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).

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