DEPARTMENT OF HEALTH

Sickle Cell Disease Issue Brief

OCTOBER 2020

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 medical organizations will be included.

Searches for published clinical trials and observational studies of cannabis therapy 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. Though the Minnesota medical cannabis program does not allow smoked or vaporized dried cannabis, studies using these forms of cannabis administration were allowed for insight they could provide. Finally, the federal government-maintained website 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

Sickle cell disease (SCD) refers to a collection of inherited, life-long red blood cell disorders that affects hemoglobin, which is a protein that carries oxygen throughout the body. Persons with SCD have abnormally shaped red blood cells (shaped like a sickle as opposed to disc-shaped) that are more inflexible (rigid) than those found in non-SCD people. This subsequently can increase the risk of blocked blood flow in SCD patients, which can lead to increased risk of stroke and infections and can be incredibly painful for these patients – both manifesting as acute pain such as pain crises (episodes of acute pain) and chronic pain. (National Heart, Lung, and Blood Institute (NHLBI); Hoppe & Heubayr, 2019). Other complications may include

pulmonary disease (e.g., asthma), cardiac disease (e.g., pulmonary hypertension), and renal disease due to sickle cell nephropathy.

Prevalence

SCD prevalence is difficult to report accurately because numbers are often estimated from newborn screening data for hemoglobinopathies and subsequently extrapolated out. Keeping these limitations in mind, it is estimated that approximately 70,000 to 100,000 people in the U.S. have SCD, with the lower bound possibly accounting for early mortality from SCD complications (Hassell 2010; Brousseau et al. 2010; Hoppe & Neumayr, 2019). Those of African ancestry are predominately affected. In the U.S., roughly 1 in 365 babies identifying as Black or African American are born with SCD (NHLBI).

Current Therapies

Of current disease-modifying therapies for SCD, hydroxyurea (HU) and glutamine are the only FDA-approved drugs for the treatment of SCD. HU treatment appears to be most effective as well as demonstrating safety, and it is approved for use in children and adults (Ware et al. 2016; Wang et al. 2011). However, long-term effects of HU use is unknown. Glutamine is a more recently-introduced therapy for SCD patients where data has shown that it may reduce the frequency of and hospitalizations from painful crises (Niihara et al. 2018).

An evidence-based report on managing sickle cell disease also recommends blood transfusion therapy for SCD patients (Yawn et al. 2014). Due to the low-oxygen carrying capacity of hemoglobin in SCD patients that can cause sickle cell anemia, blood transfusions can increase the oxygen-carrying capacity within the body of an SCD patient. This allows for better flow of blood within the body to ease SCD complications as well as anemia. However, this can require patients to receive transfusions fairly frequently (~every 3-4 weeks), which can be a burden on patients to do consistently, particularly if they suffer from more severe SCD complications.

Preclinical Research

Data from preclinical research is very limited with overall results indicating that there may be a role of the endocannabinoid system in affecting SCD-related pain. One such representative study is discussed below.

Kohli DR, Li Y, Khasabov SG, et al. Pain-related behaviors and neurochemical alterations in mice expressing sickle hemoglobin: modulation by cannabinoids. *Blood*. 2010; 116:456-465.

Mouse models of human sickle cell disease were used to investigate the effects of cannabinoids and opioids on pain-related behaviors. Two mouse models of human sickle cell disease (BERK and hBERK1) were compared to control mice (HbA-BERK) on the following four pain-related behaviors: deep tissue hyperalgesia (measured by grip force); mechanical hyperalgesia (enhanced pain responses from mechanical stimulation, as measured by paw withdrawal thresholds and paw withdrawal frequency (PWF)); heat hyperalgesia (enhanced pain responses from heat administration, as measured by paw withdrawal latency (PWL)); and cold

hyperalgesia (enhanced pain responses from cold administration, measured by PWL and PWF). The four pain-related behaviors were expected to be greater in the SCD mouse models compared to controls. In addition, the authors hypothesized that administration of morphine or a cannabinoid receptor agonist (CP 55940) would decrease pain-related behaviors in the SCD mouse models. The study proceeded in two main phases: first, all mice (BERK, hBERK1, HbA-BERK) were injected with complete Freund adjuvant (CFA) in the left hind paw to induce inflammation in that limb, and all mice were subsequently measured on the four pain-related behaviors. The second phase of the study involved the SCD mice groups only (BERK and hBERK1), with half receiving morphine and the other receiving cannabinoid receptor agonist CP 55940, after which one of the four pain-related behaviors was measured again (grip force) at various intervals after administration.

