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Abstracts

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Conflict of Interest Statement

Top Abstracts: Oral Presentations

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Cannabis Use and Young Adults in Florida: User Characteristics, Patterns of Use, and its Implications

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To our knowledge, there is no research on cannabis use among young adults in Florida. Understanding young adults' attitudes and patterns of use about cannabis can assist healthcare providers, and the State to determine trends in this population. Thus, the overarching aim of this study is to characterize a typical young cannabis user in Florida.

To archive this, we are proposing the following aims. First, to compare attitude and demographic characteristics between CBD-dominant and THC-dominant young adults, and second, asses the relationship between CBD-dominant use and patterns of use and mental health.

We used the Florida Young Adult Cannabis Study, which included a total of 415 medical cannabis patients and 485 non-patient cannabis users. Demographic and bivariate association we conducted among the two groups (CBD-dominant and THC-dominant), multivariable logistic regression was used to build three models to identify factors associated with CBD-dominant cannabis use.

Close to 49% of young adults were THC-dominant and 51% were CBD-dominant users. Black young adults (AOR = 1.64, 95% CI = 1.11, 2.41) were more likely to be CBD-dominant users than White young adults. College students/graduates (AOR = 1.75, 95% CI = 1.24, 2.45), young adults with an income over $75,000 (AOR = 1.68, 95% CI = 1.10, 2.57), and medical cannabis patients (AOR = 2.71, 95% CI = 1.99, 3.69) were all more likely to be CBD-dominant users. Young adults who had insurance coverage (AOR = 1.56, 95% CI = 1.06, 2.28) were more likely to be CBD-dominant users. While young adults who self-reported fair or poor overall health (AOR = 0.53, 95% CI = 0.31, 0.90) were less likely to indicate CBD-dominant use, and finally, CBD-dominant cannabis use was also more likely among young adults who indicated having a cannabis use disorder (AOR = 1.87, 95% CI = 1.18, 2.96).

The current research addresses an important gap in the literature by identifying characteristics associated with CBD-dominant use among a sample of young adult cannabis users. This is important given the possible therapeutic effects associated with CBD use.

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Medical Marijuana Treatment Availability in Florida Communities with Higher Proportions of Older Adults

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Objective: Medical marijuana must be dispensed via licensed Medical Marijuana Treatment Centers (MMTCs) and treatment authorization must originate from authorized physicians in Florida. Recent studies have demonstrated that a significant proportion of medical marijuana users are older adults. The purpose of this study was to compare concentration of medical marijuana availability (MMTCs and physicians) with proportion of older adults in Florida counties. **Methods:** Two measures of medical marijuana treatment availability were defined for all counties: MMTCs/100,000 older residents and authorized physicians/100,000 older residents. Treatment locations from 2020 were downloaded from Florida Department of Health's Office of Medical Marijuana Use (OMMU) public database. Census Bureau data for the year 2020 was used to calculate the proportion of residents age ≥65 years in each county. Counties comprised of >33% older adults were classified as having a large aging population. Of those with large aging populations, treatment availability measures were calculated as a ratio of physicians or MMTCs per 100,000 older residents. Pearson correlations were calculated for treatment availability measures and proportion of older residents, then measures were mapped using Tableau software. **Results:** There were a total of 2,234 authorized physicians and 239 MMTCs in 2020. On average, older adults comprise 23% of the population in Florida counties, with 6 out of 67 counties comprised of a large aging population (>33% older adults). Florida counties had 31 authorized physicians/100k older residents [range: 0 to 102], but correlation was not significant (Pearson R=-0.11; p-value=0.38). The highest concentrations of authorized physicians were in Sarasota (45 per 100k) and Indian River (39 per 100k) counties. Florida counties had 4 MMTCs/100k older residents [range: 0 to 25], but correlation was not significant (Pearson R=-0.16; p-value=0.19). The highest concentrations of MMTCs among aging populations were Sarasota (6 per 100k) and Charlotte (4 per 100k) counties. **Conclusion:** Medical marijuana treatment availability, as estimated by MMTC and authorized physician concentration, is widely available in areas with large aging populations in Florida. Risk and benefits of medical marijuana treatment, especially related to potential interactions between marijuana and prescription medications, should be tailored for this population to prevent adverse events.

3

Effects of the non-psychoactive cannabinoid cannabidiol in acute and chronic migraine-like states

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Objective: Migraine is a debilitating disorder characterized by recurrent headaches accompanied by symptoms of anxiety and abnormal sensory sensitivity, including photophobia. Migraine is often inadequately managed by existing treatments. Thus, additional treatment options with improved efficacy and reduced side effects are a research priority. Surprisingly, despite the extensive historical use of Cannabis in headache disorders, there is limited research on the non-psychoactive cannabidiol (CBD) for migraine and there is no scientific evidence to prove that CBD is an effective treatment. Here, we test the efficacy of CBD in preventing and treating prominent symptoms of acute and chronic, pharmacologically-evoked, migraine-like states in mice. **Methods:** We developed and characterized in our laboratory an animal model of acute and chronic migraine that involved measures of periorbital allodynia associated with intraperitoneal (i.p.) administration of the migraine-triggering agent calcitonin-gene related peptide (CGRP, 0.1 mg/kg). Periorbital allodynia was assessed through mechanical stimulation of the mouse periorbital region using von Frey filaments applied according to an up down method. CBD (10 and 30 mg/kg, i.p.) was tested for its ability to decrease this and other CGRP-induced migraine-like symptoms, including facial grimace, photophobia and anxiety in male and female C57BL/6J mice. **Results:** A single administration of CGRP induced facial hypersensitivity in both male and female mice. Repeated CGRP treatment produced progressively increased levels of basal hyperalgesia in females, but not male mice. A single CBD administration protected mice from hyperalgesia induced by a single CGRP injection, in both males and females. Repeated CBD administration prevented increased levels of basal hyperalgesia induced by repeated CGRP treatment in female mice. CBD, injected after CGRP, reversed CGRP-evoked allodynia. CBD also reduced spontaneous pain traits induced by CGRP administration in female mice. CBD failed in providing protection from CGRP-induced photophobia. Finally, CBD blocked CGRP-induced anxiety in male mice. **Conclusion:** Collectively, these results demonstrate the efficacy of CBD in preventing episodic, as well as chronic headache, particularly in female subjects. Importantly, CBD may serve as an abortive agent for treating migraine attacks. CBD also shows efficacy for headache-related conditions such as anxiety and spontaneous pain, but does not seem to protect from photophobia.

