DEPARTMENT OF HEALTH

Age-Related Macular Degeneration

SEPTEMBER 2019

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 medical organizations will be included.

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

Definition

Age-related macular degeneration (AMD) is a leading cause of visual impairment and severe vision loss. How it develops isn't completely understood, but involves dysregulation of the body's complement, lipid, angiogenic, inflammatory, and extracellular matrix pathways, resulting in deterioration of cells that support the light-detecting rod and cone cells that line the back of the eye (retina). As the disease progresses the light-detecting cells also become injured and sometimes die. The consequence is vision loss, especially in the central part of the visual field (Mitchell 2018).

Its early stage involves characteristic deposits within layers of the retina and retinal pigment anomalies. Late-stage AMD is defined by the presence of signs indicating new growth of abnormal – often leaky – blood vessels (neovascular AMD) or loss of retinal pigment epithelial cells (atrophic AMD) (Mitchell 2018). Based on studies of white populations, neovascular AMD appears to be somewhat more common than atrophic AMD (Smith 2001).

Early AMD is often asymptomatic. Some patients notice mild central distortion, particularly when reading, and reduced reading ability with low light. Late AMD affects central vision and can progress rapidly (weeks or months) in the neovascular form, and more slowly (years or decades) in the atrophic form. The earliest symptoms of AMD include distorted vision when reading, driving, or watching television, and a dark or grey patch in the central vision, with difficulty recognizing faces. If only one eye is affected, symptoms might not be apparent until the good eye is covered (Mitchell 2018).

As might be expected, AMD has widespread impact on quality of life. AMD has been associated with increased risk of functional disability, falls and other injuries, cognitive impairment (Mitchell 2018) and depression (Brody 2001).

Prevalence

A decade ago, AMD was estimated to account for more than 54% of all vision loss in the white population in the USA. An estimated 8 million Americans are affected with AMD, of whom over 1 million will develop advanced AMD within the next 5 years (Coleman 2008). Because of improvements in treatment of neovascular AMD over the past decade, these figures are now probably substantially lower (Mitchell 2018).

Prevalence of AMD is strongly age-related. Combined results from three population studies in the 1990s (Wisconsin, the Netherlands, and Australia) showed prevalence of late-stage AMD to be 0.2% in patients aged 55-64 years, 0.85% in those aged 65-74, 4.59% in those aged 75-84, and 13.05% in those 85+ (Smith 2001). Prevalence of early AMD is higher in people of European ancestry than in Asians, and prevalence of early and late-stage AMD is higher in people of European ancestry than in those of African ancestry. Estimate of global prevalence of early, late, and any AMD among the population age 45-85 years are 8.0%, 0.4%, and 8.7%, respectively (Wong 2014).

There is a strong genetic component to AMD and over the past decade more than 50 gene variants have been found to be associated with increased risk for AMD. Smoking is the strongest modifiable risk factor for AMD, associated with a two-times increased risk for developing late AMD and around a 10-year younger age at onset (Mitchell 2018).

Current Therapies

Prevention and Delay of AMD Progression

Clinical trials have shown high-dose zinc and anti-oxidant vitamin supplements can slow the progression from early-stage to late-stage AMD by about 20%. High-dose statin therapy is being investigated to delay progression, but at this point evidence remains mixed (Mitchell

2018).

Treatment of Neovascular AMD

Effective treatment for neovascular AMD is based on inhibition of the angiogenic protein vascular endothelial growth factor (VEGF), which is produced in the retina and induced by hypoxia and other conditions. VEGF increases retinal vascular permeability and promotes formation of new blood vessels - neovascularization. A few different anti-VEGF agents are used in clinical practice. An anti-VEGF agent is typically injected into the eye monthly or every few months for an extended period of time (Mitchell 2018). Monthly injections of VEGF inhibitors are expensive and they are burdensome to patients (Day 2011). And there is a lot of variability among patients in effectiveness of anti-VEGF therapy – perhaps as a function of genetic characteristics (McKibbin 2012). Research continues on alternative, longer-acting, and personalized anti-VEGF therapies (Mitchell 2018).

Treatment of Atrophic AMD

Currently there is no effective therapy for atrophic AMD, but several agents are being investigated in clinical trials, especially drugs targeting the complement pathway related to inflammation. Use of stem-cell-based therapies is being explored for potentially replacing dead or dysfunctional retinal pigment epithelium with healthy retinal pigment epithelium (Mitchell 2018).

