

Dry Eye Management

With
**Stimulating
Natural Approaches**



Faculty



Stephen C. Pflugfelder, MD (Chair)

Professor of Ophthalmology
James and Margaret Elkins Chair
Baylor College of Medicine
Houston, Texas



Nathan Lighthizer, OD

Associate Dean and Associate Professor
Chief, Specialty Care Clinics
Northeastern State University
College of Optometry
Tahlequah, Oklahoma



Selina McGee, OD, FAAO

Visionary Founder and CEO
BeSpoke Vision
Edmond, Oklahoma

Original Release: May 15, 2025

Expiration: May 15, 2026

This continuing medical education activity is provided by MedEdicus LLC.

MedEdicus

This continuing medical education activity is supported through an educational grant from Viatrix Inc.

Distributed with **REVIEW**
of OPTHALMOLOGY

Activity Description and Purpose

Recent advances in dry eye disease (DED) management have introduced therapeutic strategies that stimulate natural tear production by activating neural pathways within the lacrimal functional unit (LFU). This educational activity provides ophthalmologists with a clinically relevant update on DED pathophysiology, with a focus on LFU's central role in tear film homeostasis and disease progression. Through faculty-led discussions and real-world case examples, the activity explores diagnostic strategies, such as tear osmolarity testing and meibography, and highlights novel neurostimulation treatments, including varenicline nasal spray and mechanical external stimulators. Participants will enhance their ability to (1) describe the role of the LFU in the pathogenesis of DED and (2) design treatment plans incorporating neurostimulation to optimize patient outcomes.

Target Audience

This educational activity is intended for ophthalmologists.

Learning Objectives

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

- Describe the role of the lacrimal functional unit in the pathogenesis of dry eye disease
- Design treatment plans for patients with dry eye disease using neurostimulation

Accreditation Statement



MedEdicus LLC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Credit Designation Statement

MedEdicus LLC designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credit™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Instructions for Obtaining Credit

To obtain *AMA PRA Category 1 Credit™* for this activity, please read the monograph, consult referenced sources as necessary, complete the evaluation form with posttest answer form, and email to info@mededicus.com. Within 14 days, a certificate will be emailed to the email address provided on the form.

Disclosure Policy

MedEdicus adheres to the ACCME's Standards for Integrity and Independence in Accredited Continuing Education. Any individuals in a position to control the content of a CME activity, including faculty, planners, reviewers, or others, are required to disclose all financial relationships with ineligible entities (commercial interests). All relevant conflicts of interest have been identified and mitigated by MedEdicus prior to the commencement of the activity.

Faculty

Nathan Lighthizer, OD, is a consultant for Diopsys, Inc, OCuSOFT Inc, Orasis Pharmaceuticals, Reichert, Inc, and Virtual Vision Health; is an advisory board member of Aerie Pharmaceuticals, Inc,

Amgen Inc, Bausch & Lomb Incorporated, Bruder Healthcare, EyePromise, Ivantis Inc, Novartis Pharmaceuticals Corporation, Orasis Pharmaceuticals, Oyster Point Pharma, Inc, Tarsus Pharmaceuticals, Inc, and Théa Pharma Inc; and is on the speakers bureau for AbbVie Inc, Avellino, Diopsys, Inc, Dompé US, Inc, Ellex, iCare USA Inc, Innova Systems, Lumenis, NIDEK USA, Inc, Novartis Pharmaceuticals Corporation, Optovue, Inc, Reichert, Inc, RVL Pharmaceuticals, Inc, Sight Sciences, Sun Pharmaceutical Industries, Inc, and Virtual Vision Health.

Selina McGee, OD, is a consultant for AbbVie Inc, Aldeyra Therapeutics, Amgen Inc, Avellino, Bruder Healthcare, Cynosure, Dompé US, Inc, Eyevance, Harrow, Inc, Kala Pharmaceuticals, Lumenis, Novartis Pharmaceuticals Corporation, Ocuphire Pharma, Optovue, Inc, Oyster Point Pharma, Inc, RVL Pharmaceuticals, Inc, ScienceBased Health, Sun Pharmaceutical Industries, Inc, Tarsus Pharmaceuticals, Inc, Théa Pharma Inc, Topcon Medical Systems, Inc, Trukera, Versant Ventures, and Zeiss; and is on the speakers bureau for AbbVie Inc, Bausch & Lomb Incorporated, Cynosure, Dompé US, Inc, Lumenis, Optovue, Inc, Oyster Point Pharma, Inc, and Tarsus Pharmaceuticals, Inc.

Stephen C. Pflugfelder, MD, is a consultant for Alcon, Dompé US, Inc, Hanall Biopharma*, Kala Pharmaceuticals, KOWA Pharmaceuticals America, Inc, and Nicox*; and is a contracted researcher for Dompé US, Inc.

* The financial relationship existed during the past 24 months but has now ended

Peer Reviewer

This activity was peer reviewed. The peer reviewer has no relevant commercial relationships to disclose.