Results from the first phase showed that the SCD mouse models had lower grip force than controls and that grip force decreased with age. This indicates greater deep tissue pain in the SCD mouse models over controls that increases with age. Paw withdrawal thresholds from mechanical stimulation were lower in the SCD mouse models compared to controls, and paw withdrawal frequency (PWF) from mechanical stimulation was higher in SCD mouse models compared to controls and increased with age. Heat administration lead to a decrease in paw withdrawal latency (PWL) in SCD mice compared to controls, which suggests increased sensitivity to heat in SCD mice than controls. Lastly, cold administration resulted in increased PWF and decreased PWL in SCD mice than controls, which indicated that SCD mice have greater sensitivity to cold than controls.

Results from the second phase with the administration of either morphine or CP 55940 showed the following on grip force on SCD mice (BERK and hBERK1 mice). For SCD mice injected with 20 mg/kg of morphine, grip force increased 1 to 4 hours after administration compared to baseline (pre-injection levels) and returned back to baseline levels by 24 hours. This effect was not found with mice injected with a smaller morphine dose (10 mg/kg). SCD mice injected with 0.3 mg/kg of CP 55940 showed an increase in grip force 0.5 to 6 hours after administration compared to baseline and vehicle, with grip force returning back to baseline levels by 24 hours. Overall results show that SCD mouse models (BERK and Hberk1) exhibit greater pain-related behaviors compared to non-SCD mice, with administration of morphine (at 20 mg/kg) or CP 55940 in SCD mice decreasing deep tissue/musculoskeletal pain (as measured by increases in grip force).

Clinical Trials

There is limited data on the effects of cannabis or cannabinoids on treating SCD symptoms in humans, particularly in relation to pain management. One clinical trial so far has been published; results did not demonstrate a reduction in pain from cannabis use, as measured by the Brief Pain Inventory (BPI). One other clinical trial was identified, which is currently in the patient recruitment stage and is sponsored by a private business and network of medical cannabis certifiers from a couple of U.S. states. They are discussed below.

Abrams DI, Couey P, Dixit N, Sagi V, Hagar W, Vichinsky E, et al. Effects of inhaled cannabis for pain in adults with sickle cell disease: a randomized clinical trial. *JAMA Network Open*. 2020; 3(7): e2010874. doi:10.1001/jamanetworkopen.2020.10874

This was a double-blind, placebo-controlled randomized clinical trial of the effects of vaporized cannabis on patients with SCD with chronic pain. In this crossover study design inpatient setting, patients were randomly assigned to receive vaporized cannabis (4.4% THC, 4.9% CBD) or placebo (vaporized cannabis removed of cannabinoids) to start for 5 days, followed by at least a 30-day washout period before crossing over to the other treatment. For each of the days of treatment, patients vaporized cannabis (or placebo) at 8 a.m., 2 p.m., and 8 p.m. using a standardized puff procedure with patients given the freedom to self-titrate their doses. The following measures were collected during the study period: 1) a 0-100 visual analogue scale (VAS) for chronic pain and 2) the Brief Pain Inventory (BPI). Patients scored their pain on the VAS on arrival for the study and for each day of the study 2 hours after their 8 a.m. treatment inhalation. The BPI was administered on the first and last study day (day one and day five). Results indicated that there were no statistically significant mean differences in pain scores between the active and placebo groups on any of the five study days, as measured by the VAS for the 23 patients who completed both arms of the study; therefore reported levels of pain were no different between active and placebo groups. Results on the BPI showed that there were no statistically significant mean differences between the active and placebo groups in pain interference, walking, sleep, and enjoyment between day one and day five, but a statistically significant reduction in pain interference on mood between days one and five. Adverse side effects were mild overall with mean scores on adverse ratings being no different between active and placebo groups.

Ongoing Clinical Trials

As of October 2020, a search on ClinicalTrials.gov on the effects of cannabis or cannabinoids on SCD yielded one study that is currently listed as recruiting. Another study had been identified through the search but it is not discussed here; results of this study have been published (see Abrams et al. 2020 above).

