



Alzheimer's Disease

ISSUE BRIEF ON ALZHEIMER'S DISEASE

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

Alzheimer's disease (AD) is a neurodegenerative disorder that is distinct from normal aging and is the most common cause of dementia. Dementia refers to 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 is observable as memory loss, diminished reasoning skills and executive functioning (decision-making, planning), and changes to personality/mood and behavior. Neuropathological characteristics of the disease include deposition of β -amyloid ($A\beta$) into what are called amyloid plaques (amyloidosis) and accumulation of tau protein into neurofibrillary tangles – both of which are implicated in neurodegenerative processes observed in AD brains (Alzheimer's Association).

Diagnosis

The National Institute on Aging and the Alzheimer’s Association (NIA-AA) recently updated their clinical guidelines for diagnosing AD in 2011. These guidelines generally mirror the typically observed progression of AD, which is: 1) preclinical AD (individual may be undergoing amyloidosis, neurodegeneration, or both processes concurrently, but person is asymptomatic for AD; Sperling et al., 2011), 2) mild cognitive impairment (MCI) due to AD (patient shows signs of cognitive impairment but at levels below a dementia diagnosis; Albert et al., 2011), and 3) clinical AD (McKhann et al., 2011).

NIA-AA’s preclinical AD guidelines are a framework for advancing research into identifying preclinical states of AD rather than providing diagnostic criteria for the clinician. Due to research indicating that there are biomarkers for AD (a measurable indicator that may be found within the brain/body (e.g, a substance) that indicates the presence of a particular disease) in the absence of any observable changes, NIA-AA recommends further advancing this area of research to find biomarkers that best predict AD. In addition, they also recognize that there may be subtle cognitive changes in preclinical AD patients—they emphasize the need to develop more sensitive neurocognitive tools to capture these changes to lead to earlier diagnosis.

NIA-AA’s criteria for diagnosing mild cognitive impairment (MCI) due to AD include concern being brought to the attention of a clinician regarding a patient’s observed change in cognition (either from the patient, someone who knows the patient well, or the clinician). The patient must also show impairments in at least one cognitive domain that would be greater than what one would expect for someone that age and of their educational background. Furthermore, these impairments cannot be attributed to some other systemic or brain disease. These individuals must still be functioning at a relatively independent level, and they must not fit criteria for a dementia diagnosis.

Diagnosis of clinical AD has two main requirements which are to 1) meet core criteria for a dementia diagnosis, and 2) satisfy criteria that would indicate that the cause of dementia is either probably AD (probable AD) or possibly AD (possible AD). Criteria for dementia includes interference in ability to function at usual activities or work, a decline from a previously-attained level of functioning, impairments in cognition as indicated in the patient’s history and through cognitive assessments, and impairments in at least two cognitive domains (acquiring and remembering new information, reasoning/judgment, visuospatial skills, language skills, or changes to personality/behavior). Probable AD criteria includes the observation that symptoms have worsened gradually (months to years as opposed to over a few hours/days) as well as a historical record of this worsening trend, and that cognitive deficits either fall into an amnesic presentation (memory impairments) or non-amnesic presentation (language, visuospatial, executive functioning impairments).

Prevalence

According to one model of AD prevalence, 6.08 million Americans had AD in 2017 (includes those with mild cognitive impairment due to AD, early clinical AD, and late clinical

AD). Those numbers are predicted to rise to 15.0 million cases in the US by 2060. According to the same model, 46.7 million Americans were in a preclinical AD state (asymptomatic individuals experiencing amyloidosis, neurodegeneration, or both amyloidosis and neurodegeneration). Preclinical AD cases are expected to rise to 75.68 million by 2060 (Brookmeyer et al., 2018).

There are certain risk factors that have been associated with an increased risk of an AD diagnosis. Those who are 60 years old and older are more susceptible to AD (Centers for Disease Control and Prevention; CDC), with 95% of all AD cases identified in patients ≥ 65 years old (Reitz & Mayeux, 2014). The rate of those with AD doubles every 5 years beyond age 65 (CDC). There also seems to be an inherited risk of developing AD if there are biological family members with the disease (CDC). Other risks include having a cardiovascular disease, Type II diabetes, high blood pressure, excessive body weight, and decreased mental stimulation (Reitz & Mayeux, 2014; CDC)

Current Therapies

There are currently four FDA-approved pharmacotherapies for treating cognitive and functional decline in AD patients, which are: donepezil, galantamine, rivastigmine, and memantine. The first three are acetylcholine esterase (AChE) inhibitors, while the last one (memantine) is an N-methyl-D-aspartate (NMDA)-receptor antagonist (Anand et al., 2014).

AChE inhibiting drugs work by inhibiting the activity of an enzyme (acetylcholine esterase) that breaks down the neurotransmitter acetylcholine (ACh). Dementia is associated with a dysfunctional cholinergic system; therefore, AChE inhibitors are prescribed to enhance ACh levels (by inhibiting AChE, this gives ACh a longer period of time to act on receptor targets). AChE drugs 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, as an NMDA-receptor antagonist (NMDA receptor is a glutamatergic receptor), is prescribed due to evidence of glutamatergic excitotoxicity in AD patients. Essentially, too much glutamate release has neurotoxic effects on cells; therefore, memantine works to block NMDA-receptor mediated activity to inhibit the perpetuation of this excessive glutamate release. 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).

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

Preclinical research on the effects of cannabis or cannabinoids on AD has focused heavily on influencing endocannabinoid (eCB) signaling for its potential to provide neuroprotective effects in AD. A review paper of this preclinical work is summarized below, followed by two preclinical studies that indicate reductions in some markers of AD pathology with the administration of Δ -9-tetrahydrocannabinol (THC) or cannabidiol (CBD).

Aso E, Ferrer I. Cannabinoids for treatment of Alzheimer’s disease: moving toward the clinic. *Front Pharmacol.* 2014; 5: 37. doi: 10.3389/fphar.2014.00037.

The authors cite the lack of effectiveness of AD-modifying treatments and highlight the potential of the endocannabinoid (eCB) system as a potential target for AD-modifying outcomes, particularly if eCB signaling can be enhanced during the asymptomatic period of AD (when pathological changes in the brain are not yet influencing observable changes in behavior and cognition). The authors subsequently review the state of the evidence on the role of the eCB system in AD pathology, which is summarized below.

Endocannabinoids (naturally occurring compounds within the brain that interact with cannabinoid receptors and affect neuronal transmission) have been documented to increase as a function of neuronal damage, suggesting that they may have a role in repair. For example, there has been evidence of increased CB2 receptor expression in post-mortem samples of AD patient brains, and this increased expression has been correlated with increased β -amyloid ($A\beta$) levels and plaque formation – both of which are associated with AD pathology. Other evidence has shown that AD brains have dysregulatory fatty acid amide hydrolase activity (FAAH; an enzyme that primarily breaks down anandamide, one of the most well-studied eCBs to date). FAAH appears to be overexpressed in AD brains which has the following consequences: 1) the eCB anandamide is metabolized more quickly in AD brains, which leads to decreased eCB signaling in AD patients than in neurologically healthy patients, and 2) increased FAAH activity

in AD brains then leads to increased accumulation of the metabolite arachidonic acid (AA; FAAH breaks down anandamide into AA). The metabolite AA has been implicated in pro-inflammatory responses within the brain and in the immune system; therefore, the overexpression of FAAH in AD brains has the consequence of contributing to inflammatory processes that are typically not found in neurologically healthy individuals.

The authors also cite evidence of cannabinoids providing neuroprotection against A β . For example, in rodents injected with A β and subsequently administered an eCB or exogenous cannabinoid showed a greater number of healthy neurons (cell viability) after a period of time compared to controls, with other evidence also pointing to a reduction in A β -induced impairments in memory. There is also evidence of eCB signaling affecting tau hyper-phosphorylation. In AD, the tau protein gets abnormally phosphorylated which has been implicated in cell death and synapse loss. A handful of studies have implicated both CB1 and CB2 receptor agonism playing a role in reducing tau hyper-phosphorylation. Evidence is also provided for the role of the eCB system in reducing neuroinflammatory responses found in AD brains. Increased proliferation and activation of microglia (a type of cell that supports central nervous system functions) signal inflammatory responses in AD, and according to evidence cited in the paper, CB2 receptor agonists and Sativex (pharmaceutical drug with 1:1 ratio of THC to CBD) seem to reduce microglial response in rodent models of AD.

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

These authors introduced the cannabinoid THC to N2a-variant amyloid- β protein precursor cells (N2a/A β PPswe) to observe for A β aggregation in vitro. A β is secreted at high levels in N2a/A β PPswe 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 A β levels, with long-term administration decreasing A β deposits in hippocampal and cortical regions. Therefore, differences in A β aggregation in N2a/A β PPswe 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 A β_{40} levels (A β isoform that is most abundantly found in the brain) after N2a/A β PPswe cells were treated with THC or caffeine for 6 hours, 24 hours, and 48 hours.

