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TEAR STIMULATION STRATEGIES ON THE HORIZON FOR DRY EYE DISEASE

FACULTY

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COPE approved for 2.0 credits for optometrists
COPE Course ID: 73412-AS
COPE Course Category: Treatment & Management of Ocular Disease: Anterior Segment (AS)

This continuing education activity is supported through an educational grant from Oyster Point Pharma, Inc.

ACTIVITY DESCRIPTION AND PURPOSE

Increased understanding of the pathophysiology of dry eye disease (DED) over the past few decades has led to advances in its diagnosis and to new treatments, with a particular focus on medications for controlling inflammation. Dissatisfaction among both patients and eye care providers with anti-inflammatory modalities for managing DED, however, suggests the need for additional treatments. New and emerging therapies for DED are aimed at increasing natural tear production. In this educational activity, experts in DED present a review of natural tear production and its importance for ocular surface health, describe new and emerging tear stimulation treatments for DED, including data from pivotal trials, and share insights on therapeutic decision making through a series of case-based discussions.

TARGET AUDIENCE

This educational activity is intended for optometrists.

LEARNING OBJECTIVES

After completing this activity, participants will be better able to:

- Review the benefits of natural tear production for ocular surface health
- Describe the mechanisms of actions of new and emerging tear stimulation treatments for dry eye disease
- Review the latest clinical trial data for new and emerging tear stimulation treatments for dry eye disease
- Identify patients who would be good candidates for tear stimulation treatments

ACCREDITATION STATEMENT

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TEAR STIMULATION STRATEGIES ON THE HORIZON FOR DRY EYE DISEASE

Introduction
Dry eye disease (DED) is a common condition. Its prevalence is rising across all ages. Increased understanding of the pathophysiology of DED over the past few decades has led to advances in its diagnosis and to new treatments, with a particular focus on medications for controlling inflammation. Dissatisfaction among both patients and eye care providers with anti-inflammatory modalities for managing DED, however, suggests the need for additional treatments.[1,2]

New and emerging therapies for DED are aimed at increasing natural tear production. This approach is consistent with current consensus recommendations for DED management that identify restoration of tear film homeostasis as the ultimate goal and cite tear film–oriented therapy to produce a healthy and stable tear film as a primary approach.[3,4]

In this educational activity, experts in DED present a review of natural tear production and its importance for ocular surface health, describe new and emerging tear stimulation treatments for DED, including data from pivotal trials, and share insights on therapeutic decision making through a series of case-based discussions.

Tear Film and Tear Homeostasis
In 2017, the Tear Film & Ocular Surface Society (TFOS) Dry Eye WorkShop (DEWS) II Definition and Classification Subcommittee issued an updated definition of DED that stated: "Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."[5] The relationship between loss of tear film homeostasis and the development of DED is understood by considering the biologic functions of tear film. In addition to providing a pure optical surface that enables clear vision and maintaining comfort, tear film serves to prevent infection, suppress inflammation, clear debris, and promote healing of the ocular surface.[6] Tear film achieves its vital functions because of its complex structure, comprising a tightly controlled mixture of water and an array of electrolytes, at least 5 classes of lipids, soluble and transmembrane mucins, and approximately 1800 proteins **(Figure 1)**.[6-8]

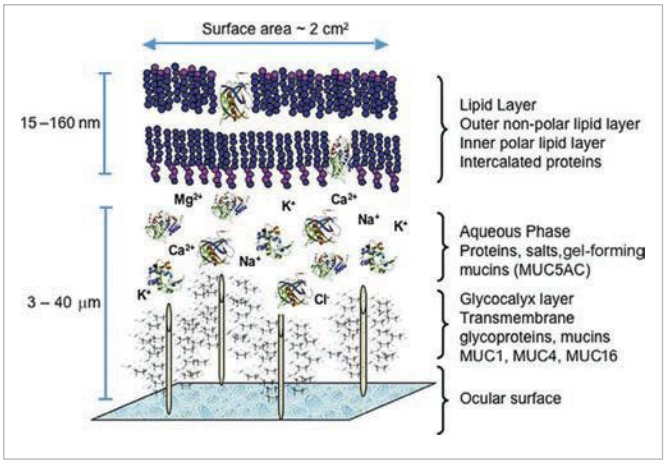

Figure 1. Model of tear film, comprising a complex mixture of lipids, proteins, and electrolytes[8]

Abbreviation: MUC, mucin.

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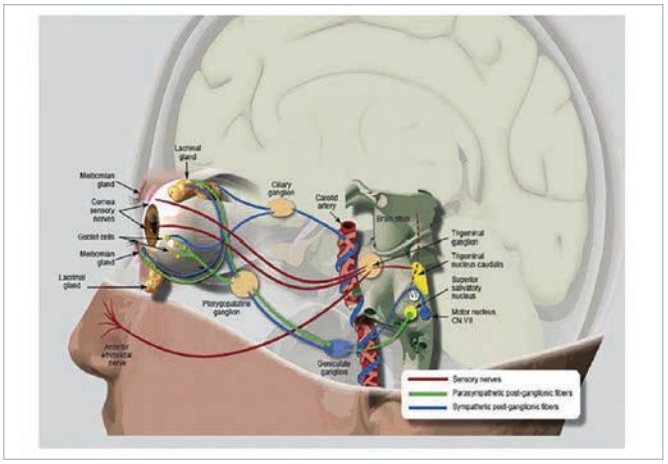

Figure 2. Structures involved in tear production[10]

Abbreviation: CN, cranial nerve.

