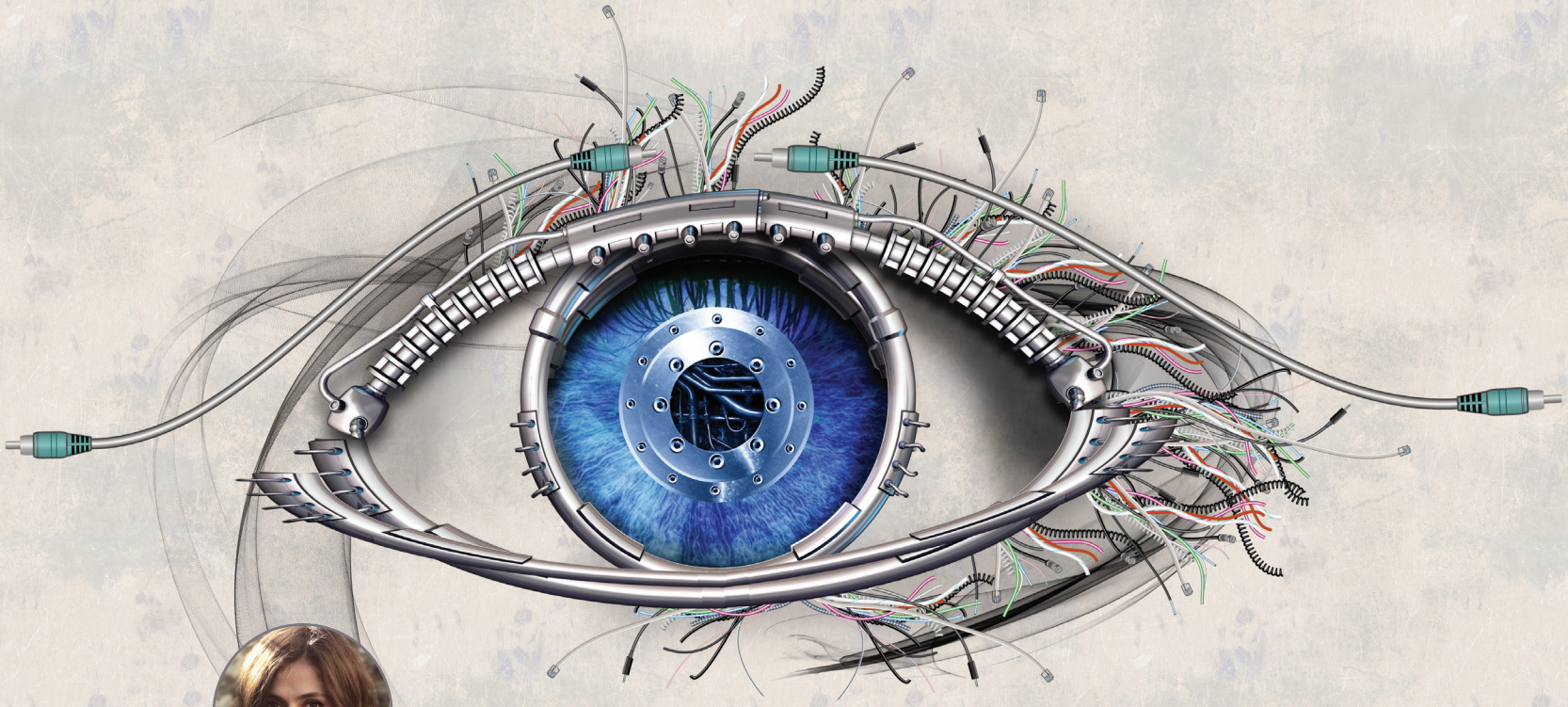

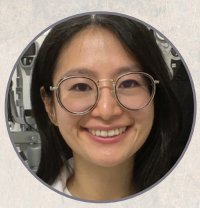

# NERVE-RELATED CORNEAL PAIN

## Understanding mechanisms, diagnosis, and treatment strategies.

BY NESLIHAN DILRUBA KOSEOGLU, MD; ISABELA YANG, MD; AND PEDRAM HAMRAH, MD

Neuropathic corneal pain (NCP)—a subtype of neuropathic pain—is relatively recently recognized, poorly defined, and underinvestigated, yet it can substantially affect patients' quality of life (QOL). This article summarizes current knowledge of the underlying mechanisms, clinical presentation, diagnostic approaches, treatment options, and perioperative management strategies for NCP.

### UNDERSTANDING NCP

Neuropathic pain, as defined by the International Association for the Study of Pain, is "pain caused by a lesion or disease of the somatosensory nervous system."[1,2] NCP refers to chronic corneal pain experienced by patients in response to nonnoxious stimuli.

