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Adverse Ocular Impact and Emerging Therapeutic Potential of Cannabis and Cannabinoids: A Narrative Review

Mostafa Bondok[1], Anne Xuan-Lan Nguyen[2], Leonardo Lando[3], Albert Y Wu[4]

[1]Department of Medicine, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada; [2]Department of Ophthalmology and Visual Sciences, University of Toronto, Toronto, ONT, Canada; [3]Ocular Oncology Service, Barretos Cancer Hospital, Barretos, Brazil; [4]Department of Ophthalmology, Stanford University School of Medicine, Stanford, CA, USA

Correspondence: Albert Y Wu, Department of Ophthalmology, Stanford University School of Medicine, Stanford, CA, USA, Email awu1@stanford.edu

Abstract: Cannabis is the most used drug worldwide with an estimated 219 million users. This narrative review aims to explore the adverse effects and therapeutic applications of cannabis and cannabinoids on the eye, given its growing clinical and non-clinical uses. The current literature reports several adverse ocular effects of cannabis and cannabinoids, including eyelid tremor, ptosis, reduced corneal endothelial cell density, dry eyes, red eyes, and neuro-retinal dysfunction. Cannabinoids may transiently impair night vision, depth perception, binocular and monocular contrast sensitivity, and dynamic visual acuity. Cannabinoids are not currently considered a first-line treatment option for any ocular conditions. Δ-9-tetrahydrocannabinol been shown to result in short-term intraocular pressure reduction, but insufficient evidence to support its use in treating glaucoma exists. Potential therapeutic applications of cannabinoids include their use as a second-line agent for treatment-refractory blepharospasm, for dry eye disease given corneal anti-inflammatory properties, and for suppression of pendular nystagmus in individuals with multiple sclerosis, which all necessitate further research for informed clinical practices.

Keywords: cannabis, cannabinoids, adverse effects, therapeutic uses, eye

Introduction

Cannabis is currently the most used drug worldwide, with an estimated 219 million users in 2021,[1] and refers to a group of plants that includes *Cannabis sativa, Cannabis indica*, and *Cannabis ruderalis*.

Studies have reported the therapeutic efficacy of cannabinoids in treating chronic pain, alleviating spasticity in multiple sclerosis, and serving as an antiemetic.[2] Research into cannabinoids' applications to treat ocular conditions have revealed its potential in treating blepharospasm[3–8] and lowering intraocular pressure in glaucoma.[9–30] Animal studies demonstrate anti-inflammatory and analgesic properties, corneal regenerative effects,[31–40] and retinal neuroprotective effects of cannabinoids.[41–54]

Several unwanted effects of medical and recreational cannabis use are described in the scientific literature, including nausea, somnolence, and hallucinations.[2] Other reports have suggested more substantial effects, including its contribution to the incidence of psychotic disorders.[55] As for its effects on the eye, adverse ocular effects of cannabinoids and cannabis reported in contemporary literature include eyelid tremor,[56–60] ptosis,[61–68] corneal opacification,[69,70] reduced corneal endothelial cell count,[71] reduced corneal revascularization,[72] neuroretinal dysfunction,[73–84] retinal vasculature abnormalities,[47–52] and impaired extraocular motility.[85–101] As ongoing research explores the therapeutic benefits of cannabinoids, the understanding of its adverse effects continues to evolve. Given the growing clinical and non-clinical uses of cannabis and cannabinoids, this article aims to identify adverse ocular effects and assess the emerging potential of cannabinoids in ocular therapeutics.

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Brief Historical Context

The growing movement towards the decriminalization and legalization of cannabis[1,102,103] necessitates a comprehensive understanding of its physiological effects. In the last decade, there has been a 23% increase in global users:[1] a growth rate more rapid than both opiates and cocaine.[104] As of 2023, cannabis, commonly referred to as marijuana, pot, weed, grass, or herb, is legal in several countries,[102] and 23 states in the United States.[103]

The use of cannabis for medical purposes has occurred for millennia, with the first historical documentation of its medical use appearing nearly 5000 years ago in Ancient Chinese texts.[105] There has been a resurgence of interest in the uses of cannabinoids, the chemical compound in cannabis, to treat several medical conditions in the last few decades.[2,106,107]

Method of Literature Search

A systematic literature search of Ovid MEDLINE, Ovid Embase, and Scopus from inception of the databases to June 25, 2023, was conducted to identify relevant papers. The search strategy was developed and validated for each database with an academic librarian using both controlled vocabulary (ie, MeSH and Emtree terms) and free-text terms. The search terms used to identify relevant articles across databases are shown in Supplementary Box 1. We further reviewed reference lists of published reviews identified through our search to ensure comprehensive coverage of relevant studies that may have been missed in the initial search. This study was exempt from requiring ethics review by the University of British Columbia Behavioural Research Ethics Board (BREB) given the use of publicly available information, as per TCPS (Article 2.2).[108] To enhance accessibility for non-eye care professionals, we have included a brief glossary of relevant ophthalmologic and pharmacologic terms for reference in Supplementary Box 2.

Inclusion and Exclusion Criteria

Studies were included if they discussed adverse ocular effects or therapeutic applications of cannabis or cannabinoids. All forms of cannabinoids were considered, including CBD, THC, as well as synthetic cannabinoids (eg, HU-308, UR-144, XLR-11, Nabilone, Dronabinol, Levoantradol, SR 141716A, WIN55,212–2, GAT211, GAT228, HU211). Any route of administration could be utilized (eg, oral, sublingual, topical). Study abstracts must be written in English, and all study designs were accepted. Observational and experimental studies on human participants were prioritized, while laboratory and animal studies were also considered for supplementation. Studies were excluded if they were not relevant to the research topic, not in English, or not peer reviewed.

Screening and Extraction

Abstracts were screened for relevance by two independent reviewers (MB, LL), and conflicts were resolved through discussion with a third reviewer (AXN). Data extraction of relevant studies was conducted descriptively, and articles were organized by topic, relevance, and conclusions through a collaborative, iterative process.

Pharmacological Effects of Cannabinoids

The cannabis plant species contains approximately 540 natural compounds, over 100 of which are classified as phytocannabinoids (plant-derived cannabinoids) based on their chemical structure.[109] The most extensively studied phytocannabinoids are Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), which are the predominant psychotropic and non-psychoactive ingredients, respectively.[109] The *C. sat*iva plant has multiple chemotypes that vary in their relative composition of THC and CBD.[110]

Chemically, phytocannabinoids are a diverse group of isoprenylated resorcinol polyketides. Phytocannabinoids are categorized based on their affinity to the two main cannabinoid receptors: Cannabinoid receptor type 1 (CB_1) and Cannabinoid receptor type 2 (CB_2).[110] CB_1 and CB_2 receptors belong to a well-known family of G protein-coupled receptors (GPCR), which plays a central role in the endocannabinoid system. CB1 and CB2 are coupled through G proteins, particularly G i/o (inhibitory G protein), to inhibit adenylate cyclase and influence mitogen-activated protein kinase signaling in some contexts.[111] CB_1 receptors are also coupled through G proteins to various calcium and potassium channels, promoting neuron hyperpolarization.[111]

Cannabinoid Receptors

The localization of CB_1 and CB_2 receptors has been delineated using several strategies, each providing unique insights.[112] These include messenger RNA in situ hybridization, immunocytochemistry, and quantitative autoradiography.[113] CB_1 receptors are mainly localized to the brain and central nervous system, while CB_2 receptors are predominately localized to the peripheral nervous system and immune system.[111,114,115]

Most CB_1 receptors are located on the pre-terminal axonal segments of neuronal axons, with fewer on other parts of the neuron.[116] CB_1 receptors can also be found on CCK-positive basket cells,[116] on many glutamatergic terminals in the brain,[117] and within some peripheral tissues, including the liver,[118] pancreas,[119] skeletal muscle,[120] and adipocytes.[121] CB_2 receptors are expressed on immune cells,[115] neuronal cells,[122] as well as cells involved in bone mass regulation.[123]

The human body produces endogenous cannabinoids called endocannabinoids.[112] The endocannabinoid system consists of cannabinoid receptors and the enzymes responsible for the synthesis and degradation of endocannabinoids.[112] Endogenous cannabinoids include arachidonoyl ethanolamide (anandamide) and 2-arachidonoyl glycerol (2-AG).[111] These endogenous cannabinoids activate CB_1 and CB_2 receptors, amongst other GPCRs and ion channels.[124] The simple conceptual framework of agonists and antagonists is not enough to understand the complex pathways within the endocannabinoid system,[112] with a complete understanding requiring an understanding of partial agonism,[125] functional selectivity,[126] and inverse agonism.[127]

