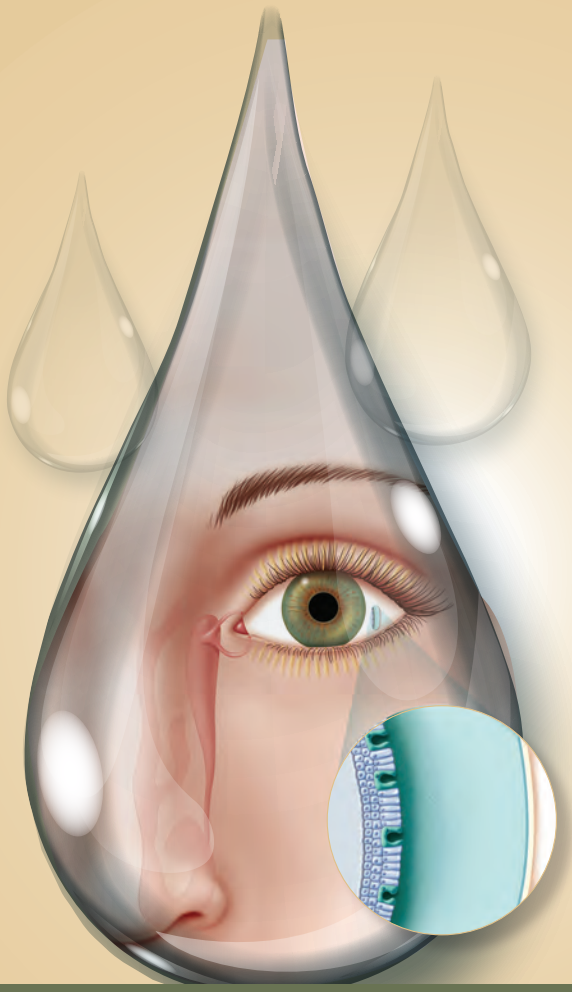

CME MONOGRAPH

EARN CREDITS CME

Tearing Up

NEW AND EMERGING THERAPY WITH TEAR STIMULATION FOR DRY EYE DISEASE

FACULTY

Michael B. Raizman, MD (Chair)

Anat Galor, MD, MSPH

David Wirta, MD

Visit https://www.tearstimCME.com for online testing and instant CME certificate.

ORIGINAL RELEASE: September 1, 2021 | EXPIRATION: September 30, 2022

This continuing medical education activity is provided by MedEdicus LLC.

MedEdicus LLC

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

Distributed with EyeNet

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 physicians 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 based on real-world situations of patients with DED.

TARGET AUDIENCE

This educational activity is intended for ophthalmologists.

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

ACCME ACCREDITED

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 1.5 *AMA PRA Category 1 Credits*™. 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, and complete the posttest and evaluation online at https://www.tearstimCME.com. Upon passing, a certificate will be made available immediately.

DISCLOSURE POLICY

MedEdicus requires that anyone who is in a position to control the content of this educational activity disclose all relevant financial relationships with any commercial interest. Financial relationship information is collected and resolved prior to the educational activity.

Faculty

Anat Galor, MD, MSPH, is a consultant for Novartis Pharmaceuticals Corporation, Oyster Point Pharma, Inc, and Tarsus Pharmaceuticals, Inc.

Michael B. Raizman, MD, is a consultant for Alcon, Eyevance, Novartis Pharmaceuticals Corporation, Oyster Point Pharma, Inc, Palatin Technologies, Inc, and Sun Pharmaceutical Industries, Inc.

David Wirta, MD, is a contracted researcher for Oyster Point Pharma, Inc.

Peer Reviewer

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

Planners and Managers

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

DISCLOSURE OF COMMERCIAL SUPPORT

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

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; Oyster Point Pharma, Inc; *EyeNet;* or the American Academy of Ophthalmology.

