DEPARTMENT OF HEALTH

# Anxiety Disorders

ISSUE BRIEF ON ANXIETY DISORDERS

## 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

According to the American Psychiatric Association, anxiety disorders include disorders with common features of excessive fear and anxiety and related behavioral disturbances. In this definition, fear refers to a response to a real or imminent threat whereas anxiety refers to anticipation of a future threat. The Diagnostic and Statistics Manual (DSM-5) defines several disorders which fall under the broad category of anxiety disorders: Separation Anxiety Disorder, Selective Mutism, Specific Phobia, Social Anxiety Disorder, Panic Disorder, Agoraphobia, Generalized Anxiety Disorder, Substance/Medication-Induced Anxiety Disorder, and Anxiety Disorder Due to Another Medical Condition, as well as Panic Attack specifier which could apply to different diagnoses (American Psychiatric Association Publishing).

**Diagnosis**

Screening and diagnosis for anxiety disorders is done by a healthcare provider using distinct sets of criteria, which are based on the features of each disorder, from the DSM-5. Clinicians frequently use validated survey tools to assess the presence and/or severity of symptoms. Phobias, including specific phobia and social anxiety disorders, represent the majority of anxiety disorders. Social anxiety disorder is characterized by marked, persistent and unreasonable fear of being observed or evaluated negatively by others in social situations; specific phobias refer to persistent and unreasonable fear or anxiety when exposed to certain situations or objects; agoraphobia refers to a fear of places or situations in which escape might be difficult or where help would not be available should a panic attack occur. Generalized anxiety disorder (GAD) and obsessive-compulsive disorders (OCD) are less prevalent; GAD is characterized by excessive anxiety and worry; OCD is characterized by recurrent obsessions or/and compulsions that cause distress or problems with functioning. Panic disorder refers to recurrent panic attacks. In children (and sometimes adults), separation anxiety disorder refers to inappropriate and excessive anxiety when separated from home or people to whom a child is attached; selective mutism refers to a failure to speak when expected in certain social situations (Bandelow 2012).

**Prevalence**

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

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

**Complications**

According to the Mayo Clinic, complications of anxiety disorders can include impairment in completing work or tasks, lack of energy and sleep disturbance. Untreated anxiety disorders can result in depression, substance abuse, insomnia, digestive problems, headaches, and cardiovascular health issues (Mayo Clinic).

# Current Therapies

The World Federation of Biological Psychiatry summarized treatment guidelines for patients with anxiety disorders in a 2012 publication (Bandelow 2012); the following highlights different anxiolytic therapies described in their review. Patients with anxiety disorders can be treated with either medication, psychotherapy, or both. The choice of treatment regimen

depends on many factors, including patient preference, severity, other psychiatric and medical comorbidities, history of previous treatment or issues like substance abuse or suicide risk, as well as therapy cost to the patient. First-line pharmacotherapy is selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and pregabalin, a calcium-channel modulator. Treatment with SSRIs is usually well-tolerated but side effects can include overstimulation, fatigue, or headache among others. Treatment with SNRIs can include side effects of nausea, restlessness, insomnia or headache as well as sexual dysfunction, discontinuation syndromes or increased blood pressure in some cases. Both SSRIs and SNRIs may require 2-4 weeks of therapy before patients begin experiencing benefit, which can present challenges for compliance. Pregabalin produces more immediate effects but can cause side effects of dizziness and somnolence.

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

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

According to data from the European Study of the Epidemiology of Mental Disorders (ESEMeD), subjects from a large non-institutionalized European cohort who had an anxiety disorder had a low level of 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 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. Included below are summaries of literature reviews on this topic that reflect the quality of evidence currently available.

**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.

**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.

**Campos AC, Moreira FA, Gomes FV, Del Bel EA, Guimaraes FS. Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders. *Philosophical Transactions of the Royal Society B* 2012;367:3364-3378.**

This review synthesized detailed summaries of existing evidence for the mechanisms of cannabidiol therapy for psychiatric disorders, focusing on anxiety, depression and psychosis.

