EXECUTIVE SUMMARIES OF FINAL REPORTS

Awardees of the 2019 Consortium grants cycle

Paul A. Borsa, PhD
Associate Professor
College of Health and Human Performance

Efficacy of a controlled short-term trial of CBD ingestion on reducing symptomatic response and facilitating recovery after induced muscle injury

Executive Summary: Many physically active Americans have reported pain-relieving effects of cannabidiol (CBD) that can reduce or eliminate use of nonsteroidal anti-inflammatory drugs (NSAIDs). Currently its biological and therapeutic effects have not been explained, and clinical research in humans regarding its effectiveness is urgently needed. We sought to investigate if a controlled short-term trial of CBD ingestion was effective in reducing a symptomatic response (e.g., musculoskeletal pain and pain-related anxiety) and facilitating functional recovery (strength loss) following induced muscle injury. Secondarily, we wanted to investigate if the therapeutic effects are dose dependent.

We have **secured Investigational New Drug (IND) status for our investigational product from the US Food & Drug Administration (FDA) Center for Drug Evaluation and Research (CDER)**. In addition, we were able to receive IRB approval from UF. Our IND approved investigational product has been manufactured and processed through a Florida-based CBD company (SunFlora, Inc, St. Petersburg, FL), which has agreed to source our hemp-derived CBD for the project as well as for future studies. Patient recruitment has commenced after initial delays due to the pandemic. Data from this study will help shape future grant applications on identifying an efficacious dose range of CBD, as well as determining the cellular and molecular mechanisms that contribute to symptom resolution and recovery.

Helen Bramlett, PhD
Professor
Miller School of Medicine

Therapeutic dosing of a cannabinoid (CBD) after mild and moderate brain injury for translation to the clinic

Executive Summary: Cannabidiol (CBD) has been shown to have anti-inflammatory, neuroprotective effects and its administration may be a therapeutic strategy in the treatment of traumatic brain injury (TBI). The objective of the present study was to assess two therapeutic doses (3 or 5mg/kg) of CBD using a clinically-relevant oral administration regimen in two pre-clinical models of brain injury: a pressure wave-induced blast injury and a fluid percussioninduced (FPI) moderate TBI. We anticipated conducting and analyzing several neurocognitive, sensorimotor, hearing, and vestibular behavioral outcome measures, as well as histological analyses evaluating neuro- and cytoprotection and inflammatory responses. All FPI and Blast TBI groups have been completed, undergone their respective behavioral testing paradigms, and tissue processed for histological analyses.

We observed several interesting trends with CBD treatment after TBI. In the moderate FPI model, there was a slight preservation of sensorimotor skills as indicated by reduced asymmetrical usage of forelimbs, albeit this was not significant. Cognitive evaluation showed no CBD effect on spatial memory acquisition and retention after injury, however short-term working memory skills trended towards sham uninjured levels. Histological assessment revealed reduced cortical atrophy and contusion volumes in animals treated with CBD. Furthermore, we qualitatively observed decreased microglia activation, a hallmark indicator of TBI-induced neuroinflammation. In the Blast experiments, there were no improved hearing outcomes at the time of assessment, which contrasted our earlier findings in similar experiments with intraperitoneal CBD administration.

In summary, in our studies, **we found that oral consumption of CBD may have reduced inflammation, protected vulnerable brain regions, and reversed certain memory and sensorimotor deficits that are observed after brain injury. The appearance of reduced microglia reactivity, led us to believe that a higher oral dose may be more efficacious in reversing neuropathological sequelae**. Further investigation, possibly coupled with higher sensitivity testing paradigms, is needed to fully evaluate CBD as a therapeutic avenue in TBI. Our plan is to continue to evaluate the use of CBD after TBI for a future grant submission to an appropriate funding agency.

Joshua Brown, PharmD, PhD, MS
Assistant Professor
College of Pharmacy

UF UNIVERSITY of FLORIDA

Characterizing community and physician-level factors associated with medical marijuana prescriber registration and patient access

Executive Summary: This project **created a dynamic data visualization tool and linkable database to cross-reference cannabis-licensed physician practices, cannabis dispensary locations, and community-level and physician-level indicators of access and health**.

We first compared physicians authorized to submit patient orders for medical cannabis in Florida versus those without authorization by specialty. Further, we compared physician specialties by authorization status for measures that assess past prescribing behaviors for opioids, benzodiazepines, and brand name drugs. The general trend observed was that authorized physicians, overall and for select specialties, prescribed more opioids and more benzodiazepines than non-authorized physicians of the same specialty. Prescribing for brand name drugs was more comparable for authorized versus non-authorized physicians. Physician prescribing, practice location, dispensary locations, and other community-level measures were overlayed using Tableau Server mapping software to visually assess patterns of geographic disparities. These community-level measures were adjusted for population and the findings revealed that, during the study period, there was lack of medical cannabis access in rural areas as compared with more densely populated areas in Florida. Additionally, we documented a strong correlation between cannabis access and utilization of opioids.