Pre-Clinical Research

Multiple review articles have been publicized summarizing research on the endocannabinoid system (ECS) in the eye (Bouchard 2016, Rapino 2018, Schwitzer 2016), but understanding the impact of manipulating components of the ECS in AMD patients has been hampered by lack of a good animal model for AMD (Frische 2014).

The ECS appears to play a role in response to injury of retinal cells, but what that role is remains somewhat unclear. Cannabinoid receptor type 1 (CBR1) and type 2 (CBR2) have been found in the human retina: CBR1 has been found in multiple layers of the retina, including photoreceptor cells and retinal pigment epithelium cells; CBR2 in retinal pigment epithelium cells. The two main endogenous cannabinoids are found in the retina: 2-AG in large amounts and anandamide in smaller amounts (Schwitzer 2016). In the next paragraph, several published experiments attempting to manipulate elements of the ECS in retinal cell cultures or in animal models of retinal injury are summarized briefly.

In a human retinal epithelial cell culture exposed to hydrogen peroxide as a model of oxidative stress, exposure to a CBR1 antagonist (blocker) rescued RPE cells from damage. The oxidative stress itself upregulated (increased) the expression of CBR1 receptors on the cells (Wei 2013). In a similar experimental model, exposure to a CBR2 agonist significantly protected human RPE cells from oxidative stress; exposure to a CBR1 agonist did not (Wei 2009). In a mouse model of continuous bright light-induced retinal damage, a CBR1 antagonist protected against both photoreceptor death and functional loss (Imamura 2017). And in a similar mouse model of

continuous bright light-induced retinal damage and a mouse RPE cell line exposed to continuous bright light, a CBR2 agonist reduced photoreceptor cell death (in vivo mouse model) and cell damage (cell culture model) (Imamura 2018). Contrasting findings were reported in another study where a human RPE cell line was exposed to oxidative stress from the chemical, hydroxynonenol. Exposure to a CBR2 agonist 15 minutes prior to the chemical exposure increased, rather than reduced, inflammation in RPE cells (Hytti 2017).

Results from these studies seem to suggest that exposure to a CBR1 agonist such as THC would not be helpful and could be harmful to retinal cells undergoing oxidative stress. THC is known to interact with the ECS in ways other than through CBR1 and CBR2 receptors, so it is possible THC could have a beneficial effect on retinal cells undergoing stress, but at present beneficial impact is undefined. Cannabidiol (CBD) is widely held to have anti-inflammatory effects and there is some evidence it can protect nerves from damage. In a rat model of diabetic retinopathy, treatment with CBD significantly reduced both oxidative stress and neurotoxicity and prevented retinal cell death (El-Remessy 2006). The degree to which this applies to AMD in humans is not clear.

Clinical Trials

No randomized, controlled clinical trials have been published for cannabis or cannabinoids as therapy for AMD.

Observational Studies

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

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Chronic Pain

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Introduction

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This research brief is a bit different from other research briefs produced by the Office of Medical Cannabis. Intractable pain, already an approved condition for the program, is a subset of patients with chronic pain. The preclinical studies and clinical trials relevant to chronic pain are also those relevant to intractable pain. Instead of summarizing the many clinical trials relevant to chronic pain individually, this brief points to other such summaries and gives brief discussion to one recent review article covering preclinical studies.

Definition

Though the term "chronic pain" is used frequently, the term does not have a single, clear definition. The International Association for the Study of Pain defines pain as, "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." It goes on to define chronic pain as pain that persists past the normal time of healing, noting this may be less than one month or, more often, more than six months. It suggests that, with non-malignant pain, three months is the most convenient point of division between acute and chronic pain but for research purposes six months will often be preferred (IASP 2011). The National Pain Strategy defines chronic pain as pain that occurs on at least half the days for six months or more (Interagency Pain Research Coordinating Committee 2016).

There are different ways of categorizing types of chronic pain: perceived location (example – headache), etiology (example – cancer pain), or the primarily affected anatomical system (example – neuropathic pain). Some diagnoses of pain defy these classification systems (example – fibromyalgia). The International Classification of Diseases, 11th revision (ICD-11)

nests several categorization schemes into its classification system, using etiology as the highest-level classification. This results in chronic pain being divided into 7 groups of categories: 1) chronic primary pain, 2) chronic cancer pain, 3) chronic post-traumatic and post-surgical pain, 4) chronic neuropathic pain, 5) chronic headache and orofacial pain, 6) chronic visceral pain, 7) chronic musculoskeletal pain (Treede 2015).