The following reflects the paper's discussion of therapies relating only to anxiety. The authors note that early preclinical studies on the use of CBD for anxiety reported mixed results, but these were later explained in a study by Guimaraes et al. showing a dose-dependent benefit where maximum benefit is achieved at lower doses and high doses are ineffective. A number of studies have found that CBD exhibits anti-anxiety effects in rat models which used the elevated plus-maze, the Vogel conflict test and contextual fear conditioning to measure impact. Additionally, other studies have found that CBD reduces defensive behaviors in response to a predator, which may model triggers for panic attack and posttraumatic stress disorder (PTSD). The authors also note that in relation to PTSD management, CBD has been shown to interfere with learning and memory of aversive events as well as promote memory extinction in some experiments. One rat model study from Elbatsh et al., however, reported that CBD treatment increased freezing in a contextual fear conditioning test which would contrast with the previously discussed findings. The authors suggest that these findings differed from others because the animals were conditioned while being treated with CBD, which could have interfered in learning or memory mechanisms.

The authors include a review of clinical evidence of an anxiolytic effect of CBD. Reviewed findings agree with animal studies and report that CBD reduces anxiety-producing effects of delta-9-tetrahydrocannabinol (THC) and is associated with less anxiety in healthy subjects exposed to anxiety-producing triggers. Finally, a study on patients with social phobia showed that 600 mg CBD was effective in reducing anxiety, cognitive impairment and discomfort during a simulation public speaking test compared to placebo treatment.

Target sites and mechanisms of CBD action are also explored in this review. A few studies report neuroimaging findings that CBD is involved in emotional processing; one avenue of activity involves controlling blood oxygenation in the amygdala and the anterior and posterior cingulate cortex, and impedes connectivity between the pre-frontal and subcortical regions. These findings align with pre-clinical studies in which CBD injected directly into brain sites related to panic or anxiety responses reduced anxiety in rats. The mechanisms of CBD's anxiolytic effects have been studied in vivo; Russo et al. found that CBD acts as a 5HT1A receptor agonist to produce neuroprotective effects; a clinical study comparing CBD to ipsapirone, a 5HT1A receptor partial agonist, found similar results in the CBD-treated group in an experiment using simulated public speaking. Finally, the authors described the promoting role of CBD in adult hippocampal neurogenesis, a process whose impediment is linked to the pathogenesis of anxiety disorders. Cannabidiol has been shown to increase proliferation of hippocampal progenitor cells, possibly by inhibiting ananadamide metabolism or uptake. The authors conclude that CBD holds therapeutic potential which may be limited by its variable bioavailability and bell-shaped dose response curve which seems to indicate a small therapeutic dose range. The authors also note that greater elucidation on the mechanisms of CBD action is needed.

# Clinical Trials

There is limited clinical data to draw on in understanding the effect of cannabis on anxiety disorders. Below are summaries of experimental studies using THC or CBD to treat

anxiety in simulated stress tests, as well as information on ongoing studies described on ClinicalTrials.gov. 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 July 2017 (Minnesota Department of Health website): http://www.health.state.mn.us/topics/cannabis/practitioners/dosagesandcompositions2017.pdf

**Bergamaschi MM, Costa Queiroz RH, Nisihara Chagas MH, Gomes de Oliviera DC, Spinosa De Martinis B, Kapczinski F, Quevedo J, Roesler R, Schroder N, Nardi AE, Martin-Santos R, Cecilio Hallak JE, Waldo Zuardi A, Crippa JAS. 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**

The New York Psychiatric Institute is sponsoring a clinical trial to study the off-label use of nabilone, a synthetic cannabinoid which mimics the action of THC, in treating adults with obsessive-compulsive disorder. The study design involves two experimental arms: in the first, patients receive 1mg nabilone daily for four weeks; in the second, patients receive 1mg nabilone daily along with cognitive behavioral therapy for four weeks. As of July 2017, the study is recruiting participants and the principal investigator is Dr. Helen Simpson at the New York Psychiatric Institute. More information can be found at *Cannabinoid Medication for Adults with OCD:*

https://clinicaltrials.gov/ct2/show/NCT02911324?term=cannabis%2C+marijuana&cond=anxiety&rank=4

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 November 2017 (as of September 2016, the study is not yet recruiting participants). 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?term=cannabis%2C+marijuana&cond=anxiety&rank=5

# Observational Studies

A number of observational studies examine the relationship between cannabis use and anxiety and report mixed findings; in some cases, anxiety appears more prevalent among cannabis users while other studies report no association. Interpreting these findings is a challenge given the differences in methodology (in some cases, adjustments are made for potential confounders but not in others) and imprecision in measuring street cannabis use (both in frequency and quantity of use). Lastly, the direction of causality is uncertain as there are indications that patients prone to symptoms of anxiety may be more likely to use cannabis as a means of mitigating their symptoms. Included below are summaries of a large observational cohort study, a review and a meta-analysis of observational studies examining this association.