FACULTY

Michael B. Raizman, MD (Chair)
Ophthalmic Consultants of Boston
Associate Professor of Ophthalmology
Director, Corneal Fellowship Training Program
Director, Cornea and Anterior Segment Services
Tufts University School of Medicine
Boston, Massachusetts

Anat Galor, MD, MSPH
Professor of Ophthalmology
Bascom Palmer Eye Institute
University of Miami
Miller School of Medicine
Staff Physician, Miami Veterans
Affairs Medical Center
Miami, Florida

David Wirta, MD
Principal Investigator and Medical Director
Eye Research Foundation, Inc
Newport Beach, California

NEW AND EMERGING THERAPY WITH TEAR STIMULATION 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 physicians 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 through neurostimulation. 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 for patients with DED

Tear Film and Tear Homeostasis

In 2017, the Tear Film & Ocular Surface Society Dry Eye WorkShop 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

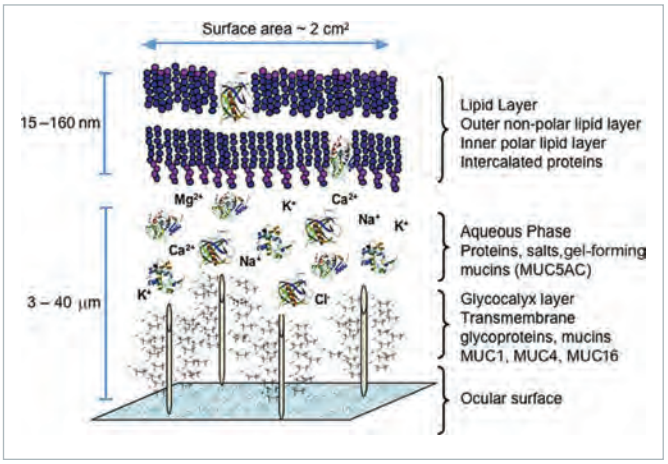

Figure 1. Model of tear film, comprising a complex mixture of lipids, proteins, and electrolytes[8]

Abbreviation: MUC, mucin.

Republished with permission of the Association for Research in Vision and Ophthalmology, from The International Workshop on Meibomian Gland Dysfunction: report of the Subcommittee on Tear Film Lipids and Lipid-Protein Interactions in Health and Disease, Green-Church KB, Butovich I, Willcox M, et al, 52, 2011; permission conveyed through Copyright Clearance Center, Inc.

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]

Homeostasis of the 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

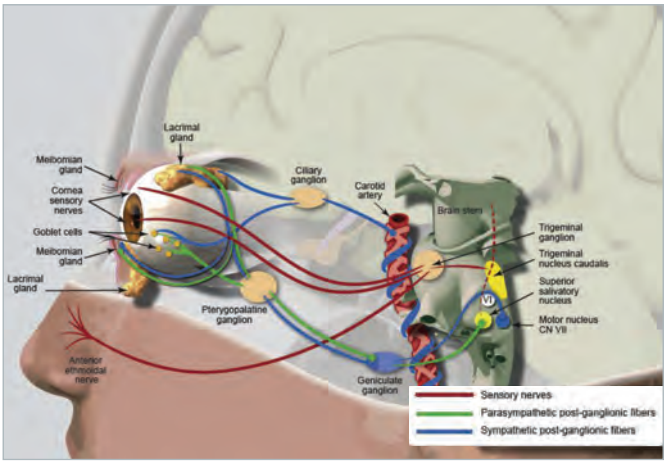

Figure 2. Structures involved in tear production[10]

Abbreviation: CN, cranial nerve.

Reprinted from *The Ocular Surface,* 17, Dieckmann G, Fregni F, Hamrah P, Neurostimulation in dry eye disease–past, present, and future, 20-27, Copyright 2019, with permission from Elsevier.

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 of the components 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 Raizman: What are the key facts about tear composition and tear production that clinicians and patients need to know to aid in their understanding of ocular surface health, DED, and DED treatment?

Dr Wirta: The Tear Film & Ocular Surface Society Dry Eye WorkShop II definition of DED describes it as a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film. With reference to this definition, it is important to consider that the ability to produce natural tears is a core factor for maintaining tear film homeostasis.

Dr Galor: Clinicians are used to looking at the eye and finding answers. While some aspects of tear health, including tear volume, tear film stability, and corneal staining, can be assessed by looking at the ocular surface, other important players, such as cornea and conjunctival nerves, cannot be directly seen. It cannot be forgotten, however, that nerves are important for maintaining a healthy ocular surface given that they sense the environment and trigger appropriate responses.

