DEPARTMENT OF HEALTH

Anxiety 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

Anxiety disorder refers to a collection of specific psychiatric disorders as classified according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5; American Psychiatric Association 2013). These disorders are characterized by the general feature of excessive fear (i.e., an emotional response to a perceived or real threat) and/or anxiety (i.e., an emotional response to a future threat), which can have negative emotional and behavioral consequences for the sufferer. The DSM-5 currently includes the following under anxiety disorders:

- Separation anxiety disorder
- Selective mutism

- Specific phobia
- Social anxiety disorder (Social phobia)
- Panic disorder
- Panic attack (Specifier)
- Agoraphobia
- Generalized anxiety disorder
- Substance/medication-induced anxiety disorder
- Anxiety disorder due to another medical condition
- Other specified anxiety disorder
- Unspecified anxiety disorder

Prevalence

Epidemiologic survey data estimates the 12-month prevalence of all anxiety disorders to be between 8-21% and lifetime prevalence of all anxiety disorders to be between 14-34% (Bandelow 2015; Kessler et al. 2012). The following 12-month and lifetime prevalence were reported by the same authors for some anxiety disorders:

- Panic disorder: 12-month prevalence 0.7-3.1%; lifetime prevalence 1.6-5.2%
- Generalized anxiety disorder: 12-month prevalence 0.2-4.3%; lifetime prevalence 2.8-6.2%
- Agoraphobia: 12-month prevalence 0.1-10.5%; lifetime prevalence 0.8-2.6%
- Social anxiety disorder: 12-month prevalence 0.6-7.9%; lifetime prevalence 2.8-13.0%
- Specific phobia: 12-month prevalence 0.8-11.1%; lifetime prevalence 8.3-13.8% (Bandelow 2015)

Current Therapies

Current therapies in the treatment of anxiety that are discussed in the 2017 Anxiety Issue Brief have not significantly changed, and readers may refer back to the summary on therapies, which is included below and can be accessed at Anxiety Disorders: Issue Brief on Anxiety Disorders (PDF) (www.health.state.mn.us/people/cannabis/docs/rulemaking/anxietybrief.pdf), from the Minnesota Department of Health Office of Medical Cannabis.

The World Federation of Biological Psychiatry summarized treatment guidelines for patients with anxiety disorders in a 2012 publication (Bandelow 2012); the following highlights different anxiolytic therapies described in their review. Patients with anxiety disorders can be treated with either medication, psychotherapy, or both. The choice of treatment regimen depends on many factors, including patient preference, severity, other psychiatric and medical comorbidities, history of previous treatment or issues like substance abuse or suicide risk, as well as therapy cost to the patient. First-line pharmacotherapy is selective serotonin reuptake

inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and pregabalin, a calcium-channel modulator. Treatment with SSRIs is usually well-tolerated but side effects can include overstimulation, fatigue, or headache, among others. Treatment with SNRIs can include side effects of nausea, restlessness, insomnia or headache as well as sexual dysfunction, discontinuation syndromes or increased blood pressure in some cases. Both SSRIs and SNRIs may require 2-4 weeks of therapy before patients begin experiencing benefit, which can present challenges for compliance. Pregabalin produces more immediate effects but can cause side effects of dizziness and somnolence.

Tricyclic antidepressants (TCAs) are also effective in treating anxiety disorders but they are associated with more severe side effects than first-line medications (sedation, slow reaction time, dry mouth, constipation, and weight gain), which hinder patient compliance. Additionally, TCAs interact with other medications and overdose can result in death. Benzodiazepines are also effective in treating anxiety disorders, and are quick-acting agents. Their side effect profile is similar to TCAs and thus patients may be impaired and therefore unable to drive or perform other tasks. Benzodiazepines pose an addiction risk and therefore are contraindicated for patients with substance abuse history. Finally, the antihistamine hydroxyzine can be effective but has sedative effects that make it unfavorable unless other treatment has been unsuccessful.

Non-medication therapy is often conducted alongside medical therapy and can be very effective. In the treatment of obsessive-compulsive disorders, specific phobias or other phobias (agoraphobia, social anxiety disorder), psychotherapies such as exposure therapy and response prevention can be very effective treatment modalities, but patients often refuse or abandon such therapies.

According to data from the European Study of the Epidemiology of Mental Disorders (ESEMeD), subjects from a large non-institutionalized European cohort who had an anxiety disorder had a low level of health care utilization: only 20.6% reported seeking treatment. Of those who sought treatment, 30.8% received drug treatment only, 19.6% received psychotherapy only, and 26.5% received both drug therapy and psychotherapy (Alonso 2007).

Overall, even with effective first-line treatments for anxiety such as antidepressants and cognitive-behavioral therapy, 40-60% of patients may still struggle to manage their anxiety adequately along with problems of treatment compliance or through difficulties in accessing treatment (Katzman et al. 2014).

Preclinical Research

There has been growing interest to investigate the role of the endocannabinoid system in state anxiety and anxiety disorders. This includes delivering phytocannabinoids (plant-derived cannabinoids such as delta-9-THC (THC) and cannabidiol (CBD)) as well as synthetic cannabinoids in animal models of anxiety. For example, there is some evidence to suggest anxiolytic properties of CBD in animal models of anxiety with a bell-shaped dose-response curve; moderate dosages of CBD show anxiolytic effects while high and low dosages of CBD are ineffective (Blessing et al. 2015). There has also been interest in manipulating the

pharmacokinetic processes of cannabinoids (e.g., metabolism of cannabinoids) with novel compounds to also improve anxiety symptomology in animal models, as well as pharmacodynamic modulation of the CB1 and CB2-receptors. For example, there is evidence to suggest that there are specific interactions between CB1-receptors, 5-HT1A serotonin receptors, and transient receptor potential vannilloid type 1 receptors that connect the endocannabinoid system more closely with emotion and anxiety regulatory processes (Papagianni & Stevenson, 2019).