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Preclinical herb-herb interaction of cannabidiol and kratom in rats

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Objective: Consumer use of cannabidiol (CBD) continues to increase. Another natural product, kratom, has also seen increased use in the western world and drawn the attention of regulatory bodies as its abuse liability is not well characterized. The major chemical component of kratom is mitragynine, an atypical opioid agonist that is being investigated as a potential aid to individuals suffering from opioid use disorder, though kratom commercial products contain many additional compounds. Individuals are beginning to combine these products, yet nothing is known about their potential to interact. The goal was to characterize the interaction between CBD and kratom. **Methods:** For the oral single-dose study, male Sprague Dawley rats (weight 250 ± 25 g) were dosed with 50 mg/kg CBD and after 30 min, 0.8 mL/kg OPMS. OPMS is a commercially available liquid kratom product with a mitragynine content of 12 mg/mL. For the multiple dose study, rats were pretreated with 25 mg/kg CBD and after 30 min received 0.4 mL/kg OPMS. This dosing schedule was repeated every 12 hr (0900 and 2100) for four days. Plasma samples collected throughout the study were analyzed for content of CBD and kratom alkaloids mitragynine, corynantheidine, speciociliatine, speciogynine, paynantheine, and 7-hydroxymitragynine. **Results:** With CBD pretreatment, the maximum concentration of mitragynine increased 2.3-fold and the exposure increased 2.8-fold. After a single oral dose an overall increase in the time to maximum concentration, the maximum concentration, and the exposure was observed for all minor alkaloids. Steady state concentrations of mitragynine and CBD showed similar behaviors as those observed after a single oral dose with an increase in both the maximum concentration achieved and the exposure. **Conclusion:** All kratom alkaloids had increased exposure with concomitant CBD administration. These results raise concerns for consumers who are taking kratom products and CBD together. The safety and toxicity of minor kratom alkaloids has not been reported but they have shown activity at a variety of receptor subtypes including adrenergic, dopaminergic, opioid, and serotonergic. Until kratom alkaloids are more widely understood and regulated caution should be taken if used in combination with CBD.

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Perinatal Cannabidiol Exposure Decreases Survival in Mice, and Impacts Anxiety-like and Obsessive Compulsive-like Behavior and Object Memory in a Sexually Dimorphic Manner When Raised to Adult

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Objective: Anxiety, attention, and memory were examined in adult mice following gestational exposure to cannabidiol (CBD), the non-psychoactive ingredient of cannabis. Administration of oral CBD to the pregnant dam was hypothesized to dampen offspring anxiety behaviors when raised to adult. **Methods:** Sexually naïve dams were trained to eat 100 mg of strawberry jam from a dish. Following acclimation and two weeks prior to mating, 100 mg/kg CBD or ethanol vehicle was mixed in the jam and administered daily to provide drug treatment throughout gestation and lactation. Once pups were born, some litters were cross-fostered to vehicle treated dams to separate any effects of CBD-induced changes in maternal behavior. At 3 months of age, offspring were behaviorally phenotyped using the buried marble, light-dark box (LDB), elevated plus maze (EPM), object memory recognition, and object attention tasks. **Results:** Pups born to CBD-treated mothers had a reduced survival – 62.2% of pups died before being weaned, whereas only 9.5% of non-drug treated pups died. We did not observe changes in litter size, maternal body weight or pup birth weight (postnatal day 0, P0), however, pups born to CBD-treated mothers weighed significantly greater by P10 and P21. In utero exposure caused mice of both sexes to bury more marbles, and females, not males, lost this behavior if they were cross-fostered to control dams. In utero exposure decreased time spent in the light compartment of an LDB apparatus when females were raised to adults, but had no effect on male mice. In utero exposure did not affect performance in an object attention task or the 1-hour object recognition test but it decreased performance of female mice in the 24-hour object recognition test. **Conclusion:** In conclusion, our data showed that gestational CBD decreases survival and may produce long-lasting anxiolytic effects for adult female mice. Gestational CBD increases obsessive compulsive-like behavior in adults, which can be reversed in females by early maternal behaviors. Gestational CBD does not alter ADHD-like behavior but decreases long-term memory in female mice as adults.

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Perceived Effectiveness of Medical Marijuana Among Adults with Chronic Pain: Findings from Interview Data in a Three-Month Pilot Study

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Objective: Patient reported outcomes are critical to evaluate effectiveness of medical marijuana (MM) as a potential alternative treatment for chronic pain. The study objective was to examine overall perceived effectiveness of medical marijuana among middle-aged and older adults who were newly initiating MM for chronic pain management. **Methods:** Interview data from participants in a three-month prospective pilot study on MM's impact on chronic pain and related outcomes were analyzed to assess perceived effectiveness of MM. Participants answered an open-ended question, "Overall how effective do you think the MM treatment is for your condition?," in a phone interview approximately one month after baseline, when participants were supposed to find a regimen with a relatively stable dose after self-titration. All responses were transcribed and analyzed using the RADaR (Rigorous and Accelerated Data Reduction) technique. **Results:** 51 adults initiating MM for chronic pain were interviewed (52.9% male, mean age 54.4, SD = 12.0), with the majority (80.3%) identifying as Non-Hispanic White followed by Non-Hispanic Black (13.7%), Multi-racial (3.9%), and Hispanic White (2.0%). Most participants (62.7%) reported MM was effective for pain reduction. The common benefits mentioned included reduction in pain intensity, improved sleep quality, and reduced need for pain and psychiatric medications. Participants also mentioned improvements in mental wellbeing such as better mood, improved focus, and less anxiety, and improvements in physical mobility. Common challenges or concerns mentioned by participants included difficulty finding a suitable product or dose (e.g., could not find the 'sweet spot'), and experiencing side effects such as 'undesired high', 'stomach issues', and a limited 'threshold of pain' treatable by product. **Discussion:** Findings suggest a majority of participants perceived MM to be effective overall for chronic pain management, with improved physical and mental functioning and reduction in other medications as commonly cited benefits. However, sides effects and difficulty in identifying proper product and dosage also warrant future investigation as MM becomes a more prevalent treatment option for chronic pain.

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Basic Science and Translational

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The Chemistry of Vaping and Dabbing Cannabinoid Acetates

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Objective: One of the newer cannabinoid compounds that is being sold to consumers is THC acetate as well as related acetylated products formed from CBN and CBD. During the lung injury outbreak that was first recognized in the summer of 2019, it had been shown that vaping vitamin E acetate led to the formation of ketene. Ketene is a highly reactive poison that was cited as a possible cause of e-cigarette or vaping product use-associated lung injury (EVALI). The objective of this study is to determine if ketene can be produced from vaping cannabinoid acetates. **Methods:** Commercial formulations and pure standards of cannabinoid acetates were aerosolized using a temperature-controlled ceramic electronic "nail", a hot surface routinely used for the flash vaporization of cannabinoid concentrate products. The vaporized aerosol was pulled through an impinger containing CDCl3 (NMR solvent) and benzylamine (ketene trapping agent). The ketene-benzylamine product (N-benzylacetamide) was analyzed by quantitative NMR. **Results:** N-benzylacetamide formation was observed for all cannabinoids studied. Exposure levels and toxicological thresholds will be presented. **Conclusion:** Vaping cannabinoid acetates leads to ketene emissions. Vaping these products thus could be putting users at risk.

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Evaluation of chronic combination oxycodone and cannabidiol treatment on pain behavior in an operant pain model

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Objective: Investigate the effect of chronic oxycodone and cannabidiol treatment, alone or in combination, on behavior using an operant orofacial reward-pain conflict model. **Methods:** Using the orofacial pain assessment device (OPAD) rats were trained to consume a positive reinforcer of a sweetened condensed milk solution under nociceptive (44.5°C) and non-nociceptive (37°C) conditions. We then investigated the effect of chronic oxycodone (0.56 mg/kg, i.p.) and cannabidiol (3.2 and 10 mg/kg, i.p.) treatment, alone or in combination, on operant responding at the different temperatures over 14 days of treatment. **Results:** Oxycodone increased responding under both thermal conditions. Neither dose of cannabidiol administered alone altered responding but when combined with oxycodone, cannabidiol dose-dependently increased responding beyond that produced by oxycodone alone. This action was more efficacious at the higher temperature, suggestive of a largely analgesic effect. **Conclusion:** These results suggest that while being devoid of any inherent activity, cannabidiol may potentiate the analgesic effect of oxycodone. As such, cannabidiol may be useful as an opioid-sparing approach to treating pain. Future work will further investigate oxycodone and cannabidiol interactions, particularly in the context of oxycodone reinforcement and reward.

