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June 29, 2022

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Kelly Garcia, Director
Iowa Department of Health & Human Services
Hoover State Office Bldg
Des Moines, IA 50319

Re: 2022 Report on Use of Medical Cannabidiol

Dear Members of the Iowa General Assembly and Director Garcia:

Pursuant to the 2014 Iowa Acts Ch 1125, §10h, enclosed is the 2022 report on Report on Use of Medical Cannabidiol.

If you have any questions or need more information, please don't hesitate to contact this office.

Sincerely

Mark J. Braun

University of Iowa Children's Hospital
University of Iowa Health Care

Pediatric Neurology

200 Hawkins Drive 2505JCP
Iowa City, IA 52242
319-356-4864 **Tel**
319-356-4855 **Fax**
www.uihealthcare.com/children

June 29th, 2022
University of Iowa

Jennifer Harbison
Director Health Policy | Office of the Vice President for Medical Affairs

Re: **2022 Report to the Department of Public Health and the Iowa General Assembly**

Recent Publications and additions since the last review submitted July 2021:

There have only been seven randomized placebo-controlled trials published since the last review. One looks at the use of cannabidiol (CBD) to help with withdrawal symptoms from stopping chronic cannabis use, another looks at medical cannabis effects on obsessive-convulsive disorder, one on anti-nausea effects during cancer treatment, one on spasticity in children with cerebral palsy. Then there are three studies that look at different aspects of treatment of pain.

- The first was published by Khalsa and coworkers [1] in 2021 in the *Journal of Addiction Medicine*. COVID-19 pandemic has resulted in devastating mortality and morbidity consisting of socioeconomic and health effects that have included respiratory/pulmonary, cardiovascular, mental health and neurological consequences such as anxiety, depression, and substance use. Extensive efforts are underway to develop preventive vaccines and therapeutics such as remdesivir, dexamethasone, convalescent plasma, and others to treat COVID-19 but many report residual mental health problems after recovery. Cannabis products such as cannabidiol (CBD) are being advertised for the treatment of COVID-19 associated mental health problems and substance use disorders. This commentary will briefly clear the myth that CBD can ameliorate a wide range of COVID-19 associated health effects including anxiety, depression, or any substance use disorder, and show that there is a clear lack of sufficient unbiased clinical evidence from well-designed double-blind, placebo-controlled clinical trials to prove the antianxiety or antidepression therapeutic properties of CBD and support its wide use as medicine to treat COVID-19- associated mental health conditions or substance use disorders. Finally, we suggest that addiction physicians must play an important role in dealing with their patients requesting CBD prescription for treating any of these conditions.
- The second study by de Almeida and colleagues [2] in 2021 in the journal *Movement Disorders* looked at whether or not medical cannabis could help improve sleep in Parkinson patients by improving rapid eye movement (REM) sleep. **Background:** REM sleep behaviour disorder (RBD) is a common non-motor feature of Parkinson's disease (PD). Cannabidiol (CBD) is one of the main non-psychoactive components of Cannabis sativa and may represent an alternative route for treating RBD. **Objective:** This study assessed the efficacy and safety of CBD for RBD in PD. **Methods:** We conducted a phase II/III, double-blind, placebo-controlled clinical trial in 33 patients with RBD and PD. Patients were randomized 1:1 to CBD in doses of 75 to 300mg or matched capsules placebo and were followed up for 14 weeks. The primary outcomes were the frequency of nights with RBD, CGI-I, and CGI-S. **Results:** CBD showed no difference to placebo for primary outcomes. Regarding secondary outcomes, we observed a significant improvement in average sleep satisfaction from the 4th to 8th week in the CBD versus placebo group with P = 0.049 and P = 0.038, respectively. **Conclusion:** CBD, as an adjunct

therapy, showed no reduction in RBD manifestations in PD patients. A transient improvement in sleep satisfaction with a dose of 300mg has been noted. © 2021 International Parkinson and Movement Disorder Society.

