SMC20-0002

pennsylvania
DEPARTMENT OF HEALTH

Qualifying Medical Conditions for Medical Marijuana Usage Application

Individual Requestor Information

Full Name: **Werkheiser** (*Last*) **Monica** (*First*) **L** (*M.I.*)

Address: **1309 Stefko Blvd** (*Street Address*) (*Apartment/Unit #*)

Bethlehem (*City*) **PA** (*State*) **18017** (*ZIP Code*)

Phone: **484-408-6122** Email **monica@keystonecannaremedies.com**

Medical License Number (if applicable): **RP443071**

Registry I.D. Number (if applicable):

Qualifying Condition Request

Name of Medical Condition **Traumatic Brain Injury**

Has this condition been approved in any other state? YES ■ NO ☐ If yes, where? **Georgia, Illinois, New Hampshire, Ohio, Washington**

References Supporting Qualified Practitioner's Opinion

Full Name: David Gordon, MD Relationship: Certifying MMJ Physician

Hospital/Agency: Phone: (888) 916-9937

Address: 798 Hausman Rd. Suite 170
Allentown, PA 18104

Full Name: Charles Harris, MD Relationship: Certifying MMJ Physician

Hospital/Agency:: Phone: (484) 602-4438

Address: 6724 Kernsville Rd.
Orefield, PA 18069

Full Name:	Alex Perez, MD	Relationship:	Certifying MMJ Physician
Hospital/Agency::		Phone:	(570) 424-2001
Address:	296 E Brown St, Suite D East Stroudsburg, PA 18301		

Documentation (clinical, medical, or scientific data) Supporting Efficacy of Medical Marijuana as Treatment for Condition

Citation: **Nguyen BM, Kim D, Bricker S, Bongard F, Neville A, Putnam B, Smith J, Plurad D. Effect of marijuana use on outcomes in traumatic brain injury. *The American Surgeon*, October 2014**

Summary:

Traumatic brain injury (TBI) is associated with significant morbidity and mortality. The objective of this study was to establish a relationship between the presence of a positive toxicology screen for tetrahydrocannabinol (THC) and mortality after TBI. This study was a 3-year retrospective review of registry data. The THC(+) group was compared with the THC(-) group with respect to injury mechanism, severity, disposition, and mortality. Overall mortality was 9.9 percent (44); however, mortality in the THC(+) group (2.4%) was significantly decreased compared with the THC(-) group (11.5% [42]; P = 0.012). After adjusting for differences between the study cohorts on logistic regression, a THC(+) screen was independently associated with survival after TBI (odds ratio, 0.224; 95% confidence interval, 0.051 to 0.991; P = 0.049). A positive THC screen is associated with decreased mortality in adult patients sustaining TBI.

Citation: **Hampson AJ, Grimaldi M, Axelrod J, Wink D. Cannabidiol and (-)Delta9-tetrahydrocannabinol are neuroprotective antioxidants. *Proc Natl Acad Sci U S A*. 1998;95(14):8268-73.**

Summary:

The neuroprotective actions of cannabidiol (CBD) and other cannabinoids were examined in rat cortical neuron cultures exposed to toxic levels of the excitatory neurotransmitter glutamate. Glutamate toxicity was reduced by both CBD and Δ^9-tetrahydrocannabinol (THC). Cannabinoids protected equally well against neurotoxicity mediated by N-methyl-D-aspartate receptors, 2-amino-3-(4-butyl-3-hydroxyisoxazol-5-yl) propionic acid receptors, or kainite receptors. The neuroprotection observed with CBD and THC was unaffected by cannabinoid receptor antagonist, indicating it to be cannabinoid receptor independent. CBD, THC and several synthetic cannabinoids all were demonstrated to be antioxidants by cyclic voltammetry. CBD and THC also were shown to prevent hydroperoxide-induced oxidative damage as well as or better than other antioxidants in a chemical (Fenton reaction) system and neuronal cultures. CBD was more protective against glutamate neurotoxicity than either ascorbate or α-tocopherol, indicating it to be a potent antioxidant. These data also suggest that CBD may be a potentially useful therapeutic agent for the treatment of oxidative neurological disorders such as cerebral ischemia.

Citation: **Panikashvili, David, Simeonidou, Constantina, Ben-Shabat, Shimon, Hanuš, Lumír, Breuer, Aviva, Mechoulam, Raphael, Shohami, Esther, An endogenous cannabinoid (2-AG) is neuroprotective after brain injury, Nature, 2001/10/04/online, VL. 13, 527, Macmillan Magazines Ltd., https://doi.org/10.1038/35097089**

Summary:

This study demonstrated that after injury to the mouse brain, 2-AG may have a neuroprotective role in which the cannabinoid system is involved. After closed head injury (CHI) in mice, the level of endogenous 2-AG was significantly elevated. When synthetic 2-AG was administered to mice after CHI, significant reduction of brain edema, better clinical recovery, reduced infarct volume and reduced hippocampal cell death was found as compared with controls. When 2-AG was administered together with additional inactive 2-acyl-glycerols that are normally present in the brain, functional recovery was

significantly enhanced. The beneficial effect of 2-AG was dose-dependently attenuated by SR-141761A, an antagonist of the CB_1 cannabinoid receptor.