Planners, Managers, and Writers

MedEdicus planners, managers, and writers have no relevant commercial relationships to disclose.

Disclosure of Commercial Support

This continuing medical education activity is supported through an educational grant from Viatrix Inc.

Off-Label Discussion

This educational activity may include discussion of unlabeled and/or investigational uses of drugs and devices. Please refer to the official prescribing information for each drug or device discussed in this activity for approved dosing, indications, and warnings.

Provider Contact Information

For questions about this educational activity, please contact MedEdicus LLC at info@mededicus.com.

To view the MedEdicus privacy policy, visit <http://mededicus.com/privacy-policy.php>.

Disclaimer

The views and opinions expressed in this educational activity are those of the faculty and do not necessarily represent the views of MedEdicus LLC, Viatrix Inc, or *Review of Ophthalmology*.

Dry Eye Management

With Stimulating Natural Approaches

Introduction

Dry eye disease (DED) is a chronic multifactorial disease that can have a significant negative impact on quality of life.¹ The disease is characterized by a loss of tear film homeostasis, and its development and progression are driven by tear film instability, hyperosmolarity, and ocular surface inflammation that interact in a self-perpetuating vicious circle.²

Tear film homeostasis is maintained by the lacrimal functional unit (LFU), which regulates tear secretion, distribution, and clearance to meet the demands of the ocular surface and maintain ocular surface health.² The LFU consists of the cornea, conjunctiva, main and accessory lacrimal glands, meibomian glands (MGs), lids, and interconnecting neural network (**Figure 1**).² 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.³ These impulses travel via the ophthalmic branch of the trigeminal nerve to the brainstem, where they connect with efferent parasympathetic fibers that innervate the lacrimal glands, goblet cells, and MGs.⁴ 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.^{3,5} 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.⁵

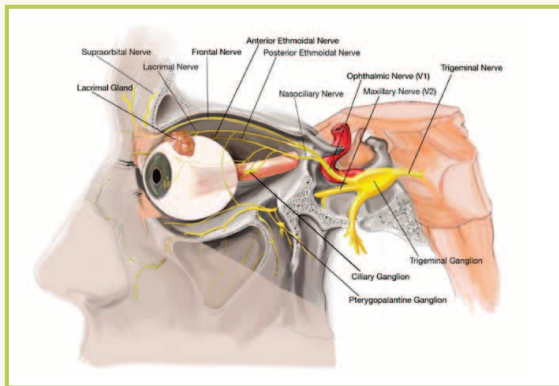


Figure 1. Schematic of the lacrimal functional unit neural network²

Reprinted from *The Ocular Surface*, 25, Pflugfelder SC, Cao A, Galor A, Nichols KK, Cohen NA, Dalton M, Nicotinic acetylcholine receptor stimulation: a new approach for stimulating tear secretion in dry eye disease, 58-64, Copyright 2022, with permission from Elsevier.

Compromised function of any LFU component can result in loss of tear film homeostasis, which stimulates an inflammatory cascade.² Inflammation damages the ocular surface, corneal nerves, and tear-producing structures. Tear film instability causes fluctuating vision, and inflammation can induce ocular burning, stinging, grittiness, and redness.

Studies analyzing molecular factors in the tear film of patients with DED show overexpression of proinflammatory cytokines.^{6,7} One recent study measuring levels of proinflammatory and anti-inflammatory cytokines in the tears of healthy individuals and patients with DED found a statistically significant correlation

between Schirmer test score (STS), Eye Dryness Score (EDS), and cytokine levels, such that a higher STS correlated with lower tear cytokine levels and a worse EDS correlated with higher tear cytokine levels.⁶ These results provide further support for the ideas that patients with symptomatic DED have ocular surface inflammation and that a better tear film is associated with less severe symptoms and a lower level of inflammatory cytokines.

Discussion

Dr Pflugfelder: When I see a patient with DED, I try to identify which LFU component is the underlying cause of the disease and use that information to guide targeted therapy.

Has the idea that DED is a consequence of LFU dysfunction affected your approach to diagnosing and/or managing DED?

Dr Lighthizer: It has because it underscores the value of intervening with a treatment that stimulates natural tear production vs relying only on artificial tears to supplement the tear film. In contrast to artificial tears, healthy natural tears are a complex mixture of water, electrolytes, lipids, mucins, and proteins and function to prevent infection, suppress inflammation, and promote healing of the ocular surface.⁹

Furthermore, understanding that the LFU is a complex system and that DED is a multifactorial disease supports the idea that effective management of DED can require an individualized, multimodal approach.

Dr Pflugfelder: Does understanding of the relationship between inflammation and DED affect your treatment approach?

Dr Lighthizer: When inflammation is more severe, I like to initiate acute treatment with a corticosteroid, which can act quickly to reduce the inflammation, while simultaneously starting a topical immunomodulator, which takes longer for onset of benefit. The study showing the correlation between cytokine levels and STS points to the value of a treatment that can stimulate natural tear production by the LFU.⁶

Dr McGee: Treatments for DED that are used to decrease inflammation or improve MG function can enable increased tear production by the LFU and thereby restore ocular surface homeostasis, but it can take time to see those benefits. Neurostimulation approaches increase LFU function directly and quickly.