Compared to control, THC-treated and caffeine-treated N2a/A β PPswe cells had lower concentrations of A β_{40} . Furthermore, these reductions in A β_{40} levels in both treatment conditions occurred in a dose-dependent manner; higher concentrations of THC and caffeine both lead to greater reductions in A β_{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 A β_{40} accumulation compared to caffeine, suggesting greater efficacy of THC in inhibiting A β production. Interestingly, incubation of both THC and caffeine in N2a/A β PPswe cells did not further enhance A β_{40} inhibition compared to THC treatment alone; this suggests the lack of a synergistic effect of both treatments to inhibit A β production. Additional experimentation with a one-time treatment or repeated treatments of THC also demonstrated that repeated treatments were more effective in A β inhibition, particularly at

higher THC doses. To establish that THC and caffeine did not have neurotoxic effects on N2a/A β PPswe cells, a 3(4,5-dimethylthiazol-2-yl)2,5-diphenyl-2H-tetrazolium bromide (MTT) conversion assay was performed. MTT assay established that THC and caffeine were not neurotoxic to N2a/A β PPswe cells indicating relative safety of these treatments. Additional study with THC-treated N2a/A β PPswe cells in a fluorometric assay was indicative of decreased A β aggregation as evidenced by decreased intensity of fluorescence in A β . Furthermore, greater reductions of fluorescence in A β 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 A β production and other markers of Alzheimer disease pathology in vitro.

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. *J Neurochem*. 2004; 89: 134-141.

This study explored potential neuroprotective effects of the cannabinoid cannabidiol (CBD) on β -amyloid (A β)-induced neurotoxicity. Alzheimer’s disease patients show accumulation of A β 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 pheochromocytoma PC12 cells in rats were treated with A β alone (A β -only) or in conjunction with CBD (A β +CBD). In the A β +CBD condition, CBD was administered immediately before A β . A third experimental condition included the administration of a CB1-receptor antagonist (SR141716A) 10 minutes prior to CBD administration (A β +CBD+SR141716A). Cell viability was measured via 3(4,5-dimethylthiazol-2-yl)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 A β for 24 hours had died (A β -only condition), supporting A β ’s neurotoxic effects. Administration of CBD immediately before A β (A β +CBD) significantly reduced cell death compared to the A β -only condition, with administration of higher concentrations of CBD leading to greater neuroprotection (fewer cell deaths). ROS accumulation had increased in A β -only cells compared to untreated cells, and A β +CBD cells showed significantly reduced ROS accumulation. The concurrent administration of CB1-receptor antagonist SR141716A in A β +CBD-treated cells (A β +CBD+SR141716A) showed similar levels of ROS attenuation as A β +CBD-treated cells, suggesting that CBD’s neuroprotective effects are not mediated via CB1 receptors. MDA levels were significantly higher in A β -only treated cells compared to untreated cells, with A β +CBD treated cells showing fewer MDA accumulation compared to A β -only cells. Higher concentrations of CBD in A β +CBD treated cells showed greater reductions in MDA accumulation. The apoptosis assay (via appearance of caspase 3

band in PC12 cells) showed that A β -only cells showed significant apoptosis within 6 hours of A β administration; administration of A β +CBD reversed those effects. Results also showed that untreated cells showed no DNA fragmentation while A β -treated cells showed fragmentation. Concurrent CBD administration (A β +CBD), especially at higher concentrations, appeared to decrease signs of DNA fragmentation. Lastly, while intracellular calcium levels were significantly elevated in A β -treated cells, calcium levels were comparatively lower in A β +CBD-treated cells. Results suggest to the authors that CBD may have neuroprotective, anti-apoptotic, and anti-oxidative effects against A β peptide toxicity.

Clinical Trials

In contrast to the preclinical research’s emphasis on manipulating the eCB system to reverse or slow down AD progression, the clinical literature has primarily investigated the role of cannabinoids in altering mood or behavior in AD patients. Therefore, there currently is a gap in the clinical literature to address whether cannabinoids can reverse or slow down the neurocognitive dysfunction that is found in AD patients.

There are some limitations in how much interpretive power the following clinical trials can provide. Firstly, sample sizes are quite small across the studies. Secondly, not all clinical trials that were found specifically focused on AD patients. Of the four clinical trials reviewed below, two of them specifically focused on AD patients (with one of those two studies only including two patients in their trial). The remaining two clinical trials focused on a broader group of dementia patients, including those diagnosed with vascular dementia or mixed dementia. Nevertheless, the justification for including these two studies is based on the composition of AD patients in the sample (majority of patients in both studies were composed of AD patients).

Volicer L, Stelly M, Morris J, McLaughlin J, Volicer BJ. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer’s disease. *Int J Geriatr 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. *J Clin Psychopharmacol*. 2011; 31(2): 256-257.

This was a very small (n=2; both diagnosed with probable AD) 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 dronabinol 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.

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; AD: n=34; Vascular dementia: n=7; Mixed dementia: n=9). 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. Tetrahydrocannabinol 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 (n=22; AD: n=18; Vascular dementia: n=1; Mixed dementia: n=3). 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.

Ongoing Clinical Trials

As of early October 2018, two ongoing clinical trials were identified via ClinicalTrials.gov that investigated the effects of cannabis or cannabinoids on AD. 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 currently listed as 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 Examination (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 currently listed as March 2019.

Observational Studies

Two observational studies were identified that investigated the role of cannabis or cannabinoids in AD patients. These two studies specifically investigated the effects of THC or dronabinol on behavioral symptoms. Both studies had small sample sizes as well as lacking a comparator group(s) for statistical comparison, which puts the evidence here as lower quality

compared to more rigorously controlled studies with larger sample sizes. It should also be noted that, while the last of the two observational studies was not restricted to AD patients, it is included in this brief since the majority were AD patients.

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. *J Alzheimers Dis.* 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.

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 in the “Clinical Trials” section of this brief, 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 measure 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.

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 Alzheimer’s Disease were found.

The National Academies of Sciences, Engineering and Medicine published a report on the health effects of cannabis and cannabinoids in 2017. This report included a review of evidence on the effects of cannabinoids on dementia, including Alzheimer’s Disease. The committee for this report concluded that “there is limited evidence that cannabinoids are ineffective treatments for improving the symptoms associated with dementia” (see Conclusion 4-13; National Academies of Sciences, Engineering, and Medicine, 2017).

References

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ISSUE BRIEF – ALZHEIMER’S DISEASE

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Chronic Hepatitis C

AUGUST | 2018

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

Chronic hepatitis C is the result of a liver infection caused by the virus hepatitis C left untreated in the acute period, leading to chronic and sometimes lifelong infection. This viral infection causes liver inflammation and can lead to permanent liver damage. Among people infected with hepatitis C, 15%-25% clear the infection without treatment; 75%-85% will develop chronic infection (CDC). Hepatitis C virus infection occurs through exposure to blood from an infected person (Mayo Clinic).

Diagnosis

Hepatitis C is diagnosed with blood tests which determine the presence of the virus; follow-up blood tests are used to determine the viral load and the virus' genotype. To assess

whether liver damage has occurred, imaging studies (magnetic resonance elastography or transient elastography) or liver biopsy can be performed (Mayo Clinic).

Complications and Consequences

Viral hepatitis (liver inflammation), depending on the severity, can be 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. 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 [Part II]). The Centers for Disease Control and Prevention (CDC) reports that for every 100 people infected with hepatitis C, 60-70 people will develop chronic liver disease; 5-20 people will develop cirrhosis over a 20-30 year period and 1-5 people will die from cirrhosis complications or liver cancer (Centers for Disease Control and Prevention).

Prevalence

The CDC estimates that in 2010 there were 3.5 million people in the U.S. with chronic hepatitis C (Centers for Disease Control and Prevention).

Current Therapies

The current standard of care for viral hepatitis treatment involves 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 (SVR)-an indicator of successful therapy- rates of 90-95% in hepatitis C patients with cirrhosis (Majumdar 2016). Patients who achieve SVR often see improvements in liver fibrosis and cirrhosis (Poynard 2002); they are also at reduced risk for need for liver transplantation and liver-related mortality (Dienstag 2011, Jezequel 2015). Treatment regimens vary based on presence and severity of cirrhosis, virus genotype, treatment history and other comorbidities and typically lasts 12-24 weeks. Side effects of DAAs can include anemia, diarrhea, fatigue, headaches, nausea, vomiting or bradycardia (healthline.com). Recent DAA regimens have a better safety profile in high-risk patients with advanced liver disease compared to previous standard-of-care therapies and clinical trials have shown low rates of discontinuation of treatment, ranging from 0-3% (Kumar 2014). Notably, DAA therapies are cost-effective but very expensive: a 2016 study reported costs for a 12-week course of DAA therapy ranging from \$54,600 to \$147,000 (Rosenthal 2016).

More advanced liver disease requires additional treatment. An expert panel published cirrhosis management guidelines in 2010 (Kanwal 2010) in which treatment diverges based on

calculated Model for End-stage Liver Disease¹ 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 disaccharides 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 broadly investigated the involvement of the endocannabinoid function on various aspects of liver disease, including development of fatty liver disease (steatosis), fibrosis, cirrhosis and liver 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. Some 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

¹ <https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/>

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 promote production of 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 CCl₄-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 (programmed cell death) 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, may improve hepatic inflammation and pruritus in liver disease, but more data are needed to support this.

Patsenker E, Stickel F. Cannabinoids in Liver Diseases. *Clinical Liver Disease*, February 2016; 7(2):21-25.

This review summarizes findings on the endocannabinoid system's interaction with chronic liver disease progression. A few studies have supported the hypothesis that CB1 activation promotes liver damage and CB2 activation protects against it. The authors discuss the role of two endocannabinoids, AEA and 2-AG, in liver disease and state that while there are indications that elevated levels of endocannabinoids are correlated with the degree of liver injury, the role of endocannabinoids is poorly understood. In animal cirrhosis models, AEA and 2-AG are involved in disease pathways of intrahepatic resistance and hepatic encephalopathy.

The authors note that clinical observational studies have found conflicting results on the association between marijuana use and hepatitis C progression but one study found that cannabis use in HIV-HCV co-infected patients was associated with less insulin resistance.

