DEPARTMENT OF HEALTH

Liver Disease

ISSUE BRIEF ON LIVER DISEASE

Introduction

Briefings such as this one are prepared in response to petitions to add new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, to members of the Medical Cannabis Review Panel, and to interested members of the public scientific studies of cannabis products as therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) will be included, especially if there are few clinical trials or observational studies. Though interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses, when published in peer-reviewed journals surveys will be included for completeness. When found, published recommendations or opinions of national organizations medical organizations will be included.

Searches for published clinical trials and observational studies are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Finally, the federal government-maintained web site of clinical trials, clinicaltrials.gov, was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

Definition

Liver disease refers to damage to the liver caused by hereditary factors or lifetime exposures, such as alcohol use, obesity or viruses, and the subsequent effects of such damage. There are a few common pathways in liver disease: alcohol-related fatty liver disease, non-alcoholic fatty liver disease, and viral hepatitis. These pathways have distinct causes but share features of disease progression. Other less common pathways in liver disease are immune system abnormalities (autoimmune hepatitis, primary biliary cirrhosis, or primary sclerosing cholangitis), genetic conditions (hemochromatosis, hyperoxaluria and oxalosis, or Wilson's disease) and cancer or other growths (liver cancer, bile duct cancer, or liver adenoma) (Mayo Clinic. Liver Problems. 2017).

Diagnosis

Liver disease can be diagnosed using different modalities. Liver function tests are blood tests of enzymes and proteins which can approximate liver function, though they cannot provide a complete diagnosis. Imaging studies, including computed tomography (CT) scan, magnetic resonance imaging (MRI) and ultrasound can be used to examine liver damage. Finally, liver tissue biopsy can also diagnose liver damage and is considered the diagnostic standard (Mayo Clinic. Liver Problems. 2017).

Complications and Consequences

Liver inflammation (hepatitis) and damage can be caused by a number of lifestyle factors as well as genetic factors, but is commonly caused by viral infection (including infections of hepatitis A, B, or C virus). Liver damage secondary to alcoholic or non-alcoholic fatty liver disease begins with steatosis, an accumulation of fat in the liver. In some cases, steatosis is benign but in others it progresses to a state of inflammation, known as steatohepatitis. The inflammation stage is reversible with appropriate diagnosis and treatment. In the absence of treatment, scarring on the liver develops and eventually replaces healthy liver tissue (fibrosis). Fibrosis can be managed successfully; in the absence of intervention, however, patients with liver fibrosis progress to cirrhosis, an irreversible disease state in which the liver's normal architecture is disrupted. Cirrhosis develops in approximately 10-12% of patients with steatohepatitis within eight years (Bhala 2009) and its potential complications are serious, including liver cancer, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, portal hypertension, variceal bleeding and hepatorenal syndrome. The final stage of liver disease is liver failure, in which the liver loses all function. This condition can progress over years and is life-threatening. (American Liver Foundation, Heidelbaugh 2006)

Prevalence

Data from the Third National Health and Nutrition Examination Survey, which collected data from 1988-1994, found the prevalence of elevated aminotransferase levels, a common laboratory indicator of liver damage, to be 7.9% in U.S. adults (Clark 2003). The Centers for Disease Control and Prevention (CDC) estimates the morbidity of chronic liver disease and cirrhosis in the U.S. to be 1.6%, with an estimated attributable 12.0 deaths per 100,000 (National Center for Health Statistics).

Current Therapies

Current viral hepatitis treatment centers around direct acting antiviral drugs (DAA), which can be single drugs or combination therapy. These antiviral therapies achieve high rates of success: a 2016 systematic review of DAA therapy found that several current treatment regimes achieve sustained virological response (an indicator of successful therapy) rates of 90-95% in hepatitis C patients with cirrhosis (Majumdar 2016).