Dr Pflugfelder: Perhaps a treatment that directly impacts LFU function should also be the goal for long-term management of DED.

How do you evaluate the LFU and tear dysfunction?

Dr McGee: We have patients complete the SPEED (Standard Patient Evaluation of Eye Dryness) questionnaire. Anyone whose score is ≥ 6 undergoes tear film osmolarity testing. Every patient is also evaluated with a slitlamp examination that includes vital dye staining. I find that sodium fluorescein strips with a No. 12 Wratten filter work best. I wait 2 minutes before assessing the cornea for staining, and take that time to appreciate the tear meniscus height and evaluate the MGs by looking at structure and pushing on glands to establish function.

Dr Lighthizer: We use the SPEED questionnaire as a quantitative instrument and have patients complete it at every visit. In addition, we have developed a qualitative questionnaire that patients complete at their first visit to obtain information on etiologic and contributory factors, including ocular and systemic medications, water intake, fish consumption, and systemic conditions.



Our examination includes all the components that Dr McGee mentioned. I like to do meibography and show patients their images because a picture is worth a thousand words. As an academic practice, we also have access to technology for measuring tear osmolarity and the matrix metalloproteinase-9 (MMP-9) assay, which can guide treatment decisions by identifying inflammation.

Treatments for Dry Eye Disease

Current consensus recommendations for DED management identify restoration of tear film homeostasis as the ultimate goal.^{9,10} Treatment options for DED have increased in recent years with the introduction of modalities that aim to reduce evaporative tear loss, control ocular surface inflammation, address meibomian gland dysfunction (MGD), or increase natural tear production by neurostimulation. Treatment based on neurostimulation of natural tear production became available in 2018 with the introduction of an intranasal electrical device stimulating sensory neurons in the nose (TrueTear), but sale of this product was discontinued by the manufacturer in 2020.¹¹ Current and emerging neurostimulation treatments use chemical or mechanical approaches for nerve activation.

Chemical Neurostimulation

Varenicline solution nasal spray was approved by the US Food and Drug Administration (FDA) in October 2021 for treatment of the signs and symptoms of DED.¹² The agent is recommended to be sprayed once into each nostril twice daily at approximately 12-hour intervals; each spray delivers 0.05 mL containing varenicline 0.03 mg.¹³

Varenicline is a highly selective nicotinic acetylcholine receptor agonist that stimulates tear production by binding to acetylcholine receptors found within the nasal mucosa and likely at ends of the ethmoid branch of the trigeminal nerve.¹³⁻¹⁵ ONSET-2, the 4-week phase 3 trial investigating varenicline nasal spray for the treatment of DED, met its primary end point, showing that 47.3% of 260 patients receiving varenicline 0.03-mg/0.05-mL spray achieved a ≥ 10 -mm improvement in STS from baseline to week 4 compared with 27.8% of 252 patients receiving vehicle control ($P < .0001$).¹⁶ The change from baseline STS to week 4 was also significantly greater in the group treated with varenicline 0.03 mg ($P < .0001$) (Figure 2).¹⁶ The most common treatment-emergent adverse events among the patients receiving varenicline 0.03-mg/0.05-mL nasal spray were sneezing (95%), followed by cough (18.8%), throat irritation (13.5%), and instillation site irritation (8.1%); most events were considered mild.¹⁶

A post hoc analysis of pooled data from ONSET-2 and an earlier phase 2b study showed that varenicline nasal spray improved tear production and DED-related symptoms in patients with self-reported autoimmune disease.¹⁷ Varenicline has also been reported to improve symptoms, corneal and conjunctival staining, tear secretion, and inflammatory cytokine levels in an open-label pilot study including patients with moderate to severe Sjögren syndrome.¹⁸ Small studies found trends for benefits of using varenicline nasal spray as an ocular surface-sparing option for managing dry eye after excimer laser refractive surgery or corneal collagen crosslinking.¹⁹⁻²¹

Although varenicline nasal spray is the only FDA-approved chemical neurostimulator for DED currently available,¹³ research is ongoing for other chemical compounds targeting ocular sensory nerves. One such investigational agent is acoltremon ophthalmic solution, 0.003% (previously known as AR-15512). Acoltremon is a potent transient receptor potential melastatin 8 (TRPM8) agonist.²² TRPM8 receptors are expressed on the sensory nerves innervating the cornea and lids, are sensitive to cold and osmolarity, and, when stimulated, trigger trigeminal signaling that induces LFU tear