Clinical Trials

Published clinical data investigating the effects of cannabis/cannabinoids on anxiety continues to be limited and generally confined to examining the effects THC or CBD on induced anxiety states. One additional study since the 2017 Anxiety Issue Brief has been published and is described below (Linares et al. 2019).

Three additional clinical trials were identified via ClinicalTrials.gov, all of which will be examining the effects of CBD on anxiety. To the best that information is provided on these studies online, two of the three trials appear to be targeting patients with a diagnosed anxiety disorder. All three studies appear to be active but "not yet recruiting."

Linares IM, Zuardi AW, Pereira LC et al. Cannabidiol presents an inverted U-shaped dose-response curve in a simulated public speaking test. *Braz J Psychiatry*. 2019 Jan-Feb;41(1):9-14.

This experimental study investigated the effects of CBD at varying doses and its psychological and physiological effects on a simulated public speaking test (SPST). Previous research utilizing the SPST on patients with generalized social anxiety disorder showed that pretreating patients with 600 mg of CBD reduced anxiety, distress, and cognitive impairment during the SPST (Bergamaschi et al. 2011). This work was conducted as an extension of this former study to further refine the potential therapeutic window of CBD in treating anxiety. A total of 57 participants were randomized in a double-blind procedure to receive either 150 mg (n=15), 300 mg (n=15), or 600 mg (n=12) prior to participation in the SPST, and their results were compared to a control group (n=15). Dependent measures were the Visual Analog Mood Scale (VAMS) and heart rate (HR) and blood pressure (BP) recordings. For VAMS, participants mark a point on a 100-mm straight line where their current subject state lies on a given affective dimension, with opposite words marking the two end points on the line (e.g., calm-excited).

VAMS, HR, and BP were measured at the time CBD (or control) was administered. VAMS, HR, and BP were measured again 90-minutes after drug administration (Pre-stress phase). Video instructions were subsequently provided to participants where they were told they would be given two minutes to prepare a four-minute speech on public transportation in their city. They were told that their speech would be recorded on video where it would later be analyzed by a group of trained psychologists. After the two-minute speech preparation phase and prior to the beginning of making the four-minute speech, VAMS, HR, and BP were measured (anticipatory anxiety stage). Two minutes into the four-minute speech, VAMS, HR, and BP were measured again (performance anxiety stage) after which point the participant could finish the remainder

of the speech. VAMS, HR, and BP were measured immediately after the conclusion of the speech and were measured once more 30-minutes after (post-stress stage).

Of the three CBD dosage level groups, the 300 mg CBD group was the only one showing lowered anxiety compared to placebo during the performance anxiety stage. This was taken as evidence that there may be a bell-shaped dose-response curve similar to some animal studies in the effects of CBD on at least performance anxiety.

Ongoing Clinical Trials

Cannabinoids for the Treatment of Anxiety Disorders: An 8-Week Pilot Study.
https://clinicaltrials.gov/ct2/show/NCT04569760

Cannabidiol for Anxiety.
https://clinicaltrials.gov/ct2/show/NCT04267679

A Clinical Trial of a Hemp-Derived Cannabidiol Product for Anxiety.
https://clinicaltrials.gov/ct2/show/NCT04286594

Observational Studies

Observational studies that have come out in the last few years generally fit within the context of existing literature that indicates some reported benefit in using cannabis/cannabinoids for treating anxiety. However, due to lack of experimental control in these studies, it is difficult to establish any direct effects of cannabis/cannabinoids on anxiety symptoms. Below are a few representative observational studies that have been published since the 2017 Anxiety Issue Brief.

Turna J, Simpson W, Patterson B, Lucas P. Cannabis use behaviors and prevalence of anxiety and depressive symptoms in a cohort of Canadian medicinal cannabis users. *J Psychiatr Res*. 2019;111:134-139.

In this survey study, patients (n=888) who had identified anxiety as a primary reason for using cannabis for medicinal purposes (CMP) were asked to complete validated screening tools that might signify the presence of anxiety-related disorders including generalized anxiety (measured by Generalized Anxiety Disorder-7 scale; GAD-7), depressive symptomology (via the Patient Health Questionnaire; PHQ-9), social anxiety disorder (SAD; via the MINI Social Phobia Inventory; Mini-SPIN), along with a few questions taken from the Panic Agoraphobia Scale (PAS) to alert for potential expression of panic disorder symptoms. (Note: screening tools do not provide conclusive evidence of having any of these disorders and does not necessarily lead to clinical diagnosis in the patient). Based on literature, authors suggested that the following proportion of patients may express clinical levels of the following: 46% for GAD, 42% for SAD, 26% for major depressive disorder, and 26% for panic disorder/agoraphobia. Roughly 64% of the patients in this sample met screening criteria for more than one disorder. Results also showed that those reporting to use 3 g/day or more of CMP had higher scores on generalized anxiety and depression screening tools; those who used at least 3 g/day of CMP scored higher on GAD-7 and PHQ-9 than either the moderate (1-2 g/day) or low users (<1 g/day). The majority

of participants (92%) seemed to agree that "anxiety, worry, fears" were improved with CMP use, along with high agreement that CMP use improved the following symptoms as well: "irritability" (76%), "difficulty falling to sleep" (72%), "anxiety attacks" (59%) and "low mood" (57%). Roughly half of participants (52%) reported Cannabis indica to provide the best improvement in their anxiety, while 32% indicated that Cannabis sativa had the most anxiogenic (anxiety-inducing) effects. While participants in this study indicate that CMP use generally improves their anxiety symptoms, the authors interestingly note that many of these patients' anxiety symptoms were screened to be at moderate levels, with authors noting that greater systematic study of the effects of CMP use on mental illness is needed.