The authors discuss CB1 and CB2 receptors as therapeutic targets for chronic liver disease and cite findings in which CB1 knockout mice had improved hepatic fibrosis and steatosis but CB2 knockout mice had increased collagen deposition, liver fat and inflammation. Finally, the authors discuss the use of rimonabant, a CB1 receptor antagonist, which has been shown in preclinical rodent studies to improve hepatic fibrosis, steatosis, inflammation and liver regeneration as well as mitigate disease progression in the presence of cirrhosis. Clinical trials with rimonabant in obese patients showed that the treatment group reduced prevalence of metabolic syndrome and related markers, but was associated with intolerable side effects which resulted in termination of the trial. The authors state that targeting the endocannabinoid system for treatment of liver diseases holds promise but the mechanisms of doing so remain undeveloped.

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.

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 chronic hepatitis C. 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 tetrahydrocannabinavirins, GWP42003 and GWP42004 for the treatment of type II diabetes for a 13-week period. Tetrahydrocannabinavarin (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§=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 petition for the addition of Hepatitis C as a qualifying condition cites a prospective observational study published in 2006 which examined the effect of recreational cannabis use on viral treatment compliance and virological outcomes in hepatitis C patients undergoing treatment for substance use at a community clinic (Sylvestre 2006). The study was conducted before the introduction of DAA as standard hepatitis C therapy and followed 71 patients treated with interferon and ribavirin. Of these 71, 22 (31%)

smoked cannabis. Patients completed questionnaires reporting illicit drug use and other behavioral variables. The rate of discontinuing treatment was significantly higher in non-cannabis users compared to cannabis users (33% versus 5%) and almost half of those who discontinued treatment did so due to intolerable side effects. The authors state that these results suggest that cannabis use can improve adherence to hepatitis C treatment which translates to higher rates of SVR and lower rates of post-treatment virological relapse. This study is observational and lacks control for confounding variables; its findings must be confirmed in more robust studies. Furthermore, the study's generalizability to current hepatitis C treatment regimens is unknown. The summaries of other recent observational studies below represent the level of observational evidence currently available to describe the effect of cannabis on measures of chronic hepatitis C 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 log₁₀ 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 liver 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/m². 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/m², alcohol abuse, tobacco use, methadone or buprenorphine treatment and high serum HCV RNA load. An activity grade of $\geq A2$ or a fibrosis stage of $\geq F2$ 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 $\geq A2$, serum HCV RNA load, genotype 3, BMI > 27 kg/m² and hyperglycemia or diabetes. Further stratification by genotype (genotype 3 versus non-genotype 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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Juvenile Idiopathic Arthritis

SEPTEMBER 2018

Introduction

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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, 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

Juvenile idiopathic arthritis (JIA), formerly known as juvenile rheumatoid arthritis, is the most common type of arthritis in children. It can cause persistent joint pain, swelling, and stiffness. In some children the symptoms last for only a few months; others have symptoms for the rest of their lives. Some types of JIA can result in serious complications, such as growth problems, joint damage, and eye inflammation. Treatment focuses on controlling pain and inflammation, improving function, and preventing joint damage (Mayo Clinic 2018).

JIA encompasses a diverse group of immune-mediated medical disorders affecting children under 16 years of age which share as a common feature arthritis lasting more than six weeks. Much remains to be discovered about what causes these diseases. Despite the unknowns, important advancements in therapy have occurred over the past 20 years. There is hope that, as the causes are better understood, therapies treating the underlying biologic processes will be developed and genetic information will help guide treatment (Eisenstein 2014).

In the late 1990s the International League of Associations for Rheumatology adopted the JIA classification of chronic childhood arthritis, effectively replacing earlier classification systems: the juvenile rheumatoid arthritis (jra) and juvenile chronic arthritis (jca) systems. The JIA classification system is based on clinical findings (example – number of joints affected), family history, and in some cases, information from a limited number of laboratory tests. Around 50% of European children have the oligoarticular form of JIA (<5 joints involved during the first six months of disease) (Eisenstein 2014).

Prevalence

JIA is the most common pediatric autoimmune musculoskeletal condition (Kessler 2014). Prevalence estimates from around the world have varied greatly. These differences might be due to a combination of true differences in different geographic regions and use of varying inclusion criteria. Studies in the United States produce estimated prevalence in the range of 1 to 10 per 10,000 children (Gewanter 1983, Helmick 2008).

Current Therapies

Over the last two decades, significant efforts have been made to improve the quality of research in children with JIA, resulting in dramatic advances in management. These efforts include the creation of better classification criteria, validated outcome measures and a definition of clinical remission for select subsets of JIA. Also, placebo-controlled clinical trials have become more acceptable to children with JIA and their families through innovative methodologies that minimize time on placebo. And development of research consortiums has aided in the ability to conduct well-defined, standardized, multi-center research protocols. Therapeutic goals have become more ambitious and physicians have higher expectations for complete remission (Wahezi 2013).

Initial therapy, primarily to manage pain and acute inflammation, is non-steroidal anti-inflammatory drugs (NSAIDs), sometimes with the addition of corticosteroids either injected into the joint or administered systemically. Though these therapies reduce suffering from symptoms, they do relatively little to slow progression or eliminate the underlying disease processes. Disease-modifying anti-rheumatic drugs (DMARDs) have the ability to reduce and prevent long-term clinical and radiological progression of disease. DMARDs are divided into two types: older non-biologic drugs and the newer biologic therapies. Each of these types of therapy are discussed below, drawing on good recent reviews by Wahezi (2013) and Kessler (2014).

Use of only NSAIDs as therapy is possible in some children with few joints involved and mild

disease activity. There are several different kinds of NSAIDs, but naproxen has become the initial drug of choice for most children with JIA due to availability in liquid preparation, limited dosing schedule and minimal side effect profile. Due to concerns regarding potential heart toxicity and because of the availability of more effective and relatively safe treatments, treatment with any NSAID is currently recommended at the lowest effective dose and for the shortest amount of time possible.

Corticosteroids are potent anti-inflammatory drugs, but due to potential toxicity systemic use is typically reserved for severe cases of certain types of JIA or in low doses as a temporary measure until disease modifying drugs take effect. For cases where few joints are involved but with high disease activity, where there is poor prognosis, or where NSAIDs didn't help enough, corticosteroids can be injected into the joints. Clinical response is typically rapid and may persist for up to 4-12 months.

Methotrexate, a non-biologic DMARD, is the most commonly used DMARD for treatment of JIA. Traditionally a second-line agent (after use of NSAIDs and steroid joint injections), it is now also recommended as initial treatment for patients with high disease activity and/or poor prognosis. There are other non-biologic DMARDs, but they are used much less frequently than methotrexate. Previously used therapies, such as gold, penicillamine and anti-malarials have not been shown to be effective and are now rarely used in the treatment of JIA.

The first class of biologic DMARD approved for use in JIA is directed against tumor necrosis factor alpha, a pro-inflammatory chemical released by macrophages, a type of white blood cell. Current guidelines suggest the use of TNF inhibitors as a second- or third-line agent in patients with JIA who continue to have persistent disease activity despite an adequate trial of initial therapeutic agents. There is concern about potential for increased risk of infection with TNF inhibitors, especially tuberculosis. There is also concern about increased risk of malignancies, though the true magnitude and nature of these risks are not clear, due to the relatively recent history of use of these agents. Another type of biologic DMARD, IL-1 inhibitors, have been shown to be effective for a sub-type of JIA that does not respond well to TNF inhibitors. There are also other biologic DMARDs in addition to TNF inhibitors and IL-1 inhibitors.

Pre-Clinical Research

No preclinical studies using tissue from patients with JIA or using animal models of JIA were found. There is a body of pre-clinical research related to rheumatoid arthritis. But it is now known that the underlying pathogenesis of JIA differs from adult rheumatoid arthritis, as well as among sub-sets of patients with JIA (Wahezi 2015). So, it is unclear to what degree findings from these studies are relevant to patients with JIA. For the sake of completeness, some of those studies are summarized below.

Cox ML, Haller VL, Welch SP. Synergy between Δ^9 -tetrahydrocannabinol and morphine in the arthritic rat. *Eur J Pharm* 2007;567:125-130.

The effects of morphine and THC, separately and in combination, were tested in a rat model of inflammatory arthritis. The model involves administering a killed mycobacterium preparation (Freund's complete adjuvant) into the skin, which results in a generalized inflammatory arthritis. Drug effect was measured by the paw pressure test. In this test the rat's hind paw is exposed to increasing mechanical pressure. The pressure at which the rat withdraws its limb is defined as the pain pressure threshold. A higher threshold is interpreted as a reduction in pain. In this study THC and morphine were found to have a synergistic interaction in pain reduction in both normal rats and the arthritic-model rats.

Smith FL, Fujimori K, Lowe J, Welch SP. Characterization of Δ^9 -tetrahydrocannabinol and anandamide antinociception in nonarthritic and arthritic rats. *Pharmacol Biochem Behav* 1998;1:183-191.

The effect of THC and the endocannabinoid anandamide were tested separately in a rat model of arthritis similar to the model used in Cox 2007. The investigators found that both THC and anandamide reduced pain in normal rats and had a similar pain-reducing effect in arthritic rats. Exploration of impact of a CB1 receptor antagonist showed different results for THC and for anandamide in pain reduction: the pain reduction produced by THC was decreased, but there was no change in the pain reduction produced by anandamide. And naloxone blocked the pain reducing effect of both THC and anandamide. These findings led the authors to conclude, "This study indicates that anandamide and THC may act at different receptor sites to modulate endogenous opioid levels in mechanical nociception."

