MDH Minnesota Department *of* Health

Minnesota Medical Cannabis Program
Petition to Add a Qualifying Medical Condition

Making your petition

- ☐ Any person may petition the Minnesota Department of Health ("the department" or "MDH") to add a qualifying medical condition to those listed in subdivision 14 of Minnesota Statutes section 152.22.

Petitions will be accepted only between June 1 and July 31, 2017.
Petitions received outside of these dates will not be reviewed.

Petitions must be sent by certified U.S. mail to:

Minnesota Department of Health
Office of Medical Cannabis
P.O. Box 64882
St. Paul, MN 55164-0882

- ☐ You must mail the original copy of the petition with an original signature.
- ☐ Complete each section of this petition and attach all supporting documents. Clearly indicate which section of the petition an attachment is for.
- ☐ Each petition is limited to one proposed qualifying medical condition. If your petition includes more than one medical condition, it will be dismissed.
- ☐ If you are petitioning for the addition of a medical condition that was considered but not approved in a prior year's petition process, you **must include** new scientific evidence or research to support your petition or describe substantially different symptoms. Please refer to our website to see which medical conditions were reviewed in prior years (http://www.health.state.mn.us/topics/cannabis/rulemaking/addconditions.html).
- ☐ If the petition is accepted for consideration, MDH will send the petition documents to the Medical Cannabis Review Panel ("Review Panel"). MDH staff will also provide information to the Review Panel about the proposed qualifying condition, its prevalence, and the effectiveness of current treatments.
- ☐ You may withdraw your petition any time before the Review Panel's first public meeting of the year by submitting a written statement to the Department stating that you want to withdraw it.

Petition review process

- ☐ An appointed citizens Review Panel will meet to review all eligible petitions.
- ☐ MDH will post notice of the public meetings of the Review Panel on its medical cannabis website.
- ☐ After the public meeting and by November 1, the Review Panel will provide the Commissioner of Health its written report of findings.
- ☐ The Commissioner will approve or deny the petition by December 1.

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Minnesota Medical Cannabis Program
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Section A: Petitioner's Information		
Name (First, Middle, Last): [redacted] o/b/o Sensible Minnesota		
Home Address (including Apartment or Suite #): [redacted]		
City: [redacted]	State: MN	Zip Code: [redacted]
Telephone Number: [redacted]	E-mail Address: [redacted]	

Section B: Medical Condition You Are Requesting Be Added

Please specify the name and provide a brief description of the proposed qualifying medical condition. Be as precise as possible in identifying the condition. **Optional:** Include diagnostic code(s), citing the associated ICD-9 or ICD-10 code(s), if you know them. *Attach additional pages as needed.*

Liver Disease.

See attached Section B.

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Section C: Symptoms of the Proposed Medical Condition and/or Its Treatment

Describe the extent to which the proposed qualifying medical condition or the treatments cause suffering and impair a person's daily life. *Attach additional pages if needed.*

See attached Section C.

Section D. Availability of conventional medical therapies

Describe conventional medical therapies available and the degree to which they ease the suffering caused by the proposed qualifying medical condition or its treatment. *Attach additional pages if needed.*

See attached Section D.

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Section E: Anticipated benefits from Medical Cannabis

Describe the anticipated benefits from the medical use of cannabis specific to the proposed qualifying medical condition. *Attach additional pages if needed.*

See attached Section E.

Section F (optional): Scientific Evidence of Support for Medical Cannabis Treatment

It will strengthen your petition to include evidence generally accepted by the medical community and other experts supporting the use of medical cannabis to alleviate suffering caused by the proposed medical disease or its treatment. This includes but is not limited to full text, peer-reviewed published journals or other completed medical studies. Please attach complete copies of any article or reference, not abstracts.

☑ ***I have attached relevant articles.*** *(check box if you have attached scientific articles or studies)*

Section G (optional): Letters in Support of Adding the Medical Condition

Attach letters of support for the use of medical cannabis from persons knowledgeable about the proposed qualifying medical condition, such as a licensed health care professional.

☑ ***I have attached letters of support.*** *(check box if you have attached letters of support)*

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Section H: Acknowledgement and Signature

Please Note: Any individually identifiable health information relating to any past, present, or future health condition or health care contained in this Petition is classified as a health record under Minnesota Statutes §144.291, and is not subject to public disclosure.

I certify that the information provided in this petition is true and accurate to the best of my knowledge.

[redacted] 07/31/2017

SIGNATURE DATE (mm/dd/yyyy)

To obtain this information in a different format, call:
(651) 201-5598 in the Metro area and (844) 879-3381 in the Non-metro.

Section A: Petitioner's Information

[redacted]

[redacted]

[redacted]

Section B: Medical Condition You Are Requesting Be Added

Clinical Information:

Condition: **Liver Disease**. The liver is a large organ that sits just under your rib cage on the right side of your abdomen. The liver is essential for digesting food and ridding the body of toxic substances.[1]

Toxic liver disease, ICD-10-CM K71, described as diseases of the liver caused by viruses, such as hepatitis A, hepatitis B (HBV), and hepatitis C (HCV); diseases caused by toxins (example: fatty liver disease, cirrhosis – scarring of hepatic tissue); liver cancer, and inherited (genetic) diseases, such as hemochromatosis and Wilson Disease. Tests are available to assess liver damage and functional capacity to determine a diagnose of liver disease.[2]

Section C: Symptoms of Proposed Medical Condition and/or Its Treatments

Symptoms of liver disease are varied and frequently include: swelling and pain in the abdomen and legs, bruising easily, changes in the color of your stool and urine, jaundice – yellowing of the skin and eyes, itchy skin, chronic fatigue, nausea or vomiting, headaches, and loss of appetite.[1]

Progression of liver disease: Per the American Liver Foundation, the primary infection or stage of liver disease is **inflammation** – it may cause discomfort or may go unnoticed. Over time, continued inflammation will continue to damage the liver leading to **fibrosis** – excess scar tissue replacing healthy liver tissue; scar tissue is unable to perform the functions of healthy tissue, and may prevent blood from flowing through one's liver (the liver may heal itself over time, if

the liver disease is successfully treated at this stage). Untreated liver disease leads to **cirrhosis,** heavy scarring, preventing the liver from healing itself.[3]