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Transcriptomic Analysis of Cannabidiol and Tetrahydrocannabivarin Revealed New Molecular Targets for Treatment of Experimental Diabetic Neuropathy

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Purpose: To identify the transcriptomic signatures of Cannabidiol (CBD) and tetrahydrocannabivarin (THCV) in Streptozotocin induced experimental diabetic neuropathy (DN). **Methods:** Animals were rendered diabetic using STZ (55 mg/kg, i.p). CBD was administered (10 & 20 mg/ kg, i.p) and THCV (15 & 30 mg/kg, i.p) during the last 4 weeks of 12-week diabetic period. The animals' pain perception was assessed using the Hargreaves plantar test, hot and cold plate method, von Frey aesthesiometer, and Randall-Selitto apparatus, and nerve functional assessment using the Laser Doppler oximeter. After the study, the animals' blood was drawn to measure blood glucose levels and their DRGs were isolated for transcriptomic studies. **Results:** Diabetic animals after eight weeks significantly ($P<0.001$) increased hypersensitivity to thermal and mechanical pain and also significantly ($p<0.001$) reduced nerve blood flow when compared to the age matched control animals. CBD and THCV treatment reversed these effects in a dose-dependent manner while having no effect on the animals' body weights or blood glucose levels. Differently expressed genes (transcriptomic analysis) have been discovered in the isolated DRGs of control, diabetic, and treated animals, with 32 genes in the control group, 33 in the THCV group, and 45 in the CBD group, all of which differ from the genes expressed in diabetic animals' DRGs. These genes regulate nerve function by affecting the RAP1 signaling pathway, MAP kinase signaling pathway, neurotrophin signaling pathway, Parkinson's disease, Alzheimer's disease, focal adhesion, insulin signaling pathway, microRNAs in cancer, and others, according to KEGG analysis. **Conclusion:** Despite the fact that CBD and THCV are non-psychoactive medical marijuana components, they differ in their ability to regulate different genes that contribute to the health of neurons in diabetic condition. More research is needed to understand how these two compounds work together to reduce diabetic pain.

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Proteomics and Transcriptomics Uncover the Molecular Targets of CBD and THCV in the Sensitization of Doxorubicin against DOX-resistant MDAMB 231 Xenografts

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Purpose: To study the chemosensitization effects of cannabidiol (CBD) and tetrahydrocannabivarin (THCV) in combination with doxorubicin (DOX) against triple negative breast cancers xenografts. **Methods:** The chemosensitization effect of CBD and THCV in combination with DOX was studied using xenotransplanted DOX resistant MDA-MB-231 cells. After subcutaneous injection of 2.5 million DOX resistant MDA-MB-231 cells in 100 μL matrigel, nude mice were randomized to one of six groups (Control, DOX alone, CBD alone, CBD+DOX, THCV alone and THCV+DOX). In the combination study, CBD (10 mg/kg, i.p.) and THCV (15 mg/kg, i.p.) were given one day before DOX (5 mg/kg, i.p.) to assess the chemosensitization effect. The treatment was repeated twice a week for 3 weeks until the control group reached 6000 mm3. Using a vernier caliper, the tumor volumes were measured. The animals were euthanized and their blood and tumors collected for further study. **Results:** CBD and THCV pretreatment effectively increased DOX's anticancer potentials, reducing tumor growth and development in mice bearing DOX resistant MDA-MB-231 tumors. Data from RNA sequencing and proteomics revealed that CBD and THCV regulate apoptosis, oxidative stress, and inflammation by targeting the PDL-1 pathway, AMPK pathway, histone proteins, serotonergic pathway, CB1 receptors, and P38-MAPKinase pathway, thereby enhancing the chemosensitization effects of DOX against MDA-MB-231 breast cancers. RT-PCR and western blot analysis were used to validate the same expression genes and proteins found in RNA sequencing and proteomics. In addition, we discovered significant changes in histone acetylations when CBD/THCV was combined with DOX. **Conclusion:** According to the results of RNA sequencing and proteomic studies, CBD and THCV appear to have a chemosensitization effect on DOX by reversing histone modifications and their downstream effectors.

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Mechanistic evaluation of combined Cannabis components cannabidiol and β-caryophyllene in reducing chronic pain in a rat SCI model

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Objective: Medical marijuana is often used to relieve pain, but there is a paucity of preclinical studies which evaluate the effects of cannabis components in a spinal cord injury (SCI) model. Previous studies in our lab have established optimal therapeutic doses of two cannabis components, Cannabidiol (CBD) and β-caryophyllene (BCP), that synergistically or additively attenuate allodynia associated with SCI. To elaborate on our previous findings, 3 aims were pursued in this study: (1) assess for adverse side effects following CBD:BCP coadministration, (2) explore possible mechanisms of action underlying pain reduction, and (3) determine whether long-term CBD:BCP administration reduces opioid-seeking behavior. **Methods:** Using male and female Sprague-Dawley rats, spinal cord injuries were induced using a clip compression model at mid-thoracic levels. To assess for adverse side effects, we evaluated disturbances in motor coordination, catalepsy, and body temperature using our highest therapeutic dose. Next, we pretreated with selective CB1, CB2 and opioid antagonists followed by coadministration of CBD:BCP at the pre-determined A50 dose and evaluated for tactile and cold allodynia. Lastly, we used the Conditioned Place Preference (CPP) test with low dose morphine as an analgesic reinforcing agent. CBD:BCP treated or controls were paired with morphine on their non-preferred side and saline on their preferred side, then assessed for CPP. **Results:** Coadministration of CBD:BCP did not produce any adverse effects in the behaviors observed. Neither administration of AM630 nor naloxone had any effect on tactile and cold allodynia. However, administration of AM251 reduced or completely blocked the beneficial analgesic effects of CBD:BCP. Furthermore, animals who received CBD:BCP coadministration showed reduced morphine-seeking behavior compared to SCI animals who received morphine only. **Conclusion:** These results suggest that CBD:BCP coadministration is both a safe and effective treatment option for SCI-related pain. Further, their use as a supplemental therapeutic agent could potentially reduce opioids needed for effective pain management. Since neither CBD nor BCP are thought to act via the CB1 receptor, our results showing reversal of CBD:BCP analgesic effects by a selective CB1 antagonist suggest potential novel interaction between the 2 components in SCI that may underlie the robust beneficial effects of this combination.