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

Dr Raizman: Relevant to treatments designed to increase natural tear production by neurostimulation, it is also helpful to understand the neuroanatomy of tear production and that intranasal neurostimulation caused by inhaled air is responsible for approximately one-third of basal tear production.[12]

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]

Discussion

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

Dr Galor: The first step in treating dry eye symptoms is identifying contributors to symptoms and recognizing that

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.

different patients will benefit from different combinations of therapies. We have a wide variety of artificial tears available that have different compounds, viscosities, and added ingredients, and I encourage patients to find the product(s) that work best for them. We have also expanded our therapeutic options for eyelid diseases with various products available to address anterior and posterior blepharitis. We have corticosteroids that can be used in the short term and immunomodulators – cyclosporine and lifitegrast – that can be used in the long term to address chronic ocular surface inflammation. However, some individuals cannot tolerate these medications because of side effects, and others have persistent symptoms despite an improvement in ocular surface inflammation. This points to the need for anti-inflammatory therapies that are better tolerated and novel medications that address other contributors to symptoms, including nerve dysfunction. Better point-of-care tests are also needed in the dry eye space that can inform clinicians which specific products may be most beneficial in an individual patient.

Dr Wirta: A positive attribute of our current armamentarium is that it contains a broad spectrum of artificial tear products. We can tailor our choice for individuals, taking into account DED subtype, severity, and patient preference. Another advantage is the expanding number of options for treating meibomian gland dysfunction (MGD), which is important, considering MGD is a common cause of DED. Although punctal plugs have drawbacks, I think they are useful as an option for maintaining the natural tear film.

There has been a lot of emphasis on inflammation in DED. Many of our currently available treatments for DED, along with those that are in development, are targeting inflammation. There are still unmet needs for anti-inflammatory treatment. Topical steroids have been used off-label as a treatment for DED, and now there is a topical steroid with an indication for treating DED.[13] Because of safety concerns, however, steroids are limited to short-term use. Cyclosporine products and lifitegrast can be used for longer-term treatment, but in my experience, only a minority of patients benefit from or are satisfied with either of those agents.

Dr Raizman: Most patients I treat with cyclosporine or lifitegrast for DED achieve significant improvement in their ocular surface condition, but these patients might also tell me that they do not feel or see significantly better. In addition, the stinging and burning that occurs with both cyclosporine and lifitegrast and the dysgeusia associated with lifitegrast can be intolerable for some patients. I agree that although anti-inflammatory treatment is a key component of DED management for many patients, our current options are lacking. Furthermore, anti-inflammatory treatment is not sufficient as a standalone approach.

Has the emphasis on inflammation in DED caused clinicians to overlook loss of tear film homeostasis as the core feature? If so, could it be contributing to underdiagnosis or undertreatment of DED?

Dr Wirta: I do not know if the focus on inflammation has necessarily led clinicians to overlook the issue of tear film homeostasis or if that is contributing to underdiagnosis. I think that when patients present with a problem, they are expecting some action from their provider; prescribing an anti-inflammatory treatment is an accessible way for meeting that expectation.

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 nasal 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.[16] 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)**,[17] 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.

FDA clearance of the iTEAR100 was based on results of 2 pivotal trials, including a double-masked, randomized, sham-controlled multicenter study and a multicenter single-arm study.[16] The design and results of the single-arm study have been published.[18] 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

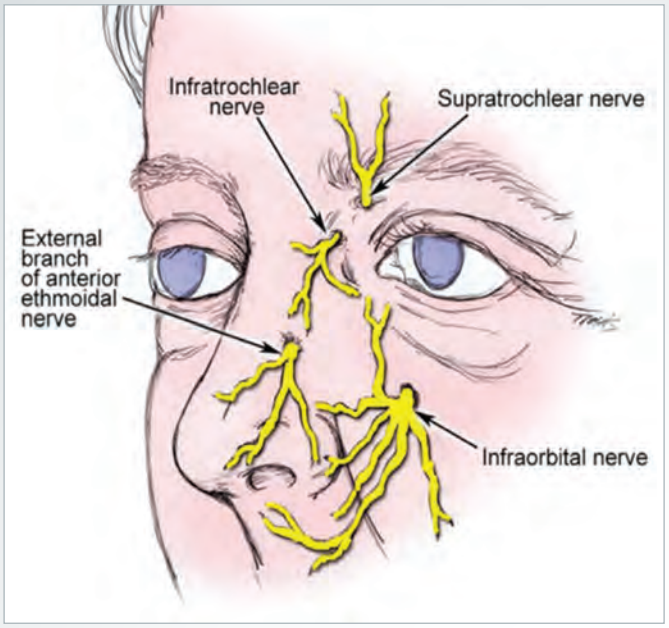

Figure 3. Location of the external branch of the anterior ethmoidal nerve (external nasal nerve)[17]

Image reproduced with permission from Medscape Drugs & Diseases (https://emedicine.medscape.com/), Nose Anesthesia, 2020, available at: https://emedicine.medscape.com/article/82679-overview

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. 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.

