Supplement to

May 2021

CRST
Cataract & Refractive Surgery Today

MILLENNIALEYE

MOAs OF DED:
Understanding the Origins of Disease and Targeted Therapies in the Pipeline

FACULTY:

Preeya K. Gupta, MD

Edward J. Holland, MD

John D. Sheppard, MD

Vance Thompson, MD

David L. Wirta, MD

Experts in dry eye disease share their approaches to diagnosis and treatment of patients with this multifactorial disease. The panel members also come an agreement on key issues related to this complex condition and discuss novel investigative therapeutics that have the potential to improve patients' quality of life.

A continuing medical education activity provided by Evolve Medical Education LLC.
This activity is supported by an unrestricted educational grant from Oyster Point Pharma.

evolve
medical education

MOAs of DED: Understanding the Origins of Disease and Targeted Therapies in the Pipeline

Release Date: May 2021
Expiration Date: May 2022

FACULTY

VANCE THOMPSON, MD
Moderator
Founder, Vance Thompson Vision
Professor of Ophthalmology
University of South Dakota Sanford School of Medicine
Sioux Falls, SD

PREEYA K. GUPTA, MD
Associate Professor of Ophthalmology
Duke University Eye Center
Durham, NC

EDWARD J. HOLLAND, MD
Professor of Ophthalmology
University of Cincinnati
Director of the Cornea Service
Cincinnati Eye institute
Cincinnati, OH

JOHN D. SHEPPARD, MD
President, Virginia Eye Consultants
Professor of Ophthalmology, Microbiology, Molecular Biology
Eastern Virginia Medical School
Partner & Board of Directors, CVT Vision Partners
Norfolk, VA

DAVID L. WIRTA, MD
Principal Investigator/Medical Director
Eye Research Foundation
Newport Beach, CA

CONTENT SOURCE

This continuing medical education (CME) activity captures content from a virtual roundtable discussion.

ACTIVITY DESCRIPTION

This panel of experts in ocular surface diseases reviews the changing approach to managing patients with dry eye based on the latest research and their clinical experience. The panel members also discuss pipeline therapies and how they may compare to current treatments.

TARGET AUDIENCE

This certified CME activity is designed for ophthalmologists.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

- **Summarize** the mechanism of action of dry eye disease (DED)
- **Describe** the significance of the trigeminal nerve in ocular surface disorders
- **Evaluate** the impact that chronic diseases, certain medications, and ocular surgery can have on the health of the ocular surface
- **Compare** the current and potential future treatments for DED

GRANTOR STATEMENT

This activity is supported by an unrestricted educational grant from Oyster Point Pharma.

ACCREDITATION STATEMENT

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

CREDIT DESIGNATION STATEMENT

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

TO OBTAIN CREDIT

To obtain credit for this activity, you must read the activity in its entirety and complete the Pretest/Posttest/Activity Evaluation/Satisfaction Measures Form, which consists of a series of multiple-choice questions. To answer these questions online and receive real-time results, please go to https://evolvemeded.com/course/2112-supplement. Upon completing the activity and self-assessment test, you may print a CME credit letter awarding 1 *AMA PRA Category 1 Credit*™. Alternatively, please complete the Posttest/Activity Evaluation/Satisfaction Form and mail or fax to Evolve Medical Education LLC, 353 West Lancaster Avenue, Second Floor, Wayne, PA 19087; Fax: (215) 933-3950.

DISCLOSURE POLICY

It is the policy of Evolve that faculty and other individuals who are in the position to control the content of this activity disclose any real or apparent conflicts of interest relating to the topics of this educational activity. Evolve has full policies in place that will identify and resolve all conflicts of interest prior to this educational activity.

The following faculty/staff members have the following financial relationships with commercial interests:

Vance Thompson, MD, has had a financial agreement or affiliation during the past year with the following commercial interests in the form of *Consultant*: Acufocus, Alcon Vision, Allergan, Allotex, Avellino, Avisi Technologies, Bausch + Lomb, BRIM Biotechnology, Carl Zeiss Meditec, Conjtac, CSO, Equinox, Euclid Systems, Expert Opinion, eyeBrain Medical, Eyedetec, EyeGate Pharma, FemtoVision, Forsight Robotics, Glaukos, Healthe, Imprimis, iVeena, Johnson & Johnson Vision, Leica, Melt Pharmaceuticals, Mynosys, Novaliq, Ocular Innovations, OneFocus, Ophtec, ORra, Oyster Point Pharma, Percept, Precision Lens, ReFocus, RxSight, Sight Sciences, Stuart Therapeutics, Tarsus Rx, TearClear, TherOptix, ThruFocus, Treehouse Health, Veracity, Viewpoint Therapeutics, Visant, and Visiometrics. *Grant/Research Support:* Acufocus, Alcon Vision, Allergan, Bausch + Lomb, Carl Zeiss Meditec, Equinox, EyeGate Pharma, Glaukos, Johnson & Johnson Vision, Ora, RxSight, and Sight Sciences. *Speaker's Bureau:* Acufocus, Alcon Vision, Glaukos, and Johnson & Johnson Vision. *Stock/Shareholder:* Acufocus, Allotex, Avellino, Conjtac, Equinox, Euclid Systems, Expert Opinion, eyeBrain Medical, Eyedetec, EyeGate Pharma, Forsight Robotics, Healthe, iVeena, Melt Pharmaceuticals, Mynosys, Ocular Innovations, Oyster Point Pharma, Percept, RxSight, Sight Sciences, Stuart Therapeutics, Tarsus Rx, TearClear, Treehouse Health, Veracity, and Visant.

David L. Wirta, MD, has had a financial agreement or affiliation during the past year with the following commercial interests in the form of *Consultant*: AbbVIe, Eyenovia, and Novartis. *Grant/Research Support:* Allergan, Novartis, Ora, and Oyster Point Pharma.

Preeya K. Gupta, MD, has had no agreements or affiliation during the past year with commercial interests.

Edward J. Holland, MD, has had a financial agreement or affiliation during the past year with the following commercial interests in the form of *Consultant*: Abingworth, Aerie Pharmaceuticals, Akros Pharma, Alcon Vision, Aldeyra Therapeutics, Allegro, Allergan, Azura Ophthalmics, BlephEx, BRIM biotech, Carl Zeiss Meditec, Claris Bio, Corneat, CorneaGen, Dompé, Expert Opinion, Eye Point Pharmaceuticals, Glaukos, Hanall, Invirsa, Kala Pharmaceuticals, Mati Therapeutics, Merck, Novartis NIBR, Novartis, Ocular Therapeutix, Ocuphire, Omeros, Oyster Point Pharma, Precise Bio, Prometic Biotherapeutics, ReGentree, Retear, Senju, Shire, Sight Sciences, Slack, Tarsus, TearLab Research, Vomaris, and W.L. Gore and Associates. *Grant/Research Support:* Alcon Vision, Mati Therapeutics, Novartis, Omeros, Senju, and Shire. *Speaker's Bureau:* Alcon Vision, Novartis, Omeros, Senju, and Shire.