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Evaluation of Cannabis constituents in a model of phantom limb pain in rats

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Objective: Phantom Limb Pain (PLP) often results from medically required limb amputation and becomes difficult to manage due to underlying inflammation and other neuropathologies, affecting up to 85% of amputees. Medical marijuana is often used for pain relief and may be beneficial for chronic pain syndromes like PLP due to the wealth of cannabinoid (CB) compounds acting via distinct or synergistic mechanisms. The goal of this study was to evaluate the analgesic potential of delta-9-tetrahydrocannabinol (THC), Cannabidiol (CBD), β-caryophyllene (BCP) and their combination in preventing or reversing PLP-like behavior. **Methods:** Using male Sprague-Dawley rats, complete sciatic nerve transection was used to replicate limb amputation. To model complex limb injuries leading to medically-indicated amputation, first chronic constriction injury (CCI) was induced using chromic gut ligatures placed around the sciatic nerve. One week later intraplantar formalin was injected 2 hours prior to performing complete axotomy. To assess for PLP, animals were observed daily using a

scale designed to capture and distinguish overall autotomy severity. Based on previous studies in our lab that established optimal synergistic CBD:BCP doses, animals were injected twice daily with either THC, CBD:BCP or THC:CBD:BCP at the following doses: 0.04 mg/kg THC, 2.0 mg/kg CBD and 16.0 mg/kg BCP. Animals were sacrificed when proximal injury appeared, with the day of termination recorded, or by 72 days post-axotomy. **Results:** Administration of all of the tested cannabis combinations showed attenuation in the severity and onset of PLP-like behaviors compared to the vehicle controls. Comparison between experimental groups showed that animals treated with either THC alone or CBD:BCP combination displayed lower autotomy scores compared to animals receiving all three together (THC:CBD:BCP). This may be due to competing partial agonist effects of one or more of the components, and will be further investigated. No overt side effects were observed following any treatments. **Conclusion:** These findings further support the novel use of cannabis constituents as therapeutic agents for the management of neuropathic pain syndromes. In particular, identification of effective combinations of mechanistically distinct cannabis components may be beneficial in preventing the development of debilitating and difficult-to-treat phantom limb pain.

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Extracellular Vesicles from Human Umbilical Cord Mesenchymal Stem Cells Loaded with Cannabidiol Alleviate Paclitaxel Induced Peripheral Neuropathy

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Objective: Chronic paclitaxel (PTX) treatment causes excruciating pain in cancer patients, limiting its use in cancer chemotherapy. Herein, neuroprotective potential of synthetic cannabidiol (CBD) and CBD formulated in extracellular vesicles (CBD-EVs) isolated from human umbilical cord-derived mesenchymal stem cells were studied against PTX-induced neuropathic pain (PIPN) in C57BL/6J mice. **Methods:** PTX (8 mg/kg, i.p) was injected every other day (four doses) to induce neuropathy in C57BL/6J mice. CBD and CBD-EVs was administered (5 mg/kg, i.p) for 6 weeks with twice a week frequency. At the end of study, behavior of the animals towards pain perception were measured using Hargreaves plantar apparatus, hot and cold tail immersion test, von Frey aesthesiometer and Randall-Selitto apparatus. Dorsal root ganglions (DRGs) were isolated from animals for molecular studies. Further, invitro studies were conducted in DRG primary cultures to study the mitochondrial effects of CBD and CBD-EVs against PTX insult. **Results:** EVs and CBD-EVs particle size, surface roughness, nanomechanical attributes, stability, and release studies were investigated. CBD-EVs treatment significantly improved mechanical and thermal hypersensitivity (P<0.001) as compared to EVs or CBD alone. PTX-treated mice dorsal root ganglions and spinal homogenates had mitochondrial dysfunction which was significantly improved by CBD and CBD-EVs by regulating the AMPK pathway (P<0.001). Blocking studies with 5HT1A receptors and AMPK demonstrated that CBD had no effect on PIPN neurobehavioral or mitochondrial function. **Conclusion:** Our results suggest that CBD-EVs can be a novel therapeutic option for the treatment of PIPN and CBD treatment activates AMPK axis in regulating PIPN.

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Clinical Drug Interaction Assessment of Cannabidiol and Methylphenidate

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Medical cannabis (MC) refers to cannabis or cannabis-based products recommended to alleviate or reduce symptoms of a medical condition or a disease. The two primary cannabinoids utilized for their therapeutic properties are cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC). MC may consist of purified single agents (e.g. CBD or THC), or complex mixtures within multiple which may be administered via a range of dosing routes. Drug-drug interactions (DDIs) are a significant cause of ED visits, hospital admissions and increased morbidity and mortality. Importantly, MC is frequently used by complex medical patients taking conventional prescription medications and the DDI potential of MC remains only partially understood. In vitro data indicate that THC and CBD can potently inhibit the drug metabolizing enzyme carboxylesterase (CES1). This finding may be significant since functional CES1 is required for both detoxification and metabolic activation of prodrugs. **Objective:** An open-label, placebo-controlled, crossover study in healthy subjects (n=12) assessed the influence of 4-days of either 750 mg CBD oral solution (Epidiolex®) twice daily vs placebo on a 10 mg dose of the CES1 substrate methylphenidate (MPH; Ritalin®). **Methods:** Following a run-in of CBD or placebo, an additional dose of CBD or placebo, and 10 mg of MPH was administered. Serial blood samples were collected over 8 hours and concentrations of MPH and CBD were measured by LCMS/MS. Pharmacokinetic parameters were summarized by noncompartmental analyses. **Results:** The MPH maximum plasma concentration (Cmax) was reached within 0.5-3 hours and for CBD within 1-6 hours. Co-administration of CBD led to a numerical increase in the exposure to MPH. The ratio (90% CI) of AUC and Cmax central values when MPH was administered with CBD versus alone were 1.09 (0.98, 1.22) and 1.08 (0.87, 1.35), respectively. The geometric mean AUC0-8 and Cmax of CBD were 1470 ng·hr/mL and 360 ng/mL, respectively. There was a trend of increased MPH exposure with CBD co-administration. **Conclusion:** CBD at the dose evaluated, produced only weak and clinically insignificant effects on MPH exposure. However, given the positive trend observed between MPH and CBD exposure, some vigilance is warranted when CBD is administered at higher doses or with CES1 substrate medications.

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Endocannabinoid modulation of the mouse Insular Cortex

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In recent years, the endocannabinoid system (ECS) has emerged as one of the most important neuromodulatory systems involved in the regulation of food intake. It has gathered significant attention as a promising therapeutic target in eating disorders. Stimulation of cannabinoid receptors with exogenous ligands has been shown to increase appetite and food intake towards food with high palatability.

In addition, the ECS has been shown to play a role in neural processing of salient stimuli important for food seeking and eating initiation. While animal studies have indicated that these effects result in part from ECS modulation of the mesolimbic reward system, less information is available on endocannabinoid influences on cortical regions important for eating behaviors.

For all these reasons, we believe that understanding the neuromodulatory effect of endocannabinoids on neural processing of food-predicting cues within the mouse Insular Cortex (IC) will increase our knowledge of the neurobiological mechanisms of cannabinoid actions and provide crucial information for the development of cannabinoid-based pharmacotherapies.

Here we will present two parts of this research. First, we are going to present neural data using a novel, genetically-encoded cannabinoid indicator that allowed us to record the endocannabinoid modulation within the IC while the animals perform a taste-related task. Second, we are going to present behavioral data of male and female mice engaged in a taste-related task, measured before and after pharmacological manipulation of the ECS in the IC.

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An Exogenous Cannabinoid Decreases Olfactory Sensitivity in Non-fasted Mice

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The endocannabinoid system is a widespread neuromodulatory network that influences numerous aspects of sensory perception including olfactory processes. Previous research in rodents has suggested that endocannabinoids may regulate food intake through an olfactory-dependent mechanism (Soria-Gómez & Bellocchio et al., 2014). Specifically, cannabinoid type-1 (CB1) receptors within the granule cell layer of the main olfactory bulb (MOB) were proposed to stimulate ingestion in fasted mice by enhancing their olfactory sensitivity.