Chronic pain is different in kind from acute pain; that is, chronic pain is not simply acute pain that lasts for months. Painful stimuli, when present over time, can trigger a prolonged but potentially reversible increase in the excitability and firing of neurons in the central nervous system – both within the spinal cord and within the brain. This phenomenon, called central sensitization, appears to be key to development and maintenance of chronic pain. It is an area of active research, but much remains to be learned (Woolf 2011). Chronic pain of some kinds is also likely to involve sensitization of peripheral (outside of the central nervous system) nerves (Graven-Nielsen 2002). Better understanding of the nature of central sensitization and how it is expressed across different pain conditions holds hope for more effective, targeted therapies (Arendt-Nielsen 2018). Some chronic pain medication therapies attempt to reverse the effects of central sensitization, but there is also emerging interest in non-medication therapies to counter central sensitization (Greenwald 2018).

The petition specifies “moderate and severe chronic pain.” Because these descriptive terms lack clear definition this report focuses on chronic pain, generally.

Prevalence

A research group used responses to a question on frequency of pain occurrence in 2016 National Health Interview Survey data to estimate the prevalence of chronic pain. Using a response of pain on most days or every day in the past six months, 20.4% of the U.S. adult population had chronic pain. Higher prevalence was associated with advancing age. Age-adjusted prevalence of chronic pain was significantly higher among women, adults who had worked previously but were not currently employed, adults living in or near poverty, and rural residents (CDC 2018).

Current Therapies

The experience of chronic pain reflects a complex interplay of emotional, psychological and social factors that contribute to an individual’s worsening ability to function. Patients suffering from chronic pain can have mood disorders, sleep disturbances and impaired social interactions. Interventions that act primarily on pain sensory receptors, such as local anesthetic, are unlikely to be successful in managing chronic pain. Rather, the best results are obtained through multimodal and rehabilitative techniques, with the goal of improving function rather than interrupting a painful stimulus (Weiner 2001).

Treatment modalities frequently used by physician pain specialists and other practitioners include: medications, regional anesthetic interventions, surgery, psychological therapies, rehabilitative/physical therapy, and complementary and alternative medicine. The following sections provides a brief overview of each of these modalities, drawn from the Institute of Medicine’s 2011 report, *Relieving Pain in America: A Blueprint for Transforming Prevention,*

Care, Education, and Research. A common source of frustration for chronic pain patients, their families, and clinicians is that it is often impossible with today's knowledge to predict which treatment or combination of treatments will work best in an individual case. Many patients are not told, or do not readily comprehend, that the road to finding the right combination of treatments for them may be a long one with many different approaches to treatment until the right match is found (IOM 2011).

Medications

A wide range of medications is used for pain management. The most common are non-opioid analgesic drugs (acetaminophen; nonsteroidal anti-inflammatory drugs, including SOX-2 inhibitors; ibuprofen; and aspirin), opioids, and a plethora of so-called "adjuvant analgesic drugs" that encompass medications used for other indications that also are used to manage pain. Most often these adjuvant medications are in the anticonvulsant or psychotropic classes. A few additional drug classes and compounds further illustrate the range: mu-opioid agonists, serotonin and norepinephrine reuptake inhibitors, and muscle relaxants. The use of opioids for chronic pain has become controversial. In fact the 2017 Institute for Clinical Systems Improvement guideline for pain management recommends avoiding use of opioids for treating patients with chronic pain (Hooten 2017).

Regional Anesthetic Interventions

Regional anesthetic interventions are invasive and include a variety of treatments, such as sacroiliac joint injections; epidural steroid injections to manage radicular pain (pain radiating along a nerve as a result of irritation of the spinal nerve root, such as sciatica); cervical, thoracic, and lumbar facet joint nerve blocks; or implantation of devices that deliver analgesic medications directly to the spinal canal. Clinical trial evidence of effectiveness for these procedures is generally slim, though some specific types of patients might benefit from certain of the procedures.