Citation: ***Lital Magid, Sami Heymann, Merav Elgali, Liat Avram, Yoram Cohen, Sigal Liraz-Zaltsman, Raphael Mechoulam, and Esther Shohami*, Role of CB2 Receptor in the Recovery of Mice after Traumatic Brain Injury, Journal of Neurotrauma 2019 36:11, 1836-1846 https://doi.org/10.1089/neu.2018.6063**

Summary:

This study demonstrates that the CB_2 receptor plays an important role in neuroprotection following brain injury. The endogenous ligands, anandamide and 2-AG, which bind to both CB_1 and CB_2 receptors, contribute to the natural defense of the CNS. In previous studies the authors demonstrated that treatment with the endocannabinoid 2-AG, which binds to both CB_1 and CB_2 receptors 1 h after traumatic brain injury in mice, attenuates neurological deficits, edema formation, infarct volume, blood–brain barrier permeability, neuronal cell loss at the CA3 hippocampal region, and neuroinflammation. With a synthesized CB_2 receptor selective ligand, these compounds exhibited potent binding and agonistic properties at the CB_2 receptors with very low affinity for the CB_1 receptor, and some were highly anti-inflammatory. In mice and rats subjected to closed-head injury and treated with these novel compounds, enhanced neurobehavioral recovery, inhibition of tumor necrosis factor α production, increased synaptogenesis, and partial recovery of the cortical spinal tract were seen.

Documentation Supporting Qualified Physicians Opinion: Benefits of Medical Marijuana Use Outweigh Health Risks for Condition

Summary:

Traumatic brain injury (TBI) is one of the leading causes of death worldwide in individuals under the age of 45. Triggered by concussions from car accidents, falls, violent contact sports, explosives or by gunshot and stab wounds, TBI affects 1.7 million Americans annually. There is emerging evidence that cannabinoids, especially CBD, can be neuroprotective following an injury to the brain. Additionally, the considerable anti-inflammatory effects of THC following an injury to the head shows promise in improving outcomes and lessening recovery times as well as preserving function following an injury to the head. A phytocannabinoid remedy that combines CBD and THC and acts at multiple targets simultaneously would seem to be an ideal therapeutic candidate to treat TBI.

At Keystone Canna Remedies, we are successfully treating patients with severe migraines, Chiari malformations, and hemicrania continua. With success in other states treating TBI with marijuana, there is research underway within the Department of Neuroscience at Thomas Jefferson University reviewing cannabinoid reactions in post concussive headaches.

Disclaimer and Signature

I certify that my answers are true and complete to the best of my knowledge.

Individual Requestor Signature: *Monica L. Werkheiser* Date: **10/13/20**

SMC20-0004

pennsylvania
DEPARTMENT OF HEALTH

Qualifying Medical Conditions for Medical Marijuana Usage Application

Individual Requestor Information

Full Name: **Shea** (*Last*) **Kevin** (*First*) **J** (*M.I.*)

Address: **1309 Stefko Blvd** (*Street Address*) (*Apartment/Unit #*)

Bethlehem (*City*) **PA** (*State*) **18017** (*ZIP Code*)

Phone: **484-408-6122** Email **kevin@keystonecannaremedies.com**

Medical License Number (if applicable): **RP444670**

Registry I.D. Number (if applicable):

Qualifying Condition Request

Name of Medical Condition **Hepatitis**

Has this condition been approved in any other state? YES X NO ☐

If yes, where? **Arizona, Arkansas, Delaware, Illinois, Massachusetts, Michigan, Missouri, New Hampshire, New Mexico, North Dakota, Ohio, Rhode Island, South Carolina, Washington**