Safety Considerations

The psychoactive cannabinoid, THC, produces many of the adverse effects of cannabis, while the non-psychoactive CBD is credited for its therapeutic effects.[107,128] Non-medical cannabinoid products have differences in their relative concentrations of CBD and THC.[110] Retailers who sell cannabinoids are not subject to the same strict regulations as medical prescriptions.[129] CBD preparations of these products are often inaccurate,[130,131] with CBD and THC concentrations often mislabeled.[132,133] Individuals who use cannabis for self-medication report treating pain, anxiety, depression, headache/migraine, nausea, and muscle spasticity.[134] The CBD concentrations from retail products are often lower levels than those used in clinical trials and may even contain THC levels that exceed legal limits.[130] Meanwhile, medical-grade cannabinoids, both synthetic or plant-derived, have more accurate concentrations of THC and CBD.[129] Plant-derived or synthetic CBD have no pharmacological differences when tested in vitro.[135]

Information on cannabinoid drug interactions is scarce,[136] which raises safety concerns. The mechanisms of these drug interactions include CBD's inhibition of drug transport,[137] enzyme inhibition,[138] and enzyme induction.[139] Cannabis and cannabinoids can have adverse psychiatric effects, such as the increased risk of psychotic disorders, anxiety or panic attacks in naïve users, structural and functional alterations to the brain, mood disturbances and depression, and risks of lung cancer when smoked.[140] Consequently, medical cannabis is contraindicated in patients with unstable cardiovascular or respiratory disease, and those with a personal or strong family history of psychosis.[141]

Cannabinoids and the Ocular Response

The primary mechanism of action of cannabinoids on the eye is through CB_1 and CB_2 receptors.[142] These GPCRs are part of the extensive endocannabinoid system throughout the body.[143] Both receptors play a crucial role in modulating the release of neurotransmitters[143] and represent a nuanced interplay between the endocannabinoid system and neuronal health.

CB_1 receptors are located in the central nervous system, including the eyes, and have been shown to provide neuroprotection to retinal cells, particularly in reducing excitotoxicity, inflammation, and oxidative stress.[142] CB_1 receptors are also located on the corneal epithelium and endothelium.[144] While activation of CB1 receptors has been associated with neuroprotective effects, chronic or excessive CB1 activation, often with the use of exogenous cannabinoids like THC, can potentially cause neurotoxicity.

While some studies suggest CB2 expression in the eyes,[145] this topic remains controversial.[142] They have been shown to mediate immune and inflammatory responses and contribute to aqueous humor turnover, which can ultimately also promote neuroprotection by suppressing inflammation and immune-mediated damage.[22,40,146]

Barriers to Ocular Drug Delivery to the Eye

On the ocular level, topical administration of drugs is preferred as it can reduce adverse effects from systemic routes of administration.[147] However, only 3–5% of the administered dose reaches the eye due to structural and dynamic barriers.[148] When drugs are administered orally, only 1–2% reach the eye,[149] and they present with greater systemic adverse effects. Furthermore, orally administrated drugs must pass through the gastrointestinal tract, traverse the blood-stream, and cross the uve-ocular barriers.[149] The eye is considered immune privileged due to these blood-ocular barriers, which consist of the blood-aqueous barrier (BAB) in the anterior segment and the blood-retinal barrier (BRB) in the posterior segment of the eye.[150] Intravenous and intramuscular routes of administration must overcome the BRB to reach therapeutic targets in the eye.

With topical drug delivery to anterior eye segment structures, only about 3–5% of the applied dose is effective due to protein interactions in the tear film, tear turnover rate, and drug removal through the blinking reflex.[151] Physiological barriers present additional challenges for therapeutic targets in the anterior segment, as drugs must pass through several layers. After administration, a drug interacts with the lacrimal fluid (tears), forming a tear film that consists of a lipophilic external, aqueous middle, and mucin inner layer containing electrolytes, lipids, and proteins, which can partially hydrolyze the drug and thus reduce bioavailability.[152] The tear turnover rate and blinking reflex result in a short contact time of the drug with ocular surface tissue. Loss of ophthalmic solution via nasolacrimal drainage or systemic absorption via the conjunctiva is a dynamic barrier to drug delivery.[152] The corneal epithelial layer comprises a single layer of basal cells and several layers of stratified squamous epithelial cells held together by tight junctions. These cells serve as a barrier against drug penetration via paracellular and transcellular transport pathways.[152] Once reaching the anterior chamber, drugs may bind to melanin pigments in the uvea, thus reducing bioavailability in the anterior chamber.[153] Topical administration is favorable in the treatment of conjunctivitis, blepharitis, glaucoma, or anterior uveitis.[154] When drugs targeting the anterior chamber are delivered systemically, they must overcome the BAB, which consists of the endothelium of the iris/ciliary blood vessels and the non-pigmented ciliary epithelium.[155]

Drug administration to the posterior segment of the eye occurs via intravitreal, transscleral, subretinal, and topical modes of administration, with the latter being less suitable due to the anatomical specificities of the eye.[156] Topical ocular administration targeting structures in the posterior segment must cross the tear film, conjunctiva, cornea, aqueous humor, and vitreous humor. For this reason, posterior segment targets typically require intravitreal and subretinal administration.[149]

Ocular Teratogenic Effects

A study using pregnant mice found that prenatal exposure to cannabis smoke for 5 minutes each day during gestation resulted in 17% thinner retinas in young adulthood, but this result normalized in older adulthood.[157] A longitudinal cohort study of 794,099 infants in Quebec, Canada revealed that prenatal substance exposure was significantly associated with childhood eye disorder hospitalization.[158] Exposure to illicit drugs in utero, including smoked cannabis, was also shown to result in reduced visual acuity, nystagmus, and delayed visual maturation in a case series of 20 patients.[159] However, these findings were not specific to cannabis exposure, as many participants in the study were known users of other illicit substances (including benzodiazepines and opiates),[159] making cannabis-related effects inconclusive.

Adverse Ocular Effects — Anterior Segment

Red Eyes in Cannabis Users

Smoked cannabis causes acute, transient conjunctival injection, or red eye, among users.[100,160] Hence, this is one of the most sensitive objective signs of cannabis use, with one study reporting that 94% of drug-impaired drivers with a positive THC blood sample have red eyes.[100] THC induces vasodilation through binding cannabinoid receptors in the eye. These on-target effects increase blood flow to the conjunctiva, leading to conjunctival redness. Animal models suggest the degree of THC-induced vasodilation is dose-dependent.[161]

Dry Eyes and Cannabis

A study on THC's role in aqueous deficiency dry eye (ADDE) found that CB_1 receptors are expressed in cholinergic neuronal axons innervating lacrimal gland cells.[162] CB_1 activation by THC reduced tearing in male mice, but this was not seen in female mice.[162] Other studies on mice have implicated endocannabinoid receptors' multi-factorial role in dry eye disease (DED).[163]. A theoretical benefit of cannabis to treat DED through THC-mediated pain relief and CBD-mediated anti-inflammation has been proposed.[163] In contrast, dry eye symptoms have been reported by cannabis users in several studies. In a study on medical cannabis users, 8.7% reported dry eyes.[164] In a randomized control trial of smoked cannabis for chronic neuropathic pain, dry eyes were one the most common drug-related adverse reactions in the group that received the 9.4% THC formulation.[165] A study of orally administered nabilone, a synthetic cannabinoid, also reported dry eyes as a side effect.[166]

Decreased Corneal Endothelial Cell Density in Cannabis Users

As discussed earlier, CB_1 receptors are predominantly located in the corneal epithelium and endothelium.[144] A study on cannabis users found a decreased corneal endothelial cell density among chronic users,[71] likely due to cannabinoid toxicity as CB_1 receptors are prominent in the anterior eye segment.

Topical THC Eyedrops Cause Corneal Opacification in Animal Studies

Experimental studies on the topical application of THC eyedrops in animal studies have demonstrated corneal opacification following administration in cats,[69,70] as shown in Table 1. This is thought to occur due to decreased corneal hydration, as activated CB_1 receptors inhibit corneal endothelial cell pumping action, attenuating aqueous humor removal from the cornea, which is needed to maintain corneal transparency.[70,167].

Cannabis Effects on Pupils

Cannabis' effects on pupil size are conflicting. Several studies suggest acute cannabis smoking causes pupillary constriction.[169–171] Meanwhile, other studies report pupillary dilation following acute cannabis smoking,[100,160,172] likely mediated by sympathetic stimulation.[172] A study of 39 synthetic cannabinoid UR-144 users found pupillary dilatation and, less commonly, pupillary constriction.[56] Other studies found that smoking cannabis promoted abnormal pupillary reactions to light,[160,171] including a decrease in contraction velocity after a light stimulus,[169] or more simply reported as a "decreased" pupillary light reflex.[160,171]

Adverse Ocular Effects — Posterior Segment

Scotopic Vision

GPR55 is expressed in rod photoreceptors and has been implicated in mediating scotopic night vision in animal models.[173] The cellular mechanism by which this occurs was delineated using tadpoles, whereby CB_1 receptor activation improved visual contrast sensitivity under low-light conditions.[174] Several reports describe anecdotal evidence of improvements in night vision after smoking cannabis,[175–177], a strategy fishermen use.[175] A study in nature evaluating self-reported vision changes after smoked cannabis found that 68% of participants had worsened glare and halos, and 74% felt smoking cannabis diminished their ability to drive at night.[178] Similarly, a study of 64 healthy volunteers found reductions in night vision when measured at 20 minutes after smoking cannabis.[179] With limited and conflicting evidence, whether cannabis transiently improves night vision in humans remains inconclusive.