Cirrhosis can lead to serious complications, such as liver cancer. In some patients, the first symptoms experienced, and their first diagnosis of liver disease are during the stage of cirrhosis. Symptoms of cirrhosis include: bleeding or bruising easily, edema - water may accumulate in legs and/or abdomen, jaundice, severe itchy skin, blood cell blockage and bursts in liver, increased sensitivity to medicines and their side effects, an increased risk of possibility in developing insulin resistance and type-2 diabetes, and impair cognitive functions. Treatment of cirrhosis focus is in preventing the condition from becoming worse; treatment may slow or stop liver damage.[3]

End Stage: Liver failure: Liver failure is life-threatening and requires urgent medical attention. Usually, it occurs after years of abusing drugs of choice and alcohol (chronic liver failure) and because of cirrhosis. Chronic liver failure may also be a result of malnutrition. Rarely, liver failure may happen within 48 hours (acute liver failure) usually resulting from a reaction to poisoning or a medication overdose. The first symptoms of liver failure may be nausea, loss of appetite, fatigue, and diarrhea. Patients may become confused, disorientated, extremely sleepy, and have an increased risk of coma or death. At this stage, the only treatment option may be a liver transplant.[3]

Liver cancer: In the early stages of liver cancer, symptoms may not be expressed, but may include: losing weight without trying, loss of appetite, upper abdominal pain, nausea and vomiting, general weakness and fatigue, abdominal swelling, jaundice, and abnormal (white, chalky) stools. **Causes**: It is not clear what causes liver cancer, in most cases. Although, evidence suggests that chronic hepatitis C infection has been a precursor to liver cancer. **Risk factors**: Chronic infection with HBV or HCV, cirrhosis, certain genetic liver diseases, diabetes, nonalcoholic fatty liver disease, exposure to aflatoxins (poisons produced by molds that grow on poorly-stored crops), and/or excessive alcohol consumption. **Diagnosis** includes blood tests, imaging tests, and liver biopsy are used to determine the presence and stage of liver cancer (I-IV or A-D). **Treatment**: surgery to remove the tumor(s), liver transplant, or localized treatments, such as heating cancer cells, freezing cancer cells, injection of alcohol into the tumor, chemotherapy, or radiation therapy, targeted drug therapy – although, more studies are need to understand how targeted drug therapy may be utilized to combat advanced liver cancer, along with supportive (palliative) care.[4]

Section D: Availability of Conventional Medical Therapies

According to staff at Mayo Clinic, treatment for liver disease depends on diagnosis and severity. Some liver problems can be treated with lifestyle modifications, such as stopping alcohol use or losing weight, typically as part of a medical program that includes careful monitoring of liver function. Other liver problems may be treated with medications or may

require surgery. Treatment for liver disease which has resulted in liver failure may ultimately require a liver transplant.[1]

Dandelion and Milk Thistle have been traditionally used to address issues of the liver, but there is no compelling evidence to support their use for any condition, according to the National Center for Complementary and Integrative Health. A few studies have been conducted with regard to utilizing milk thistle, but little is known of its efficacy in treating people with liver disease.[2]

Transjugular Intrahepatic Portosystemic Shunt (TIPS): TIPS create a tract within the liver using x-ray guidance to connect two hepatic veins. The shunt is kept open by the placement of a small, tubular metal device commonly called a stent.[2]

During a TIPS procedure, interventional radiologists use image guidance to make a tunnel through the liver to connect the portal vein (the vein that carries blood from the digestive organs to the liver) to one of the hepatic veins (three veins that carry blood away from the liver back to the heart). A stent is then placed in this tunnel to keep the pathway open.

Patients who typically need a TIPS have portal hypertension, meaning they have increased pressure in the portal vein system. This pressure buildup can cause blood to flow backward from the liver into the veins of the spleen, stomach, lower esophagus, and intestines, causing enlarged vessels, bleeding, and the accumulation of fluid in the chest or abdomen. This condition is most commonly seen in adults, often as a result of chronic liver problems leading to cirrhosis. Portal hypertension can also occur in children, although children are much less likely to require a TIPS.

- Benefits:
  - A TIPS is designed to produce the same physiological results as a surgical stunt or bypass, without the risks that accompany open surgery.
  - TIPS is a minimally invasive procedure that typically has a shorter recovery time than surgery.
  - A patient's TIPS should have less of an effect than open surgical bypass on future liver transplantation surgery because the abdomen has not been entered, thus there is no scar tissue formed in the abdomen.
  - The stent that keeps the shunt open (TIPS) is contained entirely inside the diseased liver, and is removed with it during a transplant operation.
  - Studies have shown that this procedure is successful in reducing variceal bleeding in more than 90 percent of patients.
  - No surgical incision is needed—only a small nick in the skin that does not have to be stitched.

- Risks:
  - Any procedure which involves skin penetration carries a risk of infection. The chance of infection requiring antibiotic treatment appears to be less than one in 1,000.
  - There is a very slight risk of an allergic reaction to the contrast material used for venograms (x-ray of the veins). Also, kidney failure (temporary or permanent) due to contrast material use is a concern, particularly in patients with poor kidney function.
  - Any procedure that involves placement of a catheter inside a blood vessel carries certain risks. These risks include damage to the blood vessel, bruising or bleeding at the puncture site, and infection. However, precaution is taken to minimize these risks.
  - Other possible complications of the procedure include fever, muscle stiffness in the neck, bruising on the neck at the point of catheter insertion, delayed stenosis, or narrowing within the stent - which is less common with the current GORE-TEX-lined stents.
    Serious complications may include: occlusion, or complete blockage, of the stent and rapid recurrence of symptoms, infection of the stent or fabric lining, abdominal bleeding that might require a transfusion, laceration of the hepatic artery - which may result in severe liver injury or bleeding that could require a transfusion or urgent intervention, heart arrhythmias or congestive heart failure, radiation injury to the skin is a rare complication, and, rarely, death. Patients with more advanced liver disease are at greater risk for worsening liver failure after TIPS.[5]