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Homeostasis of tear film composition is maintained by the lacrimal functional unit (LFU), which consists of the cornea, conjunctiva, main and accessory lacrimal glands, meibomian glands, lids, and interconnecting innervation.[9] The meibomian glands produce lipids, goblet cells in the conjunctiva secrete mucins, and the aqueous component of the tear film and electrolytes comes mainly from the main and accessory lacrimal glands and cells in the conjunctiva. Basal tear flow is controlled through neural reflex arcs that are initiated by sensory stimulation of trigeminal nerve endings located in the cornea, conjunctiva, eyelid margins, and nose **(Figure 2)**.[10]

Sensory impulses arising from afferent nerves in the cornea, conjunctiva, and eyelid margins travel via the ophthalmic branch of the trigeminal nerve to the superior salivatory nucleus in the brainstem, where they connect with efferent parasympathetic fibers that innervate the lacrimal glands, goblet cells, and meibomian glands.[10] The anterior ethmoidal nerve, which is also a branch of the ophthalmic division of the trigeminal nerve, represents the afferent pathway for the nasolacrimal reflex arc by which nasal stimulation results in increased tear production.[11] Intranasal stimulation of the internal branch of the anterior ethmoidal nerve by inhaled air is thought to be responsible for 34% of basal tear production.[12] Compromise of the function of any component of the LFU—which can occur because of disease, injury, or aging—can affect tear production, resulting in loss of tear film and ocular surface homeostasis with the development of DED.

Discussion

Dr Karpecki: The neuroanatomy of tear production is somewhat complex. Do you think optometrists have sufficient knowledge of this topic, or is it even something they need to understand?

Dr Hauswirth: I expect that most clinicians have not thought much about the neural regulation of tear production since they learned about it in optometry school. It is not something you would be likely to keep in the forefront of your mind clinically given some of the more traditional teachings about dry eye and current therapeutic approaches.

Dr Nichols: I believe it is useful for clinicians to have basic knowledge of tear composition and tear production because it is a foundation for understanding how some of our DED therapies work and how they can be combined to create an optimized approach to DED management. I think clinicians know that aqueous, lipids, and mucin are the 3 main components of the tear film and where each component comes from. Although they may no longer recall the details of the neural pathways that are involved in production of the tear components, education can easily address that gap.

Dr Vollmer: I agree that it is important for clinicians to have some basic understanding of the complexity of natural tears and the neuroanatomy of tear production because the information provides the rationale for new neurostimulation treatments for DED. I also think the knowledge is valuable for helping clinicians counsel patients about these treatments. Patients might question how a treatment that is applied to the nose will help their DED, so education will be important for achieving patient acceptance and compliance with these new modalities.

Dr Nichols: I agree that patient education will be important for the success of neurostimulation treatments. Giving an example that patients can relate to would probably be particularly useful for helping them understand how the treatment works. Asking patients if they have noticed their eyes start to water after they breathe in deeply through the nose could help them appreciate the connection between nasal stimulation and tear production.

Current Treatments for Dry Eye Disease

Historically, treatment of DED focused on tear film replenishment with artificial tears and tear film retention with punctal plugs. The approval of cyclosporine emulsion, 0.05%, for DED combined with findings from research establishing the role of inflammation in DED led to a focus on controlling inflammation and the development of new treatments targeting inflammation. Current options for DED management include an array of medications with anti-inflammatory or immunomodulatory activity **(Table 1)**.[13,14] Decisions to use these agents, other medications, and/or procedure-based or surgical interventions are guided according to determination of the DED subtype and the presence of any identifiable underlying causes **(Table 2)**.[15]

Table 1. Anti-Inflammatory Drugs Used to Treat Dry Eye Disease

Drugs Indicated to Treat Dry Eye Disease[13]		
Generic Name	**Preparation**	**Indication**
Cyclosporine, 0.05%	Emulsion	Indicated to increase tear production in patients whose tear production is presumed to be suppressed by ocular inflammation associated with keratoconjunctivitis sicca
Cyclosporine, 0.09%	Emulsion	Indicated to increase tear production in patients with keratoconjunctivitis sicca
Lifitegrast, 5%	Solution	Indicated for the treatment of the signs and symptoms of dry eye disease
Loteprednol etabonate, 0.25%	Suspension	Indicated for the short-term (up to 2 weeks) treatment of the signs and symptoms of dry eye disease

Drugs Used Off-Label to Treat Forms of Dry Eye Disease[14]	
Generic Name	**Preparation**
Azithromycin	Oral
Azithromycin, 1%	Solution
Doxycycline/ Minocycline	Oral
Fluorometholone acetate, 0.1%	Suspension
Loteprednol etabonate (multiple concentrations)	Gel drops, ointment, suspension
Prednisolone acetate, 1%	Suspension

Discussion

Dr Karpecki: What are the benefits of our current therapies? In what areas do you think the armamentarium is lacking?

Dr Vollmer: Our current therapies stand out for the number of different options available for targeting different aspects of DED. For example, numerous treatments are specific to blepharitis or meibomian gland disease as root causes of inflammation.

Dr Hauswirth: I think the number of options available for addressing inflammation is also a strength because controlling inflammation when it exists is probably requisite for achieving the goal of restoring tear film and ocular surface homeostasis. Going forward, however, I see a movement toward using multiple therapies for restoring tear film homeostasis and not just relying on inflammation control.

Dr Karpecki: It is my impression that some clinicians approach DED management with a "silver bullet mentality". They have the mindset that all they have to do is treat one component of DED, such as inflammation, and then try something else only if treating the inflammation is not effective. DED, however, is a multifactorial disease with different subtypes. The most expeditious and effective way to manage DED in any particular patient is by using a multimodal approach that addresses all of its components. These treatable components include obstructed oil glands, inflammation, and the tear film, which still keeps management relatively simple.

Do you think that the potential complexity of proper management for DED contributes to DED underdiagnosis?

