CME Monograph

DRY EYE DISEASE

IMPROVING DIAGNOSIS AND TREATMENT DURING THE DIGITAL AGE

EARN CREDITS CME

Visit https://tinyurl.com/modernDED for online testing and instant CME Certificate.

ORIGINAL RELEASE: June 1, 2020 **EXPIRATION:** June 30, 2021

FACULTY

TERRY KIM, MD (Chair)
Professor of Ophthalmology
Duke University School of Medicine
Chief, Cornea and External Disease Division
Director, Refractive Surgery Service
Duke University Eye Center
Durham, North Carolina

ALICE T. EPITROPOULOS, MD
Assistant Professor
Department of Ophthalmology
Ohio State University
Ophthalmic Surgeons and Consultants of Ohio, Inc
Columbus, Ohio

MARJAN FARID, MD
Professor of Ophthalmology
Director of Cornea, Cataract, and Refractive Surgery
Vice Chair of Ophthalmic Faculty
Gavin Herbert Eye Institute
University of California, Irvine
Irvine, California

CHRISTOPHER E. STARR, MD, FACS
Associate Professor of Ophthalmology
Director, Refractive Surgery Service
Director, Ophthalmic Education
Weill Cornell Medicine
New York, New York

CME REVIEWER FOR NEW YORK EYE AND EAR INFIRMARY OF MOUNT SINAI

PRITI BATTA, MD
Assistant Professor of Ophthalmology
Icahn School of Medicine at Mount Sinai
Director, Medical Student Education
New York Eye and Ear Infirmary of Mount Sinai
New York, New York

LEARNING METHOD AND MEDIUM

This educational activity consists of a supplement and ten (10) study questions. The participant should, in order, read the learning objectives contained at the beginning of this supplement, read the supplement, answer all questions in the post test, and complete the Activity Evaluation/Credit Request form. To receive credit for this activity, please follow the instructions provided on the post test and Activity Evaluation/Credit Request form. This educational activity should take a maximum of 1.5 hours to complete.

ACTIVITY DESCRIPTION

Dry eye disease (DED) is increasing in prevalence among people of all ages, and the use of digital devices is a major contributor to this trend. Diagnosis and treatment of DED is important to limit its deleterious consequences, which can include reduced visual function, decreased quality of life, and worse outcomes after cataract and refractive surgery. The desired results of this activity are for ophthalmologists to have a better understanding of the epidemiology of DED, screening techniques, advances in diagnostic testing, and approaches to individualized management.

TARGET AUDIENCE

This educational activity is intended for ophthalmologists.

LEARNING OBJECTIVES

Upon completion of this activity, participants will be better able to:

- Review the epidemiology of DED
- Recognize the quality of life burden of DED
- Select appropriate diagnostic tests for evaluating DED
- Review the implications of inflammation in DED on treatment
- Apply evidence of DED treatments for individualized care of patients

ACCREDITATION STATEMENT

ACCME ACCREDITED

The **New York Eye and Ear Infirmary of Mount Sinai** is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. This educational activity was developed and implemented in collaboration with **MedEdicus LLC**.

AMA CREDIT DESIGNATION STATEMENT

The **New York Eye and Ear Infirmary of Mount Sinai** 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.

GRANTOR STATEMENT

This continuing medical education activity is supported through an unrestricted educational grant from Novartis Pharmaceuticals Corporation.

This continuing medical education activity is provided by **New York Eye and Ear Infirmary of Mount Sinai.** This educational activity was developed and implemented in collaboration with **MedEdicus LLC**.

New York Eye and Ear Infirmary of Mount Sinai

MedEdicus

This continuing medical education activity is supported through an unrestricted educational grant from Novartis Pharmaceuticals Corporation.

Distributed with
Ophthalmology Times

DISCLOSURE POLICY STATEMENT

It is the policy of **New York Eye and Ear Infirmary of Mount Sinai** that the faculty and anyone in a position to control activity content disclose any real or apparent conflicts of interest relating to the topics of the educational activity in which they are participating. They are also required to disclose discussions of unlabeled/unapproved uses of drugs or devices during their presentations. **New York Eye and Ear Infirmary of Mount Sinai** is committed to providing its learners with quality CME activities and related materials that promote improvements in healthcare and not the proprietary interests of a commercial interest and, thus, has established policies and procedures in place that identify and resolve all conflicts of interest prior to the execution or release of its educational activities. Full disclosure of faculty/planners and their commercial relationships, if any, follows.

DISCLOSURES

Alice T. Epitropoulos, MD, had a financial agreement or affiliation during the past year with the following commercial interests in the form of *Receipt of Intellectual Rights/Patent Holder:* EpiGlare Tester; *Consultant/Advisory Board:* Abbott Medical Optics; Allergan; Bausch & Lomb Incorporated; Bio-Tissue; Bruder Healthcare; Dompé US, Inc; EyePoint Pharmaceuticals; Eyevance; Johnson & Johnson Vision Care, Inc; Kala Pharmaceuticals, Inc; Novartis Pharmaceuticals Corporation; Ocular Therapeutix, Inc; Omeros Corporation; Physician Recommended Nutriceuticals; and Sun Pharmaceutical Industries; *Contracted Research:* Bausch & Lomb Incorporated; Kala Pharmaceuticals, Inc; Ocular Therapeutix, Inc; Physician Recommended Nutriceuticals; and TearLab Corporation; *Honoraria from promotional, advertising or non-CME services received directly from commercial interests or their Agents (eg, Speakers Bureaus):* Abbott Medical Optics; Allergan; Bausch & Lomb Incorporated; Bio-Tissue; Dompé US, Inc; Eyevance; Johnson & Johnson Vision Care, Inc; Kala Pharmaceuticals, Inc; Novartis Pharmaceuticals Corporation; Ocular Therapeutix, Inc; Physician Recommended Nutriceuticals; and Sun Pharmaceutical Industries, Inc.

Marjan Farid, MD, had a financial agreement or affiliation during the past year with the following commercial interests in the form of *Consultant/Advisory Board:* Allergan; Bio-Tissue; CorneaGen; Dompé US, Inc; EyePoint Pharmaceuticals; Eyevance; Johnson & Johnson Vision Care, Inc; Kala Pharmaceuticals, Inc; and Shire.

Terry Kim, MD, had a financial agreement or affiliation during the past year with the following commercial interests in the form of *Consultant/Advisory Board:* Aerie Pharmaceuticals, Inc; Alcon; Allergan; Avedro, Inc; Avellino Labs; Bausch & Lomb Incorporated; BlephEx; CorneaGen; Dompé farmaceutici SpA; Eyenovia, Inc; Johnson & Johnson Vision Care, Inc; Kala Pharmaceuticals, Inc; NovaBay Pharmaceuticals, Inc; Novartis Pharmaceuticals Corporation; Ocular Therapeutix, Inc; Omeros Corporation; Presbyopia Therapies; Shire; Sight Sciences; Surface Pharmaceuticals Inc; and Zeiss; *Ownership Interest (Stock options, or other holdings, excluding diversified mutual funds):* Avellino Labs; CorneaGen; Eyenovia, Inc; Kala Pharmaceuticals, Inc; NovaBay Pharmaceuticals, Inc; Ocular Therapeutix, Inc; Omeros Corporation; and Presbyopia Therapies.

Christopher E. Starr, MD, had a financial agreement or affiliation during the past year with the following commercial interests in the form of *Consultant/Advisory Board:* Allergan; Bausch & Lomb Incorporated; BlephEx; Bruder Healthcare; Dompé farmaceutici SpA; EyePoint Pharmaceuticals; Eyevance; Johnson & Johnson Vision Care, Inc; Kala Pharmaceuticals, Inc; Novaliq GmbH Germany; Novartis Pharmaceuticals Corporation; Quidel Corporation; Shire; Sight Sciences; Sun Pharmaceutical Industries, Inc; TearLab Corporation; and Verily Life Sciences LLC; *Ownership Interest (Stock options, or other holdings, excluding diversified mutual funds):* TearLab Corporation.

NEW YORK EYE AND EAR INFIRMARY OF MOUNT SINAI PEER REVIEW DISCLOSURE

Priti Batta, MD, has no relevant commercial relationships to disclose.

EDITORIAL SUPPORT DISCLOSURES

Cheryl Guttman Krader; Melissa Carter-Ozhan, MS; Cynthia Tornallyay, RD, MBA, CHCP; Kimberly Corbin, CHCP; Barbara Aubel; and **Michelle Ong** have no relevant commercial relationships to disclose.

DISCLOSURE ATTESTATION

The contributing physicians listed above have attested to the following:

1) that the relationships/affiliations noted will not bias or otherwise influence their involvement in this activity;
2) that practice recommendations given relevant to the companies with whom they have relationships/affiliations will be supported by the best available evidence or, absent evidence, will be consistent with generally accepted medical practice; and
3) that all reasonable clinical alternatives will be discussed when making practice recommendations.

OFF-LABEL DISCUSSION

This CME activity includes discussion of unlabeled and/or investigative uses of drugs. Please refer to the official prescribing information for each drug discussed in this activity for FDA-approved dosing, indications, and warnings.

New York Eye and Ear Infirmary of Mount Sinai Privacy & Confidentiality Policies
https://www.nyee.edu/education/cme

CME Provider Contact Information
For questions about this activity, call 212-870-8125.

TO OBTAIN *AMA PRA CATEGORY 1 CREDIT™*

To obtain *AMA PRA Category 1 Credit™* for this activity, read the material in its entirety and consult referenced sources as necessary. Please take this post test and evaluation online by going to https://tinyurl.com/modernDED. Upon passing, you will receive your certificate immediately. You must score 70% or higher to receive credit for this activity and may take the test up to 2 times. Upon registering and successfully completing the post test, your certificate will be made available online and you can print it or file it.

