JCRS ASCRS ESCRS
JOURNAL OF CATARACT & REFRACTIVE SURGERY
Volume 49 Issue 11 November 2023

REVIEW/UPDATE

# Topical analgesics for acute corneal pain: current options and emerging therapeutics

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Acute corneal pain is a common complaint that causes significant distress to patients and continues to challenge therapeutic avenues for pain management. Current topical treatment options have marked limitations in terms of both efficacy and safety, thus often prompting the adjunctive use of systemic analgesics, including opioids. In general, there have not been extensive advancements in pharmacologic options for the management of corneal pain over the past several decades. Despite this, multiple promising therapeutic avenues exist which hold the potential to transform the ocular pain landscape, including druggable targets within the endocannabinoid system. This review will summarize the current evidence base for topical nonsteroidal anti-inflammatory drugs, anticholinergic agents, and anesthetics before focusing on several potential avenues in the setting of acute corneal pain management, including autologous tear serum, topical opioids and endocannabinoid system modulators.

*J Cataract Refract Surg 2023; 49:1160–1167* 

Acute corneal pain represents a complex and debilitating nociceptive state commonly arising from disruption of the ocular surface, such as from acute trauma, surgery, or infection.[1] Despite its high prevalence, acute corneal pain continues to present challenges in effective pain management. In large part, our inability to overcome said challenges stems from limitations with the efficacy and safety of currently available topical and systemic agents. Compounding this problem is a defined lack of progress in both the development of new agents and the improvement of existing agents.

Mechanistically, corneal pain begins with the release of inflammatory mediators subsequent to corneal trauma.[2] These mediators lower the action potential firing threshold of corneal nociceptors, and pain signals are subsequently transmitted to higher centers by polymodal nociceptors (Ad and C fibers) by the ophthalmic division of the trigeminal nerve.[3] A failure of inflammation to resolve, and of wound healing to progress by anti-inflammatory processes and epithelial/stromal regeneration and remodeling, leads to the propagation of pain transmission and can precipitate fibrosis, the abnormal regrowth of neurons, and the development of neuropathic pain.[4] Neuropathic pain involves peripheral and/or central neuronal damage and sensitization, leading to the generation of pain from nonpainful stimuli (allodynia) and/or exaggerated pain after a painful stimulus (hyperalgesia).[5] Where nociceptive pain generally stems from direct damage to tissues and inflammation and is transient in nature, neuropathic pain is generally chronic (Figure 1).[1,6]

This review will provide an update on the safety and efficacy of currently available and emerging topical ocular therapeutics for acute pain management after common corneal surgical procedures and corneal abrasions. Broadly, the healing and pain time course for corneal epithelial disruption can range from days to beyond a week, depending on various factors including the extent of the corneal surface affected. Whereas most corneal abrasions will heal within 2 to 3 days, complications such as infection or development of a corneal ulcer can significantly delay resolution. Two common corneal surgeries, photorefractive keratectomy (PRK) and epithelium-off (epi-off) corneal crosslinking (CXL), can result in moderate-to-severe pain for a 3 to 5-day period, with peak pain between 24 hours and 36 hours.7 Epi-off CXL is a U.S. Food and Drug Administration (FDA)-approved treatment used to prevent progression of disease processes involving corneal ectasia (eg, keratoconus, post–laser-assisted in situ keratomileusis [LASIK], pellucid marginal degeneration).8 After PRK/CXL, patients often describe a burning, tearing, and foreign-body sensation. Whereas PRK may have some specific advantages over LASIK, PRK is associated with higher pain levels and slower recovery, making it the less commonly performed procedure in the United States.[9]

Notably, achieving adequate ocular analgesia is important not only in the management of acute pain but also for longterm clinical outcomes—where it functions to decrease the risk of subsequent development of a chronic ocular pain state.[10] Data regarding the incidence and prevalence of chronic ocular pain are variable and limited for

Submitted: October 14, 2022 | Final revision submitted: May 17, 2023 | Accepted: May 18, 2023

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M.E.M. Kelly acknowledges funding from the Canadian Institutes of Health Research (PJT-166150).