Dr Nichols: Selecting appropriate treatment can be complicated. Dry eye treatment failures can and do occur for various reasons. Patients might not adhere to dosing instructions and discontinue on their own. There were failures with cyclosporine when it first became

Table 2. Treatment Options for Dry Eye Disease Subtypes[15]

Aqueous Tear Deficiency	Blepharitis/MGD (Evaporative or Nonevaporative)	Goblet-Cell Deficiency/Mucin Deficiency	Exposure-Related DTS
• Tear supplements (ie, drops, gels, ointments, sprays, and lubricating inserts) • Nutritional supplements • Topical cyclosporine • Topical lifitegrast • Topical steroids • Topical secretagogues • Moisture chamber eyewear	• Tear supplements and lubricants (ie, drops, gels, ointments, sprays, and lubricating inserts) • Lid hygiene and lid scrubs (ie, cleansers, warm compresses, and massage) • Nutritional supplements • Topical cyclosporine • Topical lifitegrast • Topical erythromycin/bacitracin • Topical azithromycin • Topical steroids or antibiotic/steroids	• Tear supplements and lubricants (ie, drops, gels, ointments, sprays, and lubricating inserts) • Topical cyclosporine • Topical lifitegrast • Vitamin A ointment – retinoic acid (compounded) • Moisture chamber eyewear • Topical secretagogues	• Tear supplements and lubricants (ie, drops, gels, ointments, sprays, and lubricating inserts) • Taping of the eyelid • Moisture chamber eyewear
• Oral secretagogues • Topical hormones (compounded) • Autologous serum (compounded) • Albumin (compounded) • Bandage contact lenses/ Scleral lenses • Topical dapsone (compounded) • Topical tacrolimus (compounded) • Topical *N*-acetylcysteine	• Oral doxycycline/tetracycline • Tea tree oil • Topical metronidazole ointment or drops (compounded) • Topical doxycycline (compounded) • Topical clindamycin (compounded) • Topical dehydroepiandrosterone (compounded) • Topical dapsone (compounded) • Topical *N*-acetylcysteine	• Scleral lenses	• Scleral lenses
• Punctal plugs • Cautery occlusion • Amniotic membrane transplantation	• In-office thermal pulsation and/or lid massage • Debridement of the lid margin • Intense pulsed light • Meibomian gland probing		• Eyelid surgery (ie, correction of lid malposition and tarsorrhaphy)

Abbreviations: DTS, dysfunctional tear syndrome; MGD, meibomian gland dysfunction.

available, possibly explained by the fact that cyclosporine was not being used in the right patients because physicians did not have the tools to look at the full ocular surface picture or they were saving cyclosporine use for patients with the most severe disease. Nevertheless, if the experience stuck in the minds of clinicians, they might have decided it was not worth diagnosing DED because there was not an effective treatment. Today, there are more safe and effective treatment options, including cyclosporine. In many cases, however, diagnosis and treatment of DED does not have to be complex. All clinicians can ask about symptoms; examine the lids and meibomian glands; look for other signs of DED at the slitlamp, including staining and tear meniscus height; educate patients about management; and recommend something more than artificial tears. Patients coming for care are bothered by their DED and likely have already tried and failed treatment with artificial tears.

At the same time, I believe that many patients with early mild DED would experience an improvement in symptoms if they used an artificial tear 4 times per day. Complying with such frequent dosing is a tall task. For many patients, a less burdensome treatment that creates natural tears might restore tear film and ocular surface homeostasis, relieve symptoms, and prevent DED from worsening.

Dr Hauswirth: Most patients who seek care probably have early DED and can be managed with a simplified approach. To Dr Nichols' point, clinicians need to detect DED and start an appropriate treatment. By doing so in the early stages, we would likely be seeing fewer patients with more advanced disease who need more complex management.

Dr Karpecki: This brings to mind the quotation: "If I had more time, I would have written a shorter letter." In the past, because knowledge of DED was limited, we did extensive diagnostic testing and recommended all kinds of treatments without a clear rationale. Now that we have more information and greater understanding of DED, we are able to create the "shorter letter" by doing a more straightforward evaluation and offering targeted treatments. The diagnostic approach introduced by TFOS DEWS II is fairly simple. It recommends beginning by asking triaging questions, uncovering risk factors, using a questionnaire to identify symptoms, and then looking for loss of homeostasis by checking osmolarity, tear breakup time (TBUT), or ocular surface staining.[16] When DED is diagnosed, based on the above testing, clinicians can determine the subtype by expressing the meibomian glands and assessing tear meniscus height (TMH).

New and Emerging Treatments Targeting Tear Production

Products aiming to increase natural tear production through activation of the nasolacrimal neural pathway include a commercially available, external, extranasal neurostimulation device—iTEAR100—and an investigational intranasal spray—OC-01.

Extranasal Stimulation

iTEAR100 is a portable, pocket-sized device that received US Food and Drug Administration (FDA) clearance in May 2020 for marketing as a treatment to temporarily increase acute tear production in adults via mechanical stimulation.[17] It features an oscillating tip that is applied bilaterally on the lateral surfaces of the nose to stimulate the external anterior ethmoidal nerve **(Figure 3)**,[18] a branch of the trigeminal nerve that serves as the afferent limb in the nasolacrimal neural pathway. The treatment is recommended to be performed on both sides of the nose for 30 seconds per side. The device has a built-in timer that pauses the oscillations every 10 seconds, which guides users to know when the 30-second treatment period has ended. Participants in premarketing clinical trials were instructed to use the device at least twice a day.

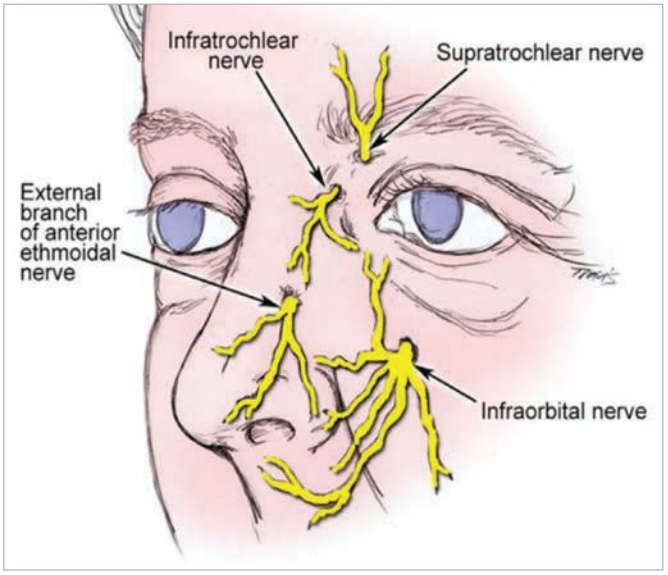

Figure 3. Location of the external branch of the anterior ethmoidal nerve (external nasal nerve)[18]