Data curation and linkage will continue with the aim of hosting the server and interactive maps on the Consortium's website permanently for use by the public and other researchers. Findings will be used for future research evaluating disparities in access as well as for investigating important potential confounding variables once the MEMORY database is established. The investigators will pursue funding from the NIH and Robert Wood Johnson Foundation with a focus on health policy as well as pharmacoepidemiological and health outcomes studies using these curated and linked data.

Andrea Cippitelli, PhD
Research Assistant Professor
College of Medicine

Cannabidiol: A potential treatment for migrainelike pain, negative emotion and photophobia

Executive Summary: Migraine is a complex condition characterized by the tendency to have headache with sensory disturbances and comorbid anxiety and depression. Based on the wide range of cannabidiol (CBD)'s pharmacological actions, including anxiolytic and antidepressant effects, modulatory effects on neuronal transmission, and pain relief, we aimed to investigate if CBD has a therapeutic role in migraine pathology.

We used a calcitonin gene-related peptide (CGRP) migraine model since peripherally administered CGRP (0.1 mg/kg) reliably provided measures of cephalic allodynia, spontaneous pain as assessed by facial signs of discomfort, altered light sensitivity (photophobia) and conditioned place aversion (CPA) in mice.

The most important finding so far is that CGRP-induced cephalic allodynia is successfully blocked by CBD treatment (30 mg/kg, ip) both in male and female C57BL/6J mice. We determined that the painful responses manifested as a facial grimace were attenuated 60 min post-CGRP injection by systemic administration of 30 mg/kg CBD in female mice, whereas signs of facial discomfort in male mice were prominent at 15 min post-injection and were not reversed by similar CBD dose. We also observed reliable photosensitivity both in male and female mice, however CBD pretreatment was not effective in blocking CGRP-induced photophobia. CGRP produced anxiogenic-like activity only in male mice, an effect reversed by CBD. Lastly, we determined that avoidance for the compartment previously associated with CGRP injection was not reversed by CBD. This experiment was conducted only in male mice.

Collectively, **our results suggest that CBD is effective in relieving migraine-like pain and anxiety comorbid to headache pain, but fails in providing protection from other symptoms experienced by migraineurs such as photophobia**. Additional preclinical research is needed to demonstrate the suitability of CBD as a treatment for migraine and to identify the mechanisms of protective effects. Results from our studies aid in the progression of MMJ research, as they inform on pharmacological and behavioral effects of CBD.

Gregory McManus, PhD
Associate Professor
College of Arts and Sciences

Rapid identification and quantification of heavy metals and microplastics in CBD oil

Executive Summary: Cannabis has shown great promise for the treatment of many medical conditions. There are, however, substantial uncertainties surrounding the nature and content of contaminants in cannabis plants. The goal of this project was to develop reliable, rapid, inexpensive techniques for the determination of key contaminants within the cannabis plant and to accelerate research in this promising industry to ensure consumer/patient safety.

The specific aims of our projects were to: develop a methodology to rapidly quantify the heavy metal contaminants, including arsenic, cadmium, cobalt, copper, lead and mercury in commercially available samples of CBD oil via Wavelength Dispersive X-ray Fluorescence (WDXRF); and identify microplastic polymer contaminants in CBD oil using coupled Thermal Gravimetric Analysis – Differential Scanning Calorimetry (TGA–DSC). For the purposes of this study we collected 25 different CBD oil samples from 15 different vendors across the country. All CBD oil samples are in the form of tinctures with CBD oil concentrations ranging between 250 mg to 3000 mg per 30 mL bottle.

Analysis showed that heavy metals were not present in the samples within the detection limits of the WDXRF instrument. However, analysis did identify the presence of trace amounts of silicon in at least 12 of the 25 samples measured. Presumably, due to the low concentrations of microplastics in the samples, no characteristic endothermic phase transition temperatures were observed for the samples.

Our conclusions are that these contaminants are not present in the over two dozen commercially available CBD oil samples we analyzed within the detection limits of our instruments. These findings should help reassure consumers and policy makers that CBD oil products are inherently safe. For future direction, we propose using coupled Thermal Gravimetric analysis and Mass Spectroscopy (TGA-MS) techniques to determine contaminates present in the marijuana vaping products. For this purpose, we will seek funding through the NIH R03 program.