- The third study was published by Spinella and colleagues [3] in 2021 in the journal *Psychopharmacology*. **Rationale:** Cannabidiol (CBD) has been reported to attenuate stress and anxiety, but little is known about the extent to which such effects result from pharmacological versus expectancy factors. **Objectives:** We evaluated whether CBD expectancy alone could influence stress, anxiety, and mood, and the extent to which beliefs regarding CBD effects predicted these responses. **Methods:** In this randomized crossover study, 43 health adults (23 women) attended two experimental laboratory sessions, where they self-administered CBD-free hempseed oil sublingually. During one session, they were (incorrectly) informed that the oil contained CBD and in the other session, that the oil was CBD-free. Following administration, participants engaged in the Maastricht Acute Stress Test (MAST). Heart rate variability (HRV) was assessed continuously, and subjective state was assessed at baseline, 90-min following oil administration, immediately following the MAST, and after a 10-min recovery period. **Results:** The CBD expectancy condition was associated with increased sedation as well as with changes in HRV that were consistent with heightened anticipatory stress regulation. Overall, there were no systematic changes in subjective stress, or anxiety, according to expectancy condition. However, participants who endorsed strong a priori beliefs that CBD has anxiolytic properties reported significantly diminished anxiety in the CBD expectancy condition. Conclusions: CBD expectancy alone impacted several subjective and physiological responses. Additionally, expectancy-related factors were implicated in anxiolytic effects of CBD for those who believed it was helpful for such purposes, emphasizing the need to measure and control for CBD-related expectancies in clinical research that involves the administration of CBD.

- The fourth study was published by Naftali and colleagues [4] in 2021 in the journal *J. Crohns Colitis*. **Aims:** Despite reports that medical cannabis improves symptoms in Crohn's disease [CD], controlled studies evaluating disease response are lacking. This study assessed the effect of cannabidiol [CBD]-rich cannabis oil for induction of remission in CD. **Methods:** In a double-blind, randomised, placebo-controlled, single-centre trial, patients received orally either cannabis oil containing160/40 mg/ml cannabidiol/tetrahydrocannabinol [CBD/THC] or placebo for 8 weeks. Disease parameters, including the CD activity index [CDAI], and simple endoscopic score for CD [SES-CD], were assessed before and after treatment. In a subgroup of patients, blood samples were collected for CBD and THC plasma levels. **Results:** The study included 56 patients, age 34.5 ± 11 years, men/women 30/26 [54/46%],30 in cannabis and 26 in placebo groups. CDAI at recruitment and after 8 weeks was 282 (interquartile range [IQR] 243-342) and 166 [IQR 82-226], and 264 [IQR 234-320] and 237 [IQR 121-271] [$p < 0.05$] in the cannabis and placebo groups, respectively. Median quality of life [QOL] score improved from 74 for both groups at baseline to 91 [IQR 85-102] and 75 [IQR 69-88] after 8 weeks in the cannabis and placebo groups, respectively [$p = 0.004$]. SES-CD was 10 [IQR 7-14] and 11 [IQR7-14], and 7 [4-14] and 8 [IQR 4-12] [$p = 0.75$] before and after treatment, in the cannabis and placebo groups, respectively. Inflammatory markers (C-reactive protein [CRP], calprotectin) remained unchanged. **Conclusions:** Eight weeks of CBD-rich cannabis treatment induced significant clinical and QOL improvement without significant changes in inflammatory parameters or endoscopic scores. The oral CBD-rich cannabis extract was well absorbed. Until further studies are available, cannabis treatment in Crohn's disease should be used only in the context of clinical trials.