Visual Acuity

The effects of cannabis on static visual acuity are not fully elucidated. Ortiz-Peregrina et al found a reduction in static vision following smoking cannabis,[178] while Adams et al found no differences in low and high-contrast conditions after smoking cannabis.[87] Brown et al demonstrated that cannabis use produces dose-dependent reductions in dynamic visual acuity.[180] At an oral dose of 20 mg, while THC provided mild analgesic effects, it also led to blurred vision in cancer

Table 1 Summary of Studies on the Effects of Cannabis on the Cornea

Study	Topic of Relevance	Design	Population	Cannabinoid and Route of Administration	Summary of Results
Colasanti et al, 1984[69]	Corneal opacification	Experimental animal study	Cats	THC eyedrops (topical)	Topical application of THC to the corneas of cats demonstrated toxicity, including sustained conjunctival chemosis, erythema, hyperemia, and corneal opacities approximating the site of drug delivery, which were visible in 3–5 days.
Colasanti et al, 1984[70]	Corneal opacification	Experimental animal study	Cats	CBD, THC (topical)	Adverse effects of THC included conjunctival erythema and chemosis as well as severe corneal opacification. These adverse effects were not present following the administration of cannabidiol.
Polat et al, 2017[71]	Decreased corneal endothelial cell density	Case-control study	60 humans	Cannabis (route unspecified)	All members of the cannabinoid group had been diagnosed with cannabinoid use disorder, with usage three or more times per week. The mean corneal density was significantly lower in the cannabinoid group compared to the healthy control group ($p < 0.01$).
Bereiter et al, 2002[36]	Therapeutic corneal effects	Experimental animal study	Rats	WIN55,212–2 (topical or intraperitoneal)	The topical cannabinoid agonist WIN55,212-2 reduces cornea-evoked trigeminal brainstem activity in the rats, which may have implications for ocular analgesia.
Murataeva et al, 2015[34]	Therapeutic corneal effects	In-vitro experimental animal study	Bovine corneal epithelial cells	WIN55212-2 (topical)	Cannabinoid agonist WIN55212-2 activates the CB_1 receptor, inducing chemotaxis of these bovine corneal cells.
Murataeva et al, 2019[32]	Therapeutic corneal effects	Experimental animal study	Mice	–	CB_2 receptor deletion impairs wound healing, and CB_2 receptors mediate chemorepulsion in corneal epithelial cells.
Murataeva et al, 2019[38]	Therapeutic corneal effects	In-vitro experimental animal study	Bovine corneal epithelial cells	Anandamide	In vitro, the activation of corneal GPR18 led to both chemotaxis and proliferation in corneal epithelial cells. Anandamide induced chemotaxis.
Patwardhan et al, 2006[35]	Therapeutic corneal effects	In-vitro experimental animal study	Trigeminal neurons	WIN 55,212-2 (topical)	WIN 55,212-2, a cannabinoid agonist, directly inhibits the transient receptor potential vanilloid 1 (TRPV1) and elicits peripheral anti-hyperalgesia effects.
Thapa et al, 2018[37]	Therapeutic corneal effects	Experimental animal study	Mice	THC, CBD, and HU-308 (topical)	The antinociceptive and anti-inflammatory effects of THC and CBD were observed and mediated primarily via CB_1 and 5-HT receptors, respectively.
Thapa et al, 2020[39]	Therapeutic corneal effects	Experimental animal study	Mice	GAT211,228,229, THC	Allosteric cannabinoid receptor ligands can modulate CB_1 receptor signaling to reduce pain and inflammation in corneal hyperalgesia.

Toguri 2014[40]	Therapeutic corneal effects	Experimental animal study	Rats	HU308 (topical)	Using CB_2 receptor agonist HU308, activation of CB_2 receptors had anti-inflammatory effects in a model of acute endotoxin-induced uveitis. This involved the reduction in NF-κB, AP-1, and other inflammatory mediators.
Yang et al, 2010[33]	Therapeutic corneal effects	In-vitro experimental human study	Human corneal epithelial cells	WIN55,212-2 and capsaicin	WIN55,212-2 and capsaicin transactivated the epidermal growth factor receptor, resulting in downstream cell proliferation and migratory increases.
Yang et al, 2013[168]	Therapeutic corneal effects	In vitro/vivo experimental study	Mice and human corneal epithelial cells	WIN55,212-2	Activation of CB_1 receptors using WIN55,212-2, a cannabinoid agonist, reduced immune cell infiltration and scarring, indicating a potential therapeutic avenue for suppressing inflammation and corneal opacification through the interaction of these receptors.
Pisanti et al, 2011[72]	Reduced corneal revascularization	In vitro/vivo experimental animal study	Rabbit corneal cells and live mice	Anandamide	CB_1 receptor inactivation using mice knockouts and pharmacologic antagonism inhibited proangiogenic effects, including endothelial proliferation, migration, and tube formation. CB_1 receptor blockade inhibited neovascular growth in the rabbit assay. These findings suggest that CB_1 receptors may be a target for antiangiogenic therapy.

Abbreviations: THC, Δ −9-tetrahydrocannabinol; CBD, cannabidiol; CB_1, cannabinoid receptor type 1; CB_2, cannabinoid receptor type 2.

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patients.[181] As for long-term effects, one study demonstrated visual acuity deficits in chronic (>10 years) cannabis users.[172] A case-control study found delayed ganglion cells action potential transmission in regular cannabis smokers.[74]

Reduced Contrast Sensitivity

Contrast sensitivity is another visual function measure. A 30% reduction in binocular and nearly 50% reduction in monocular contrast sensitivity has been demonstrated following smoking cannabis,[178,179] even after consideration of the potential contributions of attention and vigilance.[182] Another study found contrast sensitivity reductions in cannabis users only in low luminance conditions.[98]

Neuroretinal Dysfunction in Cannabis Users

Neuroretinal dysfunction was a documented effect of cannabis on the retina through several studies involving humans. Hallucinogen Persisting Perception Disorder (HPPD), a condition whereby users of hallucinogens continue to experience perceptual disorders for months to years after discontinued drug use, has been reported following heavy cannabis smoking[73] (Table 2). One study reported relative and absolute scotomas in five subjects measured through campimetry, as well as pathological changes identified on visual evoked potential (VEP) and electroretinogram (ERG) testing in individuals with polysubstance use disorders.[75] However, in addition to using cannabis, most study participants also used cocaine, and all used heroin.[75] Another case report found transient alternations in photoreceptor function on ERG following acute cannabis inhalation.[76] In a case report of a 25-year-old chronic cannabis smoker with unilateral blurred vision and several subretinal blebs, subretinal blebs resolved after cannabis smoking cessation.[77] It is difficult to ascertain whether this was due to the cannabis smoking, as the patient was not re-challenged to see if the blebs reappear if cannabis use was reinitiated.[77] A study that involved 60 former synthetic cannabinoid users found no significant retinal changes on OCT.[78]

Pattern and flash ERGs have helped investigate synaptic transmission abnormalities in cannabis users. Case-control studies of long-term cannabis smokers have reported ganglion cell dysfunction through delayed action potential transmission,[74,80] which was found to occur at the central retinal level[82] (Table 2). A later study found the degree of this dysfunction to be associated with the quantity of cannabis smoked.[83] In addition, other studies have found sustained abnormal visual transmission through decreased amplification by amacrine cells in long-term cannabis smokers.[79] Delayed bipolar cell neuroretinal processing has also been delineated,[80,81] and confirmed to be due to On and Off pathway dysfunction in cannabis smokers[81] (Table 2). Furthermore, a study on mice found functional loss and increased apoptosis in photoreceptor cells following 1 or 2 mg/kg intraperitoneal THC exposure daily for two months.[84]

Retinal Vasculature Abnormalities in Cannabis Users

Several case reports have proposed associations between cannabis use and abnormalities in retinal vasculature. One case report demonstrated central retinal vein occlusion only minutes following cannabis smoking in an otherwise health 18-year-old male.[48] Another case reported branch retinal artery occlusion and acute maculopathy in a 21-year-old man, and suggested this may be due to long-term heavy cannabis smoking[183] (Table 2). A case report of monocular vision loss following hemorrhagic macular infarction in a 55-year-old man was suggested as being associated with his long-term cannabis smoking[33]; however, the event seems to be more temporally related to his pregabalin and alcohol overdose in a suicide attempt the previous night.[47] Given the lack of observational studies or larger case series to substantiate these findings, the proposed associations between cannabis use and retinal vascular abnormalities should be interpreted cautiously until more robust, population-based research is available.