References Supporting Qualified Practitioner's Opinion

Full Name: David Gordon, MD Relationship: Certifying MMJ Physician

Hospital/Agency: Phone: (888) 916-9937

Address: 798 Hausman Rd. Suite 170
Allentown, PA 18104

Full Name: Charles Harris, Relationship: Certifying MMJ Physician

Hospital/Agency:: Phone: (484) 602-4438

Address: 6724 Kernsville Rd.
Orefield, PA 18069

Documentation (clinical, medical, or scientific data) Supporting Efficacy of Medical Marijuana as Treatment for Condition	
Citation:	**Adeyinka Charles Adejumo, Oluwole Muyiwa Adegbala, Kelechi Lauretta Adejumo, and Terence Ndonyi Bukong, "Reduced Incidence and Better Liver Disease Outcomes among Chronic HCV Infected Patients Who Consume Cannabis," Canadian Journal of Gastroenterology and Hepatology, vol. 2018, Article ID 9430953, 9 pages, 2018. https://doi.org/10.1155/2018/9430953.**
Summary:	Researchers investigated the effect of cannabis use on chronic liver disease (CLD) from Hepatitis C Virus (HCV) infection. They analyzed hospital discharge records of adults (age ≥ 18 years) with a positive HCV diagnosis. Records were evaluated from 2007 to 2014 of the Nationwide Inpatient Sample (NIS). The study revealed that cannabis users (CUs) had decreased prevalence of liver cirrhosis (aPRR: 0.81[0.72-0.91]), unfavorable discharge disposition (0.87[0.78-0.96]), lower frequencies of higher Baveno4 score and lower total health care cost ($39,642[36,220-43,387] versus $45,566[$42,244-$49,150]), compared to non-cannabis users (NCUs). Cannabis users had decreased frequencies of ascites and portal hypertension. The frequency of mortality and liver cancer were similar between cannabis users and nonusers.
Citation:	**Nordmann S, Vilotitch A, Roux P, Esterle L, Spire B, Marcellin F, Salmon-Ceron D, Dabis F, Chas J, Rey D, Wittkop L, Sogni P, Carrieri P; ANRS CO13 HEPAVIH Study Group. Daily cannabis and reduced risk of steatosis in human immunodeficiency virus and hepatitis C virus-co-infected patients (ANRS CO13-HEPAVIH). J Viral Hepat. 2018 Feb;25(2):171-179. doi: 10.1111/jvh.12797. Epub 2017 Nov 20.**
Summary:	Researchers aimed to study whether cannabis use in the HIV and HCV coinfected patient population, was associated with a reduced risk of steatosis, measured by ultrasound examination. A cross-sectional analysis was conducted using data from the first visit where both ultrasound examination data for steatosis (positive or negative diagnosis) and data on cannabis use were available. A logistic regression model was used to evaluate the association between cannabis use and steatosis. Among study sample patients (n = 838), 40.1% had steatosis. 14% reported daily cannabis use, 11.7% regular use and 74.7% no use or occasional use ("never or sometimes"). Daily cannabis use was independently associated with a reduced prevalence of steatosis (adjusted odds ratio [95% CI] = 0.64 [0.42;0.99]; P = .046), after adjusting for body mass index, hazardous alcohol consumption and current or lifetime use of lamivudine/zidovudine. Daily cannabis use may be a protective factor against steatosis in HIV-HCV-co-infected patients.
Citation:	**Sylvestre, Diana L; Clements, Barry J; Malibu, Yvonne. Cannabis use improves retention and virologic outcomes in patients treated for hepatitis C. European Journal of Gastroenterology & Hepatology: October 2006 - Volume 18 - Issue 10 - p 1057-1063**
Summary:	This study was conducted to define the impact of cannabis use during HCV treatment. The researchers conducted a prospective observational study of standard interferon and ribavirin treatment in 71 recovering substance users, of whom 22 (31%) used cannabis and 49 (69%) did not. A total of 21 out of 71 (30%) had a sustained virologic response: 12 of the 22 cannabis users (54%) and nine of the 49 non-users (18%) (P=0.009), corresponding to a post-treatment virologic relapse rate of 14% in the cannabis users and 61% in the non-users (P=0.009). Overall, 48 (68%) were adherent, 29 (59%) non-users and 19 (86%) cannabis users (P=0.03). Although cannabis users were no more likely than non-users to take at least 80% of the prescribed interferon or ribavirin, they were significantly more likely to remain on HCV treatment for at least 80% of the projected treatment duration, 95 versus 67% (P=0.01). Results suggest that modest cannabis use may offer symptomatic and virologic benefit to some patients undergoing HCV treatment by helping them maintain adherence to the challenging medication regimen.
Citation:	**Iris Lavon, Tatiana Sheinin, Sigal Meilin, Efrat Biton, Ayelet Weksler, Gilat Efroni, Avi Bar-Joseph, George Fink and Ayelet Avraham A Novel Synthetic Cannabinoid Derivative Inhibits Inflammatory Liver Damage via Negative Cytokine Regulation Molecular Pharmacology December 2003, 64 (6) 1334-1341; DOI: https://doi.org/10.1124/mol.64.6.1334**

Summary:	In this study, they investigated the mechanism of action of a novel synthetic cannabinoid to determine the therapeutic potential of cannabinoids. Treatment with PRS-211,092 significantly decreased Concanavalin A-induced liver injury in mice that was accompanied by: 1) promotion of early gene expression of interleukin (IL)-6 and IL-10 that play a protective role in this model; 2) induction of early gene expression of the suppressors of cytokine signaling (SOCS-1 and 3), followed by 3) inhibition of several pro-inflammatory mediators, including IL-2, monocyte chemoattractant protein-1 (MCP-1), IL-1β, interferon-γ, and tumor necrosis factor α. These results allowed the researchers to propose a mechanism by which PRS-211,092 stimulates the expression of IL-6, IL-10 and the SOCS proteins that, in turn, negatively regulates the expression of pro-inflammatory cytokines. Negative regulation by PRS-211,092 was further demonstrated in cultured T cells, where it inhibited IL-2 production and nuclear factor of activated T cells activity. These findings suggest that this cannabinoid derivative is an immunomodulator that could be developed as a potential drug for hepatitis as well as for other short- or long-term inflammatory diseases.	