To further explore this phenomenon, we used an operant conditioning go/no-go assay with highly reproducible odor stimulus delivery to measure olfactory thresholds in mice. Infusions of the CB1 agonist, WIN 55,212-2, (WIN) directly into the granule cell layer (GCL) of the MOB in these animals, yielded a significant decrease in behavioral sensitivity as compared to vehicle or no manipulation ($p = 0.001$). Intrabulb infusions of the CB1 antagonist, AM251, into the GCL did not have a significant effect on olfactory sensitivity compared to vehicle ($p = 0.35$).

Further, peripheral injections of WIN also did not influence odor detection ($p = 0.76$), contrary to previous findings utilizing this manipulation. These results indicate that exogenous cannabinoids acting on granule cells, blunt rather than enhance olfactory sensitivity, at least in non-fasted mice. Additional research is needed to uncover how metabolic state (e.g., fasting) influences cannabinoid signaling within the olfactory bulb and ultimately odor perception.

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Synthetic cannabinoids as a host-targeting approach to reduce inflammation and clear intracellular infection

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Salmonella Typhimurium is a Gram-negative intracellular bacterium that causes foodborne illness, characterized by robust inflammation of the gastrointestinal tract. Salmonella infects a variety of cells, including antigen-presenting cells such as macrophages. Our laboratory discovered that host lipid metabolism is a critical process targeted by this pathogen. Specifically, Salmonella affects the host endocannabinoid (eCB) metabolism involved in the cell's anti-inflammatory status.

Upon the highly proinflammatory infection with Salmonella that causes damage to the epithelial cells of the small intestine, there is a critical need for the host macrophage to shift from an M1 phenotype to M2. M2 phenotype is associated with resolving inflammation and improvement in tissue healing. Our study has demonstrated that eCBs and synthetic cannabinoids (CBs) prime macrophages towards a more phagocytic and less inflammatory M2 phenotype. Hence, the CBs are expected to help with bacterial clearance and reduce inflammation.

This study aimed to determine if synthetic CBs can modify innate immune responses directed against Salmonella and help maintain homeostasis during this highly inflammatory infection. Towards this goal, we infected RAW264.7 or bone marrow-derived primary macrophages (BMDMs) with S. Typhimurium, followed by exposure to such CBs as noladin ether and WIN55,212-2. The cytokine analysis was done at 2- and 24-hours post-infection, revealing that WIN55,212-2 can completely block proinflammatory TNF-alpha responses. Additionally, we evaluated the effect of CBs on bacterial clearance, where WIN55,212-2 was shown to increase bacterial clearance.

Overall, our results suggest that CBs can be used to decrease inflammation and promote host pro-phagocytic functions during Salmonella infection.

Education, Quality, and Safety

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Evaluation of administrators' and clinicians' knowledge of, attitudes about, and barriers to medical marijuana (MMJ) utilization in Florida's long-term care settings

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Objective: To evaluate administrators' and clinicians' knowledge of, attitudes about, and barriers to medical marijuana (MMJ) utilization in Florida's long-term care settings. **Methods:** A survey was developed, peer-reviewed, and delivered to clinicians and administrators in nursing homes and assisted living facilities throughout the state mainly via email. From November 2021 through February 2022, data on respondents' age, sex, race/ethnicity, and title, as well as type and size of facility were collected. Questions were grouped to reflect 1) attitudes; 2) knowledge; 3) barriers. Frequencies of respondent characteristics were described, and correlations were calculated between factors. **Results:** During this period, 117 responses were collected: 21.1% were physicians, 36.8% were nurses, and 42.1% were other professionals; 52% reported having an administrative role. The mean age of respondents was 47.2 years (SD=13.5); 74.4% identified as female, with 5.4% identifying as Black or African American and 73% as Caucasian/White. Regarding ethnicity, 17.6% identified as Hispanic, Spanish or Latinx. About half of the facilities had under 150 beds, with the median number of residents at 150. Significant ($p<0.05$) correlations were found between belief that MMJ is a viable therapy and a) having received adequate training on MMJ, b) understanding differences between MMJ and CBD, c) awareness of different routes of MMJ administration and d) knowing how to obtain an MMJ card in FL. Older respondents were more likely to indicate that MMJ was not helpful for managing certain symptoms (e.g. insomnia). Females were more likely to have reported receiving inadequate MMJ training and inexperience discussing MMJ with patients; however, males were more likely to disagree that healthcare professionals should receive MMJ training. Latinx respondents were more likely to disagree that providers should recommend MMJ for some conditions and that MMJ could have concerning interactions with other therapies. The most frequently selected barriers to recommending MMJ for patients were not having enough training and lack of clinical guidelines. **Conclusion:** These observations indicate substantial need for training and clinical guidelines for clinicians in residential, long-term care in Florida. Given the prevalence of symptoms known to respond to MMJ among older adults, facilitating access to MMJ would be helpful.

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Performance Assessment Measures: Florida A&M University (FAMU) Medical Marijuana Education and Research Initiative (MMERI) Public Education Plan

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Objective: Florida A&M University (FAMU) established the Medical Marijuana Education and Research Initiative (MMERI) to educate minorities about marijuana for medical use and the impact of the unlawful use of marijuana on minority communities, pursuant to Section 381.986 Florida Statutes (F.S.). This presentation provides an overview and update on ongoing assessment measures of how MMERI's Public Education Plan (Education, Community Engagement, and Communication) has educated and engaged individuals using education courses, print and broadcast media, public service announcements, virtual technologies, including e-Newsletters and virtual forums. This presentation also presents the evaluation of the statewide impact of MMERI's engagements, programs, courses, and activities. In July, 2020, the FAMU MMERI launched an integrated Public Education Plan for the fiscal year 2020-2021 and 2021-2022. It includes results-based approaches to educate, learn and talk about marijuana with minority and diverse audiences statewide. **Methods:** Assessment measures, such as, descriptive statistics with comparative analyses using quantitative and qualitative data, are used to organize, summarize and report on selected activities. These data are extracted from formative and summative data results and reported in the required legislative Quarterly Reports. The FAMU MMERI Core Metrics for the three key components of the Public Education Plan, include material downloads; consumer e-newsletter signups; requests for information, digital and social media analytics, including reach, impressions, click-through rate, downloads, and user engagement; estimated listenership and circulation of print, radio, and outdoor advertising; audience attendance at events, programs, and activities (virtual and in-person); responses to pre- and post-activity surveys and questionnaires, and audience sentiment, share of voice, and public commentary. It includes results-based approaches to educate, learn and talk about marijuana with audiences statewide. **Results:** FAMU's MMERI educated minorities about marijuana for medical use and the impact of the unlawful use of marijuana, pursuant to Section 381.986 Florida Statutes. However, the invaluable data extracted from assessment and surveys provided critical insight showing participants not only moved from one level of competency to a higher one in the cognitive domain, but in the affective domain as well.

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Institutional Review Board Challenges Associated with Contemporary Cannabis-based Proposals

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The primary purpose of an institutional review board (IRB) is to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in research. (Grady 2015) As noted by Grady, the research landscape has grown and evolved since the inception of the IRBs in 1974 and is likely one of the reasons inconsistencies in the IRB review, and in the application of federal regulations. has led to the dissatisfaction of investigators.