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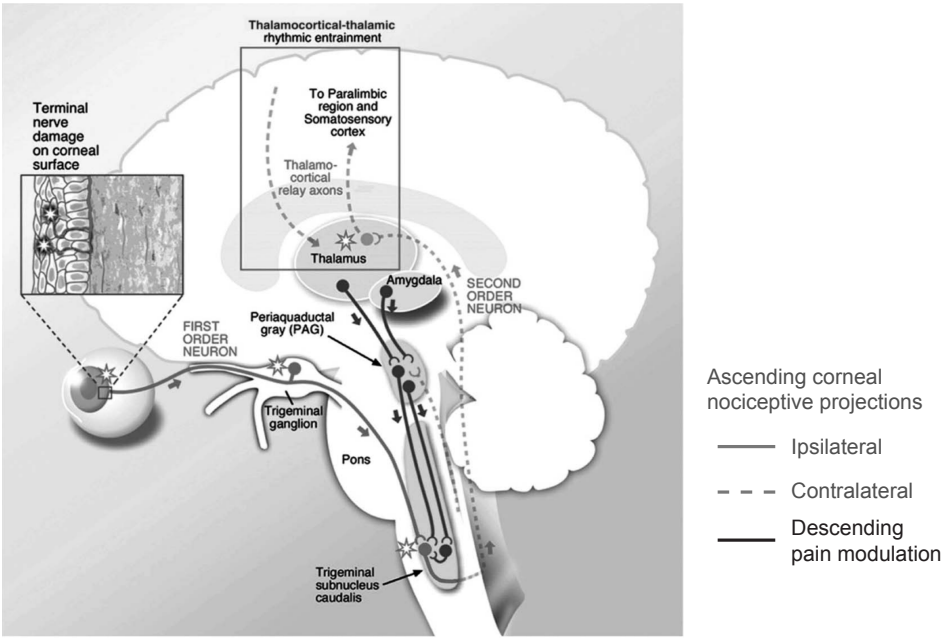


**Figure 1.** Simplified schematic of ocular sensory pathways conveying nociceptive signal from the cornea to the central nervous system. Corneal disruption/damage stimulates nerve endings of trigeminal neurons (sensory first-order neurons, ipsilateral; solid red line), with cell bodies located in the trigeminal ganglion. Nociceptive signals propagate to the brain stem where first-order neurons synapse with second-order neurons, which then decussate to the contralateral thalamus (contralateral; dashed line). From the thalamus, third-order neurons travel to supraspinal centers, including the somatosensory cortex, where pain is perceived. Descending pain modulation pathways are also depicted (blue lines). Figure used with permission from Galor.[6]

specific settings (such as postoperative), in part on account of diagnostic overlap with dry-eye disease (DED).[11,12] To our knowledge, no cases of chronic pain after CXL have been reported in the literature.[13]

Despite the range of available topical ocular and systemic analgesics, no one strategy is sufficient to control acute corneal pain across all clinical settings (Figure 2). In addition to addressing the limitations of these drugs, several repurposed and new topical ocular therapies will be discussed, including autologous tear serums, opioid system modulators, and endocannabinoid system (ECS) modulators.

## TOPICAL NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly studied and used topical analgesics for acute corneal pain, among other inflammatory and nociceptive ocular conditions. These agents are welltolerated and exert anti-inflammatory actions through the inhibition of cyclooxygenase-1 and 2 enzymes at the ocular surface, leading to decreased production of inflammatory and pronociceptive mediators.

