Cannabinoids for treatment of glaucoma

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Purpose of review
The purpose of this article is to review the current status of cannabis in the treatment of glaucoma, including the greater availability of marijuana in the USA.

Recent findings
The potency of marijuana, as measured by the concentration of Δ^9-tetrahydrocannabinol, has increased from ~2 to 3% in the 1970s to ~20% today. Many US states have passed laws allowing either medicinal or recreational use of marijuana.

Summary
The pharmacology of marijuana and its effect on intraocular pressure has not changed since the research in the 1970s and 1980s. Marijuana is an effective ocular hypotensive agent. However, cardiovascular and neurological effects are observed at the same dose, and may theoretically reduce the beneficial effect of lowering intraocular pressure by reducing ocular blood flow. The clinician must be cognizant of this potential in diagnosis, prognosis, and therapy.

Keywords
cannabinoids, glaucoma, intraocular pressure, marijuana

INTRODUCTION

The use of complementary and alternative therapies in western cultures is increasingly being recognized. In particular, the use of complementary medicine in the treatment of glaucoma is of interest – both for ocular hypotensive and neuroprotective effects [1–3]. One estimate is that 5% of patients with glaucoma use complementary and alternative medicines [4].

Marijuana is increasingly available via legal means as states in America pass either medicinal or recreational marijuana laws. Thus, it behooves eye care professionals and patients to know the efficacy, safety, and therapeutics of use of marijuana to treat glaucoma.

CONTROLLED STUDIES WITH MARIJUANA

The effects of marijuana and cannabinoids on intraocular pressure were reviewed by the Institute of Medicine in 1999 [5]. Key studies from that report are provided in this review.

In 1971, Hepler and Frank [6] evaluated the effect of marijuana smoking in normal volunteers. They found a decrease in intraocular pressure (IOP) of ~30%. Merritt and colleagues at Howard University and the University of North Carolina conducted controlled studies on the influence of marijuana on IOP and other physiological measures in the late 1970s and 1980s. In one placebo-controlled study, using marijuana obtained from the National Institute of Drug Abuse, they found that mean IOP in unmedicated patients was reduced from ~28 mmHg to ~22 mmHg, with a peak action at 2 h, and a duration of 3.5 h (Fig. 1). In this study, they found a concomitant substantial increase in heart rate (+45 beats/min, peaking at 0.5 h), and decrease in blood pressure [7,8]. The physiological effects of marijuana are also seen with oral ingestion. Tolerance to at least some of the effects is seen with repeated dosing [5,9].

TOPICAL TREATMENT

Δ^9–Tetrahydrocannabinol (THC) or vehicle alone was applied topically to one eye of normal volunteers. No fall in IOP was found. Toxicity was limited

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KEY POINTS

- Marijuana is increasingly available via legal means as states in America pass either medicinal or recreational marijuana laws.
- Marijuana is an effective ocular hypotensive agent, at least upon single administration, although tolerance may develop with repeated doses.
- Cardiovascular and neurological effects are observed at the same dose, and may theoretically reduce the beneficial effect of lowering IOP by reducing ocular blood flow.
- Adequate coverage of elevated IOP with marijuana would require frequent, and possibly costly, dosing.

to minor conjunctival injection that was short in duration (less than 60 min) and occurred with both drug and vehicle alone. Subjective responses indicated a sensation of minor burning and/or tearing. A small (1 mm) but statistically significant mydriasis occurred in both the treated eye and untreated eye and was not drug related [10]. In another study, volunteers were given either THC or vehicle alone (light mineral oil) four times daily for a week. Five volunteers, four of which used vehicle alone, discontinued the study because of burning sensation and lid swelling. In the 23 volunteers who completed the study, there was no difference in IOP between eyes treated with 1% THC and controls [11]. There is some preclinical evidence that low intraocular bioavailability of this lipophilic molecule may be solved by formulation [12].

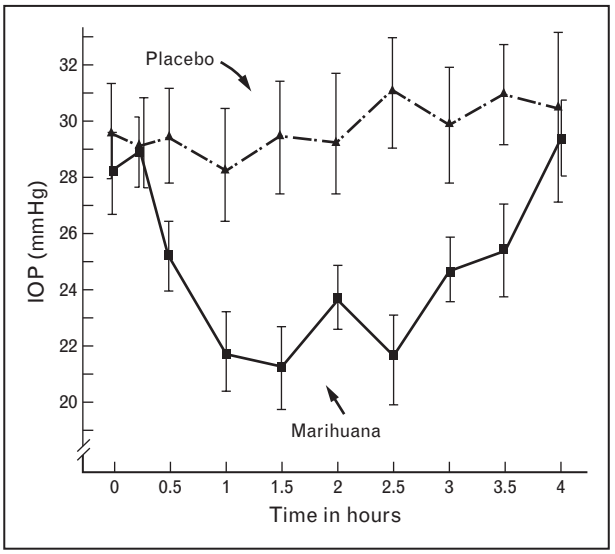

FIGURE 1. Intraocular pressure (mean ± standard error) in glaucomatous eyes after smoking marijuana or placebo. Reproduced with permission from the publisher from [7].

