

Anxiety Disorder Review

OFFICE OF MEDICAL CANNABIS

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Anxiety Disorder Review

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Executive Summary

Anxiety disorder is a mental health condition which affects approximately 31% of all adults at some point in their lifetime (National Institute of Mental Health, 2017). The manifestation can vary from mild symptoms to debilitating symptoms which can significantly alter a person's way of living. Persons with anxiety disorder can be effectively treated with medications, such as anti-depressants (SSRIs), to manage their symptoms. The best course of treatment is psychotherapy for the patient to understand their triggers and learn how to effectively respond and manage them. However, access to mental health services, such as therapists and psychiatrists, can be very difficult for many individuals across the state. In addition, some patients experience side effects from SSRIs. Some may require more intensive medications, such as benzodiazepines which have a high risk for addiction and overdose. During 2000 – 2018, Minnesota experienced a 70% increase in deaths from benzodiazepine overdoses. It is also estimated only 50.1% of adults with mental illness in Minnesota receive any form of treatment (National Institutes of Health: Substance Abuse and Mental Health Services Administration, 2020). This may be due to lack of access, unfavorable side effects from medication, or other issues. Untreated mental illness is a known cause of suicide. In Minnesota, the incidence of suicide has risen to 830 deaths in 2019.

Since 2016, anxiety disorder or panic disorder have been petitioned to be included as a qualifying condition for medical cannabis. Each petition has been denied due to lack of clinical evidence and the desire to avoid any unintended consequences. At the conclusion of the 2020 petition cycle, the Commissioner of Health requested the Office of Medical Cannabis take a more in-depth look at the issue.

A three-prong approach was initiated to evaluate the impact of adding, or not adding, anxiety disorder to list of qualified conditions for medical cannabis. The three sources of information were a review of the current literature and research, interviews with states which have added, or denied, anxiety disorder as a qualified condition, and a work group of professionals with expertise in anxiety disorder to obtain their perspectives and opinions.

Available published research shows mixed outcomes on efficacy due to variations in study design. More recent studies focus on cannabidiol (CBD), which appears to have anxiolytic effects and may be dose dependent. Most of the research thus far has involved healthy individuals, which is not representative of the targeted population. A retrospective meta-analysis showed persons with anxiety disorder did not experience progression disorder after using cannabis, however, more research is necessary. At present, cannabis is labeled as a schedule 1 drug, which complicates research efforts. Currently five trials out of over 1,100 for anxiety disorder involve cannabis (clinicaltrials.gov).

Four states have included anxiety disorder as a qualifying condition. Three states (Pennsylvania, Nevada, and New Jersey) added anxiety disorder through their respective petition processes and one state (North Dakota) included anxiety disorder at the initiation of their program. All four states saw a rapid rise in the number of individuals participating in their respective programs who have a diagnosed anxiety disorder, to the point where anxiety disorder became either the top or second most common qualifying condition. Only one state reported removal

of individuals from their program who experienced significant mental health issues following the use of medical cannabis.

Professional clinical opinions obtained through a work group vary widely on the topic of including anxiety disorder as a qualifying condition for medical cannabis. Clinicians who practice internal medicine were more open to considering anxiety disorder, some preferring to limit inclusion to the sub-diagnoses which have severe, life-altering manifestations. However, clinicians who practice psychiatry were more cautious and advocated for evidence-based outcomes to be in place first in order to shape policy. Clinicians and professionals who provided therapy and work in the field of substance use disorder acknowledged a potential harm-reduction benefit medical cannabis may offer, particularly to those who use illicit marijuana or other street drugs to manage their symptoms. All were of the opinion it is imperative to protect the developing brains of young adults as well as acknowledging medical cannabis has the potential to become addictive.

Three courses of action were identified: maintain status quo, approve medical cannabis for a limited set of anxiety disorder sub-conditions, or approve for all anxiety disorder sub-conditions. Each course of action has benefits and risks. At present, public opinion on the use of medical cannabis for anxiety disorder may be based upon isolated, personal experiences rather than the result of rigorous scientific and clinical study. Given the current restrictions at the Federal level, these barriers are unlikely to be eased anytime soon.

Therefore, considerations to include, or not include, anxiety disorder as a qualifying condition are complex. In the absence of clinical evidence, other factors may contribute to the decision such as the experience of other states, professional experience and opinions, as well as harm and risk-reduction strategies.

Background and Approach

1. Need for the Project

The Office of Medical Cannabis (referred to as the Program) offers a petition process for the public to request a medical condition for inclusion in the list of qualified conditions. Anxiety disorder was petitioned in 2017, 2019 and 2020. Panic disorder, a sub-condition of anxiety disorder, was petitioned in 2018. Over 100 comments were submitted regarding anxiety disorder during the 2020 petition cycle. The overwhelming majority of the comments were in favor of adding anxiety disorder (103 supportive vs 4 unsupportive). Those who expressed concern cited the lack of available clinical research. Many provided personal testimony sharing cannabis allowed them to sleep, slowed their racing thoughts, diminished their anxiety, and felt they could function normally. Some also noted they do not tolerate current pharmaceuticals.

On December 1, 2020, the Commissioner announced the decision to deny anxiety disorder as a qualifying medical condition. The reasons underlying this denial were the lack of solid evidence about the potential impacts of adding anxiety disorder and the desire to avoid unintended consequences. As part of the denial, however, the commissioner committed MDH to take a more in-depth look at the issue.

2. Approach

A three-prong approach was taken to provide an in-depth look at current clinical knowledge of the impacts of cannabis use on anxiety disorder, its efficacy in managing anxiety disorder, and any potential adverse consequences.

The three sources of information were:

A literature and research review

The experience of other states which either approved or denied anxiety disorder as a qualified condition

A work group of professionals with expertise in anxiety disorder to obtain their perspectives and opinions

Literature and Research Review

1. Research Landscape

According to the Food and Drug Administration's (FDA) classification, cannabis is identified as a Schedule I drug due to its high potential risk for addiction (Food and Drug Administration, 2020) and lack of accepted medical use. To complicate research opportunities further, cannabis is an illegal substance according to Federal laws. As a result, advancing research can be challenging due to various limitations, such as:

- The Drug Supply Program products available through the University of Mississippi do not reflect the products available in different parts of the country, which can limit broader utility of the study findings.
- Available funding is primarily focused on substance use disorder, as opposed to therapeutic uses.
- Many layers of review are necessary to facilitate a study

It is important to note these constraints apply to any qualifying condition and are not unique to anxiety disorder.

5 out of 1,100+

Studies for anxiety disorder in the US include cannabis

At present there are very few active cannabis studies underway in the United States. To illustrate the challenge, as of May 14, 2021, over 1,100 active clinical trials for anxiety disorder were posted in www.clinicaltrials.gov. Of the total, five involved cannabis (flower or edible, CBD only, or high CBD/low THC) as the study medication.

Facilitating cannabis clinical research has its own inherent challenges, such as:

- Study subjects may have varying preferences for the routes of administration (tincture, edible, whole flower, etc.).
- Standardized medication delivery can be difficult, depending upon the route selected. For example, smoking as route of administration is challenging to standardize because it is difficult to measure the dose inhaled.
- Placebos can be difficult to disguise, which can influence the subject's response. For example, smoked cannabis has a distinct odor and gives a sensation which are difficult to duplicate in a placebo.

- Finally, relying on a subject's self-report of prior use may not be accurate and could skew the findings. For example, under-reporting prior use may impact the dosing results.

The agency has approved one cannabis-derived medication (Epidiolex) for seizures in persons over the age of two diagnosed with Lennox-Gestaut syndrome or Dravet syndrome and three synthetic cannabis-related products (Marinol, Syndros, and Nabilone) for the treatment of nausea and anorexia associated with cancer chemotherapy or weight loss due to AIDS. It is worth noting none of these medications and products are approved for mental health disorders.

2. Current Research

Clinical research underway over the last few years has been focused primarily on the efficacy of cannabidiol (CBD) in treating anxiety disorder through the reduction of anxiety symptoms (Zuardi A. W., 1993) (Bergamaschi, 2011) (Hurd, 2019) (Masataka, 2019). Several studies indicate the anxiolytic properties of CBD might be dose-dependent, with the moderate dosages being most effective in reducing symptoms, whereas the low and high doses were ineffective or increased symptoms among healthy individuals or persons with social anxiety disorder (Zuardi A. W., 2017) (Linares, 2019). One study suggests CBD may offset the anxiogenic effects of tetrahydrocannabinol (THC) (Bhattacharyya, 2018).

A meta-analysis of 12 cohort studies showed nine of the studies did not find a relationship between cannabis use and the development of an anxiety disorder. Of interest to this project, two cohort studies examined the progression of anxiety disorder with cannabis use. Neither study found cannabis use to contribute to disorder progression (e.g., remission rates, treatment outcomes) (Botsford, 2020).

Overall, the available published research provides mixed evidence of efficacy. Comparing findings from observational cohort studies is limited because the collected variables are not consistent, which highlights the need for greater standardization. While human studies indicate some signal that cannabinoids, particularly CBD, may have anxiolytic properties, only limited evidence indicates this outcome may be dose dependent. Secondly, a limited number of studies specifically focus on individuals with a diagnosed anxiety disorder. Most of the data collected thus far is from healthy individuals, which is not representative of the potential patient pool. Finally, differences in study design make comparisons across studies difficult due to the different tasks used to induce anxiety in the study groups as well as the measures of anxiety used.