Animal studies have demonstrated the dose-dependent effects of abnormal cannabidiol (abn-CBD), a synthetic CBD, through pre-contracted retinal arteriole vasodilation.[51,184] This is consistent with a cross-sectional study of 8 participants, whereby an oral dose of 7.5 mg dronabinol, a synthetic cannabinoid and THC derivative, significantly decreased retinal arteriovenous passage time.[52] This effect was further verified in a randomized clinical trial of 24 individuals, which found increased optic nerve head blood flow following 5 mg oral administration of dronabinol.[50] An observational study on 106 young adults found that mean arteriolar diameter was significantly wider amongst frequent cannabis smokers compared

Table 2 Summary of Studies on the Effects of Cannabis on the Retina and Retinal Vasculature

Study	Topic of Relevance	Design	Population	Cannabinoid and Route of Administration	Summary of Results
Faure et al, 2016[77]	Neuroretinal dysfunction	Case report	1 human	Cannabis (inhaled)	A healthy 25-year-old man presented with unilateral blurred vision of the right eye. Imaging studies revealed several subretinal blebs. He was a chronic hashish smoker (5 joints per day) since the age of 16. After comprehensive investigations, the author suspects that this hashish use is the most probable cause of his condition.
Onur et al, 2016[78]	Neuroretinal dysfunction	Case-control study	90 humans	Synthetic cannabinoids (route unspecified)	Healthy controls were compared to a group of former chronic synthetic cannabinoid users. Cannabinoids reduced intraocular pressure and choroidal thickness in the acute/subacute phase of synthetic cannabinoid use while not having any visible retinal changes on OCT.
Pérez et al, 1995[75]	Neuroretinal dysfunction	Case-control study	30 humans	Cannabis (route unspecified)	All the subjects in the drug user group used heroine, 12 used cannabis and 12 used cocaine. Campimetry showed relative and absolute scotoma in five subjects. VECP was moderately pathological in 6 cases and pathological in 7 cases, suggesting an optical pathway or cortical center alteration. ERG showed non-specific altered traces in 11 cases.
Polli et al, 2021[79]	Neuroretinal dysfunction	Case-control study	85 humans	Cannabis (route unspecified)	ERG oscillatory potentials in regular cannabis users demonstrated abnormalities in amacrine cell functioning. The dopaminergic transmission was similar to that found in Parkinson's disease.
Schwitzer et al, 2016[76]	Neuroretinal dysfunction	Case report	1 human	Cannabis (mostly inhaled)	A 47-year-old heavy cannabis user had neuroretinal dysfunction evaluated through effects on photoreceptor functioning. There was a decrease of up to 48% in the a-wave amplitude of the full-field ERG 30 minutes after cannabis smoking for all scotopic responses compared to 5 hours after smoking.
Schwitzer et al, 2017[74]	Neuroretinal dysfunction	Case-control study	52 humans	Cannabis (mostly inhaled)	Pattern and flash electroretinogram studies demonstrated a delay in ganglion and bipolar cell responses in cannabis users, which may reflect a delayed transmission of visual information from the retina to the brain.
Schwitzer et al, 2018[80]	Neuroretinal dysfunction	Case-control study	82 humans	Cannabis (mostly inhaled)	Using pattern and flash electroretinogram, cannabis users showed delayed ganglion and bipolar cell responses in cannabis users compared to healthy controls.
Schwitzer et al, 2020[82]	Neuroretinal dysfunction	Case-control study	70 humans	Cannabis (mostly inhaled)	Utilizing multifocal electroretinogram, differences between cannabis users and controls suggest a delay in visual information transmission from the central retina to the near periphery in cannabis users, possibly affecting precise and color vision.
Schwitzer et al, 2021[81]	Neuroretinal dysfunction	Case-control study	68 humans	Cannabis (mostly inhaled)	Through assessment of the On and Off pathway function using On-Off ERG, cannabis users showed a significant increase in the latencies of both the b- and the d-waves, demonstrating the impact of cannabis on the post-receptor cones pathway at the level of bipolar cells.

(*Continued*)

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Table 2 (Continued).

Study	Topic of Relevance	Design	Population	Cannabinoid and Route of Administration	Summary of Results
Schwitzer et al, 2022[83]	Neuroretinal dysfunction	Prospective study	40 humans	Cannabis (mostly inhaled)	Using recorded flash and pattern electroretinograms, the neuroretinal dysfunction from cannabis may be reversed, as a reduction in cannabis use was associated with fewer ERG anomalies amongst chronic, heavy cannabis users.
Zhang et al, 2020[84]	Neuroretinal dysfunction	Experimental animal study	Mice	THC (intraperitoneal)	BALB/c mice were treated with 1 or 2 mg/kg THC daily. After two months, this induced inflammatory responses and oxidative stress, leading to apoptosis and functional loss within the retinal layers.
Zobor et al, 2015[73]	Neuroretinal dysfunction	Case-control study	5 humans	Cannabis (inhaled)	A 23-year-old male who is a heavy cannabis user was eventually diagnosed with Hallucinogen Persisting Perception Disorder (HPPD) and found to have abnormal electrooculography (EOG) and electrically evoked phosphene thresholds (EPT), suggesting a direct effect of cannabinoids on the retina and retinal pigment epithelium function, which may be involved in disturbances of the visual function experienced after drug consumption.
Aktaş et al, 2016[47]	Retinal vasculature	Case report	1 human	Cannabis (inhaled)	A 55-year-old male with painless and sudden vision loss in the right eye developed a hemorrhagic macular infarction. However, this was deemed to be more temporally related to his pregabalin and alcohol overdose in a suicide attempt the previous night.
Corvi et al, 2014[48]	Retinal vasculature	Case report	1 human	Cannabis (inhaled)	An otherwise healthy 18-year-old male presented with reduced visual acuity and was diagnosed with central retinal vein occlusion (CRVO), thought to be associated with an acute increase in cannabis use following a comprehensive investigation of other potential etiologies.
Hill et al, 2020[49]	Retinal vasculature	Case-control study	106 humans	Cannabis (inhaled)	Retinal imaging found that the mean arteriolar diameter was significantly wider for cannabis users, even after excluding participants who smoked cannabis in the last 24 hours. This might represent a residual vasodilatory effect of recent cannabis use or impaired autoregulation resulting from chronic cannabis use.
Hommer et al, 2020[50]	Retinal vasculature	Randomized-control trial (RCT)	24 humans	Dronabinol (oral)	Following administration of 5 mg dronabinol, a synthetic THC, measured optic nerve head blood flow (ONHBF) found that dronabinol significantly increased ONHBF at rest while placebo did not.
MacIntyre et al, 2014[51]	Retinal vasculature	Experimental animal study	Rats	Abn-CBD	The study demonstrated how abnormal cannabidiol (Abn-CBD) inhibited endothelin 1 (ET-1) induced vasoconstriction in retinal arterioles, demonstrating the role of endocannabinoids in retinal vasoactivity.
Plange et al, 2007[52]	Retinal vasculature	Cross-sectional study	8 humans	Dronabinol (oral)	After administering 7.5mg dronabinol, a synthetic THC, the retinal arteriovenous passage time decrease was statistically significant, suggesting its potential benefit in ocular circulatory disorders.

Ramtohul et al, 2022[183]	Retinal vasculature	Case report	1 human	Cannabis (inhaled)	A 21-year-old healthy man described the acute onset of superior visual field loss in his right eye. He smoked 15 grams of cannabis daily for several weeks and following comprehensive retinal imaging and systemic workup, he was diagnosed with branch retinal artery occlusion associated with paracentral acute middle maculopathy on spectral-domain OCT thought to be associated with his heavy cannabis use.
Su et al, 2015[184]	Retinal vasculature	In vitro experimental animal study	Porcine retinal arteriole	Abn-CBD (intraluminal and extraluminal)	Abnormal cannabidiol (abn-CBD) mediated vasorelaxation was seen only in precontracted retinal vessels, illustrating that abn-CBD induced a vasoactive response which highly depended on vascular tone.
Araújo et al, 2017[185]	Retinal neuroprotective effects	In vitro experimental animal study	Chick retinal cells	WIN 55212–2 and AM251/O-2050 or AM630	Following retinal ischemia in an oxygen and glucose deprivation model, the agents used decreased lactate dehydrogenase release. The increased availability of endocannabinoids, together with cannabinoid receptor antagonists, had a neuroprotective effect.
Chen et al, 2018[41]	Retinal neuroprotective effects	In vitro experimental animal study	Photoreceptor degeneration mouse model	SR141716A	Administration of SR141716A, CB_1 receptor antagonist, recovered photoreceptor loss, decreased glial reactivity and reduced abnormal vascular complexes in this mouse model, suggesting potential therapeutic effects in retinal degeneration diseases (eg, retinitis pigmentosa).
Kalenderoglu et al, 2020[53]	Retinal neuroprotective effects	Case-control study	156 humans	Cannabis (route unspecified)	Retinal nerve fiber layer (RNFL) thickness was higher in the cannabis use disorder group than in controls, which may represent the neuroprotective effect of cannabis.
Liu et al, 2014[43]	Retinal neuroprotective effects	Experimental animal study	Rats	Cannabinoid HU-211 (intravitreal)	In a rat model of glaucoma, intravitreal injection of HU-211 resulted in less apoptosis and damage to the retinal ganglion cell (RGC) neurons.
Pinar-Sueiro et al, 2013[44]	Retinal neuroprotective effects	Experimental animal study	Rats	WIN 55212-2 (topical)	In an ischemic model of retinal ganglion cell (loss, topical administration of WIN 55212-2 showed a neuroprotective effect on RGC degeneration after ischemia-reperfusion).
Spyridakos et al, 2021[54]	Retinal neuroprotective effects	Experimental animal study	Rats	WIN 55212-2 (intravitreal)	Rats given intravitreal WIN 55212-2 demonstrated neuroprotective and anti-inflammatory properties.
Yoles et al, 1996[45]	Retinal neuroprotective effects	Experimental animal study	Rats	Synthetic THC HU-211	Using a calibrated crush injury of rat optic nerves, HU-211 reduced injury-induced metabolic and electrophysiological deficits, thus having neuroprotective effects.
Zalish et al, 2003[46]	Retinal neuroprotective effects	Experimental animal study	Rats	Synthetic THC HU-211 (intraperitoneal)	Using a crush-injured rat optic nerve model, transmission electron microscopic analysis of the excised optic nerves in rats treated with HU-211 showed unmyelinated and thinly myelinated axons at the injury site, while controls did not. This is possibly indicative of regenerative growth.