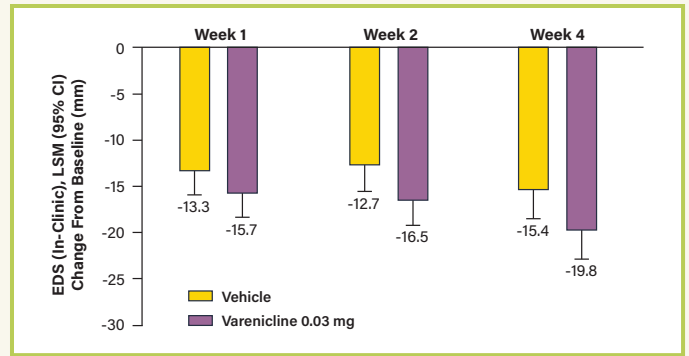


Figure 2. Least squares mean difference between varenicline 0.03 mg and vehicle in Eye Dryness Score change from baseline to week 4 showed nominal significance (-4.4 ; $P = .038$)¹⁶

Abbreviations: CI, confidence interval; EDS, Eye Dryness Score; LSM, least squares mean.

production.²³ Alcotremon has demonstrated efficacy and safety in phase 3 trials.²⁴

Mechanical Neurostimulation

iTEAR 100 received FDA clearance in May 2020 for marketing as a treatment to temporarily increase tear production in adults via mechanical stimulation.²⁵ Application of its oscillating tip on the lateral surfaces of the nose increases tear production through the nasolacrimal reflex arc by stimulating the external nasal nerve.²⁶ Recommended usage is 30 seconds on each side of the nose twice daily.²⁷

An open-label pivotal trial evaluated the device, with a primary end point of change from unstimulated to stimulated tear production as measured by a 5-minute anesthetized Schirmer test at day 30.²⁶ A total of 101 patients had a mean 9.4-mm increase in Schirmer index; 34% of these patients achieved a > 10 -mm increase. Ocular Surface Disease Index (OSDI) score decreased significantly by an average of 14.4 points from baseline. Adverse events judged definitely related to the device occurred in 2 patients, were mild, and consisted of intermittent nose soreness in 1 patient and slight headache/sneezing/tickling sensation in the other patient.

Discussion

Dr McGee: What do the results of the clinical trials reveal about the potential benefits of using a neurostimulation approach to manage DED?

Dr Lighthizer: The data from the studies of neurostimulation reporting improvements in STS, ocular surface staining, and EDS scores show that this approach meets our patients' desire for symptomatic relief while also improving DED-related signs,^{16,18} which may be the end point that clinicians most focus on to determine treatment benefit.

Dr Pflugfelder: The fact that neurostimulation treatments improve both signs and symptoms of DED suggests that this approach improves tear composition as a whole and not just aqueous production.^{16,18,26} In addition, anecdotal observations indicate that neurostimulation results in anatomic improvements in goblet cells, corneal nerve density, and MG function. I believe that data from a longitudinal study documenting these changes would be very compelling evidence for increasing acceptance of neurostimulation strategies.

Dr McGee: Is there a learning curve that clinicians and/or patients must overcome when using neurostimulation treatments?

Dr Pflugfelder: I think that patients need counseling on the mechanism of action when offered DED treatments that target the nose.

Dr Lighthizer: Implementing the nasal route to treat DED is a sea change. I think that it can take time for patients and clinicians to get on board with something that is a major shift from the existing paradigm. It is important to educate clinicians on neurostimulation so that they are comfortable recommending it to patients and committed to providing the necessary counseling on its use. I think that patients can simply be told that the intranasal spray stimulates nerves in the nose that are connected to parts of the eye that are involved in natural tear production. Telling patients about the expected benefits also helps promote acceptance.

Dr McGee: I agree that we should keep our patient education simple. When I encounter clinicians who are hesitant to use the intranasal spray, I remind them that many people are already using a nasal spray for some other indication, and I ask how many of their patients enjoy putting drops in their eyes. Although it may seem incongruous to us to treat the eye via the nose, many patients already familiar with and comfortable using nasal sprays may also appreciate not needing another eye drop, which can be difficult to instill and cause stinging and burning.

Are there certain disease or patient characteristics that influence you to recommend neurostimulation for DED treatment?

Dr Lighthizer: I like to recommend nasal neurostimulation to patients who are already on other topical ophthalmic medications, such as those with glaucoma or who are on a multimodal regimen for DED that is not providing sufficient improvement. In these situations, neurostimulation avoids exacerbating ocular surface adverse effects from topical treatments and the complexity of the topical treatment regimen. Small studies found trends for benefits of using varenicline nasal spray as an ocular surface-sparing option for managing dry eye after excimer laser refractive surgery or corneal collagen crosslinking.¹⁹⁻²¹ Nasal neurostimulation can also be a user-friendly approach to managing DED in patients who are contact lens wearers because it does not require contact lens removal.

Dr McGee: I see many specialty contact lens patients, and keeping the front surface of a scleral lens lubricated is essential for good vision. I find neurostimulation very helpful to address that need.

