mn 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

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Autism Spectrum Disorder (ASD)

ISSUE BRIEF ON AUTISM SPECTRUM DISORDER (ASD)

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 of cannabis therapy are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Though the MN medical cannabis program does not allow smoked or vaporized dried cannabis, studies using these forms of cannabis administration were allowed for insight they could provide. Finally, the federal government-maintained web site of clinical trials, clinicatrials.gov, was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

Definition

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is characterized by sustained social impairments in reciprocal social communication and interactions; and repetitive behaviors, interests, or activities. These essential markers of autism spectrum disorder present in early childhood and limit everyday functioning. The word "spectrum" is used to define ASD since the disorder manifests itself in diverse ways, depending on varying symptom severity, the individual's development level, and chronological age (American Psychiatric Association 2013.

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) is the 2013 update to the American Psychiatric Association's classification and diagnostic tool. In the U.S. the DSM serves as the primary authority for psychiatric diagnosis. In the latest version of the DSM, several disorders have now been incorporated into the ASD definition, such as Kanner's autism and Asperger's disorder, among others. To be diagnosed with ASD, a person needs to fulfil the following criteria (American Psychiatric Association 2013):

1. Persistent deficits in social communication and interaction across multiple contexts, as demonstrated by all of the following:
    1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and inability to have normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
    2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
    3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.
    4. (These criteria can be currently occurring or have occurred in the patient's past. Examples are illustrative, not exhaustive.)
2. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following:
    1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., repetitive hand flapping, lining up toys or flipping objects, delayed or immediate parroting of others' speech, idiosyncratic phrases).
    2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).
    3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., a child who is extremely attached to a spoon, an adult who spends hours rewriting specific phrases).
    4. Extremely exaggerated or dulled reactions to sensations or unusual interest in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).
    5. (These criteria can be currently occurring or have occurred in the patient's past. Examples are illustrative, not exhaustive.)

3. Symptoms must be present in the early developmental period. Though, symptoms may not become fully apparent until social demands exceed limited capacities. Symptoms may also be masked by learned strategies in later life.
4. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
5. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur. Social communication should be below what is expected for general developmental level, in order to make comorbid diagnoses of autism spectrum disorder and intellectual disability.

Prevalence

The Centers for Disease Control and Prevention estimates that 1 out of every 68 children in the United States has autism spectrum disorder. ASD is roughly 4.5 times more common among boys than girls (Christensen 2016). Since 2006, the prevalence of childhood ASD has increased by 23%, becoming a major public-health concern. This increase in prevalence can be attributed to better screening and the DSM-5's broader definition of ASD, among other issues (Harrington and Allen 2014).

Among both children and adults, roughly 3.5 million Americans live with autism spectrum disorder. Annually, costs associated with children who have ASD are $61 billion in the United States. Adults living with ASD cost the U.S. $196 billion per year (Buescher 2014).

Current Therapies

Several behavioral, educational, and pharmaceutical treatments are used to manage ASD. Pharmaceutical treatments mostly target comorbid health problems, which are common in children living with ASD (McPheeters 2011).

Behavioral and developmental interventions are the primary treatments for ASD (Ospina 2008). There is a great variety in the kinds of behavioral and developmental interventions, which are organized into smaller subcategories (Ospina 2008). For example, within the continuum of behavioral and developmental interventions, applied behavioral analysis (ABA) is designed to teach socially appropriate behaviors and to decrease challenging behaviors (Harrington 2014, Ospina 2008). Another kind of behavior and developmental intervention is social skills training (SST), which targets social deficits (White 2007).

ABA-based therapies have demonstrated positive effects on language, adaptive, cognitive, and educational outcomes (Hanley 2001, Lovaas 1987, Warren 2011). However, there is a lack of high-quality randomized controlled trials (Warren 2011). The studies that do evaluate behavioral and developmental interventions are methodologically weak, include few participants, and do not evaluate long-term effects of interventions (Ospina 2008). Therefore,

the evidence to determine which behavioral interventions are most effective in children with ASD is inadequate (Warren et al., 2011). Studies on SST interventions are similarly low-quality, though evidence from several small, initial studies indicate that SST is potentially beneficial to children with ASD (White 2007).

Common comorbidities in children with ASD include intellectual disability, constipation, sleep disorders, anxiety, ADHD, and seizure disorders (Harrington and Allen, 2014; McPheeters 2011). Treating comorbid mental-health issues in children with ASD is more challenging than treating common medical problems, such as constipation and sleep problems (Harrington 2014). Antipsychotic medications, serotonin-reuptake inhibitors, and stimulants are among the pharmaceuticals used to treat mental-health comorbidities (McPheeters 2011). However, despite the fact that medications are used to treat many children with ASD, there is little evidence to indicate that these pharmaceuticals are effective (McPheeters 2011). Drugs that do demonstrate benefits for challenging or repetitive behaviors, are unfortunately associated with adverse effects, limiting their use to patients with severe impairments or risk of injury (McPheeters 2011).

Turning to adolescents and young adults with ASD, studies examining the effectiveness of behavioral, pharmaceutical, and other therapies in this population are poor-quality (Taylor 2012). There is a dramatic lack of evidence on the best way to treat adolescents and young adults who have ASD (Dove 2012, Taylor 2012).

Pre-Clinical Research

A September, 2017 review by Zamberletti et al (Zamberletti 2017) provides a good overview of the lines of evidence from animal studies suggesting the endocannabinoid system (ECS) plays a role in autism. Recently, at least three articles (Doenni 206, Servadio 2016, and Wei 2016) have reported on studies that manipulated the ECS in mouse models of autism.

Zamberletti E, Gabaglio M, Parolaro D. The endocannabinoid system and autism spectrum disorders: Insights from animals. *Int J Mol Sci* 2017;18(9). pii: E1916. doi: 10.3390/ijms18091916

This review provides evidence of involvement of the ECS in autism through modulation of autism-like behaviors and research suggesting possible mechanisms of action.

Genetic-based models:

- Fragile X syndrome (FXS) is the most common known genetic cause of ASD. A mouse model of FXS has been developed: the Fmr1 knockout mouse. Fmr1 mice have been shown to have dysregulated endocannainoid signaling. And studies that inhibited different enzymes that degrade endocannabinoids showed improvement in autism-consistent behaviors.

- Inbreeding has produced a group of mouse strains used as a model for idiopathic (cause unknown) autism because the mice exhibit behaviors consistent with those seen in humans with ASD, but with no known gene mutation causing the behaviors. Prominent among these strains is the BTBR mouse model. Treatment to increase the level of one

endocannabinoid (AEA) resulted in reduced ASD-like behavior.

Environmental-based models – environmental manipulations in rodents conducted using the same agents that have been correlated with human autism:

- The valproic acid (VPA) rat model has been used extensively to evaluate the possible involvement of the endocannabinoid system in ASD. VPA is an anti-epileptic drug. Several studies have shown use of VPA during pregnancy may cause neural tube defects and cognitive impairment in children. In animal studies, offspring of rats administered VPA during pregnancy show lower social interaction, increased repetitive/sterotyped behaviors, early signs of neurodevelopment impairment, and abnormal responses to painful and non-painful stimuli. Studies have been done administering to rats exposed to VPA in utero substances that inhibit the breakdown of an endocannabinoid (AEA). Results showed decrease in the autism-model behaviors, with greater decrease seen in males.

- Both viral and bacterial infections during pregnancy have been linked to an increased risk to develop ASD in the offspring. Injection of pregnant rodents with the substance, polyinosine:cytosine (LPS), which mimics the immune activation seen with the influenza virus, produces ASD-like behaviors in the offspring. These include impairments in social interaction and communication, stereotyped patterns of behavior, anxiety, and impaired learning and memory. These behaviors in the offspring were accompanied by distinctive changes in brain neuron structure and function. The tie to the endocannabinoid system comes with studies that administered LPS to rodents soon after birth. This resulted in decreased social play, reduced CB1 (cannabinoid receptor 1) binding, and increased levels of the endocannabinoid, AEA.

Possible mechanisms of action:

- Studies have shown elements of the ECS interact with oxytocin, a neuropeptide that promotes parental and social bonding. Oxytocin stimulates endocannabinoid release in a relevant part of the brain (nucleus accumbens) and there is evidence endocannabinoid signaling is required for the prosocial effects of oxytocin.

- mTOR signaling is involved in memory consolidation and normalization of mTOR signaling in the hippocampus reduces the cognitive deficits caused by cannabinoid receptor 1 blockade of Fmr1 (fragile X Syndrome model) mice. Dysregulation of mTOR signaling appears to be a feature common to a subset of ASD. (mTOR is an enzyme that controls cell growth and metabolism).

- There is evidence that endocannabinoids might modulate ASD symptoms via interaction with immune system cells. Changes in endocannabinoid metabolism and in expression cannabinoid receptors (CB2) on certain white blood cells have been seen in ASD pateints.

The authors conclude, "Although preclinical findings seem to suggest that pharmacological interventions aimed at modulating the EC system could be beneficial for relieving symptoms associated with ASD, their preliminary nature does not allow any definitive conclusions to be

drawn concerning potential therapeutic exploitation."

Doenni VM, Gray JM, Song CM, Patel S, Hill MN, Pittman QJ. Deficient adolescent social behavior following early-life inflammation is ameliorated by augmentation of anandamide signaling. *Brain Behav Immun* **2016;58:237-247.**

Inflammation was induced in 14-day old rats with administration of a lipopolysaccharide. Control rats received a saline injection. Subsequent differences in social behavior tests and in endocannabinoid system were studied. LPS-injected rats exhibited a lower level of social behavior. Oral administration of an inhibitor of the enzyme that degrades the endocannabinoid AEA resulted in none of the social behavior impairment expected in LPS-injected rats. Control rats were unaffected.

Servadio M, Melancia F, Manduca A, di Masi A, Schlavi S, et al. Targeting anandamide metabolism rescues core and associated autistic-like symptoms in rats prenatally exposed to valproic acid. *Transl Psychiatry* **2016;6 e902 doi:10.1038/tp.20616.182.**

The following is from the article's abstract. Anandamide is one of the primary endocannabinoids. "VPA-exposed rats showed early deficits in social communication and discrimination, compromised sociability and social play behavior, stereotypies and increased anxiety, thus providing preclinical proof of the long-lasting deleterious effects induced by prenatal VPA exposure. At the neurochemical level, VPA-exposed rats displayed altered phosphorylation of CB1 cannabinoid receptors in different brain areas, associated with changes in anandamide metabolism from infancy to adulthood. Interestingly, enhancing anandamide signaling through inhibition of it degradation rescued the behavioral deficits displayed by VPA-exposed rats at infancy, adolescence and adulthood. This study therefore shows that abnormalities in anandamide activity may underlie the deleterious impact of environmental risk factors on ASD-relevant behaviors and that the endocannabinoid system may represent a therapeutic target for the core and associated symptoms displayed by autistic patients."

Wei D, Dinh D, Lee D, Anguren A, Moreno-Sanz G, et al. Enhancement of anandamide-mediated endocannabinoid signaling corrects autism-related social impairment. *Cannabis and Cannabinoid Research* **2016;1:1, 81-89, DOI:10.1089/can.2015.0008.**

Effect of administering an inhibitor of the enzyme that degrades the endocannabinoid AEA was tested on two distinct mouse models of ASD. The two models were a strain with a mutation that models human Fragile-X Syndrome and the BTRT mouse strain – an inbred strain with behaviors similar to ASD not known to be caused by a mutation. Social impairment was tested with a previously established method: the three-chambered social approach task. First the mice were habituated to the center chamber for ten minutes with the doors to the other two chambers closed. Then the mice were tested in a ten-minute session. Subjects were offered a choice between a novel object and a novel mouse in opposing side chambers. The novel object was a clear, empty inverted pencil cup and the novel social stimulus mouse was a sex, age, and weight-matched mouse constrained by a clear, empty inverted pencil cup. Chamber time scoring was automated using image analysis. Sniffing time was scored by trained assistants who were unaware of treatment conditions. Administration of a drug that inhibits FAAH, an enzyme that degrades AEA, completely reversed the social impairment found in both strains.

Clinical Trials

No randomized, controlled clinical trials have been completed for cannabis or cannabinoids as therapy for ASD. However, two have been registered on www.clinicaltrials.gov. and are now under way (see descriptions below). Though internet blogs and discussion forums have numerous accounts of use of cannabis and cannabinoids in persons with autism, the following case history was the only publication found for therapeutic use of a cannabinoid or cannabis product for autism.

Kurz R, Blaas. Use of dronabinol (delta-9-THC) in autism: a prospective single- case-study with an early infantile autistic child. *Cannabinoids* 2010;5:4-6.

In this study, synthetic delta-9-THC (dronabinol) was studied as a supplemental therapy in an autistic Austrian child. The child at the center of this study was diagnosed with early infantile autism at the age of three. He was six years old when the study was conducted. The study lasted six months. During the study period, the child initially received dronabinol drops at a dosage of one drop every morning (0.62 mg THC). On a day-to-day basis, the dosage was gradually increased, reaching a maximum tolerated dose of 3.62 mg THC per day (two drops in the morning, one drop at midday, and three evening drops).

At the end of the six months, the boy's symptom severity significantly decreased in five different categories: hyperactivity, lethargy, irritability, stereotypic behavior, and inappropriate speech. Based on these findings, the authors argue that dronabinol may be a therapeutic for treating early infantile autism. Dronabinol may not replace other therapies, but it is a potential, additional therapy. Larger, controlled studies on cannabinoids and autism are needed to further understand their findings, say the authors.

Cannabinoids for Behavioral Problems in Children with ASD (CBA): NCT02956226 (registered on www.clinicaltrials.gov)

This is a double blind randomized placebo-controlled clinical trial of two cannabis fomulations to treat disruptive behaviors in children and young adults (age 5-21) with ASD. It is being carried out in Israel. Estimated enrollment is 120 patients, who will be assigned to one of three olive oil-based solutions for a three-month treatment period: 1) 99% CBD and 99% THC in a ratio of 20:1 CBD:THC; 2) whole plant extract with a CBD:THC ratio of 20:1; or, 3) placebo. Primary outcome is change from baseline Home Situations Questionnaire-Autism Spectrum Disorder score, at 3 months (it is a 24-item parent-rated measure of noncompliant behavior in children with ASD). There are several other outcome measures. Recruitment began January, 2017. Estimated study completion date is July, 2019.

Cannabidivarin (CBDV) vs. Placebo in Chldren with Autsim Spectrum Disorder (ASD): NCT03202303 (registered on www.clinicaltrials.gov)

This double blind placebo-controlled clinical trial of CBDV to treat children (age 5-18 years) will be carried out in New York City. Estimated enrollment is 100 patients, who will be assigned to either 800 mg/day (400 mg twice/day) CBDV or placebo capsule for a 12-week treatment period. Primary outcome is change from baseline Aberrant Behavior Checklist-Irritability Subscale, at 12

weeks. There are several other outcome measures. Recruitment will begin October, 2017. Estimated study completion date is September, 2021.

Observational Studies

De Alwis D, Agrawal A, Reiersen AM, Constantino JN, Henders A, Martin NG, & Lynskey MT. ADHD symptoms, autistic traits, and substance use and misuse in adult Australian twins. *J Stud Alcohol Drugs* **2014;75:211-221.**

Substance use among people with autism spectrum disorders (ASD) is hypothesized to be rare, since those with ASD lack the social skills that would bring them into contact with others who use drugs and since people with ASD have less novelty-seeking behaviors than average. However, there are few studies to test this hypothesis. This study uses a cross- sectional interview and self-reported questionnaire to elucidate the relationship between people with autism traits, substance use, and substance abuse. The interview and questionnaire's study sample size was 3,028 white, Australian twins born between 1972 and 1979. The study participants' drug use, abuse, and misuse were assessed through the interview. The self-reported questionnaire collected data on the participants' autistic traits.

Surprisingly, the results of the analysis indicate that cannabis use is associated with having autistic traits in a statistically significant manner. Cannabis abuse/dependence were also significantly associated with high levels of autistic traits.

Several factors limit interpretation of this finding, however. From a demographic perspective, the study sample is racially homogenous, and its findings may not be replicated in more diverse study samples. Causal relationships cannot be determined because of the study's cross-sectional design. Last, formal diagnostic criteria were not used to determine an autism spectrum disorder diagnosis: only autistic traits were studied.

National Medical Organization Recommendations

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the management of autism spectrum disorder were found.

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OF HEALTH

Corticobasal Degeneration

ISSUE BRIEF ON CORTICOBASAL DEGENERATION

Introduction

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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

Corticobasal degeneration (CBD) is a rare, progressive neurodegenerative condition due to pathological accumulation in brain neurons of tau protein. Patients with a combination of symptoms suggestive of the disorder are often referred to as having 'corticobasal syndrome' (CBS), while CBD is used strictly to describe cases verified by pathology studies after death. Clinical diagnosis of CBD can be difficult as symptoms are variable and often resemble those of other types of neurodegenearative disorders (Armstrong 2016).

Patients typically develop symptoms in their 6th or 7th decades with a mean age of onset of 64 years and mean survival of 6 to 7 years (Lamb 2016).

The most common presenting symptom is limb clumsiness affecting one side of the body, initially with or without accompanying rigidity or tremor. Subsequently, the disease spreads to affect gait and there is slow progression to influence the arm and leg on the same side where symptoms first appeared. Eventually, major clinical features include apraxia

(difficulty carrying out intended movements) and dementia, parkinsonism (tremor, slow movement, and rigidity), palsy (weakness or paralysis), and myoclonus (spasmodic contractions of muscle groups) (Armstrong 2016).

Prevalence

Prevalence of CBD is estimated at 4.9 – 7.3 per 100,000 (Mahapatra 2004).

Current Therapies

Despite many efforts, disease-modifying treatment is not yet available for CBD. Active research is ongoing to find treatments for CBD and related neuropathological disorders (Marsili 2016).

In the absence of disease-modifying therapies for CBD, management is based on relieving symptoms and assisting patients with their activities of daily living. Advanced care planning and non-pharmacological supportive therapies are very important. Non-pharmacological supportive therapies include diet consultation (due to frequency of swallowing difficulty and poor appetite), physical therapy to safely maintain strength and balance, and speech and occupational therapy. Most patients will be trialed on L-DOPA and amantadine, although there is only limited evidence that some patients may experience modest improvement in Parkinsonism with these drugs. A wide variety of other drugs are used to treat symptoms common in CBD. Examples include sertraline and citralopram (for depression), clomipramine and trazodone (for depression and behavioral symptoms), and diazepam (for dystonia and myoclonus) (Lamb 2016).