Abbreviations: OCT, optical coherence tomography; VECP, visual evoked cortical potential; ERG, Electroretinogram; THC, Δ-9-tetrahydrocannabinol; CBD, cannabidiol.

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to controls,[49] which may represent residual vasodilatory effects from cannabis smoking or impaired autoregulation resulting from chronic cannabis use[49] (Table 2).

Adverse Ocular Effects — Adnexal Structures

Cannabis and Cannabinoids May Cause Transient Eyelid Tremors

Several studies have reported transient eyelid tremors as a physical symptom after synthetic cannabinoid[56,59] and cannabis use[58,59] (Table 3). Eyelid tremor is an umbrella term referring to involuntary and intermittent eyelid muscle spasms.[61] While both blepharospasm and eyelid tremor involve abnormal eyelid movements, they are different in their underlying causes, associated symptoms, and clinical presentation.[61] These reports do not provide clinical detail about the cannabis and cannabinoid related eyelid tremors and may instead refer to temporary tremors distinct from true blepharospasm,[56–59,61] as demonstrated in Table 3. One study of 302 participants noted eyelid tremors in 86.1% of subjects with THC blood levels greater than 1 µg/L by a drug recognition expert (DRE) examination,[59] while another study demonstrated 6 out of 18 individuals in driving cases who tested positive for synthetic cannabinoid XLR-11 had eyelid tremors.[57] In a study of drug-impaired driving cases, 39 participants with UR-144 concentrations ranging from trace levels to 17 ng/mL, eyelid tremors were among the most reported signs[56] Stress and fatigue are common causes of eyelid tremors,[186] which may be a confounder to the presence of eyelid tremors in the drug-impaired drivers within these studies.[56–59]

An interventional study of 5 patients with dystonic movement disorder received oral CBD at doses starting at 100 mg/day, up to 600 mg/day over 6 weeks and found dose-related improvement of dystonia, with maximal improvement ranging from 20–50%[4] (Table 3). Benign essential blepharospasm (BEB) is a bilateral focal dystonia characterized by episodic contraction of the eyelid protractor muscles that causes progressive spasms. In a retrospective study of 5 patients with Benign Essential Blepharospasm (BEB) refractory to botulism toxin injections (defined by the researchers as patients with residual symptoms despite being on long-term botulinum toxin therapy), participants received varying doses of oral CBD (5 to 47.5mg) and THC (2.5 to 25 mg) and all but one patient discontinued treatment due to cost, side effects, or lack of treatment efficacy.[6] A case report of a woman with severe BEB refractory to botulism toxin injections received oral dronabinol 25 mg for several weeks and reported improved pain and functional status.[8] More recently, a randomized controlled trial involving 6 patients with blepharospasm demonstrated the efficacy of 3.2% THC and 0.1% CBD containing drops administered sublingually in the treatment of blepharospasms, as a second-line therapeutic option in patients who repeatedly fail (eg, showed no improvement) first-line treatment using botulinum toxin injections[7] (Table 3).

Cannabinoids May Result in Ptosis or Droopy Eyelid

Ptosis, also known as droopy eyelid or blepharoptosis, is characterized by an abnormally low upper eyelid margin position, which may cause visual disturbances or lead to cosmetic concerns.[187] Ptosis in the setting of cannabinoid use is classified as having an acquired etiology, as opposed to congenital or involutional causes. One human study of impaired drivers found that 85.6% of blood THC-positive drivers had ptosis identified on field sobriety tests[100] (Table 3). This study did not define how ptosis was measured or defined.

Animal model studies have demonstrated ptosis resulting from intraperitoneal Anandamide,[63] intraperitoneal SR 141716A,[62] as well as cannabinoids administered intravenous or intramuscularly[65,67,68] (Table 3). Meanwhile, others have reported ptosis as part of cannabinoid withdrawal.[64,66] While most of these studies defined ptosis, whether this effect is chronic, or transient has not been described. Similarly, murine models demonstrated that ptosis resulted from intraperitoneal anandamide, an endogenous cannabinoid.[63,66] In a study of non-human primates, rhesus monkeys developed ptosis following acute exposure to intravenous Δ-9-THC but not Δ-11-THC.[65,68] Another study on cynomolgus monkeys treated with intramuscular levonantradol, a synthetic THC analog, at doses ranging from 0.01 to 0.03 mg/kg experienced ptosis, but this did not reach statistical significance.[67] Overall, animal studies have demonstrated strong evidence that cannabinoids may be associated with ptosis. Observational studies on cannabinoids and cannabis users may provide further insight into potential unwanted effect in humans.

Table 3 Summary of Studies on the Effects of Cannabis on the Eyelids

Study	Topic of Relevance	Design	Population	Cannabinoid and Route of Administration	Summary of Results
Adamowicz et al, 2017[56]	Eyelid tremor	Cross-sectional study (DRE evaluation)	39 humans	UR-144 (route unspecified)	Synthetic cannabinoid UR-144 concentrations ranged from trace levels to 17 ng/mL. The most common symptoms in cases positive for UR-144 were slurred speech, poor coordination, body and eyelid tremors, and bloodshot, watery eyes.
Hartman et al, 2017[59]	Eyelid tremor	Cross-sectional study (DRE evaluation)	302 humans	Cannabis (route unspecified)	Eyelid tremors occurred in 57.9% of cases during the Modified Romberg Balance (MRB) test, and an additional 28.1% displayed eyelid and body tremors.
Louis et al, 2014[57]	Eyelid tremor	Cross-sectional study (DRE evaluation)	18 humans	XLR-11 and/or UR-144 (route unspecified)	Six cases were positive for synthetic cannabinoids UR-144, eight for synthetic cannabinoids XLR-11, and four for both. Body and eyelid tremors occurred in 12 of 17 drivers who consented to testing.
Porath et al, 2019[58]	Eyelid tremor	Cross-sectional study (DRE evaluation)	1512 humans	Cannabis (route unspecified)	Using a statistical model that includes 13 drug-related indicators, eyelid tremors were good predictors of cannabis versus no-drug cases, with an odds ratio of 0.26 (95% CI: 0.13–0.54).
Zawar et al, 2021[60]	Eyelid tremor	Case report	2 patients with Jeavons Syndrome (JS)	CBD (oral)	A 20-year-old female with poorly controlled seizures tried CBD oil 4mg thrice daily and noted increased eyelid myoclonus. A 14-year-old female with poorly controlled seizures tried CBD oil at 5–10 mg/kg/day, which worsened her eyelid myoclonus.
Consroe et al, 1986[4]	Blepharospasms	Interventional Study	5 patients with dystonic movement disorders	CBD (oral)	Oral doses of CBD ranging from 100 to 600 mg/day were administered to patients over 6 weeks and titrated upwards. Dose-related improvement of the dystonia was demonstrated, with maximal improvement ranging from 20 to 50%.
Fox et al, 2002[5]	Blepharospasms	Randomized-control trial (RCT)	15 patients with primary dystonia	Nabilone (oral)	A single dose of cannabinoid receptor agonist, nabilone, or placebo at 0.03 mg/kg was administered orally (double-blind). Nabilone failed to significantly reduce dystonia when measured 1–3 hours after administration. However, four patients reported subjective improvement of dystonia severity, most pronounced at 2–3 days after Nabilone administration.
Gauter et al, 2004[8]	Blepharospasms	Case report	1 patient with BEB	Dronabinol (oral)	In the case of a woman with severe blepharospasm refractory to sustained benefit from other therapies, treatment with 25 mg Dronabinol, a cannabinoid receptor agonist, for several weeks was self-reported to improve the patient's pain and functional status.
Radke et al, 2017[6]	Blepharospasms	Retrospective study	5 patients with BEB	Non-specific cannabis products (oral)	Patients with BEB receiving standard botulinum toxin injections were eligible for inclusion. Three out of four patients (75%) reported symptomatic improvement as measured by objective scales. Eventually, 4 out of 5 patients dropped out due to cost, side effects, or lack of treatment efficacy.