A summary of the current available research can be found in the Appendix.

3. Minnesota's PTSD Experience

The Program added PTSD as a qualifying condition in 2017. An analysis of 5,200 enrolled in the Program with the diagnosis of PTSD showed 96% self-reported moderate to severe anxiety symptoms at baseline. Within four months, 40.9% reported a significant

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improvement in their symptoms and 62% were able to maintain the symptom improvement at the next four-month reporting period.

This experience may be a useful indicator for the potential relief medical cannabis may provide to persons with anxiety disorder who experience moderate to severe symptoms.

Experience of Other States

1. Introduction

States which have either added anxiety disorder as a qualifying condition through their medical cannabis programs, or recently considered anxiety disorder, were contacted by email and interviews were requested. Representatives from all four states (Nevada, New Jersey, North Dakota, and Pennsylvania) which have approved or included anxiety disorder as a qualifying condition responded and participated in an interview. Representatives from two states (Hawaii and Ohio) which have denied petitions also responded and participated in an interview. Specific interview questions can be found in the Appendix.

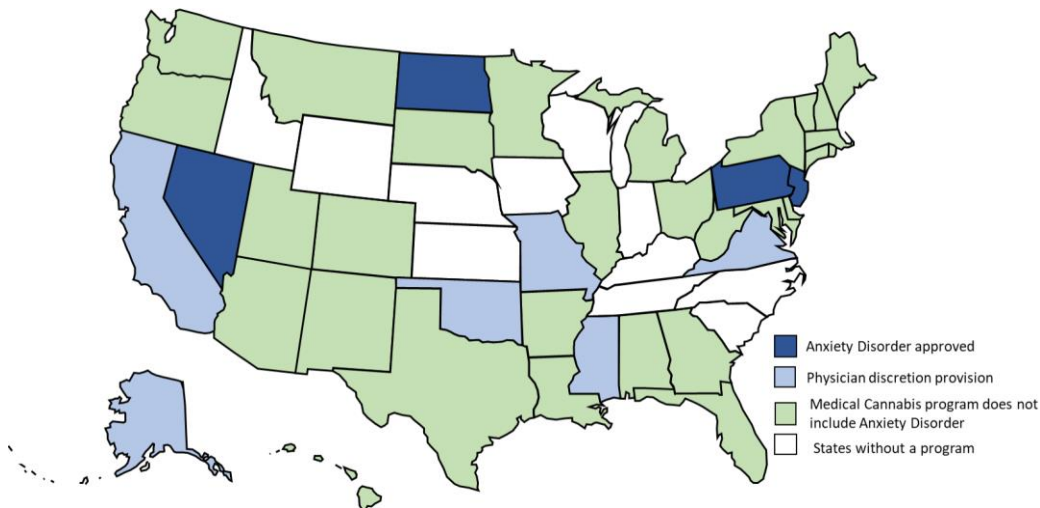
Representatives were asked questions addressing:

- The process used to evaluate anxiety disorder as a qualified condition.
- The impact adding anxiety disorder created for the program or the reasons anxiety was denied when petitioned.
- Patient experience and public reaction.

2. Individual State Details

Thirty-eight states have or will have a medical cannabis program by July 2021 (Texas Health Services, 2021) (ProCon/Encyclopaedia Britannica, Inc., 2021). Four states have either added anxiety disorder as a qualified condition through a petition process, through legislation, or through a combination of both processes. These states are Nevada, New Jersey, North Dakota and Pennsylvania.

Graphic 1: States with Medical Cannabis Programs and Anxiety Disorder Status



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One state, North Dakota, added anxiety disorder through legislative order at the establishment of their medical cannabis program. The other three states were petitioned (New Jersey and Pennsylvania) or petitioned and then submitted to the legislature for formal action (Nevada) to add anxiety disorder. The DSM-5 definition of anxiety disorder was applied in each case, however sub-conditions were not distinguished. In all four states, anxiety disorder quickly rose to either the top or second most common condition for which medical cannabis is dispensed. Within the first year of including anxiety disorder as a qualified condition, the percentage of individuals registered in the various state programs with this diagnosis ranged from 14% to 25%. None of the states have formal data collection practices in place, however one state noted a few cases have been reported where patients developed significant mental health issues following the use of medical cannabis. In these cases, care was coordinated with the individuals' respective providers and subsequently removed from the program. It is worth noting none of the states reported public concern following the approval of anxiety disorder as a qualifying condition. Table 1 summarizes these findings.

Table 1: States which have added Anxiety Disorder as a Qualified Condition

State	First Attempt Year Added	Method To Add	Decision Maker	% of Qualified Conditions	Collect Patient Impact Data?
Nevada	2019	Hybrid	Legislature	14%	No
New Jersey	2018	Petition	Board recommendation, Health Commissioner decision	24% (year 1) 58% (year 2)	No
North Dakota	2019	Legislative	Legislature	25%	No
Pennsylvania	2019	Petition	Board recommendation, Secretary of Health decision	15%	No

In a unique approach, the Pennsylvania Secretary of Health was proactive and engaged the medical community across the state. She positioned medical marijuana as a “tool in the toolbox”. The Secretary provided professional recommendations through a press release, which she stated medical cannabis is not a first line treatment, is intended for short term use, low THC/high CBD products preferred, and is not recommended for children, adolescents, or pregnant women (McNelis, 2019) (Associated Press, 2019).

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Two states – Hawaii and Ohio – have received petitions to add anxiety disorder as a qualified condition. Both states have denied the requests, citing a lack of clinical evidence as the reason for denial. Concerns over adding a mental health disorder was noted by Hawaii and the representative from Ohio stated a condition cannot be removed once added, therefore, their board is also very cautious to add a condition unless published clinical evidence exists.

It is important to note six additional states either have a provision which allows physician discretion to recommend cannabis outside of the qualifying conditions (Alaska, California, Mississippi, and Missouri) or have no pre-determined qualifying conditions (Virginia and Oklahoma). Therefore, patients could obtain medical cannabis for anxiety disorder in these states. It is important to note Virginia does not have a medical cannabis program, but instead authorizes its residents to possess medical cannabis products.

Work Group of Healthcare Professionals

1. Introduction

The purpose of the work group was to conduct a provider-based review of the potential benefits and potential harms of adding, or not adding, anxiety disorder as a qualifying condition.

The process included an in depth look at current medical knowledge of the impacts of cannabis use on anxiety disorder, its efficacy in managing anxiety disorder, any potential adverse consequences, and experiences of other states that recognize anxiety disorder as a qualifying condition.

a. Participant Identification and Selection

Seven professionals with expertise in anxiety disorder were identified and invited to participate in the work group. A wide balance of opinions was desired and all were asked to maintain an open mind to the topic. Their backgrounds included general practice, psychiatry, therapy and substance use. Two are program certifiers, two are familiar with the program and two are not associated with the program. One non-clinical stakeholder with expertise in substance use participated. A psychologist was invited to participate but did not respond. Participant, speaker and other attendee biosketches can be found in the Appendix.

Meetings were held March 29, April 19 and April 26, 2021. Each meeting was held virtually and lasted two hours. Agendas are included in the Appendix.

b. Overview of Topics Reviewed and Discussed

The following topics were reviewed and discussed over the course of the work group sessions:

- Purpose of the work group and the Commissioner's goals.
- Program background and research to date.
- Manufacturer's experience with PTSD and anxiety disorder.
- Discussion topics:
 - Current treatment standards for the sub-conditions.
 - Risks of adding or not adding anxiety disorder to the list of qualifying conditions.
 - Benefits of adding or not adding anxiety disorder.

- Recommended modifications to current data collection practices to identify if medical cannabis offers relief and improves functional outcomes for current patients experiencing anxiety.
- The professional opinion of each participant.

Copies of the meeting agendas can be found in the Appendix.

2. Anxiety Disorder

Anxiety disorder is a mental health disorder, of which the causes are not fully understood. It often involves intense, excessive, and persistent worries and fears over daily experiences and situations. Persons with anxiety disorder often experience repeated episodes of sudden feelings of intense anxiety and fear or terror. In some instances, the reactions can come on suddenly with extreme intensity. For some individuals, these feelings of anxiety and panic can interfere with their daily activities, can be difficult to control and may be out of proportion to the real danger. For many patients, treatment is necessary to effectively manage the symptoms and identify the triggers which can induce the episodes (Mayo Clinic, 2018). According to the National Institute of Mental Health, an estimated 19.1% of the adults in the US experienced an anxiety disorder each year and approximately 31.1% of all US adults will experience any anxiety disorder at some time in their lives (National Institute of Mental Health, 2017).

Anxiety disorder can be further defined by sub-conditions. The following is the list of sub-conditions, as identified in the DSM-5.

- Generalized Anxiety Disorder: Persistent nervousness or tension, with or without a cause, which rarely subsides.
- Social Anxiety/Social Phobia: Intense shyness, thoughts of socializing causes anxiety and fear. Demonstrate avoidance behaviors.
- Panic Disorder: Debilitating, severe feelings of doom which can cause mental and physical symptoms.
- Specific Phobias: Intense feelings of fear, generating disaster thinking or avoidance behaviors.
- Separation Anxiety Disorder: Intense worry over separation; avoid being separated and alone from their attachment figures.
- Agoraphobia: Often associated with panic disorder; can be debilitating if they never leave their home or severely limit their travel.