Evidence for the use of NSAIDs in the management of corneal pain is derived from a small body of randomized trials. Systematic reviews by Thiel et al. and Yu et al. evaluated 10 and 33 clinical trials, respectively, concluding that NSAIDs were more efficacious than either local anesthetics or cycloplegics alone in the control of pain after corneal abrasions.[14,15] Within the NSAIDs used for ocular indications, studies yield variable results for analgesic efficacy, with some studies reporting that nepafenac had improved therapeutic outcomes as compared with ketorolac.[16] Other studies report equal analgesic efficacy between topical NSAID agents in the management of postoperative pain.[17–19] For example, topical diclofenac and ketorolac had equal analgesic efficacy when evaluated at 24 and 72 hours after PRK.[19] Interestingly, when topical ketorolac was compared with oral naproxen sodium (220 mg), both administered every 12 hours for 72 hours, the topical NSAID was associated with a superior analgesic effect.20 Ketorolac (0.45%) is also effective at reducing post-PRK pain as assessed immediately postoperatively and on postoperative day 3 when applied as a soaked bandage contact lens.21 In the setting of CXL, two NSAIDs (diclofenac and ketorolac) administered 30 minutes preoperatively provided comparable analgesia at 36 hours postoperatively.[22]

At the same time, recent systematic reviews using more stringent pain indices for study inclusion and analysis have failed to identify analgesic efficacy with NSAID use. For example, a 2017 Cochrane review by Wakai et al. evaluated the analgesic efficacy of NSAIDs for corneal abrasion, with a primary outcome to assess whether the reduction in pain intensity was equal to or greater than 30% or 50%—where these thresholds represent a clinically relevant reduction in pain experience.[23,24] Of nine studies which met inclusion criteria, no significant analgesic effects of topical NSAIDs were identified, as measured using 30%/50% thresholds.[23] A decrease in the use of rescue oral analgesics in patients treated with topical NSAIDs was, however, observed and is consistent with previously reported findings.[14,15,23]

Most randomized controlled trials to date have not reported significant adverse effects from the use of topical NSAIDs in the setting of corneal abrasion and PRK/CXL.[16,25–29] Although generally welltolerated, there are documented safety considerations with the use of topical NSAIDs, including corneal haze, infiltrates, corneal melt, and delays in reepithelization of the cornea.[18,30] Corneal melt, in particular, is a serious complication and has been described after topical NSAID use in numerous case reports.[31,32] The emerging evidence indicates that the risk of corneal melt is associated with frequent dosing intervals and/or prolonged use.[31,32] For chronic corneal pain, patients may benefit from treatment with topical NSAIDs when pain arises, in part, from ongoing inflammation—while acknowledging that their side-effect profile may limit long-term use.

## TOPICAL ANESTHETICS

Topical anesthetics induce a transient blockade of sodium channels, which reduces pain transmission from the target tissue. Although efficacious for pain originating from the corneal surface, many experts suggest that the use of topical anesthetics should be limited to a controlled clinical setting because of their potential to delay corneal epithelial growth and to induce corneal ulceration, toxic keratopathy, and corneal melt.[33] This long-standing dogma has been chalenged by

