CME MONOGRAPH

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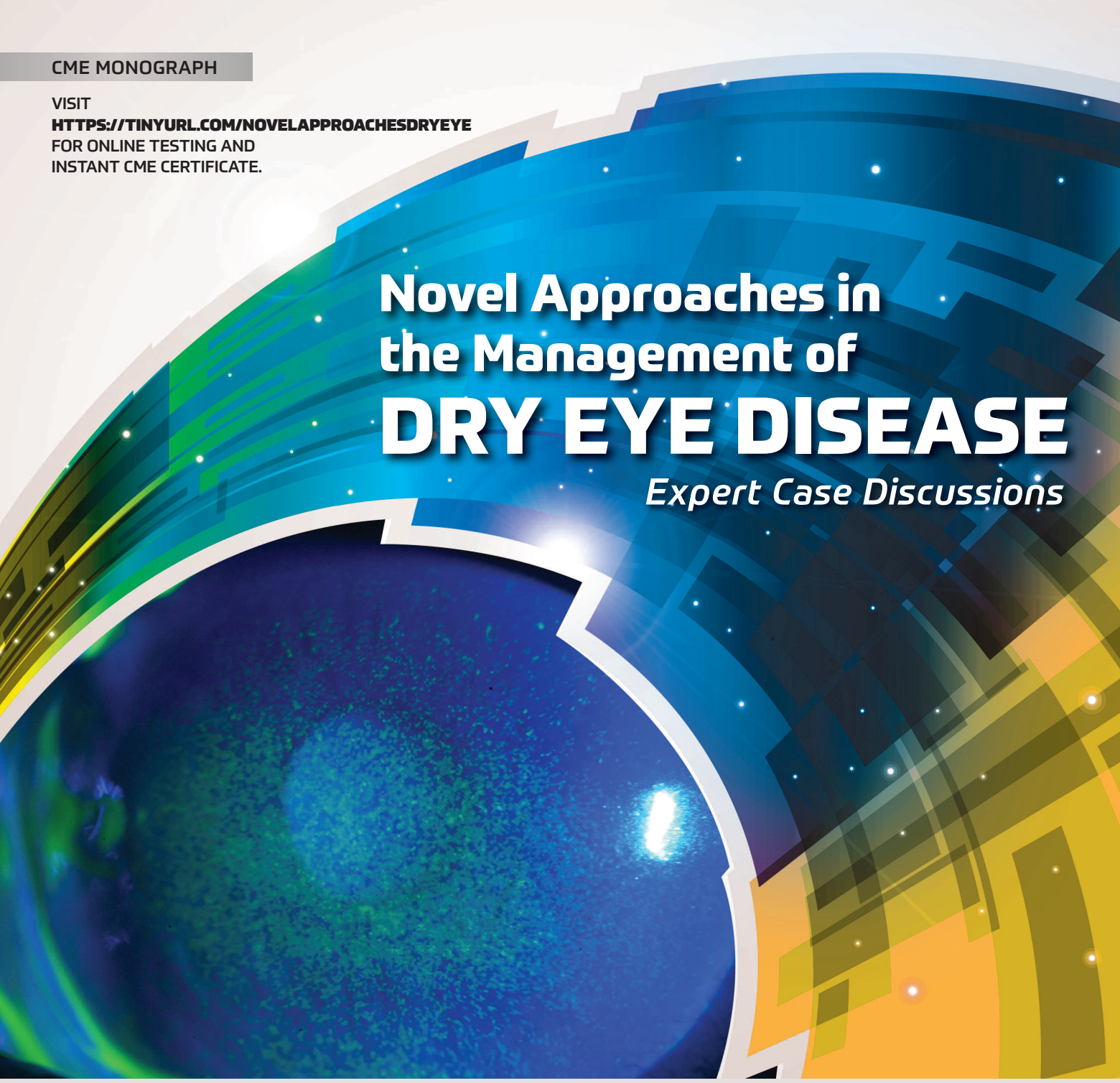
Novel Approaches in the Management of DRY EYE DISEASE

Expert Case Discussions



PROCEEDINGS FROM A CME SYMPOSIUM

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FACULTY

Elisabeth M. Messmer, MD, FEBO (Chair)
Stefano Barabino, MD, PhD
Anat Galor, MD, MSPH
Pr Marc Labetoulle, MD, PhD
Guillermo Rocha, MD, FRCSC

FACULTY

Elisabeth M. Messmer, MD, FEBO
(Chair)
Professor of Ophthalmology
Ludwig Maximilian University
Munich, Germany

Stefano Barabino, MD, PhD
Associate Professor
Department of Neurosciences, Ophthalmology, and Genetics
Clinica Oculistica
University of Genoa
Genoa, Italy

Anat Galor, MD, MSPH
Associate Professor of Clinical Ophthalmology
Department of Ophthalmology
Bascom Palmer Eye Institute
Miller School of Medicine
University of Miami
Miami, Florida

Pr Marc Labetoulle, MD, PhD
Ophthalmology
Bicêtre Hospital
South Paris University
Le Kremlin-Bicêtre, France

Guillermo Rocha, MD, FRCSC
Associate Professor
University of Manitoba
Medical Director
Ocular Microsurgery & Laser Centre
Brandon, Canada

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
Assistant Director, Comprehensive Ophthalmology Service
New York Eye and Ear Infirmary of Mount Sinai
New York, New York

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This continuing medical education (CME) activity captures content from a CME symposium held on October 14, 2016, in Chicago, Illinois.