**Danielsson A, Lundi A, Agardh E, Allebeck P. Cannabis use, depression and anxiety: A 3-year prospective population-based study. *Journal of Affective Disorders* 2016;196:103-108.**

This study used data from the Mental Health, Work and Relations study, a Stockholm population-based prospective cohort to examine whether depression and anxiety were associated with cannabis use, as captured at baseline. The study was conducted via mailed questionnaire at baseline and three years later. Included were adults age 20-64 who responded to the initial survey (53%) and follow-up survey (n=8,613, 83% of initial respondents). The exposure of interest, cannabis use, was captured as ever vs. never use and most recent cannabis use (within 12 months versus 12 months or longer). Depression was measured using

the Major Depressive Inventory (MDI); anxiety at baseline was measured using the Sheehan Patient-Rated Anxiety Scale (SPRAS) with additional questions about panic attacks from the DSM-IV. At follow-up, anxiety was measured using the Symptom Checklist items for Anxiety.

The authors adjusted for potential confounding on other substance use, educational background and childhood adverse circumstances, as well as geographic location and ethnicity. Patients with depression or anxiety at baseline were excluded. Associations were examined between cannabis use and depression or anxiety and other covariates and blocks of potential confounders were included in multivariate models (age, sex, family tensions, other illicit drug use, and alcohol consumption).

Overall, 16.5% of subjects had ever used cannabis at baseline; cannabis users tended to be male, younger and raised in Stockholm, and also were more likely to report family tension, higher illicit drug and alcohol consumption and alcohol-related problems. After adjustment for age and sex, cannabis use at baseline was significantly associated with depression and anxiety at follow up (anxiety relative risk (RR)=1.22, 95% CI: 1.06-1.42; depression RR=1.38, 95% CI: 1.26-1.50). After adjustment for family tension, the association between cannabis use and depression onset was no longer significant; similarly, after simultaneous adjustment for all confounders the association between cannabis use and anxiety onset was no longer significant.

Reversing the proposed direction of association, the authors found that after adjustment for age, depression or anxiety at baseline increased the risk of cannabis onset at follow-up (depression RR= 1.62, 95% CI: 1.28-2.03; anxiety RR= 1.63, 95% CI: 1.28-2.08). After adjustment for other illicit drug use, the associations were no longer statistically significant. The authors conclude that cannabis use at baseline is not associated with depression or anxiety after three years of follow-up. Limitations of this study include lack of information on age of initiating cannabis use, relatively lower prevalence of cannabis use in Sweden compared to other countries, and the use of different anxiety assessment tools at baseline versus three years later. The authors note that previous studies on this topic have produced mixed results; they suggest that this may be due to the inconsistent controlling of potential confounders and differences in measuring cannabis usage.

**Kedzior KK, Laeber LT. A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population- a meta-analysis of 31 studies. *BioMed Central Psychiatry* 2014;14:136.**

This meta-analysis examined the relationship between anxiety and cannabis use and use disorders, as reported in longitudinal or cross-sectional studies to date. Of 267 studies identified, 31 met the inclusion criteria of sampling from a non-institutionalized general population, capturing anxiety diagnoses based on clinical guidelines or standardized scoring systems, capturing cannabis use information, reporting odds ratios for cannabis use relative to presence/absence of anxiety or vice versa, and reporting enough data to calculate other effect sizes. Studies were excluded if they did not include data on healthy controls or if their population included a heavy burden of substance use and/or abuse or other mental illness comorbidity (other than depression).

Meta-analysis was performed using the random-effects model. Odds ratios (OR) and 95% confidence intervals (CI) were calculated or extracted from included studies; these effect

sizes were then weighted using the method of moments, which gives lower weights to smaller studies. Overall mean weighted ORs were calculated and classified as small, moderate or large. Sensitivity analyses and publication bias analyses were also performed.

