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The benefits of medical Tetrahydrocannabinol on glaucoma

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THE BENEFITS OF MEDICAL TETRAHYDROCANNABINOL ON GLAUCOMA

ABSTRACT

Introduction: This paper explores the potential therapeutic benefits of medical Tetrahydrocannabinol (THC) on glaucoma management, particularly in terms of intraocular pressure (IOP) reduction, ocular blood flow, and symptom management. Glaucoma, characterized by increased IOP and progressive optic nerve damage, is a leading cause of irreversible blindness. Current treatments focus on IOP control but may have inadequate efficacy or intolerable side effects, necessitating alternative approaches such as medical THC.

Methods: The study hypothesis posited that medical THC could significantly reduce IOP, enhance ocular blood flow, and improve symptom management in glaucoma patients. To test this hypothesis, a literature review supplemented by a semi-structured interview with an experienced optometry practitioner was conducted. Research from 2015 to 2024 was reviewed using the PRISMA approach, analyzing findings from both primary and secondary sources.

Results: Results indicated a reduction in IOP after THC administration, with studies reporting an approximate 25% decrease. Ocular blood flow was also positively affected, evidenced by increased vasodilation post-THC administration. Furthermore, patient-reported outcomes suggested improved pain management with THC use. Despite these promising findings, the effects were transient, and significant side effects, including hypotension and altered perception, were noted.

Discussion: The interview reflected cautious optimism about THC's potential, emphasizing the importance of further research given the lack of long-term data and concern over psychoactive side effects. Regulatory challenges due to THC's Schedule I status also emerged as a significant barrier to both research and clinical use. The study's limitations include its English language restriction, limited database usage, potential researcher and publication biases, and the absence of long-term outcome data. These factors may affect the generalizability of the findings. Practical implications suggest that while medical THC could be an adjunct therapy for glaucoma, careful patient selection, monitoring, and regulatory changes are imperative. The pharmaceutical development of cannabinoid-based treatments with minimal psychoactive effects could revolutionize glaucoma therapy.

Conclusion: In conclusion, medical THC shows potential in managing glaucoma, but its integration into treatment protocols requires further extensive and controlled research. This study supports the hypothesis to a degree but acknowledges the need for additional investigations to fully validate the therapeutic role of medical THC in glaucoma management.

Keywords: Glaucoma, Intraocular Pressure, Medical Tetrahydrocannabinol, Ocular Blood Flow, Symptom Management, Tetrahydrocannabinol.

INTRODUCTION

Glaucoma, a progressive optic neuropathy that has been characterized by increased intraocular pressure (IOP), has remained a significant cause of irreversible blindness globally. Glaucoma can be characterized by a progressive degeneration of the optic nerve with loss of retinal ganglion cells (Wang & Danesh-Meyer, 2021). Approximately 57.5 million people globally in 2020, suffered from primary open-angle glaucoma (Allison et al., 2020). Those with an increased risk of glaucoma have included, elderly people, relatives of people who have glaucoma, as it can be hereditary, diabetics, steroid users, and those with hypertension (Allison et al., 2020).

In 2020, the disease affected more than 76 million people around the world, with an estimated 3 million in the United States (U.S.) alone. Also, there is no cure because retinal neurons do not regenerate once they are dead, however, the progression of the disease can be slowed when medications intended to lower IOP have been prescribed (Križaj, 2019). The economic burden, nearly $3 billion per year, has been estimated to double when considering indirect costs associated with productivity loss, physical consequences, and decreased quality of life (Križaj, 2019).

Despite advancements in treatment modalities, managing glaucoma has posed challenges, particularly in cases where conventional therapies have been inadequate or associated with intolerable side effects such as, a toxic effect on tear film, diuresis, headache, electrolyte imbalance, anaphylaxis, cardiovascular overload, intracranial hemorrhage, pulmonary edema, and renal failure (Bhagat & Trivedi, 2020). Treatment options have depended on the starting level of IOP, the change of IOP over time, whether the disease was in advanced stages or not, how fast the disease was progressing, how it was currently being treated, and how it was treated in the past. Treatment options include medical, surgical, and laser procedures. All the currently available treatments are targeted toward IOP control because it is a main risk factor for disease progression (Butt et al., 2016).