There are currently no approved medications for treatment of nonalcoholic fatty liver disease (NAFLD) and data or recommendations on medical therapy are therefore off-label. Treatment of low-risk NAFL disease, in which no fibrosis is present, focuses on lifestyle modifications like exercise and diet changes. A recent systematic review found that dietary and physical activity intervention found that a 5% weight loss in NAFLD cases or a 7-10% weight loss in nonalcoholic steatohepatitis cases, achieved by combined dietary restriction and exercise, had therapeutic benefit (Kenneally 2017). In higher-risk NAFLD cases with steatohepatitis with some fibrosis, the recommended first-line treatment is vitamin E; other agents with demonstrated therapeutic benefit are pioglitazone (a peroxisome proliferator-activated receptor-γ agonist), liraglutide (a GLP-1 agonist) and metformin (an insulin sensitizer) (Banini 2017).

Patients who develop cirrhosis are managed similarly, regardless of underlying etiology. An expert panel published cirrhosis management guidelines in 2010 (Kanwal 2010) in which treatment diverges based on calculated Model for End-stage Liver Disease[1] scores; patients with scores of >15 or ≤15 in the presence of complications should be considered for liver transplant. Short of consideration for transplant, treatment focuses on surveillance for and management of disease complications.

Ascites treatment involves salt restriction and diuretic therapy (typically a combination of spironolactone and a loop diuretic). Spontaneous bacterial peritonitis, a complication related to untreated ascites, is treated with antibiotics. Patients with hepatic encephalopathy are graded on severity of encephalopathy as well as reversible factors, which include constipation, noncompliance, infection, electrolyte imbalance, gastrointestinal bleeding and benzodiazepine use, should be mitigated. If hepatic encephalopathy persists, the patient should be medically treated with dissacharides or rifaximin. Finally, if the patient develops or presents with bleeding esophageal varices, the patient should be treated with beta blockade. In the case of acute bleeding, more aggressive treatment with antibiotics and hospitalization may be necessary (Starr 2011).

When liver damage reaches the point of loss of function and failure, the treatment goal is preservation of remaining liver function or liver transplant if preservation is not possible. Liver transplantation can be complicated by infection or rejection of the transplanted liver; one large study reported survival at one, five, and ten years post-transplant to be 79%, 67% and 57%, respectively (Jain 2000).

Pre-Clinical Research

The endocannabinoid system, which includes the endogenous cannabinoids (endocannabinoids) as well as the cannabinoid receptors (CB1 and CB2) to which cannabinoids bind, is still a relatively new field of scientific inquiry. A number of recent studies have investigated the involvement of the endocannabinoid function on various aspects of liver disease, including development of fatty liver disease (steatosis), fibrosis, cirrhosis and liver

---

[1] https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/

failure in the presence of different underlying etiology. General findings suggest that upregulation of CB1 receptors is associated with onset of liver disease and increased markers of disease progression; some studies find that CB2 receptor activation is also associated with liver disease progression but others suggest that CB2 receptor activation may play a role in reversing disease progression. Several studies focus on rimonabant, a CB1 receptor antagonist, to understand CB1 receptor's role. The studies summarized below are representative of current published evidence on the impact of cannabinoids and the endocannabinoid system on liver function.

Gabbay E, Avraham Y, Ilan Y, Israeli E, Berry EM. Endocannabinoids and liver disease- review. *Liver International* 2005; 25:921-926.

The authors review existing literature at the time of publication regarding the involvement of the endocannabinoid system on various manifestations of liver disease. Summarizing studies on the effects of endocannabinoids or their receptor antagonists on hemodynamics as part of liver disease, the authors note that ascites, or accumulation of fluid in the peritoneal cavity most commonly linked to cirrhosis, is associated with increased plasma levels of lipopolysaccharide (LPS), a bacterial endotoxin. Studies have shown LPS levels to be inversely associated with liver function and linked to worse short-term survival. As peripheral CB1 receptor activation by macrophage- and platelet- derived substances has been found to promote hypotension, the relationship between anandamide and hemodynamic instability was explored by the authors in previous work. The authors found that platelets and macrophages generate different endocannabinoids which may both mediate endotoxin-induced hypotension by activating vascular CB1 receptors. Further studies found that CB1 receptor antagonism improved hypotension in rats with biliary cirrhosis and CCl_4-induced cirrhosis; similar effects were observed on arterial pressure and peripheral resistance in another rat study. The authors also cite a study that found that in cirrhotic liver samples, CB1 receptors were three times more prevalent on endothelial cells as compared to healthy liver samples, and conclude that in cirrhosis, monocytes increase endocannabinoid production which contributes to hemodynamic deterioration, with a probable mechanism of mediating between endotoxins and blood vessels.