Outcomes Mandate National Integration With Cannabis as Medicine for Prevention and Treatment of COVID-19 (OMNI-Can). https://clinicaltrials.gov/ct2/show/NCT03944447

This is a Phase 2, multi-state, multi-clinical study sponsored by OMNI Medical Services (a business and network of medical cannabis certifiers serving residents of FL and OH; omnidoctors.com) investigating the effects of medical cannabis on an array of medical conditions with chronic pain as a symptom, including SCD. In addition, it will investigate COVID-19 infection rates among medical cannabis users and the general population as well as the severity of persistent symptoms from COVID-19 between medical cannabis users and the general population. This study is projected to be administered over a five-year period, with data being collected through an online questionnaire from patients certified at OMNI Medical Services clinics. The Brief Pain Inventory (BPI) will be administered to patients with various medical conditions at three-month intervals, with change in the BPI being compared to baseline. Infection rate data will be collected from medical cannabis patients and will be compared to Johns Hopkins University Coronavirus Research Center data infection rates. In addition, medical cannabis patients with an active infection or testing positive for COVID-19 antibodies will be administered questions that address persistent symptoms for flu-like viruses.

This will be compared to national and international survey data on persistent symptoms from COVID-19. This study will primarily target adult patients.

Observational Studies

Observational studies primarily focused on assessing rationale in using cannabis in SCD patients, particularly for pain management. While data suggests that some SCD patients use cannabis to manage SCD symptoms (primarily pain), the actual evidence of any clinical benefits of cannabis on relieving SCD symptoms or reducing SCD-related complications is limited and inconclusive.

Roberts JD, Spodick J, Cole J, Bozzo J, Curtis S, Forray A. Marijuana use in adults living with sickle cell disease. *Cannabis Cannabinoid Res*. 2018;3.1:162-165. doi:10.1089/can.2018.0001.

This was an observational study on cannabis use conducted from a medical center in Connecticut that provides primary, secondary, and tertiary care for SCD patients. Approximately 130 SCD adult patients were identified from the center (those visiting the sickle cell clinic at least twice within an 18-month period), and 58 of those patients were invited to participate in an anonymous survey on cannabis use (those who had gone through urine drug testing through the clinic which are patients who are prescribed significant amounts of opioids). All 58 patients (45% of patients) invited to the study completed the survey. Forty-two percent of patients indicated in the study that they had used cannabis in the last two years, with 79% of them indicating that their use reduced the use of pain medications. The majority of the patients selected medical reasons for using cannabis that were listed on the survey, which included for the following reasons: pain (92%), anxiety (71%), mood (67%), sleep (71%), and appetite (63%). A third (33%) of the patients also reported cannabis use to get high.

Howard J, Anie KA, Holdcroft A, Korn S, Davies SC. Cannabis use in sickle cell disease: a questionnaire study. *Br. J. Haematol*. 2005;131:123-128. doi:10.1111/j.1365-2141.2005.05723.x

This was a survey study conducted in London on SCD patients. Patients were recruited from a single clinic where they were asked about their history of cannabis use, their pattern of use, its reason for use, any side effects from use, whether they used it medicinally or recreationally, and whether they wouldd be interested in participating in future clinical trials on the effects of cannabis on SCD patients. Roughly 34% of adult patients who were eligible to participate (n=86) completed the survey (n=86), with 36% of them (n=31) having ever used cannabis and 64% (n=51) being non-users. Seventy percent of the survey patients had HbSS, 20% had HbSC, and 10% had HbSβthalassaemia. Between users and non-users there were no differences between the number of painful episodes they experienced within the last year. In addition, there were no differences between cannabis users and non-users on SCD severity. When users were asked about when they last used cannabis, 39% (n=12) had used cannabis within the past week, 19% (n=6) had used it within the past month, 6% (n=2) had used within the past 6 months, and 26% (n=8) had not used cannabis for over a year. The median age of cannabis first use was age 16. For cannabis users, nearly all users (n=28) had smoked cannabis while the remaining 10% indicated that they used cannabis via the oral route. For detailed questions about their

cannabis usage, 13% had reported daily usage, 32% used weekly, 13% used monthly, and the remaining 42% had used occasionally. Roughly half of all users (52%; n=16) reported using cannabis for medical reasons, which, in this study, was tallying responses to the following: using cannabis to decrease/prevent acute or chronic pain or reduce the amount of painkillers that were needed for pain. Of the group using cannabis for medical reasons, none reported using to get "high". Thirty-nine percent (n=12) of users indicated using cannabis to relax, increase sleep quality, reduce depression or anxiety, or to improve mood. Of the 13% (n=5) who indicated using for recreational reasons, three of them also indicated using to reduce/prevent acute or chronic pain, with the remaining two indicating they used it to relax and improve sleep quality. Two (6%) provided no reason for using cannabis, and one (3%) had reported using cannabis out of curiosity (these last three were among participants that had not used within the previous year). Sleepiness and mood changes were the most frequently reported side effects.