Surgery

Surgical therapies overlap with interventional techniques, such as implantation of spinal cord stimulation systems and spinal analgesic infusion pumps, but include more invasive procedures, such as spinal decompression procedures (e.g. laminectomies, discectomy), disc replacement, and spinal fusion, which are used to treat neck, low back, and radicular pain. Joint replacement surgery is another frequently used surgical intervention for pain. Others include nerve decompression (e.g., for carpal tunnel syndrome or trigeminal neuralgia) and ablative surgeries that disrupt the flow of nociceptive pain in the nervous system, such as nerve section and cordotomy. Surgery usually is undertaken only after other treatments fail, and different procedures vary in their effectiveness.

Psychological Therapies

Psychological therapies include cognitive-behavioral treatment, behavioral treatment alone, biofeedback, meditation and relaxation techniques, and hypnotherapy. There is a substantial body of evidence showing effectiveness of these therapies, though no clear indication that one type of therapy is more effective than the others.

Rehabilitative/Physical Therapy

Rehabilitative/physical therapy is undertaken in inpatient, ambulatory care, and home-based settings. Inpatient pain rehabilitation programs are interdisciplinary, include a physical medicine and rehabilitation component, and provide education as well as treatment. A meta-analysis found such programs achieved significant reductions in both pain intensity and use of pain medications. Rehabilitation methods available to patients living at home or in other setting include stretching, strengthening, and mobility exercises. Rehabilitation/physical therapy has increasingly been found to reduce pain even in end-of-life situations, such as advanced cancer, although consistent adherence to exercise regimens may be difficult for many patients. Physical modalities of therapy include physical and functional restoration techniques, massage ultrasound, neurostimulators (such as transcutaneous electrical nerve stimulation, or TENS).

Complementary and Alternative Medicine (CAM)

There is not a universally accepted set of treatment modalities included within CAM. Acupuncture, chiropractic spinal manipulation, magnets, massage therapy, and yoga often are considered CAM pain treatments. According to the National Institutes of Health's (NIH) National Center for Complementary and Alternative Medicine, additional CAM therapies used for pain include dietary supplements, such as glucosamine and chondroitin intended to improve joint health; various herbs; acupuncture; and mind-body approaches, such as meditation and yoga. Research on CAM therapies for specific pain conditions is incomplete but accumulating.

There are numerous barriers to successful management of chronic pain. The IOM report (IOM 2011) discusses some of them: frustration with interim failures and overall time it takes to discover the complement of modalities successful for a particular patient, overemphasis on biological rather than the psychosocial causes and effects of illness, overemphasis on drugs as sole modality therapy, inadequate training – especially continuing education – on current models of pain management, and inadequate insurance coverage – especially for psychological therapies. Also, the side effects of drugs used as part of chronic pain management can cause patients to discontinue their use – sometimes without their clinicians' knowledge.

Pre-Clinical Research

There is a relatively large literature describing changes to the endocannabinoid system (ECS) in animals concurrent with pain as well as studies of the effect of manipulating the ECS in animal models of pain. A recent review (Vuckovic 2018) describes many of these published reports. For example, there are studies of animal models of neuropathic pain describing how cannabinoid receptors become more numerous in nerve structures associated with pain as well as increased levels of endocannabinoids in regions of the spinal cord and brain stem. And there are numerous studies of effect of administering cannabinoids or agents that reduce enzymatic degradation of an animal's endocannabinoids (thus increasing their levels). Some of these appear to be quite effective in animal models of pain. However, as the authors acknowledge, a number of promising therapeutic targets identified in animal studies have not been confirmed when attempted in human clinical trials. This important caution might be due in part to the difficulty of developing good animal models of chronic pain.

Clinical Trials

In 2016 the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine convened a committee of experts to conduct a comprehensive review of the literature regarding the health effects of using cannabis and/or its constituents. The committee's report *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*, was published January, 2017. The committee identified five good-to fair-quality systematic reviews on the question of whether cannabis or cannabinoids are an effective treatment for the reduction of chronic pain. In addition to identifying clinical trials from those review articles, the committee also did a primary search of the literature, yielding 30 trials using a variety of agents: oromucosal cannabis extraction products (17), smoked or vaporized plant flower (7), synthetic THC (5), and oral extracted THC (1). After assessing the reviews and the trials the committee came to this conclusion, "Conclusion 4-1: There is substantial evidence that cannabis is an effective treatment for chronic pain in adults." The report goes on to acknowledge, "While the use of cannabis for the treatment of pain is supported by well-controlled clinical trials as reviewed above, very little is known about the efficacy, dose, routes of administration, or side effects of commonly used and commercially available cannabis products in the United States. Given the ubiquitous availability of cannabis products in much of the nation, more research is needed on the various forms, routes of administration, and combination of cannabinoids" (National Academies 2017).