ACTIVITY DESCRIPTION
Findings of epidemiologic studies show that between approximately 4% and up to approximately 34% of adult populations in countries around the world are affected by dry eye disease (DED). Understanding of the pathophysiology of this common condition has provided a foundation for developments in diagnostic modalities and therapies, although approaches to evaluation and management may vary internationally, depending on access to these new options. The purpose of this activity is to update ophthalmologists on the pathophysiology of DED, along with strategies for diagnosis and treatment in different countries, taking into account disease type and severity.

TARGET AUDIENCE
This educational activity is intended for European and US ophthalmologists caring for patients with DED.

LEARNING OBJECTIVES
Upon completion of this activity, participants will be better able to:
- Diagnose and monitor DED with appropriate assessment tools and techniques
- Describe the implications of inflammation in DED for diagnosis and management
- Apply evidence-based approaches for the treatment of DED
- Describe clinically relevant results for new and emerging treatments for DED

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LAST REVIEW
June 1, 2017

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INTRODUCTION

Studies of the prevalence of dry eye disease (DED) show that it is a global problem. Understanding of its potential to be progressive and affect function and quality of life underscores the importance of identification and management. Newer technologies are enabling diagnosis, and new treatments are emerging. In particular, understanding of the role of inflammation in DED pathogenesis has focused attention on anti-inflammatory treatment. The availability of different diagnostic and therapeutic modalities, however, varies internationally.

In a series of short narratives from expert faculty, this continuing medical education monograph provides updates on DED epidemiology, pathophysiology, and methods for diagnosis and treatment in the United States, Europe, and Canada. Several cases are also discussed to illustrate clinical approaches for patient evaluation and management. Readers will be able to gain insights they can apply in their own practice settings.

EPIDEMIOLOGY OF DRY EYE

Elisabeth M. Messmer, MD, FEBO

Dry eye disease is a common ocular condition, but studies evaluating its prevalence report a wide range of results.[1] The variability in the findings may be explained, in part, by differences in the populations studied and in the definitions used for DED. Considering the latter, it is interesting to look at prevalence rates reported by studies conducted before and after 2007, the year when the Dry Eye WorkShop (DEWS) introduced a new definition for DED.[2]

Summarizing population-based epidemiologic studies published before DEWS **(Table 1)**,[1] the DEWS Epidemiology Committee cited 4 studies conducted in the United States that reported DED prevalence rates ranging from 4.3% to 14.6%.[3-6] Two Australian studies were identified that reported similar prevalence rates of 5.5% and up to 16.6%.[7,8] Two Asian studies reported much higher prevalence rates: 27.5% and 33.7% **(Table 1)**.[9,10] Interestingly, the study reporting the 27.5% prevalence included younger patients than any of the other investigations (age range, ≥ 21 years vs ≥ 40 years to ≥ 65 years).[3,7,9]

European studies published before 2007 include a German study defining dry eye by the presence of a foreign body feeling, which reported a peak prevalence of 11.2% among men aged 45 to 49 years and a peak prevalence of 22.8% among women aged 55 to 59 years.[11] A Danish study of persons aged 30 to 60 years reported a DED prevalence of 8% to 11%, with the highest prevalence in persons aged 50 to 59 years.[12] The study also reported a very low prevalence of Sjögren syndrome, which ranged from 0.2% to 2.1%, depending on the diagnostic criteria.

One other European study published before DEWS considered patients managed by ophthalmologists and reported a low DED prevalence of < 0.1% in each of the 6 countries that were included.[13] The authors concluded that DED did not create a direct health care expenditure burden, although they recognized the potential for underestimating the total economic burden because DED is often self-treated.

Studies reported after DEWS from the United States include the Beaver Dam Offspring Study, in which the DED prevalence was 14.5% overall, but higher in women than in men at 17.9% vs 10.5%, respectively.[14] Multivariate analyses identified female sex, current contact lens use, allergies, arthritis, thyroid disease, antihistamine

Table 1. Summary of Population-Based Epidemiologic Studies of Dry Eye[1,6]