John D. Sheppard, MD, has had a financial agreement or affiliation during the past year with the following commercial interests in the form of *Consultant*: Aerie Pharmaceuticals, Alcon Vision, Aldeyra Therapeutics, Allergan, Allysta Pharmaceuticals, Avedro, Bausch + Lomb, Bio-Tissue, Bruder Healthcare, Clementia Pharmaceuticals, Dompé, EyeGate, EyePoint Pharmaceuticals, Glaukos, Hovione, Johnson & Johnson Vision, Kala Pharmaceuticals, Lacri Sciences, LayerBio, Mallinckrodt, Novaliq, Novartis, Noveome Biotherapeutics, Ocular Therapeutix, Omeros, Oyster Point Pharma, Quidel, Science Based Health, Shire, Sun Pharmaceutical Industries, Takeda Pharmaceuticals USA, TearLab, Tear Solutions, and TopiVert. *Grant/Research Support:* Alcon Vision, Bausch + Lomb, Chengdu Kanghong Pharmaceutical Group, Clearside Biomedical, EyeGate, Hovione, Kala Pharmaceuticals, Mallinckrodt, and Visus Pharmaceuticals. *Speaker's Bureau:* Alcon Vision, Bausch + Lomb, Bio-Tissue, Dompé, and Mallinckrodt. *Stock/Shareholder:* Claris Bio, Doctors Optimal Formula, Eyedetec Medical, EyeRxResearch, Eyevance, Lacrisciences, LayerBio, Noveome Biotherapeutics, Oyster Point Pharma, ProVision Network, Rapid Pathogen Screening, Scientifically Developed Solutions, Strathspey Crowne, and TearLab.

EDITORIAL SUPPORT DISCLOSURES

The Evolve staff and planners have no financial relationships with commercial interests. Michelle Dalton, writer, and Nisha Mukherjee, MD, peer reviewer, have no financial relationships with commercial interests.

OFF-LABEL STATEMENT

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. The opinions expressed in the educational activity are those of the faculty. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

DISCLAIMER

The views and opinions expressed in this educational activity are those of the faculty and do not necessarily represent the views of Evolve, *Cataract & Refractive Surgery Today*, *MillennialEYE*, or Oyster Point Pharma.

DIGITAL EDITION

To view the online version of the material, please go to https://evolvemeded.com/course/2112-supplement.

evolve
medical education

PRETEST QUESTIONS

PLEASE COMPLETE PRIOR TO ACCESSING THE MATERIAL AND SUBMIT WITH POSTTEST/ACTIVITY EVALUATION/SATISFACTION MEASURES FOR CME CREDIT.

1. Please rate your confidence in your ability to summarize the mechanism of action of dry eye disease (DED) (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

2. Please rate how often you utilize the latest treatments in DED (based on a scale of 1 to 5, with 1 being never and 5 being always).

a. 1
b. 2
c. 3
d. 4
e. 5

3. _____ is the primary instigator of DED.

a. Inflammation
b. Tear film instability
c. Lack of homeostasis
d. Hyperosmolarity

4. What percentage of patients may have mixed etiology DED?

a. 70%
b. 60%
c. 50%
d. 40%

5. _____ is becoming a more common trigger of DED, as seen in today's clinic settings.

a. Screen time/computer use
b. Smoking
c. Increased air condition use
d. Allergies

6. Why might the signs and symptoms of DED not align? Select all that apply.

a. Dry eye diagnostics are not sensitive enough to diagnose DED.
b. Patients are not forthcoming with reporting their dry eye symptoms.
c. Patients with late-stage disease may not be symptomatic but will have significant clinical signs.
d. Patients with early-stage dry eye will not have corneal staining but will be highly symptomatic.

7. What role does the trigeminal nerve play in DED?

a. The trigeminal nerve stimulates the three components of the tear film.
b. The trigeminal nerve is an autoregulator of the diurnal curve in tear secretion.
c. The trigeminal nerve causes dry eye symptoms due to the release of inflammatory mediators on the ocular surface.
d. The trigeminal nerve is responsible for basal tear production through neurostimulation.

8. Which dry eye algorithm is preferred in real-world settings?

a. TFOS DEWS II
b. CEDARS
c. ASCRS Preoperative Ocular Surface Disease Algorithm
d. None is preferred; patients need personalized treatment

9. It is estimated that _____ of patients seen in an eye care setting have dry eye episodes.

a. 60%
b. 70%
c. 80%
d. 90%

10. Which of the following statements is true?

a. DED is uncommon in children or adolescents.
b. DED is uncommon in postmenopausal women.
c. DED is becoming common in children and adolescents.
d. The rates of DED have remained stable for decades.

MOAs of DED: Understanding the Origins of Disease and Targeted Therapies in the Pipeline

AN INTRODUCTION TO DRY EYE DISEASE

The Complex Mechanism of Action of Dry Eye Disease

Defining define dry eye disease (DED) has perplexed clinicians for the past 2 decades. DED is multifactorial, affecting all ages and demographic groups, although it's most common in patients age 65 and older.[1] Because DED is frequently underdiagnosed, its prevalence varies widely and may be has high as 75%.[2] Its multifaceted character and constellation of symptoms has caused a great deal of confusion among clinicians, as no single diagnostic test or set of diagnostic tests can make a diagnosis. Its etiology is related to myriad factors, such as aging, hormonal finesse, the environment, contact lenses, medications, and surgery.

"Dry eye is a hyposecretory condition, as well as numerous, often concomitant and synergistic, etiologies that idiosyncratically respond to a wide variety of environmental, local, and systemic interventions, despite careful analysis of history, examination, and targeted testing parameters," said John D. Sheppard, MD, President of Virginia Eye Consultants, Norfolk, VA. "Dry eye is certainly inflammatory. It is a hypersecretory condition as well as a disease of meibomian gland dysfunction."

The recognition of inflammation as a key driver of DED marked a significant advance in its understanding and treatment.[3] Importantly, in 2017, the Tear Film and Ocular Surface Society and International Dry Eye Workshop II (TFOS DEWS II) included inflammation in its updated definition of DED, which now reads:

"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."[1,4]

For Preeya K. Gupta, MD, Associate Professor of Ophthalmology at the Duke University Eye Center, Durham, NC, a critical phrase from the TFOS DEWS II definition is "loss of homeostasis."

"Anything can disrupt homeostasis," she explained. "It's not one particular condition or aspect that causes that disruption. It can be a series of things that change over months, years, or perhaps even day to day."

It's generally accepted that tear osmolarity values of 315 ± 11 mOsm/L to 336 ± 22 mOsm/L indicate mild to severe DED,

"When I think about the TFOS DEWS II definition, one phrase that resonates with me is loss of homeostasis."

Preeya K. Gupta, MD

"The newest environmental trigger we are dealing with is increased screen time."

– Edward J. Holland, MD

with values of 302 ± 8 considered normal.[5] Fluctuations in osmolarity readings are a marker of homeostasis disruption, with changes of 33 mOsm/L or more considered clinically significant.[6]

Once homeostasis loss is identified, finding the cause is critical to managing DED, as it's rarely a singular issue. TFOS DEWS II recognizes two primary DED subtypes—evaporative and aqueous deficient—each of which has a different pathophysiology. For example, evaporative dry eye is typically caused by meibomian gland dysfunction or tear film instability due to the evaporation of tears and hyperosmolarity. Aqueous deficient dry eye can be caused by chronic autoimmune disorders (Sjögren syndrome), systemic conditions such as lymphoma or viral infections, lacrimal gland ablation, and ocular surface aging, among others.[7]

Importantly, David L. Wirta, MD, Principal Investigator/ Medical Director of Eye Research Foundation, Newport Beach, CA, noted that although some people fit well into a DED subtype, many patients have a mixture of both. "There are some patients, such as patients with Sjögren syndrome, that clearly have aqueous deficient dry eye with nearly zero tears," he said. "Other very symptomatic patients have a normal Schirmer score, inflamed lid margins, and poor meibum secretion. But another subset of patients blends the two, which is where the multifactorial aspect of DED comes in."