Obsessive-Compulsive Disorder was re-classified in the DSM-5 is no longer considered a sub-condition of anxiety disorder. Table 2 summarizes the sub-condition, standard treatment, and prescribed medications.

The severity of anxiety disorder can vary widely from easily manageable to severely debilitating. Researchers are finding both genetic and environmental factors may contribute to the risk of developing an anxiety disorder, such as temperamental traits of

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shyness or behavioral inhibition in childhood, exposure to trauma, family history of anxiety disorders. Some physical health conditions may produce or aggravate anxiety symptoms (National Institute of Mental Health, 2018). Table 2 provides an overview of the sub-conditions of anxiety disorder, the standard treatments, and common prescribed medications.

Table 2. Sub-conditions of Anxiety Disorder, Standard Treatment and Medications (Source: Work Group Participants)

Sub-Condition	Standard Treatment	Medications Most Often Prescribed
Generalized Anxiety Disorder	Therapy to address the triggers, medications to manage symptoms	SSRIs and benzodiazepines
Social Anxiety/Social Phobia	Primarily therapy, medications are rarely prescribed	SSRIs, however, medications are rarely prescribed
Panic Disorder	Therapy to address the triggers, medications to manage symptoms	SSRIs, beta-blockers, and benzodiazepines
Specific Phobia	Exposure therapy works very well and has a high compliance rate	None, because exposure therapy is effective
Separation anxiety disorder	Therapy to understand the attachment triggers, medications to manage symptoms Therapy to learn healthy nurturing and attachment	SSRIs and possibly benzodiazepines
Agoraphobia	Therapy to address the triggers, medications to manage symptoms	SSRIs and benzodiazepines

3. Common Themes



Over the course of the work group sessions, six major common themes emerged through the discussion which represented the areas of greatest alignment among the participants. The following were heavily discussed:

- **Protect the developing brain:** significant concerns exist among the providers over protecting the brains of young adults, citing the human brain continues to develop until the age of 25. Exposure to high THC products can induce psychosis, leaving the individual with long-term psychological effects.
- **Safer alternative to benzodiazepines:** all participants agreed benzodiazepines can be dangerous due to their high risk for addiction as well as death if overdosed.
- **Therapy is the standard:** Therapy is the preferred treatment for all anxiety disorders; however patients may be unwilling to participate in therapy and/or experience limited access to therapists and psychiatrists.
- **Health equity:** Known disparities exist in the level of care available for anxiety disorder among historically disadvantaged communities. Medical cannabis may offer these individuals the option for an alternative to current medications, however this view was not shared by all participants.
- **Limited research:** the ability to study cannabis through the normal channels is not readily possible due to its status as a Schedule 1 drug as determined by the FDA. Concerns were raised public opinion to accept cannabis in our society is ahead of any known science to date.

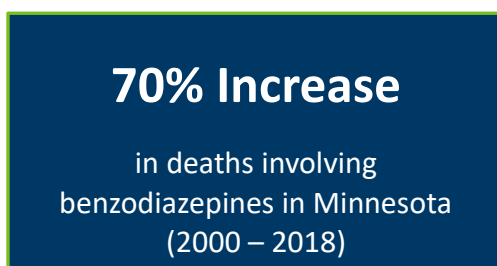
- **Harm reduction:** approving medical cannabis for anxiety disorder may offer a safer option and potentially reduce harm among individuals seeking illicit drugs to manage their symptoms.

4. Work Group Discussion Results

Over the course of the work group sessions, the opinions and perspectives of the participants were collected and distilled into benefits and risks of adding anxiety disorder as a qualifying condition.

a. Benefits

The work group identified several benefits medical cannabis may offer patients with anxiety disorder.



- Medical cannabis may be a preferred alternative to benzodiazepines due to reduction in addiction, overdoses and fatalities. From 2000 to 2018, Minnesota experienced a 70% increase in deaths involving benzodiazepines (Minnesota Department of Health, 2020).
- Medical cannabis is known to relieve symptoms. The PTSD cohort within the Program has demonstrated anxiety symptom relief from medical cannabis.
- Medical cannabis may be a bridge to therapy.
- In a harm reduction strategy, medical cannabis is preferred over illicit marijuana and other street drugs for patients managing their anxiety symptoms.
- From a health equity perspective, medical cannabis for symptom management may offer a legal alternative to high-risk medications and illegal drugs among historically disadvantaged communities and among those suffering from substance use disorder.
- In mental health, a person-centered approach allows a patient to determine their care and treatment pathway which has the greatest opportunity for success. Medical cannabis may lend itself to a patient-centered approach because it can serve as an alternative to medications which may have undesirable side effects or other risks.

b. Risks

Likewise, approving anxiety disorder as a qualified condition may pose potential risks to patients.

1 in 6

Patients with Generalized Anxiety Disorder will drop out of therapy

- Patients may no longer avail themselves to therapy if regularly using medical cannabis or may deter themselves from seeking therapy. Nationwide, approximately 1 in 6 patients with Generalized Anxiety Disorder will drop out of therapy (Gersh, 2017). This ratio could increase if medical cannabis is used, therefore, hampering any potential for patient's to properly manage their disorder.
- Patients may perceive illicit marijuana as safe for managing their anxiety, placing themselves at risk for worsening their symptoms or psychosis if the THC content is too high.
- Research is limited on other potential harms, such as the development of a new addiction or other unknown long-term health risks.

c. Areas of consistency and divergence of opinion

The table below summarizes the areas of consistency among the opinions of the participants as well as areas of divergence. In general, the participants were in alignment among the standard treatment approach of therapy, although access varies across the state and communities, and recognize current medications have known side effects as well as serious risks. Concerns were expressed if medical cannabis were available for anxiety disorder, some members of the community may not be able to afford it and will remain disadvantaged. Definitive clinical research remains elusive, and participants noted approval of medical cannabis for anxiety disorder may give the false impression illicit marijuana is safe for symptom management due to public misinformation. The advantage the Program brings is the mechanism to control, monitor and manage proper CBD/THC dosing, however primary care clinicians and therapists all believed they would benefit from precisely knowing the dosages their patients were receiving. Finally, all participants were aligned on the need to protect young adults from the dangers of high THC products, which could induce psychosis.

On the other hand, opinions were divergent in the areas of health equity and if access to medical cannabis for anxiety disorder would improve the lives of the most disadvantaged as well as whether medical cannabis would encourage or discourage someone from seeking and/or participating in therapy. Opinions also varied on the addictive potential medical cannabis, primarily if its use is intended to be short term and if not, do long-term consequences exist as well as if it offers any sustainable benefit to any sub-condition. It is important to note anxiety disorder can be diagnosed and treated

by a variety of disciplines, which may influence the treatment options and individual perspectives.

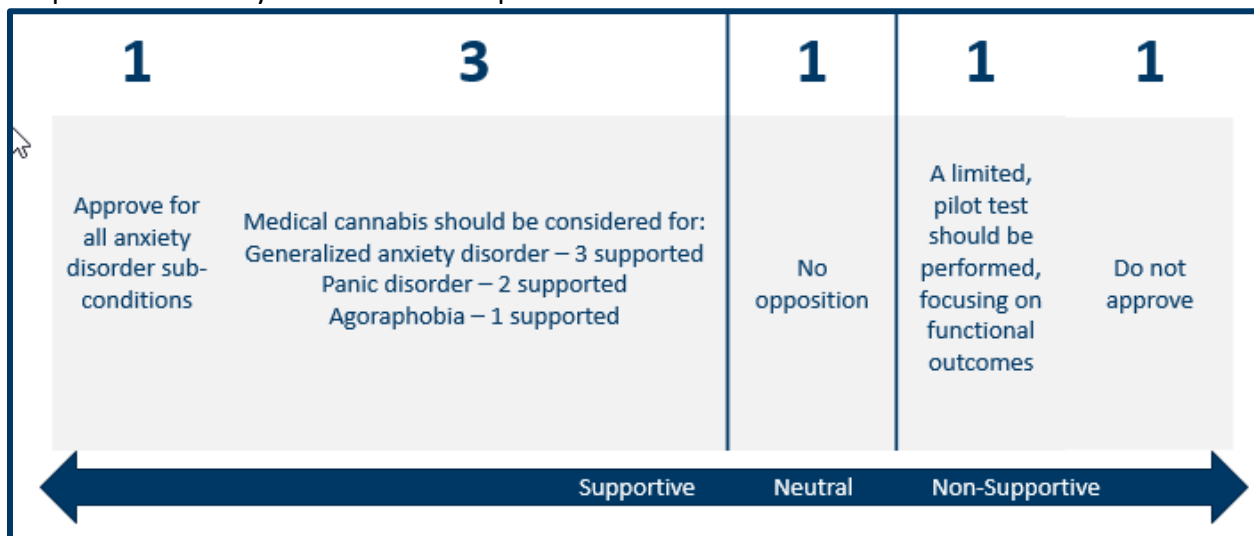
Table 3: Areas of Consistency and Divergence of Professional Opinions

Consistency	Divergence
<ul style="list-style-type: none"> • First line approach is therapy; medications are prescribed to manage symptoms. • Access to therapy varies; low income and/or BIPOC persons tend to experience greatest disparities. • Access to medical cannabis may cause new problems for disadvantaged communities, such as ability to afford a prescription. • Current medications have side effects and known risks. • Clinical research on the benefits of medical cannabis is limited. • Prevention of inducing psychosis from THC exposure among young adults is critical. • A mechanism to control, monitor and manage dosing is important. • Primary care clinicians would benefit from knowing the CBD/THC concentration prescribed to their patients. • Concerns approval for anxiety disorder may perpetuate misinformation that all marijuana is safe and effective for anxiety disorder symptom management. 	<ul style="list-style-type: none"> • Medical cannabis has the potential to improve health equity among persons in historically disadvantaged communities who have anxiety disorder. • Medical cannabis may build trust with a provider and encourage therapy, or patients may experience de-motivation to seek or continue therapy. • The overall addictive potential and side effects of medical cannabis, including whether medical cannabis offers short-term relief or if long-term usage could be damaging. • Long-term therapeutic potential for any of the sub-conditions. • The range in disciplines among provider types who diagnose and treat anxiety may result in the variation in approaches to treatment.