Study	N	Age Range, Years	Dry Eye Assessment	Prevalence, %
US Studies				
Salisbury Eye Study	2420	≥ 65	At least 1 of 6 symptoms (dryness, gritty/sandiness, burning, redness, crusting on lashes, eyes stuck shut in morning), occurring at least often	14.6
Beaver Dam	3722	≥ 48	"For the past 3 months or longer have you had dry eyes?" (If needed, described as foreign body sensation with itching, burning, and sandy feeling, not related to allergy)	14.4
Women's Health Study	36,995	≥ 49	Severe symptoms of dryness and irritation, either constantly or often, and/or the physician's diagnosis of dry eye as volunteered by the patient	7.8
Physician's Health Studies I and II	25,665	≥ 50, 55	Severe symptoms of both dryness and irritation either constantly or often and/or the physician's diagnosis of dry eye as volunteered by the patient	4.3
Australian studies				
Blue Mountains	1075	≥ 50	At least 1 of 4 symptoms, regardless of severity, or at least 1 symptom with a moderate-to-severe ranking (dryness, grittiness, itchiness, discomfort)	16.6 (at least 1 symptom) 15.3 (3 or more symptoms)
Melbourne Visual Impairment Project	926	≥ 40	At least 1 of 6 "severe" symptoms, not attributed by the subject to hay fever (discomfort, foreign body, itching, tearing, dryness, photophobia)	5.5
Asian studies				
Shihpai	2038	≥ 65	At least 1 of 6 symptoms, often or all of the time (dryness, gritty/sandiness, burning, sticky, tearing, redness, discharge, eyes stuck shut in morning)	33.7
Sumatra	1058	≥ 21	At least 1 of 6 symptoms, often or all of the time (dryness, gritty/sandiness, burning, redness, crusting on lashes, eyes stuck shut in morning)	27.5

use, and steroid use as risk factors for DED. Analyses of data from men participating in the Physicians' Health Care Studies found DED in 3.9% of men aged 50 to 54 years and 7.7% of men aged 80 years and older.[15] In this study, DED risk factors were high blood pressure, benign prostate hyperplasia, and use of antidepressant, antihypertensive, and benign prostate hyperplasia medications. The authors estimated that in 2030, approximately 2.8 million men in the United States will be affected by DED.

There is also 1 post-DEWS DED prevalence study from Europe. It included 654 adults with a mean age of 63.6 years and determined that DED, defined by the presence of symptoms and at least 1 sign, affected 11% of the population overall and was more common among women than men at 11.9% vs 9.0%, respectively.[16] In this study, the presence of signs of DED was associated with autoimmune disease, rosacea, and computer use.

In summary, the reported prevalence of DED did not change much after the DEWS report. The research shows DED prevalence increases with age and is higher in Asia than in the United States, Australia, or Europe. Dry eye disease is also more common among women than men, and risk factors for DED appear to differ by sex.

PATHOPHYSIOLOGY OF DRY EYE DISEASE

Stefano Barabino, MD, PhD

To understand the pathophysiology of DED, it is first important to recognize that DED is not just an abnormality defined by an inadequate quantity or quality of the tear film. Rather, it is a disease of the lacrimal functional unit that is composed of the components of the ocular surface (tear film, corneal and conjunctival epithelium, and meibomian glands), lacrimal glands, and interconnecting nerves.[17]

Dry eye disease is a complex, multifactorial disease, with numerous potential triggers that initiate and exacerbate the condition by driving a vicious cycle. As a simplification, etiologic factors can be divided into 4 categories according to whether they lead to lid margin inflammation/meibomian gland dysfunction (MGD), ocular surface inflammation, tear film insufficiency/inadequate lubrication, or ocular surface damage.[18] Each of these 4 features, however, will be present, at least to some degree, in eyes with DED and can interact with one another **(Figure 1)**. Therefore, all 4 must be targeted by treatment to interrupt the vicious cycle that perpetuates DED.

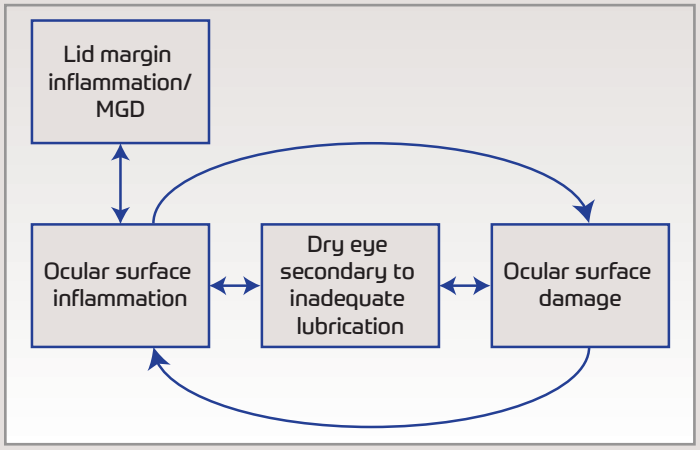


Figure 1. Four key factors of the dry eye vicious cycle[18]
Abbreviation: MGD, meibomian gland dysfunction.

The presence of inflammation in DED may not always be easy to establish clinically, but it has been shown in multiple studies in humans and animal models.[19] Although hyperemia is a sign of inflammation, inflammation may be present in the absence of a red eye. Although inflammation may be demonstrated by the presence of elevated levels of various inflammatory cytokines and chemokines in tear samples, variability in tear collections can explain why there are inconsistent results across published studies.