Lemp et al found that patients are 3 times more like to have evaporative than aqueous deficient dry eye, but that 30% of patients have a mixture of both types.[8] The prevalence of mixed etiology DED may be as high as 70%.[9] The mixed etiology may be caused by the "vicious circle" of DED, one that once the patient enters, regardless of the initial cause, becomes difficult to escape due to the interplay between tear film instability, hyperosmolarity, and inflammation, which continues in a self-perpetuating cycle.[10]

"Tear film instability leads to hyperosmolarity, which leads to cell damage and apoptosis, which then leads to inflammation and the release of the inflammatory mediators we know are in the cells and the ocular surface," said Edward J. Holland, MD, Director of the Cornea Service, Cincinnati Eye institute, Cincinnati. "This is a chronic cycle that keeps propagating dry eye."

UNDERSTANDING DRY EYE EPISODES AND CORRESPONDING TRIGGERS

Although DED is considered a chronic condition, the vast majority of patients have fluctuating disease with periods of stability interlaced with episodes. Lienert et al studied the natural history of DED over a year and found that patients reported symptom fluctuations.[11]

"Dry eye is not stable," Dr. Wirta said. "A patient has good days and bad days."

"We now know that 80% of patients with dry eye have episodes," Dr. Holland said. "They fall into two categories. They only have episodes, which could last 7 to 14 days and they have no symptoms in between episodes, or they have episodes on top of their chronic dry eye."

Because DED is multifaceted, increases in signs and symptoms, such as ocular irritation, redness, excessive tearing, itching, and soreness, can be caused by a plethora of triggers.[7] For example, environmental factors, such as reduced humidity and exposure to increased heat, wind, air conditioning, smoke or smoking, and allergens may aggravate dry eye symptoms.[12-15]

"The newest environmental trigger we are dealing with is increased screen time," Dr. Holland said.

Patients who spend more time reading and using the computer or smartphones have more DED symptoms.[16]

"Often the symptoms of dry eye and allergy can become intertwined and confused, such as itching and dry eye or tearing for a patient who has allergies," Dr. Sheppard said.

This is particularly important when evaluating children and adolescents, as DED can occur at any age. A landmark study of 99 children from Gupta et al found relatively high level of mild meibomian gland atrophy in a pediatric population, likely due to digital device use.[17] Another study from Tichenor et al found symptomatic meibomian gland dropout in 15% of 225 adolescent patients.[18]

"Clinicians must take a fantastic history on any patient who may have OSD," Dr. Sheppard said. "You want to know what they do in their work. Are there circumstances in the outdoors or in a factory that trigger the dry eye and make it episodic on weekdays as opposed to weekends? Are they a heavy user of digital display devices? People have decreased blink rates when they stare at devices. Occupational and avocational triggers are very important

EXPERT PANEL CONCLUSION #1:

"The panel supports the TFOS DEWS II definition: 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."[1, 4]

TABLE. Characteristic Findings of DED Diagnostics.[7]

TEST	FINDINGS
Tear osmolarity	Elevated; test-to-test variability; intereye differences considered abnormal
Matrix metalloproteinase-9	Indicates presence of inflammation, which dictates treatment
Aqueous tear production (Schirmer test)	10 mm or less considered abnormal
Fluorescein dye disappearance test/tear function index	Test result is compared with a standard color scale
Tear break-up time	Less than 10 seconds considered abnormal
Ocular surface dye staining	Staining of inferior cornea and bulbar conjunctiva typical
Lacrimal gland function	Decreased tear lactoferrin concentrations

because they occupy the majority of the patient's time."

Secondary factors, such as rheumatoid arthritis (RA), medications, and cataract and refractive surgery also play an important role. Wolfe et al examined self-reported dry eye symptoms in nearly 10,000 patients with RA, finding that 11% of RA patients experienced persistent dryness and 17% reported episodic symptoms.[19] Cataract and refractive surgery are known to exacerbate dry eye symptoms, especially in the 3-month postoperative period.[20,21]

"Medications such as antihypertensives and antidepressants certainly can increase dry eye," Dr. Holland said. "Surgical procedures, whether it's glaucoma surgery, cataract surgery, or corneal refractive surgery, cause some neurotrophic change and that results in dry eye in these patients."

The expert panel noted several ways to reduce surgical dry eye triggers, such as reducing injury to the cornea.

"We have to concentrate on cutting the cornea as little as possible," Dr. Sheppard said. Particularly during refractive surgery, "we have to remember that the SMILE procedure may be far gentler on the corneal nociceptors than traditional LASIK or even PRK. When we look at patients who have penetrating keratoplasty, we realize that virtually all of the corneal nerves are cut. These patients become profoundly neurogenically dry, and they need to receive a special level of care typically reserved for our sickest ocular surface patients."

To reduce cataract surgery triggers, clinicians must ensure the ocular surface is healthy enough for surgery. The American Academy of Ophthalmology recommends that all patients considering cataract and refractive surgery undergo a full dry eye examination, including tear film and ocular surface evaluation, and that any ocular surface issues are resolved preoperatively.[7]

Undiagnosed dry eye is prevalent in this patient population. The PHACO study found that of 136 patients scheduled for cataract surgery, the majority (62%) had a tear break-up time of 5 seconds or less, 77% had positive corneal staining, and 50% had positive central corneal staining. Yet nearly 60% never complained of a foreign body sensation, a common DED symptom.[22] Trattler et al estimated that 20% of the study population would never have been diagnosed with DED had they not presented for a cataract surgery evaluation. Gupta et al further confirmed this high prevalence, estimating that 80% of patients having a cataract surgery evaluation have ocular surface dysfunction, which is largely undiagnosed.[23]

SYMPTOMS AND SIGNS OF DRY EYE DON'T ALWAYS ALIGN

Part of the challenge for clinicians is the poor association between the signs and symptoms of DED; patient-reported symptoms do not align well with clinical measures.[24,25]

"The two most important dry eye patients I see are the surgical patient and the complaining patient," Dr. Sheppard said. "For the surgical patient, I don't care how good or bad they feel—they often feel fine—I care about how they look and how it affects their biometry. I have to get their dry eye under control at all costs."

If a patient is highly symptomatic, it's important to listen to their complaints carefully.

"They may say they are dry but that could mean different things to different people," Dr. Sheppard said. "It may be that the patient has photophobia or is having trouble reading or driving at night because of ocular surface irregularities. They may be tearing and don't know that's a symptom of DED. To each patient, their chief complaint is the most important one to them. It's not just dry eye, it's one of many subcategories of that complaint set, that symptom set, that the patient is focusing on and looking upon their ophthalmologist and their optometrist to fix."