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

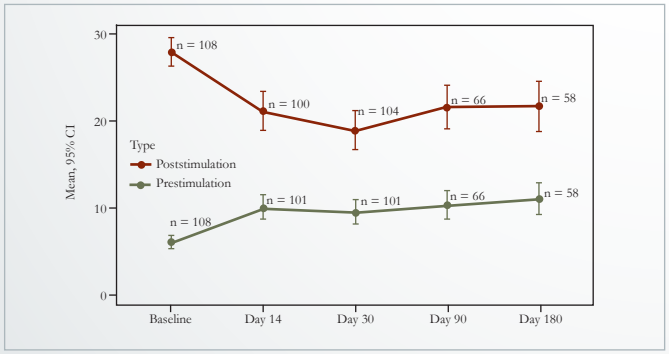

Figure 4. Prestimulation and poststimulation Schirmer scores at baseline and follow-up visits in the single-arm pivotal trial investigating the extranasal tear stimulation device[18]

Abbreviation: CI, confidence interval.

Reproduced with permission from Ji MH, Moshfeghi DM, Periman L, et al. Novel extranasal tear stimulation: pivotal study results. *Transl Vis Sci Technol.* 2020;9(12):23.

baseline,[18] which exceeds the change of > 7 points that is considered to represent a minimal clinically important difference.[19] 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.[18] Statistically significant improvements were also seen in exploratory end points analyzing change from baseline to day 30 in meibomian gland expression, meibum quality, tear breakup time (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 said they were dissatisfied with the treatment.

Adverse events judged to be definitely related to the device occurred in 2 patients.[18] 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, 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.[20] 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.[21,22]

ONSET-2, the multicenter phase 3 study investigating OC-01, enrolled 758 subjects 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.[20,23] Eligible participants had to have used and/or desired to use an artificial tear within the preceding 6 months.[24] The study met its primary end point, showing that the percentage of participants 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)**.[20,23] 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).

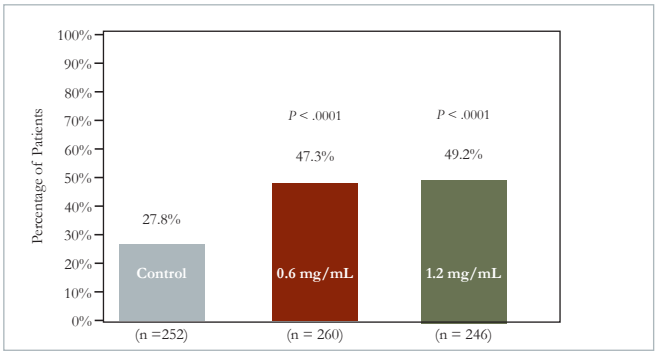

Figure 5. Patients receiving OC-01 0.6 or 1.2 mg/mL in ONSET-2 had significantly improved Schirmer scores after 4 weeks of treatment compared with those receiving placebo[20,23]

Reprinted with permission from Raizman M, Nau J, Gibson A, Shah P. ONSET-2 phase 3 study of OC-01 nasal spray for the treatment of dry eye disease. *Invest Ophthalmol Vis Sci.* 2021;62(8):1331.

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)**.[20,23] In addition to mean change in baseline EDS through day 28, mean change in baseline EDS in the Controlled Adverse Environment chamber at day 28 was also evaluated as a secondary end point.[20] There were no significant changes from baseline to day 28 in EDS in the Controlled Adverse Environment chamber.