The authors also include data on serum cannabinoids to note that in endotoxic shock during liver disease progression, serum endocannabinoid levels are markedly higher than non-diseased controls. They also cite a study pointing to pro-apoptotic effects of anandamide, an endocannabinoid. In neurological features of liver disease, the authors note that CB1 receptor blockade can improve neurologic function in mice with induced liver failure accompanied by hepatic encephalopathy. Finally, the authors cite a study involving PRS-211,092, a synthetic, non-psychoactive cannabinoid which showed reduction in liver injury in mice upon treatment with PRS-211,092. The authors cite two clinical studies: the first is a cross-sectional study on patients in Brazil using cannabis, with or without use of alcohol or crack cocaine. The study found that chronic marijuana use may have hepatotoxic effects. The second study, a case series of three patients with intractable cholestatic-related pruritis, found that administration of Marinol, a synthetic THC medication, reduced pruritis and improved sleep in all three patients.

The authors conclude their review by stating that while little is known about the effect of endocannabinoids and blockade of their receptors on liver physiology and disease, there is evidence they play a role in hemodynamic compromise in the presence of cirrhosis, likely due

to increased endocannabinoid production which results in vasodilation. They also note that increase in serum anandamide is linked to acute and chronic liver disease, and anandamide exerts an apoptotic effect on liver cells. They note that certain cannabinoids, possibly PRS-211,092,m may improve hepatic inflammation and pruritus in liver disease, but more data are needed to support this.

Purohit V, Rapaka R, Shurtleff D. Role of Cannabinoids in the Development of Fatty Liver (Steatosis). *American Association of Pharmaceutical Scientists Journal*, **June 2010; 12(2):233-237.**

This review article from the National Institute on Drug Abuse summarizes a number of pre-clinical and observational studies examining the role of CB1 and CB2 receptor activation in the development of fatty liver, an early stage of alcoholic and non-alcoholic fatty liver disease and hepatitis C. They examine the roles of CB1 and CB2 receptor activation in non-alcoholic and alcoholic fatty liver disease.

Regarding the role of CB1 receptors in development of fatty liver disease, the authors examine a study by Jeong et al. in which wild-type mice were exposed to ethanol and, in contrast to a control group, developed fatty liver and corresponding elevated disease markers (2-AG) as well as increased expression of genes encoding CB1 receptors in liver tissue; however mice treated with rimonabant, a CB1 receptor antagonist, did not develop fatty liver after ethanol exposure. Subsequent experiments examining ethanol exposure in wild-type versus global and hepatocyte-specific CB1 receptor knockout mice showed that the effects of ethanol on liver disease markers (transcription factor-SREBP-1c and fatty acid synthase) were blunted among all CB1 receptor knockout mice.

To examine CB1 receptor activation in non-alcoholic fatty liver, the authors cite a study by Osei-Hyiaman et al. in which wild type mice and global CB1 knockout mice are given a high-fat diet to cause non-alcoholic fatty liver; the wild type mice become obese and develop fatty liver while the CB1 receptor knockout mice remain lean and do not develop fatty liver. Additionally, wild type mice who were treated with rimonabant did not experience increased rates of fatty acid synthesis when fed a high-fat diet. The authors conclude that this study points to an inhibitory effect of a CB1 receptor antagonist on fatty liver development and a promoting effect of CB1 receptor agonist on fatty liver development. The authors also cite a study by Gary-Bobo et al. on the role of CB1 receptors in the development of obesity-induced fatty liver in genetically obese rats. This study found that rimonabant treatment had a protective effect against fatty liver: liver slices of rimonabant treated obese rats were found to be histologically similar to those of lean rats.