Pre-Clinical Research

No preclinical studies of cannabis or cannabinoids relevant to CBD or related neurodegenerative disorders were found.

Clinical Trials

No clinical trials of cannabis or cannabinoids relevant to CBD or related neurodegenerative disorders were found.

Observational Studies

No observational studies of cannabis or cannabinoids relevant to CBD or related neurodegenerative disorders were found.

National Medical Organization Recommendations

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the management of endocannabinoid deficiency were found.

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3

Dementia

ISSUE BRIEF ON DEMENTIA

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

Dementia is a general term to describe a decline in cognition (compared to a previously attained level of cognition) – to the point where it affects day-to-day life and social functioning. This decline can manifest as memory loss, diminished reasoning skills and executive functioning, and changes in personality and behavior.

One assessment may not adequately diagnosis dementia; therefore, clinicians may perform a variety of assessments. For the purposes of this brief, diagnostic criteria from the most recent publication of the Diagnostic and Statistical Manual of Mental Disorders is presented here (DSM-5; American Psychiatric Association, 2013). According to the DSM-5, dementia is introduced by a new term: *Major Neurocognitive Disorder*. Diagnostic criteria for Major Neurocognitive Disorder is taken verbatim from the DSM-5 and presented below:

A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
   1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and
   2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

B. The cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications.

C. The cognitive deficits do not occur exclusively in the context of a delirium.

D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

The section on Major Neurocognitive Disorder in the DSM-5 allows clinicians to further code by the origins of the neurocognitive disorder. These include: Alzheimer's disease, Frontotemporal lobar degeneration, Lewy body disease, Vascular disease, Traumatic brain injury, Substance/medication use, HIV infection, Prion disease, Parkinson's disease, Huntington's disease, Another medical condition, Multiple etiologies, and Unspecified. Definitions/criterion for these diseases are further provided in the DSM-5.

For the purposes of this issue brief, the term Dementia will be used over Major Neurocognitive Disorder because of the wider public's familiarity with the term and incorporation into common vernacular.

Prevalence

Approximately 47 million people were living with dementia worldwide according to 2015 estimates. Those numbers are expected to triple by 2050, with 9.9 million new cases projected to appear every year (Prince et al., 2015; World Health Organization, 2017). Patients with Alzheimer's Disease (AD) account for 60-80% of all dementia cases followed by those with vascular dementia. Other less prevalent conditions associated with dementia are dementia with Lewy bodies and frontotemporal dementia (Ahmed, 2016; Stevens et al., 2002).

Dementia is most prevalent among the aging population (Ferri et al., 2005) and is a major cause of dependency and disability among the elderly. It has been estimated to cost society $818 billion annually (Prince et al., 2015).

Current Therapies

Currently there are both pharmacologic and non-pharmacologic therapies available for dementia patients. A review of some common therapeutic options will be discussed below.

Pharmacological Interventions

Cholinesterase inhibitors are commonly prescribed as pharmacotherapy in dementia patients with mild to moderate cognitive and functional decline, including Alzheimer's dementia (Epperly et al., 2017), vascular dementia (Farooq et al., 2017), and Lewy body dementia (Velayudhan et al., 2017). This is because a dysfunctional cholinergic system often manifests in dementia patients. Cholinesterase inhibitors essentially slow the degradation of acetylcholine thereby allowing more of the neurotransmitter to be available for neuronal transmission. Common cholinesterase inhibitors include donepezil, rivastigmine, and galantamine, and these are relatively affordable treatments that are generally well-tolerated (Birks 2006). While cholinesterase inhibitors appear to be moderately effective in improving cognitive and functional status, the clinical meaningfulness of those changes are sometimes debated in the literature (Livingston et al., 2017; Epperly et al., 2017). In other words, a statistically significant change in dementia symptom scores may not necessarily translate into an observable, clinically significant improvement in dementia.

Memantine is another treatment used to manage cognitive decline and, to a lesser degree, neuropsychiatric symptoms (e.g., agitation). Glutamatergic neurotransmission may have a role in dementia (too much glutamate release has neurotoxic effects on cells). Therefore, memantine inhibits glutamate release as an N-methyl-D-aspartate (NMDA) receptor antagonist. According to a Cochrane review of memantine on dementia, evidence points to moderate efficacy of this drug on cognition and agitation in moderate to severe Alzheimer's disease patients and is well tolerated (McShane et al., 2009).

Neuropsychiatric symptoms associated with dementia (i.e., depression, agitation) have been treated with antipsychotics (primarily for agitation) and antidepressants (for depression and agitation). However, neuropsychiatric symptoms are poorly managed overall due to low evidence of efficacy (Bains et al., 2002; Nelson & Devanand, 2011) or harms when prescribed to dementia patients. For example, there has been evidence to suggest increased risk of mortality and cerebrovascular events with antipsychotic use in dementia patients (Schneider et al., 2005; Schneider et al., 2006).

Non-pharmacological Interventions

There has been some interest in investigating the benefits of physical exercise and cognitive engagement in dementia patients. According to Forbes et al. (2015), there is little evidence to suggest that incorporating regular, physical exercise will improve cognition or neuropsychiatric symptoms in dementia patients. However, exercise may improve the ability for dementia patients to perform daily activities (Forbes et al., 2015).

Interest in cognitive engagement in dementia patients operates under the general idea that being cognitively stagnant accelerates cognitive decline. A couple Cochrane Reviews suggest that while highly structured cognitive tasks (some which focused on training in a particular cognitive domain) showed little evidence of improving cognitive function, more generalized cognitive engagement that exposed patients to a wide range of activities improved cognitive and social functioning (Bahar-Fuchs et al., 2013; Woods et al., 2012).

Preclinical Studies

There are a number of preclinical studies that suggest the role of the endocannabinoid system in dementia, particularly Alzheimer's pathology. While clinical studies (which are discussed a later section) focus on managing dementia-related symptoms, a perusal of preclinical publications suggests great interest in manipulating the endocannabinoid system to control and even reverse the progression of dementia pathology. Since the focus of preclinical dementia research is quite variable – from methods to interfere with endocannabinoid metabolism to the development of a cannabinoid receptor knockout mouse model – this brief presents some studies that are most relevant to MN's program. More precisely, the preclinical research below all investigate the role of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) specifically – the primary cannabinoids found in MN's medical cannabis products.

Iuvone T, Esposito G, Esposito R, Santamaria R, Di Rosa M, Izzo AA. Neuroprotective effect of cannabidiol, a non-psychoactive component from Cannabis Sativa, on β-amyloid-induced toxicity in PC12 cells. *Journal of Neurochemistry*. 2004; 89: 134-141.

This study explored potential neuroprotective effects of the cannabinoid cannabidiol (CBD) on β-amyloid (Aβ)-induced neurotoxicity. Alzheimer's disease patients show accumulation of Aβ peptide which induces oxidative stress on cells thus leading to an inflammatory response and apoptosis (programmed cell death). Therefore, these investigators examined whether the administration of CBD may reverse those effects. Cultured pheocromocytoma PC12 cells in rats were treated with Aβ alone (Aβ-only) or in conjunction with CBD (Aβ+CBD). In the Aβ+CBD condition, CBD was administered immediately before Aβ. A third experimental condition included the administration of a CB1-receptor antagonist (SR141716A) 10 minutes prior to CBD administration (Aβ+CBD+SR141716A). Cell viability was measured via 3(4,5-dimethylthiazol-2yl)2,5-diphenyl-2H-tetrazolium bromide (MTT) conversion assay. Reactive oxygen species (ROS) formation and malondialdehyde (MDA) accumulation (respectively indicators of cellular oxidation and lipid peroxidation) were also measured. Investigators also observed for presence of caspase 3 protein as well as any evidence of DNA fragmentation (both are markers of apoptosis).

Close to 40% of PC12 cells incubated with Aβ for 24 hours had died (Aβ-only condition), supporting Aβ's neurotoxic effects. Administration of CBD immediately before Aβ (Aβ+CBD) significantly reduced cell death compared to the Aβ-only condition, with administration of higher concentrations of CBD leading to greater neuroprotection (fewer cell deaths). ROS accumulation had increased in Aβ-only cells compared to untreated cells, and Aβ+CBD cells showed significantly reduced ROS accumulation. The concurrent administration of CB1-receptor antagonist SR141716A in Aβ+CBD-treated cells (Aβ+CBD+SR141716A) showed similar levels of ROS attenuation as Aβ+CBD-treated cells, suggesting that CBD's neuroprotective effects are not mediated via CB1 receptors. MDA levels were significantly higher in Aβ-only treated cells compared to untreated cells, with Aβ+CBD treated cells showing fewer MDA accumulation compared to Aβ-only cells. Higher concentrations of CBD in Aβ+CBD treated cells showed greater reductions in MDA accumulation. The apoptosis assay (via appearance of caspase 3 band in PC12 cells) showed that Aβ-only cells showed significant apoptosis within 6 hours of Aβ

administration; administration of Aβ+CBD reversed those effects. Results also showed that untreated cells showed no DNA fragmentation while Aβ-treated cells showed fragmentation. Concurrent CBD administration (Aβ+CBD), especially at higher concentrations, appeared to decrease signs of DNA fragmentation. Lastly, while intracellular calcium levels were significantly elevated in Aβ-treated cells, calcium levels were comparatively lower in Aβ+CBD-treated cells. Results suggest to the authors that CBD may have neuroprotective, anti-apoptotic, and anti-oxidative effects against Aβ peptide toxicity.

Eubanks LM, Rogers CJ, Beuscher AE, Koob GF, Olson AJ, Dickerson TJ et al. A molecular link between the active component of marijuana and Alzheimer's disease pathology. *Molecular Pharmacology*. 2006; 3(6): 773-777.

This study examined the role of acetylcholinesterase (AChE) – an enzyme that metabolizes (breaks down) the neurotransmitter acetylcholine (Ach) – in β-amyloid (Aβ) accumulation. One of the hallmarks of Alzheimer's disease is cholinergic dysfunction, specifically a decrease in cholinergic transmission in Alzheimer's patients. Previous research has shown that AChE may actually induce and accelerate Aβ formation in Alzheimer's disease and that AChE activity may be inhibited by compounds that can bind to the AChE peripheral anionic site (PAS; located on surface of AChE). This suggests that PAS of AChE may be a possible therapeutic target to inhibit AChE activity and, thereby prevent further Aβ formation. For example, propidium, a ligand that can bind to PAS of AChE has been shown to decrease human AChE activity and further prevent Aβ accumulation in vitro (Bartolini et al., 2003). Based on the chemical and structural characteristics of the cannabinoid THC, the authors hypothesized that THC may also be able to bind to PAS of AChE to inhibit AChE activity and prevent Aβ accumulation. AChE activity was measured via colorimetric determination assay, and Aβ peptide aggregation was measured via the thioflavin T-based fluorometric assay (more Aβ aggregation manifests as greater fluorescence in this assay).

Results revealed a proposed docking site of THC to mouse AChE. More importantly, THC was shown to inhibit AChE, with greater concentrations of THC associated with greater AChE inhibition. Additional experiments mixing AChE with THC + propidium revealed that the addition of propidium (a PAS ligand like THC is proposed to be) doesn't lead to greater inhibition than mixing AChE with THC only. This suggests that THC and propidium cannot bind to AChE simultaneously (PAS binding can occur for either compound but not at the same time). Lastly, the fluorometric assay analysis suggested that THC – like propidium – can inhibit AChE-induced Aβ aggregation; mixing AChE with THC showed decreased Aβ staining/fluorescence compared to controls.

Cao C, Li Y, Liu H, Bai G, Mayl J, Lin X, et al. The potential therapeutic effects of THC on Alzheimer's disease. *Journal of Alzheimer's Disease*. 2014; 42(3): 973-984.

These authors introduced the cannabinoid THC to N2a-variant amyloid-β protein precursor cells (N2a/AβPPswe) to observe for Aβ aggregation in vitro. Aβ is secreted at high levels in N2a/AβPPswe cells; therefore, these cells were chosen as an exploratory target for THC action. A prior study by Cao et al. (2009) showed evidence that caffeine suppressed brain Aβ

levels, with long-term administration decreasing Aβ deposits in hippocampal and cortical regions. Therefore, differences in Aβ aggregation in N2a/AβPPswe cells was measured in THC-only, caffeine-only, and THC+caffeine experimental conditions compared to control. Enzyme-linked immunosorbent assays (ELISA) were conducted to measure $Aβ_{40}$ levels (Aβ isoform that is most abundantly found in the brain) after N2a/AβPPswe cells were treated with THC or caffeine for 6 hours, 24 hours, and 48 hours.

Compared to control, THC-treated and caffeine-treated N2a/AβPPswe cells had lower concentrations of $Aβ_{40}$. Furthermore, these reductions in $Aβ_{40}$ levels in both treatment conditions occurred in a dose-dependent manner; higher concentrations of THC and caffeine both lead to greater reductions in $Aβ_{40}$. This was true for all incubation time periods (6 hrs vs. 24 hrs. vs 48 hrs). Data also showed that lower doses of THC was necessary to establish dose-dependent decreases in $Aβ_{40}$ accumulation compared to caffeine, suggesting greater efficacy of THC in inhibiting Aβ production. Interestingly, incubation of both THC and caffeine in N2a/AβPPswe cells did not further enhance $Aβ_{40}$ inhibition compared to THC treatment alone; this suggests the lack of a synergistic effect of both treatments to inhibit Aβ production. Additional experimentation with a one-time treatment or repeated treatments of THC also demonstrated that repeated treatments were more effective in Aβ inhibition, particularly at higher THC doses. To establish that THC and caffeine did not have neurotoxic effects on N2a/AβPPswe cells, a 3(4,5-dimethylthiazol-2yl)2,5-diphenyl-2H-tetrazolium bromide (MTT) conversion assay was performed. MTT assay established that THC and caffeine were not neurotoxic to N2a/AβPPswe cells indicating relative safety of these treatments. Additional study with THC-treated N2a/AβPPswe cells in a fluorometric assay was indicative of decreased Aβ aggregation as evidenced by decreased intensity of fluorescence in Aβ. Furthermore, greater reductions of fluorescence in Aβ was associated with higher THC concentrations. Lastly, because overexpression of glycogen synthase kinase 3 (GSK-3) and tau is associated with Alzheimer's disease pathology, additional assays were performed to measure their expression with THC treatment. Data showed a dose-dependent effect of THC on GSK-3 and tau levels; greater THC concentrations decreased their expression. Overall, results suggest that THC and caffeine may be safe treatment options that can inhibit Aβ production and other markers of Alzheimer disease pathology in vitro.

Clinical Trials

A small handful of clinical trials were identified for dementia with all of them focusing on management of neuropsychiatric symptoms, particularly agitation. Overall safety profile of cannabinoids appears favorable in the treatment of dementia patients. However, the lack of consistent results across studies limits the strength of the evidence (Krishnan et al. 2009). Future studies would benefit by increasing sample sizes, greater efforts to standardize across study protocols, increasing treatment duration, and possibly increasing cannabinoid dosing in dementia patients.

van den Elsen GA, Ahmed AI, Verkes R-J, Kramers C, Feuth T, Rosenverg PG, et al. Tetrahydrocannabinol for neuropsychiatric symptoms in dementia: a randomized controlled trial. *Neurology*. 2015; 84(23): 2338-2346.

This was a randomized, double-blind, placebo-controlled multi-center study with dementia patients exhibiting neuropsychiatric symptoms (n=50). The authors explored the idea that THC may be a pharmacological alternative to treating neuropsychiatric symptoms. Participants were randomly assigned to one of two treatment arms (parallel design)—either 4.5 mg THC tablet (Namisol) daily (split into three 1.5 mg doses at specific times of the day) or placebo tablet. The primary measure was scores on the Neuropsychiatric Inventory (NPI), which was measured at baseline, 14 days, and 21 days after the start of treatment. Participants diagnosed with Alzheimer's disease, vascular dementia, or mixed dementia were eligible for the trial as long as they had an NPI score of at least 10 and also experienced agitation/aggression, and atypical motor behavior at least a month before the screening. NPI scores had decreased in both treatment groups at day 14 and 21, but these scores between the THC (n = 24) and placebo (n = 26) groups were not statistically different from each other. Therefore, THC did not improve neuropsychiatric symptoms over placebo. The authors concluded that the lack of a treatment effect would likely not have changed had they been able to recruit the initial target number of patients (design goal was 130 patients) by way of conditional power analysis. Lastly, results indicated that a 4.5 mg daily dose was well tolerated in this patient group, encouraging the authors to suggest further study with increased dosing in this patient population.

van den Elsen GA, Ahmed AI, Verkes R-J, Feuth T, van der Marck MA, Rikkert MGM. Tetrahydrocannbinol in behavioral disturbances in dementia: A crossover randomized controlled trial. *Am J Geriatr Psychiatry*. **2015; 23(12): 1214-1224.**

This was a randomized, double-blind, placebo-controlled repeated crossover study with dementia patients exhibiting neuropsychiatric symptoms. The primary objective of the study, similar to the research paper listed directly above, was to examine the efficacy of THC (in tablet form; Namisol) in treating neuropsychiatric symptoms. Participants underwent 6 treatment blocks in which each block consisted of an active treatment arm for 3 days and placebo for 3 days, followed by a 4-day washout period. Within each block, the order of treatment was randomized. THC dosage for blocks 1-3 was 1.5 mg split into two doses (0.75 mg twice daily), with an increase in dosage in blocks 4-6 to 3 mg (1.5 mg twice daily). Participants with Alzheimer's disease, vascular or mixed dementia were eligible for the study if they scored at least a 10 on the Neuropsychiatric Inventory (NPI) and also experienced agitation or aggression. A total of 20 participants completed the study. Results showed no improvements in neuropsychiatric symptoms over placebo at both the low (1.5 mg daily) and high doses (3 mg daily). Neuropsychiatric symptoms, as measured by the NPI, had worsened for both placebo and THC groups over the 12-week study period. In addition, THC did not lead to decreases in agitated behavior or caregiver burden compared to placebo. Adverse events were similarly distributed across THC and placebo arms and were of mild to moderate severity.