Dr Pflugfelder: I look for patients who have a reduced tear volume but the capacity to produce tears. I find that neurostimulation can be very helpful for patients with early Sjögren syndrome. I also try neurostimulation in patients with early-stage neurotrophic keratitis who still have some corneal sensitivity, but which is reduced so there is insufficient LFU stimulation. Patients with ocular surface exposure, which may be related to external ophthalmoplegia, Bell palsy, or trauma, among other causes, are also good candidates because increasing tear production by neurostimulation helps to keep the cornea moist and lubricated.

Dr McGee: Are there situations in which you would not use neurostimulation to manage DED?

Dr Pflugfelder: I would not consider it for patients who do not have the ability to respond to neurostimulation, such as those with end-stage Sjögren syndrome or Stevens-Johnson syndrome.

Dr McGee: I have encountered patients who did not respond to neurostimulation because the targeted nerve was severed during rhinoplasty or sinus surgery. The only way to know if neurostimulation will be effective in patients with that type of surgical history, however, is to give it a try. It may be that the treatment induces the desired response when applied to one side of the nose but not the other.

Case 1

From the Files of Nathan Lighthizer, OD

A 47-year-old postmenopausal female presented with red, puffy eyes and concerns of dryness throughout the day. She stated, "I don't know what's happened with my eyes over the last 6 to 9 months, but I've fallen off a cliff eyewise." She was experiencing fluctuating vision, light sensitivity, headaches, blurred vision, and grittiness, and reported using artificial tears approximately every hour, a lubricating ointment at bedtime, and a mask at night, which she said provided some very transient relief. She was wearing upper eyelash extensions, using a computer or other digital devices for more than 3 hours per day, and taking hormone replacement therapy.

Her OSDI score was 77. Findings on examination were best-corrected visual acuity (BCVA) of 20/20- OU; lagophthalmos; grade 2 bulbar injection OU; grade 2 diffuse inferior superficial punctate keratitis (SPK) OU; osmolarity of 318 mOsm/L OD and 317 mOsm/L OS; MMP-9 positive OU; low tear meniscus height; noninvasive tear breakup time (TBUT) of 11 seconds OU (**Figure 3**); ocular rosacea; and expression of cloudy meibum from most MGs, with some thickened material.

Recommendations for treatment were to continue artificial tears as needed and to start using loteprednol etabonate gel, 0.38%, 4 times daily, a Bruder mask, and a series of 4 monthly intense pulsed light (IPL) treatments.

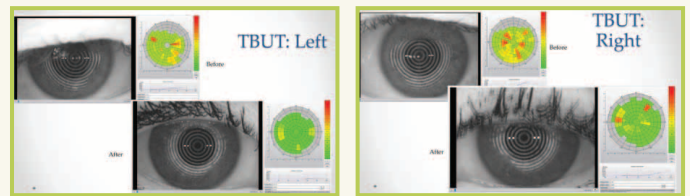


Figure 3. Noninvasive tear breakup time of the patient in Case 1 showing improvement

Discussion

Dr Lighthizer: I think about 4 issues when planning treatment for DED: LFU/tear production, inflammation, MGs, and eyelid disease, including *Demodex* and other types of blepharitis. At this first visit, I prescribed loteprednol for the inflammation, the Bruder mask for the MGs, and IPL, which targets both the MGs and inflammation. Artificial tear use was recommended for supplemental lubrication.

Is there anything else you would have done?

Dr McGee: The fact that the patient had intact MGs is encouraging because it is easier to treat DED if there is no significant gland dropout. I think it is useful to query patients about their use of cosmetic and cleansing products around the eyes because it can reveal a contributor to MGD.

Because the patient's tear osmolarity level was elevated, I would have started a topical immunomodulator that she would continue after stopping the corticosteroid.

Dr Lighthizer: I did not start an immunomodulator because I did not want to overwhelm her with too many treatments initially. In hindsight, it turned out to be a good decision because when she returned 3 weeks later, I learned that she was not happy using the topical treatments.

Dr Pflugfelder: I am a big proponent of omega-3 fatty acid supplements to treat DED and MGD because they have anti-inflammatory activity and improve meibum quality.²⁸ We perform



several in-office treatments for MGD that help to relieve obstruction and increase the amount of meibum that can be expressed manually.

Dr Lighthizer: The patient refused an omega-3 supplement, saying she did not like the “burp” they cause. IPL is the only in-office treatment we do for MGD because it seems the most affordable for patients based on costs for disposables.

Case Continued

At follow-up, the patient reported using artificial tears 4 to 5 times a day, the Bruder mask at bedtime and occasionally in the morning, and loteprednol 2 or 3 times a day, but she had stopped using the corticosteroid eye drops 4 to 5 days earlier, stating she hated that it messed up her makeup. Her OSDI score was 66. Other findings were BCVA of 20/20 OU; grade 1 bulbar conjunctival injection; and grade 1 SPK on the inferior one-fourth of the cornea OU (OS > OD).