Lemp et al compared the clinical usefulness of several DED diagnostics, including bilateral tear osmolarity, tear film break-up time, corneal staining, conjunctival staining, Schirmer test, and meibomian gland grading and found that, with the exception of tear osmolarity, the tests had either poor sensitivity (corneal staining, 54%; conjunctival staining, 60%; meibomian gland grading, 61%) or poor specificity (tear film break-up time, 45%; Schirmer test, 51%).[26] Other studies have found that tear osmolarity has the lowest variability among tests,[27] but the results are still inconsistent, with no single test capable of diagnosing DED.[28]

"The lack of correlation between clinical signs and patient-reported symptoms make dry eye challenging for both patients

and clinicians," Dr. Holland said. For example, a patient with early-stage DED from contact lens intolerance may be highly symptomatic but has no corneal staining upon examination.

"Corneal staining is not an early sign of dry eye," Dr. Holland explained. "That's a sign of moderate to severe dry eye. Therefore, a patient who is highly symptomatic may have minimal to no signs. Many clinicians don't recognize this type of patient as having significant dry eye because she's early in the course of her condition and hasn't had the chronicity to develop the classic signs we think about."

On the other hand, a patient with chronic, long-term dry eye becomes less symptomatic as their disease progresses due to neurotrophic changes. Although they may not complain of pain, they may have severe meibomian gland disease and a very unstable tear film with a rapid tear break-up time.

"These patients are complaining or poor quality of vision or fluctuating vision," Dr. Holland said. "There is a big disconnect between lots of discomfort and minimal signs in the early dry eye patient, and a lot of clinical signs but minimal symptoms of discomfort in the chronic dry eye patient."

Dr. Gupta stressed that there are many more diagnostic tests beyond corneal staining that clinicians should look to when assessing a patient for DED. In addition to corneal staining, the American Academy of Ophthalmology recommends osmolarity, matrix metallopeptidase 9, Schirmer without anesthesia, fluorescein dye disappearance, tear break-up time, and lacrimal gland function to assess the health of the ocular surface.[7] The Table details the characteristic findings for DED diagnostics.

These diagnostics, in combination with patient-reported symptom questionnaires such as Ocular Surface Disease Index, Dry Eye Questionnaire, Impact of Dry Eye on Everyday Living, National Eye Institute's Visual Function Questionnaire, among others, will aid clinicians in making an accurate diagnosis.

1. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II Definition and Classification Report. *Ocular Surf.* 2017;15(3):276-283.
2. Stapleton F, Alves M, Bunya VY, et al. TFOS DEWS II Epidemiology Report. *Ocular Surf.* 2017;15(3):334-365.
3. Pflugfelder SC, de Paiva CS. The Pathophysiology of Dry Eye Disease: What We Know and Future Directions for Research. *Ophthalmology.* 2017;124(11s):S4-s13.
4. Craig JP, Nelson JD, Azar DT, et al. TFOS DEWS II Report Executive Summary. *Ocul Surf.* 2017;15(4):802-812.
5. Sullivan BD, Whitmer D, Nichols KK, et al. An objective approach to dry eye disease severity. *Invest Ophthalmol Vis Sci.* 2010;51(12):6125-6130.
6. Eperjesi F, Aujla M, Bartlett H. Reproducibility and repeatability of the OcuSense TearLab osmometer. Graefes Arch Clin Exp Ophthalmol. 2012;250(8):1201-1205.
7. Akpek EK, Amescua G, Farid M, et al. Dry Eye Syndrome Preferred Practice Pattern. *Ophthalmology.* 2019;126(1):286-334.
8. Lemp MA, Crews LA, Bron AJ, et al. Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort: a retrospective study. *Cornea.* 2012;31(5):472-478.
9. Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy Report. *Ocul Surf.* 2017;15(3):575-628.
10. Bron AJ, de Paiva CS, Chauhan SK, et al. TFOS DEWS II pathophysiology report. *Ocul Surf.* 2017;15(3):438-510.
11. Lienert JP, Tarko L, Uchino M, et al. Long-term Natural History of Dry Eye Disease from the Patient's Perspective. *Ophthalmology.* 2016;123(2):425-433.
12. Lopez-Miguel A, Teson M, Martin-Montanez V, et al. Dry eye exacerbation in patients exposed to desiccating stress under controlled environmental conditions. *Am J Ophthalmol.* 2014;157(4):788-98.e2.
13. Alves M, Novaes P, Morraye Mde A, et al. Is dry eye an environmental disease? *Arq Bras Oftalmol.* 2014;77(3):193-200.
14. Galor A, Kumar N, Feuer W, Lee DJ. Environmental factors affect the risk of dry eye syndrome in a United States veteran population. *Ophthalmology.* 2014;121(4):972-3.
15. Iyer JV, Lee SY, Tong L. The dry eye disease activity log study. *ScientificWorldJournal.* 2012;2012:589875.
16. Karakus S, Mathews PM, Agrawal D, et al. Impact of Dry Eye on Prolonged Reading. *Optom Vis Sci.* 2018;95(12):1105-1113.
17. Gupta PK, Stevens MN, Kashyap N, Priestley Y. Prevalence of Meibomian Gland Atrophy in a Pediatric Population. *Cornea* 2018;37(4):426-30.
18. Tichenor AA, Ziemanski JF, Ngo W, et al. Tear Film and Meibomian Gland Characteristics in Adolescents. *Cornea.* 2019;38(12):1475-1482.
19. Wolfe F, Michaud K. Prevalence, risk, and risk factors for oral and ocular dryness with particular emphasis on rheumatoid arthritis. *J Rheumatol* 2008;35(6):1023-1030.
20. Woodward MA, Randleman JB, Stulting RD. Dissatisfaction after multifocal intraocular lens implantation. *J Cataract Refract Surg.* 2009;35(6):992-997.
21. Iglesias E, Sajnani R, Levitt RC, et al. Epidemiology of Persistent Dry Eye-Like Symptoms After Cataract Surgery. *Cornea* .2018;37(7):893-898.
22. Trattler WB, Majmudar PA, Donnenfeld ED, et al. The Prospective Health Assessment of Cataract Patients' Ocular Surface (PHACO) study: the effect of dry eye. *Clin Ophthalmol.* 2017;11:1423-1430.
23. Gupta PK, Drinkwater OJ, VanDusen KW, et al. Prevalence of ocular surface dysfunction in patients presenting for cataract surgery evaluation. *J Cataract Refract Surg.* 2018;44(9):1090-1096.
24. Begley CG, Chalmers RL, Abetz L, et al. The relationship between habitual patient-reported symptoms and clinical signs among patients with dry eye of varying severity. *Invest Ophthalmol Vis Sci.* 2003;44(11):4753-4761.
25. Bartlett JD, Keith MS, Sudharshan L, Snedecor SJ. Associations between signs and symptoms of dry eye disease: a systematic review. *Clin Ophthalmol.* 2015;9:1719-1730.
26. Lemp MA, Bron AJ, Baudouin C, et al. Tear osmolarity in the diagnosis and management of dry eye disease. *Am J Ophthalmol.* 2011;151(5):792-8.e1.
27. Sullivan BD, Crews LA, Sonmez B, et al. Clinical utility of objective tests for dry eye disease: variability over time and implications for clinical trials and disease management. *Cornea.* 2012;31(9):1000-1008.
28. Sullivan BD, Crews LA, Messmer EM, et al. Correlations between commonly used objective signs and symptoms for the diagnosis of dry eye disease: clinical implications. *Acta Ophthalmol.* 2014;92(2):161-166.