Volicer L, Stelly M, Morris J, McLaughlin J, Volicer BJ. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *International Journal of Geriatric Psychiatry*. **1997; 12: 913-919.**

This was a double-blind, placebo controlled crossover study where the primary objective was to investigate the effects of dronabinol (synthetic THC) on anorexia in Alzheimer's disease patients. In this 12-week study, patients were randomly assigned to one treatment arm (dronabinol capsule or placebo) for the first half (6 weeks) and were switched to the other treatment in the second half of the study (6 weeks). 5 mg of dronabinol was administered daily in two doses (2.5 mg each). Body weight, caloric intake, and skin-fold measures were dependent measures in this study. In addition, agitation (Cohen Mansfield Agitation Inventory; CMAI) and mood measures (Lawton Observed Affect Scale) were also collected in this study. A total of n = 12 patients were included in the analysis. While the amount of calories consumed did not change over the course of the study (nor were there any differences in caloric intake between treatment groups), body weight increased over the 12-week period with greater gains found in the patients who started on dronabinol first. Tricep skin fold thickness also showed an increase over the 12-week study and was not affected by treatment order. More importantly, for the purposes of this research brief, there was a decrease in agitated behavior compared to baseline during the dronabinol treatment phase as measured by the CMAI. In addition, for patients who received dronabinol first, the decrease in agitated behavior persisted during the placebo phase that followed (authors do not explain what may underlie this persistence in the absence of any active treatment). Lastly, there was a decrease in negative affect over the 12-week study with this decrease being more pronounced during dronabinol treatment. Those who received dronabinol first showed a greater decrease in negative affect than those receiving placebo first.

Walther S, Schüpbach B, Seifritz E, Homan P, Strik W. Randomized, controlled crossover trial of dronabinol, 2.5 mg, for agitation in 2 patients with dementia. *Journal of Clinical Psychopharmacology.* 2011; 31(2): 256-257.

This was a very small (n=2) randomized, double-blind crossover study investigating the effects of dronabinol on nighttime agitation and circadian disturbances. The study period was for 4 weeks in which one of the patients was randomly assigned to receive dronabinol for the first half (first 2 weeks) followed by placebo (second 2 weeks). The second patient had the opposite treatment order as the first patient. For the active treatment arm, a daily 2.5 mg evening dose of dronabinol was administered to patients. Patients wore a device on their wrist (worn like a wristwatch) to monitor nighttime agitation and circadian disturbances (continuous wrist actigraphy). Actigraphy was monitored from 9 pm to 6 am. In addition, the neuropsychiatric inventory (NPI) was administered weekly for patients to measure behavioral disturbances. The patient who received dronabinol first showed decreases in nocturnal motor activity (as measured by continuous wrist actigraphy) from baseline but saw a rebound to baseline levels by the 4th week (2nd week of placebo arm). The patient who received dronabinol last (3rd week of study, 1st week on dronabinol) saw a decrease in nocturnal activity in that 1st week but then saw an increase in nocturnal activity again. Nonparametric circadian rhythm analysis (NPCRA) showed that dronabinol improved circadian rhythms; both patients showed decreased fragmentation in circadian rhythms, stronger rhythms, and more stable interdaily rhythms during dronabinal treatment. Lastly, while NPI scores showed some decline during the study period (more apparent in the patient receiving dronabinol first), the authors

noted that behavioral changes were very small clinically speaking across all NPI subdomains. The authors do not discuss results specifically on the agitation subdomain of the NPI. The major limitation of this study is the sample size which prevents results being analyzed statistically (conclusions based on descriptive analysis). Compared to the preceding clinical studies discussed above, it is also important to note that agitation as defined here is conceptually different from the studies above (nocturnal motor activity = agitation at night). Overall, apart from a potential signal of dronabinol having a regulatory role in circadian rhythms, the conclusions that can be drawn in this study are minimal due to study limitations.

Ongoing Clinical Trials

As of mid-August 2017, two ongoing clinical trials were identified via ClinicalTrials.gov that investigated the effects of cannabis/cannabinoids on dementia, particularly dementia-related agitation. They are discussed below to the extent information is available through the ClinicalTrials.gov website.

Trial of Dronabinol Adjunctive Treatment of Agitation in Alzheimer's Disease (AD) (THC-AD) (THC-AD). https://clinicaltrials.gov/show/NCT02792257

This is a randomized, parallel assignment in-patient study of Dronabinol or placebo to Alzheimer's patients (age 60-90) exhibiting agitation (Agit-AD). Investigators state that there are no FDA-approved meds for Agit-AD—"off-label" meds commonly given for Agit-AD (i.e., antidepressants, antipsychotics). Study purpose is to see how agitation in AD patients is affected by Dronabinol vs. placebo, with hypothesis that agitation will be decreased with Dronabinol. Treatment duration is for 3 weeks, with patients in the 1st week receiving 5 mg daily (split into two doses), then increasing to 10 mg daily (split into two doses) for the 2nd and 3rd week. Primary measures are: 1) Pittsburgh Agitation Scale, and 2) Neuropsychiatric Inventory (NPI). Secondary measure is 1) adverse events. Principal investigators are Drs. Paul Rosenberg and Brent Forester respectively of Johns Hopkins University and Mclean Hospital. Estimated study completion date is December 2020.

Safety and Efficacy of Nabilone in Alzheimer's Disease
https://clinicaltrials.gov/show/NCT02351882

This is a randomized, double blind, crossover study of Nabilone vs. placebo and its effects on agitation in AD patients (long-term care patients or outpatients, ≥55 years old). Participants will be in one treatment arm for 6 weeks followed by a one-week washout period, followed by the other treatment arm for 6 weeks (dosages not stated). Primary measure is 1) Cohen-Mansfield Agitation Inventory (CMAI). Secondary measures are: 1) Neuropsychiatric Inventory (NPI), 2) Standardized Mini-mental State Examiniation (xMMSE), 3) Severe Impairment Battery (SIB), 4) Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog), 5) Alzheimer's Disease Cooperative Study – The Clinician Global Impression (ADCS-CGIC). They will also monitor pain, nutritional status, heart rate, blood pressure, and monitor specific biomarkers. Principal investigators are Drs. Krista Lanctot and Nathan Herrmann respectively of Sunnybrook Research Institute and Sunnybrook Health Sciences Centre. Estimated study completion date is December 2017.

Observational Studies

Two observational studies examining the effects of cannabinoid administration on behavioral and neuropsychiatric symptoms were identified in dementia patients. These studies had small sample sizes limiting statistical power in addition to lacking a control group for comparative analysis. Authors from both papers suggest further study utilizing higher quality double-blind, randomized control trials with increased sample sizes.

Walther S, Mahlberg R, Eichmann U, Kunz D. Delta-9-tetrahydrocannabinol for nighttime agitation in severe dementia. *Psychopharmacology (Berl).* 2006; 185(4): 524-528.

This was an uncontrolled, open-label study investigating the effects of dronabinol on nighttime agitation and neuropsychiatric behavior in dementia patients (n=6). Preceding the Walther et al. (2011) randomized control trial discussed previously, this was a relatively short-term study involving dronabinol treatment for 2 weeks. Patients diagnosed with dementia (5 Alzheimer's dementia, 1 vascular dementia) and experiencing circadian rhythm disturbances and nighttime agitation were recruited for this study. A wrist actometer was worn by patients for the duration of the study to measures changes in nighttime motor activity (monitored activity counts) compared to baseline. In addition, the neuropsychiatric inventory (NPI) was measured at baseline and once again at the end of treatment. Dronabinol was administered as a 2.5 mg daily evening dose for 2 weeks. Motor activity counts were aggregated daily within 3 different data collection periods for the duration of the study: evening (3 pm-9 pm), nighttime (9 pm-6 am), and the diurnal period (6 am-9 pm). Motor activity counts during the last 5 days compared to baseline was the primary outcome measure. Overall results showed that activity counts had decreased by the end of the treatment period and was observed for the 3 different data collection periods (evening, nighttime, diurnal). Nocturnal motor activity had, on average, decreased by 59% compared to baseline levels. Total NPI scores had also decreased by the end of the study with the following NPI subscores showing decreases by end of treatment: agitation, nighttime behaviors, aberrant motor behavior, irritability, and appetite disturbances. The numeric change in NPI scores was not provided in the paper to assess whether this decrease fell in a clinically meaningful range.

Shelef A, Barak Y, Berger U, Paleacu D, Tadger S, Plopsky I, et al. Safety and efficacy of medical cannabis oil for behavioral and psychological symptoms of dementia: an open-label, add-on pilot study. *Journal of Alzheimer's Disease*. 2016; 51(1): 15-9.

This was an uncontrolled, open-label study looking at the effects of THC in oil form on neuropsychiatric symptoms, mental state, and global improvements in Alzheimer's patients. Patients (n=11) in this study underwent a 4-week treatment with 1.65% potency THC oil derived from cannabis flowers (cannabinoid profile verified via laboratory testing). Patients were started on a daily 5 mg THC dose split into two doses (8 am and 8 pm). Patients' daily dose was increased to 10 mg THC (5 mg twice daily) after two days if they experienced no adverse events or experienced minimal improvements. If the patient still experienced no adverse events or minimal improvements, patients could max out at 15 mg THC (7.5 mg twice daily). During the study, only 3 patients tolerated a dose increase while the others (n=7) remained at the minimal

dose during the 4-week treatment period. The following primary measures were collected at baseline and at the end of the second and fourth week of treatment: the neuropsychiatric inventory (NPI), Mini-Mental State Examination to measure cognitive impairment (MMSE), Clinical Global Impression Improvement (CGI-I), and Clinical Global Impression Severity (CGI-S). A total of 10 patients were included in the analysis (n=1 discontinued treatment). Total NPI scores showed improvements in neuropsychiatric symptoms as a function of treatment. Compared to baseline, total NPI scores had decreased in the second and fourth week indicating improvements in neuropsychiatric symptoms. Analysis of NPI subdomains showed overall improvements in the following: agitation/aggression, disinhibition, irritability/lability, aberrant motor behavior, caregiver distress, delusions, and sleep and nighttime behavior disorders.

National Medical Organization Recommendations

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the management of dementia were found.

The National Academies of Sciences, Engineering and Medicine published a report on the health effects of cannabis and cannabinoids in 2017. The committee for this report concluded that the evidence for cannabis/cannabinoids improving dementia-related symptoms is "limited due to the small number of patients enrolled, limits in the study design and reporting, and inconsistent effects. The current limited evidence does not support a therapeutic effect of cannabinoids" (see Conclusion 4-13; National Academies of Sciences, 2017).

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Clinical Endocannabinoid Deficiency

ISSUE BRIEF ON CLINICAL ENDOCANNABINOID DEFICIENCY

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

Clinical endocannabinoid deficiency (CED) has been proposed as a cause of several conditions, but at this point it remains a theory; no criteria have been proposed for making a diagnosis of CED. The idea of CED was presented in 2001 in two publications by Russo and more thoroughly explored in a 2004 article (Russo 2004) that has been cited frequently in the literature. The theory of CED was based on the concept that many brain disorders are associated with neurotransmitter deficiencies – for example dopamine deficiency in parkinsonian diseases – and that a comparable deficiency in endocannabinoid levels might be manifest similarly in certain disorders that display predictable clinical features as sequelae of this deficiency (Russo 2016). In his 2004 article, Russo described similarities in clinicopathological features and overlap in occurrence for three disorders as suggestive evidence of CED: migraine, fibromyalgia, and irritable bowel syndrome. The similarities cited

included hyperalgesic states that must be clinically diagnosed based on subjective criteria; lack of characteristic tissue pathology or laboratory findings; each is a diagnosis of exclusion that often generates extensive negative diagnostic work-ups; each has an increased incidence of anxiety and depression; and each has been labeled as psychosomatic in origin or a wastebasket diagnosis by skeptical clinicians (Russo 2004). Since 2004 many other disorders have been cited as possibly falling under the CED rubric (Russo 2014).

Identification of the parts of the endoncannabinoid system (ECS) and how they interact with each other and with other body systems remains an active area of investigation. Much remains unknown. The ECS consists of cannabinoids made by the body (endocannabinoids), enzymes that break down those cannabinoids, receptors that interact with endocannabinoids, and receptors and other cell structures that appear to be activated independently of endocannabinoids. Due to this complexity, the causes of an underperforming ECS could be many and could be different for different disorders. Simplistically, correcting CED could be approached in three ways, 1) increase the body's production of endocannabinoids (or administer plant-derived cannabinoids), 2) decrease endocannabinoid breakdown, and 3) increase or decrease receptor density or function (McPartland 2014). A recent review discusses a variety of approaches to enhancing the endocannabinoid system (McPartland 2014), including impact of over-the-counter and prescription drugs, dietary supplements and herbal remedies, chronic stress reduction practices, lifestyle modifications, and use of cannabis. The review outlines evidence of different effects of plant cannabinoids from acute versus chronic exposure and different impacts of THC, CBD, and other cannabis constituents. McPartland and Guy proposed that the many constituents of cannabis work, in part, by "jump-starting" the ECB system (McPartland 2004).

Prevalence

Migraine, fibromyalgia, and irritable bowel syndrome – as well as some of the other disorders suggested as results of ECD – are relatively common. However, the proportion of these disorders that might be primarily caused by an endocannabinoid deficiency is unclear.

Current Therapies

The recent review by McPartland et al (McPartland 2014) suggests a variety of strategies for enhancing the functions of the ECS, as described above.

Pre-Clinical Research

Numerous pre-clinical studies describe involvement of parts of the ECS in disorders suggested as resulting from CED. For a review, see Russo 2014.

Clinical Trials

Few or no clinical trials of cannabis or cannabinoids have been carried out for disorders suggested as resulting from CED. See Russo 2014.

Observational Studies

Few or no observational studies of cannabis or cannabinoids have been carried out for disorders suggested as resulting from CED. See Russo 2014.

National Medical Organization Recommendations

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the management of endocannabinoid deficiency were found.

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Liver Disease

ISSUE BRIEF ON LIVER DISEASE

Introduction

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Definition

Liver disease refers to damage to the liver caused by hereditary factors or lifetime exposures, such as alcohol use, obesity or viruses, and the subsequent effects of such damage. There are a few common pathways in liver disease: alcohol-related fatty liver disease, non-alcoholic fatty liver disease, and viral hepatitis. These pathways have distinct causes but share features of disease progression. Other less common pathways in liver disease are immune system abnormalities (autoimmune hepatitis, primary biliary cirrhosis, or primary sclerosing cholangitis), genetic conditions (hemochromatosis, hyperoxaluria and oxalosis, or Wilson's disease) and cancer or other growths (liver cancer, bile duct cancer, or liver adenoma) (Mayo Clinic. Liver Problems. 2017).

Diagnosis

Liver disease can be diagnosed using different modalities. Liver function tests are blood tests of enzymes and proteins which can approximate liver function, though they cannot provide a complete diagnosis. Imaging studies, including computed tomography (CT) scan, magnetic resonance imaging (MRI) and ultrasound can be used to examine liver damage. Finally, liver tissue biopsy can also diagnose liver damage and is considered the diagnostic standard (Mayo Clinic. Liver Problems. 2017).

Complications and Consequences

Liver inflammation (hepatitis) and damage can be caused by a number of lifestyle factors as well as genetic factors, but is commonly caused by viral infection (including infections of hepatitis A, B, or C virus). Liver damage secondary to alcoholic or non-alcoholic fatty liver disease begins with steatosis, an accumulation of fat in the liver. In some cases, steatosis is benign but in others it progresses to a state of inflammation, known as steatohepatitis. The inflammation stage is reversible with appropriate diagnosis and treatment. In the absence of treatment, scarring on the liver develops and eventually replaces healthy liver tissue (fibrosis). Fibrosis can be managed successfully; in the absence of intervention, however, patients with liver fibrosis progress to cirrhosis, an irreversible disease state in which the liver's normal architecture is disrupted. Cirrhosis develops in approximately 10-12% of patients with steatohepatitis within eight years (Bhala 2009) and its potential complications are serious, including liver cancer, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, portal hypertension, variceal bleeding and hepatorenal syndrome. The final stage of liver disease is liver failure, in which the liver loses all function. This condition can progress over years and is life-threatening. (American Liver Foundation, Heidelbaugh 2006)

Prevalence

Data from the Third National Health and Nutrition Examination Survey, which collected data from 1988-1994, found the prevalence of elevated aminotransferase levels, a common laboratory indicator of liver damage, to be 7.9% in U.S. adults (Clark 2003). The Centers for Disease Control and Prevention (CDC) estimates the morbidity of chronic liver disease and cirrhosis in the U.S. to be 1.6%, with an estimated attributable 12.0 deaths per 100,000 (National Center for Health Statistics).

Current Therapies

Current viral hepatitis treatment centers around direct acting antiviral drugs (DAA), which can be single drugs or combination therapy. These antiviral therapies achieve high rates of success: a 2016 systematic review of DAA therapy found that several current treatment regimes achieve sustained virological response (an indicator of successful therapy) rates of 90-95% in hepatitis C patients with cirrhosis (Majumdar 2016).

There are currently no approved medications for treatment of nonalcoholic fatty liver disease (NAFLD) and data or recommendations on medical therapy are therefore off-label. Treatment of low-risk NAFL disease, in which no fibrosis is present, focuses on lifestyle modifications like exercise and diet changes. A recent systematic review found that dietary and physical activity intervention found that a 5% weight loss in NAFLD cases or a 7-10% weight loss in nonalcoholic steatohepatitis cases, achieved by combined dietary restriction and exercise, had therapeutic benefit (Kenneally 2017). In higher-risk NAFLD cases with steatohepatitis with some fibrosis, the recommended first-line treatment is vitamin E; other agents with demonstrated therapeutic benefit are pioglitazone (a peroxisome proliferator-activated receptor-γ agonist), liraglutide (a GLP-1 agonist) and metformin (an insulin sensitizer) (Banini 2017).

Patients who develop cirrhosis are managed similarly, regardless of underlying etiology. An expert panel published cirrhosis management guidelines in 2010 (Kanwal 2010) in which treatment diverges based on calculated Model for End-stage Liver Disease[1] scores; patients with scores of >15 or ≤15 in the presence of complications should be considered for liver transplant. Short of consideration for transplant, treatment focuses on surveillance for and management of disease complications.