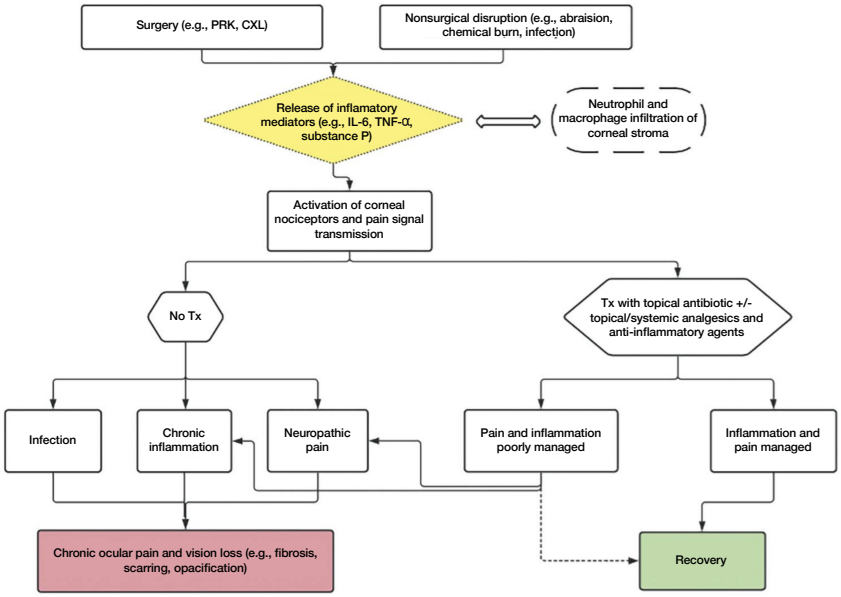


**Figure 2.** SInflammatory and nociceptive cascade after surgical or nonsurgical disruption of the cornea. Flowchart depicts recovery outcomes and potential complications (infection, chronic inflammation, neuropathic pain, vision loss, etc.) arising when the condition is either adequately treated (with analgesic + antibiotic + anti-inflammatory) or undertreated. CXL = corneal cross-linking; IL-6 = interleukin 6; TNF-a = tumor necrosis factor a; Tx = treatment

the literature which suggests that the short-term use of lower concentration topical anesthetics may be safe and efficacious for outpatient pain management after PRK or corneal abrasion.[34] Specifically, in the setting of corneal abrasion, short-term use of lower concentration tetracaine (0.5% every 30 minutes for 24 hours; as compared with placebo) was found to reduce ocular pain on a visual analog scale at 24 and 48 hours after corneal abrasion.[34] Similarly, after PRK, a higher concentration of tetracaine, also used for a short term (1% every 30 minutes for 24 hours), reduced ocular pain 10 hours postoperatively.[35] Overall, there is limited evidence to support topical anesthetic efficacy for ongoing pain management, including for managing chronic ocular pain.[14,15,36,37]

Evidence underlying claims of safety concerns from on-going administration of topical anesthetics primarily stems from isolated case reports, case series, and animal studies.[33,38–42] Some case reports detail patients having acquired the anesthetic independently (eg, through online sources) before applying them over a prolonged period (2+ weeks) without awareness of the potential negative effects.[39,40,42] This prolonged use resulted in keratitis, endothelial toxicity, and epithelial defects, which led to severe keratopathy necessitating corneal transplant.[39,40,42,43] Even at lower concentrations, long-term use of topical anesthetics has been reported to result in punctate keratitis, epithelial defects, and peripheral infiltrates.[44] In reviews assessing the toxicity of topical anesthetics, there is a consensus that although safety is excellent in a controlled clinical setting, the potential for outsourcing and misuse of topical anesthetics in an outpatient setting remains a major concern.[33,41]

Specifically, regarding adverse effects after topical anesthetic use in the setting of corneal abrasion or PRK, there was one study identified in the current review that reported delayed wound healing 24 hours after administration of 1% tetracaine (every 30 minutes for 24 hours) after corneal abrasion.[45] This study used multiple measures of safety including assessment of corneal topography and measurement of epithelial wound closure using a high-resolution imaging system. Similar studies primarily relied on only 1 measure of safety, most commonly the qualitative assessment of fluorescein uptake, and many did not specify how safety was determined.[34,35] Overall, the safety concerns for topical anesthetics significantly limit clinical utility.[15,33,41]

## TOPICAL ANTICHOLINERGICS: CYCLOPLEGICS

Cycloplegics paralyze muscles of the ciliary body and the pupillary sphincter via blockade of muscarinic acetylcholine receptors. This action relieves pain and photophobia which result from muscle spasm secondary to ocular inflammation. Mydriasis from anticholinergics also acts as a prophylactic for the development of synechiae in conditions involving ocular inflammation.

While cycloplegics are recommended in the setting of abrasion and uveitis, their potential role after refractive surgery remains unclear. Current evidence indicates that homatropine and cyclopentolate do provide some degree of analgesia for acute corneal pain after PRK and CXL.14,46,47 Specifically, homatropine (4 times a day) significantly reduced pain scores at 24 hours and 48 hours after PRK as compared with placebo.47 Cyclopentolate (3 times a day) was similarly reported to significantly decrease pain scores after PRK and CXL.46 A reduction in pain was not observed in the setting of corneal abrasion, using homatropine every 6 hours for 18 hours or homatropine applied once at initial examination of the abrasion.48,49 It is likely that, in part, this finding reflects the lower degree to which inflammatory-driven pain occurs after mild-to-moderate corneal abrasions, where higher levels of inflammation are likely to occur with PRK and CXL procedures. It is also worth noting that homatropine was not as effective as topical NSAIDs in the setting of corneal abrasion and PRK.49,50 The potential therapeutic role of cycloplegics in the setting of either PRK/CXL or significant corneal abrasion is likely as an adjunctive agent, rather than as a monotherapy.