The authors report small positive associations between anxiety and cannabis use (OR = 1.24, 95% CI: 1.06-1.45), anxiety and cannabis use disorders (OR = 1.68, 95% CI: 1.23-2.31) and anxiety with depression and cannabis use (OR = 1.68, 95% CI: 1.17-2.40). There was little evidence for publication bias and "one-study removed" sensitivity analysis showed that the anxiety and cannabis use analysis and the anxiety and cannabis use disorder analysis were robust against individual study effects. However the anxiety plus depression and cannabis analysis resulted in a nonsignificant OR with the removal of one influential study. There was moderate-high heterogeneity among ORs of included studies; the authors suggest this is due to systematic differences among studies such as OR adjustment for confounders, clinical diagnosis versus standardized tool score for anxiety diagnosis, and year of publication which could affect statistical methodology used. As a result, subanalyses were performed to account for confounder adjustment and a small positive effect was still found between cannabis use and anxiety, suggesting the association was not only due to use of other substances, psychiatric comorbidities or demographic features. Finally, the authors examined five studies which provided longitudinal data and concluded that they trended toward a small and positive relationship between cannabis use at baseline and anxiety at follow-up, reporting ORs of 1.21-1.44. The authors stress the limitations of observational data in drawing assumptions of causality and state that the main finding is that patients with anxiety are more likely to use cannabis or have a cannabis use disorder.

**Crippa JA, Zuardi AW, Martin-Santos R, Bhattacharyya S, Atakan Z, McGuire P, Fusar-Poli P. Cannabis and anxiety: a critical review of the evidence. *Human Psychopharmacology* 2009;24:515-523.**

This review included studies reporting on the relationship between cannabis use and anxiety, and focused on evidence related to recreational cannabis use in which the exact drug constituents are unknown. The authors report a well-documented acute anxiety-producing effect of cannabis, seen in observational and experimental settings. High doses of THC (>5mg oral) have been shown to cause intense fear and anxiety in some cases; a few studies report that 20-30% of cannabis users experience acute anxiety episodes after smoking cannabis. The authors note that anxiety –related side effects are most common in cannabis-naïve patients or in the presence of environmental stress; the risk factors associated with cannabis-induced anxiety were found to be individual/genetic vulnerability and personal traits, gender, frequency of use, dose and quantity consumed, proportions of cannabinoids, especially THC and CBD, history of previous episodes of anxiety or presence of anxiety disorders/symptoms, basal anxiety states, abstinence states, and environment and context of use.

In contrast to these findings, the authors report that long-term cannabis users often report a reduction in anxiety related to cannabis use. Other evidence seems to indicate a link between long-term cannabis use and onset or worsening of anxiety symptoms: frequent cannabis users were found to have higher anxiety levels than non-users, though not necessarily to have a diagnosed anxiety disorder. One study found that 21% of cannabis users with a use history of 10+ years had high levels of anxiety; another report described increasing severity of

anxiety symptoms with ongoing cannabis use among Italian army draftees. Other studies on subjects with cannabis dependency, including adolescents, found associations between presence or exacerbation of anxiety symptoms and cannabis use.

Drawing on preclinical data, the authors propose mechanisms by which THC may produce anxiogenic effects but also suggest that the relationship may be indirect: chronic cannabis use early in life may be associated with lower educational attainment or other psychosocial factors which increase risk of anxiety disorders. The authors also propose that, based on prospective observational data, there is evidence that symptoms of anxiety lead to self-medication with cannabis, rather than the reverse direction of causality. Finally, they note that there are common factors which predispose individuals to both experience anxiety and use cannabis, concluding that the true relationship between anxiety and cannabis remains to be adequately elucidated.

## National Medical Organization Recommendations

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

## Minnesota Medical Cannabis Program Data

Data is routinely collected on patients in the Minnesota Medical Cannabis program who purchase medical cannabis. At the time of each purchase, patients complete a self-evaluation in which they are asked to rate various symptoms they have experienced in the past 24 hours on a scale from 0-10 (10= the worst imaginable). In the first program year, 1,512 patients enrolled in the program and made at least one purchase. At baseline, 1,185 (73.4%) patients reported a score of 4 or greater on the symptom scale for anxiety, and were therefore considered to be experiencing moderate or severe anxiety. Of these patients, 53.8% reported a 30% reduction in reported anxiety (as measured by the symptom scale) four months after the first medical cannabis purchase. Information on clinical diagnoses of anxiety disorders was not routinely collected on patients, so the proportion of patients who meet formal criteria for such diagnoses is unknown (Minnesota Department of Health: Patient Experiences from the First Program Year).