- The fifth study by Vela and coworkers [5] appeared in the journal of *Pain*. Cannabidiol (CBD) is increasingly used as analgesic medication although the recent International Association for the Study of Pain Presidential Task Force on cannabis and cannabinoid analgesia found a lack of trials examining CBD for pain management. This trial examines CBD as add-on analgesic therapy in patients with hand osteoarthritis or psoriatic arthritis experiencing moderate pain intensity despite therapy. Using a randomized, double-blind, placebo-controlled design, patients received synthetic CBD 20 to 30 mg or placebo daily for 12 weeks. The primary outcome was pain intensity during the past 24 hours (0-100 mm); safety outcomes were percentage of patients experiencing adverse events and a characterization of

serious adverse events. Explorative outcomes included change in Pittsburgh Sleep Quality Index, Hospital Anxiety and Depression Scale, Pain Catastrophizing Scale (PCS), and Health Assessment Questionnaire Disability Index. One hundred thirty-six patients were randomized, of which 129 were included in the primary analysis. Between-group difference in pain intensity at 12 weeks was 0.23 mm (95% confidence interval -9.41 to 9.90; P = 0.96). Twenty-two percent patients receiving CBD and 21% receiving placebo experienced a reduction in pain intensity of more than 30 mm. We found neither clinically nor statistically significant effects of CBD for pain intensity in patients with hand osteoarthritis and psoriatic arthritis when compared with placebo. In addition, no statistically significant effects were found on sleep quality, depression, anxiety, or pain catastrophizing scores.

- The sixth study by Gilman and coworkers [6] was published in the journal of *Neuropscyhopharmacology*. The primary cannabinoid in cannabis, Δ9-tetrahydrocannabinol (THC), causes intoxication and impaired function, with implications for traffic, workplace, and other situational safety risks. There are currently no evidence-based methods to detect cannabis-impaired driving, and current field sobriety tests with gold-standard, drug recognition evaluations are resource-intensive and may be prone to bias. This study evaluated the capability of a simple, portable imaging method to accurately detect individuals with THC impairment. In this double-blind, randomized, cross-over study, 169 cannabis users, aged 18-55 years, underwent functional near-infrared spectroscopy (fNIRS) before and after receiving oral THC and placebo, at study visits one week apart. Impairment was defined by convergent classification by consensus clinical ratings and an algorithm based on post-dose tachycardia and self-rated "high." Our primary outcome, prefrontal cortex (PFC) oxygenated hemoglobin concentration (HbO), was increased after THC only in participants operationalized as impaired, independent of THC dose. ML models using fNIRS time course features and connectivity matrices identified impairment with 76.4% accuracy, 69.8% positive predictive value (PPV), and 10% false-positive rate using convergent classification as ground truth, which exceeded Drug Recognition Evaluator-conducted expanded field sobriety examination (67.8% accuracy, 35.4% PPV, and 35.4% false-positive rate). These findings demonstrate that PFC response activation patterns and connectivity produce a neural signature of impairment, and that PFC signal, measured with fNIRS, can be used as a sole input to ML models to objectively determine impairment from THC intoxication at the individual level. Future work is warranted to determine the specificity of this classifier to acute THC impairment.
- The seventh study by Bloomfield and colleague [7] in 2021 in the *Psychopharmacology* looked at the benefits of CBD in treating anxiety. **Rationale:** There is growing interest in the therapeutic potential of cannabidiol (CBD) across a range of psychiatric disorders. CBD has been found to reduce anxiety during experimentally induced stress in anxious individuals and healthy controls. However, the mechanisms underlying the putative anxiolytic effects of CBD are unknown. Objectives: We sought to investigate the behavioural and neural effects of a single dose of CBD vs. placebo on a range of emotion-related measures to test cognitive-mechanistic models of its effects on anxiety. **Methods**: We conducted a randomised, double-blind, placebo-controlled, crossover, acute oral challenge of 600 mg of CBD in 24 healthy participants on emotional processing, with neuroimaging (viewing emotional faces during functional magnetic resonance imaging) and cognitive (emotional appraisal) measures as well as subjective response to experimentally induced anxiety. **Results:** CBD did not produce effects on brain responses to emotional faces and cognitive measures of emotional processing, or modulate experimentally induced anxiety, relative to placebo. **Conclusions:** Given the rising popularity of CBD for its putative medical benefits, these findings question whether further research is warranted to investigate the clinical potential of CBD for the treatment of anxiety disorders.
- The eighth study by Schnieider and colleagues [8] in 2022 in the *Pain* looked at pain response. Preclinical studies have demonstrated the analgesic potential of cannabidiol (CBD). Those suggesting an effect on pain-processing receptors have brought CBD back into focus. This study assessed the effect of CBD on acute pain, hyperalgesia, and allodynia compared with placebo. Twenty healthy volunteers were included in this randomized, placebo-controlled, double-blinded, crossover study assessing pain intensities (using numeric rating scale), secondary hyperalgesia (von Frey filament), and allodynia (dry cotton swab) in a well-established acute pain model with intradermal electrical stimulation. The authors