Liver transplant: the most common reason for a transplant in adults is cirrhosis. During the procedure, a surgeon removes a diseased liver (lobes or "parts") and replaces it with a healthy liver or liver-tissue. With a successful transplantation, the patient will be placed on lifelong immunosuppression therapy to reduce the risk of transplant rejection. Patients are closely monitored by their doctor to better avoid rejection.[2]

Possible complications that may result from a transplant or transplant rejection include: certain cancers (due to taking strong immune suppressing drugs), infections, loss of function in the transplanted organ/tissue, or severity of side effects of immune-suppressing medicines.[2]

Hepatitis treatments: Most people with hepatitis A or E will get well after bed rest, abstaining from alcohol, and taking medication to help relieve discussed symptoms of liver disease. Hepatitis B is treated with drugs, such as lamivudine (Epivir) and adefovir dipivoxil (Hepsura). Hepatitis C treated, with guidance from a Hep. C Specialist, by use of a combination of lediasvir and sofosbuvir (Harvoni), for 8-24 weeks, daily treatment. Chronic hepatitis C may require a liver transplant, if severe cirrhosis is present.[2]

Common side effects of Epivir include: diarrhea, headache, fatigue, fever, chills, loss of appetite, trouble sleeping, depression, stuffy nose, cough, muscle pain. Serious side effects include: rash, vomiting, nausea, ongoing abdominal pain – may spread to back, and numbness, tingling, or burning in the fingers or toes. This is not a complete list of possible side-effects, as each patient's health is unique. Missed doses may cause complications in treatment.[6]

Common side effects of Hepsura include: nausea, vomiting, diarrhea, gas, stomach pain, mild skin rash or itching, weakness, or headaches. Emergency help should be sought if signs of allergic reaction, such as hives; difficulty breathing; swelling of one's face, lips, tongue or throat, are present. Lactic acidosis (build-up of lactic acid in the body, which may be fatal) is possible; symptoms include: muscle pain or weakness, numb or cold feeling in one's arms and legs, trouble breathing, dizziness or severe weakness, stomach pain, nausea with vomiting, or fast or uneven heart rate – emergency help is immediately required. Other, potentially serious side effects include: urinating less than usual or not at all, nausea, pain in upper stomach, itching, loss of appetite, dark urine, clay-colored stools, or jaundice.[7]
Common side effects of Harvoni include: fatigue, headaches, and general weakness. Serious side effects may include: interactions with anti-viral drugs, interactions with medicine used to treat certain heart problems – such as amiodarone – causing bradycardia (slow heart rate); medical assistance must be sought immediately if patients taking both amiodarone and Harvoni experience the following symptoms: fainting or near-fainting, dizziness or lightheadedness, not feeling well, weakness, extreme fatigue, shortness of breath, chest pains, confusion, or memory problems. Harvoni has a 94-97% success rate in curing Hep. C when patients adhere to treatment.[8]

Section E: Anticipated Benefits from Medical Cannabis

Anticipated benefits from medical cannabis include the amelioration of liver damage and reduced progression of liver disease, relief from symptoms of liver disease, and relief from symptoms associated with the treatment of liver disease. Symptomology which may benefit from medical cannabis treatment include: inflammation, pain in the abdomen and legs, muscle pain, joint pain, itchy skin, chronic fatigue, weight loss, nausea or vomiting, headaches, depression, and loss of appetite.

Endocannabinoids and Liver Disease

In a scientific review of studies up to the year 2005 by the Department of Metabolism and Human Nutrition, Hadassah-Hebrew University Medical School, The Liver Unit, Hadassah-Hebrew University Medical Center in Jerusalem, Israel, the authors described the major findings relating to endocannabinoids and liver disease. It was found that alterations to the liver due to hemodynamic changes resulting from cirrhosis (scarring of the liver from chronic inflammation) are moderated by CB1 receptors located on splanchnic (abdominal organs) and hepatic vascular endothelium (membrane lining the interior surface of blood and lymphatic vessel; in this case, blood vessels within the liver). The scientists referenced a study completed in 2001 indicating

that when compared with non-cirrhotic controls, in cirrhotic human livers there was a three-fold increase in CB1 receptors on isolated vascular endothelial cells indicating up-regulation of these receptors in chronic liver disease. [16] Cannabis has been shown to modulate the inflammatory process and neurological function due to cirrhosis via the endocannabinoid receptors. As previously described in the petition, inflammation of the liver is a precursor to liver disease - resulting in cirrhosis, if not addressed. Complications of cirrhosis include portal hypertension with a possibility of systemic vasodilation further complicating this condition, causing a decrease in effective blood volume, hypotension, fluid and salt retention, worsening ascites, and deterioration of renal function. Ascites (retention of fluid in the peritoneal cavity – causing abdominal swelling) is associated with increased plasma levels of the bacterial endotoxin lipopolysaccharide (LPS). LPS has been shown to increase with the progression of liver disease, and can cause hypotension (low blood pressure) and tachycardia (increased heart rate). Hypotension in the liver can lead to complications in blood flow and disease. The authors referenced a study, cited number 44, on LPS-treated donor rats where hypotension was shown to be prevented by pretreatment of the recipient rat with the CB1 receptor antagonists SR141716A – a synthetic cannabinoid.[9] Δ9-tetrahydrocannabinol (THC) is an agonist at both the CB1 and CB2 receptors. THC, and it's synthetic, was shown to not have a vasodilator effect in rat models – vasodilation can lead to hypotension and ascites. In a separate study referenced 66 in the authors' review, THC was shown to decrease pruritus (itchiness) in human and rodent models – suggesting a benefit for treating pruritus with the analgesic effect of THC in patients with liver disease. (Topical cannabis medicines are available August 1st, 2017 in Minnesota). As this specific review is from 2005, the authors stated that some epidemiological data supports the notion of a hepatotoxic effect for marijuana; however, methodological problems preclude conclusion in this context. Further, more current studies will be reviewed and will explain that cannabis does not lead to hepatoxicity in patients with liver disease and co-infections. Conclusions from the authors., suggest there is convincing evidence for the role in the hemodynamic compromise, as seen in cirrhosis, that "certain cannabinoids may improve hepatic inflammation and pruritus secondary to liver disease" – due to the possible synergistic or "entourage" effect of cannabinoids.[10]