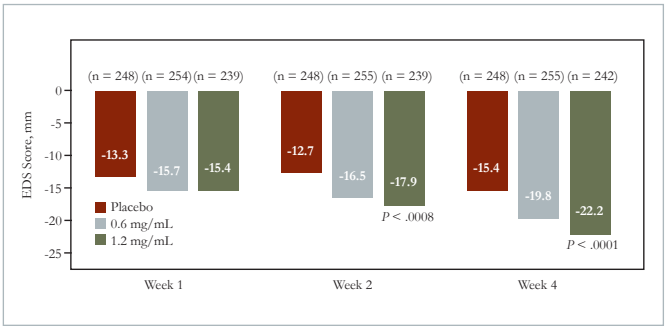

Figure 6. Mean Eye Dryness Score at follow-up visits in ONSET-2[20,23]

Abbreviation: EDS, Eye Dryness Score.

Reprinted with permission from Raizman M, Nau J, Gibson A, Shah P. ONSET-2 phase 3 study of OC-01 nasal spray for the treatment of dry eye disease. *Invest Ophthalmol Vis Sci.* 2021;62(8):1331.

OC-01 was well tolerated in the ONSET-2 study.[20,23] 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.[25] Other reported adverse events in the OC-01 0.6- and 1.2-mg/mL groups occurring at a rate > 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).[20] 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.[25] There were no serious adverse events.[20]

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.[26] 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 Raizman: Are both neurostimulation and tear stimulation accurate terms for describing the externally applied treatment and OC-01 nasal spray? Is one term better than the other?

Dr Galor: Both terms are accurate and highlight that by stimulating nerves, signals are sent up to the brainstem and back down through the efferent parasympathetic system to elicit tear stimulation.

Dr Wirta: I also think that both terms are accurate. Nerve stimulation is the underlying mechanism of action for both treatments, although it occurs through different pathways. OC-01 acts as a receptor agonist, and the external device stimulates the nerve through an electromechanical action. Both treatments have been shown to stimulate tear production.[18,20,23] Perhaps "tear stimulation" is the preferred term for patient counseling discussions. Patients may not understand the connection between nasal nerve stimulation and the eyes. I think they are more likely to appreciate that their eyes are dry because they do not have enough tears and will therefore understand the rationale for a treatment that stimulates tear production.

Dr Raizman: I think both are appropriate and useful terms. As Dr Wirta explained, the 2 treatment modalities can be distinguished by whether their mechanism of stimulation is mechanical or pharmacologic.

When discussing these treatments with patients, it will also be important to explain the benefits of natural tears vs

artificial tears. Patients should understand that natural tears are replete with a huge array of proteins and other factors that are critical for ocular surface health and that artificial tears do not come close to matching the composition of natural tears.

Dr Wirta: Another nice thing about the tear-stimulating treatments is that some patients might find them easier to use and more comfortable than artificial tears. Many people have difficulty getting eye drops into the eye and are bothered by stinging and burning. Nasal sprays are familiar to some, and the electromechanical stimulator is an easily applied noninvasive treatment.

Dr Raizman: An intranasal electrical neurostimulator was approved in 2018 to produce tears to treat dry eye symptoms until the manufacturer discontinued its use.[27] How do the new treatments differ from the previously available intranasal electrical neurostimulator?

Dr Wirta: The intranasal device had to be inserted fairly high up into the nostril, whereas the tip of the OC-01 nasal spray bottle is inserted just inside the opening of the nose, and the electromechanical stimulator is used externally. In addition, there was a fair amount of care required for patients using the intranasal neurostimulator. It had a disposable tip that had to be removed and replaced every 48 hours, and the tip and other parts had to be cleaned with alcohol wipes after each use.

Dr Raizman: Even patients who seemed to benefit from the intranasal stimulator found it cumbersome to use. I think there will be fewer logistical challenges for using either the external neurostimulator or the nasal spray.

Practical Insights on Implementation for Patient Care

Dr Raizman: Let us discuss the place of the tear-stimulating treatments in clinical practice for managing patients with DED.

I think they could be appropriate as monotherapy for mild DED in some patients, such as those who are doing well using artificial tears alone or who have dry eye related to contact lens wear in the absence of other issues who otherwise need to use an artificial tear compatible with contact lenses or use an artificial tear only when their lenses are out. Tear stimulation could also have a role for patients who have a generally healthy ocular surface but experience dryness in certain environments or that is related to use of medications that decrease aqueous tear production, such as antihistamines or antidepressants with anticholinergic activity.