compared the effect of 800-mg orally administered CBD on pain compared with placebo. They further examined the effect on hyperalgesia and allodynia. Cannabidiol whole blood levels were also measured. Pain ratings (mean ± SD) did not differ significantly after CBD application compared with placebo (5.2 ± 0.7 vs 5.3 ± 0.7, P-value 0.928), neither did the areas of hyperalgesia and allodynia differ significantly after CBD application compared with placebo (hyperalgesia 23.9 ± 19.2 cm2 vs 27.4 ± 17.0 cm2, P-value 0.597; allodynia 16.6 ± 13.1 cm2 vs 17.3 ± 14.1 cm2, P-value 0.884). The CBD whole blood level (median, first to third quartile) was 2.0 µg/L (1.5-5.1) 60 minutes and 5.0 µg/L (4.0-10.4) 130 minutes after CBD application. Although the oral application of 800-mg CBD failed to show a significant effect, it is important to focus future research on different dosing, routes of administration, and CBD as a part of multimodal treatment strategies before negating its effects on acute pain.

- The ninth study by Arout and colleagues [9] in 2022 in the *British Journal of Clinical Pharmacology* looked at pain response with different doses of CBD. **Aims:** Preclinical studies demonstrate that cannabidiol (CBD) elicits an antinociceptive response in animal models of neuropathic pain; in humans, limited data are available to support such analgesic effects. Few studies have examined CBD's analgesic effects when administered without other compounds, and little is known regarding dose-dependent effects in noncannabis users**. Methods:** This double-blind, placebo-controlled, within-subject outpatient clinical laboratory study sought to determine the analgesic effects, abuse liability, safety and tolerability of acute CBD (0, 200, 400 and 800 mg orally) in healthy noncannabis-using volunteers (n = 17; 8 men, 9 women). Outcomes included experimental pain threshold and pain tolerance using the cold pressor test (CPT), subjective ratings of CPT painfulness and bothersomeness, subjective ratings of abuse liability and mood, and cardiovascular measures, which were assessed at baseline and several time points after drug administration. Data analyses included repeated measures analysis of variance (ANOVA) with planned comparisons. **Results:** CBD failed to consistently affect pain threshold and tolerance in the CPT relative to placebo. All doses of CBD increased ratings of painfulness compared to placebo ($P < .01$). Further, CBD had dose-dependent, modest effects on mood and subjective drug effects associated with abuse liability. Oral CBD was safe and well tolerated, producing small decreases in blood pressure ($P < .01$). **Conclusion:** CBD did not elicit consistent dose-dependent analgesia and in fact increased pain on some measures. Future studies exploring CBD-induced pain relief should consider using a more extensive pain assessment paradigm in different participant populations.

Bottom line from these studies:

- There is a lack of evidence to support the use of medical cannabis for any COVID symptoms.
- Medical cannabis does not help with the REM sleep disorder associated with Parkinson's Disease.
- A study in Crohn's disease showed that after 8 weeks of CBD that the patients felt better and experienced a better quality of life, but none of their disease markers had improved.
- Two studies looked at stress and anxiety. The one study showed that there was not much improvement from stress, and that it was no different than placebo. The other study found that it was not beneficial for treating anxiety.
- One study looked at intoxication associated with THC and alcohol. Compared to placebo both resulted in impairment in driving simulation and the two combined had an increased effect on driving impairment
- Three studies looked at pain. One reported that it did not appear to be effective in relieving the pain associated with hand and psoriatic arthritis. Another looked at CBD alone (without THC) and did not find that it was very effective in treating pain. The third evaluated CBD alone in healthy volunteers using a cold-pain threshold model and they also did not find a consistent dose-response in relieving pain.