Marijuana Use is not Associated with Progression to Advanced Liver Fibrosis in HIV/HCV Coinfected Women

The endocannabinoid system is an important impactful player on a variety of liver related conditions; fibrosis, steatosis, regeneration, and portal hypertension. Endocannabinoid ligands are pervasive and interact with cannabinoid receptors 1 and 2 (CB1 and CB2), which have high affinity for tetrahydrocannabinoid (THC). Under normal physiologic conditions, hepatic expression of CB1 and CB2 is absent or weak. However, both receptors are upregulated in a variety of liver diseases, including alcoholic and non-alcoholic liver disease, liver fibrosis, chronic hepatitis C, primary biliary cirrhosis and hepatocellular carcinoma.

Use of THC in HIV/HCV coinfected patients is common. Given that cannabis is becoming more widely available and more regularly consumed, it is critical to assess its clinical effects including any negative impact of THC use on liver fibrosis progression.

Chronic liver disease modulates hepatic cannabinoid receptor expression. CB1 is upregulated in chronic liver disease, and CB2 is also upregulated in chronic liver disease and prevents fibrosis progression. It is this balance between CB1 vs CB2 activation which may modulate fibrosis progression in patients with liver disease. If over-expression of both receptors is balanced, there is no change in liver fibrosis.

This 2016 longitudinal study of HIV/HCV co-infected women shows THC was not associated with progression to significant liver fibrosis on univariable or multivariable analyses in light or heavy users. Mean THC use per week during the observation period was not independently associated with a greater risk of progression to significant fibrosis in multivariable analysis when evaluated as a continuous variable. Similarly, no association between fibrosis progression and THC use was detected when mean THC use per week was treated as a categorical variable. There was no association between THC use and fibrosis progression among those women with fibrosis at entry. Of the 489 participants, with at least two years of follow up, 15% reported weekly or greater THC use and 6% daily use for two years or more. Among these women, neither duration nor frequency of THC use was found to be predictive of significant fibrosis for weekly THC use compared to no use. Similarly, no association was detected between the number of intervals with weekly THC use and significant fibrosis when compared to abstainers with a similar length of follow-up. Similar results were seen in the subgroup of women with baseline fibrosis at entry of study.[11]

Prolonged Excretion Half-Life of 11-nor-9-Carboxy-Δ9-THC Following Cessation in a Chronic, Heavy Marijuana User: Implications for Liver Transplant Assessment

Per a 2011 case report from The Academy of Psychosomatic Medicine, many transplant programs require a toxicology screening as part of the transplant candidacy evaluation. This case describes a heavy cannabis user who demonstrated an apparent half-life of 73 days. The patient was a 51-year-old obese, Caucasian male with a history of substance abuse. Assessment for liver transplantation was required due to alcoholic liver disease with concurrent hepatitis C infection. The patient had consistently maintained a dialogue with his medical providers that he had quit cannabis use one month prior to liver transplant evaluation – the patient's providers and the scientist all believed this to be true. It was suggested that the reasoning for the patients longer than normal half-life of THC was due to chronic use and obesity. THC is metabolized by the liver, but may be stored throughout the body. Weight was found to be the primary reason for prolonged cannabinoid excretion, as cannabinoids may be stored in fat deposits and released once again upon exposure to more cannabis. It's stated that only 25% of liver transplant programs don't require abstinence of cannabis use prior to transplant. It may take months after cessation of cannabis use for a patient to screen negative for THC in a toxicology screen. This case study is important for liver transplant teams evaluating patients who use cannabis as potential transplant candidates. It is stated that unregulated cannabis use (from the illicit market) has been associated with infections, immunosuppression, and certain types of cancer – most likely, as an indirect result of not regulating whole-flower cannabis use - as bioaerosols and chemical contaminants on unregulated/untested cannabis can be dangerous to

patients who have compromised immune systems and/or need a liver transplant. Currently, most patients in Minnesota's Medical Cannabis Program are still using whole-flower from the illicit market; whole-flower should be accessible to patients, as to avoid any negative side-effects from untested cannabis flower. The development of therapeutic modalities based on cannabinoids depends on their safety (access to tested cannabis) as well as efficacy. The authors state further research into the effects of obesity and liver dysfunction on the pharmacokinetics of THC will be valuable.[12]

A Novel Synthetic Cannabinoid Derivative Inhibits Inflammatory Liver Damage via Negative Cytokine Regulation