By 2023, attention has turned to exploring alternative therapeutic approaches, with a focus on the potential role of medical cannabis, specifically Tetrahydrocannabinol (THC), in glaucoma management. Several human studies have been conducted on healthy subjects and patients with glaucoma to test the effect of THC, on IOP. These studies reported an approximate 25% decrease in IOP in 11 healthy subjects one hour after smoking 18 mg of Δ^9-THC (Lindner et al., 2023).

The pharmacological properties of cannabinoids, including THC, have been extensively studied in various medical contexts, ranging from pain management to neurological disorders

(Amin & Ali, 2019). Cannabis contains nearly 540 compounds including 100 phytocannabinoids, identified due to their shared chemical structure. The predominant psychoactive component is Δ^9-tetrahydrocannabinol (Δ^9-THC), and the main non-psychoactive component is cannabidiol (CBD) (Amin & Ali, 2019).

THC, as the principal psychoactive component of cannabis, has garnered attention for its potential to modulate intraocular pressure, a key pathophysiological factor in glaucoma. While the precise mechanisms underlying THC's ocular effects had still been being elucidated, preliminary research had suggested its ability to lower IOP [AC1] by 20-40% (Cvenkel & Kolko, 2020).

Medical THC has been a sweeping movement throughout the U.S. As many states have legalized medical THC, 36 states as of 2023, with the largest number of medical patients was Florida with over 800,000 patients followed by Pennsylvania with approximately 700,000 patients (Marijuana Policy Project, 2023). Also, Medical THC has played a key role in the economy as it is projected to account for over $11 billion (Brightfield Group, 2021).

Despite promising preclinical data on THC's ocular hypotensive properties, translating these findings into clinical practice has presented challenges. Effective glaucoma management requires balancing the reduction of intraocular pressure to prevent optic nerve damage while minimizing potential side effects and psychotropic effects associated with THC. Moreover, regulatory constraints, such as its classification as a Schedule 1 drug, mean there are no accepted medical applications, and the drug has a high abuse potential, therefore human research is limited (Piomelli et al., 2019).

Schedule I substances cannot be prescribed and can only be lawfully dispensed and possessed in research that is federally approved. Researchers must obtain a registration to handle

Schedule 1 drugs. Many states require a state Schedule 1 research license as well. These requirements can be challenging. The research registration is both substance and protocol specific (Mead, 2017).

Also, even though cannabis use is becoming more normalized, the fact that many users still hide their use, suggests there is a discriminatory view on medical THC and this view surrounding cannabis-based therapies has hindered widespread acceptance and integration into conventional glaucoma treatment protocols as many Christians and capitalists view medical THC as immoral and promoting laziness (Reid, 2020). THC also has related adverse side effects. The *Cannabis* plant contains the mind-altering THC compound, THC is the main psychoactive component of cannabis. When consumed, it can cause dopamine levels to increase in several regions of the brain, resulting in effects such as altered senses, hallucinations, paranoia, changes in mood, difficulty in thinking and problem-solving, and impaired memory and learning (Sun et al., 2015).

The purpose of this research was to analyze the use of medical THC and its benefits for treating patients suffering from Glaucoma to assess its effects on intraocular pressure, vasodilation, and pain and symptom management.

METHODOLOGY

The working hypothesis was that patients suffering from Glaucoma would see a reduction in intraocular pressure, improved ocular blood flow, and better symptom management with the use of medical THC.

The conceptual framework for this research was based on methods developed by Sevigny et al. (2021). The framework illustrates the effect that laws surrounding the liberalization of cannabis have on health, safety, and socioeconomic outcomes. When investigating whether medical THC would allow people suffering from glaucoma to have better symptom management, the laws surrounding medical THC must be understood as those laws have influenced the markets and the attitudes of the population, which leads to determining health outcomes (Figure 1). This conceptual framework was suitable for this study as it demonstrated the relationship between changes in laws and the health and socioeconomic outcomes of the population.

The methodology used was a literature review complemented by a semi-structured interview of Dr. Kimberly Epling, experienced practitioner of optometry. Questions for the interview can be found in the Appendix. The interview was recorded, and only relevant answers were used to support the information found in the literature review. The interview was approved by the Marshall University Internal Research Bureau.

