DEPARTMENT OF HEALTH

Panic Disorder

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Introduction

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

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

Definition

Panic disorder (episodic paroxysmal anxiety) is defined as a disorder where an individual experiences recurrent, unexpected panic attacks along with persistent fear of having additional panic attacks (ICD 10 Data). Panic attack symptoms include a sense of impending doom, fear of losing control or of death, rapid heart rate, sweating, trembling or shaking, shortness of breath, chills or hot flashes, nausea, chest pain, dizziness or lightheadedness, numbness or tingling, or a feeling of unreality of detachment. Individuals with panic disorder may find that the greatest burden of this condition is the intense fear of having a panic attack (Mayo Clinic Panic Disorder: Symptoms and Causes). The Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-V) defines diagnostic criteria for panic disorder as A) recurrent panic attacks; B) At least one of the attacks having been followed by either one month or more of persistent concern or worry about additional panic attacks or their consequence or a significant maladaptive behavior

change due to panic attacks; and C) the disturbance is not attributable to substance use or another medical condition (American Family Physician).

Diagnosis

Panic disorder is diagnosed by first ruling out other conditions which may cause panic attack-like symptoms and subsequent psychological evaluation. Clinicians determine whether a patient is experiencing panic attacks through detailed interviews and the use of assessments such as the Panic Disorder Severity Scale (Furukawa 2009).

Complications and Consequences

Untreated panic disorder may pervasively impact quality of life, including development of specific phobias, avoidance of social situations, other psychiatric comorbidities like depression or other anxiety disorders, risk of suicide or suicidal thoughts, substance abuse and difficulty functioning at work or school. In general, an untreated anxiety disorder can result in depression, substance abuse, insomnia, digestive problems, headaches, and cardiovascular health issues (Mayo Clinic: Panic Disorder Symptoms and Causes).

Prevalence

A 2005 cross-sectional study found that the 12-month prevalence of panic disorder in the US adult population was 2.7%; it found lifetime prevalence to be 4.7% (Kessler 2005).

Current Therapies

Panic disorder can be treated with first line medical therapies of antidepressants including selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) or tricyclic antidepressants (TCAs). 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. Tri-cyclic antidepressants are associated with more severe side effects (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. Second-line therapies include benzodiazepines which are effective as quick-acting agents. They are generally not favored for long-term therapy because they are associated with more harmful side effects, similar to TCAs and are habit-forming which makes them contraindicated in patients with substance abuse history (Mayo Clinic: Panic Disorder Diagnosis Treatment). Medication therapy is often used in combination with psychotherapy, such as cognitive behavioral therapy (CBT). Combination therapy is not always indicated, based on the patient's medical history and symptoms, but CBT has shown improved outcomes in anxiety patients with medication-resistant symptoms (Campbell-Sills 2016).

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 healthcare 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).

Preclinical Studies

The endocannabinoid system, which includes the endogenous cannabinoids (endocannabinoids) as well as the cannabinoid receptors (CB1 and CB2) to which cannabinoids bind, is still a relatively new field of scientific inquiry. Several studies have examined various mechanisms of cannabinoid involvement in psychiatric and mood disorders and highlighted processes in which endocannabinoids and CB1 and CB2 receptors are involved; additionally, the effects of phytocannabinoids have been studied in animal models as well as in noninvasive human studies. General findings on anxiety symptoms indicate that both delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) exert dose-dependent effects; at low or moderate doses, THC has anxiolytic effects; at high doses it produces anxiogenic effects. In contrast, CBD is anxiolytic at low to moderate doses but ineffective at high doses. Few studies specifically model panic symptoms; therefore the included summaries review evidence of the effect of cannabis on general anxiety symptoms in animal models, some of which could be related to panic symptoms.

Moreira FA, Wotjak CT. (2009) Cannabinoids and Anxiety in Stein MB, Steckler T (Ed.) *Behavioral Neurobiology of Anxiety and Its Treatment, Current Topics in Behavioral Neurosciences 2*, (pp 429-450). Springer-Verlag Berlin Heidelberg.