The authors also reviewed studies on the role of CB2 receptors on fatty liver development but noted that relative to the role of CB1 receptors, it is underinvestigated. They cite findings from Mendez-Sanchez et al. that showed upregulation of CB2 receptors in liver samples from patients with steatosis. Another study by Deveaux et al. found that hepatic CB2 receptor knockout mice did not develop severe fatty liver after being given a high-fat diet, in contrast to wild type mice which developed the disease after being given a high-fat diet.

Finally, the authors include a study by Hezode et al. that found daily cannabis smoking to be an independent predictor of steatosis in patients with chronic hepatitis C. Summarizing

the reviewed findings, the authors conclude that upregulation of CB1 receptors plays a role in fatty liver development and upregulation of CB2 receptors may also play a similar role, though evidence is not sufficient to determine this.

Avraham Y, Grigoriadis NC, Poutahidis T, Vorobiev L, Magen I, Ilan Y, Mechoulam R, Berry EM. Cannabidiol improves brain and liver function in a fulminant hepatic failure-induced model of hepatic encephalopathy in mice. *British Journal of Pharmacology* **2011;162:1650-1658.**

This study examined the effect of cannabidiol on mice treated with a hepatotoxin to induce acute liver failure, the end-stage progression of liver disease. The mice were randomly assigned to groups of 10 and half were injected with thioacetamide (TAA) in saline to induce liver failure; the other half were injected with vehicle saline to serve as controls. Cannabidiol extract was injected into half of the TAA-treated rats and half of the vehicle-treated mice in a single dose of 5mg/kg. The other half were treated with the cannabidiol (CBD) vehicle solution to serve as controls. Neurological function (10-point scale based on reflexes and task performance); activity, cognitive function (assessed by maze performance), brain histopathology and immunochemistry, liver histopathology and serum ammonia, liver enzymes and bilirubin levels were assessed after treatment. The study found that the mice treated with CBD and TAA had improved neurological scores and cognitive function, as well as reduced astrogliosis in brain samples as compared to mice treated with a vehicle control and TAA. Furthermore, treatment with TAA showed increased markers of liver dysfunction (ammonia, bilirubin and liver enzymes aminotransferase and alanine aminotransferase) compared to controls, but the mice treated with CBD were less susceptible to the effect of TAA with regard to hepatic encephalopathy, a grouping of neuropsychiatric abnormalities often observed in tandem with liver failure. The authors conclude that CBD appears to exhibit a multifactorial beneficial effect on liver failure and may be a future therapeutic agent.

Clinical Trials

Currently there are no clinical trials, either complete or underway, examining the effect of whole plant cannabis, THC, or CBD on liver disease. There are a few ongoing and completed trials involving cannabinoids or CB1 receptor antagonists for the treatment of liver disease which are outlined below. Additionally two safety and efficacy studies on Rimonabant, a selective CB1 antagonist, for the treatment of nonalcoholic steatohepatitis which were terminated when the medication was withdrawn, are also described below.

GW Pharma completed a preliminary safety and efficacy pilot study examining the combined and independent effects of two tetrahydrocannabivarins, GWP42003 and GQP42004 for the treatment of type II diabetes for a 13-week period. Tetrahydrocannabivarin (THCV) is a cannabinoid typically present in small amounts in cannabis. THCV is a homologue of THC. It has a propyl side chain instead of THC's pentyl group, which makes it produce different effects than THC. Primary outcome is change in mean serum high density lipoprotein cholesterol concentration, and secondary outcomes include change in mean percent liver fat. The study results are not published, but the results reported on the study's ClinicalTrials.gov website show no differences ($P > 0.05$) in change from baseline to end of study in mean percent liver fat in each of the following comparisons 1) 1:1 GWP42003:GWP42004 to placebo; 2) 20:1

GWP42003:GWP42004 to placebo; 3) GWP42003 and placebo to placebo; 4) GWP42004 and placebo to placebo. More information about this trial can be found at:

GWMD1092 – GQP42003: GWP42004 Together Plus Alone in Type II Diabetes:
https://clinicaltrials.gov/ct2/show/results/NCT01217112?term=cannabis&cond=liver&rank=4&sect=X01256