DISCLAIMER

The views and opinions expressed in this educational activity are those of the faculty and do not necessarily represent the views of **New York Eye and Ear Infirmary of Mount Sinai**, **MedEdicus LLC**, Novartis Pharmaceuticals Corporation, or *Ophthalmology Times.*

DRY EYE DISEASE

IMPROVING DIAGNOSIS AND TREATMENT DURING THE DIGITAL AGE

INTRODUCTION

Beginning in early childhood and across the age spectrum, people are spending an increasing amount of time staring at digital device screens. Recently, a group of experts in corneal disease and cataract and refractive surgery gathered to review the effects of today's digital device–based lifestyle on the epidemiology of dry eye disease (DED) and to share their insights on its implications for DED screening and management. This activity presents the highlights of their discussion.

DRY EYE DISEASE: EPIDEMIOLOGY

DED ranks as a leading cause for patients seeking eye care, and is a common problem according to results of published studies, which report its prevalence ranges from 5% to 50%.[1,2] The wide variation in prevalence estimates of available research may be explained by differences in the criteria used to identify individuals with DED and also in the populations studied.

A recent cross-sectional study of adults in the United States reported that approximately 16.4 million people had been diagnosed with DED.[3] In an age-based analysis, DED prevalence was estimated to be 2.7% among people aged 18 to 34 years and 18.6% among people aged ≥ 75 years, and it was almost twice as common in women as in men (8.8% vs 4.5%).[3] DED is more common in Asians than in whites, in females than in males, and with increasing age.[2-6] Considering historical data, the study findings supported the idea that DED prevalence is increasing in men and women in all age groups. Similarly, an increase in DED prevalence over time in all demographic groups was identified in a retrospective analysis of data collected between 2003 and 2015.[6]

The cause for the rising prevalence is thought to be due in part to the increasing use of digital visual displays.[2,7] Research shows associations between increased smartphone use and increases in both DED and meibomian gland dysfunction (MGD) in the pediatric population and between the use of visual display terminals and DED in adults.[7-10]

Dr Kim: Have you noticed a change over time in the demographic characteristics of the patients you are seeing with DED?

Dr Farid: I am in an academic practice at a university with a large undergraduate population. We are seeing a growing number of students with symptoms of DED, including eye discomfort, contact lens intolerance, and eye pain. I believe the transition from using hard-copy textbooks to electronic versions is a major reason for this trend. We are also seeing more older patients with DED; of these, a higher proportion have more severe disease, which I also believe may be a consequence of digital device usage. I do not regularly see younger children in my practice, but when I do see them, they usually have some concomitant issue, such as ocular allergy.

Dr Starr: I see patients aged ≥ 18 years in my practice and am amazed by the number of young adults I am seeing with DED. Many of these patients are students in graduate degree programs who are likely spending a lot of time reading on a digital device. Some have severe ocular surface disease (OSD), which makes me wonder at what age the problem started.

Dr Epitropoulos: The decreased blink rate and incomplete blinking that occur with digital device usage result in increased tear film instability, which is a core mechanism in the development of DED.[11] I am also seeing a growing number of patients of all ages with DED. This is partly because I am using newer modalities for diagnosis, including tear film osmolarity, the matrix metalloproteinase-9 (MMP-9) assay, and meibography. In my experience, using a combination of these diagnostic point-of-care tests can help identify DED earlier than traditional diagnostic techniques.

Dr Kim: I recently witnessed a child who was approximately 2 years old who did not blink for up to 3 minutes while watching a video on a smartphone. It is possible to set screen-time limits for some digital devices, and some smartphones can report daily screen time. Perhaps in the future, we will be asking patients with DED to show us these types of data.

Dr Epitropoulos: I suggest that patients with DED use an app that measures their device time. For those who have significant screen time, there are apps that provide reminders to blink and include education on how to perform blinking exercises and therefore minimize dry eye.

Dr Kim: I also expect that children are not likely to complain about DED symptoms, and this raises questions regarding the need to educate pediatricians about the rising prevalence of DED in children and screening to allow early detection and intervention.

Dr Farid: I think it is essential for any eye care provider who sees children to have a heightened awareness of the problem and of the newer diagnostics, which are safe for use in the pediatric population. Point-of-care testing such as MMP-9 and tear osmolarity works well and is easy to use in the pediatric population.

BURDENS OF DRY EYE DISEASE

Mild to moderate DED affects visual function and can interfere with work performance, recreational activities, willingness to drive at night, and success with contact lens wear.[12] The impact of severe DED on quality of life has ranked similar to that of severe angina and dialysis.[13,14] DED also carries a huge economic burden, and has been estimated in the United States to be responsible for $3.8 billion in direct health care costs and $55.4 billion in indirect costs related to loss of work productivity.[15] In relation to DED's effect—particularly the effect of DED symptoms—on the workplace, work performance (presenteeism) and productivity are reduced by approximately 30%.[16]

Dr Kim: Do you assess the potential effects of DED on quality of life or daily activities when you screen patients for DED?

Dr Starr: When querying patients about symptoms, I always try to assess their severity and impact on life in general. Some patients will say they cannot work or leave the house. Others are obviously depressed because of the problems they are experiencing or their failure to find adequate treatment after seeing multiple other physicians. Currently, our screening questionnaire does not include any items specific to quality of life impact.

To best help patients with DED, we have to understand the effects of their disease. The office visit can be lengthy, and some clinicians might dismiss patients with DED because they do not want to take the time needed for evaluation and counseling. Patients with DED may also be dismissed by clinicians who perceive them as complainers or as those shopping for someone who will complete the paperwork for a false disability claim. It is important to recognize that DED can cause real suffering.

Dr Farid: I also see patients who I know are experiencing a severe impact on quality of life according to their history and complaints. Patients say they have problems keeping their eyes open and being outdoors, and a fair number of them ask to have disability papers completed. Many of the latter need to work at a computer all day, but they are unable to do so because of DED-related discomfort and light sensitivity.

DIAGNOSING DRY EYE DISEASE

Underdiagnosis of DED continues to be a problem. A proactive approach to screening and the use of newer diagnostic tools may increase recognition of DED and provide information to guide appropriate management.

Dr Kim: How does digital screen usage factor into your strategies for diagnosing DED?

Dr Farid: Excessive digital screen time in a patient's history automatically puts that individual into a high-risk category for having DED and for disease progression, prompting point-of-care diagnostic testing.

Dr Epitropoulos: We have patients fill out a dry eye questionnaire and determine the need for point-of-care testing on the basis of their scores, but even those who are asymptomatic should be screened for signs of DED. I added a question about device screen time, and our technicians initiate DED testing for patients reporting as much as 5 hours a day of screen time. Testing for these patients includes meibography because of increasing evidence showing an association between digital device use and MGD.[9,17] In fact, I am including meibography in my dry eye protocol because MGD has been observed in 86% of patients with DED.[18]

Dr Kim: Which of the traditional and more modern tools for DED diagnosis do you find most valuable in practice?

Dr Farid: Nothing takes the place of a thorough slit-lamp examination. An approach described in the American Society of Cataract and Refractive Surgery (ASCRS) Cornea Clinical Committee algorithm for the preoperative diagnosis and treatment of OSD represents a way to quickly examine the ocular surface for evidence of OSD.[19] The steps are summarized by the mnemonic LLPP, which stands for:

- **L**ook at blinks, lids, lashes, and the interpalpebral surface
- **L**ift the superior eyelid and examine for signs of OSD
- **P**ull to identify lid laxity and to see into the fornices
- **P**ush the meibomian glands (MGs) to assess meibum quality and flow

I also measure tear breakup time (TBUT) with fluorescein to assess tear film stability. I augment the clinical examination with tear film osmolarity; the MMP-9 assay, which is done prior to instilling drops; and meibography. I like those newer modalities because they provide objective diagnostic information that helps patients understand they have DED, which makes them more likely to accept and comply with treatment.

We also have the platform that does meibography and includes a noninvasive TBUT and Objective Scatter Index, which is a measure

of intraocular scattering. We stopped using the platform for logistical reasons because it is located in a room outside of the usual patient workflow area. Another commercially available multimodal platform that we do not have provides noninvasive TBUT, tear meniscus height, lipid layer analysis, topography, and meibography.

Dr Starr: The newer tools that I use include tear film osmolarity and the MMP-9 assay, both of which have a higher positive predictive value than some traditional tests used to diagnose DED **(Table 1)**.[20-27] I also use meibography. I think noninvasive TBUT is a great test, but I do not yet have access to a device with that function yet.

Some clinicians believe the slit-lamp examination is all that is needed to diagnose DED, and it is an important component. I find, however, that the objective tests add to my understanding of the cause of a patient's OSD, and they are helpful in educating patients. For example, even with moderate MGD, patients may be asymptomatic and therefore might not accept that they have a problem needing treatment. The diagnosis and importance of intervention to preserve function of the remaining glands resonates with them if they see a comparison of their meibography image with that of a healthy lid.

Table 1. Diagnostic Performance of Traditional and Advanced Modalities for Identifying Dry Eye Disease

Test	Sensitivity, %	Specificity, %	PPV
Schirmer I < 10 mm[20]	83	68	31
TBUT < 10 s[20]	72	62	25
Rose bengal staining[20]	25	90	31
Tear meniscus height ≤ 0.35 mm[20]	93	67	33
Osmolarity > 308 mOsm/L[21-24]	75-95	88	89
MMP-9 ≥ 40 ng/m[25]	85	94	97
Conventional Sjögren biomarkers[26]	40-60	40-60	NA
Lipid layer thickness ≤ 60 nm[27]	48	90	NA
New Sjögren markers[26]	91	80	NA

Abbreviations: MMP-9, matrix metalloproteinase-9; NA, not available; PPV, positive predictive value; TBUT, tear breakup time.