Most studies on cycloplegics have not assessed measures of safety; however, when assessed, no adverse effects were noted at the level of the ocular surface.46,48–50 Expected side effects with the use of cycloplegics include transient blurred vision and photophobia due to loss of accommodation and mydriasis, respectively.46 Regarding chronic ocular pain, the use of cycloplegics is not mechanistically supported in the setting of neuropathic ocular pain and there is a lack of studies examining their use in this setting. There may, however, be some benefit to their use when chronic ocular pain involves ongoing inflammation that triggers ciliary spasm.

## EMERGING AND NEW THERAPEUTICS

Various lines of research present an opportunity to use topical-only

regimens in the management of corneal pain, of varying severity and etiology. We are presenting the current evidence on select agents that demonstrate a potential for clinical application in the setting of acute corneal pain. Although outside the scope of this review, it is important to acknowledge significant advances in ocular drug

delivery. For topical applications, goals include increasing both ocular surface residency time and corneal drug permeation, while minimizing the drug's side/adverse effect profile.[51] It is also important to note the potential for nonpharmacological approaches to managing postsurgical pain. For example, application of a cold pack to the eye for 24 hours after PRK was associated with decreased pain scores at 8 hours, 16 hours, and 24 hours, in addition to decrease in use of pain medication.[52] It should be noted that application of cold packs is associated with ocular physiologic changes, which, in particular, may adversely affect certain patient populations (eg, angle-closure glaucoma).[53]

## Autologous Serum Tears and Human Nerve Growth Factor

Autologous serum (AS) tears are derived from a patient's serum and possess bactericidal, analgesic, and wound healing actions—driven by a range of growth factors and other mediators. For example, AS tears contain epidermal growth factor, nerve growth factor, fibronectin, and vitamin A— which contribute to neuronal regrowth and promote epithelial proliferation, migration, and adhesion in the cornea.[54,55]

To date, AS tears have primarily been trialed in patients with chronic ocular pain associated with persistent epithelial defects, recurrent epithelial erosions, and superior limbic keratitis.[56–58] AS tears are also commonly used in the treatment of DED—a multifactorial ocular surface condition characterized by ocular surface inflammation and tear film instability.[59] Treatment with AS tears (every 4-6 hours for 23 months) was shown to reduce punctate epithelial erosions, persistent epithelial defects, and subjective sensations of ocular irritation for DED secondary to systemic autoimmune disease.60 Despite demonstrating promise for DED, a recent meta-analysis concluded that it was not yet possible to make definitive conclusions regarding the efficacy of AS tears in this setting.[61]

Despite an overall paucity of evidence, AS tears have been shown to reduce acute ocular pain after both CXL and PRK procedures.[62,63] After CXL, treatment with AS tears (4 times a day for 7 days) was associated with decreased pain levels on postoperative days 1 and 2, in addition to reducing the average epithelial closure time—indicative of improved corneal wound healing.[62] After PRK, AS tears (every 3.5 hours for 2.2 days) similarly increased epithelial healing rates, and patients reported cessation of ocular pain 0.8 days earlier than those in the control groups.[63]

In addition to providing analgesia and supporting epithelial wound healing, AS tears have been found to improve corneal neuron growth. Specifically, nerve growth factor in AS tears may play a key role in resprouting and restoration of function in injured neurons.[55] This may have treatment implications for patients with neuropathic corneal pain. For example, treatment with AS tears decreased pain in a study of patients with severe neuropathic pain, where over half of the cohort had developed this condition after LASIK or PRK.[64] In the acute corneal pain setting, AS tears may play a role in postsurgical healing and pain management, including as a prophylactic therapy aimed at preventing the development of chronic neuropathic pain.