Using flow cytometry to analyze conjunctival samples collected with impression cytology, we found immune cells in the superficial layer of the conjunctiva and evidence of increased inflammation in specimens from eyes with DED.[19] Compared with healthy controls, cells from eyes with DED had a significantly increased CD4/CD8 ratio and a significantly greater number of CD14+ cells (macrophages). In addition, expression of human leukocyte antigen D related (HLA-DR) was increased in CK19+ conjunctival epithelial cells in the DED group.

Although the cornea remains transparent in most eyes with DED, it also harbors immune cells.[20] Activated antigen-presenting cells (APCs) have been shown to be present, along with increased lymphatic vessels, in eyes with chronic DED. The lymphatics allow APCs to reach the lymph nodes, where they generate autoreactive T cells. The T cells travel to the ocular surface tissues, where they become activated after binding to antigens on the APCs. Cytokines, enzymes, and other chemical factors released by the activated T cells cause damage to ocular surface tissues that perpetuate the immunoinflammatory response, thereby establishing chronic DED. Understanding of the immunoinflammatory pathogenic pathway of DED underscores the importance of treatment that targets the immune response and inflammation to disrupt the vicious cycle.

DIAGNOSIS AND TREATMENT UPDATE: UNITED STATES

Anat Galor, MD, MSPH

Diagnosis of DED is challenging because the disease can manifest with various symptoms and signs and from different underlying causes. Understanding that inflammation is often present in DED supports evaluation to detect its presence to identify patients who may benefit from anti-inflammatory treatment. This is now possible using a commercially available test that assays a tear sample for an elevated level of matrix metalloproteinase-9 (MMP-9).[21] This in-office test is easy to use and will generate a positive result, which is denoted by the appearance of a red line when the level of MMP-9 concentration is ≥ 40 ng/mL.[21] Although the test does not provide a quantitative measurement of MMP-9, the intensity of the red line can be interpreted as a gross indication of the level of MMP-9 (inflammation intensity) in the tear film.

In 2 separate studies, only approximately 40% of patients with DED diagnosed according to symptoms and/or clinical examination findings had a positive MMP-9 assay.[22,23] These data suggest that the MMP-9 assay provides unique information that may be important for guiding decisions on anti-inflammatory therapy for DED.

Hyperosmolarity of the tear film is another consequence of DED-related inflammation and can be identified with another commercially available in-office test.[24] An osmolarity value > 308 mOsm/L is considered abnormal.[24,25] It is not just the absolute number, however, that is important. Because a healthy ocular surface system can maintain homeostasis and stable osmolarity, intraeye and intereye variability is also evidence of an abnormal tear film.[26]

Although it has yet to be proven, it is reasonable to expect that anti-inflammatory treatment for DED would be more effective in eyes with inflammation than in those without inflammation. New choices for anti-inflammatory treatment in the United States include a multidose preservative-free preparation of cyclosporine emulsion, 0.05%, and topical lifitegrast, 5.0%. The multidose cyclosporine product features a proprietary dispensing tip design that incorporates a unidirectional valve and air filter technology to maintain sterility.[27]

Lifitegrast is a lymphocyte function-associated antigen-1 antagonist. It blocks binding of T cells to intercellular adhesion molecule 1 on APCs, vascular endothelial cells, and epithelial cells, and thereby prevents T-cell activation and extravasation into ocular surface tissues.[28,29] Lifitegrast was investigated in 3 placebo-controlled pivotal trials, in which it was well-tolerated and demonstrated significant differences compared with placebo for improving DED signs and symptoms.[30-32] Notably, lifitegrast provided significant symptom relief by day 14 **(Figure 2)**.[30,31] It is indicated for the treatment of the signs and symptoms of DED.[33]

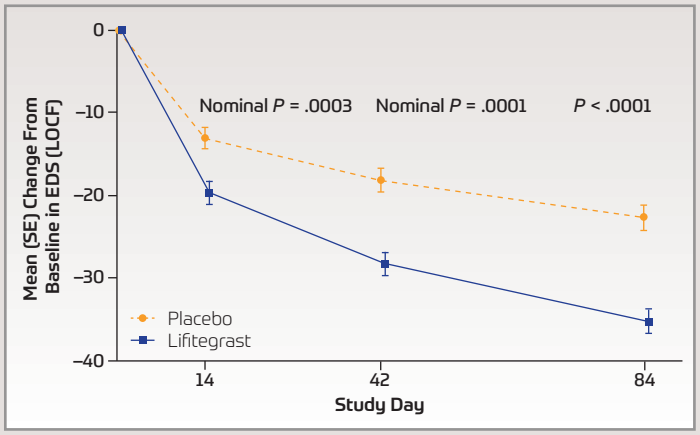


Figure 2. Change from baseline to day 84 in symptom scores in the placebo and lifitegrast groups in OPUS-2. Eye dryness score (EDS) was a coprimary end point.[30]

Abbreviations: LOCF, last observation carried forward; SE, standard error.