Yang K, Moore A, Nguyen K, Nafsu R, Kaufmann C. Cannabis Use for anxiety among older patients. *Am J Geriatr Psychiatry*. 2020;28:4S.

Due to evidence that older adults are using cannabis in increasing numbers, this survey study was conducted to understand whether this group uses cannabis medically to relieve anxiety-related symptoms. Patients being followed up at a geriatrics clinic in California were administered a survey that asked them to report on characteristics of their cannabis use and the perceived effectiveness of using cannabis for medical purposes. Of the 568 patients included in the study, 14% (n=82) reported being recent users (defined as use within the past 3 years). Among this group (n-82), twenty (24%) participants indicated using cannabis to treat anxiety, with 70% of them (n=14) reporting that cannabis was extremely or somewhat helpful in alleviating anxiety symptoms. Results also showed that the older adults using cannabis to treat anxiety were more likely to use products containing THC compared to older adults using cannabis for other symptoms. In addition, compared to other older adults using cannabis for treating other symptoms, older adults using cannabis to treat anxiety were more likely to use edibles and vape flower.

Purcell C, Davis A, Moolman N, Taylor SM. Reduction of benzodiazepine use in patients prescribed medical cannabis. *Cannabis Cannabinoid Res*. 2019;4(3):214-218.

In this retrospective study, patients who had reported benzodiazepine use at the start of their medical cannabis treatment were identified, and their responses to a survey at roughly two, four, and six months into their medical cannabis treatment were analyzed. This study was conducted by a medical cannabis certifying clinic in Canada where participating health care practitioners prescribe medical cannabis to patients. Since health care practitioners typically wrote prescriptions in two-month intervals, patients' benzodiazepine use was surveyed over three follow-up visits with their certifying health care practitioner, roughly corresponding to data collection at two, four, and six months into their medical cannabis treatment. Data showed that of the 146 patients included in the study (those who completed three follow-up visits since starting medical cannabis), 30% (n=44) were able to discontinue their benzodiazepine use within two months of starting medical cannabis. Within four and six months of starting medical cannabis treatment, a total of 44% (n=65) and 45% (n=66) of patients had discontinuing benzodiazepine treatment. A notable limitation of this study is that the patients do not report on the medical condition(s) for which benzodiazepines were prescribed except that there is a general statement that 32% were prescribed to treat "psychiatric conditions." While it is possible that a proportion of those patients were prescribed

benzodiazepines for anxiety symptoms, the lack of information on what those psychiatric conditions are means that it is unclear whether medical cannabis treatment may reduce reliance on benzodiazepines in treating anxiety.

National Medical Organization Recommendations

The National Academies of Sciences, Engineering, and Medicine produced a report on the health effects of cannabis in 2017 and the committee found limited evidence that cannabidiol improves anxiety symptoms, as measured by a public speaking test, in patients with social anxiety disorder (Conclusion 4-17). The committee also found limited evidence of a statistical association between cannabis use and the development of any anxiety disorder other than social anxiety disorder and increased symptoms of anxiety (with near daily cannabis use) (Conclusion 12-9). Finally, the committee found moderate evidence that anxiety is not a risk factor for the development of problem cannabis use (Conclusion 13-2b) (National Academies of Sciences 2017).

Minnesota Medical Cannabis Program Data

The patient self-evaluation (PSE) is administered through Minnesota's medical cannabis online registry to all enrolled patients and assesses symptoms that are experienced in patients in the program as well as any side effects they attribute to the use of medical cannabis products. Every time a patient would like to make a medical cannabis purchase from one of the two manufacturers of medical cannabis products in Minnesota, the patient must complete the PSE. This allows for data capture that follows the patient's participation in the program and provides some indication of their baseline functioning at the outset of their program participation.

On the PSE, patients are asked to rate the severity of their symptoms in the past 24 hours using a 0-10 numerical rating scale (0=symptom not present; 10=symptom is as bad as one can imagine). Most notably, one of the symptoms patients are asked to report on in the PSE is anxiety. Since the publication of the 2017 Anxiety Issue Brief from the Minnesota Department of Health's Office of Medical Cannabis, which reported on symptom changes in participants who enrolled in the first year of program operation (n=1512), an update to that report has been published to include a greater number of patient responses (n=6924); see Benefits Reported on the Patient Self-Evaluation: Patients with First Enrollment July 2015-June 2017 (PDF) (www.health.state.mn.us/people/cannabis/docs/about/cohort/c2015_2017_benefitspse.pdf). Of those who enrolled in the program for the first time between July 2015-June 2017 (n=6924), 76% (n=5270) scored their anxiety at moderate to severe levels at baseline (score of 4 or higher). Of those patients, 56% of them (n=2972) reported at least a 30% reduction in anxiety within 4 months of their first medical cannabis purchase, with over half of those patients who achieved that threshold (58%; n=1724) maintaining that level of improvement in the next 4-month follow-up window. Limitations in reporting include the self-report aspect of the study along with the potential for response bias in the sample of patients who are represented in the data. For example, patients may drop out early in their program participation for a variety of reasons, one of which might be from not finding medical cannabis to be sufficiently effective for

the management of their symptoms; in this case, those voices may not be represented in the data. (Minnesota Department of Health Office of Medical Cannabis).

References

Alonso J, Lepine J, ESEMeD/MHEDEA 2000 Scientific Committee. Overview of Key Data from the European Study of the Epidemiology of Mental Disorders (ESEMeD). *J Clin Psychiatry.* 2007;68(suppl2):3-9.

Bergamaschi MM, Queiroz RH, Chagas MH, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. *Neuropsychopharmacology*. 2011;36:1219-26.

Blessing EM, Steenkamp MM, Manzanares J, et al. Cannabidiol as a potential treatment for anxiety disorders. *Neurotherapeutics*. 2015;12:825-836.