INFLAMMATORY COMPONENT OF OCULAR SURFACE DISEASE

Tear Film Homeostasis and its Effect on Dry Eye Disease

Tear film instability is the basis for dry eye. Hyperosmolarity activates the inflammatory pathways, causing aqueous tear deficiency or chronic meibomian gland disease.[1]

"This hyperosmolarity then leads to inactivation of antigen-presenting cells and the stimulation of the inflammatory cycle," said Edward J. Holland, MD. "Activated T cells then release the inflammatory mediators that occur on the ocular surface to give the patients dry eye symptoms. Tear film instability leads to inflammation in that vicious circle of dry eye."

The tear film has three main layers: aqueous, lipid, and mucin.[2] Tears are secreted through the trigeminal nerve—brainstem—facial

"The trigeminal nerve and its function have a large bearing on how the patient perceives their disease."

– David L. Wirta, MD

nerve—lacrimal gland reflex arc. The trigeminal nerve is the largest cranial nerve and is important, not just for homeostasis, but for the many symptoms that occur with trigeminal nerve hyperstimulation.

"When we think about the trigeminal nerve, it really wasn't until a few years ago that we understood the neural aspects or the feedback groups that were there to protect the ocular surface," Preeya K. Gupta, MD said. "The trigeminal nerve is constantly surveilling the ocular surface, bringing in those sensory inputs, which then go to the brainstem and trigger an afferent pathway that then targets the lacrimal functional unit. That trigeminal pathway is very important for providing reflexive protection and contributing to a healthy and complete tear film."

Importantly, tears are not just balanced saline; the tear film provides nutrients to the ocular surface.

"Tears are a very complex mixture of hopefully homeostatically regulated and consistently secreted beneficial proteins and immunoglobulins," John D. Sheppard, MD, said. "The protective proteins include lactoferrin and lysozyme as well as microquantities of proteins like lacritin, which is a universal stimulant of proliferation of epithelial cells on the ocular surface."

Homeostasis is the balance of beneficial proteins, anti-inflammatory cytokines, immunoglobulins, mucins, lipids and electrolytes in the tear film.

"Any alteration in any portion of what we call the ocular surface unit can disturb that homeostasis," Dr. Sheppard said. "This is an orchestra that's only as functional as its weakest musician."

For example, if the parasympathetic nervous system (PNS) and the fifth cranial nerve are dysfunctional, there is less simultaneous secretion of the three components of the tear film that are stimulated by the PNS. The PNS is most easily accessed through the nasal passages, and 34% of basal tear production is caused by sensory stimulation from air moving through the nose.[3] This is an important learning point, as several devices and agents use nasal neurostimulation for dry eye disease (DED) treatment.

"The trigeminal nerve and its function have a large bearing on how the patient perceives their disease. If they have poorly functioning sensation, they might have more signs, more staining, more breakdown of the corneal epithelium," said David L. Wirta, MD.

CURRENT PHARMACOLOGIC ANTIINFLAMMATORY TREATMENTS

Inflammation is a core mechanism in the vicious circle of DED.[4] Pharmacologic treatments indicated for dry eye, such as cyclosporine (cyclosporine 0.05%, Restasis, Allergan; cyclosporine 0.09%, Cequa, Sun Pharma), lifitegrast, and loteprednol 0.25%, specifically address the inflammatory component of DED.

Clinical trials have indicated that cyclosporine may be disease modifying, with a systematic review showing that Restasis dosed twice daily significantly improved both objective and subjective outcomes in patients with DED.[5] Cequa is also a cyclosporine, but is dosed at a higher level than Restasis and includes a nanomicellar formulation that better penetrates the aqueous layer, thereby improving drug absorption.[6] The pivotal phase 3 trial showed clinically significant improvements in tear production and ocular surface integrity with Cequa, although the long-term efficacy is unknown. The long-term efficacy of lifitegrast is also unknown, but studies show the agent improves both signs and symptoms of DED.[7]

Despite these clinical trial successes, Dr. Wirta calls these agents "somewhat effective" in the real world.

"Certainly, there are patients who benefit from them, but the average patient does not," he said. "Twenty-five percent of patients have some sort of positive response and improvement with them."

The perceived lack of efficacy in the real-world setting could be due to several factors including the vehicle, patient selection, and their delayed onset of action. Side effects such as stinging and burning may discourage their use, despite their effectiveness. With Restasis, for example, 17% of patients have ocular burning upon instillation. Lifitegrast also causes stinging and burning, but at a lesser rate. Younger patients with inflammatory ocular surface and aqueous tear deficiency typically have the most robust response to cyclosporine and lifitegrast, but it still takes several months for them to work.

"Lifitegrast works a little faster than Restasis, and I tend to go to that one first," Dr. Holland said.

Rapid symptom relief is critically important to patients, and Dr. Gupta noted that this is a significant gap in current maintenance treatments for DED. A potential game-changer in this regard is the approval of loteprednol 0.25% for dry eye, which just became available in the United States in January 2021.[8] Loteprednol 0.25% is a nanoparticle that penetrates the mucus layer at a lower concentration than other anti-inflammatory

EXPERT PANEL CONCLUSION #2:

The trigeminal nerve is an autoregulator of the diurnal curve in tear secretion. Patients are dependent upon the normal and proper function of this efferent and efferent regulator of tear secretion.

agents, making it less likely to cause spikes in intraocular pressure.[9] It's specifically indicated for short-term treatment of DED, with the pivotal STRIDE trials showing improvements in ocular discomfort, corneal staining, and conjunctival hyperemia at day 15.

"I think loteprednol 0.25% will be a breakthrough treatment for dry eye," Dr. Holland said. "We know that 80% of our patients have dry eye episodes. If you have an episode, a maintenance therapy with cyclosporine or lifitegrast is not going to manage that, whereas a good topical steroid would. That's where loteprednol 0.25% fits in."

Dr. Holland anticipates a change in the DED treatment paradigm where clinicians begin with a topical steroid like loteprednol 0.25% to manage dry eye episodes and then transition patients to maintenance therapy with either lifitegrast or cyclosporine. Sheppard et al looked at loteprednol induction therapy for 2 weeks followed by maintenance cyclosporine, finding that approach provided more rapid relief of dry eye signs and symptoms with greater efficacy than either agent alone.[10]