Absence of inflammation in most patients with DED prompts interest in identifying other therapeutic targets; one of these targets is somatosensory dysfunction. Some patients complaining of DED symptoms may have neuropathic pain that arises from underlying nerve dysfunction.[34] A corneal somatosensory pathway exists, in which signals are transmitted from the cornea to areas in the brain, including the primary somatosensory cortex that senses pain, along the amygdala within the limbic system, which might explain why patients with DED also experience emotional disorders, such as depression and anxiety. Currently, there is no test for diagnosing the presence of a neuropathic pain component. Pain specialists, however, have determined that patients with neuropathic pain are likely to report specific symptoms that include hot burning pain, hyperalgesia, and allodynia, which in the eye may manifest as sensitivity to wind and light, respectively.[34,35] Research in patients with DED shows that these findings are also more likely in individuals whose disease course follows a chronic course.[35]

It is important to consider neuropathic pain in patients with a consistent clinical picture because clinicians may expand their treatment regimen to include medications that can alter or improve nerve function. Anti-inflammatory medications are 1 such option because nerves are sensitized by the presence of inflammation.[35] Autologous serum tears that contain nerve growth factors and other mediators thought to normalize and improve function may also be beneficial.[36]

Topical treatment with tavilermide, which is a neurotrophin mimetic that acts as a partial agonist of the nerve growth factor receptor, is being investigated as a more specific treatment.[37] Other novel treatments for DED that act on the neural component include an investigational agonist of TRPM8 (transient receptor potential melastatin 8), which affects the activity of peripheral sensory nerves,[38] and an intranasal device for stimulating natural tear production by modulating nerve function.[39] The intranasal device was cleared by the US Food and Drug Administration and approved for marketing in the United States in April 2017.[40] The primary effectiveness end point of increased tear production measured by Schirmer score was met in 2 pivotal trials.[40] Potential clinical benefit derived from the temporary increase in tear production was not assessed, but significant reductions in corneal and conjunctival staining and symptom scores have been reported in an open-label study enrolling 40 patients with mild-to-severe DED who used a prototype of the intranasal neurostimulation device at least 4 times daily for 180 days.[39,40] There were no serious device-related adverse events in any of the 3 trials. The most common nonserious device-related adverse events recorded in the pivotal trials were nasal pain, discomfort, or burning (10.3%); transient electrical discomfort (5.2%); and nosebleed (5.2%).[40]

Currently, pain specialists treat neuropathic pain using various oral medications, including calcium channel alpha-2-delta ligands (pregabalin, gabapentin), serotonin-norepinephrine reuptake inhibitors (duloxetine), and tricyclic antidepressants.[34] These agents may be useful for some patients with DED and neuropathic pain complaints.

In summary, DED is not 1 disease. It has multiple components that may be addressed using different modalities. As new treatments emerge, clinicians can look forward to advances in diagnostic tools that will help identify DED subtypes and thus guide targeted treatment.

DIAGNOSTIC AND TREATMENT UPDATE: EUROPE

Pr Marc Labetoulle, MD, PhD

The potential for discordance in the severity of signs and symptoms of DED and in the rate at which signs and symptoms improve after treatment initiation complicates DED diagnosis and management. Recognizing this disparity, a simplified decision-making schema for DED diagnosis and treatment was developed, which categorizes patients into 3 groups based on the relative severity of their DED signs and symptoms **(Figure 3)**.[41]

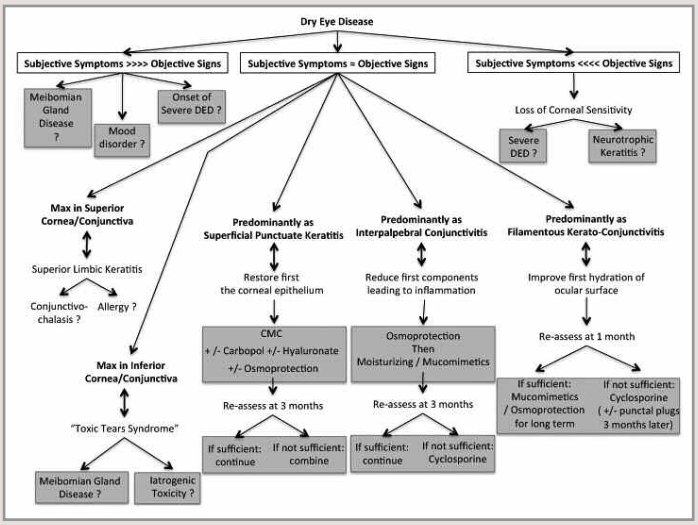


Figure 3. Simplified decision-making schema to guide treatment selection for dry eye disease[41]

Abbreviations: CMC, carboxymethylcellulose; DED, dry eye disease.
Permission request submitted.

According to this schema, patients who have signs of DED that are much more severe than their subjective symptoms may be suspected to have loss of corneal sensitivity, which can be evaluated with an esthesiometer.[42] Two potential causes for this clinical picture include neurotrophic keratitis, which can be secondary to surgery or herpes zoster infection, and severe, end-stage DED.

