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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