References

1. Khalsa JH, Bunt G, Maggirwar SB, Kottilil S. COVID-19 and Cannabidiol (CBD). *J Addict Med*. 2021 Sep-Oct 01;15(5):355-356. doi: 10.1097/ADM.0000000000000771. PMID: 33323690.
2. de Almeida CMO, Brito MMC, Bosaipo NB, et. al. Cannabidiol for Rapid Eye Movement Sleep Behavior Disorder. *Mov Disord*. 2021 Jul;36(7):1711-1715. doi: 10.1002/mds.28577. PMID: 33754375.
3. Spinella TC, Stewart SH, Naugler J, et. al. Evaluating cannabidiol (CBD) expectancy effects on acute stress and anxiety in healthy adults: a randomized crossover study. *Psychopharmacology* (Berl). 2021 Jul;238(7):1965-1977. doi: 10.1007/s00213-021-05823-w. PMID: 33813611.
4. Naftali T, Bar-Lev Schleider Let. Al.. Oral CBD-rich Cannabis Induces Clinical but Not Endoscopic Response in Patients with Crohn's Disease, a Randomised Controlled Trial. *J Crohns Colitis*. 2021 Nov 8;15(11):1799-1806. doi: 10.1093/ecco-jcc/jjab069. PMID: 33858011.
5. Vela J, Dreyer L, Petersen KK, et. al. Cannabidiol treatment in hand osteoarthritis and psoriatic arthritis: a randomized, double-blind, placebo-controlled trial. *Pain*. 2022 Jun 1;163(6):1206-1214. doi: 10.1097/j.pain.0000000000002466. PMID: 34510141.
6. Gilman JM, Schmitt WA, Potter K, et.al. Identification of Δ9-tetrahydrocannabinol (THC) impairment using functional brain imaging. *Neuropsychopharmacology*. 2022 Mar;47(4):944-952. doi: 10.1038/s41386-021-01259-0. PMID: 34999737.
7. Bloomfield MAP, Yamamori Y, Hindocha C, et. al. The acute effects of cannabidiol on emotional processing and anxiety: a neurocognitive imaging study. **Psychopharmacology (Berl)**. 2022 May;239(5):1539-1549. doi: 10.1007/s00213-022-06070-3. PMID: 35445839.
8. Schneider T, Zurbriggen L, Dieterle M, et. al. Pain response to cannabidiol in induced acute nociceptive pain, allodynia, and hyperalgesia by using a model mimicking acute pain in healthy adults in a randomized trial (CANAB I). *Pain.* 2022 Jan 1;163(1):e62-e71. doi: 10.1097/j.pain.0000000000002310. PMID: 34086631.
9. Arout CA, Haney M, Herrmann ES, et. al. A placebo-controlled investigation of the analgesic effects, abuse liability, safety and tolerability of a range of oral cannabidiol doses in healthy humans. *Br J Clin Pharmacol*. 2022 Jan;88(1):347-355. doi: 10.1111/bcp.14973. PMID: 34223660.

Sincerely,

Ronald A. Herman

Dr. Ron Herman PhD
Clinical Professor, University of Iowa
College of Pharmacy | Dept. of Pharm. Practice & Science
180 South Grand Ave. | 349 CPB
Iowa City, IA 52242

From a clinical standpoint there has been an added indication for cannabidiol in the area of patients with tuberous sclerosis complex.

Sincerely,

Michael Ciliberto, MD
Assistant Professor
Division of Pediatric Neurology
Stead Family Department of Pediatrics
University of Iowa Children's Hospital