Documentation Supporting Qualified Physicians Opinion: Benefits of Medical Marijuana Use Outweigh Health Risks for Condition

Summary:	
	Patients diagnosed with hepatitis C frequently report using cannabis to ease both symptoms of the disease such as pain and decreased appetite as well as the nausea associated with antiviral therapy. As HCV progresses, marijuana has been shown to help alleviate complications, especially portal hypertension and liver cancer without worsening liver cirrhosis, complications of cirrhosis, mortality, liver cancer, and unfavorable discharge disposition. Marijuana may also help to prevent progression of steatosis or at least not contribute to worsening steatosis. While marijuana alone cannot treat hepatitis C, it can be used in a complementary way along with physician-prescribed medications to provide a higher likelihood of treatment success for hepatitis C patients.

Disclaimer and Signature

I certify that my answers are true and complete to the best of my knowledge.

Individual Requestor Signature: *Kevin Shea* Date: **10/15/20**

Patients diagnosed with hepatitis C frequently report using cannabis to ease both symptoms of the disease such as pain and decreased appetite as well as the nausea associated with antiviral therapy. As HCV progresses, marijuana has been shown to help alleviate complications, especially portal hypertension and liver cancer without worsening liver cirrhosis, complications of cirrhosis, mortality, liver cancer, and unfavorable discharge disposition. Marijuana may also help to prevent progression of steatosis or at least not contribute to worsening steatosis. While marijuana alone cannot treat hepatitis C, it can be used in a complementary way along with physician-prescribed medications to provide a higher likelihood of treatment success for hepatitis C patients.

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SMC21-0001

pennsylvania
DEPARTMENT OF HEALTH

Qualifying Medical Conditions for Medical Marijuana Usage Application

Individual Requestor Information

Full Name: **Shea** (*Last*) **Kevin** (*First*) **J** (*M.I.*)

Address: **1309 Stefko Blvd** (*Street Address*) (*Apartment/Unit #*)

Bethlehem (*City*) **PA** (*State*) **18017** (*ZIP Code*)

Phone: **484-408-6122** Email **kevin@keystonecannaremedies.com**

Medical License Number (if applicable): **RP444670**

Registry I.D. Number (if applicable):

Qualifying Condition Request

Name of Medical Condition **Hepatitis C**

Has this condition been approved in any other state? YES X NO ☐

If yes, where? **Arizona, Arkansas, Delaware, Illinois, Massachusetts, Michigan, Missouri, New Hampshire, New Mexico, North Dakota, Ohio, Rhode Island, South Carolina, Washington**

References Supporting Qualified Practitioner's Opinion

Full Name: David Gordon, MD Relationship: Certifying MMJ Physician

Hospital/Agency: Phone: (888) 916-9937

Address: 798 Hausman Rd. Suite 170
Allentown, PA 18104

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Hospital/Agency:: Phone: (484) 602-4438

Address: 6724 Kernsville Rd.
Orefield, PA 18069

Documentation (clinical, medical, or scientific data) Supporting Efficacy of Medical Marijuana as Treatment for Condition	
Citation:	**Adeyinka Charles Adejumo, Oluwole Muyiwa Adegbala, Kelechi Lauretta Adejumo, and Terence Ndonyi Bukong, "Reduced Incidence and Better Liver Disease Outcomes among Chronic HCV Infected Patients Who Consume Cannabis," Canadian Journal of Gastroenterology and Hepatology, vol. 2018, Article ID 9430953, 9 pages, 2018. https://doi.org/10.1155/2018/9430953.**
Summary:	Researchers investigated the effect of cannabis use on chronic liver disease (CLD) from Hepatitis C Virus (HCV) infection. They analyzed hospital discharge records of adults (age ≥ 18 years) with a positive HCV diagnosis. Records were evaluated from 2007 to 2014 of the Nationwide Inpatient Sample (NIS). The study revealed that cannabis users (CUs) had decreased prevalence of liver cirrhosis (aPRR: 0.81[0.72-0.91]), unfavorable discharge disposition (0.87[0.78-0.96]), lower frequencies of higher Baveno4 score and lower total health care cost ($39,642[36,220-43,387] versus $45,566[$42,244-$49,150]), compared to non-cannabis users (NCUs). Cannabis users had decreased frequencies of ascites and portal hypertension. The frequency of mortality and liver cancer were similar between cannabis users and nonusers.
Citation:	**Nordmann S, Vilotitch A, Roux P, Esterle L, Spire B, Marcellin F, Salmon-Ceron D, Dabis F, Chas J, Rey D, Wittkop L, Sogni P, Carrieri P; ANRS CO13 HEPAVIH Study Group. Daily cannabis and reduced risk of steatosis in human immunodeficiency virus and hepatitis C virus-co-infected patients (ANRS CO13-HEPAVIH). J Viral Hepat. 2018 Feb;25(2):171-179. doi: 10.1111/jvh.12797. Epub 2017 Nov 20.**
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Citation:	**Iris Lavon, Tatiana Sheinin, Sigal Meilin, Efrat Biton, Ayelet Weksler, Gilat Efroni, Avi Bar-Joseph, George Fink and Ayelet Avraham A Novel Synthetic Cannabinoid Derivative Inhibits**