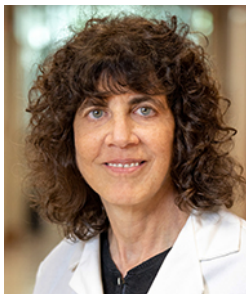
Mandip Singh Sachdeva, PhD
Professor
College of Pharmacy

Hyaluronic acid functionalized, Cannabidiol-loaded Mesenchymal Stem Cells (MSC)-Derived Exosomes for Drug Resistant Cancers

Executive Summary: About 10-14 % of all breast cancers are triple negative (TNBC), which represents an important clinical challenge, as these tumors often develop resistance to conventional chemotherapeutics. While cannabidiol (CBD) may have favorable effects in various cancers, poor solubility and increased metabolism by cytochromes P450 (CYP) enzymes limit the bioavailability of CBD.

In our laboratory, we observed that CBD besides having anticancer activity against MDA-MB-231, MDA-MB-468 and DOX-resistant MDA-MB-231 cells was also a sensitizer for anticancer drugs like doxorubicin and docetaxel. Exosomes derived from human mesenchymal stem cells (hUCMSCs-EX) have shown their potential clinical applications in various diseases including cancer. Exosomes derived from hUCMSCs were fully characterized and were formulated with CBD. CBD Exosomes significantly decreased the proliferation of MDA-MB-231 and MDA-MB-468 cells. We further functionalized these exosomes by using Hyaluronic acid (HA) and it was observed that these exosomes significantly decreased the proliferation of MDA-MB-468 cells (i.e., IC50 value: 1.76 µM) with significant increase in G1 phase cell cycle arrest when compared to CBD alone at similar doses.

Our results demonstrate **significant benefits of CBD in TNBC. Further, hUCMSCs-EX were found to be a suitable delivery system for CBD to make it a clinically feasible formulation**. Further studies using tumor models in animals will determine the benefits of the HA coated CBD-EX, which are in progress.



Jacqueline Sagen, PhD, MBA
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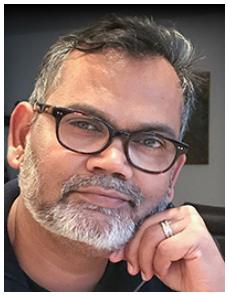
UNIVERSITY OF MIAMI

Evaluation of medical marijuana for the treatment of chronic spinal cord injury pain using a rat central neuropathic pain model

Executive Summary: Although the most frequently reported use of MMJ is for pain relief, there has been a paucity of preclinical studies evaluating the effects of cannabis in chronic pain models. Chronic pain following spinal cord injury (SCI) occurs in a majority of patients and can be so severe that it is their top quality of life concern. The goal of this study was to rigorously evaluate the effects of the two major but mechanistically distinct cannabis components, CBD and THC, and their potential synergistic pain-relieving combination, using a preclinical SCI rodent model. However, the work was hampered by the inability to obtain THC due to delays resulting from the Covid-19 pandemic. Therefore, another prominent component of Cannabis, the sesquiterpene β-caryophyllene (BCP) was substituted for these initial studies. BCP is a major component (up to 35%) in the essential oils of Cannabis sativa. It acts as a CB2-receptor-selective agonist and has shown pain-reducing effects in rodent models. Thus, its potential pain-reducing mechanism is distinct from CBD and THC and may be a valuable addition in SCI pain management.

The chronic SCI pain-reducing effects of CBD and BCP were evaluated using a battery of behavioral tests for neuropathic SCI pain in both male and female rats with clip compression spinal injury. Dose-response analyses were done for both drugs and the A50s (doses producing half-maximal effect) were calculated. Since CBD and BCP act via distinct receptors to reduce pain, their combination in appropriate ratios may provide further beneficial effects at lower doses of each. To determine this, dose-response evaluations of the combination based on the fixed ratio of the A50s were done, and potential synergism assessed using isobolographic analysis. Results showed that the CBD/BCP combination synergistically reduced cold allodynia in both male and female rats with chronic SCI neuropathic pain. The combination produced additive effects in reducing tactile allodynia.

Thus, **the combination of two major Cannabis components, CBD and BCP, show promise in furthering a pain management treatment for SCI neuropathic pain**. These results and further development will be pursued via the National Center for Complementary and Integrative Health (NCCIH) special interest program in Analgesic Properties of Minor Cannabinoids and Terpenes. In addition, once the THC is obtained, it will be tested in combination with CBD and BCP, in order to select the most potent SCI pain-reducing ratios and targeted for future NIDA/NINDS pain funding programs.



Krishna Vaddiparti, PhD, MPE, MSW
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College of Public Health and Health Professions & College of Medicine

UF UNIVERSITY of FLORIDA

A feasibility study of real-time monitoring of Posttraumatic Stress Disorder related sleep disturbances and other symptoms among patients on medical marijuana

Executive Summary: In the US several states permit the medical use of marijuana by individuals with Posttraumatic Stress Disorder (PTSD) but, at this point, we lack evidence on the appropriateness of marijuana as

a therapy for PTSD. The goal of this pilot grant is to demonstrate the feasibility of recruiting and retaining patients with PTSD on MMJ in a prospective study and examine in real-time how MMJ affects PTSD related sleep disturbances and recovery from PTSD symptoms and distress, using Ecological Momentary Assessment (EMA) delivered via smartphone and surveys.