This Israeli study, published by The American Society for Pharmacology and Experimental Therapeutics in 2003, studied the mechanism of action of a synthetic cannabinoid (PRS-211,092) on female mice with injections of concanavalin A (con. A) - inducing an immune-mediated liver injury (mimicking liver disease), by expressing pro-inflammatory cytokines. Control mice were injected with saline. Con. A was used as a model for hepatitis mediated by cellular immunity. Blood was drawn from the mice prior and post injection of con A. After drug administration, the liver and spleen of the mice were removed, and a quantitative real-time polymerase chain reaction was conducted to quantify gene expression in the liver and spleen samples of con. A-injected mice and samples from saline-injected control animals. Liver tissue was observed under a microscope and evaluated for the degree of vascular congestion, dilatation, and telangiectasia (a.k.a. spider veins) in the portal tract, the degree of vascular congestion and dilatation in the centrilobular area, and the degree of inflammatory cell infiltration, liver cell degeneration, and necrosis in the midzone liver parenchyma. Statistical analysis and average scores 0 (normal) – 4 (highest severity) were performed (histopathology scoring). It was indicated that treatment with PRS-211,092 diminished con. A-induced liver damage demonstrated by decreased plasma levels of alanine aminotransferase (enzyme found in liver; ALT). When compared to animals only treated with con. A, efficacy of PRS-211,092 pretreatment and posttreatment of con. A were both effective in reducing ALT levels. High ALT levels are indicative of liver health issues. It was also shown that PRS-211,092 reduced disruption of liver tissue confirmed by the histopathology scoring for the "degree of vascular congestion and dilatation as well as inflammatory cell infiltration and liver cell degeneration."[12] During severe inflammation, acute phase proteins are secreted by hepatocytes. High levels of cytokines are toxic to the liver. Treatment with PRS-211,092 inhibited the expression of acute phase proteins by half. It was also determined that PRS-211,092 affects cytokine levels in spleen and plasma by increasing interleukin-6 (IL-6) and interleukin-10 (IL-10) gene expressions (anti-inflammatory proteins). The anti-inflammatory actions of IL-6 and IL-10 involves stimulation of suppressors of cytokine signaling (SOCS), SOCS-1 and -3 (proteins). Treatment with PRS-211,092 increased SOCS-1 and -3 expression significantly in the spleen and liver, indicating PRS-211,092 inhibits inflammatory damage via negative cytokine regulation (increased suppressors of cytokine signaling). It is suggested by the researchers that the negative feedback control of cytokine signaling by the SOCS may be a generic feature of cannabinoids. The researchers conclude that PRS-211,092 is "highly effective in diminishing

Con. A-induced liver damage" and may provide a basis for developing immunomodulatory treatment for hepatitis and other short- or long-term inflammatory disease, utilizing cannabis.[13]

Cannabidiol Improves Brain and Liver Function in a Fulminant Hepatic Failure-induced Model of Hepatic Encephalopathy in Mice

A study from Hadassah-Hebrew University Medical School, Jerusalem, Israel of 2010 investigated the effects of cannabidiol (CBD) and its anti-inflammatory properties on 20 mice in a model of induced hepatic encephalopathy associated with fulminant hepatic failure and 20 mice in a model of control - injected with saline. Hepatic encephalopathy is a neuropsychiatric disorder caused by acute or chronic liver failure, usually observed in patients with end-stage liver disease. The CBD utilized was extracted from cannabis resin and mixed with ethanol, emulphor and saline with a ratio of 1:1:18. It was determined that CBD, derived from *Cannabis sativa* activates the 5-hydroxytryptamine receptor (5-HT). CBD did not activate 5-HT in control animals, but was shown to be an agonist of the 5-HT receptor ameliorating brain damage in a chronic model of hepatic encephalopathy induced by bile duct ligation (resulted obstructive jaundice model – symptom of an underlying disease such as liver disease). Female mice were injected with either saline or thioacetamide (induces liver failure with hepatic encephalopathy), and were then treated with either saline or CBD. After the induction of hepatic failure, the brains and livers were removed for histopathological analysis and blood was taken for analysis of plasma liver enzymes. Cognitive function of a separate group of mice were tested. Neurological and motor functions in thioacetamide-treated mice were evaluated, and it was concluded that cognitive functions were restored by CBD while motor activity was partially restored by CBD. Increased plasma levels of ammonia, bilirubin, liver enzymes, and 5-HT levels were normalized following CBD treatment. The researchers concluded that CBD restores liver function and improves brain pathology. It is inferred that the effects of CBD may be due to a combination of its actions in the liver and brain because of CBDs ability to cross the blood-brain barrier – indicating CBD acting both centrally and peripherally. The researchers note that in previous studies both CB1 receptor antagonist (CBD) and a CB2 receptor agonist (THC) have been shown to diminish brain and liver damage that occurs with liver disease. Their results indicated that CBD has a neuroprotective role in hepatic encephalopathy induce by fulminant hepatic failure. The researchers concluded that "CBD improves the symptoms of fulminant hepatic failure by affecting both brain histopathology and liver function, and thus may serve as therapeutic agent for treating human hepatic encephalopathy."[14]

Cannabis Use and Reduced Risk of Insulin-resistance in HIV-HCV Infected Patients: A Longitudinal Analysis

A French study from 2015 examined whether cannabis use was consistently associated with reduced insulin-resistance (IR) risk in 703 HIV-Hepatitis C Virus infected patients, utilizing self-administered questionnaires every 12 months over 60 months of follow-up data for patients with at least one medical visit where IR and cannabis use were assessed. A mixed logistic regression model evaluated the association between IR risk and cannabis use (occasional, regular, daily). IR and an increased risk of diabetes is frequent in HIV-HCV co-infected patients

and associated with the progression of liver disease. The researchers state that "although cannabis use can increase appetite, it has been associated with a reduced risk of obesity and therefore IR in the general population." Data collected from the study included: HIV RNA plasma viral load (detectable or not), CD4 count, and a measure of degree liver fibrosis combined with data on HCV treatment initiation. The researchers also gathered HCV genotype, fibrosis stage, HCV plasma viral load, body mass index, history of HCV and HIV treatment, fasting glycemia (blood glucose level assessment), insulinemia (associated with type-2 diabetes), lipid panel, and comorbidities (diabetes, hypertension, cardiovascular problems, and renal dysfunction). Three sensitivity analyses showed that cannabis use (whether occasional, regular, or daily) was dramatically associated with lower risk of IR. The scientists also noted that their research is in line with previous studies in humans and animal models. It's stated that "when administered to obese rats, cannabis was associated with weight reduction and an increase in the weight of the pancreas, implying beta-cell protection."[15] It was determined by the researchers that cannabis use is associated with a lower IR risk in HIV/HCV-coinfected patients.[15]

