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November 1998, Vol 116, No. 11 &gt;

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Clinical Sciences | November 1998

## Marijuana Smoking vs Cannabinoids for Glaucoma Therapy FREE

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Arch Ophthalmol. 1998;116(11):1433-1437. doi:10.1001/archophth.116.11.1433.

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### ABSTRACT

**ABSTRACT** | MEDICAL EFFECTS | OCULAR EFFECTS | MARIJUANA SMOKING AS TREATMENT FOR GLAUCOMA | CANNABINOIDS FOR GLAUCOMA TREATMENT | ARTICLE INFORMATION | REFERENCES

**Objective** To discuss the clinical effects, including toxicological data, of marijuana and its many constituent compounds on the eye and the remainder of the body. A perspective is given on the use of marijuana and the cannabinoids in the treatment of glaucoma.

**Results** Although it is undisputed that smoking of marijuana plant material causes a fall in intraocular pressure (IOP) in 60% to 65% of users, continued use at a rate needed to control glaucomatous IOP would lead to substantial systemic toxic effects revealed as pathological changes.

**Conclusions** Development of drugs based on the cannabinoid molecule or its agonists for use as topical or oral antiglaucoma medications seems to be worthy of further pursuit. Among the latter chemicals, some have no known adverse psychoactive side effects. Smoking of marijuana plant material for the reduction of elevated IOP in glaucoma is ill-advised, given its toxicological profile.

PREVIOUS REVIEWS of the ocular and toxic effects of marijuana<sup>1-6</sup> have provided considerable background on general human responses. Use of marijuana for medicinal purposes decreased markedly in Western civilizations during the 1930s and 1940s, due to the variable potency of these herbal preparations and the parallel development of specific medications that were more potent and targeted toward specific symptoms. This philosophical alteration in medical therapy reflected changes that occurred in all branches of medicine.<sup>7</sup> Only in the latter part of this century has marijuana been used as a pleasure-inducing substance during liberalization of ethics and social behavior in many cultures.<sup>8-10</sup> After tobacco, alcohol, and caffeine, it is probably the most widely used drug in society.

More recently, legislation has been passed by certain states (with subsequent revocation in 1 state) that has led to a resurgence of interest in the evaluation of possible medical uses of marijuana. Extensive evaluations have resulted in 1 report to the director of the National Institutes of Health,<sup>11</sup> and will result in another from the Institute of Medicine of the National Academy of Sciences.



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Furthermore, a meeting on this topic held in March 1998 at New York University School of Medicine, New York, will result in publication of a book in the spring of 1999.<sup>12</sup> In many areas of interest, there is little but anecdotal material on which to rely, but in the area of glaucoma, there exists a substantial literature.

## MEDICAL EFFECTS

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A number of health hazards of marijuana have been identified, but some are difficult to document completely.<sup>9,10,13</sup> Acute effects are increased pulse rate, orthostatic hypotension, euphoria, and conjunctival hyperemia.<sup>14,15</sup> Long-term clinical effects in humans include respiratory, hormonal, and pulmonary toxic effects, although effects on many other organ systems, including the brain, have been noted.<sup>14-28</sup> Marijuana smoking leads to emphysemalike lung changes that are caused by the products of marijuana burning (ie, cannabinoids) or through the release of tars, carcinogens, and other volatile materials, as occurs with tobacco smoke.<sup>16,17</sup> The latter products, however, occur in greater concentration than in tobacco smoke.<sup>19</sup> The cognitive effects induced by marijuana are of equal concern; these assume greater relevance with chronic, repetitive exposure, especially in the age group in which glaucoma is most prevalent.<sup>18,20-28</sup> These factors must be considered when potential chronic use of cannabis is considered as a treatment. This is especially true of glaucoma, where continuous use would be necessary to control this 24-hour-a-day disease, requiring as many as 2920 to 3650 marijuana cigarettes per year.