Pfizer completed a trial on CP-945598 (otenabant) a high affinity, selective CB1 receptor antagonist for the treatment of non-alcoholic steatohepatitis. This was a Phase 1 trial investigating the steady-state safety, tolerability and pharmacokinetics of the medication; it was first received by ClinicalTrials.gov in June 2008 and last updated in August 2009 without posting study results. Primary outcome measures were Urine 6-β-hydroxycortisol:cortisol ratio, adverse event monitoring, physical examinations, sitting vital sign measurements, 12-lead electrocardiograms and laboratory safety assessments, and pharmacokinetic data on the medication and its primary metabolite. Published data on the study is not available. More information can be found at:

Phase 1 Pharmacokinetic Study of CP-945598 In Patients with NASH:
https://clinicaltrials.gov/ct2/show/NCT00706537?term=cannabis&cond=liver&rank=1

Sanofi-Aventis sponsored two trials to investigate the safety and efficacy of Rimonabant in treating non-alcoholic steatohepatitis; one study focused on patients with Type II diabetes and the other focused on non-diabetic patients. Both studies were first posted on ClinicalTrials.gov in December 2007; as of April 2016, both trial websites report that the trials were terminated by Sanofi-Aventis in compliance with national health authorities. No data on primary outcomes (mean change per year in non-alcoholic fatty liver disease activity score) or secondary outcomes (change from baseline in hepatic fibrosis score, change from baseline in serum hyaluronate and hepatic transaminases) were reported for either study. More information on these studies can be found at:

An Efficacy and Safety Study of Rimonabant for Treatment of Nonalcoholic Steatohepatitis (NASH) in Patients Without Diabetes:
https://clinicaltrials.gov/ct2/show/NCT00576667?term=cannabis&cond=liver&rank=3

An Efficacy and Safety Study of Rimonabant for Treatment of Nonalcoholic Steatohepatitis (NASH) in Patients With Type 2 Diabetes:
https://clinicaltrials.gov/ct2/show/study/NCT00577148?term=cannabis&cond=liver&rank=2&view=record

Observational Studies

A small number of cross-sectional and longitudinal studies also examine the relationship between liver disease progression and cannabis use in selected populations, with conflicting findings. Some studies report that cannabis use is linked to prevalence of steatosis while others, including a few longitudinal cohort studies, find no association or a protective effect of cannabis against incidence or progression of liver disease. The summaries below represent the level of observational evidence currently available to describe the effect of cannabis on measures of liver disease burden.

Kelly EM, Dodge JL, French AL, Glesby MJ, Golub ET, Augenbraun M, Plankey M, Peters MG. Marijuana Use Is Not Associated With Progression to Advanced Liver Fibrosis in HIV/Hepatitis C Virus-coinfected Women. *Clinical Infectious Diseases* 2016; 63:512-518.

This prospective observational study followed 575 females co-infected with HIV and hepatitis C virus (HCV) and enrolled in the Women's Interagency HIV study to examine whether cannabis use was associated with liver disease progression. Cohort patients are seen in follow-up every six months as part of the study; this includes collection of medical data, physical examination, biological specimen collection and sociodemographic and behavioral data collection. Aspartate aminotransferase to platelet ratio index (APRI) and the fibrosis-4 score (FIB-4) were used as noninvasive measures of liver fibrosis to assess disease progression. Marijuana use (described by the authors as tetrahydrocannabinol (THC) use) was assessed at each follow-up interview and use patterns were defined as less than once a month, more than once per month but less than once per week, once a week, 2-3 times a week, 4-6 times a week, or 1 or more times per day.

Predictors of progression to advanced fibrosis (FIB-4 > 3.25) were evaluated using Cox proportional hazards regression with backward elimination to determine a final model. Of the 575 patients who were included in this analysis, mean follow-up was 11 years. The study group was mostly African American (63%) with HCV genotype 1 (88%) and had a mean HCV viral load of 6.1 $\log_{10}$ IU/mL, mean HIV RNA of 4.1 IU/mL and CD4 count of 375 cells/µL at study entry. At baseline, 2% of study patients had significant fibrosis and were eliminated from the analysis. Comparison of patients by THC usage group showed that all groups were generally similar in demographics and baseline clinical characteristics, but THC users were more likely to use cigarettes, alcohol and intravenous drugs. Among included patients, 83% were ever-THC users at the time of enrollment; 44% had used THC within 6 months of enrollment and 19% used THC weekly or more frequently.