In Florida, the Consortium for Medical Marijuana Clinical Outcomes Research (CMMCOR) was established in 2019 for the purpose of conducting, sharing, and supporting research on the effects of medical marijuana on health conditions and symptoms. The CMMCOR is comprised of selected Universities across the state and works to contribute to the understanding of medical marijuana. In accordance with the US regulatory requirements, each institution board must include a scientific member amongst the diverse make-up of at least 5 in total, whose responsibilities include evaluating research acceptability related to laws, regulations, institutional commitments, and professional standards. This includes determining the levels of risk and anticipated benefits of a proposed study. Given recent financially-supported cannabis research initiatives in Florida and the complexity of regulations surrounding marijuana laws, in addition to the limited expertise of institutional faculty, it is proposed to establish a centralized review model where the combined Florida institutions form an alliance to create a new central IRB for the sole purpose of most-accurately reviewing cannabis-based research proposals.

Federal regulations permit such centralized review boards for the primary purposes of minimizing redundant reviews, alleviating the overall burden, reducing delays in reviews, and facilitating member expertise for a given research focus area. Resistance to adopting a central review has been based on the importance of local context, local accountability, liability, discomfort with relinquishing control over the review, uncertainty of the quality of the review, and logistical concerns of cost-sharing. It is proposed that for the purposes of effectively studying medical marijuana under one state program that a centralized IRB would serve the initiative well.

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R/THCO: A Rapid Netnographic Examination of THC-O-Acetate

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The use of rapid online ethnographic assessment represents a novel exploration into the growing phenomenon of semi-synthetic cannabinoids. This research outlines the emergence of an online community dedicated to the consumption and distribution of the substance, THC-O-Acetate.

The role of prosumers of these products as mediators of knowledge and substances is explored, to contextualize the nature of the broader growth of semi-synthetic cannabinoid markets. Observations about the perceived safety and potency of these substances are noted in the context of the overarching regulatory landscape in which these substances are emerging, with implications for their regulation discussed in the conclusion.

While the use of rapid ethnographic methodologies has been explored in design processes [Heinonen and Medberg 2018] and medical settings (Ackerman et al., 2015), the utilization of online field sites and social media networks as subject communities reflect the more integrated technological approach known as netnography (Kozinets 2010). As rapid ethnographic engagement is usually limited temporally, the utilization of digital networks of information and community allows for a more elaborate picture, especially when combined with other methods of "Time Deepening" (Millen 2000).

An important distinction between more traditional ethnography and the methods utilized for this research is that the researcher did not use data collected from personal engagements, interviews, or focus groups in order to avoid ethical complications that may arise from the author's own embedded position as a cannabis industry stakeholder. The remainder of this section will explain the motivations behind site choice, and the background of the community will be explored.

Population Health and Clinical

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Factors Associated with the Perceived Effectiveness of Marijuana for Anxiety Among People Living with HIV

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Among people living with HIV (PLWH), the prevalence rates of marijuana use range between 20 to 60%, with more than half using marijuana to manage anxiety symptoms. However, not all PLWH perceive marijuana as an effective treatment for anxiety. Understanding which factors are associated with perceived marijuana effectiveness has the potential to improve therapeutic recommendations for PLWH.

Thus, this study aimed to identify specific characteristics (i.e., demographic and health conditions) associated with perceived marijuana effectiveness for anxiety among PLWH. This was a cross-sectional study using baseline data from the Marijuana and Potential Long-term Effects (MAPLE) Study. Demographic characteristics included age, sex, sexual orientation, and health conditions (e.g., physical, mental). The effectiveness score was dichotomized into two categories, not very effective (0-8) and very effective (9-10). The descriptive analysis was done using Chi-Square and Fisher's exact tests for categorical variables (N %) and

the Mann-Whitney test for numerical variables (Median IQR). The multivariate logistic regression analyses were performed to identify characteristics associated with perceived effectiveness using the backward elimination method.

A total of 187 participants who self-reported anxiety (Yes/No) or had a GAD-7 score ≥ 10, or those who reported using cannabis for anxiety/stress were included in the analysis. The median (IQR) age was 50 (39, 57), 62% were males, 62% were African Americans, and 57% were heterosexual. In the bivariate analysis, perceived marijuana effectiveness for anxiety was significantly greater in women, LGBTQ, and self-report schizophrenia, cancer, and chronic lung disease (p≤0.05).

In the adjusted analysis, PLWH who were LGBTQ (OR 0.26, 95% CI .10 - .67) or reported diabetes (OR 0.14, 95% CI .02 -.95), depression (OR 0.37, 95% CI .14-.97), or schizophrenia (OR 0.12, 95% CI .02-.64) were less likely to report marijuana as very effective; whereas those with PTSD (OR 3.7, 95% CI 1.10-12.6) and cancer (OR 11.7, 95% CI 1.1 – 128.5) were more likely to report marijuana as very effective for anxiety. No other variables were significant in the bivariate or multivariate analyses.

The current research addressed an important gap in the literature by identifying characteristics associated with perceived marijuana effectiveness among PLWH who reported anxiety.

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The co-presence of opioids in Cannabinoid-related mortality during the COVID-19 pandemic in Florida

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Background: As more Americans died from opioid overdoses (more than half a million opioid deaths in the US since 1999 and 75,673 during the COVID-19 pandemic's initial year), medication-assisted treatment (MAT) to curb opioid overdoses was one of the top priorities. The MAT treatment includes methadone, buprenorphine, and cannabinoids. Some studies implicate the role of cannabinoids in opioid use disorder or its analgesic properties to reduce opioid use. However, research on the co-use of opioids in cannabinoid-related mortality (CRM) is limited. **Purpose:** This study reports the co-presence of opioids in cannabinoids as a cause of death during the COVID-19 pandemic in Florida. (A drug is considered the cause of death when it plays a causal role in the death of a person through autopsy and toxicology results). **Methods:** We used retrospective analysis of people who died from cannabinoids as a cause of death with the co-presence of opioids in their system. We used descriptive statistics in describing the co-presence of opioids in CRM using the Florida Department of Law Enforcement data in 2020. **Results:** 42 decedents died from cannabinoids as a cause of death in Florida in 2020. Age range from 17-74 years, mean age of 39.52 (SD=14.829). Most decedents were male (83.3%), non-Hispanic whites (n=33 or 78.6%). All 42 decedents died in accidents, 16 of 42 from vehicular motor accidents and, 21 of 42 from polysubstance use while under the influence of cannabis, 17 of 42 active tetrahydrocannabinol or THC (no dosage reported). Twelve cases involved morphine, 11 cases with fentanyl,

6 cases with heroin, 3 cases with codeine, 2 cases with oxycodone and buprenorphine, and a case with hydrocodone. Heroin involvement accounts for 6 cases. **Implications:** Cannabinoid-related mortality is indeed a serious problem. The co-presence of opioids such as morphine and fentanyl is notable, warrants further study. Until a safety level of the analgesic effect of cannabinoids is proven safe, the public is warned about the potential adverse effects of using the drugs concurrently.

