

Marijuana for Glaucoma: A Recipe for Disaster or Treatment?

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Marijuana has been shown to lower intraocular pressure (IOP[†]) but with limited duration of action and numerous adverse effects. Use of marijuana to lower IOP as a means of glaucoma treatment would require frequent use throughout the day, leading to significant adverse effects, possible progression toward Cannabis Use Disorder (CUD), and/or withdrawal symptoms. The treatment of glaucoma based on the cannabis plant or drugs based on the cannabinoid molecule should be considered carefully before being prescribed. Considerations should include the adverse physical and psychological adverse effects, including substance abuse. Currently, the deleterious effects of marijuana outweigh the benefits of its IOP-lowering capacity in most glaucoma patients. Under extremely rare circumstances, a few categories of glaucoma patients may be potential candidates for treatment with medical marijuana. Further studies on alternate routes and more focused means of cannabinoid molecule delivery to the eye for glaucoma treatment are needed.

INTRODUCTION

Medical marijuana (medical cannabis) is the use of *Cannabis sativa* and its derivatives, such as Δ^9 -tetrahydrocannabinol (Δ^9 -THC), as medical drugs to treat diseases or alleviate symptoms. Recent U.S. government policies paved the way for the legalization of the medicinal use of marijuana [1]. As of 2015, medical marijuana is legal in 23 U.S. states and the District of Columbia, while an additional nine states have pending legislation for its legalization. Indications for medical marijuana use include pain related to cancer, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), Parkinson's disease, multiple sclerosis or spinal cord injuries, Crohn's disease, post-traumatic stress disorder (PTSD), and glaucoma [2]. However, the American Medical Association (AMA) [1], the American

Society of Addiction Medicine, American Glaucoma Society (AGS) [3], and other organizations [4,5] have issued statements and comprehensive reviews [6] that oppose medical marijuana usage due to extensive adverse effects. The disaccord between lawmakers and physicians on use of medical marijuana makes this topic complex and challenging for physicians to address with their patients. However, with the expanding legalization of this substance, more glaucoma patients are inquiring about marijuana as a treatment option. Therefore, a review of medical marijuana's benefits and shortcomings in the treatment of glaucoma is necessary. This study aims to systematically review and summarize evidence of medical marijuana's role in the treatment of glaucoma, while also investigating its addictive potential and long-term health consequences.

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†Abbreviations: Δ^9 -THC, Δ^9 -tetrahydrocannabinol; AMA, American Medical Association; AGS, American Glaucoma Society; IOP, intraocular pressure; DSM-V, Diagnostic and Statistical Manual of Mental Disorders; CUD, Cannabis Use Disorder; CWS, Cannabis Withdrawal Syndrome; POAG, primary open-angle glaucoma; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; PTSD, post-traumatic stress disorder.

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THERAPEUTIC EFFECT OF MARIJUANA IN GLAUCOMA

Glaucoma describes a multiplicity of ocular disorders, all having in common a characteristic optic neuropathy with resultant visual field deficits. It is most commonly associated with elevated intraocular pressure (IOP) and causes irreversible vision loss. There is evidence that the blood-pressure lowering effect of marijuana mediates the temporary reduction in IOP [7]. This mechanism of action could be harmful in glaucoma, as it may lead to poor perfusion of the optic nerve. An alternative hypothesized mechanism by which Δ^9 -THC lowers IOP is through acting on ciliary body cannabinoid receptors and lowering aqueous humor production, rather than lowering blood pressure [8,9]. While peripheral vision is more commonly lost first, if left untreated, glaucoma can lead to blindness. This condition is a leading cause of blindness in the United States and affects more than 3 million Americans [10]. Though older people tend to be at higher risk for this disease, young adults, children, and infants can develop glaucoma. At present, the only known modifiable risk factor for glaucoma progression is increased IOP. Typically, IOP above 21 mmHg is considered ocular hypertension, and such patients are monitored for progression to glaucoma. However, some patients have pressure within the average physiologic range but may still sustain optic nerve damage at these lower IOP levels [11]. Medical marijuana can be considered as a potential treatment for glaucoma, as studies have shown that marijuana and Δ^9 -THC can lower IOP when administered orally, intravenously, or by smoking [12,13]. It has been shown to lower IOP by approximately 25 percent in 60 to 65 percent of both glaucoma and non-glaucoma patients [6,13,14]. Additionally, the absolute change in IOP seemed to have a dose-response relationship, with increasing dose associated with greater reduction in IOP from baseline. However, the effect was found to last only 3 to 4 hours. There was no relationship between dose and duration of effect [6].