(*Continued*)

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Table 3 (Continued).

Study	Topic of Relevance	Design	Population	Cannabinoid and Route of Administration	Summary of Results
Zloto et al, 2022[7]	Blepharospasms	Randomized-control trial (RCT)	6 patients with BEB	Cannabis (sublingual)	Patients with benign essential blepharospasm refractory to botulinum toxin injections were eligible for inclusion. In the treatment group, an average of 6.27 drops were used daily in the last six weeks, containing 3.2% THC and 0.1% CBD. There were 61 spasm events in the treatment group, compared to 94 spasm events in the placebo group ($p = 0.05$) in the last six weeks of this 12-week study.
Aceto et al, 1998[63]	Ptosis	Experimental animal study	Rats	Anandamide (intraperitoneal)	Anandamide is an endogenous cannabinoid agonist. Continuous intraperitoneal infusion of rats with Anandamide at an increasing dose of 50–200 mg/kg/24hr produced ptosis (50% or greater eyelid closure), especially at higher doses.
Aceto et al, 1996[64]	Ptosis	Experimental animal study	Rats	SR 141716A (intraperitoneal)	SR 141716A is a CB_1 receptor antagonist. Continuous intraperitoneal infusion of rats at an increasing dose ranging from 0.5–200 mg/kg/24h within three experimental groups found that ptosis (50% or greater closure of the eyelids) was a significant sign of withdrawal.
Beardsley et al, 1987[68]	Ptosis	Experimental animal study	Rhesus monkeys	Δ 9-THC and Δ9-11-THC (intravenous)	Δ 9-THC produced signs of ptosis, sedation, and ataxia in all the rhesus monkeys, while Δ9-11-THC did not.
Costa et al, 2000[66]	Ptosis	Experimental animal study	Rats	Anandamide (intraperitoneal)	Anandamide is an endogenous cannabinoid agonist. Rats were injected with anandamide at 20 mg/kg daily for two weeks to assess for physical dependence and withdrawal signs/symptoms. Ptosis was one of the most common withdrawal signs.
Hutcheson et al, 1998[62]	Ptosis	Experimental animal study	Mice	SR 141716A (intraperitoneal)	SR 141716A is a CB_1 receptor antagonist. Mice in the experimental group receiving 20 mg/kg of THC displayed a notably increased occurrence of ptosis compared to the control group after SR 141716A injection. This effect did not occur in the group receiving 10 mg/kg of THC.
Meschler et al, 2000[67]	Ptosis	Experimental animal study	Cynomolgus monkeys	Levonantradol (intramuscular)	Levonantradol is a CB_1 receptor agonist. In isolation, administering levonantradol at doses ranging from 0.01 to 0.3 mg/kg resulted in sedation, ptosis, and reduced overall movement and activity. The decrease in ptosis was not statistically significant; however, this may be attributable to a single monkey that did not experience sedation when given levonantradol.
Young et al, 1981[65]	Ptosis	Experimental animal study	Rhesus monkeys	Nantradol and Levonantradol (intravenous)	The doses of nantradol and levonantradol studied ranged from 0.03 to 0.3 mg/kg. The acute effects of these drugs were characterized by five main signs: pupil dilation, ataxia, ptosis, doxing, and attenuated reactivity to external stimulated.

Abbreviations: DRE, drug recognition expert; BEB, benign essential blepharospasm; CBD, cannabidiol.

Topical THC Eyedrops and Eyelid Swelling

One study exploring whether topical 1% THC eyedrop administration can decrease intraocular pressure (IOP) reported that 4 out of 28 participants dropped out due to acute burning sensation and "lid swelling".[14] However, 3 out of 4 participants who dropped out were in the control group that received light mineral oil, not THC.[14] Based on these findings, it cannot be concluded that THC drops cause acute eyelid swelling.

Oculomotor Control

Cannabis and cannabinoid effects on extraocular motility have been examined in the context of intoxication from recreational use and as side effects following medical uses[85–101] (Table 4). Early investigations compared the impact of smoked cannabis and drinking alcohol on ocular movements, and found that alcohol impaired saccades and smooth pursuit, while cannabis did not.[85,86,191] Long-term heavy cannabis use may influence static visual acuity, potentially affecting visual performance and promoting changes in psychomotor performance, including ocular motor control.[96] Long-term studies by Huestegge et al investigated inhaled cannabis' persistent effects on oculomotor function and eye movement control during reading in a cross-sectional study. In the study, 20 long-term cannabis users (without acute THC intoxication) had prolonged fixation time, increased text revisiting, and longer word viewing times compared to non-users, suggesting that even subtle deficits in essential oculomotor control can impact reading performance[89,90] (Table 4). Potential sustained alterations, including increased fixation time, delayed response times, altered saccadic amplitudes, extended text recheck, and elongation of word visualization were also identified in chronic cannabis users.[89,90]

Stereopsis

A reduction in three-dimensional vision following smoking cannabis was demonstrated through a deterioration in stereoacuity[178,179] (Table 4), defined as the ability to detect differences in the depth of field.[178] Other studies have shown a reduction in binocular depth inversion, a sensitive measure of impaired visual information processing, for up to 192 hours after cannabis resin at a dose of 3.0–4.0 mg/kg in seven healthy volunteers[192] and permanent reductions in chronic cannabis smokers when measured using a random-dot stereogram.[193] As cannabinoids' effects on extraocular motility implicate a complex interplay with various aspects of visual functioning, including ocular tracking, gaze stability, and nystagmus, further research is needed to investigate these effects.

Gaze Stability and Nystagmus

Beyond gaze stability, cannabinoids have been associated with eye deviation,[91] possibly due to alterations of neural pathways involved in eye movement coordination and control.[91,93] One case reported conjugate dextrodeviation of the eyes from cannabis intoxication after inadvertent ingestion, with effects lasting six weeks[91] (Table 4). Several studies of impaired drivers found horizontal gaze nystagmus a common sobriety examination finding,[58,189] which was later tested on 44 human participants, 43 (98%) of which exhibited HGN after smoking cannabis within the three-hour impairment window[190] (Table 4).

Thyroid Storm

A case was reported on a 25-year-old man with Graves' disease who passed away following a thyroid storm, which was thought to have been triggered by smoking synthetic cannabinoids the morning of his presentation to the hospital.[194] No other cases have been reported.

Therapeutic Applications of Cannabis and Cannabinoids

Corneal Anti-Inflammatory Properties in Animal Studies

Studies have demonstrated potential therapeutic effects through acute 'cannabinoid-associated anti-inflammatory, analgesic, and regenerative effects on the cornea,[31–40,168] as summarized in Table 1. These include topical cannabinoid receptor agonist WIN55,212-2.[34–36,168] Furthermore, in vitro human and in vivo animal studies have demonstrated reduced

Table 4 Summary of Studies on the Effects of Cannabis on Extraocular Muscle Functioning

Study	Topic of Relevance	Design	Population	Cannabinoid and Route of Administration	Summary of Results
Adams et al, 1975[87]	Ocular movements	Randomized-control trial (RCT)	10 humans	THC (inhaled)	Effects of oral Δ −9-tetrahydrocannabinol (THC) were examined on dynamic visual acuity, finding that THC alters various aspects of this type of eye control, affecting spatial attention shifts, volitional saccade accuracy, spatial working memory, and inhibitory control.
Baloh et al, 1979[86]	Ocular movements	Interventional study	24 humans	Cannabis (inhaled)	Effects of alcohol and cannabis (THC) on eye movements were examined, with alcohol alone significantly impairing various aspects of eye movement, including saccades, smooth pursuit, and optokinetic nystagmus. The addition of THC did not produce statistically significant additional impairment, indicating that alcohol had a more pronounced impact on eye movements in this study.
Fant et al, 1998[88]	Ocular movements	Prospective study	10 humans	Cannabis (inhaled)	Acute and residual effects of smoking cannabis showed that active doses (1.8% and 3.6%) of cannabis users had robust immediate subjective and physiological effects, including changes in heart rate and pupillary response, as well as impairments in smooth pursuit eye tracking, but these effects returned to baseline within hours, indicating minimal residual effects the following day.
Flom et al, 1976[85]	Ocular movements	Interventional study	10 humans	Cannabis (oral or inhaled)	Frequent alcohol and cannabis users observed a moving spot on a 7.5-degree field with their eyes; alcohol, but not cannabis or a placebo, reduced the frequencies at which smooth and saccadic eye movements broke down, with alcohol affecting smooth tracking by increasing processing time and saccadic tracking by altering velocity and latency times.
Huestegge et al, 2009[89]	Ocular movements	Case-control study	40 humans	Cannabis (inhaled)	Long-term cannabis users without acute THC intoxication were compared to 20 control subjects, with cannabis users had significant delays in response times and altered saccade amplitudes, indicating long-term deficits in temporal processing and visuospatial working memory, potentially affecting everyday tasks like visual search, spatial navigation, and reading.
Huestegge et al, 2010[90]	Ocular movements	Case-control study	40 humans	Cannabis (inhaled)	Eye movements during sentence reading were compared in 20 long-term cannabis users (without acute THC intoxication) and 20 control participants, indicating that cannabis users showed prolonged fixation durations, more revisiting of text, and longer word viewing times, suggesting that even subtle deficits in essential oculomotor control can impact reading performance.
Zuurman et al, 2008[97]	Ocular movements	Randomized-control trial (RCT)	12 humans	THC (inhaled)	Δ-9-THC administration via an intrapulmonary THC delivery system (Volcano®) method showed low between-subject variability in plasma concentrations and dose-dependent effects. No changes were seen in saccadic eye movements, smooth pursuit, and adaptive tracking performance.
Moskowitz et al, 1976[188]	Ocular movements	Prospective study	37 humans	Cannabis (inhaled)	Alcohol significantly altered visual search behavior (dwell, pursuit, saccade, and blink), whereas cannabis had no discernible effect on visual scanning behavior.

