

# Canadian Ophthalmological Society issues statement on use of medical cannabis

While much research is pointing to possible therapies involving medical cannabis and multiple conditions including glaucoma, the Canadian Ophthalmological Society issued a statement in the February issue of the *Canadian Journal of Ophthalmology* that it does not support the medical use of cannabis to treat glaucoma. The Canadian Glaucoma Society also endorsed this position.

## History of relieving pain

The statement notes that smoked delta-9 tetrahydrocannabinol (THC) was first associated with the alleviation of intraocular pressure (IOP) in 1971, and this effect has been substantiated in the ensuing years by clinicians using a variety of cannabis delivery methods, including oral, intravenous, sublingual, and topical.

While topical application might seem like the best method, ocular penetration has been complicated by the low aqueous solubility among of available cannabinoid

extracts, among other factors. When taken orally, the duration of effect is limited to three or four hours. Inhaling the smoke of burning cannabis also comes with a number of hazards (emphysema and possibly lung cancer) and undesired side effects (euphoria, dysphoria, decreased short-term memory, cognitive impairment, time distortion, decreased coordination, sleepiness, tachycardia, palpitations, systemic hypotension, and conjunctival hyperemia).

## Limited potential

According to the statement, the clinical potential of cannabis is limited by the undesired “neuropsychological and behavioural effects” that adhere to the use of a medical cannabis product containing THC.

The Canadian Ophthalmological Society is also concerned about the public health risks with the government-regulated production, sale, and distribution of cannabis in Canada, citing a rise in motor vehicle accidents after legalization in Colorado and noting that emergency room vis-

its for injuries and psychiatric episodes are reported to be higher in users of cannabis, as opposed to non-users.

The brief statement concludes with the following position: “The Canadian Ophthalmological Society does not support the medical use of cannabis 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.”

—Aaron Lowinger,  
CJMC Correspondent

**The Canadian Ophthalmological Society (COS) is a leading authority on eye and vision care. For more information regarding this statement from the COS, please visit <https://www.cos-sco.ca>**

## Commentary **Alex Straiker, PhD** Bloomington, Ind. U.S.A.

**PART OF THE PROBLEM** is that there’s been an assumption based on the first studies back in the late seventies, early eighties, that somehow cannabinoids are useless as an approach. I think that’s a mistake. If I was going to pursue this, I would use a drug discovery approach: find out what the targets are and then develop drugs that are best suited to that rather than just trying THC and hoping for the best.

Targeting those receptors themselves: CB1, GPR18, particularly and actually GPR119 as well, I think could bring important developments. There’s also a lot of interest right now in other related compounds, all of the hundred or so minor phytocannabinoids. It’s something we’re looking into because they’re basically uncharacterized—we don’t know how they work.

From my perspective as a neuropharmacologist, what I would say is let’s figure out how they work. And then, again, use a drug discovery approach to try and find an optimal way to activate these receptors. None of these drugs are likely to be perfect. If you could separate out the psychoactivity from THC, for example, that

would be great. CBD is an immunosuppressant and so it has some great effects in epilepsy, but there’s a price there. I think finding the target and designing drugs for that [target], that’s the best way to go.

We’ve encountered a lot of resistance to [cannabis] and part of the problem is that there are already six classes of drugs available for glaucoma, so you have to have some sort of an edge over the others. Some [of the therapies] are better than others and really only one of them is newer than 20 years.

From a marketing stance, if generics are available for a lot of these compounds, how does it make financial sense for you to introduce a new drug class? That’s what a lot of resistance has been. I was kind of surprised at that.



*Dr. Alex Straiker is a senior research scientist at Indiana University Bloomington in the Department of Psychological and Brain Sciences.*

*Dr. Straiker earned his PhD at UC San Diego and his primary research goal is to characterize cannabinoid signalling in the brain and the eye.*



# Investigating the effects of THC and CBD on the regulation of intraocular pressure

As reported in

**Investigative Ophthalmology & Visual Science**

2018; Dec 3:59.