One of the main challenges surrounding the use of AS tears is the lack of accessibility, including high cost and the lack of insurance coverage, in addition to limited suppliers—arising, in part, from the fact that AS tears have not yet gained approval by the FDA. There is also a lack of standardized production procedures and guidelines for treatment.[61] Overall, the complex biochemical makeup of AS tears merits further study to both optimize efficacy and safety, as well as to expand our understanding of the potential mechanisms through which AS tears mediate ocular surface healing and analgesia.

An isolated recombinant human nerve growth factor product (cenegermin; Oxervate) was approved in the United States in 2018 for the treatment of neurotrophic keratitis. Despite evidence from clinical trials supporting efficacy in corneal wound healing, analgesic efficacy has not been assessed and pain was a commonly reported (16%) side effect through the standard 2-month course of treatment.[65,66] Notably, this agent is one of the most expensive prescription drugs currently available on the US market, which may pose a significant access barrier for patients.

## Topical Ocular Opioid Receptor Modulators

Opioid ligands are key agents in the management of moderate to severe pain of various etiologies, despite their wellrecognized side effects and risk of tolerance and dependence with long-term use.[67] The analgesic effects of endogenous opioids (ie, endorphins, enkephalins, and dynorphins) or exogenous ligands (eg, morphine, hydromorphone, fentanyl) are mediated through the activation of G-protein–coupled opioid receptors (m, k, d), expressed in the central nervous system (CNS) and peripheral tissues, including the eye.[68] The activation of opioid receptors leads to the suppression of excitatory neurotransmitter release (substance P, norepinephrine) with subsequent inhibition of signal transduction in nociceptive pathways. In the periphery, this action is amplified under inflammatory conditions through the upregulation of opioid receptors and through increased production of opioid peptides by infiltrating immune cells.[69,70]

Topical ocular use of opioids for pain is limited, although the existing evidence supports their use. For example, Faktorovich and Basbaum reported that post-PRK administration of topical ocular morphine (0.5% every 2 hours on the first day and 4 times a day for 3 days thereafter) reduced average and maximum pain scores across the recovery period.[71] This regimen did not appear to significantly affect wound healing or have significant side effects based on daily assessment until day 4 and monthly assessments up to 3 months postoperatively.[71] Another study assessed the analgesic effect of topical 1% nalbuphine (every 2 hours on the day of PRK then 4 times a day for 1-4 days), a k-opioid receptor agonist and m-receptor partial agonist/antagonist, against a topical NSAID (0.1% nepafenac; every 2 hours on the day of PRK then 4 times a day for 1-4 days) administered to the contralateral eye.[72] Nalbuphine displayed comparable analgesic efficacy with nepafenac and was associated with an increased rate of epithelial healing.[72] Notably, topical opioids have not been assessed in the setting of chronic ocular pain. Although the use of systemic opioids after ocular surgery (ie, PRK and epi-off CXL) is common, their efficacy is rarely evaluated as the primary outcome in the relevant literature.[73,74]

In summary, the use of topical opioids merits further exploration. Nonetheless, topical delivery of opioids offers another avenue to manage corneal pain. Topical ocular administration of opioids minimizes the risk of centrally mediated side effects and notably is not associated with receptor desensitization and tolerance, as is observed with systemic use.[70] Topical opioids do, however, face potential access barriers because of their controlled drug status, as well as the potential for misuse—in particular stemming from their liquid formula-

tion.[75–77] This being said, the use of biased opioid agonists (ie, agents that activate specific signaling pathways as compared with other ligands at the same receptor, or the same receptor type in different tissues), modulators of endogenous opioid peptides (ie, degradative enzymes inhibitors), and peripherally restricted agents (ie, which fail to effectively enter the CNS) stands to improve both the safety of and opioid-induced analgesia from topical opioid receptor agonists.[78]

## ECS Modulators

Analogous to the opioid system, the ECS is a ubiquitous endogenous signaling system which holds considerable therapeutic potential, in particular for ocular disease in terms of antinociceptive, anti-inflammatory, neuroprotective, and intraocular pressure-modulating actions.[79,80] A range of potential therapeutic benefits of ECS modulation have been observed in the setting of neurodegenerative states, inflammatory-driven diseases, epilepsy, and cancer, among others.[81–83] On top of its actions in pain signaling, the ECS is believed to play a pivotal role in the regulation of tissue repair and fibrosis, both of which are of particular interest for the management of acute corneal pain and wound healing.[84]