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FDA clearance of the iTEAR100 was based on results of 2 pivotal trials: a double-masked, randomized, sham-controlled multicenter study and a multicenter single-arm study.[17] The design and results of the single-arm study have been published.[19] Patients enrolled in this study were adults aged ≥ 21 years with a 5-minute anesthetized Schirmer score of ≤ 10 mm in at least 1 eye. In addition, they had to demonstrate the ability to produce tears poststimulation with a > 10-mm change in Schirmer score. The primary efficacy end point was Schirmer index (change from unstimulated to stimulated tear production as measured by the 5-minute anesthetized Schirmer test) at day 30. Of the 108 enrolled patients, 101 were evaluated at day 30. **Figure 4** shows the mean Schirmer scores from patients seen at baseline and at days 14, 30, 90, and 180.[19] Mean prestimulation and poststimulation Schirmer scores were 6 and 28 mm, respectively, at baseline and 9.4 and 18.8 mm, respectively, at day 30. The mean Schirmer index at day 30 was 9.4 mm (95% confidence interval, 7.6-11.3), and 34% of patients achieved a > 10-mm increase.

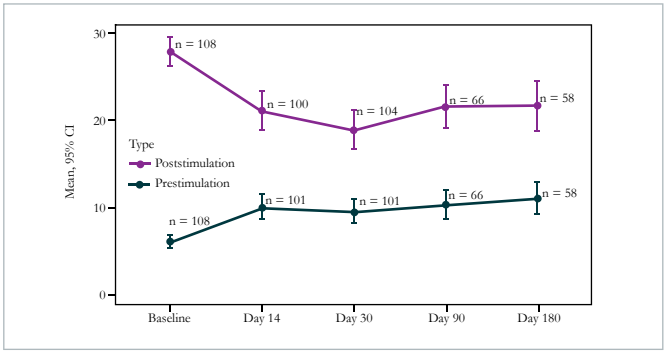

Figure 4. Prestimulation and poststimulation Schirmer scores at baseline and follow-up visits in the single-arm pivotal trial investigating the extranasal tear stimulation device[19]

Abbreviation: CI, confidence interval.

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Improvement in the OSDI (Ocular Surface Disease Index) score was assessed as a secondary end point and decreased (improved) significantly by an average of 14.4 points from baseline,[19] which exceeds the change of > 7 points that is considered to represent a minimal clinically important difference.[20] At study entry, 54 patients were using artificial tears; 44% of those participants decreased their use of artificial tears, and 23% stopped using artificial tears.[19] Statistically significant improvements were also seen in exploratory end points analyzing change from baseline to day 30 in meibomian gland expression, meibum quality, TBUT, and corneal and conjunctival staining. Almost all patients found the device easy to use after reading the instructions and receiving brief training. At day 30, 81% of 101 patients were "satisfied" or "very satisfied". Four patients (4%) who felt their symptoms did not improve were dissatisfied with the treatment.

Adverse events judged to be definitely related to the device occurred in 2 patients.[19] The events were rated as mild and consisted of intermittent nose soreness in 1 patient and slight headache, sneezing, and tickling sensation in the second patient. There were no serious device-related adverse events. Seven patients experienced adverse events considered possibly related to the study device. Five were rated as mild, 1 as moderate, and 1 as a serious unanticipated adverse event, consisting of nausea, headache, lightheadedness, and dizziness after baseline treatment in 1 patient, which led that patient to exit the study.

Intranasal Stimulation

OC-01, also known as varenicline, is being developed as a preservative-free nasal spray to treat the signs and symptoms of DED.[21] OC-01 is a highly selective nicotinic acetylcholine receptor agonist that stimulates the afferent limb of the nasolacrimal reflex pathway by binding to acetylcholine receptors found within the nasal mucosa, and likely at ends of the ethmoid branch of the trigeminal nerve.[22,23]

ONSET-2, the multicenter phase 3 study investigating OC-01, enrolled 758 patients across 22 centers and randomized participants 1:1:1 to receive placebo, OC-01 0.6 mg/mL, or OC-01 1.2 mg/mL.[21,24] Eligible patients had to have used and/or desired to use an artificial tear within the preceding 6 months.[25] The study met its primary end point, showing that the percentage of patients achieving a ≥ 10-mm improvement in Schirmer score from baseline to postinstillation on day 28 was significantly greater in the OC-01 0.6- and 1.2-mg/mL groups than in the placebo group (47.3%, 49.2%, and 27.8%, respectively; $P < .0001$ for both OC-01 groups vs placebo) **(Figure 5)**.[21,24] Mean change in Schirmer score from baseline to day 28 was also significantly greater in the OC-01 0.6- and 1.2-mg/mL groups than in the placebo group (11.3 and 11.5 mm vs 6.3 mm, respectively; $P < .0001$ for both OC-01 groups vs placebo).

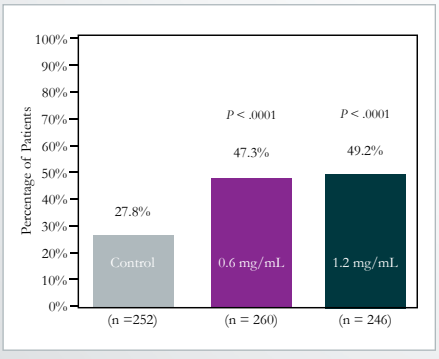

Figure 5. Patients receiving OC-01 0.6 or 1.2 mg/mL in ONSET-2 had significantly improved Schirmer scores after 4 weeks of treatment compared with those receiving placebo[21,24]

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Treatment with OC-01 was also associated with a robust and nominally significant reduction in Eye Dryness Score (EDS) in the 0.6-mg/mL group at day 14 and in the 1.2-mg/mL group at day 28 compared with that measure in the placebo group **(Figure 6)**.[21,24] In addition to mean change in baseline EDS through day 28, mean change in baseline corneal fluorescein staining and EDS in the Controlled Adverse Environment chamber at day 28 were also evaluated as secondary end points.[21] There were no significant changes from baseline to day 28 in EDS in the Controlled Adverse Environment chamber.