This chapter by Moreira and Wotjak covers the role of the endocannabinoid system in fear and anxiety, summarizing preclinical work relating to endocannabinoids, the endocannabinoid system and non-endogenous cannabinoids. The following is a brief condensation of the authors' discussion of preclinical findings relating to fear and anxiety and cannabinoids. The authors differentiate between the effects of THC and CBD, noting that the impact of THC on anxiety has been investigated using elevated plus maze and light-dark box animal experiments. The findings support the existence of a biphasic effect where at low doses (<1 mg/kg), THC exhibits anxiolytic effects and at higher doses (up to 10 mg/kg) THC has anxiety-producing effects. Additionally, similar results have been seen with some synthetic cannabinoids which mimic THC: HU210, WIN-55212-2 and CP-55940. Cannabidiol has been investigated separately and found to also have anxiolytic effects as seen in the elevated plus-maze and the Vogel conflict test. The authors suggest that cannabinoids have varying effects because depending on the dosage, they may inhibit GABA or glutamate activity in the brain which produces opposite effects through modulating different neurotransmitters. An alternate theory is that cannabinoids differentially affect CB1 receptors in different brain sites which regulate fear and anxiety, thus producing different effects.

The authors also discuss the role of the endocannabinoid system in fear and anxiety, and note that clinical trials involving the CB1 receptor antagonist rimonabant found that the medication produced anxiety, depression and an increase in suicidal thoughts among a significant proportion of subjects and the medication was ultimately withdrawn due to safety concerns revolving around psychiatric side effects. The endocannabinoid receptors have been shown to play a role in fear extinction in the context of conditioned fear: one study found that inhibiting endocannabinoid uptake or degradation promoted conditioned fear extinction. Other studies

suggest that the endocannabinoid system is only activated in this capacity when stimuli meet a certain threshold of aversion, which could imply that it operates to mitigate extreme responses to fear. The authors also state that the endocannabinoid system operates with an upper threshold of stimulation as well, which results in mechanisms that promote fear responses. They propose a "high- and low-pass filter" model in which the endocannabinoid system inhibits extreme reactions to low-aversion stimuli while not curtailing extreme reactions to high-aversion stimuli.

Soares VP, Campos AC. Evidences for the Anti-panic Actions of Cannabidiol. *Current Neuropharmacology* 2017; 15:291-299.

This review covers preclinical and clinical studies investigating the role of CBD in moderating panic responses and symptoms. The authors review a clinical study where a single dose of CBD (300 mg) decreased anxiety after the simulated public speaking test in healthy volunteers; another study by Bergamaschi et al (which is included in this brief under "Clinical Trials") found that CBD administration (600 mg) in patients with social anxiety led to significantly reduced anxiety during a speech performance.

The review discusses animal models of panic attacks (flight and freezing defensive responses to threat) and the role of CBD in these models. In a predator-prey model with a mouse encountering a snake, acute administration of CBD reduced expression of panic-related behaviors. In another study, local administration of CBD in rats inhibited the escape response when the rats were subjected to the elevated T-maze or brain stimulation. These and other preclinical findings suggest that the amygdala, hippocampus, hypothalamus and cingulate cortex may be target sites for CBD panic-reducing activity. The authors also include a discussion of pharmacological mechanisms of CBD, mainly indirectly through interaction with the serotonin 5-HT1A receptor, which has been shown in rodent models to reduce panic-like responses. The authors conclude that CBD shows anti-panic properties and may provide an alternative to medicines with more harmful side effects; clinical trials are needed to further support this possibility.

Blessing EM, Steenkamp MM, Manzanares J. Cannabidiol as a Potential Treatment for Anxiety Disorders. *Neurotherapeutics* 2015;12:825-836.

This review summarizes 49 preclinical, clinical and observational studies describing the effect of CBD on various anxiety disorders. The authors note that CBD has a number of well-documented therapeutic benefits and is widely tolerated in human studies. Cannabidiol interacts with several receptors known to be involved in fear and anxiety behaviors, notably, the CB1 receptor, the serotonin 5-HT1A receptor and the transient receptor potential vanilloid type 1 receptor. A number of studies have examined the effect of CBD in animal models of generalized anxiety, including the elevated plus maze, Vogel-conflict test and elevated T maze; injection of CBD into the dorsal periaqueductal gray, the bed nucleus of the stria terminalis (BNST) and the central nucleus of the amygdala, sites known to regulate fear and responses to threat, produced anxiolytic effects in these tests. However, in the prelimbic cortex, injected CBD was anxiogenic in unstressed rats but anxiolytic in stressed rats. Early animal model studies found CBD to produce anxiolytic effects in low doses and no effect at high doses; later studies found that moderate dosing was effective but higher dosing was not.

In stress-induced anxiety models, mixed results were found, depending on the administration of CBD (systemically administered CBD reduced stress while microinjected CBD in the BNST increased stress). The authors state that prior stress may modulate CBD's anxiogenic effects where CBD administration to stressed animals reduces stress while CBD administration to unstressed animals produces anxiety.