HU-444, A Novel, Potent Anti-Inflammatory, Non-Psychotropic Cannabinoid

Inflammation is a significant concern in the progression of liver disease, as well as with the symptoms experienced as a result of liver disease or treatment of liver disease. In a 2015 published study from Israel, it is reported that a cannabidiol (CBD) derivative, HU-444, had an anti-inflammatory effect in both *in vitro* (experiments outside of living organisms; done with macrophages) and *in vivo* (research within a living organism; in this case: mice models for both autoimmune hepatitis and rheumatoid arthritis) anti-inflammatory assays. The synthetic pathway from CBD to HU-444 is short, but the yield is relatively low. Anti-inflammatory activity was expressed in both *in vitro* and *in vivo* models of experimentation, with *in vivo* leading to the suppression of production of tumor necrosis factor-alpha (TNF-α) (a pro-inflammatory cytokine) and amelioration of liver damage as well as lowering of mouse collagen-induced arthritis. Con. A was used to induce liver damage in mice, promoting the increase of the liver enzymes interleukin-2 and inflammatory cytokines. Con. A-induced hepatitis is considered to mimic autoimmune hepatitis in humans. Con. A treated mice experienced a reduction in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and TNF-α levels were greatly reduced following the injection of HU-444. In studying the effects of HU-444 on con. A-induced liver damage, histopathological evaluations of the livers were performed. Con. A treatment was associated with liver damage with necrosis and mononuclear cell infiltration. After the administration of the CBD derivative, HU-444, it was observed that HU-444 significantly diminished liver damage and reduced mononuclear infiltration, leading to an optimally preserved normal liver histology. The authors also provided clinical benefits in terms of protecting joints and the prevention of damage caused by disease. Other studies have noted amelioration of hepatitis by HU-444, suggests a promising curative therapeutic role for CBD in human autoimmune hepatitis disease – according to the researchers.[16]

Conclusion:

It is important for the well-being of patients with compromised immune systems to have access to safe, regulated, and tested medicinal cannabis. Based on the evidence presented on the ability of cannabis to heal or reverse liver damage, and cannabis' ability to provide relief of symptoms of liver disease and treatments of liver disease, it is recommended that liver disease be approved as a qualifying condition in Minnesota's Medical Cannabis Program.

Arizona, Arkansas, Delaware, Illinois, Maine, Massachusetts, Michigan, New Hampshire, New Mexico, North Dakota, Ohio, Rhode Island, and Washington specifically allow hepatitis C (virally-induced inflammation of the liver) as a qualifying condition; with a few other states allowing symptoms associated with liver disease, determined by a physician, as qualifiers for medical cannabis.

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Section F (optional): Scientific Evidence of Support for Medical Cannabis Treatment

The following scientific literature is submitted with this petition:

Avraham, Y., Grigoriadis, N., Poutahidis, T., Vorobiev, L., Magen, I., Ilan, Y., Berry, E. 2011. Cannabidiol improves brain and liver function in a fulminant hepatic failure-induced model of hepatic encephalopathy in mice. British Journal of Pharmacology, 162(7), 1650-1658. DOI:10.1111/j.1476-5381.2010.01179.x.

Batkai, S., Jarai, Z., Wagner, J. A., Goparaju, S. K., Varga, K., Liu, J., . . . Kunos, G. (2001). Endocannabinoids acting at vascular CB1 receptors mediate the vasodilated state in advanced liver cirrhosis. Nature Medicine, 1(7). DOI:10.1038/89953.

Carrieri, M., Serfaty, L., Vilotitch, A., Winnock, M., Poizot-Martin, I., Loko, M., Dabis, F. 2015. Cannabis use and reduced risk of insulin-resistance in HIV-HCV infected patients: a

longitudinal analysis. Clinical Infectious Diseases Advance Access. DOI:10.1093/cid/civ217.

Chaiffetz, D., Dimartini, A., & Venkataramanan, R. 2011. Prolonged excretion half-life of 11-nor-9carboxy-Δ^9-THC following cessation in a chronic, heavy marijuana user: implications for liver transplant assessment. Psychosomatics. DOI: 10.1016/j.psym.2010.12.005.

Gabbay E, Avraham Y, Ilan Y, Israeli E, Berry EM. "Endocannabinoids and Liver Disease". Liver Int. 2005 Oct;25(5):921-6. Review. PMID: 16162147.

Haj, C. G., Sumariwalla, P. F., Hanus, L., Kogan, N. M., Yektin, Z., Mechoulam, R., Gallily, R. 2015. HU-44, a novel, potent anti-inflammatory, non-psychotropic cannabinoid. JPET Fast Forward. DOI:10.1124/jpet.115.226100.

Kelly, E. M., Dodge, J. L., Sarkar, M., French, A. L., Tien, P. C., Glesby, M. J., Peters, M. G. (2016). Marijuana use is not associated with progression to advance liver fibrosis in HIV/HCV coinfected women. Oxford University Press for the Infectious Diseases Society of America. DOI:10.1093/cid/ciw350

Lavon, I., Sheinin, T., Meilin, S., Bitōn, E., Weksler, A., Efroni, G., . . . Avraham, A. (2003). A Novel Synthetic Cannabinoid Derivative Inhibits Inflammatory Liver Damage via Negative Cytokine Regulation. *Molecular Pharmacology,64*(6), 1334-1341. doi:10.1124/mol.64.6.1334

Section G (optional): Letters in Support of Adding the Medical Condition

A letter of support is included from Dr. Jacob Mirman.

Additionally, the following individuals indicated their support for the addition of Liver Disease as a qualifying condition to Sensible Minnesota and Marijuana Policy Project. Commentary is as sent, except for minor modifications for clarity.

[redacted]

Physician

[redacted]5

Patients that need marijuana for their conditions face many difficulties obtaining it. This is unfair and hurts patients.