This review utilized the PRISMA approach and incorporated both primary and secondary research studies. Databases like Google Scholar, PubMed, and ProQuest were used as well as the Google search engine. Keywords used in this research include ‘Medical THC’ OR ‘Medical Cannabis’ AND ‘Glaucoma’ AND ‘Intraocular Pressure’ OR ‘Ocular Blood Flow’ OR ‘Symptom Relief’. There were 30 references used in this research and they were limited to the English language between the years 2015-2024.

Utilizing a PRISMA diagram to show the results, there were 330 records identified from the search for title and abstract review, there were also 40 results from websites, resulting in 370 total citations found. Of that total, 30 citations were included in the research paper. There were

15 articles used in the results and 15 references in the rest of the paper (Figure 2) (Adapted from Page et al., 2020).

The literature search was conducted by HK. It was validated by AC who acted as a second reader and verified the references met the study inclusion criteria.

RESULTS

Impact Of Medical THC On Intraocular Pressure

Rossi et al (2020) reported that when given THC, participants saw a decrease in IOP by nearly 3 mmHg from 14.4 mmHg to 11.1 mmHg after 6 months and also a reduction of more than 1 mmHg after two months which is significant because, for every 1 mmHg decrease, progression risks decrease by nearly 10% in patients (Rossi et al, 2020).

Chakrabarti et al (2022) reported that inhalational cannabinoids reportedly caused a 2.1 mm Hg drop in IOP from baseline 80 min after administration of cigarettes containing 12 mg Delta 9 THC and that inhalational administration of Delta 9 THC led to higher IOP reduction compared to oral administration. However, the IOP reduction was noted to be short term with a significant decrease in IOP (4.1 ± 1.5 mmHg) at 30 min that peaked at 90 min (6.6 ± 1.5 mmHg). The most common side effect was a significant decrease in systolic and diastolic blood pressures resulting in postural hypotension (Chakrabarti et al, 2022)

Mosaed et al (2022) reported that before administration of THC, IOP was averaged at 17.5 mmHg. After 30 minutes, a 15% decrease was seen and the average IOP was measured at 14.9 mmHg and it decreased another 1% by the 60-minute mark where it was measured at 14.6

mmHg before starting to increase steadily back to 16.4 mmHg after 5 hours as seen in Figure 3 (Mosaed et al, 2022).

Pescosolido et al (2018) reported, in a study of 5 people, patients were administered topical Bediol (containing 3–6 mg/mL of delta-9-THC and 4–8 mg/mL of cannabidiol) for 30 days. Then, after one month of washout, the patients were then switched to topical Bedrocan (containing 18–23 mg/mL of delta-9-THC and 1.2–18 mg/mL of cannabidiol) for an additional 30 days. IOP didn't show any significant lowering in 4 out of 5 patients. Only one patient, affected by intractable uveitic glaucoma, showed a significant IOP reduction after treatment with Bedrocan (IOP lowering of 20% from baseline) (Pescosolido et al, 2018).

MacMillan et al (2019) reported that the average IOP decrease at 90 minutes was 6.6 ±1.5 mm Hg in the treatment group with no difference in the placebo group in the same time frame ($p<0.05$). The reduction lasted for approximately three hours, but there were various side effects (e.g. altered perception) with the worst being severe hypotension. One patient had their blood pressure drop precipitously to the point where their IOP was 1-2 mm Hg in their right eye. A second patient had a similar blood pressure response with their IOP dropping to 3 mm Hg in their left eye and 14 mm Hg in their right eye (normal IOP range 12-22 mm Hg). Both patients had their blood pressure spontaneously restored via a reclining position (Macmillan et al, 2019).

Passani et al (2020) reported IOP reduction after 30 min from oral administration of 5, 10, or 20 mg delta-9-THC ranged from 10% to 24% depending on the dosage. A significant IOP reduction was noted in the 8 mg subgroup (mean reduction of 6 mmHg) as well as in the 12 mg subgroup (mean reduction of 9 mmHg). IOP lowering started 1 hour after drug administration and reached a maximum 4 hours after drug administration (Passani et al, 2020)

Zhang and Netland (2021) reported in 9 of 11 normal humans, IOP was reduced by 25% 1 hour after smoking marijuana, containing approximately 18 mg of THC. When patients with glaucoma were tested, 7 of 11 subjects showed a reduction in IOP of nearly 30%. The maximum decrease of IOP was 6.6 mmHg, nearly 23% lower than baseline, 90 minutes after smoking marijuana. Through various human studies, the maximum IOP decrease occurred 60-90 minutes after smoking and lasted around 5 hours. On average, smoking marijuana reduces IOP in at least 60-65% of user (Zhang & Netland, 2021).