The widespread effects of the cannabinoids and marijuana on many biological systems have been attributed to direct effects on certain biochemical processes, perturbations in cell membranes, or attachment to 1 of the 2 identified cannabinoid receptors, CB1 and CB2. The CB1 receptor is located in the central nervous system, whereas CB2 receptors occur in immune system tissues, such as spleen.<sup>29-33</sup> Through use of cannabinoid agonists such as WIN5512-2 and methanandamide, identification of cannabinoid receptors, and evaluation of their role in reflecting the biological activity of the cannabinoids, a better and more complete picture has arisen of the effects of these compounds.<sup>29-38</sup>

## OCULAR EFFECTS

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Inhalation of marijuana smoke or smoke of cigarettes laced with  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC), intravenous injection of cannabinoids, or ingestion of  $\Delta^9$ -THC or marijuana ("brownies") causes conjunctival hyperemia and decreased lacrimation.<sup>1-4,6,39-41</sup> Ocular side effects include diplopia, impairment of accommodation, photophobia, nystagmus, and blepharospasm. The ocular effects of long-term marijuana inhalation seem to be similar.<sup>42,43</sup> Pupillary effects appear to differ depending somewhat on the circumstances of marijuana intake.<sup>44,45</sup>

Different cannabinoids reduce intraocular pressure (IOP) in about 60% to 65% of humans, and marijuana and  $\Delta^9$ -THC (inhaled or taken orally) also decrease IOP in the same percentage of nonglaucomatous volunteers<sup>4,39,41,42</sup> and of volunteer patients with glaucoma.<sup>4,41,46</sup> Orthostatic hypotension and 50% decreased lacrimation occur quickly after inhalation of 2%  $\Delta^9$ -THC cigarettes,<sup>41</sup> as noted with a synthetic THC homolog. An apparent dose-response relationship occurred between cannabinoids or marijuana and IOP when groups were evaluated. Although the peak fall in IOP was dose related, the time of maximal change was unchanged. The IOP fell, on average, by about 25% (range, -45% to +5%) after smoking 2% marijuana through a water-cooled pipe.<sup>39</sup> Duration of the reduction of IOP is about 3 to 4 hours, by which time the IOP approaches the presmoking level.<sup>1-4,6,39,41</sup> The major difficulty with marijuana smoking was to separate the reduction in IOP and the euphoric effect. These findings confirmed the physiological and pharmacological effects found in experimental animals after intravenous drug administration.<sup>47-50</sup>

Studies in patients with primary open-angle glaucoma (POAG) indicated a reduction of IOP in 60% to 65% of the population after marijuana smoking or  $\Delta^9$ -THC ingestion.<sup>4,39,41,46</sup> Seven of 11 patients in 1 study showed a reduction in IOP of about 30% after smoking 2% marijuana cigarettes.<sup>46</sup> More quantities of oral drug or marijuana were needed compared with inhaled drug, presumably due to the poorer absorption by the former route.

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About 300 volunteers (nonglaucomatous subjects or patients with POAG) overall have participated in studies to examine the acute effects of marijuana smoking or cannabinoid use (topical, oral, or intravenous). Since the largest individual group was about 40 persons, this constitutes a large number of groups and a range of conditions under which marijuana or 1 of its constituents reduced IOP.

Topical  $\Delta^9$ -THC was examined in rabbits, dogs, and primates for pharmacological activity<sup>1-6,50-55</sup> and toxic effects<sup>56</sup> before being tested in humans.<sup>57-60</sup> The best vehicle identified for delivery of the lipophilic agent in the early 1980s<sup>55</sup> has been superseded by vehicles that permit internalization of lipid-soluble compounds into other materials that are themselves water soluble. This provides an excellent delivery mode of a lipophilic drug through the aqueous tear environment to the lipid corneal epithelium. Other approaches have entailed water-soluble esters of a maleate salt of a  $\Delta^9$ -THC-related compound.<sup>5</sup> This prodrug approach offers a new modality for encouraging greater drug penetration to the site of action. The development of nonpsychoactive, cannabinoid-related drugs also has resulted in separation of IOP reduction from euphoric effects, at least in experimental animal tests,<sup>61</sup> and holds promise for more future developments. In humans,  $\Delta^9$ -THC drops were ineffective in reducing IOP in single- or multiple-drop studies, due to the induction of ocular irritation.<sup>59,60</sup> This effect was revealed only in humans.

