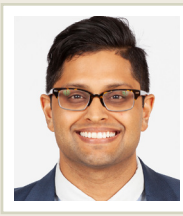
Contact Lens Update
CLINICAL INSIGHTS BASED IN CURRENT RESEARCH

What is neuropathic ocular surface pain and what can we do about it?

June 28, 2022

Anat Galor, MD, MSPH is a cornea and uveitis trained specialist with a dual appointment at the Miami Veterans Affairs (VA) medical center and the Bascom Palmer Eye Institute, University of Miami Miller School of Medicine. Dr. Galor currently runs the ocular surface program at the Miami VA and has focused her research on understanding mechanisms of pain in dry eye, with an emphasis on studying new diagnostic and treatment modalities.



Sneh Patel, MD, MPH is a recent graduate of the University of Miami Miller School of Medicine who has conducted research with Dr. Galor.

Ocular Surface Pain and Its Origin

The International Association for the Study of Pain (IASP) defines pain as:

> ***An unpleasant sensory and/or emotional experience associated with, or resembling that associated with, actual or potential tissue damage.***[1]

As the eye is an organ that should normally not be felt, this definition can be extended to ocular surface pain, which is often described as a sensation of dryness, burning, aching, irritation, and/or tenderness. As a major cause of disability, morbidity, and negative impact on quality-of-life, interest in ocular surface pain has intensified given its positive relationship to number of clinic visits and ophthalmic healthcare costs across the world.[2]

Ocular surface pain can be driven by nociceptive, neuropathic, or mixed mechanisms.

> ***Nociceptive pain is defined as pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.***[1]

When applied to the ocular surface, nociceptive pain occurs due to noxious stimuli that directly activate nociceptors at the level of the ocular surface. Nociceptive pain can be transient, as is the case with a corneal abrasion, or chronic, due to a variety of insults including tear film abnormalities (e.g., decreased tear production, elevated tear osmolarity, inflammation), environmental factors (e.g., air pollution and climate), abnormal anatomy, or direct damage by irritants or surgery.[3]

> ***Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system.***[1]

When applied to the ocular surface, neuropathic pain is a result of pathologic abnormalities within the trigeminal nerve that innervates the cornea and periocular tissue (peripheral neuropathic pain) or in higher order neurons that connect the ocular surface to the brain (central neuropathic pain). As ongoing (e.g., chronic aqueous tear deficiency) or severe (e.g., surgical nerve injury) nociceptive sources of pain can lead to peripheral and central nerve abnormalities, it is not surprising that ocular surface pain often has a mixed etiology, with both nociceptive and neuropathic contributors.[3]

What We Know: Workup

While much less is known about neuropathic pain compared to nociceptive ocular pain, growing interest in the topic has provided a rough framework for diagnosing and treating a patient with neuropathic symptoms. It is important to highlight that our current knowledge base and diagnostic capabilities are limited; as such, it is crucial that further research on neuropathic ocular surface pain is conducted. This will allow for a more complete understanding of its origins and provide stronger tools for diagnosis that will facilitate individualized patient care. Current difficulties include clinical metrics that are not consistently assessed across patients, a limited number of clinical tests available to examine corneal nerve function, and no 'gold standard' definition for neuropathic ocular surface pain.

Taking these into consideration, a focus on conducting a thorough assessment to examine potential nociceptive sources of pain, while at the same time looking for clues that neuropathic mechanisms contribute to pain, is warranted in assessing our patients. The first step is to obtain a thorough history that captures information on co-morbid ocular and systemic conditions and medications. This is helpful, as specific systemic conditions are associated with specific ocular surface manifestations. For example, rheumatoid arthritis is more closely associated with aqueous tear deficiency and ocular surface inflammation, while migraine is more closely linked to neuropathic ocular surface pain.[4] Sleep apnea (and concomitant continuous positive airway pressure treatment), on the other hand, are most closely related to anatomic abnormalities (e.g., eyelid laxity) and ocular surface disruption.