Covid-19 restrictions have caused a slight delay in launching the study as we had to amend the study methods and procedures that involve face-to-face interactions with the participants to virtual methods. Also, the travel of research assistants to MMJ clinics was restricted to physically station at the clinic and screen referrals. To test our hypothesis, we recruited 15 patients with confirmed PTSD seeking to start MMJ for their PTSD symptoms from cannabis clinics in North-Central Florida and assessed them at different phases of MMJ treatment.

Our preliminary analysis suggests that **there were significant improvements in sleep and mental health well-being, and decreases in PTSD symptoms and nightmares, with effects lasting at least 70 days after initiation of MMJ**. This pilot study also confirms that patients with PTSD on MMJ could be recruited and retained in longitudinal real-time monitoring research.

Jenny L. Wilkerson, PhD
Research Assistant Professor
College of Pharmacy

Marijuana-derived terpenes for the treatment of chemotherapy-induced pain

Executive Summary: Paclitaxel, commonly used to treat breast, lung and other cancers, can also produce persistent and debilitating side effects such as chemotherapy induced peripheral neuropathy (CIPN). Anecdotal reports suggest marijuana may be an effective analgesic. The primary constituent of marijuana, Δ-9 tetrahydrocannabinol, produces most of its physiological actions via cannabinoid type 1 receptors (CB1R), predominately distributed on neurons, and cannabinoid type 2 receptors (CB2R), predominately distributed on immune cells. Marijuana also contains a multitude of other compounds (i.e., terpenes) that have not been well studied and may hold therapeutic promise as pain therapeutics. We examined the ability of a subset of terpenes found in marijuana: γ-terpinene, α-terpineol, β-caryophyllene to reduce a common behavior associated with CIPN pain in mice. Each terpene reversed this pain-related behavior in paclitaxel-treated mice.

We found differential cannabinoid receptor involvement underlying each terpene's ability to produce antipain effects in paclitaxel-treated mice. Further, each terpene relied on downstream inflammatory factors to produce analgesia. **Cannabis-based terpenes possess a pharmacological profile that may yield new efficacious analgesics.**

These data open exciting research questions on numerous fronts. The first new question may be that additional chemical modifications may be made to these terpenes to enhance the therapeutic dosing window of these compounds. Another exciting question involves the examination of the pharmacokinetic profile of these terpenes alone and in combination. Both questions have initiated collaborations using pilot data generated from this award, with the intention of submitting an R01 to NIDA. An additional collaboration with the UF Cancer Center is underway to examine the potential of these terpenes to co-treat both cancer-induced pain as well as cancer-induced cellular senescence; a R01 to NCI is expected as well.

Ali Yurasek, PhD
Assistant Professor
College of Public Health and Health Professions

The Relationship between State Medical Marijuana Laws, Substance Use and Mental Health Disorder Diagnoses, and Associated Health Care Costs

Executive Summary: Despite the potential of MMJ to assist with mental health conditions, marijuana use is also associated with increased participation in substance use treatment and risk for the development of psychosis and mood-related disorders. Yet, whether the passage of MMJ laws is associated with changes in substance use, mental health diagnoses or healthcare costs remains unclear. The purpose of this study was investigating the trends of substance use diagnosis, mental health diagnosis, and treatment utilization in states with and without MMJ laws between 2012-2018.

As of 2020, there are 38 states that have passed MMJ laws. Our preliminary analyses examined the treatment costs associated with 8 different mental health disorder diagnosis in 2012, including Opioid Use Disorder (OUD), Cannabis Use Disorder (CUD), Alcohol Use Disorder (AUD), Post-Traumatic Stress (PTSD) related disorders, Anxiety Disorders (AD), Depressive Disorders (DD), Psychosis related disorders (PD), and Sleep Disorders (SD). In 2012, 19 states had passed MMJ laws. In 2012, states that passed MMJ laws had higher rates of OUD, CUD, AUD, PTSD, DD, and PD (ps <.001) than those that did not yet pass MMJ laws. Similarly, the healthcare costs were significantly higher across all disorders examined in states with MMJ laws compared to those without MMJ laws. Additional analysis will be conducted to examine within-state changes in these costs across the 5-year timespan, as well as changes in the prevalence of these different diagnoses over time and in states with and without MMJ laws.

Findings will provide policy-relevant information about the influence of MMJ laws on health care utilization for substance use and mental health diagnoses.