5. Recommendations

Participants were asked their opinion if anxiety disorder should be approved as a qualifying condition. The table below summarizes and sorts the opinions of the participants, from supportive to unsupportive.

Graphic 2: Summary of Professional Opinions



The opinions of the participants varied widely, as illustrated in the above graphic. Among the providers who recommended limiting approval to sub-conditions, Generalized Anxiety Disorder was agreeable by all. Panic Disorder and Agoraphobia were also recommended as potential sub-conditions for consideration. Most of the participants expressed significant concerns over potentially introducing new risks to the patient population, such as addiction.

The statements below provide greater context to the opinions expressed by the participants.

Participants in support of approving medical cannabis as a treatment option for persons with anxiety disorder:

- One recommended approving for all sub-conditions, citing experience observing patients who have reduced symptoms following use of medical cannabis. The provider also noted distinguishing between sub-conditions can be challenging and many patients are currently diagnosed with an unspecified anxiety disorder.
- Three recommended approving for sub-conditions which have known potential for severe debilitation and are more likely to be prescribed benzodiazepines.
- One had no opposition because medical cannabis is used to treat other conditions. From a substance abuse disorder perspective, they believe

persons may turn to chemicals to cope with their anxiety. Thus, medical cannabis may be a safer alternative.

Participants in opposition of approving medical cannabis as a treatment option for persons with anxiety disorder:

- One was not willing to recommend until more information is available, or a limited pilot study is conducted which evaluates functional outcomes. In their opinion, the pilot study should focus on Generalized Anxiety Disorder and Panic Disorder. The study outcomes would then determine if medical cannabis is beneficial and should be approved.
- One would not recommend medical cannabis under any circumstances. Their concerns include use may create the potential for addiction, use may demotivate patients from seeking therapy, medical cannabis for a broad condition such as anxiety disorder sends a message of normalization of marijuana usage, and the overall complexity in diagnosing anxiety disorders.

6. Data Collection

If anxiety disorder is approved, the participants recommended the Program consider enhancements to the data collection practices in place to further understand if medical cannabis is successful at offering relief and improving lives. The participants suggested:

- Incorporate a recognized scale to assess symptoms over time. The scale would be sufficient for publication in a peer-reviewed journal.
- Past and current medical, psychiatric, and family histories, including past medications and therapy.
- Current living situation, including support systems, and other social determinants of health.
- Illicit drug use screening, including past marijuana usage, other drug(s) and frequency.
- Changes in symptoms and therapy over time.
- Cross-reference patient functional outcomes information with other available data sources (e.g., PMP, Unemployment data, Worker's Comp, Health records, etc.).

Data should be collected under informed consent and at the following time points:

- Initial referral
- First refill
- Six (6) months
- Annually while enrolled

If anxiety disorder is not approved, the participants suggested expanding the current data collection practices to identify functional outcomes improvements in the cases where anxiety is a known secondary condition, such as the PTSD co-hort. These data points may provide important insights in lieu of evidence-based research. The participants recommended:

- If the patient shares they've experienced anxiety, ask probing questions regarding medications, therapy, and the patient's ability to function (work, school, etc.).
- Understand the patient's alcohol or other drug use consumption.
- Understand the patient's use of the healthcare system, including any recent hospitalizations.
- Implement a comprehensive screening tool for all patients to capture primary and secondary anxiety conditions.
- Review data available throughout the various state systems to identify if medical cannabis has improved the daily function of patients.

7. Summary

The participants were requested to maintain an open mind throughout the sessions. Two participants openly shared their beliefs about cannabis for anxiety disorder evolved during the sessions. All the participants found the experience to be useful and appreciated the opportunity to learn from each other.

In summary, three providers recommended approving medical cannabis for anxiety disorder with limitations and one recommended without restrictions. Most of the participants believe medical cannabis may offer a harm-reduction approach by either reducing use of benzodiazepines and/or reducing the use of illicit substances to manage anxiety symptoms, especially among high-risk populations. All participants recognize the risk of benzodiazepines and desire safer alternatives. In addition, all participants expressed concern over protecting young adults from the damaging effects of THC on the developing brain and the potential for causing psychosis, which could be damaging among those with an underlying undiagnosed mental disorder such as schizophrenia.

8. Insights for Consideration

The work group generated deep and thoughtful discussions regarding anxiety disorder, focusing on patient care, the impacts of cannabis use in society and substance use disorder as well as the potential for expanding research and influencing future policy.

a. Patient Care

50.1%

of adults with mental illness in Minnesota receive any form of treatment from either public or private providers (2017-2019)

Medications used for anxiety disorders, such as SSRIs and benzodiazepines, are intended to provide temporary relief to symptoms; they are not curative. The ideal treatment is therapy; however, this is not readily available to all patients and some patients may not be amenable to therapy. In Minnesota, only 50.1% of adults with mental illness receive any form of treatment (National Institutes of Health: Substance Abuse and Mental Health Services Administration, 2020). Members of the work group shared their patient population experiences, noting lower income and BIPOC communities often do not have consistent access to proper mental health care and often lack good, accurate information.

Providers expressed interest in reducing the overall use of benzodiazepines because they can be addictive and fatal if overdosed.

b. Cannabis Use and Substance Use Disorder

Most of the providers encountered patients who have used illicit marijuana to manage their symptoms. They noted some patients develop psychosis due to overuse of marijuana and high THC levels in illicit products. As a result, these experiences may promote negative general perceptions about medical cannabis.

4.6%

Marijuana use disorder rate of 18
– 25-year-olds in Minnesota
(2017-2019)

Some of the providers expressed concern approving medical cannabis for anxiety disorder may give the impression illicit marijuana is safe for managing symptoms. Approximately 40.7% of young adults in Minnesota used marijuana in the past year, as published in the Federal Substance Abuse and Mental Health Services Administration 2019 Barometer report. This reported also noted the marijuana disorder rate among the same population was 4.6% and was relatively unchanged from the prior reporting period (2002 – 2004) and is lower than the national average of 5.6% (National Institutes of Health: Substance Abuse and Mental Health Services Administration, 2020).

Harm reduction and person-centered care are a focus among substance use disorder professionals and community-based care providers. In the area of substance use

disorder, interest exists to understand if the use of medical cannabis reduces or eliminates long-term use of other harmful substances, such as opioids, heroin and other street drugs some patients may use to manage their symptoms.

c. Research and Policy

5

Active trials studying anxiety disorder and cannabis or cannabidiol in the US

Current research on anxiety disorder and cannabis is very limited due to the FDA’s classification as a Schedule 1 drug. The ability to advance research at the Federal level at the rate necessary to answer critical questions is difficult. A search of clinicaltrials.gov revealed only 5 active trials are underway in the US studying cannabis or cannabidiol and anxiety disorder.

However, collecting functional outcomes data from patients presently enrolled in the Program may be an important strategy to demonstrate cannabis effectiveness, especially conditions where anxiety is known to be experienced, such as PTSD. Provider experience may also provide important observational data points to gain insights.

In addition, the work group discussion illuminated a potential opportunity to conduct collaborative research with an academic institution. This approach may offer the Program the opportunity to collect data prospectively, using recognized tools and instruments, and publish findings in a peer-reviewed journal. The Program may need to seek legislative authorization to perform such research on existing patients enrolled in the program.

d. Professional Association Opinions

Professional associations representing areas of practice which may be directly impacted by a medical cannabis are noted below. All have legislative initiatives, including active “day-on-the-hill” events. However, only three have posted public position statements regarding medical cannabis.

Minnesota Medical Association (MMA) - Published 2020

Until the FDA approved medical cannabis for clinical use and is no longer classified as a schedule I drug by the Drug Enforcement Agency (DEA), the MMA cannot support the use of medical cannabis outside of a clinical trial.

www.mnmed.org/MMA/media/Hidden-Documents/policycompendium.pdf

Minnesota Psychiatric Society (MPS) – Published 2019

MPS believes scientific findings should be the basis for developing policy decisions regarding marijuana. The organization’s position paper focuses primarily on the generalized use of marijuana by young adults, citing negative

impacts such as lowered academic achievement, arrests, and engaging in high risk behaviors. The paper also cites an increased risk of psychotic disorder development, depression and anxiety as well as long term intellectual and emotional impacts. ([mps 2019 position statement - marijuana 3-7-19 1 .pdf \(mnpsychsoc.org\)](#))

American Academy of Family Physicians (AAFP) – Published 2019

AAFP believes family physicians play a key role in addressing marijuana, cannabinoid, and cannabis use; reducing barriers to research; and advocating for appropriate policy to protect the health of patients and the public. AAFP believes family physicians should partner with public health and policy professionals to advance evidence-based approaches which address both medical and recreational use. ([www.aafp.org/about/policies/all/marijuana-position-paper.html](#))

Association for Addiction Professionals (NAADAC) – Publication date unknown

NAADAC does not currently support the use of cannabis as medicine or for recreational purposes. The organization encourages research to be performed at the same rigor as medications to allow evidence-based and scientifically supported policy changes to occur. ([NAADAC Position Statement on the Medical and Recreational Use of Cannabis](#))

Position statements were not published by:

National Alliance for Mental Illness (NAMI)

Mental Health Minnesota

Minnesota Psychological Association (MPA)

e. Anticipated Responses

Since 2016, anxiety disorder has been petitioned primarily by the general public and cannabis advocates for inclusion as a qualifying condition. The patient voice, expressed in written comments and formal testimony, has consistently supported the addition of anxiety disorder as a qualifying condition. It is anticipated a high level of public interest will remain for the immediate term, primarily by patients and advocates for whom current standard of care is either not accessible and/or tolerated.