Loteprednol was discontinued. The patient was told to continue with the Bruder mask, artificial tears, and IPL, and was prescribed varenicline nasal spray twice daily. It was explained that the varenicline would increase her natural tear production, which could decrease any need for eye drops that “messed up” her makeup.

The patient returned 1 month later and commented that her symptoms were much improved since she started varenicline. She said she loved having “many more tears” and not having to use so many eye drops. Her OSDI was 48, she was using artificial tears once or twice a day, and she reported good compliance with using the Bruder mask. Examination findings were good meibum quality; no blepharitis; trace injection OU; trace SPK OU; noninvasive TBUT of 16+ seconds OU; and osmolarity of 305 mOsm/L OD and 302 mOsm/L OS.

Two months later, the patient had completed 4 IPL sessions and was very happy. She was told to continue using varenicline, the Bruder mask, and artificial tears as needed, and to return every 3 to 6 months to determine the need for additional IPL.

Case 2

From the Files of Selina McGee, OD, FAAO

A 68-year-old retired female presented for a dry eye consultation. She said her eyes seemed gritty, burned, and itched. She said she loved to sit and read later in the day, but it was difficult because her vision was blurry and worsening as the day went on. Her medical history was unremarkable. Past treatment for DED included artificial tears; cyclosporine emulsion, 0.05%; and TrueTear. Her SPEED score was 6/28. Other findings were osmolarity of 335 mOsm/L OD and 309 mOsm/L OS; TBUT of 3.8 seconds OD and 4.2 seconds OS; scattered punctate corneal staining; MMP-9 negative OU; MG expression of 3/5 × 3, with mostly cloudy expression; and no lid telangectasia or lash debris.

The patient was diagnosed with moderately severe keratoconjunctivitis sicca OU. She did not want to try immunomodulatory drops again. The iTEAR 100 was discussed because the patient indicated she had liked using TrueTear. She was told to use the external neurostimulator at least 4 times a day and up to 10 times a day if she felt it was needed. Because the patient lived 90 miles away, she was told to return in 6 months rather than after the typical 4-week interval.

Findings at her next visit were SPEED score of 4/28 and osmolarity of 309 mOsm/L OD and 294 mOsm/L OS. The patient was told she could use the iTEAR 100 just twice daily, but to increase the frequency as needed. She was prone to seasonal allergies and was told that increasing use of the neurostimulator to produce her own real tears could help flush allergens from the ocular surface.

At follow-up 6 months later, her SPEED score was 1/28, osmolarity was 295 mOsm/L OD and 292 mOsm/L OS, and the patient was very happy.

Dr McGee: It was impressive to see how this patient’s symptoms and hyperosmolarity improved using neurostimulation alone. I think her case demonstrates the opportunity for success when intervening early for DED.

This patient readily accepted treatment with the external neurostimulator because she liked the intranasal device. I think this case also points to the fact that many patients are interested in trying novel technologies. Therefore, there is an onus on the clinician to offer them.

When prescribing neurostimulation with the extranasal device or intranasal spray, I always inform patients that sneezing is a potential adverse effect and can be intense enough to cause urinary incontinence in an at-risk population. I also recommend that to increase comfort when using the external device, patients place the applicator on the cheek first and then slide it toward the nose.

Case 3

From the Files of Stephen C. Pflugfelder, MD

A 45-year-old female college professor presented with neurogenic DED related to left-side Bell palsy. She was initially treated with valacyclovir and facial nerve stimulation that led to recovery of some cranial nerve VII function over the next month that allowed partial closure of the left upper eyelid. She was currently using preservative-free artificial tears frequently, a lubricating ointment at bedtime, and a sleep mask. She had concerns about almost constant foreign body sensation and blurred vision. Examination showed orbicularis muscle weakness, incomplete eyelid closure, and lagophthalmos (~2 mm) OS; TBUT of 10 seconds OD and 5 seconds OS; corneal fluorescein staining (National Eye Institute scale) of 0/15 OD and 12/15 OS; and visual acuity of 20/20 OD and 20/40 OS.

Treatment discussed included placement of a gold weight in the left upper lid, partial tarsorrhaphy, or fitting of a hydrogel or a scleral lens. The patient chose a scleral lens and experienced immediate improvement in both irritation and vision while she was wearing the lens. When she returned 1 month later, however, she had concerns that her left eye vision had worsened after wearing the lens for approximately 2 hours. She said vision improved if she used artificial tears and removed and cleaned the lens, which was impractical. The lens was covered with mucus/protein, and the patient noted the coating worsened in the afternoon. A dissolvable punctal plug was placed in the left lower punctum but caused unpleasant epiphora. Varenicline nasal spray twice daily was prescribed and led to a marked reduction of lens coating to a tolerable level.

The patient was happy. She reported improved vision and said her eye felt comfortable without the scleral lens.

Dr Pflugfelder: I recommended nasal neurostimulation for this patient to address both her cornea exposure and the scleral lens coating.