Δ^9 -THC in the form of topical application and eye drops has also been investigated, but these forms were found to be less effective than oral, intravenous, or smoked marijuana [15,16]. The topical oil was ineffective in reducing IOP in humans due to ocular irritation and stimulation of tears that rinsed the medication from the eye, preventing absorption [16]. As an eye drop, Δ^9 -THC requires an effective delivery system [7,17], due to low water-solubility of active molecules [16]. Recent discovery of ocular cannabinoid receptors [11] and the lowering of IOP through the endocannabinoid system [18] has stimulated new research into development of this drug in topical eye drop form, which would minimize the harmful systemic adverse effects of *Cannabis sativa*.

ADDICTIVE EFFECTS OF MARIJUANA USE

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V) combined the DSM-IV

categories of cannabis abuse and substance dependence into a single disorder: Cannabis Use Disorder (CUD) [19]. The severity of the disorder is based on the number of symptoms. Table 1 shows the diagnostic features of CUD. In this article, cannabis or marijuana addiction and dependence are used interchangeably to refer to CUD.

In most cases, single-time users of marijuana do not become addicted to the drug, though there is evidence that occasional and recreational users start becoming addicted and developing morphological changes in brain regions such as the nucleus accumbens [20]. According to the National Institute on Drug Abuse, long-term, daily use of marijuana has strong potential for addiction and drug abuse, with medical marijuana users being no exception [21]. A population-based study involving 8,098 participants showed that approximately 1 in 11, or 9 percent, of marijuana users in the general population were dependent on marijuana [22-24]. However, the study assessed dependence based on DSM-III criteria that included problems with law enforcement as a criterion. Since then, this criterion has been removed from the DSM-V, given cultural and legal system differences that makes the criterion difficult to apply across the United States and internationally. Another population-based study showed that among people who started using marijuana as teens, the rate of addiction increased to 17 percent, while among daily marijuana users, 25 to 50 percent of people were addicted [22]. The limitation of these population-based epidemiology studies is that their validity depends on participants being forthcoming about their substance use to an interviewer with whom they have no relationship. Therefore, these studies may have underestimated the rates of CUD.

In order to achieve a consistent decrease in IOP, glaucoma patients who use medical marijuana would have to smoke at least six to eight doses a day. This dosing recommendation is based upon the duration of the IOP lowering effects (3 to 4 hours) [25] and would force the glaucoma patients to become heavy, daily marijuana users, placing them at risk for substance dependence. Even for patients who do not follow this dosing recommendation, prescription of medical marijuana could lower their inhibitions toward use and may lead to drug abuse followed by addiction [26]. There is some support that the patients develop a tolerance to marijuana, resulting in progressively reduced therapeutic effect with a specific dose. In a non-randomized clinical trial involving nine patients who were treated with inhaled marijuana or Δ^9 -THC capsule every 4 hours while awake for 1 to 9 months, an initial IOP reduction was observed in all patients. All except two patients have lost the beneficial effects of treatment on their IOP at the time of termination due to treatment tolerance [12]. Similarly, in an early report, IOP reduction was inversely associated with duration of marijuana use [27]. For glaucoma patients who are dependent on medical marijuana, abruptly stopping the treatment can lead to Cannabis Withdrawal Syndrome (CWS), as recently recognized in the DSM-V. CWS is de-

Table 1. Diagnostic features of Cannabis Use Disorder as published by the American Psychiatric Association [19].

Cannabis Use Disorder (DSM-V)	
Definition	A problematic pattern of cannabis use leading to clinically significant impairment or distress
Time requirement	Within a 12-month period
# of Criteria	Meet 2 of the following criteria
Criteria	<ol style="list-style-type: none"> 1. Tolerance 2. Withdrawal 3. Taken in larger amounts or over a longer period than intended 4. Persistent desire or unsuccessful efforts to cut down or control cannabis use 5. Great deal of time is spent in activities necessary to obtain cannabis, use cannabis, or recover from its effects 6. Important social, occupational, or recreational activities are given up or reduced because of cannabis use 7. Continued cannabis use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of cannabis 8. Continued cannabis use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by cannabis 9. Recurrent cannabis use in situations in which it is physically hazardous 10. Recurrent cannabis use resulting in a failure to fulfill major role obligations at work, school, or home 11. Craving or a strong desire or urge to use cannabis
Severity	
Mild	2-3 symptoms
Moderate	4-5 symptoms
Severe	6 or more symptoms

defined as having three or more of the following symptoms within 1 week after cannabis cessation: irritability, sleep difficulty, poor appetite/weight loss, anxiety, restlessness, depressed mood, and physical symptoms such as abdominal pain [28]. These symptoms will usually peak around the third or fourth consecutive day after drug cessation [28]. The majority of these withdrawal symptoms will subside after about 2 weeks [28]. Currently, there is no treatment besides behavioral counseling for marijuana addiction, and there are limited treatment options for CWS [29].