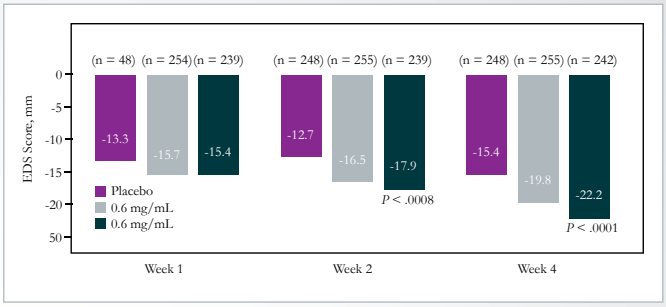

Figure 6. Mean Eye Dryness Score at follow-up visits in ONSET-2[21,24]

Abbreviation: EDS, Eye Dryness Score.

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OC-01 was well tolerated in the ONSET-2 study.[21,24] Sneezing was the most common adverse event associated with OC-01, occurring in 95.0% of 260 patients in the OC-01 0.6-mg/mL group, in 96.7% of 245 patients in the OC-01 1.2-mg/mL group, and in 29.1% of 251 patients in the placebo group. The sneezing usually remitted within the first minute following administration and was rated mild and generally not bothersome to patients.[26] Other reported adverse events in the OC-01 0.6- and 1.2-mg/mL groups occurring at a rate of > 5% included cough (18.8% and 21.6%, respectively), throat irritation (13.5% and 18.0%, respectively), and instillation site reaction (7.3% and 14.3%, respectively).[21] These events were also transient and occurred at a rate of ≤ 2% in the placebo group. Overall, < 2% of patients in either OC-01 treatment group experienced a treatment-emergent adverse event leading to treatment discontinuation.[26] There were no serious adverse events.[21]

The effect of treatment with OC-01 on goblet cell degranulation and meibomian glands in patients with DED was investigated in a small study that randomized 18 patients 2:1 to a single administration of OC-01 1.2 mg/mL or placebo.[27] The results showed significant reductions in goblet cell area and perimeter in the OC-01 group compared with the control group, which suggests OC-01 was associated with goblet cell degranulation. OC-01 was not associated with a significant effect on meibomian gland area or perimeter, although the investigators noted that judging from their baseline meibomian gland area, the study participants may have more severe meibomian gland disease and therefore be less likely to show any significant change after an acute treatment.

Discussion

Dr Karpecki: Are both neurostimulation and tear stimulation accurate terms to describe the mechanism of action for the external stimulator and the OC-01 nasal spray?

Dr Vollmer: I think the terms go hand in hand because neurostimulation causes tear stimulation.

Dr Nichols: Neurostimulation is the afferent process that creates the efferent response of tear stimulation.

Dr Karpecki: Neurostimulation to treat DED is not new because an intranasal electrical neurostimulator was approved in 2018 to produce tears to treat dry eye symptoms until the manufacturer discontinued its use.[28] Do you think discontinuation of the intranasal electrical neurostimulator has affected clinicians' perceptions of neurostimulation as a strategy for DED management?

Dr Nichols: The decision to stop production/promotion of the intranasal neurostimulator likely had little to do with efficacy or safety.[29] I believe that a variety of business-related issues developed when the device was being introduced that created challenges for its commercial success, and the technology was ahead of its time. I consider it unfortunate that the intranasal electrical neurostimulator was not able to reach its full potential because I believe that neurostimulation of tear production has value for treating DED.

Nevertheless, the electrical device was somewhat awkward to use because the probe had to be inserted deep within the nose, and it was recommended for 4-times-daily use. I think there might be greater acceptance for the external device, which is easier to use than the intranasal neurostimulator, and for the nasal spray, which uses an administration route that is familiar to most patients. In addition, both the external device and nasal spray are used just twice daily.

Dr Hauswirth: I find it exciting to see the continued industry interest in neurostimulation for tear production. I think these approaches are useful for patient care and also for allowing researchers to better understand the neural pathways regulating meibum release and goblet cell degranulation. I agree that the external neurostimulator and nasal spray are easier and more comfortable to use than an internal device. For these reasons, I expect they will be met with higher patient acceptance.

Dr Karpecki: What do you see as the benefits of using the new and emerging products to stimulate production of natural tears vs using artificial tears?

Dr Hauswirth: Natural tears contain a myriad of components that are essential for tear film stability and ocular surface homeostasis. Artificial tears do not come close to replicating the composition of natural tears.

Dr Karpecki: Artificial tears are now a mainstay of managing all DED. Do you think treatments that stimulate natural tear production should replace artificial tears, or will they be something that should be added if a patient does not achieve sufficient benefit using artificial tears?

Dr Nichols: Practically speaking, the answer to that question will be determined by how insurance coverage affects patient access to the new treatments. One situation in which I think a nasal treatment that stimulates natural tear production could be especially useful would be to manage DED related to contact lens wear because patients could then limit or avoid the need for using topical eye drops when their lenses are in.

Dr Vollmer: The neurostimulator modalities would also be a good option for patients who have difficulty administering eye drops or who do not like using eye drops for any reason. Also, the external neurostimulator might appeal to patients who prefer drug-free options.

Dr Hauswirth: I see these treatments being used as a supplement to other therapies that provide the benefits of natural tears along with a reduction in drop burden and preservative exposure.

Dr Nichols: Figure 4 showing the prestimulation and poststimulation Schirmer scores from the baseline and follow-up visits in the external neurostimulator trial suggests there was some leveling out of response with time.[19] Did patients notice any loss of effectivity?

Dr Karpecki: Perhaps the baseline measurement reflects an exaggerated response to initial use. It may be more reasonable to consider the data collected at day 14 as the reference for evaluating if the response diminishes over time because the results from day 14 onward were stable. Six of the 7 patients I enrolled in the study purchased the device when it became commercially available. I continue to see these patients regularly. After 9 to 12 months of use, none are reporting any loss of effect. Furthermore, considering that tear production is constantly stimulated by air inhaled through the nose, I would not expect the development of tolerance to a product that is used just twice daily.

Dr Vollmer: The data from the study show that not only did the treatment induce tear production, but according to the prestimulation Schirmer score data, it was associated with an increase in basal tear secretion.[19] This benefit is consistent with experience showing that after chronic use of neurostimulation devices to treat other disease, there is a buildup of effect that translates into a benefit extending beyond the time of application.