Ploner et al, 2002[93]	Ocular movements	Prospective study	12 humans	THC (oral)	A dose of 10mg THC modified saccade control in terms of spatial attention shifts, fine-tuning of voluntary saccades, spatial working memory, and inhibition of inappropriate saccades, suggesting the involvement of the cannabinoids in controlling saccades and associated cognitive functions.
Mohan and Sood, 1964[91]	Strabismus	Case report	1 human	Cannabis (inhaled)	A patient developed conjugate dextrodeviation of the eyes from cannabis intoxication after inadvertent ingestion, resolving effects after six weeks.
Moskowitz et al, 1972[92]	Attention and visual perception	Prospective study	12 humans	Cannabis (inhaled)	Cannabis effects detection of peripheral light stimuli, and linearly correlated to changes in peripheral vision performance.
Yoon et al, 2019[96]	Attention and visual perception	Prospective study	53 humans	Cannabis (route unspecified)	Subjects with cannabis use disorders showed more inhibitory control deficits and attentional bias toward cannabis stimuli than controls, suggesting these measures' potential utility in research and interventions with substance users.
Mikulskaya et al, 2018[98]	Attention and visual perception	Case-control study	41 humans	Cannabis (route unspecified)	Cannabis users displayed reduced spatial contrast sensitivity in low luminance conditions and increased motion coherence thresholds, potentially linked to lower dopamine levels, raising concerns about driving safety in cannabis users, especially in low visibility conditions.
Pradeep et al, 2008[94]	Nystagmus	Case report	1 human	Cannabis (inhaled)	A patient using smoked cannabis for about three weeks improved visual acuity by 2–3 log Mar lines and reduced congenital nystagmus intensity by 10–44% for different positions.
Schon et al, 1999[101]	Nystagmus	Prospective study	1 human	Cannabis (oral)	Smoking cannabis resin significantly suppressed the nystagmus and improved visual acuity in a patient with multiple sclerosis, whereas nabilone tablets and orally administered cannabis oil capsules had no therapeutic effect.
Chase, 2016[189]	Horizontal gaze nystagmus	Retrospective study	133 humans	THC (route unspecified)	Drivers under the influence of synthetic cannabinoids were more frequently impaired with confusion, disorientation, incoherent, slurred speech, and horizontal gaze nystagmus compared to those under the influence of cannabis.
DeGregorio, 2021[190]	Horizontal gaze nystagmus	Cross-sectional study	74 humans	Cannabis (inhaled)	A new method for detecting recent cannabis use and impairment after smoking was tested on 74 participants. Fourty-four individuals were assessed for horizontal gaze nystagmus (HGN), 43 (98%) of which exhibited HGN after smoking cannabis within the three-hour impairment window.

Abbreviations: THC, Δ-9-tetrahydrocannabinol; HGN, horizontal gaze nystagmus.

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corneal neovascularization through CB_1 receptor antagonism.[72,195] Additional studies investigating these potential therapeutic effects are needed.[196]

Pterygium

Cannabinoid receptor differential expression in patients with pterygium, a wedge-shaped fibrovascular outgrowth that originates in the conjunctiva and extends into the cornea,[197] has been reported. This may imply a potential role of cannabinoid targets in the understanding of pterygium.[197]

Retina Neuroprotective Effects in Animal Studies

The therapeutic potential of cannabinoids on the retina has been explored through several animal studies. A 2008 study that claimed neuroprotective and anti-inflammatory CBD effects on the retina was retracted in 2014 by the journal editors as the findings were not supported by the presented research data.[198] Rat model glaucoma studies have demonstrated that intravenous THC or synthetic cannabinoid HU-211 injections significantly reduce retinal ganglion cell (RGC) death,[42,43] likely mediated by IOP reduction[42] (Table 2). Topical administration of cannabinoid receptor agonist WIN 55212-2 has demonstrated similar neuroprotective effects in rat ischemic models of retinal ganglion cell loss.[44] Two studies demonstrated the neuroprotective effects of intraperitoneal synthetic cannabinoid HU-211 injections in rats following optic nerve crush injuries, including a metabolic and electrophysiological deficit reduction,[45] and regenerative growth following injury[46] (Table 2). Accordingly, while cannabinoid retinal neuroprotective effects have been illustrated in animal studies, this has yet to be demonstrated in the human retina.

Retinal ischemia plays a role in various ocular pathologies, including diabetic retinopathy and glaucoma.[185] One study demonstrated that the TRPA1 receptor is a critical element in cell death following the early stages of ischemia.[185] By using synthetic cannabinoid receptor agonists, a decrease in lactate dehydrogenase (LDH) was demonstrated in chick retinal models.[185] LDH was used as a cell death marker in the study.[185] The therapeutic potential of cannabinoids in retinal degenerative etiologies has been explored using animal models. A mouse model study utilizing the CB_1 agonist SR141716A found photoreceptor loss recovery following degeneration[41] (Table 2).

Applications in Diabetic Retinopathy

Differential expression of endocannabinoids in the ocular tissues of diabetics has been documented, including differences in endocannabinoid concentrations in diabetic patient aqueous humor[146] and higher endocannabinoid (AEA and 2-AG) levels in specific anatomical locations within ocular tissue in the post-mortem eye tissue of diabetic retinopathy patients.[188] Differential levels of endocannabinoids in the aqueous humor of diabetic and non-diabetic patients may offer a novel therapeutic target for diabetic retinopathy. Given previous studies suggesting endocannabinoids may offer neuroprotection through anti-inflammatory activity, elevated levels of endocannabinoids may be a mechanism for counteracting inflammation in diabetic retinopathy.[188]

Applications in Glaucoma

Glaucoma is a heterogenous group of irreversible diseases characterized by damage to the optic nerve.[199] Therapies focused on reducing IOP are still the primary strategy to prevent disease progression, as IOP remains one of the few modifiable risk factors for glaucoma management.[199] Therapeutic and adverse effects of cannabinoids on IOP have been researched by nine groups involving a total of 112 individuals,[9–30] with most studies focusing on primary open-angle glaucoma (Table 5).

Cannabinoids have been shown to promote an IOP decrease in animal and clinical investigations which date back to the 1980s. In 1976, Cohen described a 30% drop in IOP levels for 4–5 hours following smoking of a mean of 103 mg THC in 7 out of 11 individuals with open-angle glaucoma.[10] In 1977, a prospective study with 10 subjects receiving intravenous (mean 1.5 or 3.0 mg), weight-adjusted THC experienced a 51% IOP-reduction from baseline.[11] It was later found that the BW146Y chemical derivative exhibited a noteworthy independent reduction in intraocular pressure, while BW29Y did not effectively lower intraocular pressure, with both compounds showing mild side effects[19] (Table 5).