OTHER CANNABINOIDS

Intravenous administration of the presumed primary active component in marijuana, tetrahydrocannabinol (THC), delta 8-tetrahydrocannabinol (Δ^8-THC), or 11-hydroxyl-delta 9 tetrahydrocannabinol (11–OH-THC) to healthy adults substantially decreased intraocular pressure, whereas cannabinol, cannabidiol (CBD), and beta-hydroxytetrahydrocannabinol (ß-OH-THC) had little effect [5,13].

Three synthetic cannabinoids were also investigated; BW29Y, BW146Y, and nabilone (later commercialized for another indication). These cannabinoids were given orally to patients who had high IOP. BW146Y and nabilone were as effective as ingesting THC or smoking marijuana, but again had a very short duration of action; BW29Y was ineffective [14,15].

CANNABINOID OCULAR PHARMACOLOGY

Some of the issues with marijuana were pointed out by Kaufman in an editorial nearly 20 years ago. The lack of efficacy of topical treatment might be either because of lack of intraocular bioavailability, or a central rather than peripheral site of action. The efficacy of repeated dosing, and whether tolerance develops to the ocular hypotensive efficacy is not known. There are concomitant physiological and psychotropic effects, including the possibility of reduced ocular blood flow at the doses which reduce intraocular pressure. The duration of action is relatively short – on the order of 3–4 h. At that time, the mechanism of ocular hypotensive efficacy was not known (although based upon a single patient, it appears to be outflow) [16]. The additivity of marijuana to other ocular hypotensive agents is also not known [17].

PUBLIC POSITION STATEMENTS AND GENERAL REVIEWS

In its 1999 report, the Institute of Medicine made this conclusion regarding the therapeutics of marijuana for the treatment of glaucoma '…Although glaucoma is one of the most frequently cited medical indications for marijuana, the data do not support this indication.'[5] They noted that at the same doses which lower IOP, patients experience tachycardia, systemic hypotension, and psychological effects – similar to earlier papers by Green [18] and Kaufman [17].

In October 1998, the Canadian Ophthalmological Society (COS) published a policy statement and guideline entitled 'Glaucoma and the use of marijuana'. They concluded that there was a lack

of evidence to support the use of marijuana for glaucoma. Recently, the COS revisited this topic, and revised their statement in 2010 (www.eyesite.ca). It reads '...the COS does not support the medical use of marijuana for the treatment of glaucoma due to the short duration of action, the incidence of undesirable psychotropic and other systemic side-effects, and the absence of scientific evidence showing a beneficial effect on the course of the disease. This is in contrast to other more effective and less harmful medical, laser, and surgical modalities for the treatment of glaucoma' [3].

In 2010, Jampel [19] published an opinion from the American Glaucoma Society as '...although marijuana can lower the IOP, its side effects and short duration of action, coupled with a lack of evidence that its use alters the course of glaucoma, preclude recommending this drug in any form for the treatment of glaucoma at the present time.'

In 2014, the American Academy of Ophthalmology reiterated its position that marijuana is not a proven treatment for glaucoma [20].

In June of 2015, there were several articles in *JAMA* regarding cannabinoids. Whiting *et al.* conducted a systematic review of the benefits and adverse events of cannabinoids. With respect to glaucoma, they included only a small crossover trial of sublingual cannabinoids. This trial found no difference between placebo and cannabinoids on measures of intraocular pressure in patients with glaucoma [21]. In their overall review, they concluded that there was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity. There was low-quality evidence suggesting that cannabinoids were associated with improvements in nausea and vomiting because of chemotherapy, weight gain in HIV infection, sleep disorders, and Tourette syndrome. Cannabinoids were associated with an increased risk of short-term AEs [22▪]. Hill [23] reviewed marijuana for treatment of chronic pain and other medical and psychiatric problems. He concluded that a few of these indications have evidence to support treatment with marijuana and many that do not. Also in June 2015, Le and Tyndale edited a multiauthored issue of *Clinical Pharmacology and Therapeutics* entitled 'Cannabinoids: Friend or Foe?' [24▪]. The issue included perspectives on the therapeutic use of natural and synthetic cannabinoids in several indications, as well as societal issues such as legalization and the impact on the healthcare system. The conclusions are exemplified by Abrams and Guzman's summary about cannabis in cancer care: '...Cannabinoids have a favorable drug safety profile, but their medical use is predominantly limited by their psychoactive effects and their limited bioavailability' [24▪,25].