During the study period, 51% of patients developed significant fibrosis, and incidence of fibrosis during follow-up did not vary between THC use groups. Independent predictors of significant fibrosis were FIB-4 score at entry, lower entry CD4 count and alcohol use. The authors examined the relationship between THC use and significant fibrosis by modeling THC use as average number of uses per week or as a categorical variable (<1 use per week, 1 use per week, 2-3 uses per week, 4-7 uses per week or no THC use) and failed to find a significant relationship. Parallel analysis was conducted on patients who entered the study with fibrosis (FIB-4 score of >1.5); among this subset, the same variables were found to be independent predictors of fibrosis and marijuana use was not associated with fibrosis in this group.

Limitations of this study include its observational nature, as well as the self-reported behavioral data which may have resulted in under-reporting of THC and alcohol use. Additionally, the study used non-invasive clinical markers of fibrosis to measure disease progression rather than liver biopsy, which would provide more accurate results.

Hezode C, Zafrani ES, Roudot-Thoraval F, Costentin C, Hessami A, Bouvier-Alias M, Medkour F, Pawlostky J. Daily Cannabis Use: A Novel Risk Factor of Steatosis Severity in Patients with Chronic Hepatitis C. *Gastroenterology* 2008;134:432-439.

This cross-sectional study examined predictors of steatosis in consecutively enrolled patients with untreated hepatitis C virus (HCV) infection who underwent liver biopsy. Inclusion criteria were positive anti-HCV antibody test documented for at least 6 months, available biopsy which confirmed chronic hepatitis C infection and available fasting glucose, triglyceride and cholesterol levels at the time of biopsy. Patients with concomitant hepatitis B infection or human immunodeficiency virus (HIV) infection or with a history of immunosuppression were excluded; patients who used illicit drugs other than marijuana or who had previously been treated for chronic hepatitis C were excluded. Demographic data and behavioral data were collected, as well as laboratory and histopathologic data from livery biopsy. Cannabis use was characterized by three classifications: 1) nonusers, 2) occasional users who smoked less than one daily cigarette and 3) daily users who smoked at least one daily cigarette. Stepwise logistic regression was used to determine independent predictors of steatosis. A total of 315 patients were enrolled from May 2003 to June 2006; patients were mostly male with a mean age at biopsy of 45 years and mean BMI of 24.8 kg/m^2. Most patients were genotype 1 (62.5%) or 3 (21.0%). Almost half (45.7%) of patients had evidence of steatosis: 14.9% had mild steatosis, 11.8% had moderate steatosis and 19.0% had marked steatosis. Most patients were cannabis nonusers (63.5%); 12.4% were occasional users and 24.1% were daily users, with a median of 82 cigarettes smoked per month. Cannabis users tended to be younger and male with a lower BMI; they were more likely to have a history of alcohol abuse or tobacco smoking than nonusers. Additionally, cannabis users were more likely to have been infected with HCV via intravenous drug use and therefore were more likely to have genotype 3 HCV.

Univariate analysis showed that marked steatosis was significantly associated with daily cannabis use, as well as genotype 3 HCV infection, hyperglycemia or diabetes, BMI ≥ 27 kg/m^2, alcohol abuse, tobacco use, methadone or buprenorphine treatment and high serum HCV RNA load. An activity grade of ≥A2 or a fibrosis stage of ≥F2 were also associated with marked steatosis. Subsequent logistic regression showed that daily use of cannabis was independently associated with marked steatosis (odds ratio of 2.1, 95% CI: 1.01-4.5) along with activity grade ≥A2, serum HCV RNA load, genotype 3, BMI > 27 kg/m^2 and hyperglycemia or diabetes. Further stratification by genotype (genotype 3 versus non-gentype 3) and separately by daily alcohol intake (<30 g/day versus ≥30 g/day) showed that daily cannabis use (versus nonusers and occasional users combined) was associated with marked steatosis after adjustment for genotype (P=0.03) and alcohol use (P=0.008).