In panic disorder and compulsive behavior models, CBD was found to reduce panic in an animal model measuring explosive escape and defensive immobility in response to a predator (predator-prey model) but it was also found to increase behaviors associated with increased anxiety (decrease in time spent outside burrow and increase in defensive attention). Compulsive behaviors were also examined in one study which focused on marble-burying behavior, a proposed analog to obsessive-compulsive disorder. In this study, CBD was found to reduce compulsive behavior for several days.

In contextual fear conditioning, fear extinction and reconsolidation blockade, CBD was found to reduce physiologic conditioned fear responses in animals. One study found conflicting results but administered the CBD prior to conditioning rather than prior to re-exposure as in the case of other studies. Additionally, CBD has been found to promote extinction of conditioned fear responses in other studies. The authors summarize preclinical evidence in stating the body of research generally supports CBD's potential as a therapeutic agent for anxiety disorders, though little is known about the effects of chronic dosing.

The authors also discuss human experimental and clinical studies. In acute psychological studies, CBD was found to reduce experiment-induced anxiety in a few studies as well as promote fear extinction in another human study. A few neuroimaging studies are also discussed which examine effects of CBD on resting cerebral blood flow (rCBF) or brain activation as seen on functional magnetic resonance imaging (fMRI); changes in rCBF due to CBD were observed but not correlated with anxiolytic effects. The fMRI experiment found that CBD attenuated activation of the left amygdala and the anterior and posterior cingulate cortex when subjects were exposed to fearful images. Finally, the authors discuss epidemiologic studies of neuropsychiatric disorders which indicate that CBD may exert a protective effect against adverse psychiatric effects of THC, including acute anxiety.

Clinical Trials

There is limited clinical data to draw on in understanding the effect of cannabis on anxiety-related symptoms. Below are summaries of experimental studies using THC or CBD to treat anxiety symptoms in simulated stress tests, as well as information on ongoing studies described on ClinicalTrials.gov. It is unclear whether these studies, which do not specifically enroll patients with panic disorder, relate to the treatment of panic disorder symptoms, but some review articles include such studies in their discussion of cannabis treatment for panic disorder or panic attacks.

Of note, clinical trials investigating the effects of THC (extracts or dronabinol) on other medical conditions, including glaucoma, pain and muscle spasms, have found that patients commonly report anxiety as a side effect or adverse effect of treatment, in some cases causing the subject to withdraw from the study (Flach 2002; Merritt 1980; Beal 1997; Muller-Vahl 2003; Hagenbach

2007; Narang 2008). More detailed information on these trials is available in A Review of Medical Cannabis Studies relating to Chemical Compositions and Dosages for Qualifying Medical Conditions May 2018 (Minnesota Department of Health website):

http://www.health.state.mn.us/topics/cannabis/practitioners/dosagesandcompositions2018.pdf

Bergamaschi MM, Costa Queiroz RH, et al. Cannabidiol Reduces the Anxiety Induced by Simulated Public Speaking in Treatment-Naïve Social Phobia Patients. *Neuropsychopharmacology* 2011;36:1219-1226.

This experimental study examined the effects of CBD on patients with social anxiety disorder in a simulated public speaking test. Twenty-four treatment-naïve undergraduate students with generalized social anxiety disorder (SAD) were identified through a self-assessment diagnostic tool and randomly assigned to the treatment group (one administration of 600 mg CBD) or placebo in a double-blind design. Twelve healthy control subjects without SAD were recruited as well. All groups were matched on gender, age, years of education and socioeconomic status. None of the subjects had used marijuana more than five times in their lives, nor did any have history of head trauma, neurological illness, substance use or other major health issues. The treatment and placebo were administered orally with gel capsules. The subjects underwent an adaptation period, were given drug or placebo, followed by instructions about the speech test. They were then given time to prepare for the speech and asked to deliver the speech. Both subjective assessments (Visual-Analog Mood Scale, Negative Self-Evaluation Subscale from the Self-Statements during Public Speaking Scale and Bodily Symptoms Scale) and physiologic measurements (skin conductance, arterial blood pressure and heart rate) were collected to assess anxiety at baseline, 80 minutes following drug administration (pretest), immediately before the speech test, during interruption of the speech and at two time points after the speech.

The placebo SAD group had significantly higher levels of anxiety, cognitive impairment, discomfort and alert compared to the healthy controls during the test. The treatment SAD group however had significantly less anxiety, cognitive impairment and discomfort (as measured by the Visual-Analog Mood Scale) compared to the placebo SAD group during speech performance; during the anticipatory period before the speech the treatment SAD group showed significantly less alert compared to the placebo group. The authors conclude that these preliminary findings suggest that a single dose of CBD can inhibit the fear of public speaking which is a key feature of SAD.