	Inflammatory Liver Damage via Negative Cytokine Regulation Molecular Pharmacology December 2003, 64 (6) 1334-1341; DOI: https://doi.org/10.1124/mol.64.6.1334	
Summary:	In this study, they investigated the mechanism of action of a novel synthetic cannabinoid to determine the therapeutic potential of cannabinoids. Treatment with PRS-211,092 significantly decreased Concanavalin A-induced liver injury in mice that was accompanied by: 1) promotion of early gene expression of interleukin (IL)-6 and IL-10 that play a protective role in this model; 2) induction of early gene expression of the suppressors of cytokine signaling (SOCS-1 and 3), followed by 3) inhibition of several pro-inflammatory mediators, including IL-2, monocyte chemoattractant protein-1 (MCP-1), IL-1β, interferon-γ, and tumor necrosis factor α. These results allowed the researchers to propose a mechanism by which PRS-211,092 stimulates the expression of IL-6, IL-10 and the SOCS proteins that, in turn, negatively regulates the expression of pro-inflammatory cytokines. Negative regulation by PRS-211,092 was further demonstrated in cultured T cells, where it inhibited IL-2 production and nuclear factor of activated T cells activity. These findings suggest that this cannabinoid derivative is an immunomodulator that could be developed as a potential drug for hepatitis as well as for other short- or long-term inflammatory diseases.	

Documentation Supporting Qualified Physicians Opinion: Benefits of Medical Marijuana Use Outweigh Health Risks for Condition

Summary:	
	Patients diagnosed with hepatitis C frequently report using cannabis to ease both symptoms of the disease such as pain and decreased appetite as well as the nausea associated with antiviral therapy. As HCV progresses, marijuana has been shown to help alleviate complications, especially portal hypertension and liver cancer without worsening liver cirrhosis, complications of cirrhosis, mortality, liver cancer, and unfavorable discharge disposition. Marijuana may also help to prevent progression of steatosis or at least not contribute to worsening steatosis. While marijuana alone cannot treat hepatitis C, it can be used in a complementary way along with physician-prescribed medications to provide a higher likelihood of treatment success for hepatitis C patients.

Disclaimer and Signature

I certify that my answers are true and complete to the best of my knowledge.

Individual Requestor Signature: *Kevin Shea* Date: **10/15/20**

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SMC21-0002

pennsylvania
DEPARTMENT OF HEALTH

Qualifying Medical Conditions for Medical Marijuana Usage Application

Individual Requestor Information

Full Name: **Werkheiser** (*Last*) **Monica** (*First*) **L** (*M.I.*)

Address: **1309 Stefko Blvd** (*Street Address*) (*Apartment/Unit #*)

Bethlehem (*City*) **PA** (*State*) **18017** (*ZIP Code*)

Phone: **484-408-6122** Email **monica@keystonecannaremedies.com**

Medical License Number (if applicable): **RP443071**

Registry I.D. Number (if applicable):

Qualifying Condition Request

Name of Medical Condition **Chronic Insomnia refractory to standard therapies**

Has this condition been approved in any other state? YES ■ NO ☐ If yes, where? **Minnesota & New Mexico**

References Supporting Qualified Practitioner's Opinion

Full Name: David Gordon, MD Relationship: Certifying MMJ Physician

Hospital/Agency: Phone: (888) 916-9937

Address: 798 Hausman Rd. Suite 170
Allentown, PA 18104

Full Name: Alex Perez, MD Relationship: Certifying MMJ Physician

Hospital/Agency:: Phone: (570) 424-2001

Address: 296 E Brown St, Suite D
East Stroudsburg, PA 18301

Documentation (clinical, medical, or scientific data) Supporting Efficacy of Medical Marijuana as Treatment for Condition

Citation: **Vigil, J.M.; Stith, S.S.; Diviant, J.P.; Brockelman, F.; Keeling, K.; Hall, B. Effectiveness of Raw, Natural Medical *Cannabis* Flower for Treating Insomnia under Naturalistic Conditions. *Medicines* 2018, *5*, 75.**

Summary:

The conclusion of this study showed the consumption of medical *Cannabis* flower is associated with significant improvements in perceived insomnia severity. This study included four hundred and nine people with a specified condition of insomnia recording a real-time ratings of self-perceived insomnia severity levels prior to and following consumption, experienced side effects, and product characteristics, including combustion method, cannabis subtypes, and/or major cannabinoid contents of cannabis consumed. The results showed an average symptom severity reduction of −4.5 points on a 0–10 point visual analogue scale. The use of pipes and vaporizers were associated with greater symptom relief and more positive and context-specific side effects as compared to the use of joints, while vaporization was also associated with lower negative effects. Cannabidiol (CBD) was associated with greater statistically significant symptom relief than tetrahydrocannabinol (THC), but the cannabinoid levels generally were not associated with differential side effects.