[redacted]

Physician, Patient's Spouse

[redacted]

[redacted]

Patient

[redacted]

[redacted]

Patient, Patient guardian of an adult

[redacted]

I have wide spread chronic pain (fibromyalgia, myofascial, muscle spasms, nerve pain, migraines) well as nausea from Mariners disease. I also have issues with anxiety, depression & PTSD. I've just started the medical cannabis program here about 1mo ago. I've noticed a major decrease in my nausea & anxiety I'm not as depressed my muscle spasms have lessened and I don't concentrate a lot on the pain but the pain is still there. I do not feel sick or lethargic like I did when I was on opiate medication. For the first time in 20 plus years I can actually sleep 4+ hours @ night. I've also noticed that I'm able to focus a better without all of the anxiety of having to remember how to move and how to be around people in public. The major drawback to this program here in Minnesota for me is that I'm low-income and have a hard time paying for the products. I would also like to see other choices such as edibles or the plant as an option. In conclusion, I would like to add that this medication would be fabulous for all of the related conditions above especially for people with Alzheimer's and Dementia to alleviate their stress of anxiety when they can't remember or become disoriented. As well as for people with autism will help with their focus and minimize the cold symptoms of anxiety and depression. Thank you for your time.

[redacted]

Patient

[redacted]

I'm on the medical program for chronic pain here in Minnesota. And marijuana works best for everything without the harsh side effects that pharmaceuticals. But this program is lacking quality, variety, and the range of conditions! If someone has an ailment and marijuana helps them best, why should there be any question who gets treatment? When it's so easy for people to get opiates and Vicodin and Percocet that kill 10's of thousands a year and this natural, broad range of multiple reliefs, with extremely limited side effects, and 0 deaths ever is so hard to get! It's stupid and ridiculous that we're even still having to fight and beg for something today is so much better than anything that big Pharma and doctors are trying to do for us!

[redacted]

Patient

[redacted]

I could use it for pain. I have liver disease and cannot take pain medication.

[redacted]

Patient

[redacted]

My chronic pain and nausea caused by migraine headaches and lower back issues are relieved by medical marijuana. Opiates are not an option in my life as I am allergic.

[redacted]

Patient

[redacted]

[redacted]

Patient

[redacted]

I have personal experience in managing chronic pain and nausea though the CBD edibles my sister has shared with me while visiting her in California, where she has a medical card and uses these regularly as a way to manage her symptoms. I have never experienced any problematic side effects, and she specifically takes the CBD edibles and tinctures as an alternative to many other pharmaceuticals that she HAS had terrible side effects with. She currently uses medical marijuana to treat the symptoms of Lupus, Ischemic Colitis, Chronic Fatigue and Fibromyalgia, as well as depression, nausea, anxiety and chronic pain from the above diseases. I believe the above conditions that include those being petitions for addition in Minnesota would greatly assist those dealing with these chronic diseases to get some relief without the terrible side effects from pharmaceuticals. My mother is experiencing dementia and liver disease as a result of long-term alcohol use and I would like to see the state offer her an alternative, healthier form of support for symptoms of these diseases as well.

[redacted]

Patient

[redacted]

I have chronic pain and liver disease. I can't take Tylenol. The liver has stressed the kidneys and I can't take anti-inflammatory meds. Narcotics make me nauseated. Tramadol did nothing. Lyrica made me feel loopy... so besides positioning, ice and warm packs...I had little to help the discomfort I gave in back and hands, feet, shoulders and hips.... besides keeping my weight low and trying to be active.....the liver disease hits me with devastating fatigue.....have to keep active...the marijuana helps. Besides all the physical therapy.... I have discomfort. Thank goodness, my Doctor let me try the medical marijuana program. It helps.

[redacted]

Patient

[redacted]

I am a patient and I use it daily it helps with my Chronic Pain and my Liver I am a transplant patient. I would like to see this help others as it has help me.

[redacted]

Patient

[redacted]

[redacted]

I need a natural treatment not a chemical one. I cannot take most pills because of my MCS. I need the plant the whole plant to be legal and to eat or smoke it.

[redacted]

Patient

[redacted]

I thought the whole legalization of marijuana in MN was all about chronic pain! I was so disheartened to find out how narrow minded our legislators were with the few medical issues that ended up qualifying. No wonder those companies aren't making any money! I hope they do it right this time around.

[redacted]

Patient

[redacted]

As a patient, I feel as though anyone who can be helped by Medical Marijuana should have the option to try to find a medicine that can help with their condition.

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[1] Liver disease. 2014. Retrieved July 31, 2017, from http://www.mayoclinic.org/diseases-conditions/liver-problems/basics/definition/con-20025300.

[2] Liver Disease | MedlinePlus. (n.d.). Retrieved July 31, 2017, from https://medlineplus.gov/liverdiseases.html.

[3] The Progression of Liver Disease. (n.d.). Retrieved July 31, 2017, from http://www.liverfoundation.org/abouttheliver/info/progression/.

[4] Liver cancer. 2016. Retrieved July 31, 2017, from http://www.mayoclinic.org/diseases-conditions/liver-cancer/symptoms-causes/dxc-20198168.

[5] Radiological Society of North America (RSNA) and American College of Radiology (ACR). (n.d.). Transjugular Intrahepatic Portosystemic Shunt (TIPS). Retrieved July 31, 2017, from https://www.radiologyinfo.org/en/info.cfm?PG=tips#benefits-risks.

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[10] Gabbay E, Avraham Y, Ilan Y, Israeli E, Berry EM. "Endocannabinoids and Liver Disease". Liver Int. 2005 Oct;25(5):921-6. Review. PMID: 16162147.

[11] Kelly, E. M., Dodge, J. L., Sarkar, M., French, A. L., Tien, P. C., Glesby, M. J., Peters, M. G. (2016). Marijuana use is not associated with progression to advance liver fibrosis in HIV/HCV coinfected women. Oxford University Press for the Infectious Diseases Society of America. DOI:10.1093/cid/ciw350

[12] Chaiffetz, D., Dimartini, A., & Venkataramanan, R. 2011. Prolonged excretion half-life of 11-nor-9carboxy-Δ^9-THC following cessation in a chronic, heavy marijuana user: implications for liver transplant assessment. Psychosomatics. DOI: 10.1016/j.psym.2010.12.005.