Physicians, psychologists and therapists are most likely to voice opposition to the inclusion of anxiety disorder. Psychiatrists, in particular, are likely to encounter patients who have experienced serious psychotic episodes from marijuana over-use and/or elevated THC levels, and may voice the most concern. Substance use disorder specialists may also have concerns over introducing a potentially addictive substance, however, professionals and clinicians practicing a harm-reduction approach may accept medical cannabis as an alternative to high-risk street drugs. Concerns will continue over the ongoing normalization of illicit marijuana usage, which is not unique to anxiety disorder but is an over-arching societal issue.

In all four states where anxiety disorder has been approved as a qualifying condition, the representatives shared in the interviews that little to no negative public reactions were experienced following approval.

f. Program Authority

Medical conditions which qualify a person to enroll in the medical cannabis program may be added by the legislature or by the commissioner. The commissioner's authorization to add, modify or remove a medical condition is found in Minnesota Statutes §152.27, subd. 2(b). A qualifying medical condition is defined as a diagnosis of a medical condition that has been identified as one that will qualify a patient to enroll in the medical cannabis program (see Minnesota Statutes §152.22, subd. 14.) To add an additional qualifying medical condition, the commissioner must evaluate if petitions received determine whether addition, modification, or removal is warranted based on evidence and research. The commissioner must then notify the chairs and ranking minority members of the legislative committees with jurisdiction over health and human services of the determination. The notification must be given by January 15 of the year the commissioner wishes to make the change. The change becomes effective August 1 of that year unless the legislature provides otherwise by law.

The Program is responsible to publishing annually recommended medical cannabis formulations and dosages for each qualifying medical condition (see Minnesota Statutes §152.25, subd. 2). Guidance documents for health care practitioners certifying [intractable pain](#) and [obstructive sleep apnea](#) diagnoses have been issued.

Conclusions

1. Potential Pathways for Consideration

The Program has three options for consideration: maintain status quo and deny future petitions until clinical evidence is available, approve a limited set of sub-conditions which are at greatest risk for debilitating illness and have the highest potential to be prescribed benzodiazepines, or approve anxiety disorder as a whole. Each option has its own respective set of benefits and risks. The table below summarizes three potential options.

Table 4. Options for Consideration

Maintain Status Quo

Benefits:

- More time for evidence to demonstrate effectiveness
- Protect young people from THC exposure
- Less signaling to society illicit marijuana is safe
- The status quo is understood and familiar

Risks:

- No opportunity for research to capture real-world data
- Loss of harm reduction potential through decreased use of benzodiazepines and/or illicit drugs
- Ignores the reality of illicit use by persons who suffer from trauma
- Persons may not seek or participate in therapy if they continue to use illicit marijuana to manage their symptoms
- Additional benzodiazepine overdoses and fatalities
- Suicides may occur due to SSRI non-response and lack of access to therapy

Approve a Limited Set of Sub-conditions

Benefits:

- Slow approach to including anxiety disorder which allows time to understand effectiveness before expanding to a broader set of sub-conditions, if at all
- Relieve symptoms for patients who are refractory to SSRIs
- Reduce benzodiazepine usage in the state
- Medical cannabis may lend itself to a patient-centered care approach because it can serve as an alternative to medications which may have undesirable side effects or other risks a patient may not be willing to take.
- Medical cannabis may create the opportunity for therapeutic engagement by building trust between the patient and the provider, especially among individuals who use illicit marijuana or other street drugs to manage symptoms

Approve a Limited Set of Sub-conditions

Risks:

- Medical cannabis may be used as a “quick fix” and patients may not avail themselves to therapy
- Further reinforces the wrong message illicit marijuana is safe and equivalent to medical cannabis
- Potential for addiction
- In young adults, cannabis may alter brain development by binding to endocannabinoid receptor; it may induce psychosis and unmask schizophrenia
- Providers may rush to a diagnosis and prescribe medical cannabis, without ensuring all standard treatments have been attempted

Approve for All Sub-conditions

Benefits:

- Same benefits as noted for a limited set of sub-conditions
- Patients with an unspecified anxiety disorder can receive treatment

Risks:

- Same risks as noted for a limited set of sub-conditions

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Addendum

1. Research Matrix

Below is a list of summarized published research in the field of cannabis and anxiety disorder.

Reference	Year	Study Type	Participants	Dose	Results
Zuardi et al.	1993	Randomized control trial (RCT); Double-blind design and placebo-controlled	Four groups of 10 participants	CBD (300 mg), diazepam (10 mg), ipsapirone (5 mg), or placebo.	CBD decreased anxiety after the simulated public speaking test (evaluated through the visual analog mood scale and state trait anxiety inventory) and was as effective as other pharmacological agents. Only diazepam was sedative.
Fusar-Poli et al.	2009	RCT; Double-blind and placebo-controlled	n=15 healthy, right-handed males	10mg THC, 600mg CBD or placebo	There was a trend for a reduction in anxiety after administration of CBD, while THC increased anxiety. CBD attenuated the blood oxygenation level-dependent signal in the amygdala and the anterior and posterior cingulate cortex, while subjects were processing intensely fearful faces, and its suppression of the amygdala and anterior cingulate responses was correlated with the concurrent reduction in skin conductance response fluctuations.
Bhattacharyya et al.	2010	RCT; Placebo-controlled, double-blind, and crossover	Fifteen healthy males for the fMRI study. Six for the behavioral study (3F,3M)	THC 10 mg, CBD 600 mg, or placebo	Pre-treatment with CBD marginally reduced the anxiolytic effects induced by THC, and these were associated with changes in amygdalar activation (increased amygdalar activation induced by THC was attenuated with CBD administration; amygdala activation is associated with emotional processing including anxiety). Other brain regions showed similar opposing effects with THC vs. CBD administration. Psychotic symptoms that were elevated with THC were attenuated with pre-treatment with CBD.
Bergamaschi et al.	2011	RCT; Double-blind	Healthy volunteers (n=12) and 24 patients with generalized social anxiety disorder (SAD)	CBD 600mg	Pretreatment with CBD in patients with social anxiety disorder (SAD) significantly reduced anxiety, cognitive impairment and discomfort in their speech performance - down to levels comparable to healthy controls.
Zuardi et al.	2017	RCT; Parallel-group, double-blind, and placebo controlled	Health volunteers (n=60)	Placebo, clonazepam (1 mg), and CBD (100, 300, and 900 mg)	Subjective anxiety measures in volunteers were reduced with CBD 300 mg, but not with CBD 100 and 900 mg, in the post speech phase after a test of public speaking in a real situation.

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Reference	Year	Study Type	Participants	Dose	Results
Childs et al.	2017	RCT; Double-blind and placebo-controlled, and crossover	Healthy volunteers with some history of cannabis use (non-daily cannabis use; n=42).	7.5 mg THC, 12.5 mg THC, or placebo.	During pre-test treatment assessment, the high THC group reported higher levels of anxiety than the low THC and placebo groups. During the post-test assessment, higher levels of THC (12.5 mg) lead to greater subjective reporting of stress on a non-stressful test and a stress test (Trier Social Stress Test) compared to placebo. In contrast, low dose of THC (7.5 mg) lead to similar levels of reported stress compared to placebo, indicating that low doses may attenuate stress.
Jadoon et al.	2017	RCT; Placebo controlled, double-blind, and crossover	Nine healthy males	CBD 600mg or placebo	CBD lowered BP (especially before and after stress), increased HR, decreased stroke volume, and caused a blunted forearm skin blood flow response to isometric exercise. In response to cold stress, subjects who had taken CBD had blunted BP and increased HR, with lower total peripheral resistance.
Bhattacharyya et al.	2018	RCT; Parallel-group, double-blind, and placebo controlled	Thirty-three medication-naive participants at CHR-P (clinical high risk for psychosis) and 19 healthy controls.	CBD 600mg	Participants receiving placebo had reduced activation relative to controls in the right caudate during encoding and in the para hippocampal gyrus and midbrain. Within these three regions, activation in the CBD group was greater than in the placebo group but lower than in the control group.
Masataka	2019	RCT; Placebo-controlled, parallel group, double-blind	Teenagers with social anxiety disorder (SAD) and avoidant personality disorder (n=37)	300mg CBD or placebo	In 4 weeks, the CBD group showed improvement on two separate social anxiety measures compared to the placebo group.
Linares et al.	2019	RCT; Double-blind and parallel group	Healthy male subjects (n=57)	CBD 150, 300, and 600mg or placebo	CBD significantly decreased anxiety at the moderate dose (300 mg) compared to placebo, as measured on a visual analogue mood scale (VAMS). Low (150 mg) and high (600 mg) doses of CBD were no different than placebo on the VAMS, suggesting anxiolytic effects of CBD may be achieved at moderate doses.
Hurd et al.	2019	RCT; Double-blind and placebo-controlled	Drug-abstinent individuals with heroin use disorder	CBD 400 or 800 mg, once daily for 3 consecutive days	Both doses of CBD significantly reduced both craving and anxiety induced by the presentation of salient drug cues, which persisted 7 days after the final CBD exposure. CBD reduced the drug cue-induced changes in HR and salivary cortisol levels.
Sultan et al.	2020	RCT; Placebo-controlled and double-blind	Healthy males (n = 13 per group)	CBD 600mg or placebo orally for 1 week	In response to stress, volunteers who had taken CBD had lower systolic BP after acute and repeated dosing.