In 1971, researchers first published results that inhaled cannabis had a beneficial effect on intraocular pressure (IOP). IOP remains the single greatest contributing factor to the development of glaucoma, a major cause of blindness. Researchers at Indiana University published a study last December on their findings using THC and CBD to treat mice.

Despite the fact that the potential link between cannabis and glaucoma has a 50-year history, researchers still don't understand the mechanism behind how cannabis affects IOP. It has been assumed that THC acts upon one of the known cannabinoid-receptors (CB1, CB2, GPR18, GPR119, GPR55) but these links have never been determined. CBD, meanwhile, has been found to be ineffective on IOP in most previous studies.

## THC use for IOP is sex-dependent

The first finding of the study was that a topical treatment of the eye with THC yielded sex-dependent results. After eight hours, male mice saw a 30% drop in IOP, whereas female mice saw a more modest reduction than males after four hours, and no effect at eight hours. To test why results were sex-dependent, researchers examined the mRNA expression of the relevant cannabinoid receptors in the eyes of male versus female mice. They found that mRNA levels of CB1 and GPR18 were lower in female mice than male mice.

Researchers also attempted to drill down on the mechanism by which THC affects IOP, using mice with CB1 receptors either knocked out or genetically removed, to see if any other cannabinoid receptors are active in controlling IOP. Interestingly, researchers found that CB1 deletion only partly reduced the effect of THC, suggesting that another receptor is active. A likely candidate is the GPR18 receptor, which has been noted to lower IOP in mice and is activated by THC.

## THC to lower IOP has a long history

Testing the theory by using a GPR18 antagonist applied topically to the CB1 knockout mice, researchers found no effect on IOP at one or four hours, making a strong case that



*"We've got these three receptors: CB1, GPR18, GPR119. Each of these is a cannabinoid family receptor. Each of them can lower pressure on its own. And I think the idea of maybe targeting those or simply targeting the endogenous system, because the body has its own cannabinoids, targeting that to lower pressure, I think is really promising."*

—Dr. Alex Straiker

THC lowers IOP through a combination of the CB1 and GPR18 receptors.

That THC can lower IOP "has been shown since the 1970s," according to Indiana University researcher Alex Straiker, PhD "No one has ever shown how it works; after 45 years we still didn't know how it worked. We showed that it works through a combination of two different receptors. We did some of the background work in the last five years and we found that there are actually three different cannabinoid receptors that each lower ocular pressure under different circumstances. It's a really complicated system. And so we found that two of those are activated by THC and that's probably why it works as well as it does because it seems to be kind of synergistic."

Looking at the role that CBD plays in IOP, researchers at Indiana University found support that CBD in male and female mice alike substantially raised IOP at one and four hours. The same experiment in CB1 knock-out mice, however, resulted in a decrease in IOP at one hour, but no change at four hours.

## Results show CBD plays two roles in IOP

The results indicate that CBD likely has two opposing effects on IOP: the dominant effect of raising IOP via the CB1 receptor, and the secondary effect of lowering IOP, most likely via the GPR18 receptor. To test this further, the team used a 50-50 CBD/THC topical application and no effect on IOP. Dr. Straiker stated that CBD on its own has been shown to increase IOP 18%, and that "the American Academy of Ophthalmology has now issued a recommendation about CBD and people who are at risk for glaucoma."

## More research needed

For Dr. Straiker, THC treatment in humans to reduce IOP remains an avenue worth exploring. "Back in the '70s, there was a big heyday of research into this long before the receptors were ever identified," he told CJMC.

As his team's research appears to reveal, "We've got these three receptors: CB1, GPR18, GPR119. Each of these is a cannabinoid family receptor. Each of them can lower pressure on its own. And I think the idea of maybe targeting those or simply targeting the endogenous system, because the body has its own cannabinoids, targeting that to lower pressure, I think is really promising."

—Aaron Lowinger, CJMC Correspondent