Citation: **Pava MJ, Makriyannis A, Lovinger DM. Endocannabinoid Signaling Regulates Sleep Stability. *PLoS One*. 2016;11(3):e0152473. Published 2016 Mar 31. doi:10.1371/journal.pone.0152473**

Summary:

The major findings of this work are that endocannabinoid signaling through the CB1 receptor is necessary and sufficient for the stability of non-rapid eye movement (NREM) sleep. Direct activation of CB1 receptor or increasing endocannabinoid tone increased the time spent in NREM sleep. Further support for the role of endocannabinoids in regulating NREM stability comes from experiments with the CB1 antagonist, where blockade of CB1 reduced the duration of NREM bouts. Thus, the major conclusion from this work is that endocannabinoids regulate sleep stability, but endocannabinoid signaling is not necessary for sleep homeostasis.

Citation: **Feinberg I, Jones R, Walker J, Cavness C, Floyd T (1976). Effects of marijuana extract and tetrahydrocannabinol on electroencephalographic sleep patterns.**

Summary:

Marijuana extract, given in daily doses containing 70 to 210 mg delta-9-tetrahydrocannabinol (THC), induced effects on sleep that were virtually identical to those produced by the same doses of relatively pure (96%) THC. Both drugs reduced eye movement density with some tolerance developing to this effect. Stage 4 tended to increase with drug administration. Abrupt withdrawal led to extremely high densities of eye movement, increased rapid eye movement (REM) durations, and a sharp but transient fall in stage 4 to baseline levels. These effects may be useful in the elucidation of the pharmacology of sleep.

Citation **Eric Murillo-Rodríguez The role of the CB1 receptor in the regulation of sleep Elsevier: Progress in Neuro-Psychopharmacology and Biological Psychiatry Published1 August 2008 doi.org/10.1016/j.pnpbp.2008.04.008**

Summary

The endocannabinoids have an active role modulating diverse neurobiological functions, such as learning and memory, feeding, pain perception and sleep generation. Experimental evidence shows that the administration of Δ^9-THC promotes sleep. The activation of the CB_1 receptor leads to an induction of sleep, this effect is blocked via the selective antagonist. Since the system of the endogenous cannabinoids is present in several species, including humans, this leads to the speculation of the neurobiological role of the endocannabinoid system on diverse functions such as sleep modulation.
Katherine A. Belendiuk, Kimberly A. Babson, Ryan Vandrey, Marcel O. Bonn-Miller,

Citation **Cannabis species and cannabinoid concentration preference among sleep-disturbed medicinal cannabis users, Addictive Behaviors, Volume 50, 2015, Pages 178-181, SSN 0306-4603, https://doi.org/10.1016/j.addbeh.2015.06.032.**

Summary

Individuals report using cannabis for the promotion of sleep, and the effects of cannabis on sleep may vary by cannabis species. This study looked at 163 adults purchasing medical cannabis for a physical or mental health condition They provided self-report of (a) whether cannabis use was intended to help with sleep problems (e.g. insomnia, nightmares), (b) sleep quality (PSQI), (c) cannabis use (including preferred type), and (d) symptoms of DSM-5 cannabis dependence. 81 participants reported using cannabis for the management of insomnia and 14 participants reported using cannabis to reduce nightmares. Individuals using cannabis to manage nightmares preferred sativa to indica strains (Fisher's exact test (2) = 6.83, $p < 0.05$), and sativa users were less likely to endorse DSM-5 cannabis dependence compared with those who preferred indica strains ($\chi^2(2) = 4.09$, $p < 0.05$). Individuals with current insomnia ($t(9) = 3.30$, $p < 0.01$) and greater sleep latency ($F(3,6) = 46.7$, $p < 0.001$) were more likely to report using strains of cannabis with significantly higher concentrations of CBD. Individuals who reported at least weekly use of hypnotic medications used cannabis with lower THC concentrations compared to those who used sleep medications less frequently than weekly ($t(17) = 2.40$, $p < 0.05$).

Citation **Tringale, Rolando, and Claudia Jensen. "Cannabis and insomnia." *Depression* 4.12 (2011): 0-68.**

Summary

This retrospective study of cannabis patients analyzed clinical data on patient-reported effects on sleep latency before and after the use of cannabis. Included in this analysis 116 subjects who reported difficulty with sleeping and 31 subjects who reported no difficulty with sleeping. The primary outcome measures were a comparison of both cohorts and the sleep latency time after the use of cannabis compared with sleep latency time without the use of cannabis. Secondary outcomes were measured by comparing sleep latency between the two cohorts, sleep quality, and effect on dreaming. Analysis was conducted by the Wilcoxon-signed rank test and the Kruskal-Wallis test. Both groups of patients reported it took them less time to sleep if they used cannabis. Even though both groups' sleep improved with cannabis, the group reporting trouble sleeping experienced a much greater effect. Among those who had reported trouble sleeping, 79% reported increased sleep quality after using cannabis. Less consistent responses were seen with respect to dreaming, with 21% reporting a decrease in dreaming, 28% reporting no change, and 44% leaving the question blank. The authors concluded that patients seeking physician approval to use cannabis commonly report benefits on decreasing sleep latency, even if a sleep disorder is not the chief complaint.