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Reference	Year	Study Type	Participants	Dose	Results
Appiah-Kusi et al.	2020	RCT; Placebo-controlled and double-blind	CHR-P (clinical high risk for psychosis) patients (n=32) and healthy controls (n=26) patients	CBD 600mg or placebo for 1 week	The change in cortisol associated with experimental stress exposure was greatest in HCs and least in CHR-P patients, with CHR-CBD patients exhibiting an intermediate response. Changes in anxiety and experience of public speaking stress were greatest in the CHR-P and least in the HC, with CHR-CBD participants demonstrating an intermediate level of change.
de Faria et al.	2020	RCT; Double-blinded, placebo-controlled, and crossover	Parkinson's disease patients (n=24)	CBD 300mg or a placebo	Acute CBD administration decreased anxiety in patients with Parkinson's disease, and there was also decreased tremor amplitude in an anxiogenic situation.
Fabre & McLendon	1981	RCT; Placebo-controlled and double-blind. Parallel design.	Patients with "psychoneurotic anxiety" (Study 1: n = 5; Study 2: n = 20).	Nabilone (synthetic cannabinoid mimicking THC) or placebo. Study 1 was conducted to assess appropriate dosage of nabilone to have anxiolytic effects (to inform Study 2 dosage design), with patients ranging from 2 mg-8 mg/day (mean dosage at end of study was 2.8 mg/day). Study 2 had a fixed dose of 1 mg nabilone/3x day.	Compared to placebo, nabilone significantly reduced anxiety as measured on the Hamilton Anxiety Scale (study 2).
Shannon & Opila-Lehman	2016	Case report	10-year-old girl with PTSD secondary to sexual abuse	CBD (25 mg) at bedtime, and 6–12mg of CBD sublingual spray during the day as needed for anxiety	A gradual increase in sleep quality and quantity and a decrease in her anxiety were noted. After 5 months, the patient was sleeping in their own room the majority of nights and handling the new school year with little difficulty.
Shannon et al.	2019	Case series	Adults (n=72) with concerns of anxiety (n = 47) or poor sleep (n = 25)	25-175mg in the morning (anxiety) or evening (sleep)	Anxiety and sleep improved for most patients, and these improvements were sustained over time.
Elms et al.	2019	Case series	Adult patients (n=11) with DSM-5-diagnosed PTSD	Mean starting dose 33mg and the mean total dose at the 8-week follow-up was 49mg (range: 2–100)	Ten of 11 patients experienced a decrease in PTSD symptom severity. Four patients continued CBD for 36 weeks or more. They had an initial mean PCL-5 score of 57.75 with a mean score at 36 weeks of 29.25. CBD also offered relief in a subset of patients who reported frequent nightmares.

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Reference	Year	Study Type	Participants	Dose	Results
Barchel et al.	2019	Observational prospective study.	Children with autism spectrum disorder (n=53; median age 11)	CBD oil dosage dependent on ASD patient. Recommended daily dose of CBD was 16 mg/kg (maximal daily dose 600 mg).	Of the 17 patients where there were anxiety reports, 47.1% of them experienced improvements in anxiety, while it worsened in 23.5% of patients.
Lackovics et al.	2020	Case report	Teenager with multiple substance use disorder, severe depression, social phobia, and narcissistic personality	CBD with an initial dosage of 50mg twice daily, gradually to 300mg twice daily	By their request, the patient discontinued sertraline after 3 weeks of CBD treatment. There were no side effects regarding HR, BP, and weight. The patient improved regarding depressive as well as anxiety symptoms, including simple phobias and symptoms of paranoia and dissociation.
Klier et al	2020	Case report	14-year-old patient with Crohn's disease with social phobia	CBD with an initial dosage of 100mg per day, gradually to 600mg per day for 19 weeks	CBD reduced the Clinical Global Impression Severity Scale from 5 to 3, and reduced the severity of symptoms of needle phobia, fear of medical intervention, and social phobia.
Gulbransen et al.	2020	Audit	Patients (n=253) presenting to Cannabis Care, New Zealand	CBD oil	Four hundred patients were assessed for CBD and 397 received a prescription. Follow-up was completed on 253 patients. Patients with non-cancer pain and mental health symptoms achieved improvements to patient-reported pain, depression and anxiety symptoms.
Hines et al.	2020	Observational birth cohort study.	Birth cohort with mean age 24 years of age (n=1087)	Cannabinoid composition unknown, with study questionnaire specifically asking about THC concentrations.	Mean age of onset of cannabis use was 16.7 years of age, with 13% of the cohort reporting high-potency cannabis use. There was a correlation between high-potency cannabis use (typically ≥10% THC, skunk, or other high potency herbal cannabis) and increased cannabis usage frequency, cannabis problems (addiction), and increased likelihood of an anxiety disorder.
Bonn-Miller et al.	2014	Cross-sectional observational study.	Adults (n = 217) who were patients at a cannabis dispensaries receiving medical cannabis in California.	Types of cannabis used not collected.	Approximately 60% of participants indicated using medical cannabis for anxiety, yet less than half (20%) reported a reduction in anxiety symptoms as a primary benefit for using medical cannabis. Social anxiety motives (e.g., "to make you feel more confident") were associated with cannabis use problems as well as perceived helpfulness of cannabis.

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Reference	Year	Study Type	Participants	Dose	Results
Bechtold et al.	2015	Longitudinal observational study	Age cohort followed from adolescence to mid-20s on cannabis use patterns and then again in the mid-30s assessing for health outcomes including anxiety (n=386).	Types of cannabis used not collected.	Results showed that early-onset chronic users, late increasing users, adolescence-limited users, and low/nonusers did not differ in the lifetime diagnosis of an anxiety disorder. In addition, results did not differ by race (black vs. white).
Gage et al.	2015	Longitudinal observational study	Birth cohort (n=1512). Cannabis use measured at 16; anxiety self-report measure at 18.	Types of cannabis used not collected.	Results showed no relationship between cannabis use at age 16 and the development of an anxiety disorder at age 18.
National Academies of Sciences, Engineering, and Medicine.	2017	An evidence-based consensus authored by a committee of experts on the health effects of cannabis and cannabinoids. This was funded by the CDC Foundation, Centers for Disease Control and Prevention, National Institutes of Health/National Cancer Institute, National Institutes of Health/National Institute on Drug Abuse, U.S. Food and Drug Administration, various US state public health departments - among others.	Comprehensive review of the current state of research on health effects of cannabis and cannabinoids, including a review of its effects on anxiety. This 487-page report is an update to the Institute of Medicine's (1999) report on the health effects of cannabis and cannabinoids.		Conclusion 4-17: "There is limited evidence that cannabidiol is an effective treatment for the improvement of anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders." Conclusion 12-8(a): "There is limited evidence of a statistical association between cannabis use and the development of any type of anxiety disorder, except social anxiety disorder." Conclusion 12-8(b): "There is moderate evidence of a statistical association between regular cannabis use and increased incidence of social anxiety disorder." Conclusion 12-9: "There is limited evidence of a statistical association between near daily cannabis use and increased symptoms of anxiety."

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Reference	Year	Study Type	Participants	Dose	Results
Botsford et al.	2020	Review paper	15 research papers on anxiety included in the review.		A literature search was conducted for papers between 1990-2018 investigating the relationship between cannabis use and the onset, progression and/or treatment of anxiety disorders. Experimental papers were included, as well as cohort studies (cross-sectional studies were excluded due to lower quality of study design). Of 12 cohort studies identified that examined the relationship between cannabis use and the onset of an anxiety disorder/symptoms, 9 of them did not find a relationship between cannabis use and the development of a future anxiety disorder. The remaining 3 cohort studies showed an increased likelihood of developing an anxiety disorder or anxiety symptoms with cannabis use. Of 2 cohort studies that examined the progression of an anxiety disorder with cannabis use (e.g., remission rates, course of treatment, etc.), one study found that cannabis use did not significantly affect remission rates compared to non-users (remission rates were not different between those groups). The other study found that cannabis use or cannabis use disorder did not differentially affect outcomes in treatment (medication, cognitive behavioral therapy) compared to non-users. Authors also discussed one experimental research paper (Bergamaschi et al, 2011) which is discussed further up in this review (see results above in the context of other experimental/RCT papers discussed in the matrix). Limitations identified in the review are the varied anxiety patient groups being examined (lack of standardization in target anxiety disorder studied). In addition, large cohort studies introduce different variables to statistically control for which further highlights greater need of standardization across studies overall.
Van Amerigen et al.	2019	Review paper	Various papers.		Authors summarize that preclinical studies appear to show some evidence that there is an interplay between the endocannabinoid system and emotional regulation centers of the brain (including anxiety), and that people self-report anxiolytic effects of cannabis. However, clinical evidence on humans is mixed.
Turna et al.	2017	Review paper	Various papers.		Authors discuss that in spite of anxiety being a very commonly reported mental health condition in North America and that anxiolytic effects of cannabis are self-reported in healthy populations, the literature is lacking on systematically studying the effects of cannabis on clinical populations.