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Cannabis use among young adults in the state of Florida: A comparison of medical cannabis patients and non-patient cannabis users

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Objective: As state laws regulating cannabis use have changed in recent years there has been a corresponding increase in the prevalence of cannabis use, particularly among young adults. Since the repeal of a ban on smoking medical cannabis in 2019, the state of Florida has seen a dramatic increase in both the number of treatment centers and qualified patients. The primary goal of the current research is to compare medical cannabis patients (MCP) to non-patient cannabis users (NPCU) along demographic characteristics, characteristics of cannabis use, and health-related conditions. **Methods:** The Florida Young Adult Cannabis Study included respondents aged 18 to 34, who had used cannabis products at least three times in the past 90-days and were residents of the state of Florida during the previous 12-months. Participants were recruited during the winter of 2020 via an online survey panel program, Qualtrics. Participants included 900 individuals who submitted complete survey data, including 415 MCP and 485 NPCU. **Results:** A sizeable portion of the sample reported motives for cannabis use that were inconsistent with their "patient" status, as 13% of MCP endorsed primarily/exclusively recreational motives, while 31% of NPCU endorsed primarily/exclusively self-treatment motives. Regarding demographic characteristics, MCP were more likely to be male, college graduates, employed, and have health insurance compared to NPCU. Additionally, MCP were more likely to report several different forms of cannabis (e.g., edibles, concentrates), to microdose, and be CBD-dominant users compared to NPCU. However, NPCU initiated regular cannabis at a younger age and reported more daily use than MCP. Regarding social characteristics of cannabis use, MCP reported more sources of cannabis, used cannabis with different groups of people, and identified more sources of information about cannabis compared to NPCU. Finally, MCP were more likely to report pain which interferes with daily activities, suicidal ideation, symptoms associated with PTSD, and COVID-19 related medical issues than NPCU. **Conclusion:** The current research identified several significant differences between MCP and NPCU and informs state-level policy. Relative to NPCU, MCP used for self-treatment motives, used safer forms of cannabis, initiated regular cannabis use at an older age, and used cannabis less frequently.

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Tracking real-time changes in anxiety/depression among Florida cannabis consumers using Releaf App and exploring user demographics connected to relief outcome

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In recent years, scientific attention has increasingly focused on the therapeutic effectiveness of cannabis use for a wide variety of physical and mental ailments. One-third of Americans will suffer from an anxiety disorder at some point in their lives, and over 20% will suffer from major depressive disorder. Traditional pharmaceutical treatments for depression and anxiety may be problematic, due to their relatively low efficacy as well as their potential for abuse.

As such, medical cannabis—now legal in some form in over 70% of U.S. states—has attracted interest due to its potential to alleviate symptoms of both conditions. Surveys of medical cannabis users across the United States have shown that relief from symptoms of anxiety and depression are among the most common reasons cited by patients for using medical cannabis.

Recently, smartphone technology has facilitated the collection of large amounts of data from cannabis users. One popular smartphone app—Releaf App™ technologies—has been used worldwide by researchers, healthcare professionals, and cannabis product manufacturers to collect data on the performance of legal cannabis and hemp-derived CBD products.

The present study used the Releaf App to review the self-reported experiences of cannabis users in Florida, with a focus on understanding how cannabis may impact anxiety and depression symptomology. Over the last three years, several hundred Releaf App users from the state of Florida provided anonymous, real-time reports of their symptoms of anxiety and/or depression immediately before and after a cannabis use session.

Changes in symptomology, gender, age, method of consumption, and dose amount were analyzed. Multilevel modeling was used to analyze the data. After controlling for symptom levels before sessions, cannabis consumption significantly reduced anxiety/depression symptomology for the majority of participants, with higher relief for depressive symptoms. Doses and method of consumption also significantly predicted symptom reduction, but gender and age did not impact findings. We also explore user demographics among those who reported positive relief (70%), no relief (25%), and negative relief (5%) outcomes.

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Medical Marijuana & Me (M3): A New Combined Cohort/Cross-sectional Study of Medical Marijuana Users in Florida

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Background: Significant knowledge gaps regarding the effectiveness and safety profile of medical marijuana (MMJ) impose challenges for MMJ-certifying clinicians who make treatment recommendations. The Medical Marijuana & Me (M3) study is proposed to collect patient-centered data from Florida MMJ users.

Objectives:
- Quantify MMJ use persistence and identify reasons for discontinuation.
- Describe outcome trajectories for primary reasons for MMJ use and determine factors associated with different trajectories among MMJ initiators.
- Describe MMJ use patterns, including consumption modes, dosing, and use frequency that patients report as "most effective," and identify characteristics associated with such use patterns.
- Describe changes in products, consumption modes, and dosing over time.
- Characterize adverse effects, including cannabis use disorder, and identify associated products and patient characteristics.
- Track alcohol, tobacco, and other substance use among MMJ initiators.
- Describe concurrent prescription medications use, and factors associated with changes in medications after initiating MMJ.
- Identify concomitant medication use with potential drug-MMJ interactions risk.

Protocol Summary: The M3 databank will house: 1) data from a prospective cohort of MMJ initiators who complete surveys at enrollment, three months, and nine months after MMJ initiation, and 2) data from a cross-sectional sample of current MMJ users. A multidisciplinary committee including researchers, physicians, pharmacists, patients, and dispensary personnel planned study protocols. We plan to recruit 1000 participants aged ≥18 years with ~50% new and ~50% current MMJ patients from clinics and dispensaries. Consented participants will be compensated with a gift card for each survey completion. Survey domains include sociodemographic characteristics, physical and mental health, marijuana use history, reasons for MMJ use and discontinuation, MMJ products and use patterns, concurrent use of prescription medications and other substances, and side effects. We pilot-tested the questionnaires on 20 randomly selected participants from the Marijuana Center Contact Registry. We established a concept system to facilitate sharing and analysis of deidentified M3 data. Linkages with other databases are planned as well. Enrollment begins in May 2022. **Conclusion:** The M3 databank will provide data to investigators affiliated with the consortium to enhance research to inform policy, clinical practice, and improvements in patient outcomes.

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Efficacy and Safety of Older Adults with Chronic Pain using Medical Marijuana

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Objective: The purpose of this study is to identify if Medical Marijuana (MMJ) is effective and safe for older adults with chronic pain, to develop an understanding of what educational materials are required to facilitate access to appropriate products at medical marijuana treatment centers (MMTC), and to provide evidence to guide policy for clinical practice. **Methods:** This study utilized an explanatory sequential mixed methods design. The quantitative phase was descriptive correlational and investigated the preparation to use MMJ, patterns of use and effects on pain relief including potential side effects. The qualitative phase used content analysis to identify emergent themes from the interview data. **Results:** Data was collected using REDCap online survey tools. 131 participants met inclusion criteria with 124 completing the questions. Thirty participants were purposely invited to the interviews with seven interviews completed and analyzed. The analysis revealed the occurrence of several common side-effects of MMJ use. The largest side effect was an increased appetite (22.3%), followed by change in lethargy (14.0%). There were also elevated levels reported in mood changes (12.4%), lack of concentration (11.6%) and dizziness (9.1%). 3 (2.5%) participants reported that they did not receive any MMJ education prior to filling their prescription, with 52.5% reporting the education was less than 20 minutes. MMJ was considered effective in reduction of overall chronic pain on a visual analog scale ranging from 0 to 100 with a decrease in average pain from 70.9 prior to MMJ use to 33.8 after use [t(79)=16.29, p<.001, d=1.82]. Six themes were identified from the qualitative interviews included: 1) reasons for using MMJ, 2) side effects of MMJ, 3) benefits, 4) lack of education about the safe use of MMJ, 5) dispensary challenges, and 6) the cost burden of obtaining the MMJ license and renewal. All seven participants confirmed their difficulty with seeking out information about MMJ on their own. **Conclusion:** These themes, in combination with the quantitative findings, suggest that state legislative bodies understand the importance of implementing mandatory MMJ education among dispensary site personnel to help address any gaps of MMJ education.