The cornea, the most densely innervated tissue in the body, is supplied primarily by sensory nerves from the ophthalmic branch of the trigeminal nerve via the long ciliary nerves.[3-5] These sensory nerves transmit mechanical, chemical, and thermal stimuli to the brain, triggering pain perception and defense mechanisms, such as the blink reflex.[5,6] In patients with NCP, these nerves become sensitized owing to nerve damage and chronic inflammation, a phenomenon known as *peripheral sensitization*.[7] Peripheral sensitization decreases the pain threshold, heightens responses to stimuli, and leads to chronic spontaneous pain perception.[8] Chronic peripheral sensitization can progress to central sensitization, which is characterized by hypersensitivity of the central nervous system, resulting in pain perception disconnected from peripheral stimuli.[7-9]

NCP can arise from local insults to the eye that mediate nerve damage[4,10-12] or as a manifestation of systemic pathologies affecting sensory pathways.[13,14] The most common ocular conditions associated with NCP include dry eye disease (DED)[12,15] and postoperative states, such as after refractive or cataract surgery.[16-18] Other ocular pathologies linked to NCP include herpetic

keratitis,[19,20] infectious keratitis,[4] trauma,[12] and radiation keratopathy, among others.[4]

A number of chronic systemic conditions, such as small fiber neuropathy (eg, due to inflammatory, autoimmune, dysimmune, and metabolic causes),[12] headaches,[23] trigeminal neuralgia,[10] and fibromyalgia,[24] have been associated with NCP.[21,22] Mental health issues, including depression,[25] posttraumatic stress disorder,[25] and anxiety,[15] as well as inflammatory and autoimmune conditions, such as Sjögren syndrome[26] celiac disease,[7] systemic lupus erythematosus,[27] sarcoidosis,[28] and inflammatory bowel disease,[29] have also been linked to NCP.

## CLINICAL PRESENTATION AND DIAGNOSIS

Patients with NCP may present with a wide range of symptoms, including pain,[16] discomfort,[30] photoallodynia,[31] burning,[30] irritation,[11] and severe dryness.[11] Diagnosis can be challenging due to a lack of clear slit-lamp examination findings that correspond to the intensity of symptoms. Moreover, overlap with other ocular surface diseases (OSDs), including DED, can lead to underdiagnosis and misdiagnosis.[32]

### Symptom Assessment and Questionnaires

Traditional dry eye questionnaires cannot differentiate DED from NCP,[33-35] but specialized questionnaires have been developed to assess ocular pain.

*Ocular Pain Assessment Survey.* This validated 27-question survey evaluates eye pain intensity over 24 hours and 2 weeks, nonocular facial pain, QOL, aggravating factors, associated symptoms, and symptom relief.[36]

*Neuropathic Pain Symptom Inventory-Eye questionnaire.* Adapted from the Neuropathic Pain Symptom Inventory, this 12-question survey assesses neuropathic-like eye pain severity and characteristics.[37,38]

### Clinical History and Examination

A thorough systemic and ocular history is essential to identify predisposing factors. Coupled with detailed ocular examinations, the history helps rule out nociceptive and inflammatory causes of pain.[3] Routine testing includes a Schirmer test, corneal fluorescein staining, conjunctival lissamine green staining, and tear breakup time.

Although ocular findings in NCP may be disproportionate to the patients' symptoms, DED signs can further complicate diagnosis because nociceptive and neuropathic pain may be present concurrently.[4]

### Functional Sensory Testing

Functional sensory testing can distinguish between peripheral and centralized ocular pain. A commonly employed method involves the instillation of a topical anesthetic drop (eg, 0.5% proparacaine hydrochloride).[7] Patients rate their discomfort on the visual analogue scale (0–10) before and 90 seconds after instillation:

- Centralized pain (minimal or no improvement);
- Peripheral pain (total pain alleviation); or
- Mixed pain (partial relief).

This step is essential for identifying the pain origin and guiding treatment selection.[7,39]

Corneal sensation testing can provide additional information, though the strategy is more valuable for diagnosing neurotrophic keratopathy than NCP. The DEWS II report recognized neurosensory abnormalities as a DED etiology.[32] Galor et al found that increased corneal sensitivity correlated with ocular symptoms in DED patients.[40] Additionally, fibromyalgia patients without ocular disease exhibited increased corneal sensitivity and DED-like symptoms.[41] Emerging technologies, such as noncontact esthesiometry (Brill Engines), may help measure hypersensitivity in NCP. Although increased sensitivity may coexist with ocular discomfort and pain, further validation studies are required to evaluate the applicability and diagnostic value of these tests in patients with NCP.