2. State Details

State representatives were interviewed and were asked the following general questions to understand the process used to either accept or deny a petition to include anxiety disorder in the list of qualifying conditions:

- What was the process used to include anxiety in the list of recognized conditions?
- If anxiety was petitioned, what were the critical factors which made for a successful petition?
- Were there any opposition to the inclusion of anxiety? If so, what were the concerns?
- Does your state have a definition for anxiety? Are there any safety restrictions?
- Are any sub-conditions specified? Are there restrictions or exclusions for any sub-condition?
- How many patients in your medical cannabis program have anxiety as a primary diagnosis?
- What has been the experience of patients with anxiety after enrolling in your program?
- Have any adverse events or side effects been reported? If so, what are they?
- What has been the reaction of the public to the inclusion of anxiety to your state's medical cannabis program?
- If anxiety disorder was denied, what were the factors which resulted in this outcome?

Representatives from the states which have approved anxiety disorder – Nevada, New Jersey, North Dakota and Pennsylvania – generously shared information about their programs. These details included information on their total enrollment, the portion which comprises anxiety disorder and other relevant insights which may be useful to the Program. The information below is a summary of those findings. The numbers were accurate as of March 17, 2021.

a. Nevada

- Number of patients in the program: 13,210
- Number (%) of patients with anxiety disorder as a primary diagnosis: 2, 913 (22%)
- Anxiety disorder as a percent of the total conditions: 14%
- Other important insights:
 - Established the Cannabis Compliance Board in 2019 to tighten the regulations. Following the gaming regulations model.
 - PTSD approved first. In 2019, legislation changed to broaden condition to include anxiety as well as PTSD.
 - When recreational use became effective in 2017, the medical program has experienced an overall reduction of approximately 54% among active card holders (28,308 in May 2017 to 13,210 in July 2020). However, some card holders returned to the program because of the product availability and cost savings.

b. New Jersey

- Number of patients in the program: 104,253
- Number (%) of patients with anxiety disorder as a primary diagnosis: not available
- Anxiety disorder as a percent of the total conditions: 24% at the end of year 1
- Other important insights:
 - The autism community played a significant role in the inclusion of anxiety disorder due to it manifesting as an underlying condition.
 - Some members of the substance use community view medical cannabis as a potential option for addressing secondary anxiety disorder in order to introduce psychotherapy.
 - The legislature is adding more conditions through a reform, thereby ending the petition process.
 - Cases of psychosis development among patients with a severe mental health disorder have been reported. In these situations, the office collaborated with the patient's prescriber to remove them from the program.

c. North Dakota

- Number of patients in the program: 3,752
- Number (%) of patients with anxiety disorder as a primary diagnosis: 1502 (40%)
- Anxiety disorder as a percent of the total conditions: 25%
- Other important insights:
 - Set a cap at 6% THC for anyone under 18 years of age

d. Pennsylvania

- Number of patients in the program: ~150,000
- Number (%) of patients with anxiety disorder as a primary diagnosis: unknown
- Anxiety disorder as a percent of the total conditions: 15%
- Other important insights:
 - The Secretary of Health was proactive and engaged the medical community across the state. She positioned medical marijuana as a "tool in the toolbox"
 - The Secretary provided professional recommendations through a press release. These recommendations include medical marijuana is not a

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first line treatment, it is for short term use, low THC/high CBD products are preferred, not recommended for children and adolescents, and pregnant women should not use medical marijuana

- Research level data would be collected through an agreement with a Pennsylvania public university

3. Work Group Participants

Below are the bio sketches of the individuals who participated in the work group sessions, including staff and others who served as speakers.

Jon Ebbert, MD - Mayo Clinic

The research of Jon O. Ebbert, M.D., focuses on the promotion of a healthy lifestyle through the treatment of substance use and abuse. Dr. Ebbert is particularly interested in the assessment and treatment of tobacco dependence and the development of novel therapeutic and pharmacological approaches to treat tobacco dependence.

Focus areas:

- Pharmacotherapy for the treatment of tobacco dependence
- Combination pharmacotherapy for the treatment of tobacco dependence
- Electronic nicotine delivery systems (ENDS)

Significance to patient care:

Dr. Ebbert's work has the potential to significantly improve the health and well-being of patients who are dependent on tobacco.

Kathleen Heaney, MD - Hennepin Health

Dr. Heaney is a psychiatrist certified in addiction and consultation-liaison psychiatry. She completed her addiction psychiatry fellowship at Mayo Clinic in Rochester.

She is a distinguished fellow of American Psychiatric Association and member of the American Academy of Addiction Psychiatry and The Academy of

Consultation- Liaison Psychiatry. She practices at Hennepin County Medical Center as well as M Health Fairview.

Wendy Jones - Minnesota Recovery Connection

Wendy Jones is a person in long-term recovery from substance use disorder. She joined Minnesota Recovery Connection (MRC) as its executive director in 2018 after a long career with the Minnesota Historical Society, where she was Director of Education. Led and governed by members of the recovery community, MRC is a grassroots nonprofit that provides peer-to-peer support services, public education, and advocacy in support of its mission to strengthen the recovery community. Wendy is a passionate advocate for breaking the stigma that surrounds addiction and is a former Humphrey Policy Fellow and a James P. Shannon Leadership Institute alumna. She is currently completing a Masters of Public Affairs from the Humphrey School of Public Affairs.

Jacob Mirman, MD, DHT, CCH, MHom - Life Medical

Dr. Mirman is a partner in Life Medical, PA, and integrative primary care clinic in St. Louis Park, MN. He is a specialist in internal medicine and homeopathy, as well as some other integrative medicine modalities. He graduated from the University of Minnesota Medical School and completed his residency in Internal Medicine at Illinois Masonic Medical Center in Chicago, Illinois. Dr. Mirman has extensive training and expertise in homeopathy. Over the years he investigated and studied numerous integrative modalities in addition to homeopathy, such as Naturopathic Medicine, Low Level Laser Therapy, NeuroResearch Protocol, Bach flower essences, Medical Cannabis, and others. Some of the therapies he found to be most effective have been incorporated in Life Medical. He also advises his patients on some of the others and gives referrals to the appropriate specialists when necessary.

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He has been certifying patients and providing regular follow-up for Minnesota Medical Cannabis Program since 2015. In 2021 he started a Cannabis Results page on Life Medical website:
<https://www.lifemedical.us/service/cannabis-results/>

Cuong Q. Pham, MD - University of Minnesota

Dr. Pham is a physician and assistant professor in the Department of Medicine and Pediatrics at the University of Minnesota Medical School. He works clinically as a hospitalist at the University of Minnesota Medical Center and as a primary care physician at the Community University Health Care Center (CUHCC). His work on academic medical education in health equity as well as with the underserved communities in the Twin Cities has led him to focus on Community-Based Participatory Research. His current research is in collaboration with the local urban American Indian community to develop a culturally-centered and family-centered approach to opioid use disorder treatment in primary care settings.

Cedric Weatherspoon, LMFT - Empower Therapeutic Support Services, PLLC

Cedric Weatherspoon is a Licensed Marriage and Family Therapist who provides mental health support to individuals, families, and couples who are experiencing life challenges related to generational and complex trauma. Cedric Weatherspoon has over a decade of experience supporting community members who live in residential community mental health homes.

Mr. Weatherspoon uses over 20 years of experience and extensive knowledge to partner with community organizations to develop innovative strategies to engage families. Implementing client-centered practices in their work with African American children and families navigating wellness.

Mr. Weatherspoon believes when community providers and community members form a working partnership based on creating access to quality healthcare and healthcare education, we can address stigmas and disparities in healthcare.

Alik Widge, MD - University of Minnesota

Dr. Widge is a psychiatrist and biomedical engineer. Clinically, he provides brain stimulation treatments for mood, anxiety, and substance disorders. These include deep brain stimulation, cortical stimulation, and transcranial magnetic stimulation. His research focuses on developing these treatments further, particularly the creation of new "closed loop" devices. These devices sense brain signals in real-time and deliver energy in a planned and rational fashion, compensating for each patient's specific brain network abnormalities. Dr. Widge's laboratory prototypes new stimulation paradigms and targets in rodent models, conducts clinical trials of these new technologies, and searches for biomarkers of illness and recovery to guide next-generation therapies. He is a nationally recognized expert in the management of difficult-to-treat mood and anxiety disorders.

Minnesota Department of Health Staff

Nick Lehnertz, MD

Dr. Nick Lehnertz is a Medical Specialist at MDH in the Division of Infectious Disease Epidemiology, Prevention and Control. He is a physician and epidemiologist with 15 years of experience working both domestically and internationally in the areas of preventive medicine and public health. He graduated from University of Minnesota Medical School, did his residency at University of Vermont and Johns Hopkins Medical Institutions, and his public health training at Johns Hopkins School of Public Health.