Dr Wirta: Increasing natural tear production is a viable therapeutic pathway that could be a standalone treatment for some patients, or a good supplement to other modalities for others. I think the tear-stimulating treatments will certainly have value as adjuncts to anti-inflammatory treatment for DED. Assuming that the patient has some lacrimal gland function, I cannot think of any situations in which it would be unreasonable to consider a treatment that stimulates natural tear production. In the setting of zero lacrimal gland function, such as post-orbital radiation, then aggressive topical lubrication possibly combined with anti-inflammatory treatments would be a better fit.

Dr Galor: I agree that neurostimulation may be appropriate in many different DED populations. In my experience with the intranasal neurostimulator, individuals with low tear production related to autoimmune disease responded and did well. For example, I saw a 56-year-old male who complained of chronic dryness and irritation in both eyes. His past medical history was significant for sarcoidosis for which he was being treated with adalimumab. On examination he had low tear production (5 mm/4 mm wetting at 5 minutes OD/OS) along with a fast TBUT (5 seconds/6 seconds OD/OS), and mild interpalpebral corneal epithelial disruption. He was started on cyclosporine emulsion, 0.05%, twice a day with a 1-month course of a corticosteroid, but he discontinued the cyclosporine because of burning on instillation. He underwent a successful in-office trial with the intranasal device, and until the device was discontinued, he used it along with preservative-free artificial tears, as needed. With this therapy, he reported his ocular dryness and irritation improved sufficiently so that his symptoms became manageable.

Individuals who are very sensitive to eye drops and find local site reactions intolerable may benefit from nasal nerve stimulation that induces tearing through a different mechanism.

Dr Raizman: Some patients seem to have a very sensitive ocular surface and experience much irritation with the use of artificial tears, and they are an important group to consider. The idea that tear stimulation treatment could benefit a broad population of patients with DED, including those with more severe disease, is supported by results of a subgroup analysis in the OC-01 pivotal trial that showed symptoms improved regardless of baseline EDS.[23] Do any of you see any situations that might favor choosing either the nasal spray or the external neurostimulator? For example, perhaps patients with arthritic hands might have difficulty administering the nasal spray, although I expect they might find the nasal spray bottle easier to manipulate than an eye drop container. I can imagine some patients might not

like the idea of stimulating their nose externally. I cannot, however, think of any scenarios in which one treatment would be more effective than the other.

Dr Wirta: There may be some intranasal anatomical features or pathologies that would limit use of the nasal spray and deem the external device a better option.

I wonder if people who have thin or sensitive skin might develop a blemish at the site of application of the external stimulator after using it for a period of time. Certain patients might be bothered by that and might be better candidates for the nasal spray.

Given the choice, I expect that some patients might have a preference for one treatment over the other. For example, the external neurostimulator might appeal to younger patients who are attracted to technology and favor something that is natural vs a medication. Older patients who are used to using medications might prefer the nasal spray because it is something familiar.

Dr Galor: Both treatments are novel for ophthalmology. Some patients like or do not mind being early adopters and would be amenable to trying either. Others like to be on the cutting edge and might favor one option if they see it as being more of an "outside the box" solution than the other. Then, there are patients who are very resistant to trying new things. They might decline either modality at first while they wait to hear more about it, perhaps from someone they know who has used it successfully.

Dr Raizman: Should there be an in-office test to evaluate response before prescribing these treatments?

Dr Wirta: The screening protocol for participation in the OC-01 clinical studies included a provocation test, in which a cotton-tipped applicator was placed up the nose to evaluate whether nerve stimulation would induce tear production.[28] I think that is a crude technique for identifying who will respond to the spray or the external stimulation, and it is also unpleasant for patients. A better approach would be to check for response with in-office use of the device or the spray. Assuming the spray is approved, it would be nice if the manufacturer would supply samples for in-office testing. Patients also need to be instructed on proper use of both treatments, and an in-office provocation test with the patient using the treatment under supervision would be a way to confirm that it is being used properly.

I do not think there should be any threshold of response in the provocation test to determine suitability for treatment. Any patient who responds with some increase in tear production after testing the nasal spray or external neurostimulator could potentially benefit from the treatment.

Dr Raizman: I agree that these treatments could be helpful for any patient with DED who has some lacrimal gland function and shows increased tear production with the treatment. I think they would also have a role in treating patients with MGD who do not have aqueous tear deficiency; but, of course, the tear stimulation treatment would need to be combined with treatment that targets the MGD.