1. Messmer EM, Bulgen M, Kampik A. Hyperosmolarity of the tear film in dry eye syndrome. *Dev Ophthalmol*. 2010;45:129-138.
2. Willcox MDP, Argueso P, Georgiev GA, et al. TFOS DEWS II Tear Film Report. *Ocul Surf*. 2017;15(3):366-403.
3. Gupta A, Heigle T, Pflugfelder SC. Nasolacrimal stimulation of aqueous tear production. *Cornea*. 1997;16(6):645-648.
4. Gupta PK, Asbell P, Sheppard J. Current and future pharmacological therapies for the management of dry eye. *Eye Contact Lens*. 2020;46 Suppl 2:S64-s9.
5. Akpek EK, Amescua G, Farid M, et al. Dry Eye Syndrome Preferred Practice Pattern. *Ophthalmology*. 2019;126(1):286-334.
6. Goldberg DF, Malhotra RP, Schechter BA, et al. A phase 3, randomized, double-masked study of otx-101 ophthalmic solution 0.09% in the treatment of dry eye disease. *Ophthalmology*. 2019;126(9):1230-1237.
7. Holland EJ, Luchs J, Karpecki PM, et al. Lifitegrast for the treatment of dry eye disease: results of a phase iii, randomized, double-masked, placebo-controlled trial (OPUS-3). *Ophthalmology*. 2017;124(1):53-60.
8. Beckman K, Katz J, Majmudar P, et al. Loteprednol etabonate for the treatment of dry eye disease. *J Ocul Pharmacol Ther*. 2020;36(7):497-511.
9. Popov A. Mucus-Penetrating particles and the role of ocular mucus as a barrier to micro- and nanosuspensions. *J Ocul Pharmacol Ther*. 2020;36(6):366-375.
10. Sheppard JD, Donnenfeld ED, Holland EJ, et al. Effect of loteprednol etabonate 0.5% on initiation of dry eye treatment with topical cyclosporine 0.05%. *Eye Contact Lens*. 2014;40(5):289-296.

OBSTACLES TO SUCCESSFUL LONG-TERM TREATMENT

How Useful are Treatment Algorithms?

Several treatment algorithms have been developed for dry eye disease (DED) to help guide clinicians through the process including Tear Film and Ocular Surface Society and International Dry Eye Workshop II (TFOS DEWS II),[1] CEDARS, and the American Society of Cataract and Refractive Surgery (ASCRS) Preoperative Ocular Surface Disease Algorithm. TFOS DEWS II recommends a stepwise approach based on questioning and diagnostic testing, recommending different treatments based on disease severity, but notes that it is more of an organizational tool than a rigid algorithm.

The ASCRS Corneal Clinical Committee recently developed an extensive algorithm to test for ocular surface disease (OSD) before cataract surgery, including the Standardized Patient Evaluation of Eye Dryness (SPEED) questionnaire, tear osmolarity analysis, corneal topography, staining, and tear break-up time and Schirmer testing.[2]

Finally, the CEDARS Dry Eye Algorithm divides DED into four categories. Each category has its own treatment stepwise treatment approach.[3]

"These algorithms are great teaching tools for those who are less experienced in treating OSD, but they created a bit of confusion," John D. Sheppard, MD, said. "It's important to keep treatment simple and as monophasic as possible so that one understands that an improvement is due to an individual intervention and that a side effect may also be due to that individual intervention. If we, on the other hand, make five recommendations and the patient gets better or worse, we're not really sure what influenced that change in the patient's clinical presentation."

Preeya K. Gupta, MD, also sees the algorithms as educational, stressing that while it is most scientific when strictly followed, everyone can participate at some level by choosing what works best to integrate into your own clinical practice.

"It's not necessarily the expectation that clinicians follow these in a stepwise fashion," she said. "Their best use is to educate clinicians on best practices from leading experts and provide the clinician with a guide of options as well as information."

One algorithm isn't better than the other, and there's not one clinicians should lean on. Instead, the expert panel recommends using them as a guide to create an individualized treatment plan based on patient signs, symptoms, and needs (Figure).

"Every patient is their own algorithm," David L. Wirta, MD, said.

EXPERT PANEL CONCLUSION #3:

Clinicians should use dry eye algorithms as a guidepost to develop an individualized care plan based on the individual's signs, symptoms, and needs.

Dr. Sheppard agreed, noting that all the algorithms are useful from the perspective of an intellectual discussion, but are not intended to be set strategies for real-world patients.

"I prefer a straightforward approach," he said. "What is the most important finding today, and what is the single best way to treat it? Isolating treatments reduces confusion regarding both efficacy and side effects. That finding may be a key sign (central corneal staining with resultant irregular astigmatism) best treated with specific meibomian gland therapy for evaporative dry eye (Omegas, lipid tears, thermal pulsation, amniotic membrane), or an adamant chief complaint of ocular irritation, perhaps best treated with high viscosity tears and punctal plugs for immediate relief and an anti-inflammatory for delayed relief."

BARRIERS TO CARE

Insurance preauthorization, patient compliance, and side effects remain significant barriers to care. To keep medication costs reasonable, the expert panel recommends clinicians select prescriptions based on the patients' insurance coverage. Clinicians must also explain to patients that treatments will not work overnight. Patients need to tolerate some amount of trial and error with therapies until they find something that works for them.

"It really does to some extent depend upon the art of medicine and our ability to instinctively evaluate a patient's concern, motivation, and their personality and intellectual ability to understand their disease and to follow through with a treatment recommendation," Dr. Sheppard said.

Many patients don't understand that dry eye is a chronic, recurring, progressive disease. DED won't be resolved in a few weeks.

"This creates a lot of frustration," Edward J. Holland, MD, said. "We need to set the patient's expectations about what dry eye is, why it's chronic, why it's episodic and recurrent, and why it's progressive. The vast majority of patients will be on lifelong treatment. When they understand that, they are apt to be more compliant."

Patients must also understand the potential side effects of DED treatment, including how preservatives such as benzalkonium chloride (BAK) impact the ocular surface.[4]

EXPERT PANEL CONCLUSION #4:

Dry eye treatments should be selected based on the patient's signs and symptoms with preservatives avoided whenever possible. Insurance coverage must also be taken into consideration.

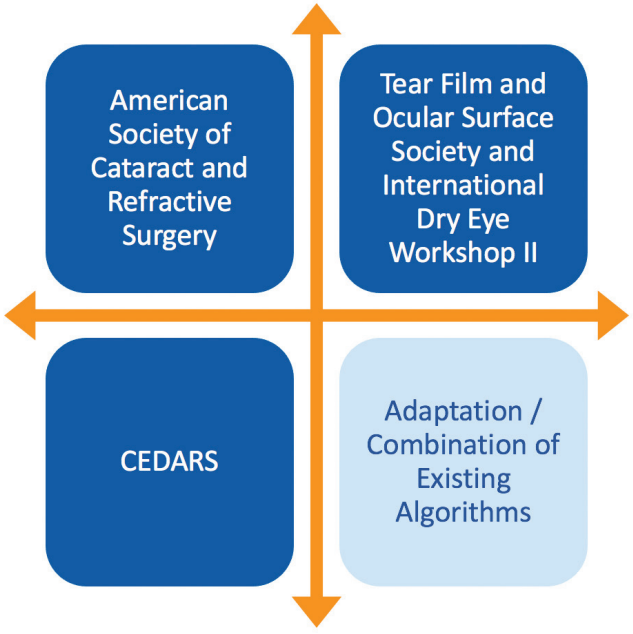

Figure. Several treatment algorithms have been developed for dry eye disease (DED) to help guide clinicians through the process. Some clinicians adapt those into one that suits their practice and patients.

"We know that BAK causes toxicity to the ocular surface over time," Dr. Gupta said. "It can break down the corneal epithelium, induce toxicity to the goblet cells, and even create neurotrophism. The inclusion of preservatives is something clinicians have control over. It's important to recognize when a patient might be on a high preservative load and go a step further to limit the amount of chronic BAK exposure, both in terms of quantity and the number of years they are exposed."