Next, standardized questionnaires should be used to quantify and characterize ocular pain. These can include dry eye specific questionnaires, such as the Dry Eye Questionnaire 5 (DEQ5) which asks about frequency and intensity of dryness and discomfort along with tears,[5] or the Ocular Surface Disease Index (OSDI) which is a multifaceted questionnaire that asks about frequency of various descriptors, impact of triggers, and effect on quality of life.[6] Others include ocular surface pain specific questionnaires such as a Likert-type numerical rating scale (NRS), the Ocular Pain Assessment Survey (OPAS) which asks about intensity of pain, descriptors, and impact on quality of life,[7] or the Neuropathic Pain Symptom Inventory-modified for the Eye (NPSI-E) which focuses on the intensity of neuropathic pain descriptors.[8]

The physical examination begins with a focus on the periocular skin, blink rate, and anatomy. Next, point of care tests can be used to assess for ocular surface inflammation or tear osmolarity, common sources of nociceptive pain. Corneal sensitivity can then be tested qualitatively with a cotton tip applicator or dental floss, and graded on a scale of 0-3 (none, reduced, normal, increased). A slit lamp exam with vital dye staining should be conducted to assess: the eyelid margin (looking for anterior blepharitis and/or features of Meibomian gland dysfunction), tear film stability (with tear break up time), corneal and conjunctival staining, and conjunctival anatomy. Tear production can be assessed with a Schirmer's test, although tear meniscus height is often used as a surrogate measure. It is important for the clinician to examine the patient prior to anesthetic placement as this can impact slit lamp examination findings; placement of the anesthetic is in itself an important clinical test. If ocular surface pain is present, the clinician should initially ask the patient to rate its intensity on a 0-10 NRS, subsequently instill anesthetic drops and then re-grade pain 30 seconds to two minutes later. Persistent pain after topical anesthesia suggests a central or non-ocular surface source of pain. Finally, imaging tests, such as in vivo confocal microscopy can be performed to examine corneal nerve morphology.

While not one-hundred-percent accurate, key findings that suggest a potential neuropathic contribution to ocular surface pain include:

1. Presence of chronic pain co-morbidities upon history (e.g. fibromyalgia, migraine, complex regional pain syndrome, chronic pelvic pain, vulvodynia)
2. Presence of specific descriptors on questionnaires (e.g. burning pain, sensitivity to wind or light, or symptoms out of proportion to signs of disease)
3. Abnormal corneal sensation (hypo- or hyperesthesia) [9]
4. Persistent symptoms despite a history of multiple therapies for nociceptive pain[3, 10-12]
5. As stated above, certain findings can hint at the location of the abnormality; most notably, persistent pain after topical anaesthetic instillation, as well as signs of cutaneous allodynia (pain to light touch around the eye) are suggestive of a centralized (e.g. CNS) abnormality.[13]

What We Know: Treatment

As the diagnosis of neuropathic pain is clinical, the first step in treating ocular surface pain is to treat all nociceptive sources of pain. If this strategy is not successful, or if the initial examination is highly indicative of neuropathic pain, treatment of neuropathic pain should be initiated.

First line therapies in patients with peripheral neuropathic pain are topical. This includes treating with anti-inflammatories and blood-derived products (e.g., autologous serum tears (AST); platelet rich plasma). In various series, anti-inflammatory therapy has been shown to improve pain symptoms,[14] tear surface abnormalities,[15] and peripheral nerve metrics such as corneal nerve density[16] in a sub-set of individuals. Topical blood products contain blood-bound neurotrophic and epithelial growth factors including nerve growth factor (NGF) and neurotrophin-3, which can promote regeneration of corneal nerves.[17] Several studies have shown improvements in pain[18] and peripheral nerve metrics[19] with AST. Pre-clinical studies are currently investigating the use of transient receptor potential cation channel subfamily V member 1 (TrpV1) modulators on the treatment of surgical[20, 21] and chemotherapy-induced[22, 23] peripheral neuropathic pain. This therapy is also being investigated in human trials in individuals with post-operative corneal induced chronic pain (see ClinicalTrials.gov: NCT04630158).