American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (5th ed.)*. Arlington, VA: American Psychiatric Publishing, 2013.

Katzman MA, Bleau P, Blier P, Chokka P, Kjernisted K, Van Ameringen M. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry*. 2014;14:S1.

Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *Int J Methods Psychiatr Res*. 2012;21:169-184.

Minnesota Department of Health Office of Medical Cannabis. *Issue Brief: Anxiety Disorder.* August 2017. Accessed October 2020. https://www.health.state.mn.us/people/cannabis/docs/rulemaking/anxietybrief.pdf

Minnesota Department of Health Office of Medical Cannabis. *Benefits Reported on the Patient Self-Evaluation: Patients with First Enrollment July 2015-June 2017*. October 11, 2019. Accessed October 2020. https://www.health.state.mn.us/people/cannabis/docs/about/cohort/c2015_2017_benefitspse.pdf.

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.

Papagianni EP, Stevenson CS. Cannabinoid regulation of fear and anxiety: an update. *Curr Psychiatry Rep.* 2019;21:38.

Purcell C, Davis A, Moolman N, Taylor SM. Reduction of benzodiazepine use in patients prescribed medical cannabis. *Cannabis Cannabinoid Res*. 2019;4(3):214-218.

Turna J, Simpson W, Patterson B, Lucas P. Cannabis use behaviors and prevalence of anxiety and depressive symptoms in a cohort of Canadian medicinal cannabis users. *J Psychiatr Res*. 2019;111:134-139.

Yang K, Moore A, Nguye K, Nafsu R, Kaufmann C. Cannabis Use for anxiety among older patients. *Am J Geriatr Psychiatry*. 2020;28:4S.

Minnesota Department of Health
Office of Medical Cannabis
85 E 7th Place, Suite 220
PO Box 64882
St. Paul, MN 55164-0882
651-201-5598
health.cannabis@state.mn.us

10/2020

To obtain this information in a different format, call: 651-201-5598.

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.

References

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

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

Brousseau DC, Panepinto JA, Nimmer M, Hoffmann RG. The number of people with sickle-cell disease in the United States: national and state estimates. *Am J Hematol*. 2010;85(1):77-78. doi: 10.1002/ajh.21570

Hassell KL. Population estimates of sickle cell disease in the U.S. *Am J Prev Med*. 2010;38(4S):S512-S521.

Hoppe C, Neumayr L. Sickle cell disease: monitoring, current treatment, and therapeutics. *Hematol Oncol Clin N Am.* 2019;33:355-371. doi:10.1016/j.hoc.2019.01.014

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

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.

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.

National Heart, Lung, and Blood Institute (NHLBI at National Institute of Health). Sickle Cell Disease. Accessed September 2020. https://www.nhlbi.nih.gov/health-topics/sickle-cell-disease

Niihara Y, Miller ST, Kanter J, et al. A phase 3 trial of l-glutamine in sickle cell disease. *N Engl J Med.* 2018;379(3):226–35.

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.

Wang WC, Ware RE, Miller ST, et al. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABYHUG). *Lancet*. 2011;377(9778):1663–72.

Ware RE, Davis BR, Schultz WH, et al. Hydroxycarbamide versus chronic transfusion for maintenance of transcranial doppler flow velocities in children with sickle cell anaemia-TCD With Transfusions Changing to Hydroxyurea (TWiTCH): a multicentre, open-label, phase 3, non-inferiority trial. *Lancet*. 2016;387(10019):661–70.

Yawn BP, Buchanan GR, Afenyi-Annan AN et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. *JAMA*. 2014;312(10):1033-1048. doi:10.1001/jama.2014.10517.

Minnesota Department of Health
Office of Medical Cannabis
85 E 7th Place, Suite 220
PO Box 64882
St. Paul, MN 55164-0882
651-201-5598
health.cannabis@state.mn.us
www.health.state.mn.us

10/2020

To obtain this information in a different format, call: 651-201-5598.

DEPARTMENT OF HEALTH

Chronic Vocal or Motor Tic Disorder 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, clinicatrials.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

Tics are sudden and repetitive twitches, movements, or sounds, which a person cannot stop themselves from doing. Persistent (chronic) vocal or motor tic disorder is defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) as the presence of one or more motor tics (examples include blinking or shrugging shoulders) or vocal tics (examples include humming or clearing the throat), but not both motor and vocal tics (American Psychiatric Association 2013). Tics vary in complexity and are often preceded by

premonitory sensations, often localized to the site of the tic; patients report that performing the tic relieves these sensations (Kurlan 2011 NEJM). To meet DSM-5 diagnostic criteria for chronic vocal or motor tic disorder, a person must have tics that occur many times a day, starting before the age of 18 and lasting over a year. These symptoms must not be caused by medication or another medical condition (Centers for Disease Control and Prevention). Chronic vocal or motor tic disorder is distinct from Tourette Syndrome in that patients experience *only* vocal or motor tics, whereas Tourette Syndrome patients experience *both* vocal and motor tics. Much of the research included in this issue brief refers to studies conducted on the impact of medical cannabis on tics in patients with Tourette Syndrome.

Tics are often preceded by premonitory sensations, often localized to the site of the tic; patients report that performing the tic relieves these sensations. Children with tic disorders often suppress tics in certain social settings, such as school, but this suppression can lead to mental fatigue. Frequency and severity of tics fluctuate over time; intensity of tics can be exacerbated by stress (Kurlan 2011).

Tic onset usually occurs before the age of 10; simple motor tics have a median onset at 5 to 6 years of age; vocal tics typically appear later, usually between ages 8-15. Tics usually worsen during early adolescence, and most patients reach their worst-ever tic severity between ages 7 and 15, followed by a lessening in severity over time. Studies have generally found that some symptoms persist into adulthood, but are associated with less psychological distress, although the physiologic reasons for these changes are not fully understood (Leckman 2003). Of note, a minority of adult patients experience severe tics (Artukoglu 2019). Other neuropsychiatric conditions, most notably Attention Deficit Hyperactivity Disorder (ADHD) and obsessive-compulsive disorder (OCD), are often present in patients with tic disorders (Bloch Sept. 2009, Bloch Dec. 2009).