Dr. Wirta estimates that 15% of the general population has a sensitivity to BAK. Clinical studies have shown that BAK is linked to worsening OSD, as patients on preserved drops have more signs and symptoms of dry eye.[5] Leung et al found that each additional BAK-containing eye drop per day was associated with 2 times higher odds of abnormal lissamine green staining results.[6] This is especially important patients with glaucoma, as many are on multiple mediations containing BAK, resulting in a significant overlap between patients with glaucoma and dry eye.

"It's key to avoid preservatives in the glaucoma population," Dr. Sheppard said. "The other consideration is in treatment-naïve patients who have been self-treating with over-the-counter drops. These are largely ineffective, and contain heavy preservatives that are deleterious to the ocular surface."

1. Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy Report. *Ocul Surf.* 2017;15(3):575-628.
2. Starr CE, Gupta PK, Farid M, et al. An algorithm for the preoperative diagnosis and treatment of ocular surface disorders. *J Cataract Refract Surg.* 2019;45(5):669-684.
3. 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.
4. Baudouin C, Labbe A, Liang H, et al. Preservatives in eyedrops: the good, the bad and the ugly. *Prog Retin Eye Res.* 2010;29(4):312-334.
5. Fechtner RD, Godfrey DG, Budenz D, et al. Prevalence of ocular surface complaints in patients with glaucoma using topical intraocular pressure-lowering medications. *Cornea.* 2010;29(6):618-621.
6. Leung EW, Medeiros FA, Weinreb RN. Prevalence of ocular surface disease in glaucoma patients. *J Glaucoma.* 2008;17(5):350-355.

DRY EYE TREATMENT OPTIONS IN THE PIPELINE

There are several novel treatments in the pipeline including neurostimulating nasal sprays and disease-modifying regenerative treatments that treat the root cause of dry eye disease (DED).

Varenicline nasal spray is selective cholinergic agonist that demonstrated statistically significant improvements in Schirmer score compared with control in the phase 3 ONSET-2 trial.[1]

"Varenicline binds to the receptors located on the trigeminal nerve in the anterior portion of the nasal cavity. After nerve activation, the lacrimal punctal unit is stimulated and produces all three layers of the tear film," Edward J. Holland, MD, said. "I think is very exciting is that you get immediate relief, and you're stimulating all three layers of the tear film."

The nasal spray approach will be convenient for patients and is an attractive alternative to eye drops for several reasons. First, patients are accustomed to using nasal sprays. Second, nasal sprays allow patients to avoid the side effects of eye drops, such as ocular irritation, discomfort, and burning. Third, many patients struggle with eye drop installation.

"I see this as a complementary mechanism to existing products," Preeya K. Gupta, MD, said. "Certainly, there are going to be patients who only need one medication, but many patients need polytherapy. Patients can use this in addition to maintenance therapy to achieve symptomatic relief."

Other agents in the pipeline may be disease modifying. Reproxalap is a small molecule RASP inhibitor that improved ocular redness and the clinical symptoms of ocular dryness and discomfort in the phase 3 TRANQUILITY trial (NCT04674358).[2] Dr. Sheppard called RASP inhibition "revolutionary."

"RASP inhibitors block an entirely different pathway in the inflammatory cascade, which appears to be effective not only in dry eye but also in allergy," said John D. Sheppard, MD. "Malonaldehyde is a product of aldehyde-based inflammation and it's found to be elevated in dry eye patients. With the application of reproxalap, we find that malonaldehyde levels decrease markedly. This highly correlative biomarker, which is directly associated with a mechanism of action of reproxalap, has been accepted as a useful and clinically significant and perhaps even a primary endpoint for subsequent studies."

Tavilermide is also being investigated for treatment of dry eye. This is a first-in-class nerve growth factor mimetic for the treatment of DED. Tavilermide is preservative-free with a unique mechanism of action, facilitating protein secretions from the conjunctival glands. A phase 3 trial is underway.[3]

"Tavilermide has been under investigation for a decade now," Dr. Sheppard said. "It's a TRK-A agonist that produces a neurostimulatory effect on the surface epithelium directly, as well as perhaps a secretory enhancement."

Lacripep, a synthetic tear protein fragment of lacritin, is also being studied for use in treating dry eye. Lacritin is a nanomolar quantity biologic that's found in everyone's tear film but is deficient in dry eye.[4]

"By augmenting lacritin, we can find enhancements of ocular surface epithelial morphology as well as increased production of more normal tears," Dr. Sheppard said.

Results of a phase 2 trial in patients with Sjögren syndrome (NCT03226444) found a statistically significant reduction in inferior corneal staining and improvement in burning and stinging symptoms after 2 weeks of treatment.

RGN-259 is a Tβ4-based sterile and preservative-free eye drop under development for DED and neurotrophic keratitis. RGN-259 reduces corneal apoptosis and inflammation through cell migration and increasing laminin-5 production. It's currently being investigated in the phase 3 ARISE-3 study (NCT03937882).

"RGN-259 gets at the nerve function and decompensation aspect of dry eye," Dr. Gupta said. "Advanced DED almost always involves some sort of decompensation of that nerve loop. This is an exciting area of ocular surface disease, and one for which we need more treatments."

Ophthalmology has entered into a biologics era for dry eye, with primitive early-stage interventions.

"Novartis is looking at the FAB fragment of a monoclonal antibody directed against tumor necrosis factor, which appears to have an outstanding effect upon ocular surface and

EXPERT PANEL CONCLUSION #5:

Investigative treatments in the pipeline for dry eye disease have unique mechanisms of action and may be disease modifying.

"There's no ideal drug, and there's no ideal tolerability profile. So, perhaps the new mechanism of action may be just as potent but safer, better tolerated, or both. That may be the new frontier in dry eye."

– John D. Sheppard, MD

perhaps intraocular inflammation," Dr. Sheppard said. "Noveome Biotherapeutics is looking at the supernatant secretome of immortalized cultured amniotic membrane cells that produce high levels of more than 400 beneficial synergistic regenerative, reparative, antiscarring, antiinflammatory and antimicrobial proteins that may be very effective for dry eye. They are taking mother nature at its best and using these really truly very primitive biologic substances very much for the benefit of the ocular surface."

The panelists agreed that a significant unmet need in the dry eye space are head-to-head clinical trials in large patient populations that directly compare molecules. Without this information, clinicians will continue to struggle with treatment personalization. For example, some agents may be well-suited for older, neurotrophic patients while others may be better for younger patients with highly symptomatic meibomian gland disease.

"Due to the heterogeneity of DED, each patient most likely responds best to a single mechanism of action, and perhaps not so often T-cell mediated disease," Dr. Sheppard said.

Dr. Sheppard also hopes these new agents in the pipeline have a better tolerability profile than current pharmacologics, as lifitegrast and cyclosporine cause ocular irritation and blurred vision, and topical steroids are known to cause cataracts and glaucoma with continued use. An improved tolerability profile will help increase compliance.

"There's no ideal drug, and there's no ideal tolerability profile," Dr. Sheppard said. "So, perhaps the rising star of a novel mechanism of action may be not only just as potent but safer, better tolerated, or both. That may be the new frontier in dry eye." ■

EXPERT PANEL CONCLUSION #6:

Investigative treatments may be more effective than current treatments due to increased convenience and tolerability.