Patients in the pivotal study were also invited to continue using the device beyond the primary end point visit. Data were analyzed from 58 patients who used the device for 180 days, and the Schirmer test and OSDI data for those patients showed no evidence of tolerance or loss of response.[19] We will have to wait to see what the experience with the device is when it is used by larger numbers of patients.

Case 1: Mild Aqueous-Deficient Dry Eye Disease

From the Files of Scott Hauswirth, OD, FAAO

A 54-year-old female business executive presented with the chief concern of increased eye discomfort at the end of the day and occasional redness for the past 6 months. She had been wearing silicone hydrogel soft contact lenses for several years but stopped approximately 9 months ago because of discomfort and redness, which she self-treated with occasional use of over-the-counter tetrahydrozoline, 0.05%, or brimonidine tartrate, 0.025%.

The patient was healthy and had no systemic medical issues. Results from her screening and diagnostic evaluation were as follows: SPEED (Standardized Patient Evaluation of Eye Dryness) score of 9, DEQ-5 (Dry Eye Questionnaire 5) score of 11, 1-2+ lissamine green staining of the conjunctiva, no corneal staining or blink abnormality, decreased TMH, 10 of 15 meibomian glands yielded moderate volume of clear liquid secretions, and TBUT of 7 seconds OU. ***Figure 7*** *shows the image results from an ocular surface analyzer.*

Dr Hauswirth: The factors that I consider when deciding on therapy for patients with DED include symptom frequency and bother, clinical sign severity and concordance with symptoms, DED subtype, inflammation, if any anatomical issues are contributing to DED and are relevant to the neurostimulator products, and if the patient had any nasal surgery or has a nerve deficiency. I also consider patient lifestyle and preference because both can certainly affect the likelihood of treatment adherence.

What are your thoughts about diagnosis in this patient?

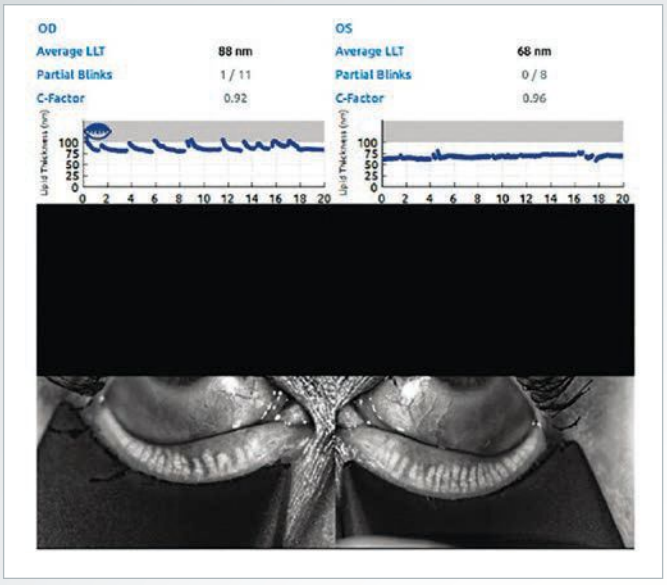

Figure 7. Results from evaluation of the patient in Case 1 with an ocular surface analyzer

Abbreviation: LLT, lipid layer thickness.

Dr Karpecki: The clinical findings are not really consistent with DED related to contact lens wear, and she does not appear to have significant meibomian gland dysfunction. Considering the conjunctival staining and decreased TMH, I believe she most likely has aqueous-deficient DED and perhaps also some contribution from decreased mucin secretion.

Dr Nichols: The patient does not appear to be overly dry and does not have severe symptoms. The worsening of symptoms at the end of the day may be related to time spent in front of a computer.

Dr Vollmer: I agree that this patient likely has aqueous-deficient DED that is unrelated to her previous history of contact lens wear. She has a relatively shortened TBUT, yet her corneas remain uncompromised. Her symptoms are also not likely attributable to significant meibomian gland dysfunction, per the results from the ocular surface analyzer.

Dr Hauswirth: A patient with these presenting features would most likely be offered an artificial tear. I thought she was a good candidate for a neurostimulation type of therapy that she could use whenever she felt symptoms developing. I did not think her DED signs and symptoms were severe enough to start immunomodulatory therapy. I did tell her to stop using the tetrahydrozoline and brimonidine. I would hope with increased tear production via neurostimulation, conscious blinking, and other good computer habits, she would likely have a significant decrease in her discomfort and redness.

Case 2: Dry Eye Disease Associated With a Systemic Inflammatory Disease

From the Files of Scott Hauswirth, OD, FAAO

A 48-year-old male presented with eye discomfort, burning, blurred vision, and foreign body sensation. His symptoms were associated with graft-vs-host disease that developed 60 days after he underwent a bone marrow transplant for acute lymphoblastic leukemia. Current medications included oral prednisone, tacrolimus, and ruxolitinib. He scored a 17 on both the SPEED and DEQ-5. His examination showed extensive corneal and conjunctival epitheliopathy ***(Figure 8)****; Schirmer I (without anesthesia) test result of 3 mm OD, 4 mm OS; SMTube 0.5 OU; and TBUT of < 1 second OU.*

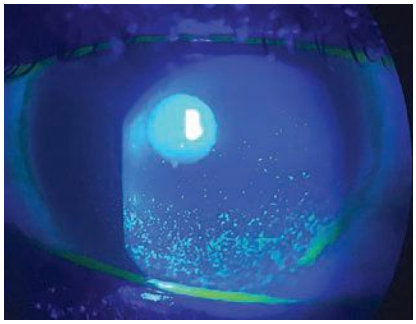

Figure 8. Slitlamp image after fluorescein staining of the patient in Case 2 shows extensive corneal epitheliopathy

Dr Hauswirth: This patient has ocular graft-vs-host disease that is not responding to his systemic medications. I started him on a topical steroid for rapid control of the inflammation and on lifitegrast, 5%, twice daily in both eyes, which I expected he would continue using long term. I think this patient would be a good candidate for a treatment that stimulates tear production. I would insert punctal plugs to retain the tears once the inflammation is under better control.