[13] Lavon, I., Sheinin, T., Meilin, S., Biton, E., Weksler, A., Efroni, G., . . . Avraham, A. (2003). A Novel Synthetic Cannabinoid Derivative Inhibits Inflammatory Liver Damage via Negative Cytokine Regulation. *Molecular Pharmacology,64*(6), 1334-1341. doi:10.1124/mol.64.6.1334

[14] Avraham, Y., Grigoriadis, N., Poutahidis, T., Vorobiev, L., Magen, I., Ilan, Y., Berry, E. 2011. Cannabidiol improves brain and liver function in a fulminant hepatic failure-induced model of hepatic encephalopathy in mice. British Journal of Pharmacology, 162(7), 1650-1658. DOI:10.1111/j.1476-5381.2010.01179.x.

[15] Carrieri, M., Serfaty, L., Vilotitch, A., Winnock, M., Poizot-Martin, I., Loko, M., Dabis, F. 2015. Cannabis use and reduced risk of insulin-resistance in HIV-HCV infected patients: a longitudinal analysis. Clinical Infectious Diseases Advance Access. DOI:10.1093/cid/civ217.

[16] Haj, C. G., Sumariwalla, P. F., Hanus, L., Kogan, N. M., Yektin, Z., Mechoulam, R., Gallily, R. 2015. HU-44, a novel, potent anti-inflammatory, non-psychotropic cannabinoid. JPET Fast Forward. DOI:10.1124/jpet.115.226100.

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07-20-2017

Minnesota Department of Health Office of Medical Cannabis
P.O. Box 64882
St. Paul, MN 55164

To the Minnesota Department of Health,

My name is Dr. Jacob Mirman, I graduated from the University of Minnesota Medical School and completed my residency in primary care internal medicine at Illinois Masonic Medical Center in Chicago. I specialize in integrative medicine and I am the Medical Director of Life Medical, an integrative medicine clinic in St. Louis Park.

I write to you today in support of the petitions to add nausea, autism, dementia, Alzheimer's disease, liver disease, and chronic pain to Minnesota medical cannabis program. As a physician treating patients for all these conditions, I believe my patients who suffer from these conditions would benefit from being added to the state's program.

I am a primary care internist. I am a not a politician, a law enforcement officer or a cannabis policy expert. Yet, as an internist with 25 years of experience working with patients, I hope you will consider my views on whether to expand Minnesota's medical cannabis program.

I have been certifying patients for medical cannabis for over a year now, and have seen a tremendous benefit to patients when they return to me for follow-ups. Notably, in addition to the medical condition that qualifies them for the program, many patients who I have certified suffer from some other ailment — including several listed above — and have seen their conditions improved with medical cannabis use.

Patients come to me because they need help. I agree to see them and do my best to help them. The buck stops with me. If I send a patient to a specialist and he or she is unable to help, the patient comes back to me and their medical care is again my responsibility.. When standard approaches do not help the patient, my responsibility as their physician does not end.

For the last few months, around 20% of my practice has involved treating patients benefiting from medical cannabis. I certify on average two-three new patients per day. Notably, many patients are finding relief for not just the condition they have been certified for, but also secondary conditions. Further, my patients are happier, suffer from less anxiety (many have

SECTION G

ceased use of anti-anxiety medication), and are significantly reducing their pain. Quite a few have gotten off of narcotics and other pain killers altogether.

Practicing integrative medicine allows me to find the best treatment for my patients, and their success stories are what make my work so much fun. The beauty of integrative medicine is that it brings together different treatment methods to get the best effect for each individual patient. We use whatever modality we consider best for each patient's case. Our patients get the benefit of customized treatment plans that include conventional and complementary therapies. We combine all possible treatment options; whatever may help the patient in the most effective and safest way. And we are seeing great results using integrative approach.

Nausea is a common symptom of many conditions, or their treatments, including cancer and pain. Migraines are often accompanied by nausea, adding nausea to the program could significantly help my patients. Nausea is also often associated with PTSD, muscle spasms, and pain, all of which are currently covered by the program. Adding nausea to the program just makes sense.

Marinol — which is pure, synthetic THC — has been approved as a prescription drug since 1985 for nausea and vomiting associated with cancer chemotherapy in patients. Like other medications, Marinol can also be prescribed for off-label uses. However, Marinol is an inadequate substitute for many nauseated patients because, as a pill it is slow-acting. Also, unlike vaporized cannabis, a patient cannot precisely titrate their dosage and many end up overly intoxicated.

Autism, dementia, and Alzheimer's disease, are all marked by anxiety. Cannabis causes people to calm down. I have seen this many times with children in particular. For example, I had a young patient with seizures who, upon being placed on cannabis, changed her behavior drastically, she became better in school, improved in gymnastics, and had a higher quality of life. Offering cannabis to patients suffering from autism, dementia, and Alzheimer's disease, will result in a reduction in their anxiety and likely benefit these patients as to other symptoms they suffer from as well.

In addition, cannabis has been helpful at reducing self-injurious and aggressive behavior in autistic individuals who have not responded to other treatments. In Texas and Georgia, parents have talked to the media about their decision to break state law to help their autistic children, who were engaging in self-harm.

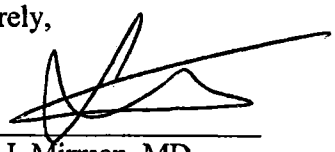
Liver disease often results in decreased appetite and nausea. Granting access for patients who suffer from this condition to medical cannabis, will likely help them battle these afflictions tremendously. Cannabis's alleviation of a decreased appetite is well-documented, and it is in the interest of my liver disease patients to have access to this important treatment option.

In my opinion, medical cannabis is the best pain medication of any pain medication available today either prescription or over the counter. It is much safer than opioids, and even safer than over-the-counter drugs like ibuprofen and Tylenol. Not only is cannabis incredibly effective, but there are few if any side effects and no risk of fatal overdose. Indeed in all my years of practicing

medicine, I have never seen a drug that has such a remarkable effect on patients with almost zero side effects.

Please add nausea, autism, dementia, Alzheimer's disease, liver disease, and chronic pain, to Minnesota medical cannabis program.

Sincerely,



Jacob I. Mirman, MD