1. 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. 2020. www.globenewswire.com/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.
2. Eyewire. Aldeyra Therapeutics announces positive top-line symptom and sign results from run-in cohort of phase 3 TRANQUILITY trial in dry eye disease. https://eyewire.news/articles/aldeyra-therapeutics-announces-phase-3-tranquility-dry-eye-disease-trial-design/.
3. Mimetogen pharmaceuticals completes enrollment of mim-728 phase 3 trial for tavilermide for dry eye disease. 2020. http://mimetogen.com/news-publications/press-releases/3910-mimetogen-pharmaceuticals-completes-enrollment-of-mim-728-phase-3-trial-for-tavilermide-for-dry-eye-disease.html
4. TearSolutions Announces Results From Primary Sjögren's Syndrome Trial and Appoints Anil Asrani President and CEO. 2020. https://eyewire.news/articles/tearsolutions-announces-results-from-primary-sjo%CC%88grens-syndrome-trial-and-appoints-anil-asrani-president-and-ceo/.

MOAS OF DED: Understanding the Origins of Disease and Targeted Therapies in the Pipeline

Release Date: May 2021
Expiration Date: May 2022

INSTRUCTIONS FOR CME CREDIT

To receive credit, you must complete the attached Pretest/Posttest/Activity Evaluation/Satisfaction Measures Form and mail or fax to Evolve Medical Education LLC; 353 West Lancaster Avenue, Second Floor, Wayne, PA 19087; Fax: (215) 933-3950. To answer these questions online and receive real-time results, please go to https://evolvemeded.com/course/2112-supplement. If you experience problems with the online test, please email us at info@evolvemeded.com. Certificates are issued electronically, therefore, please provide your email address below.

Please type or print clearly, or we will be unable to issue your certificate.

Full Name_____ ❑ MD/DO participant ❑ OD ❑ non-MD participant

Phone (required) _____ ❑ Email (required) _____

Address/P.O. Box _____

City _____ State/Country____ Zip/Postal Code_____

License Number _____ OE Tracker Number _____

DEMOGRAPHIC INFORMATION

Profession
___ MD/DO
___ OD
___ NP
___ Nurse/APN
___ PA
___ Other

Years in Practice
___ >20
___ 11-20
___ 6-10
___ 1-5
___ <1

Patients Seen Per Week (with the disease targeted in this activity)
___ 0
___ 1-15
___ 16-30
___ 31-50
___ >50

Region
___ Northeast
___ Northwest
___ Midwest
___ Southeast
___ Southwest

Setting
___ Solo Practice
___ Community Hospital
___ Government or VA
___ Group Practice
___ Other
___ I do not actively practice

Models of Care
___ Fee for Service
___ ACO
___ Patient-Centered Medical Home
___ Capitation
___ Bundled Payments
___ Other

LEARNING OBJECTIVES

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Summarize the mechanism of action of dry eye disease (DED)	_____	_____	_____
Describe the significance of the trigeminal nerve in ocular surface disorders	_____	_____	_____
Evaluate the impact that chronic diseases, certain medications, and ocular surgery can have on the health of the ocular surface	_____	_____	_____
Compare the current and potential future treatments for DED	_____	_____	_____

POSTTEST QUESTIONS

PLEASE COMPLETE AT THE CONCLUSION OF THE PROGRAM.

1. Based on this activity, please rate your confidence in your ability to summarize the mechanism of action of dry eye disease (DED) (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

2. Based on this activity, please rate how often you plan to utilize the latest treatments in DED (based on a scale of 1 to 5, with 1 being never and 5 being always).

a. 1
b. 2
c. 3
d. 4
e. 5

3. _____ is the primary instigator of DED.

a. Inflammation
b. Tear film instability
c. Lack of homeostasis
d. Hyperosmolarity

4. What percentage of patients may have mixed etiology DED?

a. 70%
b. 60%
c. 50%
d. 40%

5. _____ is becoming a more common trigger of DED, as seen in today's clinic settings.

a. Screen time/computer use
b. Smoking
c. Increased air condition use
d. Allergies

6. Why might the signs and symptoms of DED not align? Select all that apply.

a. Dry eye diagnostics are not sensitive enough to diagnose DED.
b. Patients are not forthcoming with reporting their dry eye symptoms.
c. Patients with late-stage disease may not be symptomatic but will have significant clinical signs.
d. Patients with early-stage dry eye will not have corneal staining but will be highly symptomatic.

7. What role does the trigeminal nerve play in DED?

a. The trigeminal nerve stimulates the three components of the tear film.
b. The trigeminal nerve is an autoregulator of the diurnal curve in tear secretion.
c. The trigeminal nerve causes dry eye symptoms due to the release of inflammatory mediators on the ocular surface.
d. The trigeminal nerve is responsible for basal tear production through neurostimulation.

8. Which dry eye algorithm is preferred in real-world settings?

a. TFOS DEWS II
b. CEDARS
c. ASCRS Preoperative Ocular Surface Disease Algorithm
d. None is preferred; patients need personalized treatment

9. It is estimated that _____ of patients seen in an eye care setting have dry eye episodes.

a. 60%
b. 70%
c. 80%
d. 90%

10. Which of the following statements is true?

a. DED is not common in children or adolescents.
b. DED is uncommon in postmenopausal women.
c. DED is becoming common in children and adolescents.
d. The rates of DED have remained stable for decades.

ACTIVITY EVALUATION/SATISFACTION MEASURES

Your responses to the questions below will help us evaluate this CME activity. They will provide us with evidence that improvements were made in patient care as a result of this activity.

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low _____

Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low _____

This activity improved my competence in managing patients with this disease/condition/symptom _____ Yes _____ No

Probability of changing practice behavior based on this activity: _____ Yes _____ No _____No change needed

If you plan to change your practice behavior, what type of changes do you plan to implement? (check all that apply)

_____ Change in pharmaceutical therapy
_____ Change in diagnostic testing
_____ Change in current practice for referral
_____ My practice has been reinforced
_____ Change in nonpharmaceutical therapy
_____ Choice of treatment/management approach
_____ Change in differential diagnosis
_____ I do not plan to implement any new changes in practice

Please identify any barriers to change (check all that apply):

_____ Cost
_____ Lack of consensus or professional guidelines
_____ Lack of administrative support
_____ Lack of experience
_____ Lack of time to assess/counsel patients
_____ Lack of opportunity (patients)
_____ Reimbursement/insurance issues
_____ Lack of resources (equipment)
_____ Patient compliance issues
_____ No barriers
_____ Other. Please specify: _____
_____

The design of the program was effective for the content conveyed. ___ Yes ___ No

The content supported the identified learning objectives. ___ Yes ___ No

The content was free of commercial bias. ___ Yes ___ No

The content was relative to your practice. ___ Yes ___ No

The faculty was effective. ___ Yes ___ No

You were satisfied overall with the activity. ___ Yes ___ No

Would you recommend this program to your colleagues? ___ Yes ___ No

Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced through your participation in this activity:

_____ Patient Care
_____ Practice-Based Learning and Improvement
_____ Professionalism
_____ Medical Knowledge
_____ Interpersonal and Communication Skills
_____ System-Based Practice

Additional comments:

_____

_____ I certify that I have participated in this entire activity.

This information will help evaluate this CME activity; may we contact you by email in 3 months to see if you have made this change? If so, please provide your email address below.

_____