ADVERSE EFFECTS OF MARIJUANA USE

The *Cannabis sativa* plant contains the mind-altering Δ^9 -THC compound, one of 483 known compounds and one of 84 other cannabinoids found in the plant [30]. Δ^9 -THC is the main psychoactive component of cannabis. When consumed, it can cause elevated dopamine levels in several regions of the brain, including striatal and prefrontal areas [31], resulting in effects such as altered senses, hallucinations, paranoia, changes in mood, difficulty in thinking and problem solving, and impaired memory and learning [32]. People with Cannabinoid Use Disorder (CUD) have higher occurrence of mental health co-morbidities, such as psychosis, which result from acute use of large doses of the drug [33,34]. Additional adverse effects from using marijuana include conjunctival hyper-

emia, impaired immune system response, impaired motor coordination, and emphysema-like lung changes [35]. Marijuana has been linked to an increased risk of airway cancer when smoked [36] and shown to be potentially teratogenic in pregnant users [37]. Heavy marijuana users reported having lower life satisfaction, poorer health, and more relationship problems when compared with non-users [32,38]. However, it is difficult to confirm the causal relationship between marijuana and quality of life. To avoid these adverse effects, drug companies have tried to market synthetic cannabinoids for glaucoma patients, but these drugs possess genotoxic properties [39].

CURRENT TREATMENTS FOR GLAUCOMA

Glaucoma is not curable, but its progression can be slowed through IOP reduction. Depending on the condition, medical, laser, or surgical treatments can be used. A number of topical prescription medications are available for use in glaucoma treatment. These eye drops cause IOP reduction by either decreasing production of aqueous humor from the ciliary body or increasing outflow of the aqueous humor through the trabecular meshwork or uveoscleral pathway, the natural drain of the eye. These major categories of topical ocular hypotensive drugs include prostaglandin analogues, β -adrenoreceptor antagonists, α_2 -adrenoreceptor agonists, carbonic anhydrase

inhibitors, and cholinergic agonists [40]. A combination of these drugs is also available to adequately control IOP in patients who require more than one agent for effective IOP reduction. When intraocular pressure remains elevated despite treatment with maximally tolerated medical therapy, laser or surgical interventions are considered. Trabeculoplasty is a form of laser treatment that stimulates the trabecular meshwork to increase its outflow facility. In terms of surgical options, trabeculectomy and glaucoma drainage device procedures are the traditional surgeries used to lower IOP. Both procedures bypass the trabecular meshwork and create alternate routes for aqueous humor in the eye to egress. In recent years, several micro-invasive glaucoma surgeries utilizing natural aqueous humor outflow pathway to facilitate drainage have emerged. In severe cases of glaucoma, both medical and surgical interventions may fail to lower IOP and prevent disease progression toward blindness [41]. However, when compared with these standard therapeutic options, medical marijuana does not seem to offer a superior therapeutic value given its significantly worse side effect profile [11].

CONCLUSION

Medical marijuana has been shown to lower the IOP for brief periods of time but carries a greater side effect profile than standard therapeutic options. The amount of daily doses to maintain the IOP-lowering effect is likely to lead to CUD and result in physical and psychological harm to the patient. There are no long-term studies on the systemic and ocular effects of marijuana use by glaucoma patients. There is also no specific data on addiction and withdrawal symptoms in glaucoma patients, as a subgroup of the general population. However, considering the addictive nature, short duration of effect, and harmful adverse effects of using medical marijuana, most patients should consider alternative treatments that offer greater medical benefits and fewer adverse effects.

While standard options are superior to medical marijuana in the management of glaucoma, there may be a role of medical marijuana use in end-stage glaucoma patients who have failed maximal medical therapy and surgery or who are poor surgical candidates. However, clinicians should be cautious in prescribing marijuana to such patients with a history of psychiatric illness, substance abuse [42], or co-morbidities such as lung diseases or chronic obstructive pulmonary disease. Lack of such risk factors or presence of other indications for marijuana use, such as HIV/AIDS or cancer, argues for potential benefits of medical marijuana in end-stage glaucoma patients who have failed all standard treatment options. New delivery methods of medical marijuana that would increase the duration of effect, such as extended release oral capsules, improved synthetic cannabinoids that can work in combination with other medication, or cannabinoids other than Δ^9 -THC that do not induce psychotropic adverse effects [43] should be investigated. Further research must be done

before medical marijuana, in any form, can be considered as a safe and effective treatment option for glaucoma patients.

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