Components of the ECS have been identified in nearly all tissues of the body, the cornea being no exception (Figure 3).[85] Along with respective synthetic and degrative enzymes, a primary receptor of the ECS, cannabinoid 1 receptor (CB1R), has been identified in the corneal epithelium stroma, and endothelium—where it acts to regulate pain transmission.[86,87] The cannabinoid 2 receptor (CB2R), on the other hand, is primarily localized to the surface of immune cells, and activation of this receptor leads to anti-inflammatory actions.[88,89]

The ECS has been explored in animal models of uveitis, proliferative vitreoretinopathy, uveoretinitis, and corneal wound healing, with results supporting the potential for therapeutic use.[88,90,91] For example, in the setting of aseptic endotoxin-induced uveitis in rats, treatment with a single topical dose of a CB2R-selective agonist (HU308) led to a decrease in several parameters of inflammation at 6 hours, including levels of leukocyte-endothelial adherence within vessels in the iris, and inflammatory mediator levels in anterior ocular tissue.[91] A single dose of a topical NSAID (nepafenac) or of a topical corticosteroid (dexamethasone or prednisolone) also did not have an effect, with the exception of reduced levels of one cytokine after prednisolone administration.[91] Activation of CB2R (via HU308) and CB1R (via $D^8$-tetrahydrocannabinol) in a corneal burn model in mice both resulted in anti-inflammatory and antinociceptive actions.[88] Although not yet explored in an ocular setting, activation of CB2R has been shown to improve wound healing and reduce fibrotic signaling in a variety of experimental models including dermal fibrosis, skin wound healing, and systemic sclerosis.[92–94]

Psychoactive effects associated with ECS modulators (eg, inability to concentrate, fatigue, memory loss, etc.) are related to CB1R activation in the CNS. As such, agents that selectively activate CB2R are not associated with these effects.[95] At the same time, because of the potential for CB1R activation as a treatment strategy for corneal pain and inflammation, the potential for systemic absorption should be considered when designing ocular therapeutics. Peripherally restricted CB1R modulators can be used to prevent central effects, as these agents are either poorly or not able to cross the blood-brain barrier because of their chemical properties.[96] This strategy reduces levels of neuropathic pain in preclinical models.[97] Tachyphylaxis is another consideration with the use of CB1R agonists, which has led to the investigation of new modulatory approaches including use of allosteric modulators, which increase or decrease binding affinity and/or efficacy of orthosteric agonists, and enzyme inhibitors.[98]

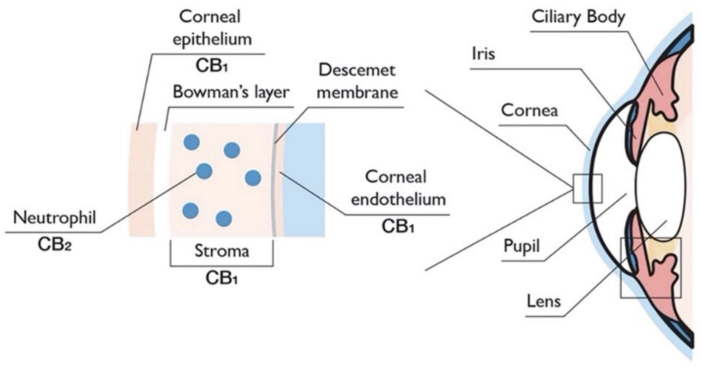


**Figure 3.** ECS localization shown in an anatomical schematic of the cornea. The 5 layers composing the cornea (anterior to posterior): epithelium, Bowman's layer, stroma, Descemet membrane, and endothelium. CB1R has been identified in the stroma, corneal endothelium, and epithelium, and CB2R is present on the surface of neutrophils that infiltrate the stroma during acute inflammation.87–89,108 CB1R = cannabinoid 1 receptor; CB2R = cannabinoid 2 receptor; ECS = endocannabinoid system