Krustev E, Reid A, McDougall JJ. Tapping into the endocannabinoid system to ameliorate acute inflammatory flares and associated pain in mouse knee joints. *Arthritis Res Ther* 2014;16:437

The effect of a synthetic inhibitor (URB597) of an enzyme (FAAH) that degrades the endocannabinoid anandamide was tested using a mouse model of inflammatory arthritis. Inhibition of the enzyme results in higher levels of anandamide. Anandamide has anti-inflammatory and analgesic qualities, and it was hypothesized that local administration of URB597 would result in evidence of decreased joint inflammation and pain. The mouse model of inflammatory arthritis was created by injecting an irritating substance (kaolin and carrageenan) into the mouse's right knee joint. White blood cell adherence and blood flow within the joint were measures of inflammation. Hind limb weight bearing and sensitivity to hair filament testing were measures of pain. Hallmarks of decreased inflammation, decreased white blood cell rolling and decreased hyperemia were seen with low doses of URB597, but not with high doses. And injection of URB597 improved both hind limb weight bearing and the hair withdrawal thresholds. This led the authors to conclude, "These results suggest that the endocannabinoid system of the joint can be harnessed to decrease acute inflammatory reactions and the concomitant pain associated with these episodes."

Fukuda S, Kohsaka H, Takayasu A, Yokoyama W, et al. Cannabinoid receptor 2 as a potential therapeutic target in rheumatoid arthritis. *BMC Musculoskelet Disord* 2014, 15:275.

This article describes both studies done on mice and studies done on human tissues:

1. A selective CB2 receptor agonist (JWH133) was tested on mice with murine-model rheumatoid arthritis. Use of JWH133, injected intraperitoneally, resulted in less synovial inflammation and bone destruction than in control mice.
2. CB2 receptor density was found to be higher in humans with RA than in humans with OA
3. Fibroblast-like synovial cells from human RA synovium were cultured and then stimulated with a chemical that stimulates production of inflammatory mediators. Co-administration of JWH133 was found to dose-dependently suppress production of the inflammatory mediators.

Malfait AM, Gallily R, Suariwalla PF, Malik AS, Adreakos E, Mechoulam R, Feldmann M. The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. *Proc Natl Acad Sci USA* 2000;97:9561-9566.

Intradermal injection of collagen derived from cows and from mice was injected deep in the skin of mice to induce either an acute (cow collagen) or chronic relapsing (mouse collagen) model of rheumatoid arthritis. At time of symptom development, CBD was administered either by intraperitoneal injection or orally. Mice with injection of collagen and administration of only the vehicle used in administering the CBD served as controls. CBD was found to exert a dose-dependent suppressive action, both on the clinical arthritis and joint damage. Additional study findings suggest that the therapeutic mechanism of CBD includes the suppression of TNF- α , the pro-inflammatory cytokine known to be a major mediator of arthritis.

Clinical Trials

No clinical trials of cannabis or cannabinoids for treatment of JIA were found. One clinical trial of a cannabinoid for rheumatoid arthritis pain has been published (Blake 2006). But, as mentioned above, it is now known that the underlying pathogenesis of JIA differs from adult rheumatoid arthritis, as well as among sub-sets of patients with JIA. So, it is unclear to what degree findings from this study are relevant to patients with JIA. For the sake of completeness, that trial is summarized below.

Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology* 2006;45:50-52.

This was a double-blind, randomized, placebo-controlled study carried out for five weeks in patients diagnosed with rheumatoid arthritis (RA) on a stable regimen of traditional therapy but who did not gain adequate pain relief from standard treatments. A total of 58 participants (12 male/46 female; average age 62.8 years) met the inclusion criteria and 31 were randomized to treatment, while 27 received placebo. The patients were instructed to limit use to evening dosing to prevent daytime intoxication from the Sativex oral spray (2.7mg THC/2.5 mg CBD per 100 μ l actuation [spray]) that was used throughout the trial. The titration schedule started with

one actuation before bed then increased by one actuation every two days, based on patient response, up to a maximum of six actuations per night.

The primary endpoint tested was based on a 0-10 pain scale assessing pain upon movement each morning and comparing the baseline rating to the average of the last 14 days of the trial. Secondary outcomes were pain at rest, sleep quality, morning stiffness, the Short Form McGill Pain Questionnaire (SF-MPQ), and the 28-Joint Disease Activity score (DAS28). All outcomes except morning stiffness and SF-MPQ intensity showed a statistically significant improvement when compared to placebo, including the SF-MPQ “pain at present” rating. Side effects were approximately twice as common in the active treatment group than in the placebo group. All but two of the side effects in the active treatment group were mild or moderate; two patients rated side effects as severe (constipation, malaise). The side effects more common in the active treatment group than in the placebo group were mild dizziness, dry mouth, light-headedness and fall. Three patients withdrew from the study because of side effects – all 3 from the placebo group. There were no serious adverse events in the active treatment group and two in the placebo group.

A recent Cochrane Review of neuromodulators for pain management in rheumatoid arthritis (Richards 2012) included the Blake 2006 study and provides detailed discussion of its strengths and weaknesses. The authors conclude there is weak evidence that oromucosal cannabis is superior to placebo in reducing pain in patients with RA, but that the potential harms from side effects outweigh any modest benefits achieved.

Observational Studies

No published observational studies of cannabis or cannabinoids for the treatment of JIA 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 JIA were found.

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JUVENILE IDIOPATHIC ARTHRITIS

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Mayo Clinic: Patient Care and Health Information - <https://www.mayoclinic.org/diseases-conditions/juvenile-idiopathic-arthritis/symptoms-causes/syc-20374082> (accessed September 13, 2018).

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Smith FL, Fujimori K, Lowe J, Welch SP. Characterization of Δ^9 -tetrahydrocannabinol and anandamide antinociception in nonarthritic and arthritic rats. *Pharmacol Biochem Behav* 1998;1:183-191.

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Opioid Use Disorder

OCTOBER 2018

Introduction

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Definition

The word "opioid" refers to chemicals derived from the poppy plant or synthetic agents based on those chemicals. Some opioids are manufactured as prescription medications, prescribed to control pain, diminish cough, or relieve diarrhea. Others are made specifically to sell illegally. In addition to the medical effects for which they are prescribed, opioids also produce feelings of euphoria, tranquility, and sedation that may lead a patient to continue to take these drugs despite the development of serious related problems. The problems include the need to increase doses in order to achieve these desired effects. At higher doses the drugs can reduce respiratory drive, leading to death (Schuckit 2016). Attempts to reduce or discontinue use after

repeated administrations leads to a highly uncomfortable withdrawal syndrome. The unpleasant physical and psychological symptoms of withdrawal produce negative reinforcement, leading to ongoing, escalating use both to produce desired effects and avoid withdrawal symptoms (Bart 2012).

The Diagnostic and Statistical Manual of Mental Disorders – fifth edition (American Psychiatric Association: DSM-5, 2013) defines opioid use disorder (OUD) as a problematic pattern of opioid use that results in significant impairment or distress on a clinical level. In order to confirm a diagnosis of OUD, at least two of the following should be observed within a 12-month period. Severity of OUD is categorized based on number of criteria met: mild (2-3), moderate (4-5), severe (6 or more).

- Opioids are often taken in larger amounts or over a longer period than was intended.
- There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
- A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
- Craving, or a strong desire or urge to use opioids.
- Recurrent opioid use resulting in failure to fulfill major role obligations at work, school or home.
- Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
- Important social, occupational or recreational activities are given up or reduced because of opioid use.
- Recurrent opioid use in situations in which it is physically hazardous.
- Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
- Tolerance, as defined by either of the following: 1) need for markedly increased amounts of opioids to achieve intoxication or desired effect, or 2) markedly diminished effect with continued use of the same amount of an opioid [not considered to be met for individuals taking opioids solely under appropriate medical supervision].
- Withdrawal, as manifested by either of the following: 1) the characteristic opioid withdrawal syndrome, or 2) the same (or a closely related) substance taken to relieve or avoid withdrawal symptoms [not considered to be met for individuals taking opioids solely under appropriate medical supervision].

The clinical course of OUD involves periods of exacerbation and remission, but the underlying vulnerability never disappears. This pattern is similar to that of other chronic relapsing conditions (e.g., diabetes and hypertension) in which perfect control of symptoms is difficult and patient adherence to treatment is often incomplete. Although persons with opioid problems are likely to have extended periods of abstinence from opioids and often do well, the risk of early death, primarily from an accidental overdose, trauma, suicide, or an infectious disease (especially HIV and hepatitis C) is increased by a factor of 20 (Schuckit 2016).

Prevalence

Over 2.5 million Americans suffer from opioid use disorder, which contributed to over 28,000 overdose deaths in 2014 (NIDA). Opioid-related deaths and hospitalizations for opioid abuse treatment in the US have increased dramatically over the past two decades and in 2013 the US Department of Health and Human Services declared opioid overdose death an epidemic (Volkow 2014).

Current Therapies

Detoxification is often an initial step in treating OUD. It involves discontinuation of the abused opioid drug while treating resulting withdrawal symptoms. A variety of drugs can be used to treat the withdrawal symptoms, which include diarrhea and dilated pupils, pain, restlessness, and anxiety. Two opioid medications are frequently used under medical supervision to reduce the withdrawal symptoms: methadone and buprenorphine. A very small proportion of persons are able to go through withdrawal without use of medications. Detoxification is usually not sufficient to avoid relapse and produce long-term recovery, but it helps the patient think more clearly and participate more effectively in their rehabilitation program (Schuckit 2016). Maintenance programs are needed after detoxification. This is due at least in part to changes in the brain caused by chronic opioid use (Bart 2012).