Dr Epitropoulos: Because of both its diagnostic use and its value for patient education, I believe meibography has been a game-changing tool. All the newer point-of-care tests can be used as a tool, but in conjunction with traditional testing and a thorough slit-lamp examination.

Dr Kim: Several groups, including the Tear Film and Ocular Society Dry Eye WorkShop II (TFOS DEWS II), ASCRS Cornea Clinical Committee, and Cornea, External Disease, and Refractive Society (CEDARS), have issued guidelines and algorithms for the evaluation and management of DED.[19,28-30] Which of these are you using for screening and diagnosis?

Dr Starr: I think they can all be used together because they are complementary. The TFOS DEWS II algorithms are designed to identify patients primarily with DED, to determine DED subtype and severity, and to guide treatment on the basis of these 2 factors.[29,30] The ASCRS Preoperative OSD algorithm is specifically geared to identify and treat visually significant OSD in patients undergoing any kind of cataract and refractive surgery.[19] The CEDARS paper provides a great overview of the different subtypes of what it refers to as dysfunctional tear syndrome, features of the various subtypes, and how to make the differential diagnosis.[28] The report is very useful in that regard because most patients have multiple issues and subtypes of OSD. The CEDARS paper also outlines treatment approaches tailored to disease subtype and severity.

Dr Epitropoulos: I agree that all the algorithms have benefits. I think they should be used as organizational tools to aid treatment decisions rather than being followed in a rigid, stepwise manner.

Dr Farid: I agree that clinicians should be aware of the approaches outlined by all 3 groups and what they provide for guiding diagnosis and management.

Dr Kim: Do you think that the newer diagnostic tests and algorithms are improving or increasing DED diagnosis?

Dr Farid: I believe most cataract surgeons recognize that the condition of the ocular surface affects outcomes with premium intraocular lenses (IOLs). I think that advances in DED diagnostics are leading to increased DED diagnosis, which is driving growth of premium IOL use. At the same time, the growth in premium IOL options is driving surgeons toward increased DED diagnosis.

Dr Epitropoulos: I believe the ASCRS algorithm has had a positive impact on the practice pattern of cataract surgeons, but DED is still underdiagnosed and undertreated.

DRY EYE DISEASE TREATMENT

The availability of more therapeutic options might also be stimulating increased efforts to diagnose DED. For a long time, only cyclosporine, 0.05%, emulsion was available. Current options include lifitegrast, 5%, solution—a novel integrin antagonist[31]—and cyclosporine, 0.09%, which is formulated in an aqueous-based solution using nanomicellar technology to increase cyclosporine bioavailability.[32]

Active research is identifying new treatments for DED. Loteprednol, 0.25%—formulated in mucus-penetrating particle technology that increases loteprednol bioavailability—is being investigated in a phase 3 study as therapy for DED.[33,34] Preliminary results of the study reveal statistically significant improvements in the primary efficacy end points of ocular discomfort severity at day 15 in the overall intent-to-treat population ($P = .0002$) and the predefined subgroup of intent-to-treat patients with more severe discomfort at baseline ($P = .0007$).[34] Other novel treatments are in phase 3 studies. NOV03 (perfluorohexyloctane) is a lipid layer stabilizer that is being investigated for treating MGD.[35] A phase 2 trial showed improvements in corneal staining at 8 weeks and as early as 2 weeks with twice-daily and 4-times-daily dosing of NOV03.[36] A trial evaluating twice-daily OC-01, an intranasal spray formulation of the nicotinic acid agonist varenicline, met its primary end point of percentage of patients gaining ≥ 10 mm in Schirmer score at week 4 (N = 758). Compared with 26% of control patients, 44% of patients receiving OC-01 0.6 mg/mL and 47% of patients receiving OC-01 1.2 mg/mL gained ≥ 10 mm ($P < .001$).[37] OC-01 was well tolerated, with transient sneeze being the most commonly reported adverse event.

Dr Kim: Have treatment advances influenced your management of DED in the digital age?

Dr Farid: I expect that patients with a digital device–based lifestyle who have symptomatic DED are going to need long-term treatment. Results from a large phase 3 study program showed that lifitegrast had impressive activity for rapidly improving DED symptoms and a good safety profile during long-term use of up to 1 year.[38,39] In the OPUS-3 trial, patients receiving lifitegrast experienced improvement in signs and symptoms of DED as early as within 2 weeks of treatment initiation.[40] The most common adverse events were mild to moderate instillation-site irritation and instillation-site reaction. According to this evidence and the convenient twice-daily dosing regimen of lifitegrast, I have a low threshold for starting lifitegrast in patients with digital device–related DED.

Dr Starr: I believe that inflammation is present whenever DED is related to digital device use, and I routinely prescribe immunomodulatory treatment in patients with this history. Because access to a particular medication can vary depending on the patient's insurance plan, it is very helpful to have several options available.

The investigational loteprednol product is exciting. Even with maintenance immunomodulatory treatment, DED exacerbations or flare-ups are not uncommon. Although topical corticosteroids, particularly fluorometholone or one of the available loteprednol preparations, are widely used in this setting, none are yet indicated specifically for treating DED or DED flares.

Dr Epitropoulos: I use a topical immunomodulatory agent, either lifitegrast or one of the cyclosporine products, to treat patients with signs of inflammation or aqueous deficiency. In a phase 3 trial, the nanomicellar formulation of cyclosporine, 0.09%, was associated with statistically significant improvements ($P < .001$) in Schirmer score within 3 months.[32] With cyclosporine emulsion, 0.05%, improvements in Schirmer score and corneal staining were observed within 6 months in phase 3 trials.[41] Like lifitegrast, the cyclosporine products can cause burning upon instillation. In addition, I address MG obstruction using a nutritional supplement, thermal pulsation device, and/or intense pulsed light. Because inflammation is a contributing factor to MGD, I will often use an immunomodulator to treat this condition.

An omega-3 nutritional supplement is a mainstay for treatment of DED in my practice. Although the results of the DREAM (Dry Eye Assessment and Management) study were controversial, showing no benefit vs the olive oil comparator agent, patients using the omega-3 supplement in the study had significant improvements from baseline in both signs and symptoms.[42] Furthermore, we published a study showing that a high-quality triglyceride-based omega-3 supplement improves tear osmolarity, DED symptoms, TBUT, and MMP-9 and the omega-3 index results.[43] In addition, a meta-analysis that reviewed data from more than 3300 patients across 17 studies, including DREAM, showed a statistically significant improvement in dry eye signs and symptoms in those taking an omega-3 supplement vs placebo.[44]

CASE-BASED DISCUSSIONS

Case 1: Digital Device–Related Dry Eye Disease in a Young Adult Patient

From the Files of Alice T. Epitropoulos, MD

A 24-year-old female presented with complaints of fluctuating vision, especially toward the end of the day; burning eyes; tearing; foreign body sensation; and contact lens intolerance. She is a graduate student who spends approximately 8 hours a day looking at a digital device screen. Findings on evaluation include a SPEED (Standard Patient Evaluation of Eye Dryness) score of 20, tear osmolarity of 295 mOsm/L OD and 324 mOsm/L OS, unstable tear film based on irregular placido rings and TBUT of 2 seconds, positive MMP-9 test result, punctate epithelial erosions (PEEs), cloudy meibum that is difficult to express, and advanced MG atrophy **(Figure 1)**.

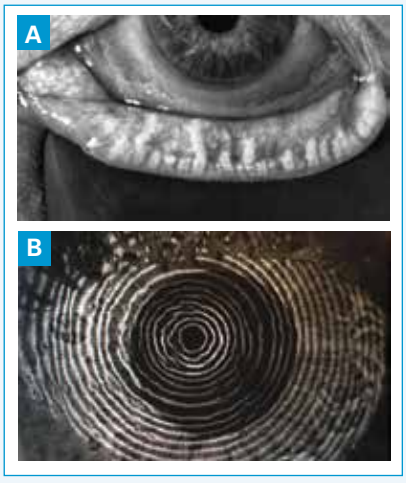


Figure 1. Diagnostic images show advanced meibomian gland atrophy (A) and evidence of an unstable tear film based on irregularity of placido rings (B)

Images courtesy of Alice T. Epitropoulos, MD

Discussion

Dr Epitropoulos: One of the main messages from this case is to be aware that more younger patients are developing MGD that appears to be related to digital device use. Furthermore, patients with significant MG loss may be asymptomatic. Failure to diagnose and manage MGD in its earliest and most treatable stages can lead to chronically compromised health of the ocular surface.

The current consensus in the literature is that once MGs have atrophied, they cannot be reactivated or regenerated. We presented results that showed visible gland structure may increase after thermal pulsation treatment at the 2019 Annual Meeting of ASCRS.[45] Our analysis also suggested that the absence of visible gland structure when imaged with infrared light may not always indicate absolute atrophy or loss of function; it may indicate loss of activity. Therefore, it is important to evaluate MGD in patients with high screen time and to intervene early.

Dr Starr: I have seen some patients with advanced MG damage who are angry that their primary eye care provider did not identify their problem earlier. Therefore, it is also a potential liability issue for providers who are not screening for MGD and DED and intervening early.

Dr Kim: We should also be educating our colleagues about referring young patients who have recurrent chalazia and styes. I believe these patients probably have anatomic abnormalities that are causing their lid problems; if these are not addressed, the patients are at risk for progressing MGD that can lead to the type of extensive damage seen in this case.[8]

Case Continued

Treatment was initiated with a multimodal strategy for MGD that included microblepharoexfoliation followed by thermal pulsation; an omega-3 supplement; lipid-based artificial tears; cyclosporine, 0.09%; and lid hygiene. In addition, the patient was educated about the

association between DED and excessive digital device use and instructed on blinking exercises, taking periodic breaks from screen time, and using glasses or a screen protector to reduce blue-light exposure.