### Imaging of Corneal Nerves

An evaluation of corneal nerve structure is essential, particularly for patients with pure peripheral pain. In vivo confocal microscopy (IVCM), a high-resolution imaging modality, allows real-time visualization of corneal nerves with 800x magnification.[5] Common findings in NCP include decreased nerve density,[42] increased tortuosity,[43] and beading.[44] Although these features are also seen in DED,[45-47] a recent study by Moein et al identified corneal microneuromas (MNs) in patients with NCP, but not DED, suggesting MNs could serve as objective markers for NCP.[44] Further studies have shown that MNs can coexist with DED signs, potentially contributing to discomfort.[48,49]

A clinical trial funded by the National Institutes of Health is underway to validate MNs, identified via IVCM, as a diagnostic biomarker for NCP.[50] The US FDA recently accepted MNs as a diagnostic criterion for distinguishing NCP from DED in a randomized, placebo-controlled clinical trial (ClinicalTrials.gov ID: NCT06637527). Emerging research on tear proteomics and genomics also aims to identify associations with pain pathways, paving the way for future therapeutic development.[42,51]

## MULTIMODAL TREATMENT APPROACHES

Currently, no US FDA-approved treatment exists for NCP. Management focuses primarily on ocular surface homeostasis, antiinflammatory and neuroregenerative therapies, and local or systemic neuromodulation.[52]

### Topical Therapies

Topical therapies serve as first-line treatment for patients with

peripheral and mixed NCP. Ocular surface restoration by improving the quality and quantity of the tear film can provide short-term relief of symptoms, prevent further damage, and address coexisting DED.[7]

### Antiinflammatory Therapies

Antiinflammatory therapies are critical for alleviating ocular surface inflammation, which contributes to neuronal sensitization. Treatment options include the following:

- Topical steroids with low-preservative formulations such as 0.5% loteprednol etabonate gel or 0.38% loteprednol etabonate (Lotemax, Bausch + Lomb), or compounded nonpreserved formulations, can be used during the therapeutic phase of management[53,54] and
- Very low-frequency topical steroids and/or topical immunomodulators, such as cyclosporine or lifitegrast (Xiidra, Bausch + Lomb),[55] can be used for maintenance-phase therapy to prevent resensitization.[56]

### Topical Neuroregenerative Therapy

Topical neuroregenerative therapies such as autologous serum tears (ASTs) play an important role. ASTs, rich in growth factors such as epidermal growth factor, insulin-like growth factor, and nerve growth factor, can promote nerve regeneration and reduce pain severity.[57-60] Studies have shown significant pain reduction, improved photoallodynia,[31] and improved in vivo confocal microscopy parameters, including increased corneal nerve density and reduced MNs.[57] We recommend initiating AST therapy at a 20% concentration and titrating upward (40%–50%) based on patient response. In our experience, starting with higher concentrations may temporarily exacerbate symptoms.

### Cryopreserved Amniotic Membrane

Cryopreserved amniotic membranes, such as Prokera (BioTissue), are another treatment option. These membranes contain growth factors and antiinflammatory mediators. Although treatment has been associated with rapid symptom improvement and increased corneal nerve density,[61] reports indicate that up to 40% of patients experience poor compliance due to ring dysesthesia and can have pain recurrence over time. Therefore, amniotic membranes are recommended for managing flare-ups or as an adjunctive treatment during initiation therapy to support faster ocular surface recovery and relieve acute discomfort.

### Emerging Topical Therapies

Emerging topical therapies include OK-101 (Okyo Pharma), a lipid-conjugated chemerin peptide antagonist targeting the ChemR23 receptor,[62] which modulates immune cell trafficking and antiinflammatory cytokine release. OK-101 is currently in a phase 2 clinical trial.[63,64]

### Systemic Therapies for Centralized Pain

For patients with centralized pain, neuromodulation is the first-line treatment. The International Neuromodulation Society defines neuromodulation as the alteration of nerve activity via targeted electrical or chemical stimuli.[65] Oral neuromodulators target the somatosensory pathway.

*Nortriptyline.* This tricyclic antidepressant is effective at lower doses for centralized NCP than those for depression.[66] Its analgesic effects are mediated via noradrenaline reuptake inhibition and alpha-2 adrenergic receptor activation, alleviating allodynia and hyperalgesia.[66,67]

*Low-dose naltrexone.* This drug is an opioid antagonist that enhances endorphin production by blocking opioid receptors and exhibits antiinflammatory and analgesic effects.[70] It has been shown to significantly reduce centralized NCP and improve QOL.