The most effective maintenance programs appear to be those that combine use of one of the FDA approved medications for treating OUD (methadone, buprenorphine, and naltrexone) in conjunction with psychosocial interventions. These are often referred to as medication-assisted therapies. Data indicate poor outcome in patients provided only psychosocial interventions (Bart 2012). Naltrexone blocks the effects of opioids and, in some highly motivated patients, can help maintain abstinence. Methadone and buprenorphine are more frequently used. Both activate the mu opioid receptor (buprenorphine activates it only partially). Though they activate the mu opioid receptor, the effects are much less strong than with most other opioid drugs. This makes them safer, though they are not without risks of their own. Overdose is possible and, in the case of methadone, a heart rhythm problem can occur. However, data suggest methadone maintenance programs decrease mortality by approximately 50% among persons with opioid-use disorders, decrease acquisition of HIV infection and hepatitis, decrease crime and illicit-substance use, improve social functioning, and increase the rate of retention in rehabilitation programs. Data also support the effectiveness of buprenorphine along these lines. Direct comparisons between methadone and buprenorphine show that both approaches improve outcomes, but most studies suggest that methadone maintenance might be associated with higher rates of patient retention (Schuckit 2016).

Methadone and buprenorphine block euphoric and sedating effects of superimposed opiates and normalize the stress response. Their role in the treatment of OUD is not simply replacement of an illicitly used opiate for a medically supervised opiate, but rather a medication that corrects many of the neurobiological processes contributing to relapse (Bart 2012). Consensus on how long a patient should continue receiving methadone or

buprenorphine therapy is lacking. Some clinicians try to taper patients off these medications after a year. Others emphasize the high rate of relapse and overdose deaths after leaving these programs and suggest that treatment should be open-ended and potentially lifelong (Schuckit 2016).

A variety of types of psychosocial therapies are used as part of medication-assisted therapy. These include cognitive-behavioral therapies, contingency management, motivational interviewing, and general supportive counseling. Systematic reviews have shown treatment that including psychosocial therapies is more effective than treatment with methadone, buprenorphine, or naltrexone alone (Dugosh 2016). In addition, patients are often encouraged to participate in support groups such as Narcotics Anonymous.

Research published in 2011 showed less than half of privately-funded substance use disorder treatment programs offered medication-assisted therapy and only a third of patients with opioid dependence at these programs actually received it (Knudsen 2011). A number of barriers contribute to the relatively low rates of access and participation in medication-assisted therapies. These include a limited number of trained, authorized prescribers, insurance limitations and requirements, and negative attitudes about addiction medications held by the public, providers, and patients. Some treatment-facility managers and staff favor an abstinence model. Studies have shown systematic prescribing of inadequate doses of methadone and buprenorphine, leading to relapse and reinforcement of a perception of ineffectiveness. Federal and state governments are taking efforts to increase access to medication-assisted therapies (Volkow 2014).

Success with medication-assisted therapy is often measured in terms of retention in treatment and reduction in illicit opioid use. Mean 1-year retention in methadone programs is around 60% and can vary based on dosing (Bart 2012). A 9-center trial of a six-month program where patients were assigned to either methadone or buprenorphine/naloxone showed retention to be higher with methadone (74% vs. 46%). Use of illicit opiates was lower with buprenorphine/naloxone during the first 9 weeks but similar thereafter at around one-third of patients (Hser 2014). There is room for improvement in treatment of patients with OUD – both in development of new therapies and in improved delivery of existing treatments. Federal and state governments and the private sector are working on both these fronts (NIDA).

Pre-Clinical Research

A recent review article summarizes pre-clinical evidence of a possible role for cannabis or cannabinoids in treating OUD (Wiese 2018). The endocannabinoid and opioidergic systems are known to interact in many different ways, from the distribution of their receptors to how activation of one system influences the function of the other. Both these systems are very complex, however, and detailed understanding of how these two systems interact is still emerging. Some rodent studies show stimulation of cannabinoid receptor 1 (CB1), as occurs with THC, decreases opioid withdrawal symptoms; others show CB1 activation increases the rewarding properties of opioids and may actually increase the severity of opioid withdrawal symptoms. In multiple studies administration of cannabidiol (CBD) has been shown to alleviate naloxone-precipitated withdrawal in morphine tolerant rats.

Clinical Trials

Information on cannabis or cannabinoids as part of OUD therapy is quite limited and is summarized in a recent review (Sloan 2017). Two small trials investigated the ability of dronabinol, synthetic THC, to alleviate opioid withdrawal side effects. They suggest that dronabinol has some effect, but the effect is likely weaker than opioid-based withdrawal therapies. The first trial randomized opioid-dependent participants to dronabinol or placebo while they were undergoing an 8-day inpatient detoxification and injectable naltrexone induction (Bisaga 2015). Dronabinol reduced the symptoms of opioid withdrawal compared to placebo, but this trial did not compare dronabinol to an active treatment. In the second trial regular opioid users were admitted to an inpatient unit for 5 weeks maintained on oxycodone, and then withdrawn from oxycodone to experimentally induce withdrawal on multiple test sessions (Lofwall 2016). Oxycodone, but not dronabinol, attenuated physical symptoms of withdrawal, including changes in heart rate, blood pressure, and pupil diameter, whereas the 20 and 30 mg doses of dronabinol induced tachycardia. The 20 and 30 mg doses reduced scores on scales of withdrawal symptom severity compared to placebo, but were substantially less effective than oxycodone. There are no published studies investigating CBD treatment in patients with OUD, though pilot data reported in a recent review suggest that CBD may blunt cue-induced craving in OUD patients who have been abstinent for at least 7 days (Hurd 2015).

Observational Studies

Two investigator groups studied medical records of patients in naltrexone treatment programs, using positive urine screening tests to assess impact of cannabis use on measures of treatment success. Both studies divided patients into three groups based on cannabis screening tests: no use, occasional use, and heavy use ($\geq 80\%$ in Raby 2009; 100% in Church 2001). Compared to patients with no use or heavy use, patients with occasional cannabis use were found to have better adherence with taking naltrexone pills (Raby 2009; Church 2001), better abstinence from opioids (Church 2001), and better retention in the treatment program (Raby 2009). Another paper reports on a retrospective medical record study of 91 patients on methadone maintenance therapy. More than half (56) of the patients had at least one positive urine screen for THC. Cannabis use during induction was associated with lower severity of withdrawal symptoms but had no association with persistent use of illicit opiates (Scavone 2013). As with all observational studies, caution is merited when interpreting the meaning of results; observed associations might not be causal.

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 opioid use disorder were found.

The American Psychiatric Association in December, 2013 released a Position Statement on Marijuana as Medicine. The document includes the following: “There is no current scientific evidence that marijuana is in any way beneficial for any psychiatric disorder. In contrast, current evidence supports, at minimum, a strong association of cannabis use with the onset of

psychiatric disorders...If scientific evidence supports the use of cannabis-derived substances to treat specific conditions, the medication should be subject to the approval process of the FDA.” (APA web site).

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Panic Disorder

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Introduction

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

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

Definition

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

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

Diagnosis

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

Complications and Consequences

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

Prevalence

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

Current Therapies

Panic disorder can be treated with first line medical therapies of antidepressants including selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) or tricyclic antidepressants (TCAs). Treatment with SSRIs is usually well-tolerated but side effects can include overstimulation, fatigue, or headache among others. Treatment with SNRIs can include side effects of nausea, restlessness, insomnia or headache as well as sexual dysfunction, discontinuation syndromes or increased blood pressure in some cases. Both SSRIs and SNRIs may require 2-4 weeks of therapy before patients begin experiencing benefit, which can present challenges for compliance. Tri-cyclic antidepressants are associated with more severe side effects (sedation, slow reaction time, dry mouth, constipation and weight gain) which hinder patient compliance. Additionally, TCAs interact with other medications and overdose can result in death. Second-line therapies include benzodiazepines which are effective as quick-acting agents. They are generally not favored for long-term therapy because they are associated with more harmful side effects, similar to TCAs and are habit-forming which makes them contraindicated in patients with substance abuse history (Mayo Clinic: Panic Disorder Diagnosis Treatment). Medication therapy is often used in combination with psychotherapy, such as cognitive behavioral therapy (CBT). Combination therapy is not always indicated, based on the patient's medical history and symptoms, but CBT has shown improved outcomes in anxiety patients with medication-resistant symptoms (Campbell-Sills 2016).

According to data from the European Study of the Epidemiology of Mental Disorders (ESEMeD), subjects from a large non-institutionalized European cohort who had an anxiety disorder had a low level of healthcare utilization: only 20.6% reported seeking treatment. Of

those who sought treatment, 30.8% received drug treatment only, 19.6% received psychotherapy only, and 26.5% received both drug therapy and psychotherapy (Alonso 2007).

Preclinical Studies

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

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

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

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

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

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

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

The review discusses animal models of panic attacks (flight and freezing defensive responses to threat) and the role of CBD in these models. In a predator-prey model with a mouse encountering a snake, acute administration of CBD reduced expression of panic-related behaviors. In another study, local administration of CBD in rats inhibited the escape response when the rats were subjected to the elevated T-maze or brain stimulation. These and other preclinical findings suggest that the amygdala, hippocampus, hypothalamus and cingulate cortex may be target sites for CBD panic-reducing activity. The authors also include a discussion of pharmacological mechanisms of CBD, mainly indirectly through interaction with the serotonin 5-HT_{1A} receptor, which has been shown in rodent models to reduce panic-like responses. The authors conclude that CBD shows anti-panic properties and may provide an alternative to medicines with more harmful side effects; clinical trials are needed to further support this possibility.