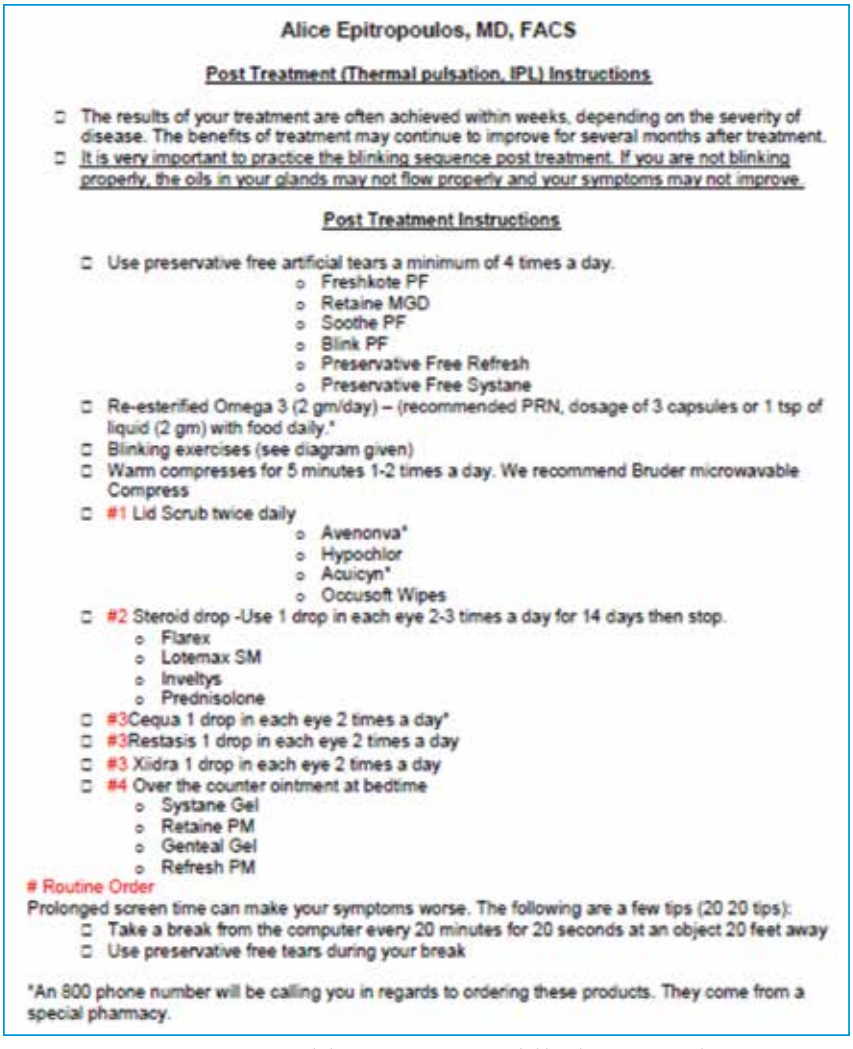
After 8 weeks, the patient's SPEED score improved to 7 and she reported less burning, less tearing, and greater comfort while wearing her contact lenses. Tear osmolarity was normal in both eyes, and the MMP-9 test result was negative. Corneal staining showed only trace PEEs, TBUT increased to 8 seconds, and MG score was improved.

Discussion

Dr Epitropoulos: The goals for treating this patient were to stabilize the tear film, reduce inflammation, and maintain function of the remaining MGs. Multiple options target the MGs, including devices that deliver heat and pulsation or massage the glands, mechanical debridement, and intense pulsed light treatment. In this case, I used a thermal pulsation device to relieve MG obstruction.

In our practice, we have a handout with posttreatment instructions for patients who had thermal pulsation or intense pulsed light treatment. All the medications and nonpharmacologic strategies that might be recommended are listed along with directions for use, and there is a checkbox for identifying those that the patient has been instructed to use **(Figure 2)**.

Dr Farid: I believe it is important to be aggressive in treating MGD in younger patients because I suspect they will not adhere to an at-home lid hygiene regimen. Therefore, I always try to do an in-office procedure to relieve MG obstruction.



Alice Epitropoulos, MD, FACS

Post Treatment (Thermal pulsation, IPL) Instructions

- ☐ The results of your treatment are often achieved within weeks, depending on the severity of disease. The benefits of treatment may continue to improve for several months after treatment.
- ☐ It is very important to practice the blinking sequence post treatment. If you are not blinking properly, the oils in your glands may not flow properly and your symptoms may not improve.

Post Treatment Instructions

- ☐ Use preservative free artificial tears a minimum of 4 times a day.
  - Freshkote PF
  - Retaine MGD
  - Soothe PF
  - Blink PF
  - Preservative Free Refresh
  - Preservative Free Systane
- ☐ Re-esterified Omega 3 (2 gm/day) – (recommended PRN, dosage of 3 capsules or 1 tsp of liquid (2 gm) with food daily.*
- ☐ Blinking exercises (see diagram given)
- ☐ Warm compresses for 5 minutes 1-2 times a day. We recommend Bruder microwavable Compress
- ☐ #1 Lid Scrub twice daily
  - Avenonva*
  - Hypochlor
  - Acuicyn*
  - Ocusoft Wipes
- ☐ #2 Steroid drop -Use 1 drop in each eye 2-3 times a day for 14 days then stop.
  - Flarex
  - Lotemax SM
  - Inveltys
  - Prednisolone
- ☐ #3Cequa 1 drop in each eye 2 times a day*
- ☐ #3Restasis 1 drop in each eye 2 times a day
- ☐ #3 Xiidra 1 drop in each eye 2 times a day
- ☐ #4 Over the counter ointment at bedtime
  - Systane Gel
  - Retaine PM
  - Genteal Gel
  - Refresh PM

Routine Order

Prolonged screen time can make your symptoms worse. The following are a few tips (20 20 tips):

- ☐ Take a break from the computer every 20 minutes for 20 seconds at an object 20 feet away
- ☐ Use preservative free tears during your break

*An 800 phone number will be calling you in regards to ordering these products. They come from a special pharmacy.

Figure 2. Posttreatment instructions provided to patients as recommended by Alice T. Epitropoulos, MD
Abbreviation: IPL, intense pulsed light.

Dr Starr: When doing thermal pulsation treatment, I first perform microblepharoexfoliation to mechanically remove keratin, scurf, collarettes, and bacterial biofilm from around the MG orifice.

Dr Kim: There is evidence that microblepharoexfoliation may help treat MGD by decreasing biofilm formation on the eyelid margin.[46,47]

Dr Epitropoulos: We performed a retrospective analysis of 177 patients with OSD who were treated with microblepharoexfoliation and found improvement in TBUT and dry eye symptom scores.[48] I believe that using a high-quality omega-3 supplement is helpful for improving meibum quality. I also recommend a lipid-containing artificial tear that helps stabilize the tear film. In addition, I discuss with patients who spend a lot of time in front of a computer about the importance of taking breaks and blinking. I consider these measures "physical therapy" for the eye.

Dr Kim: I like the idea of using that term physical therapy because it is a familiar term and concept, especially in the area of orthopedic injuries. I think patients understand that physical therapy can have a role in helping with recovery; then, they will have a mindset that they should be doing things to manage their condition in addition to using medications.

Dr Starr: Prolonged use of digital screens can result in a constellation of eye and vision-related problems that are collectively termed computer vision syndrome or digital eye strain.[11] The 20-20-20 rule, which instructs people to look away from the computer every 20 minutes for 20 seconds or more at an object that is at least 20 ft away, is often recommended as a preventive strategy. The 20-20-20 rule helps reduce the accommodative stress and eye strain associated with digital device use, but it does not address the dry eye that can develop with prolonged digital screen use. Therefore, I talk to patients about my modification, dubbed the 20-20-20-20 rule, which includes closing the eyes for 20 seconds as an added last step. I also suggest they keep a bottle of an ocular lubricant next to their screen as a reminder to blink more, to take breaks, and to use the drops as needed for symptoms. In addition, I recommend massaging the eyelids or doing forced blinks periodically because those maneuvers will stimulate meibum release, help stabilize tears, and reduce evaporation when the blink rate decreases.

Dr Kim: An interesting study evaluating blinking, tear film, and corneal-staining characteristics found that computer use was associated with a greater negative impact than was smartphone use **(Table 2)**.[49]

Dr Starr: The explanation might have to do with differences in head position when using various devices and screen sizes. For instance,

Table 2. Summary of Reported Impact of Smartphone and Computer Use on Blinking and the Ocular Surface[49]

Blinking and Ocular Surface	Smartphone Use	Computer Use
Blinking		
Rate	Decreases, increases, and no change reported	Decreases
Amplitude	Insufficient data	Decreases
Tear film		
Volume	Both increases and no change reported	Decreases
Stability	Decreases and no change reported	Decreases
Composition	Insufficient data and no change reported	Increases osmolarity, decreases mucin, increases inflammatory mediators
Corneal staining	Insufficient data	Increases and no change reported

most patients look down at their smartphones, which potentially decreases ocular surface exposure because of the lower position of the upper lid in downgaze. This is contrary to computer use, in which the head position (along with the upper lid) is typically higher, potentially increasing the area of ocular surface exposure.

Dr Kim: Do you think blue-light emission plays a role?