Impact Of Medical THC on Ocular Blood Flow

Hommer et al (2020) reported that vasodilation was increased by nearly 9.5% after the administration of THC compared to the placebo group where there was an increase of less than 0.5% throughout the experiment. This was measured using Laser Doppler Flowmetry, a technique, which illuminated the blood vessels using lasers and allowed for increases to be measured in terms of units (Hommer et al, 2020). This increase can be seen in Figure 3, which is a chart showing the % increase in vasodilation after administering THC to both the placebo and the experiment groups.

Baranowska-Kuczko et al (2019) reported that administration of marijuana showed a 63-120% increase in vasodilation among the experimental group with the only group not reaching maximum effect being the obese group which was reported at 20% less than the maximum.

Kicman and Toczek (2020) reported that in humans, CBD slightly increased (at dose of 40 mg, but not 20 mg, given sublingually) or decreased resting BP (600 mg, p.o.) after acute dosing, but not after repeated dosing (600 mg for 7 days, p.o.). Conversely, no tolerance for hypotensive effect of CBD was observed after its chronic oral dosing rising from 100 to 600 mg/day over 6 weeks in patients with dystonic movement disorders (Kicman & Toczek, 2020).

Impact of Medical THC on Symptom Management

Wang et al (2021) reported evidence from twenty-seven studies that when tested against a placebo, non-inhaled medical cannabis results in a minimal increase in the proportion of patients experiencing pain relief at or above the need to spell it first time modeled risk difference MID: 10% modeled risk difference (95% CI 5% to 15%) for achieving at least the MID of 1 cm, based on a weighted mean difference (WMD) of −0.50 cm on a 10 cm VAS (95% CI −0.75 to −0.25 cm) (2021). Also, in 10 studies, non-inhaled medical cannabis resulted in a higher proportion of patients experiencing ≥30% pain reduction with medical cannabis versus placebo (relative risk (RR) 1.21, 95% CI 1.004 to 1.47; RD 7%, 0.1% to 16%) (Wang et al., 2021).

Heng et al (2018) reported that of those who used marijuana, 90% believed that it reduced symptoms of pain, and 81% believed that it reduced the amount of opioid pain medication they used (Heng et al., 2018).

Boehnke et al (2020) reported Light use participants were more likely to take concomitant pain medications (though not opioids or benzodiazepines). In pairwise analysis, light-use participants reported significantly lower pain severity scores than moderate or heavy-use participants (5.4 vs 6.2 and 6.2, respectively, P<.0001) and lower pain interference scores than moderate or heavy-use participants (4.4 vs 5.4 and 5.5, respectively, P<.0001). Light-use participants also reported lower positive affect (23.5 vs 25.2, P= .037) and negative affect (24.7 vs 26.8, P= .011) than heavy-use participants (Boehnke et al, 2020).

Solomon et al (2020) reported 29% of patients reported a meaningful reduction in pain with medical marijuana use compared to 26% with placebo use. This means that 24 patients need to be treated with medical marijuana for one patient to have a benefit greater than the placebo (number needed to treat [NNT] = 24; odds ratio [OR], 1.46). The improvements in pain scores were meaningful (30% reduction in pain) in about half of the studies of neuropathic pain (Solomon et al., 2020). Also, meaningful pain improvement with medical marijuana treatment was reported in 9% of patients, improvement with placebo or no treatment was reported in 25% of patients, and no improvement was noted in 66% of patients. Contrast this with amitriptyline treatment, for which meaningful pain improvement was reported in 25% of patients, improvement with placebo or no treatment was reported in 25% of patients, and no improvement was noted in 50% of patients. With high-dose opioid treatment (oral morphine 60 to 110 mg per day), meaningful pain improvement was reported in 18% of patients, improvement with placebo or no treatment was reported in 25% of patients, and no improvement was noted in 57% of patients. With gabapentin treatment, meaningful pain improvement was reported in 15% of patients, improvement with placebo or no treatment was reported in 25% of patients, and no improvement was noted in 60% of patients (Solomon et al., 2020).

DISCUSSION

The purpose of this research was to investigate the potential benefits of medical THC on glaucoma, particularly its effects on intraocular pressure (IOP), ocular blood flow, and symptom management. The hypothesis posited that medical THC could reduce IOP, improve ocular blood flow, and manage symptoms effectively in glaucoma patients.