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## MARIJUANA SMOKING AS TREATMENT FOR GLAUCOMA

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Use of marijuana smoking as a treatment for glaucoma is not desirable for several reasons. Although drug absorption is maximum with smoking, and the user or patient can titrate the drug to a level of euphoria indicative of a pharmacological response, this approach is poor. The pathological effects on the lung already described, exposure to carcinogens, and the other pulmonary and respiratory changes at the organ and cellular levels<sup>6,17,19</sup> all make smoking a nonviable mechanism. The systemic toxic effects that result in pathological changes alone seem sufficient to discourage smoking marijuana.

Primary open-angle glaucoma is a 365-day-a-year disease, and since the marijuana-induced fall in IOP lasts only 3 hours, the drug consumption conceivably needed to reduce and keep IOP at a safe level would be very high. The IOP is the only readily measurable parameter that one can use as an index of POAG and is still the major indicator of what is essentially a neuropathogenic disease.<sup>62</sup> No indication has been obtained or reported that those highly limited number of persons who consume marijuana cigarettes as a compassionate investigational new drug have shown any maintenance of visual function or visual fields or stabilization of optic disappearance.

Since marijuana reduces IOP for 3 to 4 hours, after which the IOP returns to baseline, control of IOP at a significantly lowered value, including maintenance of IOP at a 2-hour minimal low value, requires a marijuana cigarette to be smoked 8 or 10 times a day (by those persons in whom IOP actually decreases). This use corresponds to at least 2920 and as many as 3650 marijuana cigarettes consumed per year.<sup>3,6</sup> It is difficult to imagine anyone consuming that much marijuana and being a productive individual who is incorporated into society and perhaps operating machinery or driving on the highways. Similarly, the systemic end-organ effects at this level of consumption have the potential of being quite high. On the other hand, the availability of once- or twice-a-day eye drops ( $\beta$ -blockers such as timolol maleate, or the prostaglandin agonist latanoprost) makes IOP control a reality for many patients and provides round-the-clock IOP reduction.<sup>62</sup>

Glaucoma treatment requires a round-the-clock reduction in IOP, and treatments are evaluated as successful if this level of activity is achieved without progression of visual field loss or optic disc changes. There has been considerable press coverage of the use of marijuana as an antiemetic<sup>63-66</sup> or as treatment for glaucoma. Dangers arise from 2 considerations of the latter. First, intermittent use would lead to a lack of IOP reduction on a continued basis, thereby permitting visual function loss to proceed. Second, full use of enough smoked marijuana leads to the need, as described above, of an average of at least 3300 cigarettes per year. Advocates of the latter approach often cite using marijuana for the relief of symptoms, whereas POAG has no symptoms until too late, when vision is irreversibly lost.

The advocates of marijuana smoking for glaucoma treatment also must contend with the lack of standardization of the plant material. The 480 chemicals, including 66 cannabinoids, in marijuana

vary depending on the site and circumstances of growth and certainly vary in content depending on which plant part is smoked.<sup>67-69</sup> This variability goes counter to the requirements of the Food and Drug Administration, Washington, DC, concerning the chemical identity and performance characteristics of specific drugs. Indeed, dronabinol (Marinol), an oral form of  $\Delta^9$ -THC, is approved by the Food and Drug Administration for the treatment of chemotherapy-induced nausea and acquired immunodeficiency syndrome wasting syndrome. Further, despite attempts by individual states to change their laws, marijuana remains a schedule 1 controlled substance, and federal law prevails.