First line therapies in patients with central neuropathic pain include oral neuromodulators such as α2δ ligands (gabapentin or pregabalin), tricyclic antidepressants (nortriptyline or amitriptyline), serotonin-norepinephrine reuptake inhibitors (duloxetine), and sodium-channel blocking anticonvulsants (carbamazepine or topiramate).[24, 25] Because these agents are neuromodulators rather than direct analgesics, pain improvement is first seen approximately three months after reaching a therapeutic dose and continues gradually over time. Thus, patients must be properly counselled on expectations, benefits, risks, and time course of treatment to ensure compliance with therapy.

Where are We Going?

Given the lack of definition, gold standard of diagnosis, and weakness in ability to determine the location of nervous dysfunction, neuropathic pain has many mysteries that have yet to be solved. Continued research is required to improve our diagnostic capabilities and guide therapy. Thankfully, emerging therapies being studied in both clinical and pre-clinical stages have shown promising results thus far.

Other therapies being studied for peripheral pain in humans include amniotic membrane transplant (AMT)[26] and recombinant human NGF.27 In the investigational stage, an open label pilot study in Korea of 15 patients with

DED-associated neuropathic pain applied TRPM8 agonist cryosim-3 four times daily. On OPAS, pain (scale 0-60) decreased at 1 week (26.47 ± 11.45; p=0.01) and 1 month (21.53 ± 10.84; p=0.02) compared to baseline (30.60 ± 12.84), while quality of life (scale 0-60) improved in a similar fashion (1 week: 27.60 ± 15.49, 1 month: 27.17 ± 16.06, baseline: 33.53 ± 14.24; p=0.003 and 0.02 respectively).[28] Meanwhile, topical formulations of TRP binding agents (agonists, antagonists, and modulators such as resiniferatoxin), [29, 30] omega-3 fatty acid derivatives (e.g. docosanoids),[31, 32] and cannabinoid agonist therapies are all being examined in pre-clinical stages.[33, 34]

Several emerging therapies are being studied for centralised pain. These include oral agents (low dose naltrexone or tramadol),[35, 36] and adjuvant therapies that target periocular afferents. For instance, periocular nerve blocks (reversible sodium channel blocker combined with a long-acting corticosteroid) have been utilized in individuals with cutaneous allodynia.[37] Given links between migraine and neuropathic ocular surface pain, strategies used in migraine have also been studied for ocular surface pain; these include botulinum toxin injections (inhibits release of neuroexcitatory transmitters)[38-40] and non-invasive neurostimulation devices such as transcutaneous electrical nerve stimulation and transcranial magnetic stimulation.[41-43] Given the close association between chronic ocular surface pain and psychological dysfunction,[44] addressing the emotional component is important; this can be achieved through cognitive-behavioral therapy, along with other stragegies.[45] Further studies are needed to identify when autonomic mechanisms contribute to chronic ocular surface pain; however, strategies to target these mechanisms, by blocking the sphenopalatine (parasympathetic) or superior cervical (sympathetic) ganglion, have been used in isolated cases. Overall, a remaining issue is the need for precision-based medicine as it is not currently possible to predict which patient will respond best to any specific therapy, whether in isolation or combination.

Summary

Our knowledge of neuropathic ocular surface pain is continuously evolving as we encounter an increasing number of affected patients and bridge the gap with our current understanding of its counterpart, nociceptive pain. Even though this is an emerging field, a framework for clinical diagnosis and initiation of therapy for neuropathic ocular surface pain has been constructed recently. Advancements in both diagnostic technologies and therapeutic algorithms remain major goals for improvement in the field. Also, discovery of more therapeutic modalities is essential, as these will solidify preventative and therapeutic techniques for improving often highly refractory symptoms. For now, patient-centred care and the use of multi-modal therapies that are applied over a long period of time with proper patient counselling, are necessary for achieving optimal outcomes.

REFERENCES:

1. IASP Terminology: International Association for the Study of Pain; 2020 [Available from: https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698.]
2. Mertzanis P, Abetz L, Rajagopalan K, *et al*. The relative burden of dry eye in patients' lives: comparisons to a U.S. normative sample. *Invest Ophthalmol Vis Sci.* 2005 Jan;46(1):46-50.
3. Mehra D, Cohen NK, Galor A. Ocular Surface Pain: A Narrative Review. *Ophthalmol Ther.* 2020;9(3):1-21.
4. Lee Y, Kim M, Galor A. Beyond dry eye: how co-morbidities influence disease phenotype in dry eye disease. *Clin Exp Optom*. 2022;105(2):177-185.
5. Chalmers RL, Begley CG, Caffery B. Validation of the 5-Item Dry Eye Questionnaire (DEQ-5): Discrimination across self-assessed severity and aqueous tear deficient dry eye diagnoses. *Cont Lens Anterior Eye*. 2010;33(2):55-60.
6. Schiffman RM, Christianson MD, Jacobsen G, *et al.* Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol.* 2000;118(5):615-21.
7. 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):1458-68.
8. 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.