Documentation Supporting Qualified Physicians Opinion: Benefits of Medical Marijuana Use Outweigh Health Risks for Condition

Summary:

Sleep is essential for maintaining mental and physical health, yet it eludes many adults. According to the National Sleep Foundation, 50 to 70 million U.S. adults experience symptoms of a sleep disorder while about 10 to 15 percent of adults deal with chronic insomnia. Although medications can play a valuable role in the management of insomnia, a subset of chronic insomnia patients may have limited or only transient improvement with medications. Many standards of therapy for insomnia have significant adverse effects, low therapeutic index, and a likelihood of tolerance and dependence.

Difficulty falling asleep and staying asleep is frequently cited as a reason that patients will use marijuana. During initial consults at Keystone Canna Remedies, many patients attest that they are not able to relax either their body or their mind enough to successfully fall asleep, and further state that marijuana will help facilitate this process more quickly. Many patients also report adverse effects to their current pharmaceutical sleep aids such as sleep walking or eating and residual drowsiness in the morning and desire to stop those medications. Utilizing medicinal cannabis in its various forms has allowed our patients an increase in quality and quantity of sleep, a decrease or stoppage of their sleep medications, and an avoidance of the above-mentioned side effects.

Disclaimer and Signature

I certify that my answers are true and complete to the best of my knowledge.

Individual Requestor Signature: *Monica L. Werkheiser* Date: **1/8/21**

SMC21-0003

pennsylvania
DEPARTMENT OF HEALTH

Qualifying Medical Conditions for Medical Marijuana Usage Application

Individual Requestor Information

Full Name: **Cook** (*Last*) **Thomas** (*First*) **J** (*M.I.*)

Address: **1309 Stefko Blvd** (*Street Address*) (*Apartment/Unit #*)

Bethlehem (*City*) **PA** (*State*) **18017** (*ZIP Code*)

Phone: **484-408-6122** Email **thomas@keystonecannaremedies.com**

Medical License Number (if applicable): **RP454072**

Registry I.D. Number (if applicable):

Qualifying Condition Request

Name of Medical Condition **Major Depressive Disorder refractory to standard therapy**

Has this condition been approved in any other state? YES ☐ NO ☒ If yes, where?

References Supporting Qualified Practitioner's Opinion

Full Name: **Dr. Philip Grieshaber** Relationship: **Certifying MD**

Hospital/ Agency: **Blue Mountain Psychiatry** Phone: (610) 253-2500

Address: 241 N. 13th Street Easton, PA 18042

Full Name: Relationship:

Hospital/ Agency:: Phone:

Address:

Full Name: _____ Relationship: _____

Hospital/
Agency:: _____ Phone: _____

Address:

Documentation (clinical, medical, or scientific data) Supporting Efficacy of Medical Marijuana as Treatment for Condition

Citation:	**Cuttler C, Spradlin A, McLaughlin RJ. A naturalistic examination of the perceived effects of cannabis on negative affect. J Affect Disord. 2018 Aug 1;235:198-205**
Summary:	Medical cannabis patients list depression as one of the three most common conditions for using cannabis. This study used subject-reported data from a mobile app (Strainprint) used to track symptoms while dosing with cannabis. The study focused on the effects of inhaled cannabis. The researchers used data from a total of 11,953 tracked inhalation sessions. Of those sessions, 561 medical cannabis patients tracked symptoms of depression 3,151 times. Patients used a scale of 0 to 10 to rate their symptoms of depression. There was a significant reduction in ratings of depression associated with cannabis use. The depression rating prior to use was 6.02±0.17 compared to 3.06±0.21 after use ($p < .001$), a decrease of almost 50%. The reduction in depression symptoms were observed in both men and women to similar extents. The largest decreases in ratings of depression were associated with the use of products with relatively low THC (<5.5%) and relatively high levels of CBD (>9.5%). Overall, cannabis use demonstrated a significant reduction the ratings of depression in a self-selected cohort of medical cannabis patients.
Citation:	**Li X, Diviant JP, Stith SS, Brockelman F, Keeling K, Hall B, Vigil JM. The Effectiveness of Cannabis Flower for Immediate Relief from Symptoms of Depression. Yale J Biol Med. 2020 Jun 29;93(2):251-264.**
Summary:	Studies on the real-time effects of cannabis on depression symptoms are limited. This study focused on patient-reported outcomes of depression symptoms recorded within a mobile app (Releaf) used to track symptoms after cannabis consumption. Patients recorded their perceived symptom intensity using a scale from 0 to 10. The study focused on treatment sessions where patients inhaled dried cannabis flower. To reflect a typical duration of effect for inhaled cannabis, session data was included when initial symptoms of depression (>0) were reported at the beginning of a session and ending symptoms were recorded within 4 hours. Over the course of the study (06/06/2016 to 07/08/2019), that inclusion criteria produced a sample size of 5,876 sessions from 1,819 subjects. Inhaled cannabis produced a statistically significant decrease in depression symptom intensity of 3.76±2.64 ($p<.001$) from 5.85±2.33 at the beginning of a dosing session to 2.08±2.07 at the end of a session (a decrease of approximately 64%). Overall, the study found that inhaled cannabis was associated with a substantial real-time decrease in patient-reported depression symptoms during a typical dosing session.
Citation:	**Denson TF, Earleywine M. Decreased depression in marijuana users. Addict Behav. 2006 Apr;31(4):738-42. doi: 10.1016/j.addbeh.2005.05.052.**
Summary:	In this study, the researchers conducted an internet survey of 4494 people who were contacted via email. The respondents ranged in cannabis experience from daily users, weekly or less users, or those who never used cannabis. The majority of respondents (3323, 75.5%) were daily users. The survey used the Center for Epidemiologic Studies Depression scale (CES-D), which measures four domains of depression: depressed affect, positive affect, somatic activity, and interpersonal symptoms. The researchers observed that people who used cannabis daily or occasionally (weekly or less) reported lower levels of symptoms of depression (i.e., less depressed mood, more positive affect, fewer somatic complaints) than people who never used cannabis. Interpersonal symptoms of depression were similar across groups. The researchers also observed that recreational users tended to have lower levels of