Lastly, there is an increasing movement at the federal and state levels to confine tobacco smoking to highly restricted areas to reduce smoking and the exposure of nonsmokers to second-hand smoke. In the face of this societal change, it is difficult to advocate increased smoking, particularly of marijuana, in settings where smoking is normally banned.

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## CANNABINOIDS FOR GLAUCOMA TREATMENT

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Oral or topical cannabinoids show promise for future use in glaucoma treatment. Newer topical delivery technologies are available for these lipophilic drugs, including the formation of microemulsions and use of cyclodextrins to increase the solubility in aqueous-based solutions. This is a marked improvement over the lipid-based vehicles that were the only ones available during earlier basic and clinical studies of topical cannabinoids.<sup>51,56,59,60,70</sup> The development of compounds related to  $\Delta^9$ -THC, such as HU211 (dexanabinol), that show a complete absence of euphoric effects while retaining IOP-reducing activity<sup>61</sup> is a major advance. Increasing knowledge concerning the topical cannabinoid receptors and ligands that reduce IOP in rabbit or monkey eyes will allow exploration of different structural analogs that may identify compounds efficacious as potential glaucoma medications.<sup>70-78</sup> Topical administration also has the advantage of permitting the use of a low mass of drug per delivery volume. Even at 5% concentration, a 30- $\mu$ L drop would contain only 1.5 mg.

Oral administration of cannabinoids that lack psychoactive effects but will reduce IOP could be a significant addition to the ophthalmic armamentarium against glaucoma. The cannabinoids that exist in the plant material<sup>67-69</sup> or as metabolites<sup>79,80</sup> do not appear to be viable candidates for oral use because of the inability to separate their euphoric and IOP-reducing effects.

Because they are readily characterized from a chemical perspective, the cannabinoids and related substances represent an area of focus for future studies. Such attention would allow the development of appropriate vehicles for these chemicals into the predominantly aqueous environment of the tears. Compounds would be identified that have no euphoric effects or at least a very high ratio of IOP reduction to euphoric effects. Such chemicals would eliminate any potential abuse problems while providing drugs that would reduce IOP by unique interaction with receptors or other membrane components that could be additive to other currently available glaucoma medications. In experiments where the action of cannabinoids in causing an IOP reduction has been sought, evidence points to an influence on increasing outflow of fluid from the eye as the major component. This is true for  $\Delta^9$ -THC and HU211, although the binding of each of these compounds to the cannabinoid receptor differs widely. The rapidity of onset of the responses strongly suggests that an effect is occurring that can undergo rapid adjustment rather than be related to slow alterations in trabecular meshwork glycoproteins.<sup>81</sup>

The perspective presented herein differs in several ways from the conclusions reached by the National Institutes of Health—assembled panel to provide a written report on medicinal use of marijuana.<sup>11</sup> The primary difference is the focus of research efforts, which the panel concluded should have marijuana smoking as its delivery mode, whereas my review recommends cannabinoids. The reasons for this divergence of opinion are given and, I believe, are compelling for glaucoma studies to focus on individual chemicals rather than a nonstandardized plant material.

The latter has no possibility, due to the inherent variability and the plant versatility, of reaching the standards required by the Food and Drug Administration in terms of chemical identity, purity, or characterization. A contemporary review of medicinal applications that evaluated the effect of  $\Delta^9$ -THC and marijuana on a broad spectrum of medical problems indicated that THC may have a role in treating nausea associated with cancer chemotherapy and in appetite stimulation. Other uses of either material were not supported.<sup>82</sup>

## ARTICLE INFORMATION

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Accepted for publication July 21, 1998.

This study was supported in part by an unrestricted departmental award and a Senior Scientific Investigator award from Research to Prevent Blindness Inc, New York, NY.

I thank Brenda Sheppard for her valuable secretarial assistance.

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