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

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

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

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

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

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

Clinical Trials

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

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

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

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

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

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

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

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

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

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

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

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

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

Ongoing Clinical Trials

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

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

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

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

<https://clinicaltrials.gov/ct2/show/NCT02548559>

Observational Studies

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

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

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

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

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

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

National Medical Organization Recommendations

There are no current recommendations from national medical organizations on the therapeutic use of cannabis for treatment of anxiety disorders, including panic disorder. The National Academies of Sciences, Engineering and Medicine produced a report on the health effects of cannabis in 2017 and the committee did not report any conclusions on the effects of cannabis on panic disorder. However, the committee found limited evidence that cannabidiol improves anxiety symptoms, as measured by a public speaking test, in patients with social anxiety disorder (Conclusion 4-17). The committee also found limited evidence of a statistical association between cannabis use and the development of any anxiety disorder *other than social anxiety disorder* and increased symptoms of anxiety (with near daily cannabis use) (Conclusion 12-9). Finally, the committee found moderate evidence that anxiety is not a risk factor for the development of problem cannabis use (Conclusion 13-2b) (National Academies of Sciences 2017).

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Psoriasis

SEPTEMBER 2018

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, 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

Psoriasis is a chronic, inflammatory skin condition that is often associated with systemic manifestations, especially arthritis. The cause of psoriasis is not fully understood, but it is known to be mediated through the immune system and there appears to be a genetic component. Approximately 90% of patients have plaque psoriasis, characterized by well-defined round or oval red, scaly plaques of varying size. The plaques can develop anywhere on the body but are most common on the extensor surfaces of the arms, legs, and trunk and on the buttocks and scalp (Weigle 2013). Microscopically, involved areas of the skin are characterized by markedly increased proliferation and incomplete differentiation of the

epidermis and a marked increase in blood flow and white blood cell infiltration (Gudjonsson 2007). In addition to often causing bothersome pruritis (itching) and pain, the lesions often cause significant social morbidity due to reactions - or perceptions of reactions - from others. This can lead to depression, isolation, problems at work and, in general, reduced quality of life. A substantial proportion of patients with psoriasis also develop psoriatic arthritis. Additional co-morbidities include metabolic syndrome, heart disease, and inflammatory bowel disease. The nature of these associations is not fully understood; they might not be directly causal. The clinical course of psoriasis is unpredictable (Weigle 2013), typically waxing and waning over time (Gudjonsson 2007).

Prevalence

In Europe and North America psoriasis prevalence is about 2 % in adults (Christopher 2001, Stern 2004), with similar prevalence in males and females (Christopher 2001, Gudjonsson 2007).

Current Therapies

Psoriasis has no known cure but many therapies can reduce severity of symptoms and slow progression of disease (Boehncke 2015). About 70-80% of patients have mild psoriasis that can be controlled using topical therapies alone (Schön 2005), primarily using vitamin D derivatives and glucocorticosteroids (Boehncke 2015).

For patients with moderate to severe disease, light exposure therapies and/or systemic therapy is needed. Phototherapies are very effective but also very time consuming and they are usually only used for short-term control of the disease. Conventional systemic non-biologic therapies in the USA for psoriasis include drugs that suppress the immune system through different mechanisms (methotrexate, cyclosporine, and apremilast [OTEZLA]) and acitretin (a vitamin A derivative thought to slow proliferation of skin cells). Most of the conventional systemic therapies can be used for long-term management of psoriasis, however, careful monitoring is needed due to frequency of drug-drug interactions and cumulative organ toxicities – not infrequently requiring discontinuation (Yeung 2013).

Over the past 15 years several biologic therapies have been developed and approved for the treatment of psoriasis. Most of the biologic therapies are monoclonal antibodies and so far they show little evidence of drug-drug interactions or organ toxicity. The most widely used biological for psoriasis is adalimumab (HUMIRA), a TNF- α inhibitor. Due to their high costs, TNF- α inhibitors are generally used after phototherapy and when conventional systemic therapies have failed, were not tolerated, or were contraindicated (Boehncke 2015). Patients' response to biologic agents can decrease over time as a result of immunogenicity and anti-drug antibodies (Menter 2008). And treatment costs are high. Estimated cost between 2007 and 2012 for biologic therapies for patients with moderate-to-severe psoriasis was over \$30,000 (Feldman 2016).

Despite the variety of therapies, there is a substantial unmet need in the treatment of

patients with mild to moderate disease, particularly those with psoriasis in difficult-to-treat areas such as the scalp, nails, and intertriginous areas (where two skin areas touch or rub together) (Boehncke 2015). According to national surveys, 23% (Stern 2004) to 52% (Armstrong 2013) of patients with psoriasis are unsatisfied with their treatment. Scores of drugs are now in clinical development for psoriasis (National Psoriasis Foundation 2018). US results from a 2012 multi-national survey found that 88% of psoriasis patients and 98% of dermatologists felt there was a strong or moderate need for better therapies (Lebwohl 2016).

Pre-Clinical Research

Separate sections are presented here for studies relevant to potential disease-modifying activity and for those relevant dealing with symptom reduction.

Disease Modification

Research into what causes psoriasis and how it might be treated has been hampered by absence of a good animal model for the disease. However, genetic modifications and immunological manipulations in rodents have resulted in hyperproliferative inflammatory skin disorders believed relevant to the study of psoriasis (Boehncke 2015).

Cannabinoid receptors are present in keratinocytes and a variety of other cell types found in the skin (Kupczyk 2009). Two published papers and an abstract suggest some cannabinoids reduce proliferation and/or differentiation of keratinocytes, the predominant cell type in the skin's outer layer. One studied the effect of cannabidiol (CBD), cannabigerol (CBG), and cannabidivarin (CBVN) on a human keratinocyte cell line often used in research because of its high capacity to replicate and differentiate. CBD and CBG reduced keratinocyte differentiation through regulation of genes that control differentiation. The effect of CBD was through CB1 receptors; the effect of CBG was independent of CB1 and CB2 receptors. CBVN did not inhibit keratinocyte differentiation (Pucci 2013). Another group studied the effect of THC, CBD, CBG, and cannabitol (CBN) on a human papilloma virus – infected keratinocyte cell line (used because of its tendency for rapid cell replication). Each of the four cannabinoids inhibited keratinocyte proliferation in a concentration-dependent manner. The mechanism of action appeared to be something other than activation of CB1 and CB2 receptors (Wilkinson 2007). An abstract with little methodologic detail states inflammation and skin barrier function in a mouse model of psoriasis was improved with topical application of a cannabinoid receptor activator (Kim 2015).

Over the past 20 years there have been important discoveries regarding interaction between the human nervous and immune systems, producing the concept of neural reflexes in inflammation and immunity. An important example is the vagus nerve, which transmits signals from the body's organs and tissues to the brain and messages from the brain to the body's organs. One consequence of increasing signals from the brain to the spleen is reduction in pro-inflammatory cytokines by a type of white blood cell called macrophages (Anderson 2012). A study was recently published showing electrical stimulation of the vagus nerve inhibits cytokine production and attenuates disease severity in patients with rheumatoid arthritis (Koopman 2016). It has been speculated that stimulation of the vagus nerve might also decrease inflammation in psoriasis patients (Derakhshan 2015). However, the impact of cannabinoids on

the vagus nerve is not altogether straightforward and not fully understood. There is some evidence that cannabis at low or moderate doses leads to decreased discharge of vagal nerve fibers from brain to organs (i.e. decreased parasympathetic tone), and at high doses these efferent messages increase (i.e. increased parasympathetic tone) (Fisher 2005). Currently, the role of cannabinoids in modulating inflammation through the vagus nerve is not well defined.

Symptom Reduction

Pruritis – itching – is a common symptom in psoriasis, and it can be very bothersome and difficult to treat. The best-known pruritis-causing substance in the body is histamine. Under certain conditions histamine is released by mast cells and keratinocyte cells in the skin. A review paper on mechanisms of itch and pain in the skin indicates endocannabinoids – cannabinoids produced by the body – reduce itch peripherally and that activation of CB1 receptors suppresses histamine-induced pruritis. The paper does not provide additional explanatory rationale (Chuquilin 2016). Another review paper (Kupczyk 2009) describes preclinical and human studies suggesting cannabinoids can reduce pruritis. Small, observational studies have shown reduced pruritis in large percentages of patients after topical application of a variety of cannabinoids. The studies described in the review paper did not use cannabinoids found in cannabis and did not involve patients with psoriasis.

Clinical Trials

No randomized, controlled clinical trials have been published for cannabis or cannabinoids as therapy for psoriasis. In March, 2017 One World Cannabis Ltd (Israel) announced in a press release “positive preliminary clinical efficacy tests results” of its proprietary topical cannabis cream to treat psoriasis and its plan to extend the size and scope of the efficacy study. It reported “up to 70% improvement in a variety of inflammation markers directly associated with psoriasis.” Publication of additional details and results of the expanded study have not been found, and the only study found on [clinicaltrials.gov](https://www.clinicaltrials.gov) is a small safety study funded by One World Cannabis Ltd (n=26; primary outcome = adverse event incidence rate; study start date = February 2017 and estimated completion date = July 2017).

<https://www.clinicaltrials.gov/ct2/show/NCT02976779?cond=psoriasis+marijuana&rank=1>).

Observational Studies

No published observational studies of cannabis or cannabinoids for the treatment of psoriasis 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 psoriasis were found.

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Traumatic Brain Injury

ISSUE BRIEF ON TRAUMATIC BRAIN INJURY

Introduction

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Definition

Traumatic brain injury (TBI), as defined by The Demographics and Clinical Assessment Working Group of the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychology Health, is "an alteration in brain function, or other evidence of brain pathology, caused by external force" (Menon et al., 2010).