Table 5 Studies on the Effects of Cannabis on Intraocular Pressure

Study	Topic of Relevance	Design	Population	Cannabinoid and Route of Administration	Summary of Results
Cohen, 1976[10]	Decreased intraocular pressure	Prospective study	30 humans	THC (inhaled and oral)	The IOP fell by 30% in 7 of 11 patients with open-angle glaucoma after THC administration (mean dose of 103 mg), with effects lasting 4–5 hr. The IOP also decreased following smoking cannabis and oral THC, but only slightly with CBD use.
Cooler and Gregg, 1977[11]	Decreased intraocular pressure	Prospective study	10 humans	THC (intravenous)	Intraocular pressure was decreased by as much as 51% from baseline, with an average decrease of 37% in 10 paid volunteers receiving intravenous medications at weight-adjusted dosages. The mean dose was 1.5 mg or 3mg THC for the first and second treatment arm, respectively.
Fischer et al, 2013[22]	Decreased intraocular pressure	Experimental animal study	Dogs	THC (topical)	Effects of 2% topical THC ophthalmic solution twice daily for nine doses compared to placebo on intraocular pressure and aqueous humor flow rate in clinically normal dogs was examined. THC resulted in a moderate reduction in mean IOP in clinically healthy dogs.
Jay and Green, 1983[14]	Decreased intraocular pressure	Interventional study	23 humans	THC (topical)	A multiple-drop study of 1% topical THC in human eyes compared to the contralateral placebo eye found no difference in intraocular pressure between eyes treated with THC versus placebo controls.
Merritt et al, 1980[15]	Decreased intraocular pressure	Interventional study	18 patients with glaucoma	THC (inhaled)	Inhaled cannabis led to heightened heart rate and lowered intraocular and blood pressure in 18 participants with glaucoma, with hypotensive effects becoming evident after 60 to 90 minutes, generally followed by a reduction in intraocular pressure.
Porcella et al, 2001[18]	Decreased intraocular pressure	Interventional study	8 patients with glaucoma	WIN55212-2 (topical)	The synthetic cannabinoid WIN55212-2 decreases IOP in patients with glaucoma who did not respond to conventional therapies at the time of the study.
Tiedeman et al, 1981[19]	Decreased intraocular pressure	Interventional study	16 patients with ocular hypertension	THC derivatives (oral)	Two chemical derivatives of Δ-1-tetrahydrocannabinol were examined, revealing that one compound (BW146Y) exhibited a noteworthy independent reduction in intraocular pressure, while the other compound (BW29Y) did not effectively lower intraocular pressure. Both compounds had mild side effects on patients.
Tomida et al, 2006[20]	Decreased intraocular pressure	Interventional study	6 patients with ocular hypertension or early primary open angle glaucoma	THC, CBD (sublingual)	In a pilot study on the effect of sublingual application of cannabinoids on intraocular pressure, a single 5 mg dose of THC reduced the IOP temporarily and was well tolerated by most patients. Sublingual administration of 20 mg CBD did not reduce IOP, whereas 40 mg CBD produced a transient increase in IOP.
Zhan et al, 2005[23]	Decreased intraocular pressure	Case report	1 patient with glaucoma	Cannabis (inhaled)	Report on a patient who requested compassionate therapy with ten cannabis cigarettes and 1–2 cannabis cookies/day for two decades, with disease stability.

Abbreviations: THC, Δ-9-tetrahydrocannabinol; CBD, cannabidiol; IOP, intraocular pressure.

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Subsequent studies have supported short-term THC IOP-reducing effects, thought to occur through aqueous humor outflow mechanisms and trabecular meshwork cell signaling.[30] In 2018, an animal study indicated that THC lowers IOP by activating CB_1 and GPR18 receptors, whereas CBD was found to potentially interfere with the IOP-related effects of THC[16] (Table 5). Altinsoy et al also investigated cannabinoids' potential counter-benefits in rabbits through the impact of anandamide on endotoxin-induced uveitis.[25] The authors eventually concluded that this endogenous cannabinoid ligand can exacerbate uveitis despite the background IOP-reducing benefit.[25] While THC has been shown to lower IOP, the effects of other cannabinoids (eg, CBD) and endogenous ligands (eg, anandamide) require further investigation.

Synthetic cannabinoids have also been tried in patients with glaucoma who have not achieved adequate IOP control (<22 mmHg) despite being on two or more topical pharmacotherapies, suggesting a potential therapeutic role in refractory cases.[17] Particularly, the synthetic cannabinoid WIN55212-2 was shown to help decrease IOP in the eyes of 8 patients with glaucoma. In 2006, Tomida et al conducted a pilot study administering sublingual CBD or THC and found a short-term reduction in IOP reduction following 5 mg THC, which was well tolerated in patients.[20] No IOP reduction was seen with 20 mg CBD, while short-term increased IOP was demonstrated with 40 mg CBD[20] (Table 5).

Given the limited evidence of long-term efficacy in treating glaucoma,[200–202] cannabinoids are considered ineffective or suboptimal therapeutic options.[203,204] This is because of their short duration of action and the incidence of undesirable psychotropic and systemic side effects.[201,203,204] Similarly, according to the National Academies of Science (NAS) report on the health effects of cannabis and cannabinoids, it was concluded that given the lack of evidence of continual IOP reducing effects, cannabinoids show limited potential in the treatment of glaucoma.[205]

Notably, a study of 18 patients with glaucoma inhaled THC led to increased heart rates and lowered intraocular and blood pressure, with hypotensive effects becoming evident after 60 to 90 minutes of use, generally followed by a reduction in intraocular pressure.[15] Until cannabinoids can be demonstrated to work at least as effectively and with fewer side effects as current glaucoma therapies, cannabis and cannabinoids have yet to be considered a reliable option for treating glaucoma.[203,204] In summary, the long-term efficacy of cannabinoids in disease control have yet to be determined.[201,202,205]

Cannabinoids in the Treatment of Blepharospasms

A childhood genetic idiopathic generalized epilepsy, Jeavons Syndrome (JS), is partially characterized by eyelid myoclonia. Oral CBD oil seemed to exacerbate eyelid myoclonus in two individuals with JS and poorly controlled seizures when trialed at 4 mg thrice daily, or 5–10mg/kg/day.[60] A double-masked randomized control trial using a single dose of 0.03 mg/kg oral nabilone, a cannabinoid receptor agonist, did not demonstrate any significant acute reduction in blepharospasm when compared to placebo[5] (Table 3). Meanwhile, other studies have demonstrated that cannabis and cannabinoids may be a potential medical treatment for patients with blepharospasms who showed no improvement following repeat treatments with conventional, first-line treatment using botulinum toxin injections[3,4,6,8] (Table 3).

Applications in Pendular Nystagmus

A case reported a 30% reduction in nystagmus at the primary position and improved visual acuity after acute smoking 10 mg cannabis in a patient with congenital horizontal nystagmus.[94] Another study reported suppressed pendular nystagmus and improved visual acuity in an individual with multiple sclerosis after smoking cannabis, but not with nabilone tablets or THC- containing capsules (trialed up to 40 mg THC per day).[101]

Limitations and Future Directions

The authors recognize that this review, by focusing on the ocular therapeutic and side effects, may have left unanswered components of cannabis' complex mechanism of action on the eye. We also recognize that less researched cannabinoids, such as cannabigerol, cannabinol, and cannabichromene, as well as terpenes, including myrcene, limonene, and pinene, were also not discussed due to the large breadth of the topics. Cannabis and cannabinoid molecular targets, active components, and functions in the eye should continue to be explored.

Future studies should consider exploring the following research areas to address current gaps in the scientific literature:

(1) What is the role of CB2 receptors in ocular tissues, particularly regarding their anti-inflammatory properties, and how might they influence therapeutic outcomes for inflammatory eye diseases? Future animal studies should aim to clarify the functions and potential benefits of CB2 receptor activation in the eye.
(2) What are the efficacy and safety profiles of cannabinoids as a second-line treatment for BEB in patients unresponsive to botulinum toxin injections? This could be assessed through studies with larger sample sizes and evaluations of optimal formulations and delivery methods, such as sublingual suspensions of CBD and THC products.
(3) Given conflicting findings regarding the role of cannabinoids in DED treatment, is there a role for cannabinoids in the treatment algorithm for patients with DED? Observational and controlled experimental studies could help determine the effectiveness and safety of cannabinoids in this context.
(4) Can cannabinoids effectively suppress pendular nystagmus in multiple sclerosis patients, as suggested by case studies following cannabis inhalation? Primary studies may consider investigating this effect further, focusing on optimal routes of administration and timing for symptom relief.

Conclusions

Cannabinoids are not currently considered a first-line treatment option for any ocular conditions. Cannabinoids may cause eyelid tremors and ptosis, while paradoxically demonstrating therapeutic potential as a second-line agent for treatment-refractory blepharospasm. Several animal studies have demonstrated cannabinoids' anti-inflammatory and regenerative effects on the cornea. Meanwhile, dry eye symptoms are a common side-effect of cannabis use. Cannabinoid retinal neuroprotective effects have only been demonstrated in animal studies. Neuro-retinal dysfunction has been substantiated in cannabis smokers, with evidence of partial reversibility with cannabis smoking cessation. Case reports have alluded to retinal vasculature abnormalities with heavy cannabis smoking. Cannabis and cannabinoids may decrease intraocular pressure in the short-term. There is insufficient evidence to support the use of cannabis and cannabinoids in glaucoma treatment given the absence of long-term therapeutic benefit, neurocognitive and systemic side-effects, and the present availability of more effective therapies. Studies have documented that cannabis and cannabinoids disrupt extraocular motility, including smooth pursuit, gaze stabilization, ocular motor control, fixation time, and eye deviation. Case reports demonstrate suppressed pendular nystagmus following smoking cannabis in individuals with multiple sclerosis.

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