Dr Epitropoulos: Prolonged use of digital devices—including tablets, computers, and smartphones—increases exposure to blue light that can result in eye strain, blurred vision, and headaches. Blue light has been reported to induce inflammation of corneal epithelial cells and to decrease corneal epithelial cell survival, thereby contributing to DED.[50] A Blue Light Summit held in 2019 identified dry eye along with sleep disruption, digital eye strain, retinal toxicity, mood disorders, impaired cognitive performance, and accelerated aging as potential hazards of blue-light emission.[51]

However, short-term exposure to blue light from normal digital displays presents minimal risk.[50] Nevertheless, a resolution was passed in California encouraging people, especially children, to reduce blue-light exposure by taking protective safety measures.[52]

Dr Kim: Some patients ask whether blue light–blocking glasses help alleviate eye strain. What are your thoughts on limiting exposure to blue light as a strategy for ocular surface health?

Dr Starr: Everyday real-life exposure to blue light from digital devices is likely not damaging to the retina or lens over long periods of time.[53] Excessive blue light may interrupt circadian rhythms and sleep patterns[54,55]; therefore, it may be beneficial to limit blue-light exposure at night. One way to do this is to turn off or dim the emittance of blue pixels on the screen, which can be done automatically with some devices (eg, using the night-shift mode on Apple devices). It is important not to create panic over blue-light exposure and to remember that the largest source of our daily blue-light exposure is the sun, not phones or computers. Blue light is also found in light emanating from light bulbs and candles.

Dr Kim: The effect of blue-light blocking on circadian rhythms was an issue that arose with the introduction of IOL materials containing blue light–blocking chromophores.[56] Anecdotally, I have not heard about sleep complaints from any of my patients with those IOL implants.

Case 2: Dry Eye Disease in a Patient Needing Cataract Surgery

From the Files of Christopher E. Starr, MD, FACS

A 74-year-old female presented for her preoperative cataract surgery visit 1 week before the scheduled date for the procedure. Keratometry data obtained using keratometry, optical biometry, and topography were not consistent with one another, and topography images showed some mild irregular astigmatism in a pattern that is typical for OSD.

The patient had a total score of 23 on the SPEED II preoperative OSD questionnaire, and she checked 16 of 18 red flags for visually significant OSD **(Figure 3)**. She also reported fluctuating vision, frequent use of ocular lubricants, blepharitis, itching, and contact lens wear. The patient identified herself as a perfectionist and indicated interest in spectacle independence and a multifocal IOL.

Further diagnostic testing showed tear osmolarity values of 343 mOsm/L OD and 332 mOsm/L OS, positive MMP-9 test result OU, and significant MG dropout on meibography.

The LLPP examination result and vital dye staining showed anterior blepharitis, MGD with very poor MG expression, rapid TBUT, conjunctivochalasis and papillae, low tear meniscus height, inferior PEEs, and severe floppy eyelids **(Figure 4)**.

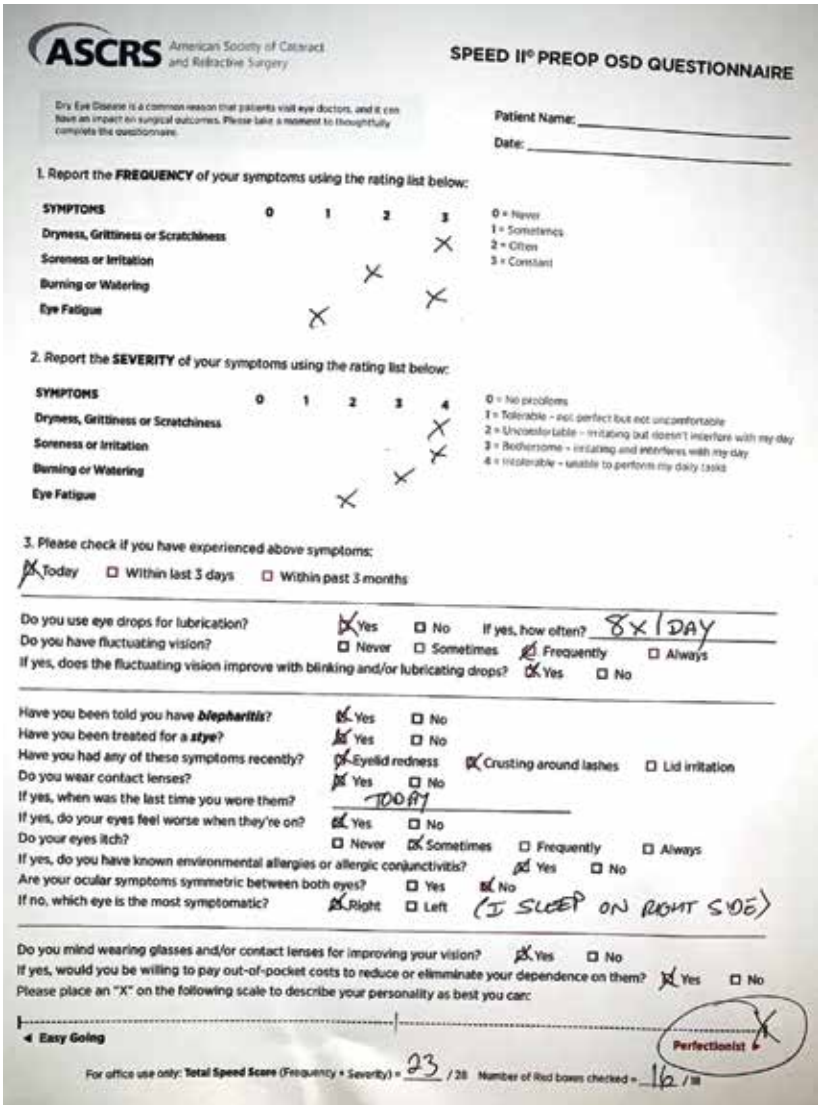
The patient was diagnosed with visually significant OSD. She was started on treatment, including lid hygiene, omega-3 supplementation, topical azithromycin, topical loteprednol, and lifitegrast, and had in-office microblepharoexfoliation followed by thermal pulsation. She was instructed to return for reevaluation after 2 to 4 weeks.

Discussion

Dr Epitropoulos: It is important to identify and treat DED in patients needing cataract or refractive surgery because this disease is a leading cause of patient dissatisfaction after these procedures.[57,58] DED affects not only visual function and patient comfort, but also affects the measurements used for surgical planning. For example, we reported that tear film hyperosmolarity was associated with higher variability in keratometry readings and showed how it affected IOL power calculations.[59] More recently, John Hovanesian, MD, Eric Donnenfeld, MD, and I conducted a study of approximately 100 patients with cataract and DED, looking at the effect of treating the ocular surface on accuracy of preoperative biometry.[60] We found that preoperative treatment with lifitegrast for significant DED in patients needing cataract surgery significantly improved the accuracy of our predicted refractive outcomes and higher-order aberrations.

Dr Starr: According to results of ASCRS Clinical Surveys, most surgeons seemed to be aware that untreated DED could have a negative effect on outcomes of cataract and refractive surgery, but only a small minority were using modern tests (eg, osmolarity and MMP-9) and advanced treatments (eg, anti-inflammatory treatments and thermal pulsation) to diagnose and manage DED preoperatively.[19] The ASCRS algorithm was developed to address this gap, and this case illustrates the algorithm in action.

The initial evaluation is done by the technician and begins with administration of the ASCRS SPEED II Preop OSD questionnaire.



ASCRS American Society of Cataract and Refractive Surgery

SPEED II® PREOP OSD QUESTIONNAIRE

Dry Eye Disease is a common reason that patients visit eye doctors, and it can have an impact on surgical outcomes. Please take a moment to thoughtfully complete the questionnaire.

Patient Name: _____

Date: _____

1. Report the **FREQUENCY** of your symptoms using the rating list below:

SYMPTOMS	0	1	2	3
Dryness, Grittiness or Scratchiness				X
Soreness or Irritation			X	
Burning or Watering				X
Eye Fatigue		X		

0 = Never
1 = Sometimes
2 = Often
3 = Constant

2. Report the **SEVERITY** of your symptoms using the rating list below:

SYMPTOMS	0	1	2	3	4
Dryness, Grittiness or Scratchiness					X
Soreness or Irritation					X
Burning or Watering				X	
Eye Fatigue			X		

0 = No problems
1 = Tolerable – not perfect but not uncomfortable
2 = Uncomfortable – irritating but doesn't interfere with my day
3 = Bothersome – irritating and interferes with my day
4 = Intolerable – unable to perform my daily tasks

3. Please check if you have experienced above symptoms:

☒ Today ☐ Within last 3 days ☐ Within past 3 months

Do you use eye drops for lubrication? ☒ Yes ☐ No If yes, how often? 8X/DAY
Do you have fluctuating vision? ☐ Never ☐ Sometimes ☒ Frequently ☐ Always
If yes, does the fluctuating vision improve with blinking and/or lubricating drops? ☒ Yes ☐ No

Have you been told you have ***blepharitis***? ☒ Yes ☐ No
Have you been treated for a ***stye***? ☒ Yes ☐ No
Have you had any of these symptoms recently? ☒ Eyelid redness ☒ Crusting around lashes ☐ Lid irritation
Do you wear contact lenses? ☒ Yes ☐ No
If yes, when was the last time you wore them? TODAY
If yes, do your eyes feel worse when they're on? ☒ Yes ☐ No
Do your eyes itch? ☐ Never ☒ Sometimes ☐ Frequently ☐ Always
If yes, do you have known environmental allergies or allergic conjunctivitis? ☒ Yes ☐ No
Are your ocular symptoms symmetric between both eyes? ☐ Yes ☒ No
If no, which eye is the most symptomatic? ☒ Right ☐ Left (I SLEEP ON RIGHT SIDE)