TBI can be focal (affecting region of impact) or diffuse (affecting areas remote from region of impact), with injury resulting in primary and secondary effects. Primary injury refers to direct tissue damage that is inflicted on the brain from the initial mechanical impact. In contrast, secondary injury refers to a cascade of effects that occur in the injured brain over a variable, undefined amount of time.

Diagnosis

TBI diagnosis typically occurs through a combination of physical assessments and structural imaging for brain abnormalities. TBIs can be classified as closed (non-penetrating) or penetrating.

The most commonly used physical assessment of TBI is the Glasgow Coma Scale (Teasdale & Jennet, 1974) which is a classification system to indicate severity of TBI based on three components: eye opening, motor response, and verbal response. A summed score is generated from these components ranging from 3-15 (<3 indicates vegetative state on down to brain death), with the following ranges respectively indicating level of severity: Mild = 13-15, Moderate 9-12, and Severe 3-8.

Neuroimaging techniques can be used to assess structural damage, with computerized tomography (CT) being the most popular first option. A commonly used CT classification of TBI is the Marshall classification system (Marshall et al., 1992) with the following classifications:

- Diffuse Injury I (no visible pathology): no visible intracranial pathology.
- Diffuse Injury II: midline shift of 0 to 5 mm; basal cisterns remain visible; no high or mixed density lesions $>25 \text{ cm}^3$.
- Diffuse Injury III (swelling): midline shift of 0 to 5 mm; basal cisterns compressed or completely effaced; no high or mixed density lesions $> 25 \text{ cm}^3$.
- Diffuse Injury IV (shift): midline shift $> 5 \text{ mm}$; no high or mixed density lesions $> 25 \text{ cm}^3$
- Evacuated Mass Lesion V: any lesions evacuated surgically.
- Non-evacuated Mass Lesion VI: high or mixed density lesions $> 25 \text{ cm}^3$; not surgically evacuated.

Prevalence

A recent estimate has indicated that approximately 2.8 million emergency department (ED) visits, hospitalizations, and deaths that occur in the US lead to a TBI diagnosis (Taylor et al. 2017). According to the Centers for Disease Control and Prevention, the number of emergency department (ED) visits in the US due to TBI went up between 2001 and 2010 (700 per 100,000 in 2010; CDC, 2016). TBI-related hospitalizations in the US have remained relatively the same during the same time period (just under 100 per 100,000), while TBI-related deaths have decreased over time (17 per 100,000 in 2010; CDC, 2016; Taylor et al., 2017). TBI is more common in males (Taylor et al., 2017; Maas et al., 2008). One US estimate put the annual cost burden of TBI at \$60 billion (Thurman, 2001).

Global rates of TBI have been increasing, particularly as developing countries are adopting greater motor vehicle use (Redelmeier et al., 2003). In developed countries where the aging population is growing, the incidence of TBI due to falls has been increasing while TBI attributed to motor vehicle accidents has decreased (Maas et al., 2008; Taylor et al., 2017). The decrease in motor vehicle-related TBI in the US has been attributed to greater public health awareness and safety initiatives.

Current Therapies

Current therapies for TBI depend on TBI severity and symptoms presented by the patient. Mild TBIs may not require any particular treatments apart from over-the-counter medications, with regular consultation with a healthcare practitioner to monitor patient's status for any worsening of symptoms (Mayo Clinic). For penetrating TBIs, surgery is common to remove hematomas (clotted blood), repair fractures in the skull, stop bleeding in the brain, or as a means of relieving intracranial pressure (decompressive craniectomy). Pharmacotherapies are chosen based on patient symptoms and may include any of the following: diuretics (to relieve swelling and intracranial pressure), antiseizure medications (for seizure control post-TBI), antidepressants and/or antianxiety medications (for controlling emotional lability), anticoagulants (for reducing blood clotting), muscle relaxants (to reduce muscle spasms), and stimulants (to increase attention or alertness; Mayo Clinic; National Institutes of Health).

There has been particular interest within the scientific community to explore existing and new pharmacotherapies for neuroprotection in TBI. This is most likely spurred by the current state of evidence showing a lack of any particular agent for improving neurological outcome in TBI patients. McConeghy et al. (2012) recently summarized the state of clinical research for neuroprotective agents, and these are discussed directly below.

Calcium-channel blockers (to prevent neuronal excitotoxicity and cell death) have generally been shown to be ineffective in TBI. Furthermore, these agents have other systemic effects that hinder TBI recovery (e.g., systemic blood pressure effects).

Corticosteroids (to prevent swelling) have shown some efficacy. However, high doses of corticosteroids make this treatment option undesirable, and some data suggests increased mortality rates in moderate to severe TBI patients on these agents compared to placebo.

Cyclosporin A (to offset calcium dysregulation) has shown some potential on improving neurological outcomes, but further investigation is necessary. Some phase II trials have indicated that cyclosporin A is relatively safe with some indication of better outcomes on the Glasgow Outcome Score-Extended (GOSE; Wilson et al., 1998) compared to placebo.

Deltibant (a bradykinin antagonist) did not show statistically improved outcomes compared to placebo, although there may be some indication that it may decrease intracranial pressure (ICP) >15 mm Hg for a longer period of time compared to placebo.

A few different agents have been investigated for their potential to attenuate excitotoxicity and excessive glutamatergic activity that is typically found in TBI. Dexanabinol, which will be discussed later in the "Preclinical Studies" and "Clinical Trials" sections of this brief, is a cannabinoid that does not have cannabimimetic effects but rather acts as a non-competitive NMDA-receptor antagonist. Dexanabinol showed some initial promise in the preclinical phase (animal models of TBI), but equal success was not evident when investigated in humans. Magnesium sulphate (to attenuate calcium influx at NMDA receptors) did not show any improved outcomes over placebo and was associated with a possible increase in mortality rates. Lastly, selfotel (a competitive NMDA antagonist) was determined to not show any favorable outcomes.

Progesterone has shown some initial promise in improving neurological outcomes and mortality rates; however, a more recent clinical trial has contradicted this finding in severe TBI patients (Skolnick et al., 2014).

Statins, which are commonly used to improve cardiovascular outcomes, have also been investigated for any role in improving TBI outcomes, and one statin (rosuvastatin) has shown, in an under-powered study, some possibility for improving memory function.

Other agents reviewed by McConeghy et al. were pegorgotein, tirilizad, and zinc supplementation – all of which did not show any particular promise in clinical trials for improving neurological outcomes over placebo or comparator groups.

Preclinical Studies

Preclinical studies on TBI tend to focus on how to manipulate the endocannabinoid system (eCB) to improve TBI outcomes. Endocannabinoids are compounds that are naturally occurring within the brain (endogenous) that influence cannabinoid receptor function and other physiological processes that subsequently affect brain functioning. This section will briefly discuss a paper summarizing preclinical work on the potential restorative role of the eCB system in TBI or related pathologies (Schurman et al. 2017). This will be followed by research on a particular cannabinoid that showed some early promise at the preclinical level (Shohami et al., 1997). This particular cannabinoid is discussed here because it is the only one found in the literature where 1) both preclinical and clinical data exists, and 2) it was not treated as a pre-treatment (prior to injury) or investigated retrospectively.

Schurman LD, Lichtman AH. Endocannabinoids: a promising impact for traumatic brain injury. *Frontiers in Pharmacology*. 2017; 8:69. doi: 10.3389/fphar.2017.00069.

This is a review paper that came out recently to summarize preclinical literature on the role of the endocannabinoid (eCB) system in TBI. The eCB system appears to be involved in several physiological processes that are implicated in repair. In particular, this review focuses on two of the most well-studied eCBs, anandamide and 2-Arachidonoylglycerol (2-AG), along with the pathways that modulate their biosynthesis and degradation.

Endocannabinoid levels have been shown to increase as a function of neuronal damage which suggests that eCB system activation may be involved in compensatory self-neuroprotection efforts. For example, slowing down the breakdown of anandamide and 2-AG in the brain (which then gives these eCBs a longer period of time to act on receptor targets) can slow down cell death. Increasing anandamide levels (by inhibiting fatty acid amide hydrolase (FAAH) activity, which breaks down anandamide) as well as 2-AG levels (by inhibiting monoacylglycerol lipase (MAGL) activity, which breaks down 2-AG) has been shown in rat models to reduce neuronal cell death. Excessive glutamate release, which is a pathology of TBI, has also been shown in preclinical research to be attenuated by increasing 2-AG levels (via inhibition of MAGL activity).

Inhibiting the enzymes FAAH and MAGL may also play a role in neuroinflammation. For example, anandamide and 2-AG share a common metabolite called arachidonic acid (AA). AA has been shown to be involved in inflammatory responses in the brain. Therefore, by inhibiting FAAH and MAGL (which decreases amount of AA in the brain), inflammatory responses can be attenuated.

The blood brain barrier (BBB) is compromised in some central nervous system insults, with TBI being one of them. Schurman et al. cite independent literature indicating that exogenous delivery of 2-AG or anandamide, or the inhibition of FAAH or MAGL can prevent BBB breakdown in various central nervous system diseases.

Shohami E, Gallily R, Mechoulam R, Bass R, Ben-Hur T. Cytokine production in the brain following closed head injury: dexamabinol (HU-211) is a novel TNF- α inhibitor and an effective neuroprotectant. *Journal of Neuroimmunology*. 1997; 72: 169-177.