Prevalence

Chronic vocal or motor tic disorder occurs in both children and adults but is more commonly found among children; estimated prevalence has been reported as high as 6% among school-aged children, with males experience greater risk (Snider 2002).

Current Therapies

The pathophysiology of tic disorders is not fully understood; however, behavioral and pharmacotherapy interventions have been found to be effective in some patients. Generally, evidence supports the efficacy of medication in managing tics, with a typical reduction of 25-50% of tics (Quezada 2018), but available pharmaceuticals hold risk of adverse events (Pringsheim 2012). The first-line treatment for chronic vocal or motor tic disorders in children over the age of 9 is behavioral therapy, and pharmacotherapy with alpha-2 agonists (most commonly clonidine and guanfacine). Behavioral therapy consists of Comprehensive Behavioral Intervention for Tics (CBIT), which has three elements: training the patient to increase awareness of tics; to perform a competing behavior when they feel the urge to tic; and making changes to daily activities to reduce tics (Woods 2016). Behavioral interventions have shown strong evidence of efficacy in reducing tics (Pringsheim 2012). In adults, botulinum toxin

injection is also considered first-line therapy. Second-line treatments include antipsychotics (risperidone and aripiprazole), which have the greatest evidence of efficacy in clinical trials, reporting up to 70% tic reduction (Quezada 2018), but are associated with more severe adverse effects, such as sedation, metabolic side effects, and drug-induced movement disorders (Artukoglu 2019). In milder cases of tic disorders, clinical observation and psychoeducation serves as adequate clinical management (Cothros 2020).

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. Preclinical data investigating the impact of cannabis on tic-based behaviors are extremely limited. Artukoglu et al. included a brief discussion of preclinical findings in their 2019 review paper, which is summarized below. Also included in this section is a paper from Ceci et al. who conducted a mouse study with indirect cannabinoid agonist URB597 to treat tic-like behavior.

Artukoglu BB, Bloch MH. The Potential of Cannabinoid-Based Treatments in Tourette Syndrome. *CNS Drugs.* 2019; 33:417-430.

In a 2019 review of current evidence for the use of cannabinoids in treatment of tics, Artukoglu et al. summarize preclinical findings by stating, “CB1 receptors are located in CNS regions that are thought to be impaired in [Tourette Syndrome]. The endocannabinoid system may regulate the direct and indirect pathways and have an inhibitory effect on the striatal dopaminergic system, which is likely overactive in [Tourette Syndrome].” They conclude that these findings hold therapeutic promise but that additional genetic, neurochemical, and neuroimaging studies are needed to understand the role of cannabinoids in modulating tics (Artukoglu 2019).

Ceci C, Onori P, Macri S, Laviola G. Interaction Between the Endocannabinoid and Serotonergic System in the Exhibition of Head Twitch Response in Four Mouse Strains. Neuroto Res 2015; 27:275-283.

This study examines the use of URB597, an indirect cannabinoid agonist that enhances endogenous anandamide levels, in reducing pharmacologically-induced tics in a mouse model. Four strains were selected to represent a broad spectrum of genetic variability; 16 adult male mice were injected with either vehicle solution or URB597 and recorded for 10 minutes. The mice were then injected with DOI, a pharmaceutical agent producing tic-like behavior, and recorded for another 10 minutes. The recordings were scored by a trained observer for head twitch response, skin jerk, bar holding, digging, immobility, grooming and movement, and exploratory behaviors. The authors found there were differences across strains in baseline movements. Once the cannabinoid agonist URB597 was administered, one of the four strains reduced sniffing behavior and one increased its sniffing behavior; no other changes were observed. Following DOI administration, all four strains of mice began to show head twitch and skin jerk behavior and URB597 administration significantly reduced frequency and duration of head twitch behavior in all four mouse strains. No effect was observed in regard to skin jerk behavior or other observed behaviors. The authors suggest that their findings support the idea that the endocannabinoid system may be a therapeutic target for tic behaviors in humans.

Clinical Trials

Clinical trial data on patients with chronic vocal or motor tic disorders including Tourette Syndrome are also limited; a few recent review papers discuss two main randomized trials published by Muller-Vahl in 2002 and 2003 and provide useful interpretation; these reviews are summarized along with the two relevant trials. One ongoing but unpublished study listed registered on ClinicalTrials.gov is briefly described.

Artukoglu BB, Bloch MH. The Potential of Cannabinoid-Based Treatments in Tourette Syndrome. *CNS Drugs*. 2019; 33:417-430.

The authors reviewed evidence for cannabinoid-based treatment of Tourette Syndrome and related tics. They found only two randomized placebo-controlled trials, one using THC as monotherapy and the other using THC as adjuvant therapy. The first trial was a double-blind crossover, single-dose trial in 12 adults with Tourette Syndrome (Müller-Vahl 2002); five of these patients were already taking psychotropic medication and maintained their previous dosages during the study. The patients were given either 5 mg, 7.5 mg or 10 mg THC according to body weight, sex, and prior marijuana use. Using the Tourette's Syndrome Symptom List (TSSL), this study found a significant reduction in tics and obsessive-compulsive disorder, which is often correlated with tic behaviors with THC treatment compared to placebo. Subjective global tic severity scores, as rated by an examiner, were lower with THC treatment but did not reach statistical significance. Five patients experienced mild side effects.