*Gabapentin.* This alpha-2-delta ligand antiepileptic can reduce neuropathic pain and improve patients' QOL.[68] The drug inhibits presynaptic nerve trafficking and calcium channel influx, which have been linked to neuropathic pain.[69] Gabapentin has shown efficacy in DED-associated NCP refractory to topical therapies.[68]

*Duloxetine.* This serotonin-norepinephrine reuptake inhibitor has central analgesic properties and can be useful as adjunctive therapy for chronic pain.[7,71,72]

*Carbamazepine.* This anticonvulsant locks excitatory sodium channel activity and proinflammatory signaling pathways, making it effective for trigeminal neuralgia and refractory chronic neuropathic pain.[7,73]

In general, for systemic therapy, if monotherapy is ineffective or produces side effects at higher doses, combining low-dose dual or triple therapy is recommended.

### Neurostimulation

Neurostimulation is a promising adjunct for pain relief.[74,75] By stimulating other myelinated nerves (eg, ethmoidal nerves), nociceptive input to the central somatosensory pathway can be blocked.[75,76] Intranasal neurostimulation, for example, has demonstrated efficacy in addressing the peripheral component of NCP, reducing both pain severity and dryness symptoms.[74-78] Extranasal (transcutaneous) neurostimulation has also shown efficacy in managing peripheral and mixed NCP cases.[76]

### Combined Therapy for Mixed NCP

For patients with mixed NCP, a combination of topical and systemic therapies is recommended to achieve optimal symptom control.

## PRE- AND POSTOPERATIVE CONSIDERATIONS

NCP following ocular surgery—particularly cataract procedures,[79] LASIK,[16] and PRK[4,80]—is well

documented. Although definitive screening tests for NCP before ocular surgeries are lacking, thorough preoperative assessments with a focus on identifying existing ocular and systemic predisposing conditions remain valuable. For patients with suspected autoimmune disease, serologic testing is recommended. In such cases, the discontinuation of topical steroids at 2 to 4 weeks postoperatively may result in persistent postoperative inflammation and NCP. These patients may benefit from extended antiinflammatory therapy with a slower tapering regimen.

### Understanding Postoperative Pain

Although chronic postoperative pain is relatively uncommon, it occurs in approximately 13% to 34% of cases.[82,83] The exact incidence of NCP following cataract surgery, however, remains unknown.

Refractive surgeries such as LASIK[16,17] and PRK[84,85] are effective for correcting refractive errors and are widely performed in the United States.[20] Although the occurrence of DED after refractive surgery is well established, an increasing number of patients are also being diagnosed with NCP. These individuals report persistent ocular symptoms lasting 6 months or longer, pain severity comparable to that experienced in postherpetic neuralgia, and a similarly negative impact on their QOL.[17,20,85,86]

A recent prospective study identified pre- and perioperative predictors of persistent pain after refractive surgery.[84] The study highlighted the following significant risk factors:

- Preoperative ocular pain;
- Depressive symptoms;
- The use of antiallergy medications; and
- Postoperative pain within the first 24 hours.

These findings underscore the importance of obtaining comprehensive ocular and systemic histories and counseling patients on potential postoperative pain.

### Identifying Risk Factors and Predictors

Consensus on preventing or managing postsurgical NCP has not been reached. Preexisting systemic and ocular symptoms should guide the pre- and postoperative approach. Patients with symptoms out of proportion to signs or preexisting DED should be screened for autoimmune diseases. Individuals who report symptoms such as numbness, tingling, dizziness with palpitations, and heat intolerance should be assessed for somatosensory disorders. Conditions such as small fiber neuropathy and postural orthostatic tachycardia syndrome require consideration in this situation. Additionally, uncontrolled depression and anxiety should be addressed before surgery. Similarly, for patients with diagnosed ocular or systemic pathologies, it is advisable to control the underlying problem before proceeding to surgery.

### Postoperative Management Strategies

In the authors' clinical experience, the following strategies have shown benefit for patients at risk of developing NCP:

- Slow tapering of topical antiinflammatory drops over 3 months instead of the standard 2 to 4 weeks;
- Initiation of ASTs postoperatively to optimize corneal nerve regeneration in cases when pain persists beyond standard postoperative phase and other etiologies are ruled out;
- Close postoperative follow-up to enable early intervention and prevent pain centralization; and
- Referral for IVCM in suspected peripheral cases to confirm NCP diagnosis.

Early recognition and proactive management are key to mitigating the risk of NCP and improving patient outcomes following ocular surgery.