Dr Vollmer: I agree. I would probably start him on loteprednol to control the ocular surface inflammation, insert punctal plugs, and recommend that he use the external neurostimulating device. Because the patient would likely benefit from an increase in basal tear production, use of twice-daily intranasal dosing of OC-01 could be recommended, if it were available, per the data from clinical trials known thus far. Its use in combination with an anti-inflammatory agent would be a welcome addition.

Dr Karpecki: Judging from the severity of staining, this patient has significant ocular surface inflammation, which, for me, is an indication for topical steroid treatment. I also think he would benefit from neurostimulation treatment that increases tear production. Evidence from the study of OC-01 and from research using the intranasal neurostimulator suggest that neurostimulation can increase mucin release from goblet cells that would be helpful for this patient.[27,30] Very few of our DED therapies provide that benefit.

Dr Nichols: This patient would likely benefit long term from being maintained on immunomodulatory therapy and potentially a treatment that could increase natural tear production. Amniotic membranes or autologous serum are options with severe corneal epitheliopathy, although they do not appear to be needed yet in this particular case.

Dr Vollmer: Do you think that if patients need to start on multiple therapies, showing their slitlamp image encourages compliance because it is a way to get them to appreciate the severity of their condition?

Dr Hauswirth: A picture is definitely worth a thousand words, although this particular patient was very motivated to be compliant because he was very uncomfortable and noticing that his symptoms were rapidly worsening. A slitlamp image would be especially helpful for a patient who is in a neurotrophic state and has severe signs of DED with minimal or no symptoms.

Dr Nichols: I like the idea of doing an in-office test to evaluate the response to neurostimulation and showing patients their TMH in slitlamp images taken prestimulation and poststimulation. As a measure

of aqueous production, TMH is also faster and more easily done than a Schirmer test.

Case 3: Refractory Autoimmune Disease–Associated Dry Eye Disease

From the Files of Scott Hauswirth, OD, FAAO

A 63-year-old retired female being treated for DED associated with systemic autoimmune disease presented with concerns of ocular burning, redness, and general discomfort. The patient was diagnosed with rheumatoid arthritis 20 years ago, had systemic lupus erythematosus, and was on methotrexate and azathioprine. Current therapy for DED included topical cyclosporine A, 0.05%, twice daily, which she started 8 years ago; nonpreserved artificial tears 6 to 8 times daily; warm compress therapy once daily; and an ocular lubricant gel at bedtime.

Findings at her visit were SPEED score of 25, DEQ-5 score of 20, 1+ lid telangiectasia OU, moderate turbid thick secretions from 9 of 15 meibomian glands, 1+ conjunctivochalasis, and TBUT of 2 seconds OD/ 3 seconds OS. Ocular surface staining shows 3-4+ lissamine green conjunctival staining and 2+ punctate epithelial keratitis (mainly inferior) ***(Figure 9)****.*

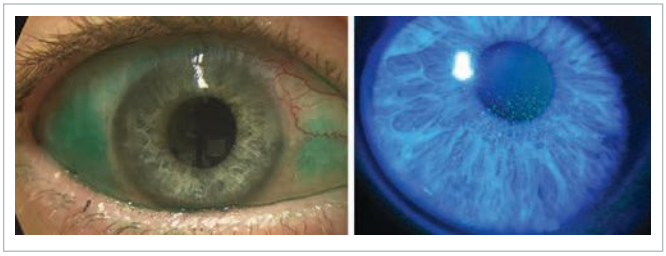

Figure 9. Ocular surface staining of the patient in Case 3

Dr Hauswirth: We know that autoimmune disease has the potential impact of decreasing overall tear production; in this case, the patient would be defined as a mixed mechanism patient with dry eye and severe conjunctival and moderate corneal epitheliopathy.

Dr Nichols: Chronic cyclosporine drops appear to be successful, although the patient's simultaneous artificial tear usage is significantly burdensome at every 1 to 2 hours. Addressing her meibomian gland dysfunction is also warranted.

Case 4: Patient With Glaucoma and Minimal Dry Eye Disease Symptoms

From the Files of Scott Hauswirth, OD, FAAO

A 43-year-old male who works in information technology presented with a concern of eye fatigue and irritation toward the end of the workday. He had bilateral LASIK (laser-assisted in situ keratomileusis) 10 years ago, and was recently diagnosed with primary open-angle glaucoma. He was using a prostaglandin analogue once daily for intraocular pressure lowering and artificial tears 1 to 3 times a day. His systemic medical history was noncontributory. On examination, slitlamp findings were unremarkable other than for slight conjunctival hyperemia OU. TBUT was 6 seconds OD/ 5 seconds OS. SPEED score was 10. DEQ-5 score was 9.

Dr Hauswirth: Two of the key pieces here are the history of LASIK, which at least temporarily disrupts the neural feedback loop for monitoring the corneal surface and likely will drop tear production, and the use of a glaucoma medication, which is also disruptive to the ocular surface. In this case I think it would be helpful to try neurostimulation as a first-line option.

Dr Karpecki: I like the idea of treating DED in this patient with neurostimulation rather than prescribing another topical medication that would add to his drop burden and potentially increase preservative exposure. Most patients with glaucoma are on preserved prostaglandin analogue therapy. The combination of a proinflammatory medication with a benzalkonium chloride preservative typically limits the use of any further agents, including DED treatments, with preservatives. In cases of nonpreserved DED treatments, adding an additional drop can sometimes confuse patients with glaucoma who are on multiple therapies. Choosing something different, such as neurostimulation, that produces more of the patient's own natural tears, may be easier in these circumstances.

Dr Nichols: I agree. The extra lubrication of the ocular surface achieved with stimulation of natural tear production could be really beneficial for patients with DED related to topical medication use.

Dr Hauswirth: Exactly. I think anything we can do here to stimulate natural tear production might be beneficial. Again, we know that natural tears would likely be better than artificial tears, providing higher amounts of growth factors and other support for a healthier ocular surface.