The second trial was a six-week double-blind parallel group trial with a maximum THC dosage of 10 mg in 24 adults with Tourette Syndrome (Müller-Vahl 2003). In the THC treatment group, there were five drop-outs, of which one was attributed to adverse effects. This study found that the THC treatment group showed significant improvement on the Yale Global Tic Severity Scale and Tourette's Syndrome Clinical Global Impressions scale after the study duration of one month, with statistically significant benefit observed at two weeks and dissipating within one day of ceasing treatment. Five subjects in the THC group experienced mild adverse effects.

The authors also describe two unpublished trials of pharmaceuticals that act on the endocannabinoid system. The first is an uncontrolled trial of palmitoylethanolamide (PEA), an agent which mimics properties of cannabis, in 16 adults with Tourette Syndrome, which suggested benefit when combined with THC. The second is a single-dose, placebo-controlled trial of monoacylglycerol lipase inhibitor (ABX-1431), which amplifies cannabinoid signaling in the endocannabinoid system. This study showed an improvement in tic severity eight hours after treatment.

The review authors conclude that clinical trial data on the efficacy of cannabinoids in treating tics is limited, and "considering the current evidence, it is premature to prescribe cannabinoid-based treatments in children given the risks for developmental adverse effects. They are also not the ideal medications to use in adults, due to the significant effects they have on driving and urine toxicology test positivity."

Koppel BS, Brust JC, Fife T. et al. Systematic review efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology.* 2013; 82(17):1556-63.

This report is a systematic review of literature on medical marijuana for treatment of symptoms of multiple sclerosis, epilepsy, and movement disorders. This review graded 34 studies which met inclusion criteria according to the American Academy of Neurology classification scheme for therapeutic articles. Only two articles were included in the discussion of Tourette Syndrome: Müller-Vahl 2002 was found to lack statistical power to enable reliable conclusions to be drawn and Müller-Vahl 2003 was found to have no significant differences between the treatment and placebo group after Bonferroni correction was applied to the results. The authors concluded: "For patients with Tourette Syndrome, data are insufficient to support or refute efficacy of THC for reducing tic severity."

Müller-Vahl KR, Schneider U, Koblenz A, Jöbges M, Kolbe H, Daldrup T, Emrich HM. Treatment of Tourette's syndrome with Delta 9-tetrahydrocannabinol (THC): a randomized crossover trial. *Pharmacopsychiatry*. 2002 Mar; 35(2):57-61.

In this randomized crossover trial with 12 patients (11 men, mean age was 34 ±13 years) with Tourette Syndrome were recruited from a clinic who were on stable medication for at least two months; exclusion included significant illness or psychiatric comorbidity. Five patients were being medicated for Tourette Syndrome. Additionally, seven patients had previously used marijuana, among whom four were regular users but were asked to stop use at least a week prior to beginning the study. The study was double-blind and placebo controlled, and patients were randomly assigned a single dose of 2.5 mg or 5 mg THC oral capsule (depending on weight, sex, and marijuana use history) or a placebo, with a four-week washout period between treatments. Blood samples were taken at six intervals in the 24 hours following treatment to collect plasma concentrations of THC and its metabolites. Patients completed self-rating scales for tic severity using the Tourette's Syndrome Symptom List (TSSL) before and three-four hours after treatment; an examiner completed the Shapiro Tourette's Syndrome Severity Scale (STSS), Yale Global Tic Severity Scale (YGTSS), and Tourette's Syndrome Global Scale (TSGS) as well as a subjective improvement rating. Treatment versus placebo TSSL scores showed a significant improvement in motor and vocal tics after THC treatment as well as in obsessive compulsive behaviors. The authors analyzed data a second time, including only patients who received 7.5 mg THC or 10 mg THC and found significant improvements measured by the TSSL and motor tics measured by the YGTSS. No subjects experienced serious adverse events; five reported mild transient adverse reactions lasting less than six hours and two patients reported mild side effects after placebo treatment. Simple linear regression showed a significant correlation between tic improvement, as measured by STSS, TSGS, and YGTSS, and maximum plasma concentration of THC metabolite 11-OH-THC. The authors note that the study's small sample size is a major limitation and its results should be considered preliminary and should be confirmed with larger placebo-controlled studies with a longer treatment period.

Muhler-Vahl KR, Schneider U, Prevedel H. Delta 9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: a 6-week randomized trial. J Clin Psychiatry. 2003;64(4)459-465.

This study was a small randomized, double-blind, placebo controlled six-week trial of the effectiveness of THC at controlling Tourette syndrome symptoms. The 24 subjects had an average age of 33 (range=18-68 years). Fifteen patients were unmedicated for at least six months prior to the study and nine were taking tic-related medications. Patients were randomly assigned to the THC group (n=12) or placebo group (n=12) and THC was administered via oral capsules with a starting dose of 2.5 mg/day. The dosage was increased by 2.5 mg/day every four days, with a target maximum dose of 10 mg/day. If a subject could not tolerate the maximum dose, an adjustment could be made by decreasing study medications up to 5.0 mg until a tolerated dose was achieved. The same dosing schedule was used to reduce medication at the end of the treatment period. Patients were examined at baseline and days nine, 20-22, 30-31, one or two days after medication stopped, and six weeks after medication stopped. At each visit, tic severity was measured using multiple clinician-rated measurement tools. Seven patients dropped out of the study or had to be excluded afterward, but only one of these did so because of side effects (anxiety and restlessness). Most rating scales demonstrated marked tic reduction at visits two, three, and four. However, Bonferroni correction (statistical adjustment for multiple measures) eliminated the statistically significant observations, except for those at day 30-31 of the study. No serious adverse reactions occurred. Five of the patients in the THC group reported mild side effects (tiredness, dry mouth, dizziness), however none of these patients reduced study medication below 7.5 mg due to these side effects because none felt seriously impaired.