The study's findings support existing evidence of the relationship between steatosis and genotype 3, as well as other known factors in steatosis (overweight or obesity, diabetes mellitus and insulin resistance). The authors noted that the study addressed potential confounding by adjusting for alcohol intake and genotype in one analysis. The authors conclude by stating that their findings support the body of evidence suggesting a CB1-mediated pathway of steatosis.

The major limitation of these findings is in the cross-sectional study design which makes any conclusions related to causality difficult to draw. Additionally, self-reported behavioral data presents risk of under-reporting of certain behaviors such as alcohol and illicit drug use.

National Medical Organization Recommendations

The National Academies of Sciences, Engineering and Medicine produced a report on the health effects of cannabis in 2017 and found limited evidence that there is no association between liver fibrosis or hepatic disease in patients with viral hepatitis C and cannabis use (National Academies of Sciences 2017).

References

American Liver Foundation. The Progression of Liver Disease. American Liver Foundation Website: http://www.liverfoundation.org/abouttheliver/info/progression/. Accessed August 14, 2017.

Avraham Y, Grigoriadis NC, Poutahidis T, Vorobiev L, Magen I, Ilan Y, Mechoulam R, Berry EM. Cannabidiol improves brain and liver function in a fulminant hepatic failure-induced model of hepatic encephalopathy in mice. *British Journal of Pharmacology* 2011;162:1650-1658.

Banini BA, Sanyal AJ. Nonalcoholic Fatty Liver Disease: Epidemiology, Pathogenesis, Natural History, Diagnosis, and Current Treatment Options. *Clinical Medicine Insights: Therapeutics* 2016;8:75-84.

Bhala N, Usherwood T, George J. Non-alcoholic fatty liver disease. *British Medical Journal*. 2009 Jul 16 339:b2474. doi: 10.1136/bmj.b2474.

Clark JM, Brancati FL, Diehl AM. The Prevalence and Etiology of Elevated Aminotransferase Levels in the United States. *The American Journal of Gastroenterology* 2003; 98(5):960-967.

Deveaux V, Cadoudal T, Ichigotani Y, Teixeira-Clerc F, Louvet A, Manin S, Nhieu JT, Belot MP, Zimmer A, Even P, Cani PD, Knauf C, Burcelin R, Bertola A, Le Marchand-Brustel Y, Gual P, Mallat A, Lotersztajn S. Cannabinoid CB2 receptor potentiates obesity-assocaited inflammation, insulin resistance and hepatic steatosis. *PLoS One* 2009 Jun 9;4(6):e5844. doi: 10.1371/journal.pone.0005844.

Gabbay E, Avraham Y, Ilan Y, Israeli E, Berry EM. Endocannabinoids and liver disease- review. *Liver International 2005*; 25:921-926.

Gary-Bob M, Elachouri G, Gallas JF, Janiak P, Marini P, Ravinet-Trillou C, Chabbert M, Cruccioli N, Pfersdorff C, Rogue C, Arnone M, Croci T, Soubrie P, Oury-Donat F, Maffrand JP, Scatton B, Lacheretz F, Le Fur G, Herbert JM, Bensaid M. Rimonaband reduces obesity-associated hepatic steatosis and features of metabolic syndrome in obese Zucker fa/fa rats. *Hepatology* 2007 Jul;46(1):122-129.

Heidelbaugh JJ, Sherbondy M. Cirrhosis and Chronic Liver Failure: Part I. Diagnosis and Evaluation. *American Family Physician* 2006 Sep 1;74(5):756-762.

Heidelbaugh JJ, Sherbondy M. Cirrhosis and Chronic Liver Failure: Part II. Complications and Treatment. *American Family Physician* 2006 Sep 1;74(5):767-766.

Hezode C, Zafrani ES, Roudot-Thoraval F, Costentin C, Hessami A, Bouvier-Alias M, Medkour F, Pawlostky J, Lotersztajn S, Mallat A. Daily Cannabis Use: A Novel Risk Factor of Steatosis Severity in Patients With Chronic Hepatitis C. *Gastroenterology* 2008;134:432-439.