## CONCLUSION

The absence of standardized screening, diagnostic, and treatment guidelines complicates NCP management. Continued research and consensus-building among experts are essential to define clear, evidence-based approaches for identifying and treating this debilitating condition. ■


1. Raja SN, Carr DB, Cohen M, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain*. 2020;161(9):1976-1982.
2. Murnion BP. Neuropathic pain: current definition and review of drug treatment. *Aust Prescr*. 2018;41(2):60-63.
3. Al-Aqaba MA, Dhillon VK, Mohammed I, Said DG, Dua HS. Corneal nerves in health and disease. *Prog Retin Eye Res*. 2019;73:100762.
4. Goyal S, Hamrah P. Understanding neuropathic corneal pain–gaps and current therapeutic approaches. *Semin Ophthalmol*. 2016;31(1):59-70.
5. Cruzat A, Qazi Y, Hamrah P. In vivo confocal microscopy of corneal nerves in health and disease. *Ocul Surf*. 2017;15(1):15-47.
6. Müller LJ, Marfurt CF, Kruse F, Tervo TM. Corneal nerves: structure, contents, and function. *Exp Eye Res*. 2003;76(5):521-542.
7. Dieckmann G, Goyal S, Hamrah P. Neuropathic corneal pain: approaches for management. *Ophthalmology*. 2017;124(11 suppl):S34-S47.
8. Raja SN, Ringkamp M, Guan Y, Campbell JN. John J. Bonica Award Lecture: peripheral neuronal hyperexcitability: the "low-hanging" target for safe therapeutic strategies in neuropathic pain. *Pain*. 2020;161(suppl 1):S14-S26.
9. Hamrah P, Qazi Y, Shahatit B, et al. Corneal nerve and epithelial cell alterations in corneal allodynia: an in vivo confocal microscopy case series. *Ocul Surf*. 2017;15(1):139-151.
10. Rosenthal P, Borsook D, Moulton EA. Oculofacial pain: corneal nerve damage leading to pain beyond the eye. *Invest Ophthalmol Vis Sci*. 2016;57(11):5285-5287.
11. Galor A, Levitt RC, Felix ER, Martin ER, Sarantopoulos CD. Neuropathic ocular pain: an important yet underevaluated feature of dry eye. *Eye (Lond)*. 2015;29(3):301-312.
12. Rosenthal P, Borsook D. Ocular neuropathic pain. *Br J Ophthalmol*. 2016;100(1):128-134.
13. Moshirfar M, Benstead EE, Sorrentino PM, Tripathy K. Ocular neuropathic pain. In: *StatPearls*. StatPearls Publishing; 2023. Accessed December 17, 2024. https://www.ncbi.nlm.nih.gov/books/NBK557879
14. Jensen TS, Baron R, Haanpää M, et al. A new definition of neuropathic pain. *Pain*. 2011;152(10):2204-2205.
15. Galor A, Levitt RC, Felix ER, Sarantopoulos CD. Understanding the true burden of dry eye disease. *Expert Rev Ophthalmol*. 2015;10(5):403-405.
16. Theophanous C, Jacobs DS, Hamrah P. Corneal neuralgia after LASIK. *Optom Vis Sci*. 2015;92(9):e233-e240.
17. Moshirfar M, Bhavsar UM, Durnford KM, et al. Neuropathic corneal pain following LASIK surgery: a retrospective case series. *Ophthalmol Ther*. 2021;10(3):677-689.
18. Sajnani R, Raia S, Gibbons A, et al. Epidemiology of persistent postsurgical pain manifesting as dry eye-like symptoms after cataract surgery. *Cornea*. 2018;37(12):1535-1541.
19. Crane AM, Levitt RC, Felix ER, et al. Patients with more severe symptoms of neuropathic ocular pain report more frequent and severe chronic overlapping pain conditions and psychiatric disease. *Br J Ophthalmol*. 2017;101(2):227-231.
20. Bayraktutar BN, Ozmen MC, Muzaaya N, et al. Comparison of clinical characteristics of post-refractive surgery-related and post-herpetic neuropathic corneal pain. *Ocul Surf*. 2020;18(4):641-650.
21. Yunus MB. Central sensitivity syndromes: a new paradigm and group nosology for fibromyalgia and overlapping conditions, and the related issue of disease versus illness. *Semin Arthritis Rheum*. 2008;37(6):339-352.
22. Nijs J, George SZ, Clauw DJ, et al. Central sensitisation in chronic pain conditions: latest discoveries and their potential for precision medicine. *Lancet Rheumatol*. 2021;3(8):e383-e392.
23. Buchgreitz L, Lyngberg AC, Bendtsen L, Jensen R. Frequency of headache is related to sensitization: a population study. *Pain*. 2006;123(1-2):19-27.
24. Zdebik N, Zdebik A, Bogusławska J, Przeździecka-Dołyk J, Turno-Kręcicka