The impact of medical THC on intraocular pressure (IOP) and ocular blood flow has been extensively investigated in the literature, providing valuable insights into its potential therapeutic effects for ocular conditions. Our review of the existing studies reveals a complex relationship between THC administration and ocular physiology, as well as its implications for symptom management.

In terms of IOP regulation, the findings from Rossi et al. (2020), Chakrabarti et al. (2022), Mosaed et al. (2022), Pescosolido et al. (2018), Passani et al. (2020), and Zhang and Netland (2021) collectively suggest that THC administration can lead to a reduction in IOP, albeit with variations in the magnitude and duration of the effect. Specifically, Rossi et al. (2020) demonstrated a sustained decrease in IOP over a six-month period, while Chakrabarti et al. (2022) and Mosaed et al. (2022) observed transient reductions in IOP following inhalational THC administration. However, Pescosolido et al. (2018) found no significant reduction in IOP in the majority of patients, except for those with specific conditions such as intractable uveitic glaucoma. Additionally, the timing and dosage of THC administration appear to influence its effects on IOP, as evidenced by the findings of Passani et al. (2020) and Zhang and Netland (2021). These results suggest that further investigation is warranted to elucidate the optimal dosing regimen and administration route for maximizing the therapeutic benefits of THC in IOP management.

The observed effects of THC on ocular blood flow, as discussed by Hommer et al. (2020) and Baranowska-Kuczko et al. (2019), provide valuable insights into the underlying mechanisms contributing to its IOP-lowering effects. Specifically, THC administration was associated with increased vasodilation, which may contribute to the regulation of IOP by improving ocular perfusion. These findings underscore the importance of considering the vascular effects of THC in the context of its therapeutic potential for ocular conditions.

Furthermore, this review of the literature highlights the potential of medical THC in symptom management, particularly in alleviating pain. Wang et al. (2021) reported significant reductions in pain severity and interference following non-inhaled THC administration, suggesting its efficacy in pain relief. Consistent with these findings, Heng et al. (2018) observed that a majority of marijuana users perceived a reduction in pain symptoms and a decrease in opioid medication usage. However, it is important to note that the efficacy of THC in symptom management appears to vary among individuals, as evidenced by the findings of Solomon et al. (2020), which reported meaningful pain reduction in only a minority of patients.

The semi-structured interview with an optometry practitioner neither supported nor rejected the findings of this review. Epling acknowledged the potential for medical THC to prove beneficial for patients with glaucoma, however, due to lack of significant human trials and acceptance by the medical community, she could not say whether medical THC can be used as a long-term solution or not.

This study was limited by the restrictions in the search strategy, such as the number of databases used, PubMed, ProQuest, and Google Scholar, and the limitation of only using sources in English from the years 2015-2024 which could have excluded relevant studies from years prior. Also, the tendency for journals to publish studies with positive results over those with negative or inconclusive results might have skewed the available literature toward studies showing the benefits of medical THC for glaucoma, thus affecting the overall analysis. Lastly, legal and regulatory constraints limited the scope of research into medical THC, potentially affecting the depth and breadth of available studies.

Medical THC could offer an alternative treatment for patients who have proven unresponsive to traditional glaucoma treatments or have shown severe side effects with treatments, however, medical THC should be monitored carefully due to its side effects. Also, the current legal status of THC as a Schedule I drug poses significant challenges to its adoption in mainstream medical practice. Changes in legislation could broaden the scope of research and allow for a more regulated and accessible treatment option. Lastly, the pharmaceutical industry could be influenced to develop more refined cannabinoid-based treatments that minimize psychoactive effects while maximizing therapeutic benefits for glaucoma.

CONCLUSION

While these findings are promising and supportive of the initial hypothesis, they also highlight the need for caution due to the side effects and the short-term nature of the benefits observed. Moreover, because of the limitations identified in the study—including potential researcher and publication bias, the limited number of databases searched, and the scope of available research—there is an acknowledgment that while the hypothesis is supported, it is not conclusively proven. Additional, more extensive research is needed to fully accept the hypothesis, particularly studies that address the limitations noted and that examine long-term outcomes, dosing strategies, and the risk-benefit profile of THC in glaucoma treatment.