Do you mind wearing glasses and/or contact lenses for improving your vision? ☒ Yes ☐ No
If yes, would you be willing to pay out-of-pocket costs to reduce or eliminate your dependence on them? ☒ Yes ☐ No
Please place an "X" on the following scale to describe your personality as best you can:

◄ Easy Going — Perfectionist ►

For office use only: **Total Speed Score** (Frequency + Severity) = 23 / 28 Number of Red boxes checked = 16 / 18

Figure 3. Ocular surface disease questionnaire[18] of the patient in Case 2 that was completed at the preoperative visit

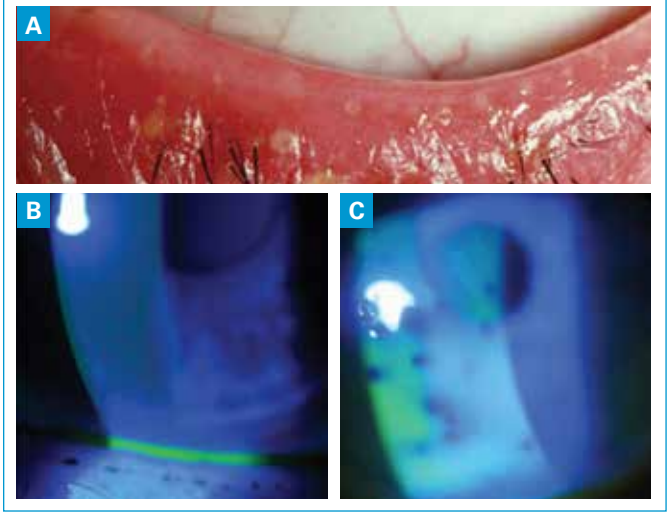


Figure 4. Slit-lamp images show anterior blepharitis (A), a low tear meniscus height, corneal punctate epithelial erosions (B), and rapid tear breakup time (C)

Images courtesy of Christopher E. Starr, MD, FACS

This questionnaire is built on the validated SPEED questionnaire, but has additional questions to help determine non-DED subtypes of OSD, the visual significance of OSD, and potential infection risk.[19] In addition, we borrowed questions from Dr Steven Dell's Cataract and Refractive Lens Exchange Questionnaire, which focuses on patient goals, willingness to pay out-of-pocket fees, and personality self-assessment.[61]

The technician reviews the questionnaire and tallies the total SPEED score and the number of checked red boxes that are considered red flags for needing preoperative treatment of OSD.[19] A SPEED score of 28 and 18/18 checked red boxes are the worst-case scenario.

Next, the technician obtains noninvasive refractive measurements and performs tear osmolarity and MMP-9 testing to identify signs of OSD.[19] All these tests should be done before any drops are put in the eye. Other objective tests, including meibography, lipid layer thickness, and noninvasive TBUT, are considered optional according to the ASCRS algorithm.

Then, the LLPP (*look, lift, pull, push*) examination is done by a clinician, followed by vital dye instillation to look for ocular surface staining and TBUT.[19] The collective findings will determine whether the patient has OSD and if it is visually significant. OSD that is not visually significant is discussed with the patient and prophylactically treated, and then scheduled surgery can proceed as planned. Because OSD often worsens following surgery, topical immunomodulators are a reasonable treatment to begin prior to surgery in patients with DED. Only cyclosporine, 0.05%, emulsion and lifitegrast were available when the ASCRS algorithm was created, and the committee recommended lifitegrast for first-line use because it could have an advantage of faster efficacy compared with cyclosporine.

Depending on its severity, patients with visually significant OSD are treated aggressively, often with a combination of prescription medications and procedural treatments. Then, they are asked to return after a minimum of 2 to 4 weeks to undergo reevaluation according to the algorithm.[19] It is important to explain to patients the reason for delaying their procedure, if necessary. Surgery scheduling and preoperative measurements are done only when the OSD is deemed no longer visually significant and unlikely to affect surgical outcomes and patient satisfaction.

The patient in this case had highly symptomatic, visually significant OSD and high expectations for her visual outcome and spectacle independence. Therefore, her surgery was delayed and she was started on aggressive multifaceted treatment for her OSD.

Case 3: Dry Eye Disease With Multifactorial Etiology

From the Files of Marjan Farid, MD

A 62-year-old female presented with worsening redness, light sensitivity, and irritation. She had been in soft contact lenses for 30 years and was used to wearing the lenses all day and occasionally would sleep without removing them. The patient now reported having to reduce the daily wear time, which was frustrating for her. She had an active lifestyle and served on multiple committees and boards in her community, which required her to view a screen for 6 to 8 hours per day. She had rheumatoid arthritis, which was diagnosed 1 year ago and controlled with methotrexate.

The patient reported trying multiple different artificial tears and contact lens rewetting drops without benefit, along with occasional use of an over-the-counter allergy drop for watery, itching eyes, but noted they had not helped recently. Examination results showed significant PEEs **(Figure 5)** and perilimbal/conjunctival injection. Ocular surface vital dye staining revealed mild epithelial dysplasia. Tear osmolarity was 319 mOsm/L OD and 310 mOsm/L OS, the MMP-9 test result was strongly positive, and she had mild MGD.

The patient was treated with loteprednol, 0.5%, gel, tapered over 1 month, and twice-daily lifitegrast. She was asked to decrease her hours of contact lens wear and switch to a daily disposable product, and was started on lid hygiene at home using hot compresses.

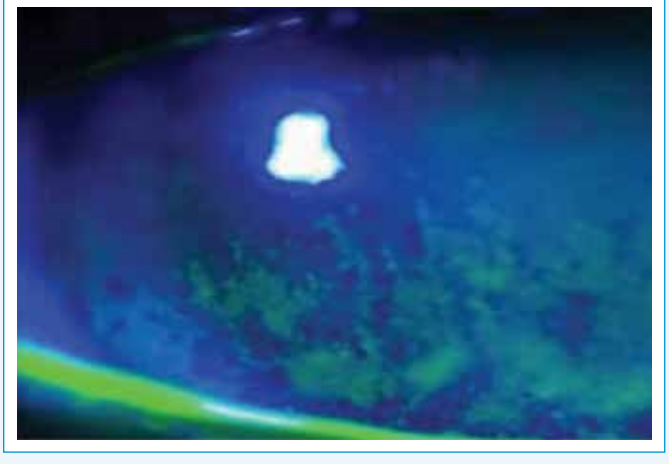


Figure 5. Image from slit-lamp examination with blue cobalt light after fluorescein instillation shows punctate keratitis in the patient in Case 3

Image courtesy of Marjan Farid, MD

Discussion

Dr Farid: Multiple endogenous and exogenous factors that cause irritation, inflammation, or that affect tear film quality or quantity are triggers for DED development or exacerbation **(Figure 6)**. The patient in this case has triggers acting through all of these mechanisms. She has irritation from the environment, her contact lenses, and medications and inflammation associated with her rheumatoid arthritis, and her tear film quality and quantity are reduced because she is postmenopausal and has MGD.

Contact lens wear, in particular, causes irritation and can lead to chronic inflammation. This factor can be associated with frequent exacerbations of comorbid DED and can also result in giant papillary conjunctivitis or even mild limbal stem cell deficiency.[62] One of the challenges for managing this patient was that she was reluctant to take a contact lens holiday.

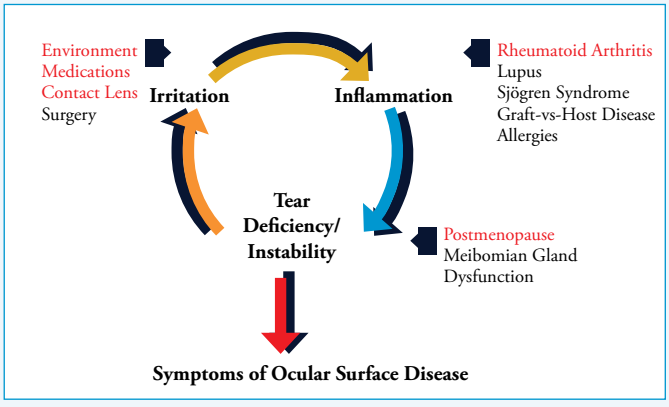


Figure 6. Dry eye disease can be triggered by multiple endogenous and exogenous factors that act through 3 basic mechanisms that interact with one another in a vicious cycle that perpetuates the condition. Factors in red are those attributed to the patient in Case 3.

Image courtesy of Mark S. Milner, MD

Dr Epitropoulos: Discontinuing contact lens wear is critical to allow the cornea to heal, and patients may be encouraged to cooperate by reiterating to them the seriousness of their condition. Patients with punctate epitheliopathy or other signs of damage to corneal tissue that do not respond to traditional treatments may be candidates for a scleral contact lens because the device does not touch the cornea, instead bathing it continuously with preservative-free saline. Such a lens may not only be therapeutic for this patient's DED, but may also help improve her quality of life.

Dr Starr: We work closely with optometrists in our group to manage patients whose DED is associated with contact lens wear. I leave it up to the optometrist to decide whether the patient needs a refitting or should be in a rigid gas permeable lens or a scleral lens.

Dr Kim: Epithelial dysplasia, which was probably seen in this patient, can be an early sign of limbal stem cell deficiency.[63] Consequently, I would expect that the patient might need to stop wearing her contact lenses for a long time and may require a scleral lens instead.

Dr Farid: I insist that patients stop wearing soft contact lenses if they have signs of limbal stem cell deficiency because soft contact lenses create a hypoxic environment for the limbus that can be disastrous.

Dr Epitropoulos: Cryopreserved amniotic membrane could be considered as another treatment option for this patient. Cryopreserved amniotic membrane creates a fetal-like environment that promotes corneal healing through its anti-inflammatory, antifibrotic, antiangiogenic, and antimicrobial properties. In addition, this patient's DED was associated with a systemic inflammatory disease. When patients have that type of comorbidity, it is important to collaborate with the physician who is treating the systemic condition to ensure it is well controlled.