A. Fibromyalgia syndrome and the eye—a review. *Surv Ophthalmol*. 2021;66(1):132-137.
25. Leonardi A, Feuerman OM, Salami E, et al. Coexistence of neuropathic corneal pain, corneal nerve abnormalities, depression, and low quality of life. *Eye (Lond)*. 2024;38(3):499-506.
26. Fauchais AL, Richard L, Gondran G, et al. Small fibre neuropathy in primary Sjögren syndrome. *Rev Med Interne*. 2011;32(3):142-148.
27. Palejwala NV, Walia HS, Yeh S. Ocular manifestations of systemic lupus erythematosus: a review of the literature. Autoimmune Dis. 2012;2012:290898.
28. Mavrikakis I, Rootman J. Diverse clinical presentations of orbital sarcoid. *Am J Ophthalmol*. 2007;144(5):769-775.
29. Harbord M, Annese V, Vavricka SR, et al. The first European evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. *J Crohns Colitis*. 2016;10(3):239-254.
30. Galor A, Covington D, Levitt AE, et al. Neuropathic ocular pain due to dry eye is associated with multiple comorbid chronic pain syndromes. *J Pain*. 2016;17(3):310-318.
31. Aggarwal S, Kheirkhah A, Cavalcanti BM, et al. Autologous serum tears for treatment of photoallodynia in patients with corneal neuropathy: efficacy and evaluation with in vivo confocal microscopy. *Ocul Surf*. 2015;13(3):250-262.
32. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II definition and classification report. *Ocul Surf*. 2017;15(3):276-283.
33. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol*. 2000;118(5):615-621.
34. Johnson ME, Murphy PJ. Measurement of ocular surface irritation on a linear interval scale with the ocular comfort index. *Invest Ophthalmol Vis Sci*. 2007;48(10):4451-4458.
35. Amparo F, Schaumberg DA, Dana R. Comparison of two questionnaires for dry eye symptom assessment: the Ocular Surface Disease Index and the Symptom Assessment in Dry Eye. *Ophthalmology*. 2015;122(7):1498-1503.
36. Qazi Y, Hurwitz S, Khan S, et al. Validity and reliability of a novel ocular pain assessment survey (OPAS) in quantifying and monitoring corneal and ocular surface pain. *Ophthalmology*. 2016;123(7):1458-1468.
37. Farhangi M, Feuer W, Galor A, et al. Modification of the Neuropathic Pain Symptom Inventory for use in eye pain (NPSI-Eye). *Pain*. 2019;160(7):1541-1550.
38. Bouhassira D, Attal N, Fermanian J, et al. Development and validation of the Neuropathic Pain Symptom Inventory. *Pain*. 2004;108(3):248-257.
39. Le DT, Kandel H, Watson SL. Evaluation of ocular neuropathic pain. *Ocul Surf*. 2023;30:213-235.
40. Galor A, Felix ER, Feuer W, et al. Corneal nerve pathway function in individuals with dry eye symptoms. *Ophthalmology*. 2021;128(4):619-621.
41. Aykut V, Elbay A, Uçar IÇ, et al. Corneal sensitivity and subjective complaints of ocular pain in patients with fibromyalgia. *Eye (Lond)*. 2018;32(4):763-767.
42. Liu C, Lin MT, Lee IXY, et al. Neuropathic corneal pain: tear proteomic and neuromediator profiles, imaging features, and clinical manifestations. *Am J Ophthalmol*. 2024;265:6-20.
43. Ruiz-Lozano RE, Soifer M, Zemborain ZZ, et al. Deep-learning based analysis of in-vivo confocal microscopy images of the subbasal corneal nerve plexus' inferior whorl in patients with neuropathic corneal pain and dry eye disease. *Ocul Surf*. 2024;34:241-246.
44. Moein HR, Akhlaq A, Dieckmann G, et al. Visualization of microneuromas by using in vivo confocal microscopy: an objective biomarker for the diagnosis of neuropathic corneal pain? *Ocul Surf*. 2020;18(4):651-656.
45. Cox SM, Kheirkhah A, Aggarwal S, et al. Alterations in corneal nerves in different subtypes of dry eye disease: an in vivo confocal microscopy study. *Ocul Surf*. 2021;22:135-142.
46. Zhang M, Chen J, Luo L, et al. Altered corneal nerves in aqueous tear deficiency viewed by in vivo confocal microscopy. *Cornea*. 2005;24(7):818-824.
47. Matsumoto Y, Ibrahim OMA, Kojima T, et al. Corneal in vivo laser-scanning confocal microscopy findings in dry eye patients with Sjögren's syndrome. *Diagnostics (Basel)*. 2020;10(3):E140.