9. Galor A, Felix ER, Feuer W, *et al*. Corneal Nerve Pathway Function in Individuals with Dry Eye Symptoms. *Ophthalmology*. 2021;128(4):619-621.
10. Ong ES, Felix ER, Levitt RC, *et al.* Epidemiology of discordance between symptoms and signs of dry eye. *Br J Ophthalmol.* 2018;102(5):674-679.
11. Kalangara JP, Galor A, Levitt RC, *et al.* Characteristics of Ocular Pain Complaints in Patients With Idiopathic Dry Eye Symptoms. *Eye Contact Lens*. 2017;43(3):192-198.
12. Galor A, Batawi H, Felix ER, *et al*. Incomplete response to artificial tears is associated with features of neuropathic ocular pain. *Br J Ophthalmol.* 2016;100(6):745-9.
13. Crane AM, Feuer W, Felix ER, *et al*. Evidence of central sensitisation in those with dry eye symptoms and neuropathic-like ocular pain complaints: incomplete response to topical anaesthesia and generalised heightened sensitivity to evoked pain. *Br J Ophthalmol*. 2017;101(9):1238-1243.
14. Devecı H, Kobak S. The efficacy of topical 0.05 % cyclosporine A in patients with dry eye disease associated with Sjögren's syndrome. *Int Ophthalmol.* 2014;34(5):1043-8.
15. Sall K, Stevenson OD, Mundorf TK, Reis BL. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group. *Ophthalmology*. 2000;107(4):631-9.
16. Levy O, Labbé A, Borderie V, *et al.* Increased corneal sub-basal nerve density in patients with Sjögren syndrome treated with topical cyclosporine A. *Clin Exp Ophthalmol.* 2017;45(5):455-463.
17. 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.
18. Ali TK, Gibbons A, Cartes C, *et al.* Use of Autologous Serum Tears for the Treatment of Ocular Surface Disease From Patients With Systemic Autoimmune Diseases. *Am J Ophthalmol.* 2018;189:65-70.
19. 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):250-62.
20. Huang YK, Lu YG, Zhao X, *et al*. Cytokine activin C ameliorates chronic neuropathic pain in peripheral nerve injury rodents by modulating the TRPV1 channel. *Br J Pharmacol*. 2020;177(24):5642-5657.
21. Kim HY, Park CK, Cho IH, *et al*. Differential Changes in TRPV1 expression after trigeminal sensory nerve injury. *J Pain*. 2008;9(3):280-8.
22. Ba X, Wang J, Zhou S, *et al.* Cinobufacini protects against paclitaxel-induced peripheral neuropathic pain and suppresses TRPV1 up-regulation and spinal astrocyte activation in rats. *Biomed Pharmacother.* 2018;108:76-84.
23. Hao Y, Luo X, Ba X, *et al*. Huachansu suppresses TRPV1 up-regulation and spinal astrocyte activation to prevent oxaliplatin-induced peripheral neuropathic pain in rats. *Gene*. 2019;680:43-50.
24. Patel S, Hwang J, Mehra D, Galor A. Corneal Nerve Abnormalities in Ocular and Systemic Diseases. *Exp Eye Res*. 2021;202:108284.
25. Patel S, Mittal R, Felix ER, *et al.* Differential Effects of Treatment Strategies in Individuals With Chronic Ocular Surface Pain With a Neuropathic Component. *Front Pharmacol.* 2021;12:788524.
26. Morkin MI, Hamrah P. Efficacy of self-retained cryopreserved amniotic membrane for treatment of neuropathic corneal pain. *Ocul Surf*. 2018;16(1):132-138.
27. Sacchetti M, Lambiase A, Schmidl D, *et al*. Effect of recombinant human nerve growth factor eye drops in patients with dry eye: a phase IIa, open label, multiple-dose study. *Br J Ophthalmol.* 2020;104(1):127-135.
28. Yoon HJ, Kim J, Yang JM, *et al*. Topical TRPM8 Agonist for Relieving Neuropathic Ocular Pain in Patients with Dry Eye: A Pilot Study. *J Clin Med*. 2021;10(2):250.
29. Venkatachalam K, Montell C. TRP channels. *Annu Rev Biochem.* 2007;76:387-417.
30. Yang JM, Wei ET, Kim SJ, Yoon KC. TRPM8 Channels and Dry Eye. *Pharmaceuticals (Basel).* 2018;11(4):125.
31. Rashid S, Jin Y, Ecoiffier T, *et al.* Topical omega-3 and omega-6 fatty acids for treatment of dry eye. *Arch Ophthalmol.* 2008;126(2):219-25.
32. Pham TL, Bazan HEP. Docosanoid signaling modulates corneal nerve regeneration: effect on tear secretion, wound healing, and neuropathic pain. *J Lipid Res*. 2021;62:100033.
33. Thapa D, Cairns EA, Szczesniak AM, *et al*. Allosteric Cannabinoid Receptor 1 (CB1) Ligands Reduce Ocular Pain and Inflammation. *Molecules*. 2020;25(2):417.