Many clinicians believe that showing patients who have MGD their images from meibography is helpful for getting them on board with treatment. I also find that there is something particularly visceral about seeing a photograph that demonstrates to patients that they have a problem. When patients think they are not benefitting from using cyclosporine or lifitegrast, I show the pretreatment and follow-up corneal staining pictures. Once they recognize the improvement, patients are motivated to continue using the treatment.

Is there anything you do to show patients they have insufficient tear production that would encourage them to use a tear-stimulating treatment?

Dr Wirta: Treatment responses in the clinical trials for these devices were based on Schirmer testing.[18,20,23] Because it is very time intensive, however, Schirmer testing is something that might be done in a practice that specializes in dry eye, but not necessarily in a general practice.

Dr Raizman: I agree. The Schirmer test is useful in many ways, but I tend not to use it in routine practice, and I think the same is true for most eye care providers. I find tear meniscus height helpful for identifying aqueous deficiency, and TBUT and staining patterns are also useful tests for quantifying severity.

Dr Galor: Despite its limitations, I do use the Schirmer test to evaluate tear production in my patients, and then I share the findings as part of my patient counseling. I discuss with patients the potential contributors to their symptoms, which can include low tear production, ocular surface inflammation, and corneal staining, among others, and then discuss the various strategies we can use to address their particular findings.