Deepa McGriff

Deepa McGriff is a Research Scientist at the Office of Medical Cannabis within the Minnesota Department of Health. She manages the survey process for program patients and certifying health care practitioners and contributes to research on the impact of the medical cannabis program. Her background includes

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clinical and population-based research. She received her Bachelor of Biomedical Engineering degree and Masters of Public Health degree in Epidemiology from the University of Minnesota.

Susan Park, PhD

Susan Park is a Research Scientist with the Minnesota Department of Health's Office of Medical Cannabis. She has been with the OMC for 5 years, primarily looking at data submitted through the Patient Self-Evaluations. She received her Ph.D. in the Cognitive & Brain Science program from the University of Minnesota's Department of Psychology.

David Rak

David Rak is the Research Manager in the Office of Medical Cannabis within the Minnesota Department of Health. With his team of two Research Scientists, he develops, manages, analyzes, and reports on all data collected from patients in the Medical Cannabis Program, and is the liaison with researchers from other sectors interested in using Medical Cannabis Program data. He received his Bachelor's degree in Journalism, and his Masters of Public Health degree with a concentration in Maternal & Child Health and Epidemiology from the University of Minnesota. He works remotely from his home office in Grand Marais on the North Shore.

Darin Teske

Darin Teske joined the Office of Medical Cannabis in August 2014. As the Legal and Policy Advisor for the medical cannabis program, his roles include communicating legal and program requirements to a variety of audiences in many different forums, helping develop policies, writing program administrative rules, and working with the day-to-day operations of the program. His background in the public sector includes labor market information, low-income energy assistance, and public utility regulation. He received a juris doctorate from William Mitchell College of Law and a master of law degree from Vermont College of Law; he also holds a master's degree in political science from Washington University in St. Louis, and a B.S.Ed. from Minot (ND) State University.

Chris Tholkes

Chris Tholkes brings over 25 years of experience working in the public, nonprofit, and philanthropic sectors. She is currently the Director for the Office of Medical Cannabis at the Minnesota Department of Health. Previously, she served as Assistant Division Director for the Office of Statewide Health Improvement Initiatives, which includes the

Statewide Health Improvement Partnership (SHIP), Tobacco Use Prevention Grants and Tribal Grants. Additional experience includes serving as a Program Officer for Otto Bremer Foundation, a staff lobbyist and Senior Policy Manager for ClearWay Minnesota, and as Director of Tobacco Control for the American Lung Association of Minnesota.

She holds a bachelors in community health education from Minnesota State Moorhead and a masters' in public administration from Hamline University.

Manufacturers

Stephen Dahmer, MD - Vireo

Dr. Stephen M. Dahmer is a board-certified family physician whose passion for health and healing has taken him around the globe. Since 2015, Dr. Dahmer has served as Chief Medical Officer of Vireo Health. He oversees clinical research affiliations, including a partnership with Montefiore Medical Center, implementing a National Institute of Health R01 \$3.8MM research grant for the first, long-term study of medical cannabis' impact on opioid use in adults with chronic pain. Dr. Dahmer is Assistant Clinical

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Professor of Family Medicine and Community Health at the Icahn School of Medicine at Mount Sinai and continues to practice Integrative Family Medicine in Scarsdale, New York.

Saurin Patel, MD - Leafline Labs

Dr. Patel trained at the University of Kansas Hospital in a combined Internal Medicine/Pediatric residency and Pulmonary/Critical Fellowship. He received an MBA from Indiana University's Kelley School of Business. He has served as Vice President of Ambulatory and Population Health - which eventually culminated in his role as system Chief Medical Officer - for North Memorial Healthcare. Dr. Patel recently started his own company to support elderly patients between their clinic visits. He is passionate about improving public health by addressing social determinants. He aspires to open a clinic and provide free care to those in need. Dr. Patel is also a father of five and prioritizes spending quality time with his family, playing monopoly, biking, fishing and traveling.

Consultants

Mary Halet - More Insight

Mary Halet is a management consultant, bringing over 25 years of experience leading teams and organizations through growth and transformation. Mary has a BS in Biology from the University of Minnesota and a MNM in Nonprofit Management from Hamline University.

Jeff Smith - More Insight

Jeff Smith is a management consultant with over 20 years of experience in the consulting across multiple industries including, public sector, medical device, and healthcare. He has specific experience assisting multiple states establish medical cannabis programs as well as addressing the unique challenges associated to their ongoing operations. Jeff has a BA in Economics and Finance from the University of St. Thomas.

4. Work Group Meeting Agendas

Agenda for March 29, 2021

Time	Topic	Duration	Facilitator/ Speaker
4:30 – 4:45	Welcome and Introductions	15 minutes	Chris Tholkes
4:45 – 4:55	Petition Process and Anxiety Review	10 minutes	Darin Teske
4:55 – 5:15	Program Background and Statistics	20 minutes	Chris Tholkes
5:15 – 5:25	Manufacturer’s Experience	10 minutes	Drs. Saurin Patel & Stephen Dahmer
5:25 – 5:35	Experience of Other States	10 minutes	Jeff Smith
5:35 – 5:50	Current state of anxiety and cannabis research	15 minutes	David Rak & Susan Park
5:50 – 6:30	Discussion	40 minutes	Jeff Smith

Agenda for April 19, 2021

Time	Topic	Duration	Facilitator/Speaker
4:30 – 4:40	Welcome and Re-cap session 1	10 minutes	Chris Tholkes
4:40 – 4:55	Review criteria used by the Commissioner to approve a condition	15 minutes	Darin Teske
4:55 – 5:35	Facilitated Discussion by Sub-Condition	40 minutes	Jeff Smith
5:35 – 6:30	Reflect and Summarize	55 minutes	Jeff Smith

Agenda for April 26, 2021

Time	Topic	Duration	Facilitator/Speaker
5:00 – 5:10	Welcome and Re-cap session 2	10 minutes	Chris Tholkes
5:10 – 6:50	Discussion	100 minutes	Jeff Smith
6:50 – 7:00	Next Steps	10 minutes	Darin Teske

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5. Summary of Sub-Conditions

The table below summarizes the standard treatment and medications most often prescribed for individuals with an anxiety disorder sub-condition, as described by the participants. The participants also identified if medical cannabis has the potential to offer benefits as well as create risks for each of the sub-conditions.

Sub-Condition	Standard Treatment	Medications most often prescribed	Potential benefits medical cannabis might offer	Potential risks medical cannabis might create
Generalized anxiety disorder	<p>Medications to manage symptoms and therapy to address the triggers</p> <p>Patients will seek help when they're in crisis</p> <p>Therapy is best when it deals with the trauma straight on, however a supportive environment where all basic needs are met are essential for effective therapy. Often these needs are not met in disadvantaged and BIPOC communities</p>	<p>SSRIs and benzodiazepines</p> <p>SSRIs are tolerated well, however they do have side effects</p> <p>Benzodiazepines can be addictive and fatal if overdosed</p>	<p>Effective symptom control</p> <p>Medical cannabis is likely safer than benzodiazepines</p>	<p>Medical cannabis may be addictive</p> <p>Use of medical cannabis may interrupt therapy progression</p>
Social anxiety and Social phobia	<p>Primarily therapy, medications are rarely prescribed</p>	<p>SSRIs, however, medications are rarely prescribed</p>	<p>Most people are treated through therapy</p> <p>If symptoms are severe enough to require medication then medical cannabis may offer benefit</p>	<p>Social anxiety can be an early indicator for schizophrenia in younger patients, therefore using a product with THC may be harmful</p>
Panic disorder	<p>Medications to manage symptoms and therapy to address the triggers</p> <p>Patients will seek help when they're in crisis</p> <p>Therapy is best when it deals with the trauma straight on, however a supportive environment where all basic needs are met are essential for effective therapy. Often these needs are not met in</p>	<p>SSRIs, beta-blockers, and benzodiazepines</p> <p>SSRIs and beta-blockers are tolerated well, however they do have side effects</p> <p>Benzodiazepines can be addictive and fatal if overdosed</p>	<p>Medical cannabis can avoid the onset of a panic attack within seconds of use</p> <p>Medical cannabis is likely safer than benzodiazepines</p>	<p>Medical cannabis may be addictive</p> <p>Use of medical cannabis may interrupt therapy progression</p>

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Sub-Condition	Standard Treatment	Medications most often prescribed	Potential benefits medical cannabis might offer	Potential risks medical cannabis might create
	disadvantaged and BIPOC communities			
Specific phobias	Exposure therapy works very well and has a high compliance rate	None, because exposure therapy is effective	None	Medical cannabis may be addictive
Separation anxiety disorder	Medications to manage symptoms and psychotherapy to understand the attachment triggers Therapy to learn healthy nurturing and attachment	SSRIs and possibly benzodiazepines SSRIs are effective yet have known side effects Benzodiazepines can be addictive and potentially fatal if overdosed	Use of medical cannabis may effectively control symptoms Medical cannabis is likely safer than benzodiazepines	Medical cannabis may be addictive Use of medical cannabis may interrupt therapy progression
Agoraphobia	Medications to manage symptoms and therapy to address the triggers	SSRIs and benzodiazepines SSRIs are tolerated well, however they do have side effects Benzodiazepines can be addictive and fatal if overdosed	Use of medical cannabis may effectively control symptoms Medical cannabis is likely safer than benzodiazepines	Medical cannabis may be addictive Use of medical cannabis may interrupt therapy progression