Ascites treatment involves salt restriction and diuretic therapy (typically a combination of spironolactone and a loop diuretic). Spontaneous bacterial peritonitis, a complication related to untreated ascites, is treated with antibiotics. Patients with hepatic encephalopathy are graded on severity of encephalopathy as well as reversible factors, which include constipation, noncompliance, infection, electrolyte imbalance, gastrointestinal bleeding and benzodiazepine use, should be mitigated. If hepatic encephalopathy persists, the patient should be medically treated with dissacharides or rifaximin. Finally, if the patient develops or presents with bleeding esophageal varices, the patient should be treated with beta blockade. In the case of acute bleeding, more aggressive treatment with antibiotics and hospitalization may be necessary (Starr 2011).

When liver damage reaches the point of loss of function and failure, the treatment goal is preservation of remaining liver function or liver transplant if preservation is not possible. Liver transplantation can be complicated by infection or rejection of the transplanted liver; one large study reported survival at one, five, and ten years post-transplant to be 79%, 67% and 57%, respectively (Jain 2000).

Pre-Clinical Research

The endocannabinoid system, which includes the endogenous cannabinoids (endocannabinoids) as well as the cannabinoid receptors (CB1 and CB2) to which cannabinoids bind, is still a relatively new field of scientific inquiry. A number of recent studies have investigated the involvement of the endocannabinoid function on various aspects of liver disease, including development of fatty liver disease (steatosis), fibrosis, cirrhosis and liver

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[1] https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/

failure in the presence of different underlying etiology. General findings suggest that upregulation of CB1 receptors is associated with onset of liver disease and increased markers of disease progression; some studies find that CB2 receptor activation is also associated with liver disease progression but others suggest that CB2 receptor activation may play a role in reversing disease progression. Several studies focus on rimonabant, a CB1 receptor antagonist, to understand CB1 receptor's role. The studies summarized below are representative of current published evidence on the impact of cannabinoids and the endocannabinoid system on liver function.

Gabbay E, Avraham Y, Ilan Y, Israeli E, Berry EM. Endocannabinoids and liver disease- review. *Liver International* 2005; 25:921-926.

The authors review existing literature at the time of publication regarding the involvement of the endocannabinoid system on various manifestations of liver disease. Summarizing studies on the effects of endocannabinoids or their receptor antagonists on hemodynamics as part of liver disease, the authors note that ascites, or accumulation of fluid in the peritoneal cavity most commonly linked to cirrhosis, is associated with increased plasma levels of lipopolysaccharide (LPS), a bacterial endotoxin. Studies have shown LPS levels to be inversely associated with liver function and linked to worse short-term survival. As peripheral CB1 receptor activation by macrophage- and platelet- derived substances has been found to promote hypotension, the relationship between anandamide and hemodynamic instability was explored by the authors in previous work. The authors found that platelets and macrophages generate different endocannabinoids which may both mediate endotoxin-induced hypotension by activating vascular CB1 receptors. Further studies found that CB1 receptor antagonism improved hypotension in rats with biliary cirrhosis and CCl$_4$-induced cirrhosis; similar effects were observed on arterial pressure and peripheral resistance in another rat study. The authors also cite a study that found that in cirrhotic liver samples, CB1 receptors were three times more prevalent on endothelial cells as compared to healthy liver samples, and conclude that in cirrhosis, monocytes increase endocannabinoid production which contributes to hemodynamic deterioration, with a probable mechanism of mediating between endotoxins and blood vessels.

The authors also include data on serum cannabinoids to note that in endotoxic shock during liver disease progression, serum endocannabinoid levels are markedly higher than non-diseased controls. They also cite a study pointing to pro-apoptotic effects of anandamide, an endocannabinoid. In neurological features of liver disease, the authors note that CB1 receptor blockade can improve neurologic function in mice with induced liver failure accompanied by hepatic encephalopathy. Finally, the authors cite a study involving PRS-211,092, a synthetic, non-psychoactive cannabinoid which showed reduction in liver injury in mice upon treatment with PRS-211,092. The authors cite two clinical studies: the first is a cross-sectional study on patients in Brazil using cannabis, with or without use of alcohol or crack cocaine. The study found that chronic marijuana use may have hepatotoxic effects. The second study, a case series of three patients with intractable cholestatic-related pruritis, found that administration of Marinol, a synthetic THC medication, reduced pruritis and improved sleep in all three patients.

The authors conclude their review by stating that while little is known about the effect of endocannabinoids and blockade of their receptors on liver physiology and disease, there is evidence they play a role in hemodynamic compromise in the presence of cirrhosis, likely due

to increased endocannabinoid production which results in vasodilation. They also note that increase in serum anandamide is linked to acute and chronic liver disease, and anandamide exerts an apoptotic effect on liver cells. They note that certain cannabinoids, possibly PRS-211,092,m may improve hepatic inflammation and pruritus in liver disease, but more data are needed to support this.

Purohit V, Rapaka R, Shurtleff D. Role of Cannabinoids in the Development of Fatty Liver (Steatosis). *American Association of Pharmaceutical Scientists Journal*, June 2010; 12(2):233-237.

This review article from the National Institute on Drug Abuse summarizes a number of pre-clinical and observational studies examining the role of CB1 and CB2 receptor activation in the development of fatty liver, an early stage of alcoholic and non-alcoholic fatty liver disease and hepatitis C. They examine the roles of CB1 and CB2 receptor activation in non-alcoholic and alcoholic fatty liver disease.

Regarding the role of CB1 receptors in development of fatty liver disease, the authors examine a study by Jeong et al. in which wild-type mice were exposed to ethanol and, in contrast to a control group, developed fatty liver and corresponding elevated disease markers (2-AG) as well as increased expression of genes encoding CB1 receptors in liver tissue; however mice treated with rimonabant, a CB1 receptor antagonist, did not develop fatty liver after ethanol exposure. Subsequent experiments examining ethanol exposure in wild-type versus global and hepatocyte-specific CB1 receptor knockout mice showed that the effects of ethanol on liver disease markers (transcription factor-SREBP-1c and fatty acid synthase) were blunted among all CB1 receptor knockout mice.

To examine CB1 receptor activation in non-alcoholic fatty liver, the authors cite a study by Osei-Hyiaman et al. in which wild type mice and global CB1 knockout mice are given a high-fat diet to cause non-alcoholic fatty liver; the wild type mice become obese and develop fatty liver while the CB1 receptor knockout mice remain lean and do not develop fatty liver. Additionally, wild type mice who were treated with rimonabant did not experience increased rates of fatty acid synthesis when fed a high-fat diet. The authors conclude that this study points to an inhibitory effect of a CB1 receptor antagonist on fatty liver development and a promoting effect of CB1 receptor agonist on fatty liver development. The authors also cite a study by Gary-Bobo et al. on the role of CB1 receptors in the development of obesity-induced fatty liver in genetically obese rats. This study found that rimonabant treatment had a protective effect against fatty liver: liver slices of rimonabant treated obese rats were found to be histologically similar to those of lean rats.

The authors also reviewed studies on the role of CB2 receptors on fatty liver development but noted that relative to the role of CB1 receptors, it is underinvestigated. They cite findings from Mendez-Sanchez et al. that showed upregulation of CB2 receptors in liver samples from patients with steatosis. Another study by Deveaux et al. found that hepatic CB2 receptor knockout mice did not develop severe fatty liver after being given a high-fat diet, in contrast to wild type mice which developed the disease after being given a high-fat diet.

Finally, the authors include a study by Hezode et al. that found daily cannabis smoking to be an independent predictor of steatosis in patients with chronic hepatitis C. Summarizing

the reviewed findings, the authors conclude that upregulation of CB1 receptors plays a role in fatty liver development and upregulation of CB2 receptors may also play a similar role, though evidence is not sufficient to determine this.

Avraham Y, Grigoriadis NC, Poutahidis T, Vorobiev L, Magen I, Ilan Y, Mechoulam R, Berry EM. Cannabidiol improves brain and liver function in a fulminant hepatic failure-induced model of hepatic encephalopathy in mice. *British Journal of Pharmacology* **2011;162:1650-1658.**

This study examined the effect of cannabidiol on mice treated with a hepatotoxin to induce acute liver failure, the end-stage progression of liver disease. The mice were randomly assigned to groups of 10 and half were injected with thioacetamide (TAA) in saline to induce liver failure; the other half were injected with vehicle saline to serve as controls. Cannabidiol extract was injected into half of the TAA-treated rats and half of the vehicle-treated mice in a single dose of 5mg/kg. The other half were treated with the cannabidiol (CBD) vehicle solution to serve as controls. Neurological function (10-point scale based on reflexes and task performance); activity, cognitive function (assessed by maze performance), brain histopathology and immunochemistry, liver histopathology and serum ammonia, liver enzymes and bilirubin levels were assessed after treatment. The study found that the mice treated with CBD and TAA had improved neurological scores and cognitive function, as well as reduced astrogliosis in brain samples as compared to mice treated with a vehicle control and TAA. Furthermore, treatment with TAA showed increased markers of liver dysfunction (ammonia, bilirubin and liver enzymes aminotransferase and alanine aminotransferase) compared to controls, but the mice treated with CBD were less susceptible to the effect of TAA with regard to hepatic encephalopathy, a grouping of neuropsychiatric abnormalities often observed in tandem with liver failure. The authors conclude that CBD appears to exhibit a multifactorial beneficial effect on liver failure and may be a future therapeutic agent.

Clinical Trials

Currently there are no clinical trials, either complete or underway, examining the effect of whole plant cannabis, THC, or CBD on liver disease. There are a few ongoing and completed trials involving cannabinoids or CB1 receptor antagonists for the treatment of liver disease which are outlined below. Additionally two safety and efficacy studies on Rimonabant, a selective CB1 antagonist, for the treatment of nonalcoholic steatohepatitis which were terminated when the medication was withdrawn, are also described below.

GW Pharma completed a preliminary safety and efficacy pilot study examining the combined and independent effects of two tetrahydrocannabivarins, GWP42003 and GQP42004 for the treatment of type II diabetes for a 13-week period. Tetrahydrocannabivarin (THCV) is a cannabinoid typically present in small amounts in cannabis. THCV is a homologue of THC. It has a propyl side chain instead of THC's pentyl group, which makes it produce different effects than THC. Primary outcome is change in mean serum high density lipoprotein cholesterol concentration, and secondary outcomes include change in mean percent liver fat. The study results are not published, but the results reported on the study's ClinicalTrials.gov website show no differences (P > 0.05) in change from baseline to end of study in mean percent liver fat in each of the following comparisons 1) 1:1 GWP42003:GWP42004 to placebo; 2) 20:1

GWP42003:GWP42004 to placebo; 3) GWP42003 and placebo to placebo; 4) GWP42004 and placebo to placebo. More information about this trial can be found at:

GWMD1092 – GQP42003: GWP42004 Together Plus Alone in Type II Diabetes:
https://clinicaltrials.gov/ct2/show/results/NCT01217112?term=cannabis&cond=liver&rank=4&sect=X01256

Pfizer completed a trial on CP-945598 (otenabant) a high affinity, selective CB1 receptor antagonist for the treatment of non-alcoholic steatohepatitis. This was a Phase 1 trial investigating the steady-state safety, tolerability and pharmacokinetics of the medication; it was first received by ClinicalTrials.gov in June 2008 and last updated in August 2009 without posting study results. Primary outcome measures were Urine 6-β-hydroxycortisol:cortisol ratio, adverse event monitoring, physical examinations, sitting vital sign measurements, 12-lead electrocardiograms and laboratory safety assessments, and pharmacokinetic data on the medication and its primary metabolite. Published data on the study is not available. More information can be found at:

Phase 1 Pharmacokinetic Study of CP-945598 In Patients with NASH:
https://clinicaltrials.gov/ct2/show/NCT00706537?term=cannabis&cond=liver&rank=1

Sanofi-Aventis sponsored two trials to investigate the safety and efficacy of Rimonabant in treating non-alcoholic steatohepatitis; one study focused on patients with Type II diabetes and the other focused on non-diabetic patients. Both studies were first posted on ClinicalTrials.gov in December 2007; as of April 2016, both trial websites report that the trials were terminated by Sanofi-Aventis in compliance with national health authorities. No data on primary outcomes (mean change per year in non-alcoholic fatty liver disease activity score) or secondary outcomes (change from baseline in hepatic fibrosis score, change from baseline in serum hyaluronate and hepatic transaminases) were reported for either study. More information on these studies can be found at:

An Efficacy and Safety Study of Rimonabant for Treatment of Nonalcoholic Steatohepatitis (NASH) in Patients Without Diabetes:
https://clinicaltrials.gov/ct2/show/NCT00576667?term=cannabis&cond=liver&rank=3

An Efficacy and Safety Study of Rimonabant for Treatment of Nonalcoholic Steatohepatitis (NASH) in Patients With Type 2 Diabetes:
https://clinicaltrials.gov/ct2/show/study/NCT00577148?term=cannabis&cond=liver&rank=2&view=record

Observational Studies

A small number of cross-sectional and longitudinal studies also examine the relationship between liver disease progression and cannabis use in selected populations, with conflicting findings. Some studies report that cannabis use is linked to prevalence of steatosis while others, including a few longitudinal cohort studies, find no association or a protective effect of cannabis against incidence or progression of liver disease. The summaries below represent the level of observational evidence currently available to describe the effect of cannabis on measures of liver disease burden.

Kelly EM, Dodge JL, French AL, Glesby MJ, Golub ET, Augenbraun M, Plankey M, Peters MG. Marijuana Use Is Not Associated With Progression to Advanced Liver Fibrosis in HIV/Hepatitis C Virus-coinfected Women. *Clinical Infectious Diseases* **2016; 63:512-518.**

This prospective observational study followed 575 females co-infected with HIV and hepatitis C virus (HCV) and enrolled in the Women's Interagency HIV study to examine whether cannabis use was associated with liver disease progression. Cohort patients are seen in follow-up every six months as part of the study; this includes collection of medical data, physical examination, biological specimen collection and sociodemographic and behavioral data collection. Aspartate aminotransferase to platelet ratio index (APRI) and the fibrosis-4 score (FIB-4) were used as noninvasive measures of liver fibrosis to assess disease progression. Marijuana use (described by the authors as tetrahydrocannabinol (THC) use) was assessed at each follow-up interview and use patterns were defined as less than once a month, more than once per month but less than once per week, once a week, 2-3 times a week, 4-6 times a week, or 1 or more times per day.

Predictors of progression to advanced fibrosis (FIB-4 > 3.25) were evaluated using Cox proportional hazards regression with backward elimination to determine a final model. Of the 575 patients who were included in this analysis, mean follow-up was 11 years. The study group was mostly African American (63%) with HCV genotype 1 (88%) and had a mean HCV viral load of 6.1 $\log_{10}$ IU/mL, mean HIV RNA of 4.1 IU/mL and CD4 count of 375 cells/μL at study entry. At baseline, 2% of study patients had significant fibrosis and were eliminated from the analysis. Comparison of patients by THC usage group showed that all groups were generally similar in demographics and baseline clinical characteristics, but THC users were more likely to use cigarettes, alcohol and intravenous drugs. Among included patients, 83% were ever-THC users at the time of enrollment; 44% had used THC within 6 months of enrollment and 19% used THC weekly or more frequently.

During the study period, 51% of patients developed significant fibrosis, and incidence of fibrosis during follow-up did not vary between THC use groups. Independent predictors of significant fibrosis were FIB-4 score at entry, lower entry CD4 count and alcohol use. The authors examined the relationship between THC use and significant fibrosis by modeling THC use as average number of uses per week or as a categorical variable (<1 use per week, 1 use per week, 2-3 uses per week, 4-7 uses per week or no THC use) and failed to find a significant relationship. Parallel analysis was conducted on patients who entered the study with fibrosis (FIB-4 score of >1.5); among this subset, the same variables were found to be independent predictors of fibrosis and marijuana use was not associated with fibrosis in this group.

Limitations of this study include its observational nature, as well as the self-reported behavioral data which may have resulted in under-reporting of THC and alcohol use. Additionally, the study used non-invasive clinical markers of fibrosis to measure disease progression rather than liver biopsy, which would provide more accurate results.

Hezode C, Zafrani ES, Roudot-Thoraval F, Costentin C, Hessami A, Bouvier-Alias M, Medkour F, Pawlostky J. Daily Cannabis Use: A Novel Risk Factor of Steatosis Severity in Patients with Chronic Hepatitis C. *Gastroenterology* **2008;134:432-439.**

This cross-sectional study examined predictors of steatosis in consecutively enrolled patients with untreated hepatitis C virus (HCV) infection who underwent liver biopsy. Inclusion criteria were positive anti-HCV antibody test documented for at least 6 months, available biopsy which confirmed chronic hepatitis C infection and available fasting glucose, triglyceride and cholesterol levels at the time of biopsy. Patients with concomitant hepatitis B infection or human immunodeficiency virus (HIV) infection or with a history of immunosuppression were excluded; patients who used illicit drugs other than marijuana or who had previously been treated for chronic hepatitis C were excluded. Demographic data and behavioral data were collected, as well as laboratory and histopathologic data from livery biopsy. Cannabis use was characterized by three classifications: 1) nonusers, 2) occasional users who smoked less than one daily cigarette and 3) daily users who smoked at least one daily cigarette. Stepwise logistic regression was used to determine independent predictors of steatosis. A total of 315 patients were enrolled from May 2003 to June 2006; patients were mostly male with a mean age at biopsy of 45 years and mean BMI of 24.8 kg/m^2. Most patients were genotype 1 (62.5%) or 3 (21.0%). Almost half (45.7%) of patients had evidence of steatosis: 14.9% had mild steatosis, 11.8% had moderate steatosis and 19.0% had marked steatosis. Most patients were cannabis nonusers (63.5%); 12.4% were occasional users and 24.1% were daily users, with a median of 82 cigarettes smoked per month. Cannabis users tended to be younger and male with a lower BMI; they were more likely to have a history of alcohol abuse or tobacco smoking than nonusers. Additionally, cannabis users were more likely to have been infected with HCV via intravenous drug use and therefore were more likely to have genotype 3 HCV.