Case Continued

At a return visit after 2 months, the epithelium was significantly smoother, symptoms were improved, and there was no conjunctival

injection, but the MMP-9 test result was still slightly positive. The patient was switched to daily disposable contact lenses, with instructions to remove them when she gets home at the end of the day. She was also started on an omega-3 fatty acid supplement and told about using a pulse of the topical corticosteroid for an exacerbation. The patient was also told to continue using the lifitegrast for long-term management of inflammatory DED. She was instructed to return every 3 to 4 months for follow-up until her symptoms were well controlled.

Discussion

Dr Farid: This patient needed aggressive treatment of her inflammation and remained on anti-inflammatory medication for her DED. I will often use both cyclosporine and lifitegrast in patients with a systemic inflammatory disease such as rheumatoid arthritis or Sjögren syndrome, although, to my knowledge, there is no evidence base to show a benefit of concomitant use. I will also add a short-term pulse of topical corticosteroid treatment during exacerbations. Because the patient still had a positive MMP-9 test result, would anyone consider adding cyclosporine to the lifitegrast?

Dr Kim: As evidenced by this case presentation, some patients have multiple risk factors for inflammatory DED that require more aggressive approaches, including off-label and combination therapies. I have used combination topical lifitegrast and cyclosporine therapy successfully with a twice-daily regimen that has been effective at controlling ocular surface inflammation. As the condition improves, I typically taper back down to one of these medications on a maintenance dosing regimen.

Dr Starr: In autoimmune patients with chronically elevated ocular surface inflammation as measured by the MMP-9 test, I do the same thing as does Dr Farid. If twice-daily immunomodulation with cyclosporine or lifitegrast is not enough, I, too, will either use both medications twice daily or increase one medication to 4 times per day (off-label) in an effort to reduce the need for intermittent pulses of topical corticosteroids.

Dr Epitropoulos: I have found that combination therapy is beneficial in some patients. Cyclosporine and lifitegrast affect T cells in different ways. Cyclosporine acts by inhibiting T cell activation, whereas lifitegrast is thought to inhibit active T cells that are already present at the ocular surface as well as the migration and activation of new T cells.[64-66] Therefore, these 2 agents may be synergistic.

TAKE-HOME POINTS

- Digital device use is contributing to an increasing prevalence of DED in both children and adults
- DED can have a significant negative effect on daily function and quality of life
- Screening for DED might include a question to identify prolonged digital device use
- DED should be identified and treated prior to cataract and refractive surgery because this disease affects surgical outcomes and patient satisfaction
- New algorithms from ASCRS, CEDARS, and TFOS DEWS II provide useful guidance on the diagnosis and management of DED
- Treatment of DED is tailored to its subtype, underlying causes, and severity, and must consider the presence of inflammation and its role in DED progression

REFERENCES

1. Bradley JL, Özer Stillman I, Pivneva I, Guerin A, Evans AM, Dana R. Dry eye disease ranking among common reasons for seeking eye care in a large US claims database. *Clin Ophthalmol.* 2019;13:225-232.
2. Stapleton F, Alves M, Bunya VY, et al. TFOS DEWS II epidemiology report. *Ocul Surf.* 2017;15(3):334-365.
3. Farrand KF, Fridman M, Stillman IÖ, Schaumberg DA. Prevalence of diagnosed dry eye disease in the United States among adults aged 18 years and older. *Am J Ophthalmol.* 2017;182:90-98.
4. Moss SE, Klein R, Klein BE. Prevalence of and risk factors for dry eye syndrome. *Arch Ophthalmol.* 2000;118(9):1264-1268.
5. Caffery B, Srinivasan S, Reaume CJ, et al. Prevalence of dry eye disease in Ontario, Canada: a population-based survey. *Ocul Surf.* 2019;17(3):526-531.
6. Dana R, Bradley JL, Guerin A, et al. Estimated prevalence and incidence of dry eye disease based on coding analysis of a large, all-age United States health care system. *Am J Ophthalmol.* 2019;202:47-54.
7. Moon JH, Kim KW, Moon NJ. Smartphone use is a risk factor for pediatric dry eye disease according to region and age: a case control study. *BMC Ophthalmol.* 2016;16(1):188.
8. Gupta PK, Stevens MN, Kashyap N, Priestley Y. Prevalence of meibomian gland atrophy in a pediatric population. *Cornea.* 2018;37(4):426-430.
9. Uchino M, Yokoi N, Uchino Y, et al. Prevalence of dry eye disease and its risk factors in visual display terminal users: the Osaka study. *Am J Ophthalmol.* 2013;156(4):759-766.
10. Hanyuda A, Sawada N, Uchino M, et al; JPHC-NEXT Study Group. Physical inactivity, prolonged sedentary behaviors, and use of visual display terminals as potential risk factors for dry eye disease: JPHC-NEXT study. *Ocul Surf.* 2020;18(1):56-63.
11. Sheppard AL, Wolffsohn JS. Digital eye strain: prevalence, measurement and amelioration. *BMJ Open Ophthalmol.* 2018;3(1):e000146.
12. Nelson JD, Helms H, Fiscella R, Southwell Y, Hirsch JD. A new look at dry eye disease and its treatment. *Adv Ther.* 2000;17(2):84-93.
13. Schiffman RM, Walt JG, Jacobsen G, Doyle JJ, Lebovics G, Sumner W. Utility assessment among patients with dry eye disease. *Ophthalmology.* 2003;110(7):1412-1419.
14. Buchholz P, Steeds CS, Stern LS, et al. Utility assessment to measure the impact of dry eye disease. *Ocul Surf.* 2006;4(3):155-161.
15. Yu J, Asche CV, Fairchild CJ. The economic burden of dry eye disease in the United States: a decision tree analysis. *Cornea.* 2011;30(4):379-387.
16. Nichols KK, Bacharach J, Holland E, et al. Impact of dry eye disease on work productivity, and patients' satisfaction with over-the-counter dry eye treatments. *Invest Ophthalmol Vis Sci.* 2016;57(7):2975-2982.
17. Wu H, Wang Y, Dong N, et al. Meibomian gland dysfunction determines the severity of the dry eye conditions in visual display terminal workers. *PLoS One.* 2014;9(8):e105575.
18. Lemp MA, Crews LA, Bron AJ, Foulks GN, Sullivan BD. Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort: a retrospective study. *Cornea.* 2012;31(5):472-478.
19. Starr CE, Gupta PK, Farid M, et al; ASCRS Cornea Clinical Committee. An algorithm for the preoperative diagnosis and treatment of ocular surface disorders. *J Cataract Refract Surg.* 2019;45(5):669-684.
20. Methodologies to diagnose and monitor dry eye disease: report of the Diagnostic Methodology Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf.* 2007;5(2):108-152.
21. 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.
22. TearLab Corporation. *TearLab™ Osmolarity System: Clinical Utility Guide.* Accessed April 6, 2020. https://www.tearlab.com/pdfs/TearLab Clinical Utility Guide.pdf
23. Khanal S, Tomlinson A, McFadyen A, Diaper C, Ramaesh K. Dry eye diagnosis. *Invest Ophthalmol Vis Sci.* 2008;49(4):1407-1414.
24. Tomlinson A, Khanal S, Ramaesh K, Diaper C, McFadyen A. Tear film osmolarity: determination of a referent for dry eye diagnosis. *Invest Ophthalmol Vis Sci.* 2006;47(10):4309-4315.
25. InflammaDry. Package insert. Rapid Pathogen Screening, Inc; 2014.