CURRENT STATUS

The potency of marijuana, which was 1.8 to 2.8% THC in the early 1980s [26], is substantially higher today. The commercial website noted above lists THC levels which are in the 20% range. In preparation for this review, I searched PubMed in April 2015 for the terms marijuana or cannabinoids' and 'glaucoma or intraocular pressure'. There were no new clinical papers.

In 1999, the Institute of Medicine made the optimistic wish that '...it might be possible to design a cannabinoid drug with longer-lasting effects on IOP and with less psychoactivity than THC' [5]. GW Pharmaceuticals received approval from the European Medicines Agency for Sativex, an oromucosal formulation of THC and cannabidiol. It is indicated '...for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis who have not responded adequately to other antispasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy (www.gwpharm.com).' Several other firms are developing cannabinoid therapeutics: CannaPharmaRx (with the mission to '...identify, analyze, and recommend the appropriate use of cannabinoid molecules in combination with existing and emerging pharmaceutical products', NEMUS Bioscience (focused on '...the discovery, development, and the commercialization of cannabis-based therapeutics'), and Zynerba Pharmaceuticals (focused on developing and commercializing proprietary next generation synthetic cannabinoid therapeutics formulated for transdermal delivery).

To date, only two cannabinoids have been approved by the US Food and Drug Administration: Marinol (dronabinol, also THC) was approved in 1985 for the treatment of anorexia associated with weight loss in patients with AIDS, as well as refractory nausea and vomiting associated with cancer chemotherapy. Cesamet (nabilone), was also approved in 1985, for the treatment of the nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. Since these approvals, other agents, including metoclopramide (dopamine antagonist) and ondansetron (serotonin antagonist) have been approved for prevention of nausea and vomiting associated with cancer chemotherapy.

PHARMACEUTICS

Marijuana is an unregulated botanical. The potency of THC, as well as of other active molecules such as cannabinol and cannabidiol, may vary from strain to strain, and from lot to lot. It may be provided as raw product or as an extract. It may be taken by various routes. Indeed, these very attributes are key to marijuana sales today. There is a potential for contaminants (e.g., pesticides). The stability of the product and its storage are not known. Dosing through inhalation of smoked product may cause lung toxicity.

Unlike drugs approved today, the following are not known about marijuana: drug–drug interactions, drug–vehicle interactions, teratogenicity, carcinogenicity, and penetration into breast milk.

COST

In the Institute of Medicine report, the cost of marijuana as glaucoma therapy was estimated at about US $60 per month. I attempted to estimate the cost with today's prices. I used a web-based cannabis distribution site, Organicann (www.organicann.com). There are a range of marijuana strains available, with a cost of approximately US $15/g. One marijuana cigarette is approximately 0.5 g. Assuming that the duration of the ocular hypotensive effect of this strain is similar to that of marijuana tested in previous decades, it would require ~3 cigarettes per day to provide daytime therapy, thus costing ~ US $23 daily. The monthly cost would be ~ US $690 or US $8,280 per year. An alternative is a concentrate, which is similarly priced on a per-gram basis, but has 3–4 times the THC potency, and thus may be more affordable.

Medical marijuana is not covered under most US medical insurance plans. That said, some organizations (e.g., Berkeley Patients Group, www.mybpg.com) provide marijuana therapy at no charge to patients unable to pay. I provide the caveat that these are estimates. They also do not take into account the effect of tolerance [5,9]. It also does not take into account bulk discounts for making larger purchases. However, it is clear that the cost of monotherapy with marijuana for glaucoma would exceed the cost of prescription pharmaceuticals, whether covered by medical insurance or not.

CONCLUSION

Our understanding of the pharmacology of marijuana, its therapeutic effect on intraocular pressure, and its effects on the cardiovascular and central nervous systems have not changed since the research conducted by Hepler, Frank, Merritt and colleagues in the 1970s and 1980s. What has changed is the greater potency, and the general availability of marijuana in the USA. Marijuana may be used therapeutically for glaucoma, therapeutically for another condition, or recreationally. Thus, the clinician must be cognizant of this potential in diagnosis, prognosis, and therapy.

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Conflicts of interest

G.D.N. consults for numerous pharmaceutical and medical device firms. He does not own stock in any.

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