Univariate analysis showed that marked steatosis was significantly associated with daily cannabis use, as well as genotype 3 HCV infection, hyperglycemia or diabetes, BMI ≥ 27 kg/m^2, alcohol abuse, tobacco use, methadone or buprenorphine treatment and high serum HCV RNA load. An activity grade of ≥A2 or a fibrosis stage of ≥F2 were also associated with marked steatosis. Subsequent logistic regression showed that daily use of cannabis was independently associated with marked steatosis (odds ratio of 2.1, 95% CI: 1.01-4.5) along with activity grade ≥A2, serum HCV RNA load, genotype 3, BMI > 27 kg/m^2 and hyperglycemia or diabetes. Further stratification by genotype (genotype 3 versus non-gentype 3) and separately by daily alcohol intake (<30 g/day versus ≥30 g/day) showed that daily cannabis use (versus nonusers and occasional users combined) was associated with marked steatosis after adjustment for genotype (P=0.03) and alcohol use (P=0.008).

The study's findings support existing evidence of the relationship between steatosis and genotype 3, as well as other known factors in steatosis (overweight or obesity, diabetes mellitus and insulin resistance). The authors noted that the study addressed potential confounding by adjusting for alcohol intake and genotype in one analysis. The authors conclude by stating that their findings support the body of evidence suggesting a CB1-mediated pathway of steatosis.

The major limitation of these findings is in the cross-sectional study design which makes any conclusions related to causality difficult to draw. Additionally, self-reported behavioral data presents risk of under-reporting of certain behaviors such as alcohol and illicit drug use.

National Medical Organization Recommendations

The National Academies of Sciences, Engineering and Medicine produced a report on the health effects of cannabis in 2017 and found limited evidence that there is no association between liver fibrosis or hepatic disease in patients with viral hepatitis C and cannabis use (National Academies of Sciences 2017).

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Nausea

ISSUE BRIEF ON NAUSEA

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

Nausea refers to a subjective, unpleasant feeling emerging from the stomach that individuals experience as an urge to vomit. Nausea may or may not be accompanied by vomiting (emesis). Causes of nausea are many and quite variable, including morning sickness due to pregnancy, infections (i.e., viral gastroenteritis), medications (e.g., chemotherapy drugs), labyrinthine causes (e.g., motion sickness), post-operative nausea, and many more (see Quigley et al., 2001 for list of causes). Due to the varied causes of nausea, emphasis on this brief concerns more common causes of nausea listed on the Mayo Clinic website including morning sickness in pregnancy, motion sickness, and viral gastroenteritis. Nausea is also commonly caused by chemotherapy treatment. However, discussion of chemotherapy-induced nausea will be excluded from this brief as nausea associated with cancer or its treatment (e.g., chemotherapy) is already a qualifying condition for MN's medical cannabis program. This

consequently severely limits the literature pool to draw on for this issue brief, as treatment for chemotherapy-induced nausea has been most extensively studied out of all nausea-inducing conditions found in the literature.

Diagnosis

Some acute cases of nausea may go away on their own and do not always warrant medical intervention (i.e., viral gastroenteritis). A patient presenting himself/herself to a health care practitioner will typically undergo a review of medical history and a physical exam to eliminate nausea of non-gastrointestinal origin. If the cause of nausea is found, treatment is targeted to treat the cause. However, in the case that a cause cannot be found, health care practitioners target treatment to ameliorating nausea and vomiting symptoms (Hasler & Chey, 2003).

Prevalence

Estimating nausea prevalence is difficult because the cause of nausea is varied. In addition, data on nausea prevalence is somewhat complicated by the fact that nausea can occur with vomiting—a separation of the two symptoms is not always clear in the literature. Nevertheless, some estimations of nausea exist. For example, a large population based study found that 12.5% of people experienced nausea that they found bothersome in the last 12 months (Haug et al., 2002). There are also some estimations of nausea prevalence for some conditions. For example, morning sickness is estimated to occur in roughly 70% of pregnant women, the majority of which occurs in the first trimester of pregnancy (Quigley et al., 2001). The prevalence of nausea in motion sickness is estimated to be anywhere between 3-60% depending on the study (Shupak & Gordon, 2006; Murdin et al., 2011; Golding, 2006). Postoperative nausea involving general anesthesia has been estimated at just under 40% (Quinn et al., 1994), although a broader range of sources indicate a wider range.

Current Therapies

Anti-emetics (anti-vomiting drugs) are typically administered for nausea regardless of whether it is accompanied by vomiting or not, and the overall consensus is that these treatments are more inconsistent in treating nausea than vomiting (Singh et al., 2016; Sanger & Andrews, 2006). The fact that anti-emetics do not ameliorate nausea and vomiting symptoms in a consistent fashion suggests differences in neural circuitry in the manifestation of these symptoms (Quigley et al., 2001; Singh et al., 2016). These drugs include antihistamines, phenothiazines, scopolamine (a cholinergic antagonist), serotonin (5-HT) antagonists (particularly 5-HT$_3$ receptor antagonists), benzamides, benzodiazepines, and corticosteroids.

While cannabinoids are discussed as current therapies in the nausea and vomiting literature, they are not discussed here as these cannabinoid treatments are currently indicated for chemotherapy-induced nausea and vomiting in cancer patients (dronabinol (Marinol), liquid dronabinal (Syndros), and nabilone (Cesamet)), which is a group of patients that already qualify for MN's medical cannabis program.

Preclinical Studies

Preclinical evidence suggests that the endocannabinoid system may be involved in non-chemotherapy related nausea and vomiting symptoms. For example, use of the anti-obesity drug rimonabant in humans – a CB_1-receptor antagonist – is associated with an increased incidence of nausea and vomiting as adverse side effects in patients (Despres et al., 2005). While there are a handful of animal models of nausea and vomiting, this brief will focus on a particular animal model which is the rat model of nausea. While there are a handful of different animal models for studying nausea and vomiting, many of them – like the ferret and shrew models – display both nausea-like behaviors and vomiting. Therefore, the delineation between nausea and vomiting is not always clear in studying a species that cannot verbally communicate. Rats, unlike ferrets and shrews, cannot vomit (non-emetic species) but still display behaviors that are associated with the same neuronal circuitry involved in vomiting that is found in emetic species. Below are a couple representative studies investigating the effects of cannabinoids in a rat model of nausea.

Parker LA, Mechoulam R, Schlievert C. Cannabidiol, a non-psychactive component of cannabis and its synthetic dimethylheptyl homolog suppress nausea in an experimental model with rats. *NeuroReport*. 2002; 13(5): 1-4.

Preclinical research has previously shown that conditioned rejection reactions in a taste reactivity (TR) test (Grill & Norgren, 1978) may be a model of nausea in rats. Conditioned rejection reactions in rats consist of stereotyped orofacial and somatic responses that occur as a result of pairing an appetitive stimulus (i.e., sugary solution) with a drug that produces illness. These rejection reactions include gaping (example shown at 40-second mark at https://youtu.be/_NdyMEvTSyE), chin rubbing, and paw treading. In this study, lithium chloride (LiCl)-induced conditioned rejection reactions were measured as a function of prior treatment with the cannabinoid cannabidiol (CBD) or vehicle solution (control). The authors hypothesized the following: If CBD can attenuate conditioned rejection reactions to LiCl, this would demonstrate CBD's anti-nausea properties. In other words, rats pretreated with CBD (Experiment 1) or the synthetic CBD dimethylheptyl homolog (CBD-DMH—a synthetic derivative of CBD; Experiment 2) should display fewer LiCl-induced conditioned rejection reactions than rats pretreated with a vehicle solution (control).

For the *conditioning* phase of the study, the delivery of a sugary solution in half of the rats was paired with LiCl and the other with saline solution. And within each of those two groups of rats, half of them received the CBD pretreatment while the other half received the vehicle pretreatment, effectively creating 4 experimental groups of rats (CBD-LiCl, vehicle-LiCl, CBD-saline, vehicle-saline).

In the *test* phase, each rat underwent two trials of the taste reactivity test upon delivery of the sugary solution alone – once preceded by CBD administration (or CBD homolog in Expt. 2) and the other preceded by vehicle administration. Results overall showed that pretreatment with CBD (Expt. 1) and CBD homolog (Expt 2) significantly reduced conditioned rejection reactions in LiCl-conditioned rats compared to those pretreated with the vehicle solution.

Parker LA, Mechoulam R, Schlievert C, Abbott L, Fudge ML, Burton P. Effects of cannabinoids on lithium-induced conditioned rejection reactions in a rat model of nausea. *Psychopharmacology*. 2003; 166: 156-162.

Unlike the previous study discussed above, which explored the role of the cannabinoid CBD (and a CBD homolog) on attenuating lithium chloride-induced nausea in rats, this study explored the role of the cannabinoid delta-9-tetrahydrocannabinol (THC) and a cannabinoid receptor agonist 11-hydroxy-delta-8-tetrahydrocannabinol-dimethyleptyl (HU-210) in conditioned rejection reactions in LiCl-conditioned rats. Similar to Parker et al. 2002, authors hypothesized that pretreatment with THC (Expt. 1) and HU-210 (Expt. 2) would attenuate conditioned rejection reactions in LiCl-conditioned rats. This study also investigated whether a CB_1-receptor antagonist (SR-141716A) could reverse conditioned rejection reactions in LiCl-conditioned rats pretreated with HU-210 (Expt. 3) or potentiate these rejection reactions with SR-141716A pretreatment (Expt. 4).

During conditioning trials, delivery of a sugary solution was paired with LiCl in half of the rats and saline solution in the other half. For those two groups of rats, half received THC pretreatment (Expt. 1) or HU-210 pretreatment (Expt. 2) and the other half received vehicle pretreatment (THC-LiCl, vehicle-LiCl, THC-saline, vehicle-saline in Expt. 1; HU-LiCl, vehicle-LiCl, HU-saline, vehicle-saline in Expt 2).

In the test phase, each rat underwent two trials of the taste reactivity test upon delivery of the sugary solution alone – once preceded by THC administration (or HU-210 in Expt. 2) and the other preceded by vehicle administration.

Results showed that LiCl-conditioned rats who received vehicle pretreatment during the conditioning phase displayed significantly more rejection reactions when given vehicle solution in the test phase than THC in the test phase. Results with HU-210, a cannabinoid receptor agonist, showed similar results as THC but only partially blocked the effects in LiCl-conditioned rats suggesting the THC may be more effective in blocking the expression of LiCl-induced nausea. Pretreatment of CB_1-receptor antagonist SR-141716A with HU-210 reversed some of HU-210's nausea reducing effects observed in Experiment 2, suggesting that nausea may be mediated by CB_1 receptors. Lastly, LiCl-condition rats pretreated with SR-141716A displayed more rejection reactions than any other group, further reinforcing CB_1-receptor involvement in nausea.

Clinical Trials

As of early September 2017, one clinical trial was identified on ClinicalTrials.gov relating to cannabis/cannabinoids as treatment for nausea unrelated to chemotherapy treatment. This particular study's main objective is to measure changes in postoperative pain with cannabinoids, but it is also measuring post-operative nausea and vomiting (PONV) as a secondary outcome. One other clinical trial had been identified on PONV and cannabis; however, this study was terminated due to a lack of a treatment effect, meaning that cannabis was not associated with any changes to PONV (NCT00695487: Does Intravenous Cannabis Reduce Postoperative Nausea and Vomiting (PONV)?).

[NCT02283281: Anesthetic Premedication With a Cannabis Extract (Cannapremed) (Cannapremed).](https://clinicaltrials.gov/show/NCT02283281) https://clinicaltrials.gov/show/NCT02283281

This clinical trial examines how well cannabinoids may help with the management of acute post-operative pain as well as nausea and vomiting. Patients undergoing an operation are given a treatment dose before anesthetic induction. Treatment arms are 1) low dose nabiximols (balanced THC:CBD product) which is 10.8 mg THC and 10 mg CBD as an oromucosal spray, 2) high dose nabiximols (21.6 mg THC and 20 mg CBD), 3) an active treatment comparator which consists of acetaminophen (1 g/50 ml vial) + midazolam (2 mg/2 ml prefilled syringe), and 4) control. The primary outcome measures are collected at multiple time points and are 1) self-reported pain ratings on a visual analog scale and 2) post-operative pain measures (number of patient-controlled morphine pushes at various time points, and total dose of morphine received in 24 hours). Secondary outcome measures are also collected at multiple time points and are 1) post-operative nausea and vomiting scores, 2) anxiety ratings on a visual analog scale, and 3) cannabinoid blood levels. Principal investigator is Dr. Elyad Davidson of Hadassah Medical Organization (Israel). Estimated study completion date is listed as February 2017; no results have yet been posted to ClinicalTrials.gov, nor have any publications have been found relating to this study.

Observational Studies

A search for observational studies examining the role of cannabinoids/endocannabinoids in nausea yielded very few studies when eliminating chemotherapy-induced nausea. The two that were found do not involve the same patient population and examined nausea induced from different conditions – one examining motion sickness in male participants (Chouker et al., 2010) and the other morning sickness in pregnancy, as well as nausea unrelated to chemotherapy (Westfall et al., 2006).

Chouker A, Kaufmann I, Kreth S, Hauer D, Feuerecker M, Thieme D. Motion sickness, stress and the endocannabinoid system. *PLOS One*. **2010; 5(5): e10752.**

This was a prospective study where participants (n = 21) who took scopolamine (anti-motion sickness drug) underwent multiple, in-flight parabolic maneuvers (PMs) in an aircraft (quick cycles of ascents and descents in the shape of an inverted-U) and observed for any developments of motion sickness. [While scopolamine was administered to all participants, please keep in mind while reading through the summary that that drug was not a treatment focus for this study. It administered to all participants on compassionate grounds to lesson motion sickness severity, as the study may have been difficult to execute otherwise]. The researchers hypothesized that participants with lower endocannabinoid signaling (as measured by peripheral endocannabinoids and cannabinoid receptor expression) would experience heightened motion sickness and stress (as measured by self-report and cortisol levels in saliva).

Blood samples were collected during the study to eventually detect for differences in endocannabinoid levels (anandamide and 2-AG) between participants who experienced motion sickness from those who did not. CB_1 and CB_2 receptor expression was also analyzed in blood samples taken before and after the in-flight experiment. Participants rated the severity of their

stress level and nausea at various time points in the study (in-flight before start of PMs, after the 10th PM, after 20th PM, after 30th PM, in-flight after the end of the PM cycles, and 24-hours after the study). Videotaping also occurred on the flight to observe for vomiting in participants. Cortisol measures were taken from saliva samples as a stress indicator.

Of all participants (n = 21), 7 (33%) subjects developed motion sickness. These 7 participants rated their stress levels significantly higher than those not experiencing motion sickness. In addition, nausea ratings were significantly higher by the 20th PM in participants with motion sickness than those who did not experience it. Most importantly, participants experiencing motion sickness had lower concentrations of circulating endocannabinoids (anandamide and 2-AG) than those not experiencing motion sickness. Pearson *r* correlations showed that nausea severity was inversely related to anandamide levels after the 30th PM but not at other time points or with 2-AG concentrations. Stress scores were inversely related to both anandamide and 2-AG by the 30th PM but not at other time points. Lastly, when comparing cannabinoid receptor expression pre- and post- flight, CB_1 receptor expression had decreased post-flight in participants who had developed motion sickness but not in participants who didn't experience it. CB_2 receptor expression did not change between the motion sickness group and the non-motion sickness group (possibly indicative of CB_2 receptors not playing a significant role in the development of motion sickness and associated nausea).

Study limitations include the small sample size and the lack of clarity on whether scopolamine – which was administered to all participants prior to the in-flight study – has any interaction with endocannabinoid signaling that wasn't measured in the study.

Westfall RE, Janssen PA, Lucas P, Capier R. Survey of medicinal cannabis use among childbearing women: patterns of its use in pregnancy and retroactive self-assessment of its efficacy against 'morning sickness'. *Complementary Therapies in Clinical Practice*. 2006; 12: 27-33.

This was an anonymous survey study of women in Canada using medical cannabis through a compassion society. The survey asked questions regarding the respondents' medical cannabis use, including for the treatment of nausea and vomiting (not necessarily pregnancy-related) as well as morning sickness during pregnancy.

Questions on the 21-item survey included the type, frequency, and quantity of medical cannabis the patients consumed and the conditions for which they were taking medical cannabis. Respondents were also asked to rate the efficacy of medical cannabis for treating nausea, vomiting, and loss of appetite for the conditions they reported taking medical cannabis for. In addition, respondents were asked if they took cannabis while pregnant for morning sickness and how effective it was for that condition. Lastly, respondents were asked to report the number of children they gave birth to and whether they had taken cannabis while pregnant – either recreationally or medically –and to assess cannabis' effectiveness for treating it.

Of the 142 women who picked up a survey (which was available through the two medical cannabis compassion societies), 84 women had completed the survey (59% response rate). All 84 women indicated they were current users of medical cannabis with 87% of them indicating they used medical cannabis at least once a day (57% of respondents indicated medical cannabis use more than once a day). Smoked form was the most common form of

administration (95% of respondents). Results provided in the paper indicated that none of the respondents had used medical cannabis for cancer. Of all respondents, 77% (n = 65) indicated using cannabis for treating nausea. Of those responding to the question on efficacy of cannabis in nausea treatment (n = 71), 54% (n = 39), 38% (n = 27), and 5% (n = 5) rated that cannabis was respectively extremely effective, effective, and somewhat effective. While not explicitly stated in the paper, the fact that there were more respondents to assessing the efficacy of cannabis as nausea treatment (n = 71) than respondents to using cannabis for nausea (n = 65) indicates that the two questions were independent of each other (one did not have to have experience using cannabis for nausea to answer the question on whether cannabis was effective for treating nausea). Ninety-four percent of total respondents (n = 79) answered questions on cannabis use during pregnancy. Of those respondents, 42% (n = 33) and 46% (n = 36) respectively indicated using cannabis recreationally and medically while pregnant. Of 59 respondents who experienced morning sickness during pregnancy, 92% rated cannabis as extremely effective or effective for treating morning sickness.

Limitations of this study include potential sampling bias and response bias in the survey, as well as the retrospective elements of the survey design.

National Medical Organization Recommendations

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the management of non-chemotherapy related nausea were found.