	depression symptoms than medical users. Overall, the study suggests that cannabis use may be associated with lower levels of depression symptoms
Citation:	**Corroon JM Jr, Mischley LK, Sexton M. Cannabis as a substitute for prescription drugs - a cross-sectional study. J Pain Res. 2017 May 2;10:989-998. doi: 10.2147/JPR.S134330.**
Summary:	The use of medical cannabis is increasing, most commonly for pain, anxiety and depression. Emerging data suggest that use and abuse of prescription drugs may be decreasing in states where medical cannabis is legal. The aim of this study was to survey cannabis users to determine whether they had intentionally substituted cannabis for prescription drugs. Researchers surveyed individuals, recruited via social media and cannabis dispensaries, through an online questionnaire. The primary goal of the study was to evaluate how cannabis is substituted for prescription medications by cannabis users. Of the study sample of 2,774 participants, 46% (1,248 individuals) indicated that they used cannabis as a substitute for one or more prescription drugs. Drug classes with the most substitutions were narcotics/opioids (35.8%), anxiolytics/benzodiazepines (13.6%), and antidepressants (12.7%). Overall, the study suggests that cannabis users (medical or non-medical) often use cannabis as a substitute for prescription medications, including antidepressants.

Future Research:	**Real-World Evidence in Patient-Reported Outcomes for Medical Cannabis (MC-RWE) (MC-RWE) - NCT04526093 (https://clinicaltrials.gov/ct2/show/NCT04526093)** With an estimated enrollment of 2000 participants, this prospective observational trial will study the effects of medical cannabis on pain, sleep, anxiety, depression, and quality of life through self-reported assessments by medical cannabis patients. The study will also track prescription medication use (including opioids, anti-depressants, etc). The study is estimated to be completed in July 2022. **Effect of Medical Marijuana on Neurocognition and Escalation of Use (MMNE) - NCT03224468 (https://clinicaltrials.gov/ct2/show/NCT03224468)** This randomized controlled trial (enrollment of 188) will compare medical cannabis patients to a waitlist control group with respect to changes in health outcomes (relief of symptoms or adverse health outcomes) or changes of the brain (based on MRI scans). Study participants will be tested at baseline and several time points for use of medical cannabis. The primary outcomes will focus on cannabis use disorders, changes in symptoms of depression and anxiety, changes in pain, and changes in sleep from baseline to 3 months. In addition to MRI scans, urinalyses will also be conducted. The study is estimated to be completed in March 2022.

Documentation Supporting Qualified Physicians Opinion: Benefits of Medical Marijuana Use Outweigh Health Risks for Condition

Summary	Depression is one of the most common mental health disorders with major depressive episodes affecting an estimated 7.1% of US adults (17.3 million adults) according to the National Institute of Mental Health (https://www.nimh.nih.gov/health/statistics/major-depression.shtml). Depressive disorders are major contributors to the global burden of disease with depressive disorders ranking as the third and fifth leading causes of year lost to disability for females and males, respectively, in 2017 (*Lancet* 2018; 392: 1789–858). Furthermore, antidepressant use is common in the US. During the period of 2015-2018, approximately 13.2% of US adults used antidepressants in the 30 days prior according to the National Health and Nutrition Examination Survey (https://www.cdc.gov/nchs/products/databriefs/db377.htm). While antidepressants have shown efficacy in treating depression, currently available drugs often have a delayed onset of response. Antidepressants are also associated with a range of potential drug-drug interactions and adverse events. Patients, therefore, are frequently looking to alternatives, particularly natural products, to treat their depression. As a result, medical cannabis patients frequently substitute cannabis for antidepressants regardless of their original qualifying condition. Available studies suggest that medicating with cannabis can help patients treat symptoms of depression.

Disclaimer and Signature

I certify that my answers are true and complete to the best of my knowledge.

Individual Requestor Signature: Thomas Cook Date: **1.8.21**