26. Shen L, Suresh L, Suh Y, Shi G. FRI0338 Evaluation of the sensitivity and specificity of the sjÖ® diagnostic test. *Ann Rheum Dis.* 2016;75(suppl 2):557.
27. Finis D, Pischel N, Schrader S, Geerling G. Evaluation of lipid layer thickness measurement of the tear film as a diagnostic tool for meibomian gland dysfunction. *Cornea.* 2013;32(12):1549-1553.
28. 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.
29. Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy report. *Ocul Surf.* 2017;15(3):575-628.
30. Wolffsohn JS, Arita R, Chalmers R, et al. TFOS DEWS II Diagnostic Methodology report. *Ocul Surf.* 2017;15(3):539-574.
31. Abidi A, Shukla P, Ahmad A. Lifitegrast: a novel drug for treatment of dry eye disease. *J Pharmacol Pharmacother.* 2016;7(4):194-198.
32. Mandal A, Gote V, Pal D, Ogundele A, Mitra AK. Ocular pharmacokinetics of a topical ophthalmic nanomicellar solution of cyclosporine (Cequa®) for dry eye disease. *Pharm Res.* 2019;36(2):36.
33. Kala Pharmaceuticals, Inc. Safety and efficacy of KPI-121 in subjects with DED (STRIDE 3). ClinicalTrials.gov. Updated May 6, 2020. Accessed May 9, 2020. https://clinicaltrials.gov/ct2/show/NCT03616899
34. Business Wire. Kala Pharmaceuticals announces statistically significant results for primary and key secondary endpoints in STRIDE 3 clinical trial evaluating EYSUVIS™ for signs and symptoms of dry eye disease. March 9, 2020. Accessed May 1, 2020. https://www.businesswire.com/news/home/20200309005294/en/
35. Bausch Health Americas, Inc. Perfluorohexylcotane (NOV03) for the treatment of signs and symptoms of dry eye disease associated with meibomian gland dysfunction. ClinicalTrials.gov. Updated April 2, 2020. Accessed April 4, 2020. https://clinicaltrials.gov/ct2/show/NCT04139798
36. Tauber J. Randomized, double-masked, comparator-controlled phase 2 trial to evaluate NOV03 (perfluorohexyloctane) for treatment of dry eye disease. Paper presented at: 2019 Annual Meeting of the American Society of Cataract and Refractive Surgery; May 3-7, 2019; San Diego, CA.
37. 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 May 11, 2020. https://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
38. Nichols KK, Donnenfeld ED, Karpecki PM, et al. Safety and tolerability of lifitegrast ophthalmic solution 5.0%: pooled analysis of five randomized controlled trials in dry eye disease. *Eur J Ophthalmol.* 2019;29(4):394-401.
39. Holland EJ, Whitley WO, Sall K, et al. Lifitegrast clinical efficacy for treatment of signs and symptoms of dry eye disease across three randomized controlled trials. *Curr Med Res Opin.* 2016;32(10):1759-1765.
40. 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.
41. Sall K, Stevenson OD, Mundorf TK, Reis BL, CsA Phase 3 Study Group. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. *Ophthalmology.* 2000;107(4):631-639.
42. Asbell PA, Maguire MG, Pistilli M, et al; Dry Eye Assessment and Management Study Research Group. n-3 fatty acid supplementation for the treatment of dry eye disease. *N Engl J Med.* 2018;378(18):1681-1690.
43. Epitropoulos AT, Donnenfeld ED, Shah ZA, et al. Effect of oral re-esterified omega-3 nutritional supplementation on dry eyes. *Cornea.* 2016;35(9):1185-1191.
44. Giannaccare G, Pellegrini M, Sebastiani S, et al. Efficacy of omega-3 fatty acid supplementation for treatment of dry eye disease: a meta-analysis of randomized clinical trials. *Cornea.* 2019;38(5):565-573.
45. Hura A, Epitropoulos A, Czyz C. Visible meibomian gland structure increases after vectored thermal pulsation treatment in dry-eye patients with meibomian gland dysfunction. Paper presented at: 2019 Annual Meeting of the American Society of Cataract and Refractive Surgery; May 3-7, 2019; San Diego, CA.
46. Perry H. Is blepharitis the progenitor of OSD? *Ophthalmology Management.* October 1, 2018. Accessed May 1, 2020. https://www.ophthalmologymanagement.com/issues/2018/october-2018/is-blepharitis-the-progenitor-of-osd
47. Epstein IJ, Rosenberg E, Stuber R, Choi MB, Donnenfeld ED, Perry HD. Double-masked and unmasked prospective study of terpinen-4-ol lid scrubs with microblepharoexfoliation for the treatment of Demodex blepharitis. *Cornea.* 2020;39(4):408-416.
48. Stoneback R. Quick hits. $12.4 million award to "audacious goals". *Ophthalmology Management.* November 1, 2016. Accessed April 16, 2020. https://www.ophthalmologymanagement.com/issues/2016/november-2016/quick-hits
49. Jaiswal S, Asper L, Long J, Lee A, Harrison K, Golebiowski B. Ocular and visual discomfort associated with smartphones, tablets and computers: what we do and do not know. *Clin Exp Optom.* 2019;102(5):463-477.
50. Zhao ZC, Zhou Y, Tan G, Li J. Research progress about the effect and prevention of blue light on eyes. *Int J Ophthalmol.* 2018;11(12):1999-2003.
51. *How to Save Your Eyes in the Digital Age: The Handbook for Eye Care and Electronics.* eyesa 73, Chapter 158 (2019). Accessed April 6, 2020. http://leginfo.legislature.ca.gov/faces/billTextClient.xhtml?bill_id=201920200SCR73
52. Porter D. Blue light and digital eye strain. American Academy of Ophthalmology. Reviewed January 16, 2020. Accessed April 16, 2020. https://www.aao.org/eye-health/tips-prevention/blue-light-digital-eye-strain
53. O'Hagan JB, Khazova M, Price LL. Low-energy light bulbs, computers, tablets and the blue light hazard. *Eye (Lond)*. 2016;30(2):230-233.
54. Porter D. Digital devices and your eyes. American Academy of Ophthalmology. Reviewed November 15, 2019. Accessed April 16, 2020. https://www.aao.org/eye-health/tips-prevention/digital-devices-your-eyes
55. Mainster MA. Violet and blue light blocking intraocular lenses: photoprotection versus photoreception. *Br J Ophthalmol.* 2006;90(6):784-792.
56. Levinson BA, Rapuano CJ, Cohen EJ, Hammersmith KM, Ayres BD, Laibson PR. Referrals to the Wills Eye Institute Cornea Service after laser in situ keratomileusis: reasons for patient dissatisfaction. *J Cataract Refract Surg.* 2008;34(1):32-39.
57. Woodward MA, Randleman JB, Stulting RD. Dissatisfaction after multifocal intraocular lens implantation. *J Cataract Refract Surg.* 2009;35(6):992-997.
58. Epitropoulos AT, Matossian C, Berdy GJ, Malhotra RP, Potvin R. Effect of tear osmolarity on repeatability of keratometry for cataract surgery planning. *J Cataract Refract Surg.* 2015;41(8):1672-1677.
59. Hovanesian JA. Treating dry eye can improve refractive prediction in cataract surgery. *Cataract & Refractive Surgery Today.* January 2020. Accessed April 6, 2020. https://crstoday.com/articles/2020-jan/treating-dry-eye-can-improve-refractive-prediction-in-cataract-surgery/
60. Dell SJ. The new Dell questionnaire. *Cataract & Refractive Surgery Today.* May 2017. Accessed April 6, 2020. https://crstoday.com/articles/2017-may/the-new-dell-questionnaire/
61. Efron N, Jones L, Bron AJ, et al; Members of the TFOS International Workshop on Contact Lens Discomfort. The TFOS International Workshop on Contact Lens Discomfort: report of the Contact Lends Interactions With the Ocular Surface and Adnexa Subcommittee. *Invest Ophthalmol Vis Sci.* 2013;54(11):TFOS98-TFOS122.
62. Termote K, Schendel S, Moloney G, Holland SP, Lange AP. Focal limbal stem cell deficiency associated with soft contact lens wear. *Can J Ophthalmol.* 2017;52(6):552-558.
63. Zhong M, Gadek TR, Bui M, et al. Discovery and development of potent LFA-1/ICAM-1 antagonist SAR 1118 as an ophthalmic solution for treating dry eye. *ACS Med Chem Lett.* 2012;3(3):203-206.
64. Semba CP, Gadek TR. Development of lifitegrast: a novel T-cell inhibitor for the treatment of dry eye disease. *Clin Ophthalmol.* 2016;10:1083-1094.
65. Donnenfeld ED, Perry HD, Nattis AS, Rosenberg ED. Lifitegrast for the treatment of dry eye disease in adults. *Expert Opin Pharmacother.* 2017;18(14):1517-1524.

INSTANT CME CERTIFICATE AVAILABLE WITH ONLINE TESTING AND COURSE EVALUATION AT **https://tinyurl.com/modernDED**

CME POST TEST QUESTIONS

To obtain *AMA PRA Category 1 Credit*™ for this activity, complete the CME Post Test and course evaluation **online** at **https://tinyurl.com/modernDED.** (Paper submissions cannot be processed.) Upon successful completion of the post test and evaluation, you will be able to generate an instant certificate of credit.

See detailed instructions at **To Obtain *AMA PRA Category 1 Credit*™** on page 2.

1. The reported prevalence of DED:
   a. Ranges from 5% to 50%
   b. Is greater in males than in females
   c. Is greater in whites than in Asians
   d. Is increasing in adolescents, teenagers, and young adults, but not in older populations

2. Digital device usage is being attributed as a cause for increased prevalence of DED in:
   a. Children
   b. Men
   c. Women
   d. All the above

3. Compared with the direct health care costs of DED in the United States, the indirect costs of DED resulting from loss of work productivity are _____.
   a. Greater
   b. Lesser
   c. Approximately the same
   d. Unknown

4. Compared with severe angina and dialysis, how has the effect on quality of life of severe DED ranked?
   a. Greater
   b. Lesser
   c. Approximately the same
   d. Unknown

5. According to recommendations of the ASCRS algorithm, which diagnostic modality should be done routinely to screen for signs of OSD in a patient who is scheduled for refractive surgery?
   a. Lipid layer thickness
   b. Meibography
   c. MMP-9
   d. Noninvasive TBUT

6. Untreated DED in a patient undergoing cataract surgery can affect the visual outcome after implantation of a _____ IOL.
   a. Monofocal
   b. Multifocal
   c. Toric
   d. Any

7. Which therapy for DED does NOT target inflammation?
   a. Topical cyclosporine
   b. Topical lifitegrast
   c. Topical loteprednol
   d. Topical perfluorohexyloctane (NOV03)

8. The 20-20-20 rule may be recommended to patients who spend a lot of time working at a computer. Which of the following is NOT one of the recommended steps?
   a. Look away every 20 minutes
   b. Look at an object 20 ft away
   c. Look away for 20 seconds
   d. Blink repeatedly for 20 seconds

9. A patient presents for her preoperative visit prior to cataract surgery. She is evaluated using the ASCRS algorithm for diagnosing OSD and is determined to have visually significant OSD. Treatment is initiated with a topical corticosteroid and topical lifitegrast. According to the ASCRS algorithm, what should the patient be told about her next scheduled appointment?
   a. She can return for surgery as planned
   b. She should call for an appointment when she notices improvement in symptoms
   c. She can return for reevaluation after 2 to 4 weeks
   d. She has to wait at least 1 month before returning for reevaluation

10. In the DREAM study, treatment with an oral omega-3 nutritional supplement significantly improved signs and symptoms of DED compared with _____.
    a. Baseline
    b. Artificial tears
    c. Oral olive oil
    d. None of the above