The National Academies of Sciences, Engineering and Medicine published a report on the health effects of cannabis and cannabinoids in 2017. The committee for this report has a statement on chemotherapy-induced nausea and vomiting specifically, which is already a qualifying condition for MN's medical cannabis program. It states that "there is conclusive evidence that oral cannabinoids are effective antiemetics in the treatment of chemotherapy-induced nausea and vomiting" (see Conclusion 4-3; National Academies of Sciences, 2017). Their statement does not extend to nausea more broadly.

Minnesota Medical Cannabis Program Data

Data is routinely collected from patients purchasing medical cannabis through participation in MN's medical cannabis program. Symptom data is collected on the Patient Self-Evaluation (PSE), which is administered prior to each medical cannabis purchase. One of the symptom measures collected on the PSE is nausea, and responses are giving using a 0-10 rating scale (0 = symptom not present; 10 = symptom as bad as patient can imagine). In the first program year, 1512 patients made at least a one medical cannabis purchase and had an observation period of at least 4 months at the time of data analysis. Of those patients, 864 of them (57.1%) experienced nausea at moderate to severe levels at baseline. Of those moderate-to-severe sufferers, just over half (55.6%) experienced at least a 30% reduction in nausea. Roughly a third (32.9%) both achieved at least a 30% reduction in nausea and maintained it, on average, for the following 4-month period. While these overall results include patients certified

for cancer, it is important to note that patients certified for cancer only accounted for a third of all moderate to severe nausea sufferers at baseline (283 out of 864 patients; 32.7%).

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Obstructive Sleep Apnea

ISSUE BRIEF ON OBSTRUCTIVE SLEEP APNEA

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

Obstructive sleep apnea (OSA) is a sleep disorder characterized by repetitive episodes of complete (apnea) or partial (hypopnea) collapse of the upper airway (mainly the oropharyngeal tract) during sleep, with a consequent cessation/reduction of the airflow. The obstructive events cause a progressive asphyxia that increasingly stimulates breathing efforts against the collapsed airway, typically until the person is awakened (Spicuzza 2015). These episodes cause acute physiological disruptions including fragmented sleep, intermittent hypoxia, and exaggerated fluctuations in heart rhythm, blood pressure, and intrathoracic pressure. Over time, the acute disruptions evolve into long-term sequelae such as hypertension and cardiovascular morbidities, reduced cognitive function, decreased mood and quality of life, impaired performance at work and while driving, and premature death (Peppard 2013).

Traditionally, OSA was considered to primarily be a problem of upper airway anatomy, where craniofacial structure or body fat decreased the size of the pharyngeal airway lumen, leading to an increased likelihood of pharyngeal collapse. It is now appreciated that multiple factors contribute to the development of OSA, including small upper airway lumen, low lung volume, respiratory instability, poor upper airway muscle function, and low arousal threshold. One or two of these causal factors might be most important for any given patient with OSA; that is, the disease occurs for different reasons in different patients. Underlying risk factors include obesity, male gender, increased age, nasal congestion, craniofacial structure, and genetics (Jordan 2014).

The International Classification of Sleep Disorders (ICSD) is a diagnostic, epidemiological and coding resource for clinicians and researchers in the field of sleep and sleep medicine. It is produced by the American Academy of Sleep Medicine in association with similar organizations in Europe, Japan, and Latin America. The most recent edition, the third, was published in 2014. It contains a section on diagnostic criteria for OSA with only minor changes from the second edition (2005). A 2014 article in the journal, *Chest*, summarized highlights and modifications in ICSD-3 (Satela 2014). Diagnosis of OSA requires either signs/symptoms (eg. associated sleepiness, fatigue, insomnia, snoring, subjective nocturnal respiratory disturbance, or observed apnea) or associated medical or psychiatric disorder (ie. hypertension, coronary artery disease, atrial fibrillation, congestive heart failure, stroke, diabetes, cognitive dysfunction, or mood disorder) coupled with five or more predominantly obstructive respiratory events (obstructive or mixed apneas, hypopneas, or respiratory effort-related arousals) per hour of sleep during polysomnography - OR - a frequency of obstructive respiratory events ≥15/hour even in the absence of associated symptoms or disorders. Data to calculate a respiratory event index, typically called apnea hypopnea index (AHI) expressing number of events per hour, can be collected during an overnight in-center sleep study or during a home sleep study. The data is interpreted and analyzed by a sleep study specialist. Subtle differences in measurement methodologies and interpretations can lead to substantial differences in diagnoses among sleep laboratories (Jordan 2014).

Prevalence

Approximately one in five adults has at least mild OSA (eg. AHI≥5) and 1 in 15 has moderate or severe OSA (eg. AHI≥15). However, >85% of patients with clinically significant and treatable OSA have never been diagnosed. Two population studies indicate the prevalence of OSA has increased over recent decades, likely due at least in part to population increases in obesity (Somers 2008). Though more common in adults, OSA can also occur in children (Sawyer 2011).

Current Therapies

Lifestyle modifications can reduce the severity of OSA and, especially in mild cases, can be sufficient management (Mayo Clinic 2017). Lifestyle modifications include losing weight, exercise, avoiding alcohol and sedative medications, sleeping on side or abdomen rather than

back, and using saline nasal spray to keep nasal passages open. However, patients with moderate to severe OSA typically need therapy beyond lifestyle modifications. Continuous positive airway pressure (CPAP), generally administered through the nose, is the gold standard of OSA treatment. It decreases the number of nocturnal obstructive events and the number of nocturnal arousals, improving sleep parameters and nocturnal oxygen saturation from the first night of treatment. Daytime and nocturnal symptoms are reversed after a short period of constant use (Spicuzza 2015). Though it is very effective, its effectiveness depends on use every day, with recurrence of symptoms after only a day or two of treatment interruption. A substantial proportion of patients who are started on CPAP find it intolerable for a variety of reasons, with adherence roughly 60-70% (Jordan 2014), or 50-80% (Weaver 2008), depending on population and how adherence is measured. There is growing attention to interventions – especially early in CPAP use – to increase adherence (Sawyer 2011). Several alternative options are available for patients in whom CPAP is unsuccessful (Spicuzza 2015). These include different ways of engineering and delivering the positive pressure, oral devices, upper airway surgery, and electrical stimulation of the hypoglossal nerve – activating the genioglossus muscle to open up the upper airway. And there are other emerging treatment options under development.

Pre-Clinical Research

A review by Carley and Radulovacki (Carley 2008) discusses evidence that stimulation of vagus nerve afferent (carries nerve impulses from sensory receptors or sense organs toward the central nervous system) pathways plays a role in sleep related breathing disorders and the presence of cannabinoid receptors in the vagus nerve's nodose ganglion. Calik and collaborators found dronabinol (synthetic THC) reduced serotonin-induced apnea and increased upper airway muscle tone (genioglossus muscle) in rats when injected into the vagus nerve's nodose ganglion (Calik 2014), but not when the injection was into the brain's right ventricle (Calik 2016). This suggests that the effects of dronabinol on apneas (at least those induced by serotonin in rats) are peripherally mediated via suppression of vagal nerve activity (Calik 2016).

Clinical Trials

Two clinical trials of a cannabinoid to treat OSA have been published. No additional trials were found on clinicaltrials.gov.

Prasad B, Radulovacki MG, Carley DW. Proof of concept trial of dronabinol in obstructive sleep apnea. *Front Psychiatry* **2013. Jan 22;4:1. doi: 10.3389/fpsyt.2013.00001.**

This was a proof of concept, single-center dose-escalation study of dronabinol (synthetic THC). Seventeen adults with a baseline Apnea Hypopnea Index (AHI)≥15/hour were enrolled. Polysomnography (PSG) was performed after a 7-day washout of continuous positive airway pressure treatment. Dronabinol was administered after baseline PSG, starting at 2.5 mg once daily. The dose was increased weekly, as tolerated, to 5 mg and finally 10 mg once daily. Repeat PSG assessments were performed on nights 7, 14, and 21 of dronabinol treatment. Change in AHI was significant from baseline to night 21 (-14.1±17.5); p=0.007). Dose was held constant if minor adverse events or new symptoms potentially related to study were reported. Two

participants remained at 2.5 mg and five remained at 5 mg dronabinol at day 21. Two participants were withdrawn due to adverse events: one due to palpitations and one due to oxygen saturation falling below 75% for >5% of the total sleep time on day 7 PSG (a participant with severe OSA at baseline, AHI=93/h). Treatment-emergent adverse events were reported in 76% of participants receiving 2.5 mg, 57% receiving 5 mg, and 75% receiving 10 mg of dronabinol. The most frequent adverse event was somnolence.

Carley DW, Prasad B, Reid KJ, Malkani R, Attarian H, Abbott S, Vern B, Xie H, Yuan C, Zee PC. Dronabinol reduces AHI and daytime sleepiness in patients with moderate to severe obstructive sleep apnea syndrome. *Sleep* **2017;40:Abstract Supplement:A207-A208(Abstract #0558).**

Results of this trial were recently published as an abstract for the SLEEP 2017 (June, 2017) conference (Carley 2017). It was a clinical trial of dronabinol (synthetic THC) versus placebo in 56 adults with BMI<45, Epworth Sleepiness Scale (ESS)>7, and polysomnography (PSG)-documented Apnea-Hypopnia Index (API) between 15 and 50. Participants were randomized to 2.5 mg dronabinol by mouth (n=19), 10.0 mg dronbinol (n=20) or placebo (n=17) daily, one hour before bedtime for 6 weeks. Repeat in-laboratory PSG followed by maintenance of wakefulness (MWT) testing was completed every 2 weeks during the treatment period. At each visit, the ESS and Treatment Satisfaction Questionnaire for Medications also were completed. Baseline AHI was 26.0±6(SD), MWT latency was 19.9±12 min, BMI was 33.8±5.4 kg/m^2 and these were equivalent among all treatment groups. ESS and age differed slightly among placebo, 2.5 mg, and 10 mg treatment groups: ESS=11.5±3.8, 10.1±3.7, 13.7±3.7 (p=0.01); Age=58.6±6.1, 52.7±7.7, 54.7±7.0 (p=0.04). In comparison to placebo, the end of treatment changes in AHI were -13.2±4.0 (p=0.001) and -9.7±4.1 (p=0.02) for the 10 and 2.5 mg dronabinol groups, respectively. ESS did not change significantly with treatment in the placebo or 2.5 mg groups, but decreased by 4.0±0.8 (p=0.0001) units for subjects receiving 10 mg dronabinol. There were no significant changes in MWT latency or BMI with treatment in any group. The above conclusions were not altered after controlling for baseline ESS and age. Subjects receiving 10 mg dronabinol also expressed the greatest overall satisfaction with treatment (p=0.02).

Observational Studies

No observational studies for use of cannabis or cannabinoids as therapy for OSA were found.

National Medical Organization Recommendations

No national medical organization recommendations were found.

The 2017 National Academy of Sciences, Engineering, and Medicine report, *The Health Effects of Cannabis and Cannabinoids*, in the "Sleep Disorders" section, describes the Prasad 2013 study and makes this statement, "Conclusion 4-19: There is moderate evidence that cannabinoids, primarily nabiximols, are an effective treatment to improve short-term sleep

outcomes in individuals associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis."

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Parkinson's Disease

ISSUE BRIEF ON PARKINSON'S DISEASE

Introduction

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Definition

Parkinson's disease (PD) is a chronic, progressive disorder that involves malfunction and death of nerve cells in the brain - neurons. It primarily affects neurons in an area of the brain called the substantia nigra. Some of the dying neurons produce dopamine, a chemical that sends messages to the part of the brain that controls movement and coordination. As PD progresses, the amount of dopamine produced in the brain decreases, leaving a person unable to control movement normally. Scientists are also exploring the idea that loss of cells in other areas of the brain and body contribute to PD. For example, researchers have discovered that the hallmark sign of PD – clumps of protein called Lewy Bodies – are found not only in the mid-brain but also in the brain stem and the olfactory bulb. These areas of the brain correlate to non-motor functions such as sense of smell and sleep regulation. The presence of Lewy bodies in these areas could explain the non-motor symptoms experienced by some people with PD before any motor sign of the disease appears. The intestines also have dopamine cells that

degenerate in PD and this may be important in the GI symptoms that are part of the disease (PDF, 2017a).

Each person with PD will experience symptoms differently. For example, many people experience tremor as their primary symptom, while others may not have tremors, but may have problems with balance. Also, for some people the disease progresses quickly and in others it does not. The diagnosis of PD depends upon the presence of one or more of the four most common motor symptoms of the disease (PDF 2017b):

- <u>Resting Tremor</u> - a shaking or oscillating movement that usually appears when the affected limb (less frequently the face or jaw) is relaxed or at rest.
- <u>Bradykinesia</u> – a general reduction of spontaneous movement, which can give the appearance of abnormal stillness and a decrease in facial expressivity (bradykinesia means "slow movement").
- <u>Rigidity</u> – stiffness and inflexibility of the limbs, neck and trunk. The rigidity can be painful.
- <u>Postural Instability</u> – a tendency to be unstable when standing upright. A person with postural instability has lost some of the reflexes needed for maintaining an upright posture and may topple backwards if jostled even slightly.

Most people with PD also experience non-motor symptoms - those that do not involve movement, coordination, physical tasks, or mobility. While a person's family and friends may not be able to see them, these "invisible" symptoms can actually be more troublesome for some people than the motor impairments of PD. Many researchers believe that non-motor symptoms may precede motor symptoms – and a PD diagnosis – by years. The most recognizable early symptoms include: loss of sense of smell, constipation, sleep disorder (REM behavior disorder), mood disorders, and orthostatic hypotension (low blood pressure when standing up). Other non-motor symptoms include excessive saliva, weight loss or gain, vision and dental problems, fatigue and loss of energy, depression, fear and anxiety, skin problems, and cognitive issues such as memory difficulties, confusion, and dementia (PDF 2017b).

Prevalence

Parkinson's disease is among the most common neurodegenerative conditions. Although its cause is unknown, many investigators believe that the diseases arises from an interaction between genetic and environmental factors. Prevalence of PD increases steadily with age. Prevalence by age grouping is as follows (all per 100,000): 41 for 40-49 years, 107 for 50-59 years, 428 for 60-69 years, 1087 for 70-79 years, and 1903 for age 80+ (Pringsheim 2014).

Current Therapies

No available therapies alter the underlying neurodegenerative process of PD, but treatments exist to treat the disease's symptoms. Levodopa, a dopamine precursor, is generally considered the most effective treatment for motor symptoms of PD. However, it has important

limitations: fluctuating effect over time and dyskinesia as a common side effect. Levodopa's beneficial effect wears off over hours and, over years, it can become decreasingly effective. There are strategies to try to minimize this fluctuation. The dyskinesia side effect can be quite severe, causing abnormal, involuntary movements. Drugs are available to try to minimize the development and severity of dyskinesia. In addition to levodopa, other types of drugs are also used to control motor symptoms, including dopamine agonists, anticholinergic drugs, beta-blockers, and monoamine oxidase type-B inhibitors. These drugs are sometimes used in addition to levodopa or instead of levodopa. Therapies are available for many non-motor symptoms including cholinesterase inhibitors for PD dementia, antidepressants and pramipexole for depression, botulinum toxin injections for excessive saliva, and clozapine for hallucinations. Axial motor symptoms, including falls, difficulty swallowing, and postural instability tend to be treatment-resistant (Connolly 2014).

Pre-Clinical Research

It is well established that the cannabinoid and dopamine signaling systems interact in the parts of the brain involved with Parkinson's disease. A review by Garcia et al (Garcia 2015) provides a readable, though rather technical, introduction to the very complex interactions between these systems. Until recently, it had been thought that the cannabinoid system exerted influence indirectly on the dopamine system, due to absence of CB1 receptors on the dopamine-producing neurons. The influence was thought to be only through nerves nearby, which have CB1 receptors, that stimulate and inhibit the dopamine neurons. Recently, research has also shown direct influence, through a receptor other than CB1 (TRVP1 and, perhaps, CB2 receptors), on dopamine neurons. It has been observed that, in parts of the brain affected in Parkinson's disease, where dopamine levels are reduced, endocannabinoid levels are elevated.

Preclinical studies using different models of experimental PD have investigated the effects of both agonists (activators) and antagonists (prevent activation) of cannabinoid receptors, as discussed in a review by Bassi et al (Bassi 2017). Studies administering different CB1 (cannabinoid receptor 1) agonists have had different results – some exacerbating but most improving motor impairment. Studies of CB1 antagonists more consistently show improvement in motor symptoms. These authors caution, "emerging contradictory results from animal models simulating PD demand development of new pharmacological tools, improved screening models, upgraded technologies, and specific ligands for evaluating the therapeutic potential of cannabinoids in PD."

There is intriguing evidence that cannabinoids protect nerves from damage through reducing oxidative injury, excitotoxicity, and calcium reflux. They are thought to also decrease inflammation by modulating glial processes that are associated with neuron survival. So there is some hope that cannabinoids may provide neuroprotection in PD through these processes (More 2015). Injection of the cannabinoid THCV in mice with an animal model of PD both improved motor symptoms and reduced the loss of dopamine-producing neurons in sections of the brain relevant to PD (Garcia 2011).

Clinical Trials

Clinical trials to date show limited evidence of effectiveness of cannabis for treating symptoms of PD or for treating levodopa-induced dyskinesia. Both completed trials are limited by small sample size and relatively short duration. The CBD trial now being organized (described below) will have a longer treatment period and larger sample size than the completed trial.

Chagas MH, Zuardi AW, Tumas V, Pena-Pereira MA, Sobreira T, et al. Effects of cannabidiol in the treatment of patients with Parkinson's disease: An exploratory double-blind trial. *J Psychopharm* **2014;28:1088-1092.**

This double-blind, placebo-controlled trial studied the effects of cannabidiol (CBD) on 21 Parkinson's disease patients with no psychiatric co-morbidities and no prior cannabis use. Three groups of participants (n=7 in each group) were randomly assigned to 300 mg CBD daily, 75 mg CBD daily, or placebo as an adjunct to their stable dosages of anti-parkinson medications. Placebo and CBD were administered in gelatin capsules with the drug dissolved in corn oil. Three assessments were done at baseline and at the end of the six-week treatment period:

- Unified Parkinson's Disease Rating Scale (UPDRS). The four parts of the UPDRS assess, 1) mentation, behavior, and mood, 2) activities of daily living, 3) motor exam, 4) complications of therapy.
- Parkinson's Disease Questionnaire-39 (PDQ-39) to assess functioning and well-being
- Udvalg for kliniske undersegelser (UKU) side effect rating scale to evaluate possible adverse effects of CBD

No statistically significant differences were observed between the three study groups in either UPDRS or UKU. The total PDQ-39 scores showed a greater improvement in the 300 mg CBD group than in the placebo group. Improvement was also significantly better in the 300 mg CBD group than in the placebo group for two of the PDQ-39 subsections: daily life activities and stigma.