This study is limited by its small sample size; additionally the study used a one-time treatment protocol and therefore more study is required to assess any long-term anxiolytic effects of CBD within this population.

Childs E, Lutz JA, de Wit, H. Dose-related effects of delta-9-THC on emotional responses to acute psychosocial stress. *Drug and Alcohol Dependence* 2017;177:136-144.

This study examined the effects of THC on healthy subjects who are asked to complete a stressful task and a non-stressful task. Healthy volunteers ages 18-40 with a history of using cannabis (at least three times ever, within the last year but not more than once per week) were

recruited from the community. Excluded from the study were patients with heavy tobacco use, serious medical or psychiatric disorders or any history substance dependence. Patients with prior history of adverse reactions to cannabis (including anxiety) were also excluded. A total of 42 subjects participated in two sessions, one with the Trier Social Stress Test (a psychosocial stress test) and one with a non-stressful task and were randomized under double-blind conditions to receive either placebo, 7.5 mg oral capsule THC or 12.5 oral capsule THC at both sessions. Subjects began the tasks 2.5 hours after ingestion and subjective assessments as well as blood pressure and salivary cortisol measurements were taken before and after task completion.

Analysis included comparison of placebo and treatment groups by demographic and behavioral features as well as current stress (assessed by the Perceived Stress Scale), trait anxiety (State Trait Anxiety Inventory) and perceived stress reactivity (Perceived Stress Reactivity Scale); no significant differences were found among groups. Patients tended to be young (mean age: 23.6 years), male and white. Mood, cardiovascular and salivary cortisol measures varied in response to the stress test (versus the non-stressful test) in accordance with previous literature. Comparing treatment groups in the pre-test period, THC-treated groups reported more subjective awareness of treatment but did not report negative perceptions of this awareness. Also in the pre-treatment period, the 12.5mg THC treatment group reported significantly increased depression, anxiety and confusion in a mood state assessment (Profile of Mood States) but showed no difference from other groups in elation, vigor, fatigue, anger or friendliness. Additionally, this group reported subjective higher distress (Visual Analog Scale) in anticipation of the task when compared to the placebo or 7.5mg THC groups.

In post-test assessment, the 12.5mg THC group reported more distress during both the non-stressful test and the Trier Social Stress Test (TSST); however a comparison of the 7.5mg THC group to placebo showed that the treatment appeared to attenuate the distress caused by the TSST during the post-test recovery period. No significant differences were seen in heart rate or salivary cortisol changes produced by the TSST across treatment groups; however in the 12.5mg THC group, treatment had a dampening effect on the increase in mean arterial pressure attributed to the TSST. The authors conclude that a low dose of THC ameliorates the negative emotional consequences of a psychological stressor among healthy (non-daily) cannabis users. Limitations of this study include its small size and the generalizability to patients with psychiatric comorbidities or with history of drug use or dependency. As this experiment only examined a one-time administration of THC, further study is required to assess any long-term anxiolytic effects of THC.

Ongoing Clinical Trials

A clinical study examining the efficacy of daily CBD oral capsules on treating anxiety disorders is listed on ClinicalTrials.gov, with an estimated completion date of August 2020. The study, which is not yet recruiting, will include 50 participants who are randomized to receive either daily 200 mg CBD oil capsules or placebo, with the possibility of dose titration to a maximum of 800 mg/day. The treatment will last eight weeks and include six clinic visits where subjects will be assessed for a range of mood and anxiety symptoms, sleep, overall functioning and drug and alcohol use. Dr. Michael Van Ameringen of Hamilton Health Sciences Corporation is listed as the

study's principal investigator. More information can be found at *Cannabidiol for the Treatment of Anxiety Disorders: An 8-Week Pilot Study*:

https://clinicaltrials.gov/ct2/show/NCT03549819

A clinical study on the effects of sublingual whole plant-derived CBD on anxiety is listed on ClinicalTrials.gov, with an estimated primary completion date of August 2019. Subjects will receive 2ml of 22:1 CBD:THC tincture three times daily for four weeks and will undergo baseline evaluation, interview, clinical, cognitive and quality of life assessments and MRI scan. Dr. Stacy Gruber of McLean Hospital in Belmont, MA is listed as the study's principal investigator. More information can be found at *Sublingual Cannabidiol for Anxiety:*
https://clinicaltrials.gov/ct2/show/NCT02548559

Observational Studies

Bricker JB, Russo J, Stein MB, et al. Does occasional cannabis use impact anxiety and depression treatment outcomes?: Results from a randomized effectiveness trial. *Depression and Anxiety 2007*; 24:392-398.