For clinical benefit, allosteric modulators have the ability to prolong receptor activation by orthosteric agonists, without contributing to receptor desensitization and downregulation.[99] For example, Thapa et al. provided new evidence in the cornea to suggest that a CB1R allosteric ligand can potentiate the antinociceptive and anti-inflammatory effects of a subthreshold dose of the orthosteric CB1R agonist, D8-tetrahydrocannabinol, in an acute model of chemical corneal injury.100 Another important avenue for ECS modulation involves the use of enzyme inhibitors. These agents lead to increased levels of endocannabinoids through inhibition of the action of enzymes which degrade them, with subsequent increases in levels of receptor signaling. Similar to allosteric modulators, the use of enzyme inhibitors, in part, has site-specific effects because

of increased endocannabinoid synthesis in tissues with active inflammation and tissue injury.[101] Specifically, inhibitors of the enzyme fatty acid amide hydrolase (FAAH) will lead to increased levels of the endocannabinoid anandamide. Similarly, inhibitors of monoacylglycerol lipase (MAGL) will lead to increased levels of the endocannabinoid 2-arachidonoylglycerol. Treatment with FAAH inhibitors has several beneficial effects in the setting of ocular pain and inflammation, including antinociceptive, analgesic, and neuroprotective actions in various preclinical models.[102,103] MAGL and dual MAGL/FAAH inhibitors have also demonstrated beneficial effects in various pain models.[104,105] Based on available evidence, it stands to reason that this therapeutic approach holds potential for acute corneal pain.

Although topical ECS modulators have yet to be assessed in the setting of chronic ocular pain, the ECS has been identified as an important potential target in the setting of neuropathic pain.[106] Mechanistically, the well-described anti-inflammatory actions of ECS modulators stand to decrease the risk of progression to a state of ocular neuronal sensitization and chronic pain when used in an acute setting, such as postoperatively. These agents could further present a safer option, as compared with steroids and NSAIDs, for the ongoing management of chronic ocular pain conditions which involve a component of inflammatory pain. The neuroprotective actions of ECS modulators further support their potential use in the setting of neuropathic pain.[80,107]

## CONCLUSION

The anatomical accessibility of the cornea presents a unique opportunity to target pain using topical modalities. Currently, available single-agent and multimodal topical approaches in the management of corneal pain and inflammation often fail to provide sufficient analgesia. As such, the use of systemic agents is frequently necessitated and remains part of the standard of care after certain corneal surgeries. Even when topical strategies fail to control pain, their use alongside systemic strategies can impart increased analgesic efficacy. Furthermore, this multiroute approach confers increased safety through lowering required dosages of systemic analgesics. The use of topical NSAIDs is supported in various clinical settings which require analgesic and anti-inflammatory actions, although safety considerations do exist. Cycloplegics may be underutilized in the postoperative realm and, despite potential for systemic anticholinergic effects, have some evidence for efficacy where pain stems from muscular spasm. Local anesthetics produce shortlived yet efficacious analgesia for pain originating from the ocular surface and are generally safe when used in the short term. Notwithstanding the treatment gap with topical agents, there have not been major advances over the past several decades in new therapeutics for acute ocular pain. Exciting lines of research in terms of topical agents for acute ocular pain include autologous serum tears, opioid modulators, and ECS modulators. Exploring new therapeutic targets while harnessing various advances in ocular drug delivery technology may have the potential to yield topical-only treatment regimens that address the sequelae of ocular trauma and surgery, including fibrosis and chronic corneal pain.


## Acknowledgments

The authors thank Laura F. Scheyer for her assistance with the graphic design of figures included in this review.


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**Disclosures:** *M.E.M. Kelly is the Chief Scientific Officer (Consultant) of Tetra Bio Pharma Inc. and is an inventor on patent WO2015/074137. J.D. Lafreniere is a Scientific Writer (Consultant) for Tetra Bio Pharma Inc. None of the other authors has any financial or proprietary interest in any material or method mentioned.*

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