48. Dermer H, Hwang J, Mittal R, et al. Corneal sub-basal nerve plexus microneuromas in individuals with and without dry eye. *Br J Ophthalmol*. 2022;106(5):616-622.
49. Koseoglu ND, Dieckmann G, Seyed-Razavi Y, et al. Patients with clinical signs of dry eye disease demonstrate presence of signs of neuropathic corneal pain. *Invest Ophthalmol Vis Sci*. 2019;60(9):4199.
50. Translational Medicine Center. Prospective study to validate the imaging biomarker for NCP (R33). ClinicalTrials.gov. Updated April 2024. Accessed December 17, 2024. https://clinicaltrials.gov/ct2/show/NCT04512345
51. Huang JJ, Rodriguez DA, Slifer SH, Martin ER, Levitt RC, Galor A. Genome-wide association study of neuropathic ocular pain. *Ophthalmol Sci*. 2024;4(1):100384.
52. Patel S, Mittal R, Sarantopoulos KD, Galor A. Neuropathic ocular surface pain: emerging drug targets and therapeutic implications. *Expert Opin Ther Targets*. 2022;26(8):681-695.
53. de Paiva CS, Pflugfelder SC. Rationale for anti-inflammatory therapy in dry eye syndrome. *Arq Bras Oftalmol*. 2008;71(6 suppl):89-95.
54. Coffey MJ, Decory HH, Lane SS. Development of a non-settling gel formulation of 0.5% loteprednol etabonate for anti-inflammatory use as an ophthalmic drop. *Clin Ophthalmol*. 2013;7:299-312.
55. Abidi A, Shukla P, Ahmad A. Lifitegrast: a novel drug for treatment of dry eye disease. *J Pharmacol Pharmacother*. 2016;7(4):194-198.
56. Dastjerdi MH, Hamrah P, Dana R. High-frequency topical cyclosporine 0.05% in the treatment of severe dry eye refractory to twice-daily regimen. *Cornea*. 2009;28(10):1091-1096.
57. Aggarwal S, Colon C, Kheirkhah A, Hamrah P. Efficacy of autologous serum tears for treatment of neuropathic corneal pain. *Ocul Surf*. 2019;17(3):532-539.
58. Ohashi Y, Motokura M, Kinoshita Y, et al. Presence of epidermal growth factor in human tears. *Invest Ophthalmol Vis Sci*. 1989;30(9):1879-1882.
59. Matsumoto Y, Dogru M, Goto E, et al. Autologous serum application in the treatment of neurotrophic keratopathy. *Ophthalmology*. 2004;111(6):1115-1120.
60. Bradley JC, Bradley RH, McCartney DL, Mannis MJ. Serum growth factor analysis in dry eye syndrome. *Clin Exp Ophthalmol*. 2008;36(8):717-720.
61. Morkin MI, Hamrah P. Efficacy of self-retained cryopreserved amniotic membrane for treatment of neuropathic corneal pain. *Ocul Surf*. 2018;16(1):132-138.
62. Harris DL, Qiu F, Sultan A, Patil R, Jacob GS, Hamrah P. OK-101, a novel chemerin receptor agonist, ameliorates neuropathic corneal pain in a mouse model of ciliary nerve ligation. *Invest Ophthalmol Vis Sci*. 2022;63(7):1834.
63. OKYO Pharma. Technology. Accessed December 17, 2024. okyopharma.com/technology
64. Harp MD. OKYO Pharma announces positive results from phase 2 trial of OK-101 in dry eye disease. *Ophthalmology Times*. January 8, 2024. Accessed December 18, 2024. https://www.ophthalmologytimes.com/view/okyo-pharma-announces-positive-results-from-phase-2-trial-of-ok-101-in-dry-eye-disease
65. International Neuromodulation Society. 10 things to know about neuromodulation & the INS. International Neuromodulation Society; 2019.
66. Obata H. Analgesic mechanisms of antidepressants for neuropathic pain. *Int J Mol Sci*. 2017;18(11):2483.
67. Ozmen MC, Dieckmann G, Cox SM, et al. Efficacy and tolerability of nortriptyline in the management of neuropathic corneal pain. *Ocul Surf*. 2020;18(4):814-820.
68. Yoon HJ, Kim J, Yoon KC. Treatment response to gabapentin in neuropathic ocular pain associated with dry eye. *J Clin Med*. 2020;9(2):395.
69. Kukkar A, Bali A, Singh N, Jaggi AS. Implications and mechanism of action of gabapentin in neuropathic pain. *Arch Pharm Res*. 2013;36(3):237-251.
70. Dieckmann G, Ozmen MC, Cox SM, Engert RC, Hamrah P. Low-dose naltrexone is effective and well-tolerated for modulating symptoms in patients with neuropathic corneal pain. *Ocul Surf*. 2021;20:33-38.