34. Thapa D, Cairns EA, Szczesniak AM, *et al*. The Cannabinoids Δ8THC, CBD, and HU-308 Act via Distinct Receptors to Reduce Corneal Pain and Inflammation. *Cannabis Cannabinoid Res*. 2018;3(1):11-20.
35. Jackson D, Singh S, Zhang-James Y, Faraone S, Johnson B. The Effects of Low Dose Naltrexone on Opioid Induced Hyperalgesia and Fibromyalgia. *Front Psychiatry.* 2021;12:593842.
36. Hutchinson MR, Zhang Y, Brown K, *et al*. Non-stereoselective reversal of neuropathic pain by naloxone and naltrexone: involvement of toll-like receptor 4 (TLR4). *Eur J Neurosci.* 2008;28(1):20-9.
37. Small LR, Galor A, Felix ER, *et al.* Oral Gabapentinoids and Nerve Blocks for the Treatment of Chronic Ocular Pain. *Eye Contact Lens.* 2020;46(3):174-181.
38. Diel RJ, Kroeger ZA, Levitt RC, *et al.* Botulinum Toxin A for the Treatment of Photophobia and Dry Eye. *Ophthalmology*. 2018;125(1):139-140.
39. Diel RJ, Hwang J, Kroeger ZA, *et al.* Photophobia and sensations of dryness in patients with migraine occur independent of baseline tear volume and improve following botulinum toxin A injections. *Br J Ophthalmol.* 2019;103(8):1024-1029.
40. Venkateswaran N, Hwang J, Rong AJ, *et al*. Periorbital botulinum toxin A improves photophobia and sensations of dryness in patients without migraine: Case series of four patients. *Am J Ophthalmol Case Rep*. 2020;19:100809.
41. Johnson M. Transcutaneous Electrical Nerve Stimulation: Mechanisms, Clinical Application and Evidence. *Rev Pain*. 2007;1(1):7-11.
42. Dieckmann G, Fregni F, Hamrah P. Neurostimulation in dry eye disease-past, present, and future. *Ocul Surf.* 2019;17(1):20-7.
43. Mehra D, Mangwani-Mordani S, Acuna K, *et al*. Long-Term Trigeminal Nerve Stimulation as a Treatment for Ocular Pain. *Neuromodulation*. 2021;24(6):1107-1114.
44. Patel S, Felix ER, Levitt RC, *et al.* Dysfunctional Coping Mechanisms Contribute to Dry Eye Symptoms. *J Clin Med.* 2019;8(6):901.
45. Otis JD, Sanderson K, Hardway C, *et al*. A randomized controlled pilot study of a cognitive-behavioral therapy approach for painful diabetic peripheral neuropathy. *J Pain*. 2013;14(5):475-82.