Dr Vollmer: I also agree. Neurostimulation would be a first-line option in this case because the patient's current drops all contain preservatives, and the nasal delivery route would not further contribute to his tear hyperosmolarity. Additionally, I agree with Dr Karpecki that compliance is likely to decrease with the addition of any more topically administered drops.

Take-Home Messages

Natural tears and DED

- Natural tears are a complex mixture of water, electrolytes, lipids, mucins, and proteins that is not replicated in any artificial tear product
- DED is characterized by a loss of tear film homeostasis
- Tear film homeostasis is maintained by the LFU, which consists of the cornea, conjunctiva, main and accessory lacrimal glands, meibomian glands, lids, and interconnecting innervation
- Afferent limbs of neural reflex arcs that mediate natural tear production include sensory nerves arising in the cornea, conjunctiva, eyelid margins, and nose
- Compromise of any of the components of the LFU affects tear production, leading to loss of tear film homeostasis

New and emerging tear stimulation treatments

- New and emerging treatments for DED target increasing natural tear production through activation of the nasolacrimal neural reflex arc
- A device applied externally to initiate the nasolacrimal neural reflex arc by stimulating the external anterior ethmoidal nerve is FDA cleared for temporarily increasing acute tear production in adults
- OC-01 (varenicline) is an investigational intranasal spray that acts to increase tear production by binding to trigeminal nerve endings in the nasal mucosa
- Clinical trial results support the efficacy and safety of the nose-based treatments for increasing aqueous tear production and improving signs and/or symptoms of DED

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1. According to the definition from TFOS DEWS II, DED is a multifactorial disease of the ocular surface characterized by:
   a. Aqueous tear deficiency
   b. Loss of homeostasis of the tear film
   c. Ocular surface inflammation
   d. Tear film instability

2. The LFU consists of:
   a. Main and accessory lacrimal glands
   b. Lacrimal glands, goblet cells, and meibomian glands
   c. Tear-producing structures and interconnecting nerves
   d. All the above

3. What nerve is the afferent part of the corneal lacrimation reflex?
   a. Optic nerve
   b. Ophthalmic branch of the trigeminal nerve
   c. Maxillary branch of the trigeminal nerve
   d. Abducens nerve

4. Air inhaled through the nose is thought to account for __ of basal tear production.
   a. 14%
   b. 24%
   c. 34%
   d. 44%

5. Which is NOT among the tests recommended by TFOS DEWS II for checking tear film homeostasis?
   a. Ocular surface staining
   b. Osmolarity
   c. Schirmer score
   d. TBUT

6. Which measure is recommended by TFOS DEWS II to identify the aqueous deficiency subtype of DED?
   a. Anesthetized Schirmer score
   b. Phenol red thread
   c. TBUT
   d. TMH

7. The external neurostimulatory device for DED received FDA clearance as a treatment for:
   a. Improving the signs and symptoms of DED
   b. Reducing inflammation associated with DED
   c. Temporarily increasing acute tear production
   d. Temporarily increasing aqueous tear production and meibum secretion

8. The tip of the external neurostimulatory device aims to stimulate the external branch of the _____ nerve.
   a. Anterior ethmoidal
   b. Lacrimal
   c. Superficial petrosal
   d. Zygomaticofacial

9. At the primary end point visit in a pivotal trial investigating the external neurostimulator, what percentage of participants achieved a > 10-mm increase in Schirmer index?
   a. 26%
   b. 34%
   c. 52%
   d. 76%

10. What was the average improvement from baseline OSDI score at the primary end point visit in the external neurostimulator pivotal clinical trial?
    a. 10.2
    b. 12.4
    c. 14.4
    d. 18.4

11. Exploratory end point analyses in the external neurostimulator pivotal clinical trial provided evidence supporting benefits for improving all the following, EXCEPT:
    a. Corneal staining
    b. Mast cell degranulation
    c. Meibomian gland expression
    d. TBUT

12. Compared with the primary end point visit at day 28, patients who continued to use the external neurostimulator for 180 days showed:
    a. Declining benefit according to Schirmer index
    b. Declining benefit according to OSDI score
    c. Continued improvement in Schirmer index and OSDI score
    d. Worsening of nasal skin irritation at the site of application

13. Which adverse event reported by 2 patients was related to use of the external neurostimulator device?
    a. Epistaxis
    b. Nasal skin erosion
    c. Rhinitis
    d. Sneezing

14. OC-01 acts as a(n):
    a. α-adrenergic receptor agonist
    b. α-adrenergic receptor antagonist
    c. Muscarinic receptor agonist
    d. Nicotinic acetylcholine receptor agonist

15. OC-01 binds to receptors on the _____ nerve.
    a. Lacrimal
    b. Nasopalatine
    c. Oculomotor
    d. Trigeminal

16. In the ONSET-2 trial, what percentage of patients in the OC-01 0.6- and 1.2-mg/mL groups achieved a ≥ 10-mm improvement in Schirmer score from baseline to postinstillation on day 28?
    a. 27.8% and 47.3%, respectively
    b. 27.8% and 49.2%, respectively
    c. 47.3% and 49.2%, respectively
    d. 47.3% and 61.2%, respectively

17. In the ONSET-2 trial, what was assessed as the symptom end point?
    a. EDS
    b. DEQ-5 score
    c. OSDI score
    d. The study investigated only improvement in signs of DED

18. In the ONSET-2 trial, what was the most common adverse event associated with OC-01?
    a. Headache
    b. Intranasal itching
    c. Rhinitis
    d. Sneezing

19. Which component of the LFU produces lipids in a normal tear film?
    a. Meibomian glands
    b. Goblet cells
    c. Conjunctiva
    d. None of the above

20. A 56-year-old female with primary open-angle glaucoma complains of eye fatigue and grittiness, especially at the end of the day. She has mild symptoms of DED: SPEED score of 12; TMH of 0.24 mm; and normal matrix metalloproteinase-9 test result. Her glaucoma is managed with 3 topical agents, but she admits to having some difficulty adhering to her treatment regimen. Which of the following treatment options for DED is likely to be most beneficial?
    a. Artificial tears
    b. External neurostimulator device
    c. Cyclosporine, 0.05%
    d. a and c