Dr McGee: As I mentioned previously, neurostimulation improves the quality of the tear film in front of the scleral lens, keeping the surface wettable so that it refracts correctly. I had a patient whose BCVA with a scleral lens was 20/60, which improved to 20/20 after starting treatment with only neurostimulation. I did not have to make any modifications to the scleral lens.

Take-Home Messages

- 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, MGs, lids, and interconnecting innervation
- **Basal tear flow** is controlled through **neural reflex arcs** that are initiated by **stimulation of trigeminal nerve endings** located 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** and an **inflammatory cascade**
- **Neurostimulation treatments for DED activate sensory neural pathways to increase natural tear production**
 - **Available options** include the following:
 - **Varenicline nasal spray**: Chemically stimulates trigeminal nerve endings within the nasal cavity
 - **External nasal nerve stimulators**: Devices that mechanically activate the external nasal nerve to trigger the nasolacrimal reflex
 - **Emerging options** under investigation include the following:
 - **Acoltremon ophthalmic solution**: A TRPM8 receptor agonist, applied topically to the eye, that has completed phase 3 trials
 - **By leveraging the body's natural reflexes, these neurostimulation therapies provide an effective mechanism to increase tear volume and help restore ocular surface homeostasis in DED**

References

1. Craig JP, Nelson JD, Azar DT, et al. TFOS DEWS II report executive summary. *Ocul Surf.* 2017;15(4):802-812.
2. Pflugfelder SC, Cao A, Galor A, Nichols KK, Cohen NA, Dalton M. Nicotinic acetylcholine receptor stimulation: a new approach for stimulating tear secretion in dry eye disease. *Ocul Surf.* 2022;25:58-64.
3. Fillmore EP, Seifert MF. Anatomy of the trigeminal nerve. In: Tubbs RS, Rizk E, Shoja MM, eds. *Nerves and Nerve Injuries*. 1st ed. Academic Press; 2015: 319-350.
4. Yu MD, Park JK, Kossler AL. Stimulating tear production: spotlight on neurostimulation. *Clin Ophthalmol.* 2021;15:4219-4226.
5. Gupta A, Heigle T, Pflugfelder SC. Nasolacrimal stimulation of aqueous tear production. *Cornea.* 1997;16(6):645-648.
6. McGee S, Macsai M, Shah P, Hendrix L, Carlson E, Wirta D. Pro- and anti-inflammatory cytokine levels in tears of dry eye subjects. Paper presented at: 2022 American Academy of Optometry Annual Meeting; October 26-29, 2022; San Diego, CA.
7. Kumar NR, Praveen M, Narasimhan R, et al. Tear biomarkers in dry eye disease: progress in the last decade. *Indian J Ophthalmol.* 2023;71(4):1190-1202.
8. Pflugfelder SC, Stern ME. Biological functions of tear film. *Exp Eye Res.* 2020;197:108115.
9. Nelson JD, Craig JP, Akpek EK, et al. TFOS DEWS II introduction. *Ocul Surf.* 2017;15(3):269-275.
10. Tsubota K, Yokoi N, Shimazaki J, et al; Asia Dry Eye Society. New perspectives on dry eye definition and diagnosis: a consensus report by the Asia Dry Eye Society. *Ocul Surf.* 2017;15(1):65-76.
11. Crabbe J. Allergan, now integrated with AbbVie, discontinues sales of TrueTear device for dry eye. Market Scope. July 17, 2020. Accessed April 23, 2025. <https://www.market-scope.com/pages/news/4658/allergan-now-integrated-with-abbvie-discontinues-sales-of-truetear-device-for-dry-eye>
12. Delaney-Gesing A. Oyster Point Pharma reports FDA approval of TYRVAYA nasal spray for DED treatment. News release. *Ophthalmology Times.* October 18, 2021. Accessed April 23, 2025. <https://www.opthalmologytimes.com/view/oyster-point-pharma-reports-fda-approval-tyrvaya-nasal-spray-for-ded>
13. Varenicline spray. Package insert. US National Library of Medicine. Updated February 12, 2024. Accessed April 23, 2025. <https://dailymed.nlm.nih.gov/dailymed>
14. Keiger CJH, Case LD, Kendal-Reed M, Jones KR, Drake AF, Walker JC. Nicotinic cholinergic receptor expression in the human nasal mucosa. *Ann Otol Rhinol Laryngol.* 2003;112(1):77-84.
15. Alimohammadi H, Silver WL. Evidence for nicotinic acetylcholine receptors on nasal trigeminal nerve endings of the rat. *Chem Senses.* 2000;25(1):61-66.
16. Wirta D, Vollmer P, Paaup J, et al; ONSET-2 Study Group. Efficacy and safety of OC-01 (varenicline solution) nasal spray on signs and symptoms of dry eye disease: the ONSET-2 phase 3, randomized trial. *Ophthalmology.* 2022;129(4): 379-387.
17. Schallhorn JM, McGee S, Nau J, et al. OC-01 (varenicline solution) nasal spray for the treatment of dry eye disease signs and symptoms in subjects with autoimmune disease: integrated data from ONSET-1 and ONSET-2. *Clin Ophthalmol.* 2023;17:725-734.
18. Gupta AS, Linaburg TJ, Iacobucci E, et al. Varenicline solution nasal spray for the treatment of dry eye disease in Sjogren's disease: a pilot study. *Clin Ophthalmol.* 2025;19:1073-1084.
19. Ferguson TJ, Messer B, Risbrudt N, Stofferahn S, Greenwood M. Varenicline solution nasal spray for the treatment of dry eye disease following LASIK. *Ophthalmol Ther.* 2024;13(6):1693-1701.
20. Ferguson TJ, Walton K, Goertz JG, Baartman BJ. Varenicline solution nasal spray 0.03 mg for the treatment of dry eye disease following photorefractive keratectomy. *Clin Ophthalmol.* 2024;18:2777-2784.
21. Ferguson TJ, Durgan D, Whitt T, Swan RJ. Varenicline nasal spray for the treatment of dry eye disease following corneal collagen crosslinking. *Ophthalmol Ther.* 2025;14(5):959-968.
22. deLong MA, Kelly CR, Sturdivant J, et al. TRPM8 agonists: a new approach to dry eye disease treatment. *Invest Ophthalmol Vis Sci.* 2023;64(8):744.
23. Belmonte C, Nichols JJ, Cox SM, et al. TFOS DEWS II pain and sensation report. *Ocul Surf.* 2017;15(3):404-437.
24. Wirta DL, Gupta PK, Pattar GR, Boehmer B, Holland E, Senchyna M. AR-15512: a novel TRPM8 agonist for the treatment of the signs and symptoms of dry eye: phase 3 pivotal study results. Paper presented at: 2024 Annual Meeting of the American Academy of Ophthalmology; October 18-21, 2024; Chicago, IL.
25. Olympic Ophthalmics receives FDA clearance for iTear100® neurostimulator. News release. PR Newswire. May 14, 2020. Accessed April 23, 2025. <https://www.prnewswire.com/news-releases/olympic-ophthalmics-receives-fda-clearance-for-itear100-neurostimulator-301058915.html>
26. Ji MH, Moshfeghi DM, Periman L, et al. Novel extranasal tear stimulation: pivotal study results. *Transl Vis Sci Technol.* 2020;9(12):23.
27. iTear®100 patient brochure. Olympic Ophthalmics Inc; 2022. Accessed April 23, 2025. <https://olympicophthalmics.com/itear100/>
28. Jo YJ, Lee JS. Effects of dietary high dose DHA omega-3 supplement in dry eye with meibomian gland dysfunction. *Int J Ophthalmol.* 2021;14(11):1700-1706.