Knight-Madden J, Lewis N, Hambleton IR. The prevalence of marijuana smoking in young adults with sickle cell disease: a longitudinal study. *West Indian Med J.* 2006;55(4):224-227.

This was a survey study conducted in Jamaica to understand prevalence of marijuana smoking in the Jamaica Sickle Cell Cohort Study (JSCCS) in 2000 and 2004. Patients in the JSCCS were born in a specific hospital between 1973 and 1981 and therefore followed since birth. Patients with homozygous SS disease (SS) and sickle cell hemoglobin-C disease (SC) were asked whether they had ever smoked marijuana with the 2000 survey asking whether they currently smoked, and the 2004 survey asking whether they had smoked in the last 12 months. Smokers were subsequently asked about if they used it for SCD and if so, what types of SCD complications they used it for. Of 185 SS genotype patients and 126 SC genotype patients, roughly 90% from both groups responded to the 2000 survey, with response rates dropping by the 2004 study (~70%-80% range), with a drop in response rate being most notable in the 2004 survey among SC genotype men. Data showed that marijuana smoking was higher among men in the study than in women, with a higher rate of smoking in SC participants. The prevalence of marijuana smoking also increased from 2000 to 2004 among both men and women. Roughly 6% of participants (n = 11) reporting on the 2004 study indicated that they smoked marijuana for SCD complications. Seven indicated using it for pain crises and one person each indicated using SCD for depression, asthma, and weight gain. Analyses also showed that the odds for smoking did not go up with increasing pain, meaning that smokers and non-smokers were no different in their pain profiles. In addition, there was little difference in the median number of pain events between smokers and non-smokers. This suggests that pain severity and the frequency of pain events does not increase the likelihood for SCD patients to smoke marijuana.

Ballas SK. The use of cannabis by patients with sickle cell disease increased the frequency of hospitalization due to vaso-occlusive crises. *Cannabis Cannabinoid Res*. 2017;2.1:197-201. doi: 10.1089/can.2017.0011

This was a retrospective study where researchers investigated whether the frequency of vaso-occlusive events (VOCs) differed between cannabis-positive and cannabis-negative SCD patients. VOCs are painful for SCD patients and are usually treated with analgesics, and since there has been increasing interest in using cannabis for pain relief, the researchers of this study wanted to investigate whether use of cannabis would affect the frequency of VOCs. More

specifically, whether use of cannabis would be associated with decreased VOCs. Patients who had been tracked through a sickle cell center supported by the Department of Health of the Commonwealth of Pennsylvania for the Philadelphia Region between 1994 and 2009 were identified. These patients had random urine drug testing data to look for the presence or absence of 11-nor-9-carboxy- Δ^9-THC, the primary metabolite of Δ^9-tetrahydrocannabinol (THC), along with detecting the presence or absence of other drugs. A total of 72 patients were included in the study who had a combined total of 270 urine drug screen tests. Males in the sample were found to be positive for cannabis significantly more often than females. In addition, males who tested positive for cannabis were found to be significantly younger than males testing negative for cannabis (no difference in age was found between female cannabis users and non-users). Data also showed that other drugs besides cannabis were more likely to be detected in users than non-users including benzodiazepines, cocaine, and phencyclidine. However, opioids amounts were similarly detected in users and non-users, meaning that cannabis usage did not change opioid usage in this sample. Lastly, while cannabis users have fewer clinic visits than non-users, cannabis users had significantly greater hospital admissions for VOCs. Emergency department admissions were no different between users and non-users. In conclusion, cannabis users were more frequently admitted to the hospital for VOCs than non-users and were more likely to have other drugs in their system. While speculative, the authors propose the possibility that the severity of SCD may be worse in cannabis users to potentially explain the greater hospital admissions for VOCs than non-users.

National Medical Organization Recommendations

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the management of SCD were found.

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