Reviews

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Doses of cannabis and cannabinoid products in clinical trials - A rapid review

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Introduction: Cannabis and cannabinoid (CaC) products are increasingly used for various medical conditions. Identifying evidence that supports safe and effective dosing is important to guide policy and clinical practice. The objective of this rapid review was to summarize doses of CaC in randomized clinical trials (RCT) investigating the effectiveness and safety of CaC products. **Methods:** To retrieve RCTs that assessed the effectiveness and safety of CaC in clinical settings we identified relevant studies from previously published reviews and updated this information with a new literature search in PubMed, Embase, and Web of Science, to retrieve recently published RCTs between November 2019 and October 2021. We excluded articles that were inaccessible or not written in English. Two reviewers (NES, SJ) extracted information about indication, route of administration (RoA), products used (e.g., tablet), agents used (e.g., cannabidiol (CBD)), doses, and publication year. We conducted a qualitative synthesis of included studies. **Results:** We identified 81 RCTs. Doses where either defined by content of delta-9-Tetrahydrocannabinol (THC) (17), CBD(8), THC and CBD(28), Dronabinol(12), Nabilone(13), Levonantradol(2), or CT3(1). Minimum and maximum daily doses as defined per protocols were 1.2–216, 20-800, 2.7/2.5–142/145.8 mg, for THC, CBD, and THC/CBD-defined products respectively. The consumed daily mean dose was reported in only 9 publications, and out of those the highest was 82.8, 74.8, and 30.8 /31.6 mg for THC, CBD, and THC /CBD defined products respectively. Investigated doses differed widely across products, RoA, and indication. For THC and THC/CBD-defined products, the maximum daily dose (216 mg , 142 /145.8 mg) was found in a trial that evaluated inhalation in patients with posttraumatic stress disorder. For CBD-defined products the maximum allowed daily dose was in patients with psychosis. **Conclusion:** CaC RCT protocols included a wide range of doses, which differed by indication, product, and RoA. However, the consumed dose was often uncertain. Investigated doses appeared generally lower than those certified for medical marijuana patients in Florida. In selected conditions, for specific RoAs and products, evidence exists to guide safe and effective dosing, but more evidence is needed for the majority of CaC products across medical conditions.

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Three theories explore why women who use cannabis regularly are twice as likely to orgasm

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Objective: Research reveals that up to 41% of women have difficulty orgasming (Laumann et al., 2005). Research also suggests that women who regularly use cannabis are twice as likely to orgasm (Lynn et al., 2019). Women, more than men report cannabis' sexual faciliatory effects (Gorzalka et al., 2010). The objective of this literature review is to explore three different theories that point to why cannabis may enhance women's ability to orgasm. If data collection supports these theories, it follows that female orgasmic disorder (FOD) could become a condition of treatment for medical cannabis. **Methods:** Literature Review **Findings:** The psychoactive chemical in cannabis, THC, alters consciousness. Altered states of consciousness were found to be strongly related to higher sexual responsiveness in women, and to a lesser extent in men (Costa et al., 2016). Altered State of Consciousness Theory proposes that women who learn to induce altered states of consciousness with cannabis are more likely to orgasm. Women, more than men, need to be in a state of absorption to orgasm (Swartz, 1994). A state of absorption can be created with an intense focus on bodily sensations and/or the imagination, both of which are stimulated by cannabis. The State of Absorption Theory proposes that a state of "absorption" is essential for high sexual arousal and orgasm in many, if not all, women. Cannabis reduces the activity in the amygdala, a part of the brain associated with hypervigilance and anxiety (Rabinak et al., 2020). A reduction in anxiety associated with a sexual encounter could improve experiences and lead to improved orgasm and satisfaction in women (Kosiba et al., 2019). The Amygdala Reduction Theory proposes that reduced amygdala activity can positively affect female orgasmic disorder. **Conclusion:** It can be hypothesized that women who use cannabis more regularly may be more comfortable with altered states of consciousness that allow deeper bodily sensations. This altered state of consciousness may lead to enhanced ability to orgasm. The researcher is collecting data to explore how and whether the use of cannabis has any impact on women's orgasmic difficulty.

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Medical Cannabis for Chronic Nonmalignant Pain Management

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Cannabis has been used since ancient times for medical and recreational research. Current cannabis research has shown that medical cannabis is indicated for symptom management for a myriad of conditions not limited to cancer, chronic pain, headaches, migraines, and psychological disorders (anxiety, posttraumatic stress disorder).

Δ9 tetrahydrocannabinol (THC) and cannabidiol (CBD) are active ingredients in cannabis that modulate a patient's symptoms. These compounds work to decrease nociception and symptom frequency via the endocannabinoid system. Research regarding pain management is limited within the United States as the Drug Enforcement Agency (DEA) classifies it as a Schedule I drug.

Few studies have found a limited medical cannabis use. This review article will document the validity of how medical cannabis can be utilized for chronic non-malignant pain management. 77 articles were selected after a thorough screening process using PubMed and Google Scholar.

The following keywords were used: "Cannabis," "Medical Marijuana," and "Chronic Non-Malignant Pain." This paper demonstrates that medical cannabis use provides adequate pain management. Patients suffering from chronic nonmalignant pain may benefit from medical cannabis use due to its convenience and efficacy.

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Medical Cannabis, Headaches, and Migraines: A Review of the Current Literature

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Cannabis has been long used since ancient times for both medical and recreational use. Past research has shown that cannabis can be indicated for symptom management disorders, including cancer, chronic pain, headaches, migraines, and psychological disorders (anxiety, depression, and post-traumatic stress disorder).

Active ingredients in cannabis that modulate patients' perceptions of their conditions include Δ9 tetrahydrocannabinol (THC), cannabidiol (CBD), flavonoids, and terpenes. These compounds work to produce effects within the endocannabinoid system to decrease nociception and decrease symptom frequency. Research within the United States of America is limited to date due to cannabis being classified as a Schedule I drug per the Drug Enforcement Agency. Few anecdotal studies have found a limited relationship between cannabis use and migraine frequency.

The purpose of the review article is to document the validity of how medical cannabis can be utilized as an alternative therapy for migraine management.

Thirty-four relevant articles were selected after a thorough screening process using PubMed and Google Scholar databases. The following keywords were used: "Cannabis," "Medical Marijuana," "Headache," "Cannabis and Migraine," "Cannabis and Headache." This literature study demonstrates that medical cannabis use decreases migraine duration and frequency and headaches of unknown origin. Patients suffering from migraines and related conditions may benefit from medical cannabis therapy due to its convenience and efficacy.

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A Review of Recent Changes to DEA Cannabis Regulations and What It Means for Medical Cannabis Research

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After years of delay, the Drug Enforcement Administration is promulgating new regulations that change the way researchers can investigate cannabis. Although still a Schedule I narcotic requiring registration with the DEA, changes in regulations mean that it is easier for researchers and clinicians to access and work with federally-legal cannabis flower, extracts and customized cannabis preparation (THC, CBD and other cannabinoid mixtures) that are more representative of what is available via state-legal programs. Although navigating DEA regulations and applications is still a challenge, there has never been a better time to pursue medical research and pharmaceutical development.

In this talk, we will review recent changes in federal regulations and what the implications are for medicinal cannabis research in the US. We will review an example of a successful application to the DEA and FDA for investigation of the antimicrobial properties of THC and other cannabinoids, and also review how recent regulatory changes influence the availability of high quality, pharmagrade cannabis, extracts, isolates and custom preparations for research.

Medical Cannabis and Cannabinoids

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