Patients with significant symptoms and minimal objective signs of DED may also have pure neuropathic pain. According to my clinical experience, however, these patients often have MGD and should be

evaluated for its presence, along with an assessment of the tear film lipid layer using interferometry tools, when available. Treatment options for MGD have traditionally been based on mechanical lid hygiene combined with topical or oral antibiotics and oral omega-3 fatty acid supplementation to improve the quality of the lipid layer.[43] Newer options include devices to relieve meibomian gland obstruction by warming the lids, with or without thermal pulsation, along with other devices and procedures for cleaning the lid margin and removing inspissated meibum.

For patients with symptom severity commensurate with their objective signs, consideration of the pattern of fluorescein staining is useful for determining the underlying etiology and appropriate treatment. For example, predominant staining in the superior cornea and conjunctiva is indicative of superior limbic keratitis, conjunctivochalasis, or allergy. Staining that is most intense inferiorly is a sign of toxic tear syndrome, for which the 2 most common causes are chronic use of preservative-containing eye drops and MGD. When the maximum staining is in the interpapillary area or there is predominant superficial punctate keratitis, patients should be assessed for DED using tear osmolarity and the MMP-9 assay to identify inflammation; those findings allow for subdividing patients according to severity.

A diagnostic algorithm developed specifically to assist with the identification of severe DED was developed by the Ocular Dryness Disease Severity (ODISSEY) European Consensus Group.[44] According to this tool, severe DED is present if the Ocular Surface Disease Index (OSDI) score is ≥ 33 and the corneal fluorescein staining (CFS) score on the Oxford Scale is ≥ 3. If only 1 of these criteria is fulfilled, then additional variables are considered.

Treatment for patients with DED depends on the severity of the ocular surface damage. If it is not severe, treatment consists of artificial tears to protect the epithelium and restore homeostasis. Patients should be reassessed after 3 months and may be continued on the same treatment if the ocular surface is improved. If there is worsening or no change and for patients with severe DED or who already show filamentous keratoconjunctivitis, anti-inflammatory treatment, including topical corticosteroids and/or topical cyclosporine, should be added to treatment with artificial tears.

A commercially available formulation of topical cyclosporine is now available only in Europe, where it is indicated for the treatment of severe keratitis in adult patients with DED, which has not improved despite treatment with tear substitutes.[45] It is a cationic emulsion with an active ingredient concentration of 0.1%,[46] which is twice the concentration found in the cyclosporine emulsion that is commercially available in the United States.[47] The cationic oil-in-water emulsion formulation prolongs residence time on the ocular surface because the positively charged nanosized droplets adhere electrostatically to the negatively charged mucins on the ocular surface.[46] Improving ocular retention improves absorption.[48] Cyclosporine cationic emulsion, 0.1%, was evaluated as a treatment for dry eye in a phase 2 study in the United States.[49]

The 6-month pivotal trial establishing the efficacy and safety of cyclosporine cationic emulsion, 0.1%, enrolled 246 patients with severe DED, defined by a CFS score ≥ 4.[50] After 3 months of treatment, patients treated with the cyclosporine cationic emulsion achieved significantly greater improvement in the CFS score than did controls **(Figure 4)**. A significant benefit for reducing HLA-DR expression compared with control was already noted after 1 month **(Figure 5)**. There was no significant improvement in symptoms as measured by change in the OSDI score.

A second supportive double-masked trial randomized 489 patients with moderate-to-severe DED and a CFS score of 2 to 4 to treatment with cyclosporine cationic emulsion, 0.1%, or vehicle for 6 months.[51] Mean changes from baseline to month 6 in CFS and

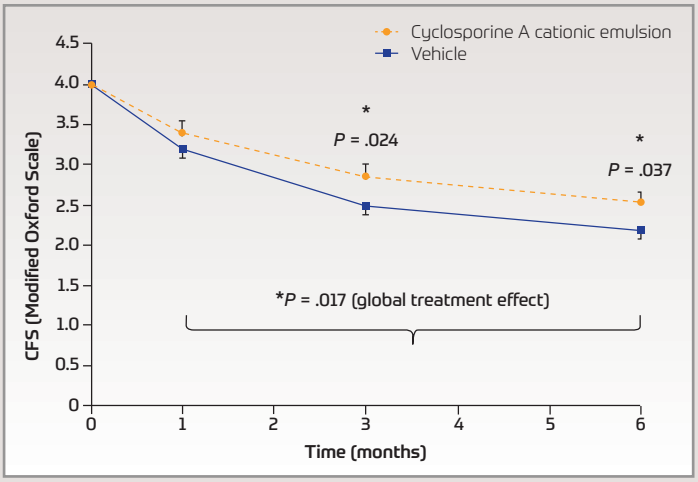


Figure 4. Mean corneal fluorescein staining (CFS) values over 6 months of randomized treatment with 0.1% cyclosporine A cationic emulsion or vehicle[50]