For CME certificate processing:

Complete the provided Evaluation Form with Posttest Answer Box and email to: info@mededicus.com



CME Posttest Questions

CME Posttest Questions

To obtain AMA PRA Category 1 Credit™ for this activity, please read the monograph, consult referenced sources as necessary, complete the evaluation form with posttest answer form, and **email to info@mededocus.com**. Within 14 days, a certificate will be emailed to the email address provided on the form.

1. By which of the following mechanisms is basal tear secretion in the LFU most directly controlled?
 - a. Cholinergic stimulation of conjunctival goblet cells
 - b. Blink-driven redistribution of the tear film
 - c. Reflex arcs involving sensory and parasympathetic nerves
 - d. Hormonal modulation of lacrimal gland secretions
2. David P, a 61-year-old retired teacher, has concerns about intermittent burning, blurred vision, and ocular fatigue that worsen with wind exposure. He has refused using nasal sprays because of past sinus surgery complications and is seeking new options. Clinical findings include TBUT of 3 seconds OD and 4 seconds OS; Schirmer score of 8 mm OU; osmolarity of 320 mOsm/L OD and 322 mOsm/L OS; and moderate SPK. MG expression shows some cloudy output, but no gland dropout. He is interested in the emerging noninvasive approaches. Which treatment option would best suit David's clinical profile and personal preference?
 - a. Acoltremon ophthalmic solution, 0.003%, twice daily
 - b. Neurostimulatory device
 - c. Varenicline nasal spray 0.03 mg/nostril twice daily
 - d. Topical cyclosporine emulsion, 0.05%, twice daily
3. Maria G, a 56-year-old teacher, presents with 12 months of gritty dryness and fluctuating vision despite frequent use of preservative-free artificial tears and successful IPL for MGD. Slitlamp examination shows trace inferior SPK; Schirmer score of 5 mm OU; and osmolarity of 318 mOsm/L OD and 320 mOsm/L OS. She dislikes eye drops that "ruin her makeup" and asks for a fast-acting, drop-sparing option. Which treatment best matches her goals?
 - a. Topical cyclosporine emulsion, 0.05%, twice daily
 - b. Varenicline nasal spray 0.03 mg/nostril twice daily
 - c. Silicone lower-punctal plugs
 - d. Oral omega-3 supplementation