The authors concluded they found no statistically significant differences concerning the motor symptoms of PD, though they found a possible effect of CBD in improving measures related to qualify of life. They acknowledge their study was limited by very small sample sizes and by not measuring specific symptoms of Parkinson's disease.

Carroll CB, Bain PG, Teare L, Liu X, Joint C, et al. Cannabis for dyskinesia in Parkinson's disease: A randomized double-blind crossover study. *Neurology* **2004;63:1245-1250.**

This paper describes a small randomized, double-blind, placebo-controlled crossover trial of an oral cannabis extract as therapy for levodopa-induced dyskinesia. The study drug was Cannador, an extract (in ethanol) of cannabis standardized to 2.5 mg Δ9-THC and 1.25 mg cannabidiol per capsule. To enroll, patients had to be on a stable anti-Parkinson's drug regimen for at least one month and remained on that mediation throughout the study. The 19 PD patients enrolled were randomized to either four weeks of active treatment followed by four weeks of placebo or vice versa, with a two-week washout interval between the two treatment periods. During the active drug treatment period patients were started on a low dose (unspecified) and the dose was increased every three days to a target of 25 mg/kg/day THC in

two divided doses. Assessments were done at baseline and at the end of the two treatment periods. The primary outcome measure was change in score for the part of the Unified Parkinson's Disease Rating Scale related to dyskinesia (Part 4; questions 32-34). There were also multiple secondary outcomes that assessed activities of daily living, quality of life, and additional dyskinesia severity scales. Two patients withdrew after the baseline assessment: one developed diarrhea (on placebo), the other had a family bereavement. Data from the remaining 17 participants were analyzed. Eleven patients failed to reach their target dose on active treatment, as did nine patients on placebo. During the active drug treatment period average dose was 0.146 mg/kg/day (range 0.034 to 0.25) THC. Results showed no evidence of treatment effect on levodopa-induced dyskinesia as assessed by the UPDRS or on any other secondary outcome measures. The authors also note there was no evidence of pro- or anti-parkinsonian effect of the cannabis extract.

A study of tolerability and efficacy of cannabidiol on tremor in Parkinson's disease: NCT02818777 (registered on www.clinicaltrials.gov)

This study will occur in two stages. Stage 1 is an open-label study of 10 Parkinson's disease patients where the dose of the study drug, an oral solution that is 98% CBD, is gradually increased to manufacturer's (GW Pharma) recommended target dose. Tolerability will be evaluated at each dose level. Based on the results of Stage 1, a target dose will be set for stage 2. The major purpose of Stage 2 is to assess the safety and tolerability of the study drug at the determined dose, and secondarily to study efficacy, particularly regarding tremor. Stage 2 is a crossover, double-blind, randomized controlled trial with 50 subjects and a 19-week treatment period. The study is being conducted in Colorado. It began in July, 2016 and is now recruiting participants. Estimated study completion date is June, 2019.

Observational Studies

Surveys and observational studies provide mixed evidence of effectiveness of cannabis on PD motor symptoms. A small study reported reduced motor symptoms after a single dose of smoked cannabis (Lotan 2014), a survey of PD patients at a movement disorder clinic in Prague (Venderova 2004) reported reduced motor symptoms in approximately one-third of PD patients, and a different survey at a Colorado movement disorder clinic indicated a smaller proportion of cannabis-using PD patients experiencing reduction in motor symptoms (Finseth 2015). The Colorado survey suggested a greater effect of cannabis on non-motor symptoms – especially sleep and mood – than on motor symptoms. The small case series of PD patients with REM sleep behavior disorder (Chagas 2014) supports the sleep-improving effect of cannabidiol for PD patients.

Lotan I, Treves TA, Roditi Y, Djaldetti R. Cannabis (medical marijuana) treatment for motor and non-motor symptoms of Parkinson disease: An open-label observational study. *Clin Neuropharmacol* 2014;37:41-44.

This single-administration study was carried out at a movement disorder clinic in Israel. It enrolled 28 Parkinson's disease patients who used cannabis daily for at least two months with no major adverse effects. Data was collected before and 30 minutes after patients smoked their

regular amount of cannabis. Six patients discontinued the dose due to severe side effects (inability to smoke, vomiting, dizziness, psychosis). On the day of testing patients were asked to arrive at the clinic without having taken their usual anti-PD medications so that their baseline motor status could be assessed. Assessments included the motor components of the Unified Parkinson's Disease Rating Scale (USPDS) and visual analog scales for non-motor symptoms. Both motor and non-motor symptoms were reported as improving significantly after the cannabis dose.

Venderova K, Ruzicka E, Vorisek V, Visnovsky P. Survey on cannabis use in Parkinson's disease: Subjective improvement of motor symptoms. *Mov Disord* **2004;19:1102-1106.**

A survey was mailed to all patients with PD registered at Prague Movement Disorders Centre (Czech Republic). The questionnaire could be returned anonymously and it asked about cannabis use, effect of cannabis on PD symptoms, use of other PD medications, and demographics. The authors note that, prior to development of the study, a PD patient's remarkable benefit from cannabis had received a lot press coverage and they observed a growing number of their patients were starting to use cannabis to relieve PD symptoms. Of 630 questionnaires sent, 339 were returned (54% response rate). Average age was 65.7 years with mean PD duration of 8.5 years. Cannabis use was reported by 85 respondents (25.1%). None had any experience with recreation use of cannabis before taking it to alleviate PD symptoms and none had been advised to use cannabis by a doctor. All continued using the antiparkinsonian therapy recommended by their neurologist. After cannabis, 39 respondents (46% of all using cannabis) described mild or substantial alleviation of their symptoms in general, 31% improvement of rest tremor, 25% alleviation of bradykinesia, 38% alleviation of muscle rigidity, and 14% improvement of levodopa-induced dyskinesias. Four patients (5%) reported that cannabis worsened symptoms. Symptom alleviation occurred, on average, 1.7 months after cannabis initiation (range=1 hour to 6 months). This relatively long period of use before symptom reduction makes placebo effect seem a less likely explanation for perceived benefit. The study's limitations include potential response bias: those responding might differ systematically from those who did not respond.

Finseth TA, Hedeman JL, Brown RP, Johnson KI, Binder MS, Kluger BM. Self-reported efficacy of cannabis and other complementary medicine modalities by parkinson's disease patients in Colorado. *Evid Based Complement Alternat Med* **2015;2015:874849. doi: 10.1155/2015/874849.**

The investigators administered a survey regarding complementary and alternative medicine (CAM) therapies to PD patients at a movement disorder clinic at the U of Colorado Hospital. They did not track refusal rate, but estimated it at 10%. The survey inquired about use and helpfulness of 23 forms of complementary and alternative medicine, including cannabis. The survey was administered between November 2012 and August 2013 – shortly after recreational cannabis was legalized in Colorado and after the state's medical program had been in place for several years. Respondents were of relatively high socioeconomic status: 82% had at least some college education and 60% reported an income above %60,000. Nine of the 207 respondents (4.3%) reported past or current use of cannabis as treatment for their PD. Five reported "great improvement" in their symptoms with cannabis. In particular, five reported improvement in their mood and sleep and two reported improvement in their motor symptoms

and quality of life. Among all 27 CAM treatment modalities, cannabis was rated among the most effective for sleep and mood improvement.

Chagas MHR, Eckeli AL, Zuardi AW, Pena-Pereira MA, Sabreira-Neto A, et al. Cannabidiol can improve complex sleep-related behaviors associated with rapid eye movement sleep behavior disorder in Parkinson's disease patients: a case series. *J Clin Pharm Ther* **2014;39:564-566.**

Persons with RBD tend to have nightmares during the REM (rapid eye movement) phase of sleep. And, instead of having the usual atonia (sleep paralysis) during REM sleep, patients with RBD exhibit such behaviors as shouting, hitting and kicking – sometimes injuring their sleeping partner. Persons with RBD are at increased risk of developing PD later in life. Four PD patients who participated in prior studies of cannabidiol therapy were identified as having RBD. During the period of CBD therapy three of the four had complete cessation of their RBD symptoms and one had a large reduction in RBD symptoms.

National Medical Organization Recommendations

In the National Academy of Sciences 2017 report, *The Health Effects of Cannabis and Cannabinoids*, there is a short section on the potential of cannabis or cannabinoids as treatment for Parkinson's disease or its symptoms. It's conclusion (Conclusion 4-11): "There is insufficient evidence that cannabinoids are an effective treatment for the motor system symptoms associated with Parkinson's disease or levodopa-induced dyskinesia" (NAS report 2017).

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Chagas MHR, Eckeli AL, Zuardi AW, Pena-Pereira MA, Sabreira-Neto A, et al. Cannabidiol can improve complex sleep-related behaviors associated with rapid eye movement sleep behavior disorder in Parkinson's disease patients: a case series. *J Clin Pharm Ther* 2014;39:564-566.

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Peripheral Neuropathy

ISSUE BRIEF ON PERIPHERAL NEUROPATHY

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

Peripheral neuropathies are common neurological disorders resulting from damage to the peripheral nervous system – the nerves that communicate information to and from the central nervous system (brain and spinal cord). There are three types of motor nerves: motor, sensory, and autonomic. Symptoms depend on whether motor, sensory, or autonomic nerves are damaged. Motor nerves control voluntary movement of muscles such as those used for walking, grasping things, or talking. Sensory nerves transmit information such as the feeling of a light touch or the pain from a cut. Autonomic nerves control organ activities that are regulated automatically such as breathing, digesting food, and heart and gland functions. Some neuropathies may affect all three types of nerves; others primarily affect one or two types (NIH Peripheral Neuropathy Fact Sheet 2017).

Symptoms vary depending on whether motor, sensory, or autonomic nerves are damaged (NIH Peripheral Neuropathy Fact Sheet 2017 for next four paragraphs)

Motor nerve damage is most commonly associated with muscle weakness. Other symptoms may include painful muscle cramps and fasciculations (uncontrolled muscle twitching visible under the skin), muscle atrophy (severe shrinkage of muscle size), and decreased reflexes.

Sensory nerve damage causes a variety of symptoms because sensory nerves have a broad range of functions. Larger sensory nerves enclosed in myelin register vibration, light touch, and position sense. Damage to large sensory fibers impairs touch, resulting in a general decrease in sensation. Since this is felt most in the hands and feet, people may feel as if they are wearing gloves and stockings even when they are not. This damage to larger sensory fibers may contribute to the loss of reflexes. Loss of position sense often makes people unable to coordinate complex movements like walking or fastening buttons, or to maintain their balance when their eyes are shut. Smaller sensory fibers without myelin sheaths transmit pain and temperature sensations. Damage to these fibers can interfere with the ability to feel pain or changes in temperature. People may fail to sense they have been injured from a cut or that a wound is becoming infected. Others may not detect pain that warns of impending heart attack or other acute conditions. Loss of pain sensation is a particularly serious problem for people with diabetes, contributing to the high rate of lower limb amputations among this population.

Neuropathic pain is a common, often difficult to control symptom of sensory nerve damage and can seriously affect emotional well-being and overall quality of life. Often worse at night, neuropathic pain seriously disrupts sleep and adds to the emotional burden of sensory nerve damage. Neuropathic pain can often be associated with an over-sensitization of pain receptors in the skin, so that people feel severe pain (allodynia) from stimuli that are normally painless. For example, some may experience pain from bed sheets draped lightly over the body. Over many years, sensory neuropathy may lead to changes in the skin and hair as well as to joint and bone damage.

Autonomic nerve damage symptoms are diverse since the parasympathetic and sympathetic nerves of the peripheral nervous system control nearly every organ in the body. Common symptoms of autonomic nerve damage include an inability to sweat normally, which may lead to heat intolerance; a loss of bladder control; and an inability to control muscles that expand or contract blood vessels to regulate blood pressure. A drop in blood pressure when a person moves suddenly from a seated to a standing position (postural hypotension) may result in dizziness, lightheadedness, or fainting. Irregular heartbeats may also occur.

Peripheral neuropathies can be classified according to categories of affected nerves into mononeuropathies, multifocal neuropathies, acute polyneuropathy, and chronic polyneuropathy. A brief example of some of the most common peripheral neuropathies within each category are presented here (Hanewinckel 2016).

*Mononeuropathies (involving only one peripheral nerve)

Carpal tunnel syndrome is the most common mononeuropathy. It results from compression of the median nerve at the wrist. Typically, patients complain of numbness, prickling or tingling sensations, and pain in the hand (sometimes extending up the arm) and sometimes weakness of the hand. Bell's palsy is paralysis of face muscles on one side due to damage to the seventh cranial nerve. The cause is unknown though it has been linked to some infections.

*Multifocal neuropathies (involves multiple nerves, but not in a symmetric fashion)

Disorders in this category are uncommon. Multifocal motor neuropathy is an immune-mediated disorder that damages the protective sheath (myelin) of motor nerves. It leads to slowly progressive, asymmetric, predominantly distal (towards hands and feet) muscle weakness and atrophy that commonly starts in the hands.

*Acute polyneuropathy

Guillain-Barre syndrome is a rapidly progressive, fairly symmetrical weakness leading to paralysis that starts in the lower legs and works its way up the legs and often involves, also, the arms and upper body. Abnormal sensations can accompany the weakness and paralysis.

*Chronic polyneuropathy

This is the category that includes some of the most common, most troublesome peripheral neuropathies. Diabetes can cause multiple types of neuropathies and it is the most common cause of chronic polyneuropathy. It is typically painful and also causes numbness, especially of the lower extremities and feet. Some types of chemotherapy characteristically cause polyneuropathy. It is predominantly a sensory polyneuropathy, but it can be accompanied by pain, autonomic dysfunction, and motor deficit. Certain nutritional deficiencies (example, thiamine) and chronic alcohol abuse (often accompanied by nutritional deficiencies) are also causes and some cases of polyneuropathy have no known cause ("idiopathic").

Prevalence

The prevalence of peripheral neuropathy in the general population is 2.4% and increases with age to an estimated 8% in those older than 55 years (Watson 2015). Pain is a very frequent symptom in peripheral neuropathy, but in some there is little pain and other symptoms predominate. Little information could be found on the proportion of peripheral neuropathy patients, overall, whose symptoms were predominantly numbness, weakness, or autonomic symptoms rather than pain. The types of peripheral neuropathy where this is clear make up a small fraction of the total number of peripheral neuropathy cases.

Current Therapies

Treatment serves primarily to prevent further progression of the neuropathic symptoms. Symptoms present at the start of treatment or when a toxic agent is removed may improve and occasionally resolve. However, more commonly patients are left with lingering symptoms from the pretreatment neurogenic injury. In these cases and in those in which the neuropathy is idiopathic or untreatable, management is symptomatic (Watson 2015).

Most of what was found about managing symptoms of peripheral neuropathy related to pain. First line agents for management of neuropathic pain include certain anticonvulsants (gabapentin and pregabalin), tricyclic antidepressants, or selective serotonin-norepinephrine reuptake inhibitors (duloxetine). Failed medication trials are commonly caused by inadequate dosing. If a patient has a partial response to a first-line agent, a second first-line agent with a

distinct mechanism of action can be added to the first agent. Combination therapy utilizing neuropathic pain medications with different mechanisms of action has been repeatedly found to be more efficacious than single-agent treatment. If a first-line agent fails, a different first-line agent can be tried. Second- and third-line agents include opioid analgesics (Watson 2015). Transcutaneous electrical nerve stimulation (TENS) and other complementary therapies, as well as orthotic devices such as orthopedic shoes, can also be helpful (NIH Peripheral Neuropathy Fact Sheet 2017).

Pre-Clinical Research

Pre-clinical research appears to have focused on the role of the endocannabinoid system and effects of exogenous cannabinoids on the pain that often accompanies peripheral neuropathy. A detailed review of animal studies is presented in Rahn 2009 and King 2017 presents a recent example of this type or research. Numerous research articles have investigated the concept that endocannabinoids can act to protect nerves in the brain and in the eye from injury. Little appears to have been published on this topic for peripheral nerves. The review by Zogopoulos et al (Zogopoulos 2013) is a relatively current overview of research related to a potential neuroprotective role for endocannabinoids.

Rahn EJ and Hohmann AG. Cannabinoids as pharmacoptherapies for neuropathic pain: from the bench to the bedside. Neurotherapeutics 2009;6:713-737.

A portion of this review article covers studies demonstrating involvement of the endocannabinoid system in animal models of peripheral neuropathy and the effect, in these animal models, of chemicals that manipulate the animal's endocannabinoid system. These chemicals include endocannabinoid receptor agonist and antagonists. The animal models of peripheral neuropathy include different forms of nerve trauma and models of diabetic, HIV, and chemotherapy peripheral neuropathy.

King KM, Myers AM, Soroka-Monzo AJ, Tuma RF et al. Single and combined effects of Δ9-tetrahydrocannabinol and cannabidiol in a mouse model of chemotherapy-induced neuropathic pain. *Br J Pharmacol* 2017;174:2832-2841.

This study investigated a potential role for cannabidiol (CBD) in treating an animal model of a peripheral neuropathy symptom: allodynia (heightened sensitivity to normal mechanical stimulation). Mice treated with three different chemotherapy agents were given either THC or CBD or both THC and CBD. Mechanical allodynia was tested over subsequent days for two weeks. The individual cannabinoids and joint administration of THC and CBD had different results for the different chemotherapeutic agents, For two of them, CBD and THC had a synergistic effect when given together. Results led the authors to conclude, "CBD may be potent and effective at preventing the development of chemotherapy-induced peripheral neuropathy, and its clinical use may be enhanced by co-administration of low doses of THC."

Zogopoulos P, Vasileiou I, Patsouris E, Theocharis S. The neuroprotective role of endocannabinoids against chemical-induced injury and other adverse effects. *J Appl Toxicol* 2013;33:246-264.