Ongoing Clinical Trials

The Hannover Medical School has posted a multi-center randomized controlled trial of nabiximols, a cannabis plant extract, in the treatment of patients with Tourette Syndrome and chronic vocal or motor tic disorders. The study design is double-blind and placebo-controlled and will enroll 96 adult patients to be randomized to the placebo arm (1-12 puffs placebo oromucosal spray per day) or experimental arm (1-12 puffs of oromucosal nabiximols spray per day) over a course of 13 weeks. The primary outcome measure is tic severity, measured by the Total Tic Score of the Yale Global Tic Severity Scale. As of October 2020, the study is recruiting participants and the principal investigator is Dr. Kirsten Müller-Vahl, who has authored the two completed clinical trials reported earlier in this section. More information can be found at *CANNAbinoids in the Treatment of TICS (CANNA_TICS):*

https://clinicaltrials.gov/ct2/show/study/NCT03087201?term=tic+cannabis&draw=2&rank=2

Observational Studies

Two published observational studies on Tourette Syndrome patients using cannabis are included in this section, along with reported data on Tourette Syndrome patients enrolled in Minnesota's Medical Cannabis Program from 2015-2017.

Abi-Jaoude E, Chen L, Cheung P, Bhikram T, Sandor P. Preliminary evidence on cannabis effectiveness and tolerability for adults with Tourette Syndrome. *J Neuropsychiatry Clin Neurosci* 2017; 29:391-400.

This retrospective observational study recruited 19 adult patients at a Toronto Tourette Syndrome clinic who had been using inhaled cannabis regularly for at least six months. On reviewing records of their adult patients, they found 22 that were currently using cannabis. One was excluded due to use less than six months and two declined to participate. In addition to medical record review, patients were brought into the office for a semi-structured interview and multiple standardized questionnaires (current and prior to cannabis use) administered by two psychiatrists. Main outcomes were mean change from baseline in the Yale Global Tic Severity Scale – Total Tic Score (YGTSS-TTS) and the percentage of patients rated as "much improved" or "very much improved" on the Clinical Global Impressions Improvement (CGI-I) Mean age of the 19 patients was 32 years (±12.3 years), 16 were male, and three female. All but one had previously been treated with medications for tics, including 14 with clonidine, 13 with at least one antipsychotic, and nine with both. The patients were found to have had 60% improvement in YGTSS-TSS (from 30.5 ±7.2 to 12.2 ±8.6, $p<0.001$) and 18 of the 19 being rated as "very much improved" or "much improved" on the CGI-I. Investigators were unable to obtain reliable information regarding cannabis strain or THC/CBD content. Using reported cannabis usage amounts, estimates of THC content, and approximated conversion of inhaled to oral THC dosing, the authors produced an estimated median dose of 250 mg equivalent of oral THC, notably, this is significantly higher than the doses used in the two extant clinical trials (which used maximum dosages of 10 mg THC). The authors note that this study is limited by likely presence of selection bias. Patients who tried cannabis and quit due to ineffectiveness or intolerable side effects would have been excluded from the study.

Thaler A, Arad S, Schleider LB, Knaani J, Taichman T, Giladi N, Gurevich T. Single center experience with medical cannabis in Gilles de la Tourette syndrome. *Parkinsonism and Related Disorders* 2019; 61:211-213.

This retrospective observational study identified Tourette Syndrome patients who were approved to use medical cannabis in Tel-Aviv, Israel. Sixty-three patients were initially identified; of these, 42 patients were included in the study (exclusion criteria were the presence of other movement disorders and use of medical cannabis for less than one year). Participants answered a structured phone questionnaire assessing subjective overall impression of efficacy of cannabis treatment (1-5 Likert scale). The subjects were mostly male (n=33) and mean age was 34.45. Mean global impression of medical cannabis efficacy was 3.85 out of 5 points; subjects reported reduction in tic severity, better sleep, and improved mood as positive therapeutic effects. Of 42 participants, all had tried at least one tic-related therapy and 17 were taking other tic-related medication along with cannabis (atypical antipsychotics (n=2), typical antipsychotics (n=1), SSRIs (n=8), benzodiazepines (n=5), methylphenidate (n=3), antidepressants (n=1) and tetrabenazine (n=2)). Four patients administered cannabis orally; 28 used inhalation, and 10 used both methods. Ten patients chose to stop medical cannabis after less than a year of treatment; four reported they stopped because they experienced no benefit on symptoms; the remaining six reported various reasons including side effects. Among all participants, side effects reported included hallucinations (n=4), irritability and confusion (n=6), subjective cognitive decline (n=7), and acute psychotic episode (n=1). This study is limited in

interpretation because THC and CBD dosage are unknown and participants were asked to report subjective global impressions; the authors note that some effects can be attributed to placebo.

Office of Medical Cannabis, Minnesota Department of Health. (2019) *Benefits Reported on the Patient Self-Evaluation: Patients With First Enrollment July 2015-June 2017*. https://www.health.state.mn.us/people/cannabis/docs/about/cohort/c2015_2017_benefitspse.pdf

Minnesota's medical program began in July 2015 and includes Tourette Syndrome as a qualifying condition. From July 2015-June 2017, 58 patients were certified by a health care practitioner as having Tourette Syndrome, and made at least two purchases of medical cannabis. These patients reported their weekly tic frequency each time they purchased medical cannabis. Their first reported weekly tic frequency was used as a baseline, and subsequent reports were compared to the baseline to assess degree of benefit. Among 58 patients included in this report, 30 (52%) achieved a 30% reduction in weekly tic frequency within four months of their first medical cannabis purchase. Additionally, 19 patients (33%) maintained this 30% reduction for four months after achieving it. This observational data lacks placebo control or dosage information, and relies on self-reported data from patients.