Kanwal F, Kramer J, Asch SM, El-Serag H, Spiegel BM, Edmunowicz S, Sanyal AJ, Dominitz JA, McQuaid KR, Martin P, Keeffe EB, Friedman LS, Ho SB. An explicit quality indicator set for measurement of quality of care in patients with cirrhosis. *Clinical Gastroenterology and Hepatology* 2010 Aug;8(8):709-717.

Kelly EM, Dodge JL, French AL, Glesby MJ, Golub ET, Augenbraun M, Plankey M, Peters MG. Marijuana Use Is Not Associated With Progression to Advanced Liver Fibrosis in HIV/Hepatitis C Virus-coinfected Women. *Clinical Infectious Diseases* 2016; 63:512-518.

Kenneally S, Sier JH, Moore JB. Efficacy of dietary and physical activity intervention in non-alcoholic fatty liver disease: a systematic review. *BMJ Open Gastroenterology* 2017;4:e000139. Doi:10.1136/bmjgast-2017-000139.

Jain A, Reyes J, Kashyap R, Dodson SR, Demetris AJ, Ruppert K, Abu-Elmagd K, Marsh W, Madariaga J, Mazariegos G, Geller D, Bonham A, Gayowski T, Cacciarelli T, Fontes P, Starzl TE, Fung JJ. Long-Term Survival After Liver Transplantation in 4,000 Consecutive Patients at a Single Center. *Annals of Surgery* 2000 Oct; 232(4):490-500.

Jeong WI, Osei-Hyiaman D, Park O, Lui J, Batkai S, Mukhopadhyay P, Horiguchi N, Harvey-White J, Marsicano G, Lutz B, Gao B, Kunos G. Paracrine activation of hepatic CB1 receptors by stellate cell-derived endocannabinoids mediates alcoholic fatty liver. *Cell Metabolism* 2008 Mar;7(3):227-235.

Majumdar A, Kitson MT, Roberts SK. Systematic review: current concepts and challengings for the direct-acting antiviral era in hepatitis C cirrhosis. *Alimentary Pharmacology & Therapeutics* 2016 June;43(12):1276-1292.

Mayo Clinic. Liver disease. Mayo Clinic Website: http://www.mayoclinic.org/diseases-conditions/liver-problems/basics/definition/con-20025300. Accessed August 11, 2017

Mayo Clinic. Liver Failure. Mayo Clinic Website: http://www.webmd.com/digestive-disorders/digestive-diseases-liver-failure#1-4 . Accessed August 16, 2017.

Mendez-Sanchez N, Zamora-Valdes D, Pichardo-Bahena R, Barredo-Prieto B, Ponciano-Rodriguez G, Bermejo-Martinez L, Chavez-Tapia NC, Baptista-Gonzalez HA, Uribe M. Endocannabinoid receptor CB2 in nonalcoholic fatty liver disease. *Liver International*. 2007 Mar;27(2):215-219.

National Academies of Sciences, Engineering and Medicine. 2017. The health effects of cannabis and cannabinoids: Current state of evidence and recommendations for research. Washington, DC: The National Academies Press.

National Center for Health Statistics. Chronic Liver Disease and Cirrhosis. Centers for Disease Control and Prevention Website: https://www.cdc.gov/nchs/fastats/liver-disease.htm. Accessed August 15, 2017.

Osei-Hyiaman D, Liu J, Zhou L, Godlewski G, Harvey-White J, Jeong WI, Batkai S, Marsicano G, Lutz B, Buettner C, Kunos G. Hepatic CB1 receptor is required for development of diet-induced steatosis, dyslipidemia, and insulin and leptin resistance in mice. *Journal of Clinical Investigation* 2008 Sept;118(9):3160-3169.

Purohit V, Rapaka R, Shurtleff D. Role of Cannabinoids in the Development of Fatty Liver (Steatosis). *American Association of Pharmaceutical Scientists Journal*, June 2010; 12(2):233-237.

Starr SP, Raines D. Cirrhosis: Diagnosis, Management, and Prevention. *American Family Physician* 2011 Dec 15;84(12):1353-1359.