This study examined the impact of occasional recreational cannabis use on anxiety and depression outcomes in participants in an effectiveness trial for combined CBT and pharmacotherapy. Patients had to meet DSM-IV criteria for panic disorder with at least one panic attack in the past week; patients with substance abuse/dependence or severely limiting psychiatric comorbidities were excluded; also, patients already seeking psychotherapy or seeing a psychiatrist were excluded. As a result, only participants who used cannabis once a week or more were less were included in the study. The 232 included adult patients were randomized to usual care or the treatment intervention, which was six CBT sessions and medications using an algorithm. Subjects were assessed at 3, 6, 9, and 12 months after baseline via phone interview for core panic symptoms, social phobia symptoms, depression symptoms and cannabis use, which was defined as once a month or more, but less than once a week ("monthly") or less than once a month ("less than monthly") at baseline. Demographic comparison showed that monthly cannabis users (n=29) tended to have lower incomes and were less likely to have a high school education or be married than less-than-monthly users (n=203) but were similar in age, gender and race. In baseline assessments, monthly cannabis users reported being more anxious and depressed, and had significantly higher social phobia. The authors found a non-significant interaction between treatment group, cannabis use (monthly vs. less than monthly) and time (3- vs. 6- vs. 9- vs. 12-month assessments), but further testing showed no interaction between treatment group and cannabis use for panic or social phobia symptoms. However, the authors found a significant interaction between cannabis use and treatment group for depression: monthly cannabis users reported worse depression levels than less-than-monthly users in the control group but no such difference was found in the treatment group. Finally, a significant interaction was found between cannabis use and anxiety sensitivity, where monthly cannabis users reported higher anxiety sensitivity scores at each time point. No significant main effects were observed between cannabis use and anxiety sensitivity or social phobia. This study is limited by the lack of control on cannabis dosing, which could vary widely at baseline and over

the course of the 12-month study. While monthly cannabis use was relatively common in this group, larger sample sizes are needed to adequately investigate this topic.

Zvolensky MJ, Lewinsohn P, Bernstein A, et al. Prospective Associations between Cannabis Use, Abuse, and Dependence and Panic Attacks and Disorder. *Journal of Psychiatry Research* 2008 October; 42(12):1017-1023.

This prospective observational study used a subset of participants from ages 14-18 from the Oregon Adolescent Depression Project, who were randomly selected and completed an initial assessment (T1), a second assessment one year later (T2), and a third assessment once they turned 24 years old (T3). In total, 941 young adults participated in all three assessments. The first assessment included a version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children; T2 and T3 included the Longitudinal Interval Follow-Up Evaluation, which asked about the course of psychiatric symptoms since the last assessment. T1 and T2, lifetime cannabis use, abuse and dependence (where abuse and dependence were mutually exclusive) were reported based on study criteria. Of all participants assessed at T2 (N=1507), 695 (43.4%) had a history of cannabis use at T2, 34 (2.3%) met criteria for history of cannabis abuse and 72 (4.8%) met criteria for history of cannabis dependence at T2.

Among participants assessed at T3 (n=941), 89 (9.3%) had a lifetime history of panic attacks and 35 (3.7%) had a history of panic disorder; excluding known cases based on T1 and T2 assessments, 32 participants (3.6%) became new cases of panic attacks and 21 participants (2.3%) became new cases of panic disorder between T2 and T3. Univariate analysis showed that cannabis use and cannabis dependence were each associated with increased odds of developing panic attacks and panic disorder between T2 and T3; no such association was found with cannabis abuse and panic attacks or disorder development. After adjustment for covariates, notably including cigarette smoking, there was no association between cannabis use/abuse/dependence and development of panic attacks or panic disorder. This study builds on previous cross-sectional research, but does not include information on cannabis dosing. While some confounders are controlled, the observational nature of this study warrants further study with controlled cannabis dosing and in a wider age range.

National Medical Organization Recommendations

There are no current recommendations from national medical organizations on the therapeutic use of cannabis for treatment of anxiety disorders, including panic disorder. The National Academies of Sciences, Engineering and Medicine produced a report on the health effects of cannabis in 2017 and the committee did not report any conclusions on the effects of cannabis on panic disorder. However, 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).

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

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