This article presents a review of in vitro (tissue culture, for example) and in vivo (effects in live animals) experimental data regarding the endocannabinoid system and its role in neuroprotection, as well as possible therapeutic perspectives. The focus is on the brain and central nervous system, but some of the findings could be relevant to the peripheral nerves.

Clinical Trials

Several clinical trials of cannabis or cannabinoids for management of symptoms in patients with peripheral neuropathy have been published. Some specifically recruited patients with peripheral neuropathy and some recruited patients with neuropathic pain more generally – so the participants included patients with peripheral neuropathy but also patients with central pain. They all focus on management of neuropathic pain. Though they typically also have, as secondary outcomes, measures of some combination of quality of life, anxiety, and sleep quality, they shed little light on the potential benefit of cannabis and cannabinoids for treating the numbness, weakness, and autonomic dysfunction that can accompany peripheral neuropathy.

Nurmikko T, Serpell MG, Hoggart B, Toomey PJ, Morton BJ, Haines D. Sativex successfully treats neuropathic pain characterized by allodynia: A randomized, double-blind, placebo-controlled clinical trial. *Pain* 2007; 133(1-3): 210-220.

This study took place over five weeks and was randomized, double-blind, and placebo-controlled involving patients with a history of nerve pain for at least six months. A total of 125 patients (74 women/51 men; average age 53 years) with unilateral peripheral neuropathy and allodynia were randomized to receive either Sativex oral spray (2.7 mg THC/2.5 mg CBD per 100 µl actuation) (n=63) or placebo (n=62) and baseline pain and sleep disturbance were recorded daily for 7-10 days prior to start of trial. All current medications, including those for pain, were continued throughout – although any current use of cannabis products were cause for exclusion.

An initial dosing test was performed: after administration of eight sprays over two hours, any patient scoring over 25 on a 0-100 Visual Analog Scale for intoxication, or presenting with any clinical concerns, was allowed no further doses. Patients who completed the initial dosing test were subsequently allowed self-titration, up to 48 sprays/24 hours (129.6 THC/120 CBD). Throughout the trial, patients recorded daily pain and sleep patterns in a journal. The primary endpoint was pain relief based on a 0-10 scale; secondary endpoints included the Neuropathic Pain Scale (NPS), mechanical allodynia testing, verbal sleep disturbance scale, Pain Disability Index (PDI), Patient Global Impression of Change (PGIC) for pain and allodynia, the General Health Questionnaire (GHQ-12) and possible cognitive decline was assessed using the Brief Repeatable Battery of Neuropsychological tests (BRB-N). Lab values and and ECG was taken prior to the study, and again at completion.

Thirteen patients from the drug arm and seven from placebo withdrew from the study prior to completion due to side effects (n=11 in treatment group; n=2 in placebo group), lack of effectiveness, and failure to comply with study requirements. The results of the primary outcome were statistically significant in favor of the drug arm and the NNT was 8.5 (50%

reduction) and 8.6 (30% reduction). All areas besides the GHQ-12 and cognitive decline showed a significant difference in favor of the Sativex arm. Fifty-seven (91%) of patients in the Sativex group experienced at least one adverse event compared with 48 (77%) in the placebo group. Most common adverse events in the Sativex group were dizziness, nausea, fatigue, vomiting, dry mouth, feeling drunk, diarrhea, somnolence, disturbance in attention, and memory deficit.

Selvarajah D, Gandhi R, Emery C, Tesfaye S. Randomized Placebo-Controlled Double-Blind Clinical Trial of Cannabis-Based Medicinal Product (Sativex) in Painful Diabetic Neuropathy. *Diabetes Care* **2010; 33(1): 128-130.**

Thirty patients (11 female/19 male; average age 56 years) with painful diabetic peripheral neuropathy (DPN), despite standard treatment with a tricyclic antidepressant, were enlisted in this randomized, double-blind, placebo-controlled study testing the effectiveness of Sativex sublingual spray (27 mg/ml THC: 25 mg/ml CBD). A two-week dose titration period was followed by a 10-week maintenance phase. All current medications were continued. Pain levels for superficial, deep, and muscular pain were documented using 100-mm Visual Analogue Scale (VAS), the Neuropathic Pain Scale (NPS), and the total pain score (TPS) at baseline and study end, as were the possible level of depression using the Hospital Anxiety and Depression Scale (HADS-D), as well as the patients' quality of life (QOL) using the McGill Pain and QOL, SE-36 Health Survey, and Euro QOL. Results showed no significant difference between the Sativex and placebo groups for change in any of the measured parameters. Of the 30 patients randomized, 6 withdrew because of adverse events.

Serpell M, Ratcliffe S, Hovorka J, Schofield M, Taylor L, Lauder H, Ehler, E. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. *Eur J* **Pain 2014;18:999-1012.**

Patients with peripheral neuropathic pain (PNP) associated with allodynia were screened and met inclusion and exclusion criteria at 39 centers in the UK, Czech Republic, Romania, Belgium and Canada. Of 303 screened patients, 128 were randomized to THC/CBD spray (nabiximols: 2.7 mg THC and 2.5 mg CBD per 100 µl spray), and 118 to placebo. Eligible patients were ≥18, had PNP ≥ 6 months, had allodynia confirmed, were receiving the appropriate treatment for their PNP, had specified causes of their PNP (PNP due to cancer or diabetes excluded), and took no analgesics on a PRN basis. At baseline they were required to have pain not entirely relieved by their analgesic regimen with a pain rating intensity ≥ 4 on a 0-10 scale. Participants had a one-week baseline period and a 14-week treatment period with visits at the end of weeks 2, 6, 10; at the end of the study (treatment week 14 or earlier if they withdrew); and 28 days after study completion or withdrawal. Participants remained on stable dosages of their concomitant analgesic medications with the exception of acetaminophen. The rescue analgesia provided contained acetaminophen, with maximum single dose of 1000 mg and maximum total daily dose of 4 grams. Participants began nabiximols at a maximum of one spray per four hour period and self-titrated to a maximum of 24 sprays per day (limit of 8 sprays per 3 hours), increasing dosage by no more than 50% from preceding day. Patients rated their pain on a 0 – 10 numeric rating scale at the end of each day. Co-primary outcome measures were, 1) proportion of patients showing ≥ 30% reduction in pain from baseline to end of study period as measured by NRS and 2) mean change in NRS score from baseline to end of study. A total of 173 of the 246 completed the study, 21 ceased treatment by remained in the study, 52

withdrew, and six were excluded as they had no on-treatment efficacy data. A total of 34 patients (28%) receiving nabiximols were classified as responders at the 30% level compared with 19 patients (16%) on placebo, achieving a statistically significant odds ratio in favor of nabiximols treatment (OR = 1.97, 95% CI = 1.05-3.70; p=0.034) in the full intention to treat (ITT) cohort and in the subset of participants who completed the study with no protocol violations likely to affect outcome measures (per protocol (PP) group: OR = 2.7 CI = 1.12-4.57 p=0.021). The adjusted mean reduction in NRS score showed a treatment difference in favor of nabiximols, but the difference didn't meet statistical significance in either the ITT or the PP groups. A variety of secondary outcome measures were used, but only two showed statistically significant change, both in favor of nabiximols: sleep quality and Global Impression of Change (general assessment of health). Side effects were common in both nabiximols (85%) and placebo (70%) groups. Most common side effects in nabiximols group were dizziness, nausea, and fatigue. Ten nabiximols patients (8%) and six placebo patients (5%) experienced serious adverse events; none were deemed related to treatment. A total of 33 patients stopped receiving study medication due to adverse effects, 25 in the nabiximols group and 8 in the placebo group.

Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, Kelly ME, Rowbotham MC, Peterson KL. Cannabis in painful HIV-associated sensory neuropathy: A randomized placebo-controlled trial. *Neurology* 2007;68:515-521.

This randomized, placebo-controlled trial included 55 patients with HIV infection and symptomatic HIV-associated sensory neuropathy with an average daily pain Visual Analog Score (VAS; 0-100) of 30 and were in stable health, with prior experience smoking cannabis (six or more lifetime exposures). Patients were given pre-rolled 3.56% cannabis and placebo cigarettes. The study included a pre-intervention phase to determine eligibility (7 days), a lead-in phase for acclimatization (2 days), an inpatient treatment phase (5 days) and outpatient post-intervention phase (7 days). Primary outcomes were daily pain VAS scores; secondary outcomes were ratings of chronic neuropathic pain VAS on days 1 and 5 of the intervention, long thermal stimulation (LTS) procedure to assess acute analgesia, and heat/capsaicin sensitization model to assess anti-hyperalgesic effects. A total of 50 patients (25 each in cannabis and placebo groups) completed the study; in the cannabis group, median daily pain reduction was 34% versus 17% in placebo (p=0.03); similarly, 52% of cannabis group patients reported a 30% or greater reduction in pain, compared to 24% of the placebo group (p=0.04). Cannabis smoking resulted in significant pain reduction after the first smoked cigarette (p<0.001); additionally, cannabis reduced experimentally-induced hyperalgesia but not pain related to heat stimulation. Reported side effects included anxiety, sedation, disorientation, paranoia, confusion, dizziness and nausea which were generally more common in the cannabis group. A non-significant reduction in mood disturbance was observed in the cannabis group when compared to placebo.

Ellis RJ, Toperoff W, Vaida F, van den Brande G, Gonzales J, Gouaux B, Bentley H, Hampton Atkinson J. Smoked Medicinal Cannabis for Neuropathic Pain in HIV: A Randomized, Crossover Clinical Trial. *Neuropsychopharmacology* 2009 Feb;34(3):672-680.

This randomized crossover trial enrolled 34 subjects with HIV infection, neuropathic pain with at least two failed trials of analgesics and an average score of 5 or higher on the pain intensity scale of the Descriptor Differential Scale (DDS). The study included five phases over 7 weeks: a

wash-in phase for baseline measurements, five days of smoked active or placebo cannabis, two weeks of wash-out, five days of smoked active or placebo cannabis, and finally two weeks of wash-out. Baseline measurements included laboratory evaluations, Total Neuropathy Score (TNS), and behavioral and mental health evaluation. Participants were given placebo and cannabis (1% to 8% THC by weight) cigarettes. During treatment phases, patients smoked cannabis or placebo cigarettes under observation by a study nurse; over four sessions, patients started with 4% THC or placebo and adjusted downwards or upwards, depending on side effects or completeness of pain relief. The primary outcome measure was pain magnitude (assessed by DDS); secondary outcomes were Sickness Impact Profile (SIP) score, Profile of Mood States (POMS) score, Brief Symptom Inventory (BSI) score, UKU Side Effect Rating Scale score for physical and psychological symptoms and Highness/Sedation Scale as well as laboratory measures for safety assessment. A total of 28 enrolled patients completed the study. Cannabis treatment significantly reduced pain compared to placebo (median difference in pain reduction was 3.3 points on DDS, p=0.016). Intent-to-treat analysis found similar results. Number needed to treat for 30% pain reduction was 3.5. No differences were observed between treatment and placebo groups in secondary outcomes. Two of the enrolled patients withdrew due to side effects (cannabis-induced psychosis in the first, intractable smoking-related cough in the second). Side effects included concentration difficulty, fatigue, sleepiness or sedation, increased duration of sleep, dry mouth and thirst; these were more common during cannabis treatment.

Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-Dose Vaporized Cannabis Significantly Improves Neuropathic Pain. *J Pain.* 2013; 14(2):136-148.

This randomized, placebo-controlled, double-blind, crossover trial included 39 patients (28 male/11 female; average age 50 years) with various diagnoses resulting in neuropathic pain (majority had peripheral neuropathy). The cannabis used was standardized to result in two products: 3.53% and 1.29% THC, as well as a placebo. The process was similar to the above article by the same researchers; however, in this trial the patients were directed to inhale four puffs at 60 minutes, followed by 4-8 puffs after the third hour of testing and used vaporized rather than smoked cannabis. They used the Foltin Puff Procedure to standardize the dosing of the vaporized cannabis. Each patient was monitored for changes in vital signs during testing.

Like their previous trial, outcomes measured were spontaneous pain relief (on a 0-100 scale, average baseline was 58), degree of pain relief (Patient Global Impression of Change), pain unpleasantness, as well as neuropathic pain (Neuropathic Pain Scale), test of allodynia, and heat pain sensitivity. Neurocognitive effects on attention, concentration, learning and memory, as well as fine motor speed (WAIS-III, HVLT, Grooved Pegboard Test and word recall tests).

Results of the pain measurements were statistically significant when both doses of THC were compared to placebo, although there was no difference between the active doses. Allodynia generally decreased, however heat sensitivity did not. Cognitive impairment was seen in both test groups. No patients withdrew due to drug and no serious adverse effects were reported; the most common side effects were mild sedation, confusion, hunger and nausea.

Frank B, Serpell MG, Hughes J, Matthews JNS, Kapur D. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain:

randomised, crossover, double blind study. British Medical Journal 2008 Jan 26;336(7637):199-201.

This randomized, double-blind crossover trial enrolled 96 patients aged 24-84 years with chronic neuropathic pain who met diagnostic criteria of sensory abnormality, allodynia, burning pain, lancinating pain and sympathetic dysfunction and had a mean pain score of at least 40 on a 0-100 VAS. Stable medication regimes, other than dihydrocodeine, were continued during the study. The study included a 6-week escalating treatment period starting with 30 mg hydrocodeine or 250 μg nabilone, with a maximum of 240 mg dihydrocodeine or 2 mg nabilone. There was a two-week washout period between treatment phases. Patients were evaluated at two-week intervals during the study and asked to fill out daily pain scores, as well as amount of sleep, sleep interruptions and amount of study drug taken. The primary outcome was mean pain VAS score during the last two weeks of treatment; secondary outcomes were mood changes, quality of life, sleep and psychometric function. A total of 73 patients had data for the available case analysis and 64 supplied adequate data and complied with the protocol and could be included in the per protocol analysis. The mean baseline pain VAS score was 69.6 mm; the mean score for the last two weeks of treatment was 6.0 mm longer for nabilone treatment compared to dihydrocodeine in the available case analysis; for the per protocol analysis, mean score for nabilone was 5.6 mm longer than dihydrocodeine. Comparison of quality life scores showed that nabilone treatment resulted in better physical domain scores but also higher bodily pain scores. Nabilone generally produced more side effects than dihydrocodeine, though no adverse events were observed.

Wilsey, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, Fishman S. A Randomized, Placebo-Controlled, Crossover Trial of Cannabis Cigarettes in Neuropathic Pain. _J Pain._ 2008; 9(6): 506-521.

A randomized, placebo-controlled, double-blind, crossover trial using cannabis (7% and 3.5% THC) and placebo cigarettes provided by the University of Mississippi and the National Institute on Drug Abuse. Thirty-eight patients (20 male/18 female; average age 46 years) with varying diagnoses were brought to clinic for administration for three six-hour sessions and dosed using a standard cued-puff procedure under supervision with a total of nine puffs each session. The approximate level of THC consumed at each session was 19 mg (3.5% THC) and 34 mg (7% THC). During the session, hourly evaluations and assessments were carried out and continued for two hours post session. All medications including those for pain were continued.

Outcomes measured were spontaneous pain relief (on a 0-100 scale, average baseline was 55), degree of pain relief (Patient Global Impression of Change), pain unpleasantness, as well as neuropathic pain (Neuropathic Pain Scale), test of allodynia, and heat pain sensitivity. Neurocognitive effects on attention, concentration, learning and memory, as well as fine motor speed (WAIS-III, HVLT, Grooved Pegboard Test and word recall tests). A significant difference was seen in all pain variables (except allodynia and heat sensitivity) when both 3.5% and 7% THC was compared to placebo. Differences were also seen in the cognitive tests were the THC products resulted in greater cognitive decline than did placebo – 7% THC showed impairment in attention, memory and learning; the 3.5% group only declined in learning and memory and to a lesser extent when compared to the 7% test groups.

Attal N, Brasseur L, Guirimand D, Clermond-Gnamien S, Atlami S, Bouhassira D. Are oral cannabinoids safe and effective in refractory neuropathic pain? *European Journal of Pain* **2004;173-177.**

This clinical study included seven patients with periphera (n=3) or central neuropathic pain with a mean Visual Analog Score (1-100) of over 40 at baseline that is refractory to at least three pharmacological classes. Current analgesic medications were continued through the study. Eight cannabis-naïve patients (4 male, 4 female) were given Dronabinol (2.5 mg THC) and started at two daily doses, with upward titration in steps of 5 mg every week if tolerated, up to 25 mg/day. If side effects occurred, the dosage was adjusted downward in steps of 2.5 mg. Patients reported daily pain VAS scores starting from one week prior to treatment, until four months after treatment initiation. The McGill Pain Questionnaire (MPQ) was used to assess sensory and affective pain dimensions. Other measurements were number of painful attacks over the previous 24 hour period, mechanical allodynia intensity as measured on a VAS, the Brief Pain Inventory (BPI), the Hospital Anxiety and Depression (HAD) scale and the Nottingham Health Profile.

Seven patients reported side effects, including somnolence, fatigue, hypotonia, blurred vision and attention/memory disorders; five patients dropped out of the study between weeks 6 and 8 due to side effects. Mean achieved dosage was 16.6 mg THC/day. No significant improvement in weekly pain VAS scores, ongoing pain and paresthesias, induced allodynia, BPI, HAD, Nottingham health profile or the sensory or affective subscores of the MPQ. A non-significant decrease in number of painful attacks after one month of treatment was observed, but this effect disappeared after two months. One patient experienced a significant decrease in the intensity of spontaneous pain and paresthesias but dropped out of the study due to side effects.

Observational Studies

No observational studies were found that focused on symptoms of peripheral neuropathy (numbness, weakness) other than pain.

National Medical Organization Recommendations

In the National Academy of Sciences 2017 report, *The Health Effects of Cannabis and Cannabinoids*, there is no discussion or conclusion statement regarding evidence of therapeutic benefit of cannabis or cannabinoids for peripheral neuropathy. In its discussion of chronic pain, the report acknowledges neuropathy was the most frequent cause of chronic pain among the trials included in Whiting's *New JAMA* review (Whiting 2015) and it includes this conclusion: "There is substantial evidence that cannabis is an effective treatment for chronic pain in adults." (Conclusion 4-1).

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