Prior research leading up to the study reviewed here had previously shown evidence of dexamabinol's (HU-211; (+)-(3S,4S)-7-hydroxy- Δ^6 -tetrahydrocannabinol 1,1-dimethylheptyl) neuroprotective effects. HU-211 is a synthetic cannabinoid that does not bind to brain CB1 receptors and does not produce cannabimimetic effects. Rather, HU-211 acts as a noncompetitive NMDA-receptor antagonist (a glutamatergic receptor) which has previously shown to decrease calcium (Ca^{2+}) neuronal influx in a rat model, thereby attenuating excitotoxic effects that may lead to cell death (brain trauma often causes an influx of Ca^{2+} into neuronal cells, which triggers excessive release of glutamate which damages cells). Other prior research using rat models has also shown that HU-211 attenuates the degradation of the blood brain barrier (BBB) as well as playing a role in decreasing cerebral edema and improving some memory functions.

In this paper, the authors explored the effects of HU-211 on tumor necrosis factor- α (TNF- α) levels. An increase in TNF- α levels in the brain had previously been documented in traumatic brain injury. HU-211 was injected into rats soon after undergoing a closed head injury, and this treatment was compared to control in the inhibition of TNF- α as well as comparing this experimental treatment to other compounds that have previously been shown to inhibit TNF- α .

A closed head injury (CHI) was induced by dropping a calibrated weight onto a defined region of the exposed skull. TNF- α levels were maximally found roughly 4 hours after CHI. For the experimental study, HU-211 was administered intravenously within 5 minutes post-CHI at a dose of 5 mg/kg (controls received a vehicle solution intravenously). TNF- α bioactivity was markedly reduced in the treatment group compared to control. Pentoxifylline (PTX) and tumor necrosis factor binding protein (TBP) administered concomitantly with rh-TNF- α (r-hTNF+TBP) – two other compounds previously shown to decrease TNF- α bioactivity – was confirmed to decrease TNF- α levels compared to control, confirming HU-211's comparative effectiveness in reducing TNF- α post-CHI. Rats were also examined on their recovery of reflexes and motor functions with a neurological severity score (NSS). All three treatments (HU-211, PTX, r-hTNF+TBP) showed changes in NSS at 24 hours post-CHI compared to controls, with HU-211 showing the most change indicating greatest recovery of reflexes and motor functions.

Evaluation of the NSS at other time points post-CHI continued to show that all 3 treatments lead to significant changes on the NSS compared to controls. All 3 treatments also showed significant reduction in cerebral edema at 24 hours post-CHI compared to controls, with HU-211 showing the greatest reduction. Blood brain barrier (BBB) integrity was also highest with HU-211 and TBP compared to control when measured 4 hours post-CHI with Evans blue (dye that allows for measuring BBB integrity). Lastly, there was a reduction in hippocampal cell death (region involved in learning/memory) with HU-211 and TBP administration, with HU-211 showing greatest reduction in hippocampal cell death.

Clinical Trials

Clinical trials investigating the effects of cannabis or cannabinoids on TBI have been restricted to the synthetic cannabinoid dexamabinol (HU-211), which is the compound that showed some promise in the preclinical literature (see “Preclinical Studies” section in this brief). However, the transition from preclinical to clinical study of this particular compound on TBI has not shown the same potential – this clinical literature is summarized below.

Knoller N, Levi L, Shoshan I, Reichenthal E, Razon N, Rappaport ZH, et al. Dexamabinol (HU-211) in the treatment of severe closed head injury: a randomized, placebo-controlled, phase II clinical trial. *Crit Care Med.* 2002; 30(3): 548-54.

This was a prospective, multi-center, randomized, double-blind study investigating the safety of dexamabinol (HU-211; a compound discussed previously in the Preclinical Studies section) compared to placebo on patients 16-65 years old with severe traumatic brain injury. A total of 67 patients participated in the study (drug treatment group: n = 30; placebo: n = 37). Roughly half had a Glasgow coma score (GCS) of 7-8 and a CT classification of 2. Patient mortality and adverse events (AEs) were reviewed after a single 48 mg dose of dexamabinol (or placebo). Those not succumbing to death or serious AEs from this group were then randomized into a higher, 150 mg dose of dexamabinol (or placebo). The following primary outcomes were measured: intracranial pressure (ICP), adverse events, cardiovascular functions including cerebral perfusion pressure (CPP), and clinical laboratory results. While this study was underpowered to detect any statistical differences on neurologic outcomes in patients, the following secondary measures were still included in the study: Galveston orientation and amnesia test (GOAT), Glasgow outcome score (GOS), and disability rating scale.

Results indicated that the mean percentage of time that ICP was <25 mm Hg was significantly lower in the dexamabinol group compared to placebo on the 2nd and 3rd day after injury, indicating that dexamabinol may be better at controlling ICP compared to placebo. In addition, the mean percentage of time that CPP was <50 was 0 on the 2nd and 3rd day after injury in the dexamabinol group compared to placebo; dexamabinol appeared to better manage CPP than placebo. Both groups reported similar number of AEs, and the AEs reported were typical of traumatic brain injury. GOS (a measure of neurologic recovery) showed improvements across patients irrespective of treatment group (meaning dexamabinol wasn't superior to placebo on GOS). The percentage of patients achieving good neurologic recovery

was significantly better at one month post-injury for the dexamabinol group compared to placebo, but this was not maintained in 3- and 6-months post-injury, indicating whatever benefit dexamabinol may afford for good neurologic recovery is lost over time.

While ICP and CPP scores appeared promising in this study, it is important to note that this was a study with a small sample size. Furthermore, due to the small sample size (which underpowers the study), interpretations on efficacy as measured by neurologic recovery are speculative until a larger scale study can support or refute those claims. Maas et al.'s (2006) study, which follows directly below, tried to address this major limitation (small sample size) to better address efficacy of dexamabinol on neurologic outcomes.

Maas AIR, Murray G, Henney H, et al. Efficacy and safety of dexamabinol in severe traumatic brain injury: results of a phase III randomized, placebo-controlled, clinical trial. *Lancet Neurol.* 2006; 5: 38-45.

This was a prospective, multi-center, randomized, double-blind parallel assignment of dexamabinol (HU-211; a compound discussed previously in the Preclinical Studies section) or placebo to adult patients who experienced severe traumatic brain injury. Inclusion criteria included patients who had a traumatic head injury within the last 6 hours and had a Glasgow Coma Motor score between 2-5. Patients were administered either 150 mg of dexamabinol or placebo intravenously within 6 hours of their injury. A total of 861 patients were randomized, with 846 of them reaching the primary outcome measure: 6-month post-injury Glasgow Outcome Scale Extended (GOSE). Secondary measures included: 1) 3-month post injury GOSE, 2) mortality rate at 10 days, 3) mortality rate at 6 months, 4) intracerebral pressure during first 74 hours since trauma, 5) neuroworsening at 10 days, 6) SF-36 quality of life scale at 6 months, and 7) Barthel index at 6 months. Results on the 6-mo GOSE showed no differences between patients treated with dexamabinol or placebo. Analyses on mortality rates, occurrences of neuroworsening, or recovery-related events were also no different between treatment groups. Intracranial pressure and cerebral perfusion pressure were also found to be no different between treatment groups. 32 patients receiving the placebo arm reported treatment-related adverse events, while 25 patients receiving dexamabinol reported treatment-related adverse events.

Ongoing Clinical Trials

As of early September 2018, no ongoing clinical trials examining the efficacy or safety of cannabis or cannabinoids on TBI were found on ClinicalTrials.gov.

Observational Studies

One observational study examining the effects of cannabis or cannabinoids on TBI was identified. As a retrospective study (more susceptible to bias and confounders relative to prospective studies), the conclusions that can be drawn are somewhat limited. The presence of

cannabis use was determined by urine toxicology screening (for presence of THC) in TBI patients, and mortality rate was retrospectively examined.

Nguyen BM, Kim D, Bricker S, Bongard F, Neville A, Putnam B, et al. Effect of marijuana use on outcomes in traumatic brain injury. *Am Surg.* 2014; 80(10): 979-83.

This study reviewed records of trauma patients (16+ years old) and identified those who were admitted to a surgical intensive care unit over a two-year period at a California hospital (January 1, 2010 - December 31, 2012). Of 7,977 trauma patients that were evaluated in this time period, 538 of them had TBI, with 82.9% of these TBI patients (n = 446) having been screened for illicit drug use. Of the 446 drug-screened patients, 82 of them tested positive for THC while the remaining 364 patients were THC-negative. Mortality rates of the THC-positive group were significantly lower than the THC-negative group. A regression analysis found that a THC-positive screen, being 45+ years old, and scoring >4 on the head Abbreviated Injury Score (Head AIS) were each independent predictors of mortality. Apart from the retrospective nature of this study being a limitation, there are limitations surrounding what can be stated regarding patient cannabis use, where THC can be detectable for days to weeks. Therefore, this study is unable to clarify the role of chronic vs. acute cannabis use in the pattern of results. Another limitation is the specific focus on mortality rates as an outcome measure for TBI; inclusion of additional outcome measures for TBI would provide a more comprehensive understanding of the potential role of cannabis on TBI prognosis.

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 TBI were found.

The National Academies of Sciences, Engineering and Medicine published a report on the health effects of cannabis and cannabinoids in 2017. This report included a review of evidence on the effects of cannabinoids on TBI or intracranial hemorrhage (the latter not necessarily always associated with TBI and can be a symptom of other disease states). The committee for this report concluded that “there is limited evidence of a statistical association between cannabinoids and better outcomes (i.e., mortality, disability) after traumatic brain injury or intracranial hemorrhage” (see Conclusion 4-15; National Academies of Sciences, Engineering, and Medicine, 2017).

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