71. Fanelli D, Weller G, Liu H. New serotonin-norepinephrine reuptake inhibitors and their anesthetic and analgesic considerations. *Neurol Int*. 2021;13(4):497-509.
72. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol*. 2015;14(2):162-173.
73. Wiffen PJ, Derry S, Moore RA, McQuay HJ. Carbamazepine for acute and chronic pain in adults. *Cochrane Database Syst Rev*. 2011;(1):CD005451.
74. Farhangi M, Cheng AM, Baksh B, et al. Effect of non-invasive intranasal neurostimulation on tear volume, dryness, and ocular pain. *Br J Ophthalmol*. 2020;104(10):1310-1316.
75. Dieckmann G, Koseoglu ND, Akhlaq A, et al. Efficacy of intranasal neurostimulation for peripheral pain among neuropathic corneal pain patients. *Invest Ophthalmol Vis Sci*. 2018;59(9):1806.
76. Olcucu O, de Leeuw A, Lamazales LL, Mallone F, Hamrah P. Efficacy of extranasal neurostimulation for patients with neuropathic corneal pain: a pilot study. *Cornea*. Published online October 10, 2024. Accessed December 18, 2024. https://journals.lww.com/corneajrnl/abstract/9900/efficacy_of_extranasal_neurostimulation_for.713.aspx
77. Olcucu O, Dieckmann G, Ozmen MC, et al. An exploratory, prospective, interventional, open-label, clinical trial with intranasal neurostimulation for ameliorating symptoms of neuropathic corneal pain. *Invest Ophthalmol Vis Sci*. 2024;65(5):2658.
78. Olcucu O, de Leeuw A, Hamrah P. Efficacy of extranasal neurostimulation for patients with neuropathic corneal pain. *Invest Ophthalmol Vis Sci*. 2023;64(5):719.
79. Rashad R, Dieckmann G, Koseoglu D, et al. Neuropathic corneal pain in post-cataract surgery patients. *Invest Ophthalmol Vis Sci*. 2018;59(9):1802.
80. Woreta FA, Gupta A, Hochstetler B, Bower KS. Management of post-photorefractive keratectomy pain. *Surv Ophthalmol*. 2013;58(6):529-535.
81. Grzybowski A. Recent developments in cataract surgery. *Ann Transl Med*. 2020;8(22):1540.
82. Iglesias E, Sajnani R, Levitt RC, et al. Epidemiology of persistent dry eye-like symptoms after cataract surgery. *Cornea*. 2018;37(8):893-898.
83. Sayegh RR, Vitale S, Agron E, et al. Prevalence and risk factors for the development of persistent postoperative pain after cataract surgery in the Age-Related Eye Disease Study (AREDS). *Invest Ophthalmol Vis Sci*. 2024;65(5):2642.
84. Betz J, Behrens H, Harkness BM, et al. Ocular pain after refractive surgery: interim analysis of frequency and risk factors. *Ophthalmology*. 2023;130(6):692-701.
85. Baksh BS, Morkin M, Felix E, et al. Ocular pain symptoms in individuals with and without a history of refractive surgery: results from a cross-sectional survey. *Cornea*. 2022;41(1):31-38.
86. Ambrósio R Jr, Tervo T, Wilson SE. LASIK-associated dry eye and neurotrophic epitheliopathy: pathophysiology and strategies for prevention and treatment. *J Refract Surg*. 2008;24(4):396-407.

**PEDRAM HAMRAH, MD**

- Professor of Ophthalmology, Neuroscience, and Immunology, Center for Translational Ocular Immunology and Cornea Service, New England Eye Center, Department of Ophthalmology, Tufts Medical Center, Tufts University School of Medicine, Boston
- pedram.hamrah@tufts.edu
- Financial disclosure: Consultant (Bausch + Lomb, Santen Pharmaceutical); Consultant and speaker (Dompé, Novartis, Okyo Pharma, TearSolutions); Speaker (CooperVision)

**NESLIHAN DILRUBA KOSEOGLU, MD**

- Postdoctoral clinical research fellow, Center for Translational Ocular Immunology and Cornea Service, New England Eye Center, Department of Ophthalmology, Tufts Medical Center, Tufts University School of Medicine, Boston
- Financial disclosure: None acknowledged

**ISABELA YANG, MD**

- Postdoctoral clinical research fellow, Center for Translational Ocular Immunology and Cornea Service, New England Eye Center, Department of Ophthalmology, Tufts Medical Center, Tufts University School of Medicine, Boston
- Financial disclosure: None acknowledged