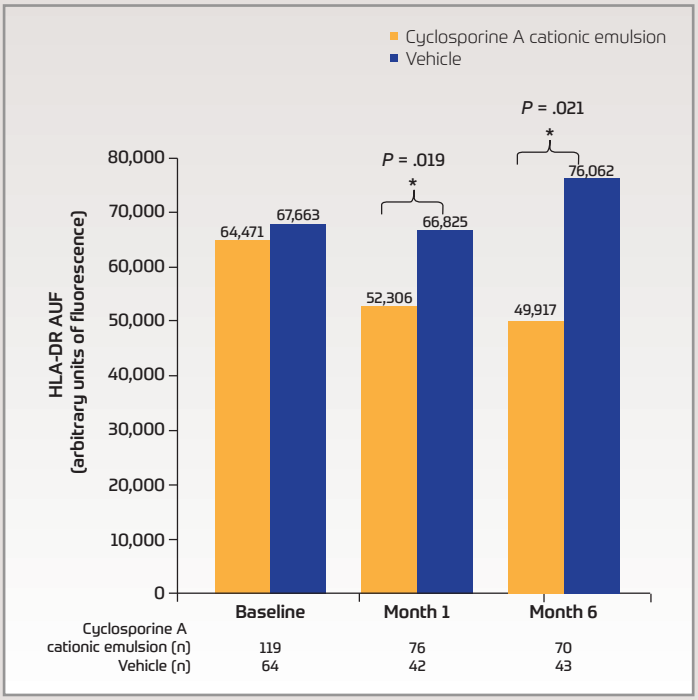


Figure 5. Change in human leukocyte antigen DR (HLA-DR) expression over 6 months of randomized treatment with 0.1% cyclosporine A cationic emulsion or vehicle[50]

global ocular discomfort were analyzed as coprimary efficacy end points. Improvements in both end points were seen in both treatment groups, but a statistically significant difference between groups, which favored cyclosporine cationic emulsion, was seen only for change in CFS. A post hoc analysis restricted to patients with a CFS score ≥ 4 at baseline found that the percentage of patients with a CFS score improvement ≥ 2 grades and a ≥ 30% improvement in the OSDI score was significantly greater in the cyclosporine cationic emulsion group than in the controls.

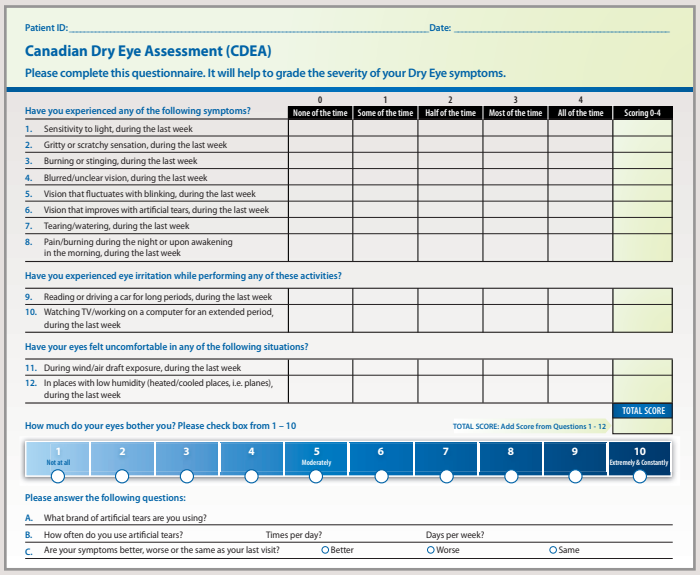
Patients with severe DED should also be evaluated for their response to treatment after 3 months. If the condition is still severe, then punctal plugs may be placed to retain tears on the ocular surface. Punctal occlusion without control of inflammation is not a reasonable option because it may increase exposure of the ocular surface to the inflammatory mediators present in tears.

Finally, the diagnosis of MGD should be considered for all patients with DED, regardless of where they fall in the diagnostic algorithm, because it may eventually develop with time, which may explain its presence in more than 80% of patients with DED.[52,53] In addition, clinicians should keep in mind that there may be outliers who are not correctly diagnosed by this algorithm. Therefore, clinicians must always listen carefully to patient complaints, consider symptoms in the context of clinical signs, and continue to reassess patients for treatment response and the possible need to modify therapy.

DIAGNOSTIC AND TREATMENT UPDATE: CANADA

Guillermo Rocha, MD, FRCSC

In 2009, I participated in a panel of Canadian ophthalmologists that was convened to develop a consensus on the management of dysfunctional tear syndrome.[54] One of the products of that meeting was the Canadian Dry Eye Assessment, a questionnaire for identifying DED-related symptoms, irritation, functional effect, and the use of artificial tears **(Figure 6)**.



Patient ID: _____ Date: _____

Canadian Dry Eye Assessment (CDEA)

Please complete this questionnaire. It will help to grade the severity of your Dry Eye symptoms.