National Medical Organization Recommendations

Pringsheim T, Okun MS, Müller-Vahl K, Martino D, Jankovic J, Cavanna AE, Woods DW, Robinson M, Jarvie E, Roessner V, Oskoui M, Holler-Managan Y, Piacentini J. Practice guideline recommendations summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders. *Neurology.* May 2019; 92(19): 896-906

The American Academy of Neurology *Practice Guideline Recommendations Summary: Treatment of Tics in People with Tourette Syndrome and Chronic Tic Disorders* states: "There is limited evidence that delta-9-tetrahydrocannabinol (THC), dronabinol, is possibly more likely than placebo to reduce tic severity in adults with [Tourette Syndrome]." The guidelines recommend that where regional legislation allows, physicians may consider treatment with cannabis-based medicine for adult patients with otherwise treatment-resistant tics or adult patients who already use cannabis as self-medication to control tics. Additionally, they recommend that physicians who prescribe cannabis-based medicine should prescribe the lowest possible dose to minimize adverse effects and should inform patients of the risks of impairment. Finally, they indicate periodically reevaluating the need for ongoing treatment (Pringsheim 2019).

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.

The National Academies of Sciences, Engineering and Medicine produced a report on the health effects of cannabis in 2017, and the committee found limited evidence that THC capsules are an effective treatment for improving the symptoms of Tourette Syndrome (Conclusion 4-8).

Pringsheim T, Doja A, Gorman D, et al. Canadian guidelines for the evidence-based treatment of tic disorders: pharmacotherapy. *Can J Psychiatry*. 2012; 57(3):133-143.

The Canadian Guidelines for the Evidence-Based Treatment of Tic Disorders: Pharmacotherapy states: "There is no evidence to support the use of cannabinoids for the treatment of tics in children or adolescents. Given this lack of evidence, as well as concerns about potential misuse, we do not recommend that cannabinoids be used for treating tics in youth. However, there is low-quality evidence that cannabinoids have modest benefits in the treatment of tics in adults."

References

American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders, 5th edition*. Arlington, VA., American Psychiatric Association, 2013.

Artukoglu BB, Bloch MH. The Potential of Cannabinoid-Based Treatments in Tourette Syndrome. *CNS Drugs* 2019; 33:417-430.

Bloch MH, Leckman JF. Clinical course of Tourette syndrome. *J Psychosom Res*. 2009 Dec;67(6):497-501.

Bloch MH, Panza KE, Landeros-Weisenberger A, Leckman JF. Meta-analysis: treatment of attention-deficit/hyperactivity disorder in children with comorbid tic disorders. *J Am Acad Child Adolesc Psychiatry*. 2009 Sep;48(9):884-893.

Centers for Disease Control and Prevention. (2020, May 13). *Diagnosing Tic Disorders*. Accessed August 1, 2020. https://www.cdc.gov/ncbddd/tourette/diagnosis.html

Ceci C, Onori P, Macri S, Laviola G. Interaction Between the Endocannabinoid and Serotonergic System in the Exhibition of Head Twitch Response in Four Mouse Strains. *Neuroto Res* (2015) 27:275-283.

Cothros N, Medina A, Pringsheim T. Review: Current pharmacotherapy for tic disorders. *Expert Opinion on Pharmacotherapy* 2020; 21(5): 567-580.

Leckman JF. Phenomenology of tics and natural history of tic disorders. *Brain Dev.* 2003 Dec;25 Suppl 1:S24-8.

Müller-Vahl KR, Schneider U, Koblenz A, Jöbges M, Kolbe H, Daldrup T, Emrich HM. Treatment of Tourette's syndrome with Delta 9-tetrahydrocannabinol (THC): a randomized crossover trial. *Pharmacopsychiatry*. 2002 Mar;35(2):57-61.

Müller-Vahl KR, Schneider U, Prevedel H, Theloe K, Kolbe H, Daldrup T, Emrich HM. Delta 9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: a 6-week randomized trial. *J Clin Psychiatry*. 2003 Apr;64(4):459-65.

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.

Office of Medical Cannabis, Minnesota Department of Health. (2019) *Benefits Reported on the Patient Self-Evaluation: Patients With First Enrollment July 2015-June 2017.* https://www.health.state.mn.us/people/cannabis/docs/about/cohort/c2015_2017_benefitspse.pdf

Pringsheim T, Doja A, Gorman D, et al. Canadian guidelines for the evidence-based treatment of tic disorders: pharmacotherapy. *Can J Psychiatry*. 2012;57(3):133-143.

Pringsheim T, Okun MS, Müller-Vahl K, Martino D, Jankovic J, Cavanna AE, Woods DW, Robinson M, Jarvie E, Roessner V, Oskoui M, Holler-Managan Y, Piacentini J. Practice guideline recommendations summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders. *Neurology* May 2019; 92(19): 896-906.

Quezada J, Coffman KA. Current Approaches and New Developments in the Pharmacological Management of Tourette Syndrome. *CNS Drugs*. 2018; 32(1): 33-45.

Snider LA, Seligman LD, Ketchen BR, et al. Tics and problem behaviors in schoolchildren: prevalence, characterization, and associations. *Pediatrics* 2002; 110:331-336.

Thaler A, Arad S, Schleider LB, Knaani J, Taichman T, Giladi N, Gurevich T. Single center experience with medical cannabis in Gilles de la Tourette syndrome. *Parkinsonism and Related Disorders* 2019; 61:211-213.

Woods D, Piacentini J, Walkup JT. (2016) *Comprehensive Behavioral Intervention for Tics (CBIT).* Tourette Association of America. https://tourette.org/media/TAACBITenglish101316final.pdf

Minnesota Department of Health
Office of Medical Cannabis
PO Box 64882
St. Paul, MN 55164-0882
651-201-5598
health.cannabis@state.mn.us
www.health.state.mn.us

10/20

To obtain this information in a different format, call: 651-201-5598. Printed on recycled paper.