Complete the CME posttest online at
https://www.tearstimCME.com

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

References

1. White DE, Zhao Y, Jayapalan H, Machiraju P, Periyasamy R, Ogundele A. Physician satisfaction with anti-inflammatory topical medications for the treatment of dry eye disease. *Clin Ophthalmol.* 2020;14:931-938.
2. White DE, Zhao Y, Jayapalan H, Machiraju P, Periyasamy R, Ogundele A. Treatment satisfaction among patients using anti-inflammatory topical medications for dry eye disease. *Clin Ophthalmol.* 2020;14:875-883.
3. Nelson JD, Craig JP, Akpek EK, et al. TFOS DEWS II introduction. *Ocul Surf.* 2017;15(3):269-275.
4. 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.
5. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II definition and classification report. *Ocul Surf.* 2017;15(3):276-283.
6. Pflugfelder SC, Stern ME. Biological functions of tear film. *Exp Eye Res.* 2020;197:108115.
7. Willcox MDP, Argüeso P, Georgiev GA, et al. TFOS DEWS II tear film report. *Ocul Surf.* 2017;15(3):366-403.
8. Green-Church KB, Butovich I, Willcox M, et al. The International Workshop on Meibomian Gland Dysfunction: report of the Subcommittee on Tear Film Lipids and Lipid-Protein Interactions in Health and Disease. *Invest Ophthalmol Vis Sci.* 2011;52(4):1979-1993.
9. Stern ME, Beuerman RW, Fox RI, Gao J, Mircheff AK, Pflugfelder SC. The pathology of dry eye: the interaction between the ocular surface and lacrimal glands. *Cornea.* 1998;17(6):584-589.
10. Dieckmann G, Fregni F, Hamrah P. Neurostimulation in dry eye disease–past, present, and future. *Ocul Surf.* 2019;17(1):20-27.
11. Fillmore EP, Seifert MF. Anatomy of the trigeminal nerve. In: Tubbs RS, Rizk E, Shoja MM, Loukas M, Barbaro N, Spinner RJ, eds. *Nerves and Nerve Injuries.* Vol 1: History, Embryology, Anatomy, Imaging, and Diagnostics. 1st ed. Elsevier; 2015:319-350.
12. Gupta A, Heigle T, Pflugfelder SC. Nasolacrimal stimulation of aqueous tear production. *Cornea.* 1997;16(6):645-648.
13. US National Library of Medicine. DailyMed. Accessed July 30, 2021. https://dailymed.nlm.nih.gov/dailymed/
14. Grant R. How—and why—to choose dry eye drugs. *Review of Optometry.* March 15, 2020. Accessed July 21, 2021. https://www.reviewofoptometry.com/article/howand-whyto-choose-dry-eye-drugs
15. Milner MS, Beckman KA, Luchs JI, et al. Dysfunctional tear syndrome: dry eye disease and associated tear film disorders – new strategies for diagnosis and treatment. *Curr Opin Ophthalmol.* 2017;27(suppl 1):3-47.
16. Olympic Ophthalmics receives FDA clearance for iTEAR100® neurostimulator. PR Newswire. May 14, 2020. Accessed July 30, 2021. https://www.prnewswire.com/news-releases/olympic-ophthalmics-receives-fda-clearance-for-itear100-neurostimulator-301058915.html
17. Lal D. Nose anesthesia. Medscape. December 9, 2020. Accessed July 30, 2021. https://emedicine.medscape.com/article/82679-overview
18. Ji MH, Moshfeghi DM, Periman L, et al. Novel extranasal tear stimulation: pivotal study results. *Transl Vis Sci Technol.* 2020;9(12):23.
19. Miller KL, Walt JG, Mink DR, et al. Minimal clinically important difference for the Ocular Surface Disease Index. *Arch Ophthalmol.* 2010;128(1):94-101.
20. Vollmer PM, Aune CA, Kabat KG. Varenicline nasal spray (OC-01) for the treatment of dry eye disease: the ONSET-2 study. Poster presented at: New Technologies & Treatments in Eye Care Summer 2021 Conference; June 11-12, 2021; Virtual.
21. 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.
22. Alimohammadi H, Silver WL. Evidence for nicotinic acetylcholine receptors on nasal trigeminal nerve endings of the rat. *Chem Senses.* 2000;25(1):61-66.
23. Raizman M, Nau J, Gibson A, Shah P. ONSET-2 phase 3 study of OC-01 nasal spray for the treatment of dry eye disease. *Invest Ophthalmol Vis Sci.* 2021;62(8):1331.
24. Evaluating the efficacy and safety of OC-01 (varenicline) nasal spray on dry eye disease. ClinicalTrials.gov. July 29, 2019. Updated August 6, 2021. Accessed August 10, 2021. https://clinicaltrials.gov/ct2/show/nct04036292
25. GlobeNewswire. Oyster Point Pharma announces positive results in ONSET-2 phase 3 trial of OC-01 nasal spray for the treatment of the signs and symptoms of dry eye disease. May 11, 2020. Accessed July 30, 2021. https://www.globenewswire.com/en/news-release/2020/05/11/2030882/0/en/Oyster-Point-Pharma-Announces-Positive-Results-in-ONSET-2-Phase-3-Trial-of-OC-01-Nasal-Spray-for-the-Treatment-of-the-Signs-and-Symptoms-of-Dry-Eye-Disease.html
26. Dieckmann G, Lopez MJ, Ozmen MC, Yavuz LS, Binotti WW, Hamrah P. OC-01 (varenicline) nasal spray induces goblet cell alterations in patients with dry eye disease. Paper presented at: 2020 Annual Meeting of the American Academy of Ophthalmology; November 13-15, 2020; Virtual. PO092
27. US Food and Drug Administration. Device classification under section 513(f)(2)(de novo). Intranasal electrostimulation device for dry eye symptoms. Updated August 2, 2021. Accessed July 30, 2021. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm?ID=DEN170086
28. PracticeUpdate. ARVO 2021: Varenicline nasal spray provides relief for dry eye disease in phase III study. May 13, 2021. Accessed August 4, 2021. https://www.practiceupdate.com/content/arvo-2021-varenicline-nasal-spray-provides-relief-for-dry-eye-disease-in-phase-iii-study/118091

Instant CME Certificate Available With Online Testing and Course Evaluation at
https://www.tearstimCME.com

CME Posttest Questions

To obtain *AMA PRA Category 1 Credit*™ for this activity, complete the CME Posttest and course evaluation online at https://www.tearstimCME.com. Upon successful completion of the posttest and evaluation, you will be able to generate an instant certificate of credit.

See detailed information at **Instructions for Obtaining Credit** on page 2.

1. According to the definition from Tear Film & Ocular Surface Society Dry Eye WorkShop 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 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

3. 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

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

5. 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%

6. 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

7. Which of the following findings would likely exclude a patient from treatment with a tear-stimulating modality?
   a. Severe eye dryness symptoms
   b. A need for short-term use to control dry eye related to an environmental issue
   c. A history of orbital radiotherapy and a 0 Schirmer score
   d. A need for topical anti-inflammatory therapy