Other reviews of cannabis and cannabinoids for treatment of chronic pain are less optimistic in their assessment. A recent systematic review and meta-analysis by Stockings et al is a good example (Stockings 2018). This group's review included 47 randomized controlled trials (RCTs) and 57 observational studies of cannabis or cannabinoids for noncancer pain. Across RCTs a significant effect was found for cannabis vs. placebo, but the effect was small. Pooled event rates across RCTs for 30% reduction in pain were 29.0% for cannabis/cannabinoids and 25.9% for placebo. The abstract of their paper concludes, "Effects suggest that number needed to treat to benefit is high, and number needed to treat to harm is low, with limited impact on other domains. It seems unlikely that cannabinoids are highly effective medicines for chronic noncancer pain."

The Office of Medical Cannabis produces an annual update to a report that summarizes clinical trials of cannabis extract products and synthetic THC for conditions included in the state's medical cannabis program. The report, *A Review of Medical Cannabis Studies Relating to Chemical Compositions and Dosages for Qualifying Medical Conditions* is posted on the Office of Medical Cannabis web site. The "Intractable Pain" section includes summaries of 16 clinical trials related to non-cancer chronic pain (there is a separate section in the report for cancer pain). Note that all or nearly all of these studies used a cannabis product (or placebo) as an adjunct (i.e. in addition) to each patient's current pain management regimen. The report (Office of Medical Cannabis 2019) can be found here: https://www.health.state.mn.us/people/cannabis/docs/practitioners/dosagesandcompositions2019.pdf.

Observational Studies

The Office of Medical Cannabis has produced a comprehensive report on the 2290 patients who enrolled in Minnesota's medical cannabis program during the first five months (Aug-Dec, 2016) intractable pain was a qualifying condition. Patients with intractable pain are a subset of patients with chronic pain. The currently qualifying condition of intractable pain is defined by the Office of Medical Cannabis as pain whose cause cannot be removed and, according to generally accepted medical practice, the full range of pain management modalities appropriate for this patient has been used without adequate result or with intolerable side effects. Use of opioid medications is not required to meet this definition. The report, *Intractable Pain Patients in the Minnesota Medical Cannabis Program: Experience of Enrollees During the First Five Months*, is posted on the Office of Medical Cannabis web site at the following address: https://www.health.state.mn.us/people/cannabis/about/ipreport.html.

Among responses to patient (54% response rate) and health care practitioner (40% response rate) surveys, a high level of benefit was reported by 61% and 43%, respectively (score of 6 or 7 on a seven-point scale). Little or no benefit (score of 1, 2, or 3) was reported by 10% of patients and 24% of health care practitioners. The benefits extended beyond reduction in pain severity, though that was the main benefit mentioned most often (64%). The main benefit listed second most often was improved sleep (27%). In other cases reduction in other pain medications and their side effects, decreased anxiety, improved mobility and function, and other quality of life factors were cited as being the most important benefit.

Prior to each medical cannabis purchase patients are required to complete a 3-item scale, the PEG scale, that asks the patient to assess, over the past week, pain intensity and its interference with enjoyment of life and general activity. Using the PEG scale data, 42% of the patients achieved ≥30% reduction in composite PEG score and 22% both achieved and maintained that level of improvement during the four months after ≥30% reduction was first achieved. The ≥30% reduction threshold is often used in pain studies to define clinically meaningful improvement.

Among the 60% of patients taking opioid medications when they began participating in the program, 63% were able to reduce or eliminate opioid usage after six months.

Survey results indicate approximately 35-40% of patients experience at least one physical or mental adverse effect, with the vast majority (approximately 90%) mild to moderate intensity. The most common adverse effects reported were dry mouth, drowsiness, fatigue, and mental clouding/"foggy brain."

National Medical Organization Recommendations

In 2015 the Neuropathic Pain Special Interest Group of the International Association for the Study of Pain published recommendations on therapies for neuropathic pain, based on a systematic review of randomized double-blind studies. They determined data for cannabinoids and several other categories of drug therapies were inconclusive and made the following recommendation: "We provide a weak recommendation against the use of cannabinoids in neuropathic pain, mainly because of negative results, potential misuse, abuse, diversion and long term mental health risks particularly in susceptible individuals" (Finnerup 2015).

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