# References

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

American Psychiatric Association Publishing. DSM® Library: Anxiety Disorders. DSM Psychiatry Online Website: http://dsm.psychiatryonline.org/doi/abs/10.1176/appi.books.9780890425596.dsm05. Accessed August 23, 2017.

Bandelow B, Sher L, Bunevicius R, Hollander E, Kasper S, Zohar J, Moller H, WFSBP Task Force on Mental Disorders in Primary Care and WFSBP Task Force on Anxiety Disorders, OCD and PTSD. Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care. *International Journal of Psychiatry in Clinical Practice*, 2012;16:77-84.

Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. *Dialogues in Clinical Neuroscience* 2015 Sept;17(3):327-335.

Beal JE, Olson R, Lefkowitz L, Laubenstein L, et al. Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia. J Pain Symptom Manage 1997;14:7-14.

Bergamaschi MM, Costa Queiroz RH, Nisihara Chagas MH, Gomes de Oliviera DC, Spinosa De Martinis B, Kapczinski F, Quevedo J, Roesler R, Schroder N, Nardi AE, Martin-Santos R, Cecilio Hallak JE, Waldo Zuardi A, Crippa JAS. Cannabidiol Reduces the Anxiety Induced by Simulated Public Speaking in Treatment-Naïve Social Phobia Patients. *Neuropsychopharmacology* 2011;36:1219-1226.

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

Campos AC, Moreira FA, Gomes FV, Del Bel EA, Guimaraes FS. Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders. *Philosophical Transactions of the Royal Society B* 2012;367:3364-3378.

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.

Crippa JA, Zuardi AW, Martin-Santos R, Bhattacharyya S, Atakan Z, McGuire P, Fusar-Poli P. Cannabis and anxiety: a critical review of the evidence. *Human Psychopharmacology* 2009;24:515-523.

Danielsson A, Lundi A, Agardh E, Allebeck P. Cannabis use, depression and anxiety: A 3-year prospective population-based study. *Journal of Affective Disorders* 2016;196:103-108.

Elbatsh MM, Assareh N, Marsden CA, Kendall DA. Anxiogenic-like effects of chronic cannabidiol administration in rats. *Psychopharmacology* 2012;221:239-247.

Flach AJ. Delta-9-tetrahydrocannabinol (THC) in the treatment of end-stage open-angle glaucoma. Trans Am Ophthalmol Soc 2002;100:215-224.

Guimaraes FS, Chiaretti TM, Graeff FG, Zuardia AW. Antianxiety effect of cannabidiol in the elevated plus-maze. *Psychopharmacology* 1990;100:558-559.

Hagenbach U, Lux S, Ghafoor N, Berger JM et al. The treatment of spasticity with delta-9tetrahydrocannabinol in persons with spinal cord injury. Spinal Cord 2007;45:551-562.

Kedzior KK, Laeber LT. A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population- a meta-analysis of 31 studies. *BioMed Central Psychiatry* 2014;14:136.

Mayo Clinic. Generalized anxiety disorder. Mayo Clinic Website: http://www.mayoclinic.org/diseases-conditions/generalized-anxiety-disorder/basics/complications/con-20024562 . Accessed August 29, 2017

Merritt, JC, McKinnon S, Armstrong JR, Hatem G, Reid LA. Oral delta 9-Tetrahydrocannabinol in Heterogenous Glaucomas. Ann Opthalmol 1980;12:947-950.

Minnesota Department of Health. A Review of Medical Cannabis Studies relating to Chemical Compositions and Dosages for Qualifying Medical Conditions. July 2017. Minnesota Department of Health Website: http://www.health.state.mn.us/topics/cannabis/practitioners/dosagesandcompositions2017.pdf .Accessed August 30, 2017.

Minnesota Department of Health. Minnesota Medical Cannabis Program: Patient Experiences from the First Program Year. May 2017. Minnesota Department of Health Website: http://www.health.state.mn.us/topics/cannabis/about/firstyearreport.pdf. Accessed August 29, 2017.

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.

Muller-Vahl KR, Schneider U, Prevedel H. Delta 9tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: a 6-week randomized trial. J Clin Psychiatry 2003;64:459465.

Narang S, Gibson D, Wasan AD, Ross EL, Michna E, Nedeljikovic SS, Jamison RN. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. *The Journal of Pain* 2008;3:254-264.

National Academies of Sciences, Engineering and Medicine. 2017. The health effects of cannabis and cannabinoids: Current state of evidence and recommendations for research. Washington, DC: The National Academies Press.

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