Have you experienced any of the following symptoms?	0 None of the time	1 Some of the time	2 Half of the time	3 Most of the time	4 All of the time	Scoring 0-4
1. Sensitivity to light, during the last week						
2. Gritty or scratchy sensation, during the last week						
3. Burning or stinging, during the last week						
4. Blurred/unclear vision, during the last week						
5. Vision that fluctuates with blinking, during the last week						
6. Vision that improves with artificial tears, during the last week						
7. Tearing/watering, during the last week						
8. Pain/burning during the night or upon awakening in the morning, during the last week						
Have you experienced eye irritation while performing any of these activities?						
9. Reading or driving a car for long periods, during the last week						
10. Watching TV/working on a computer for an extended period, during the last week						
Have your eyes felt uncomfortable in any of the following situations?						
11. During wind/air draft exposure, during the last week						
12. In places with low humidity (heated/cooled places, i.e. planes), during the last week						
						TOTAL SCORE

How much do your eyes bother you? Please check box from 1 – 10 TOTAL SCORE: Add Score from Questions 1 - 12

1 Not at all	2	3	4	5 Moderately	6	7	8	9	10 Extremely & Constantly

Please answer the following questions:

A. What brand of artificial tears are you using? _____

B. How often do you use artificial tears? _____ Times per day? _____ Days per week?

C. Are your symptoms better, worse or the same as your last visit? ○ Better ○ Worse ○ Same

Figure 6. On the basis of the Ocular Surface Disease Index, this questionnaire is designed for simple assessment of DED symptoms[54]

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Establishing a formal diagnosis of DED and its severity takes into account the Canadian Dry Eye Assessment score together with findings from the history, including understanding of the psychosocial and functional effect of DED, and clinical examination of the ocular surface, lids, and face. Traditional objective tests for DED include tear break-up time (TBUT), ocular surface staining, and Schirmer score. Since the Canadian consensus recommendations were released, tear osmolarity and the MMP-9 assay have become available. In a recent study, the performance of 3 commercially available devices for measuring tear osmolarity were compared.[55] This was an in vitro study using contrived tear samples with known osmolarity, and it was found that results recorded with 2 of the devices, one an impedance osmometer (TearLab Osmolarity System, TearLab Corporation) and the other a vapor pressure osmometer (Wescor 5520 Vapro Pressure Osmometer, Wescor Inc), strongly correlated with the known values. The osmolarity values reported with the third device (i-Pen, i-Med Pharma), however, only weakly correlated with the expected results under the experimental testing conditions.

Subsequent to the Canadian consensus panel meeting, new diagnostic tools that provide meibomian gland imaging, lipid layer interferometry, and quantitative tear film analyses have also emerged. At our center, we have been using 1 tool that provides all these functions, thereby providing a very comprehensive picture of the ocular surface condition. With this instrument, the examiner can visualize the tear film as it breaks up, the tear meniscus, and characteristics of tear film dynamics. The machine also measures noninvasive TBUT and tear meniscus height. Interferometry of the lipid layer provides a qualitative analysis of lipid layer thickness, and it has a meibography function that quantifies the area of meibomian gland drop-out, dilation, or truncation and provides an image that we have found to be very useful for educating patients about MGD. All the information obtained is contained in a summary report that uses a color-coded scheme to describe the severity of the individual parameters.

Treatment for DED recommended by the Canadian consensus panel follows a classic approach that includes the use of medications with anti-inflammatory activity, including topical cyclosporine, topical corticosteroids, and oral tetracyclines, along with secretagogues (eg, pilocarpine).[54] The treatment algorithm also follows a stepwise approach, taking into account disease severity, and it recognizes the possible need to treat lid disease and rosacea in all patients with DED **(Figure 7)**.

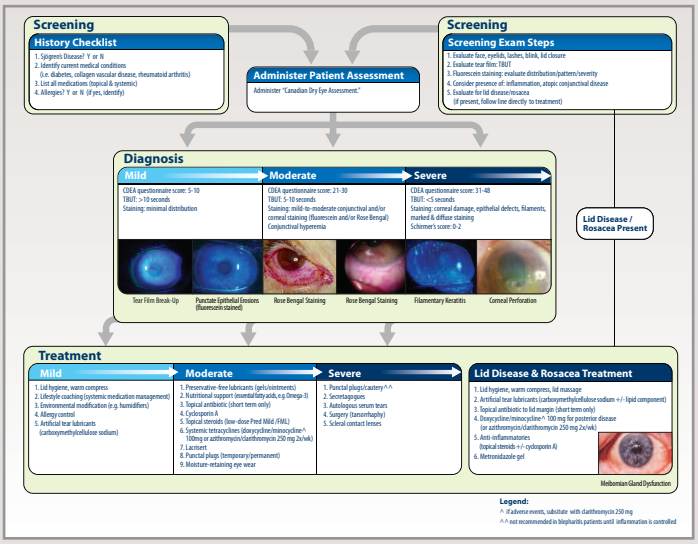

Figure 7. Treatment algorithm for ocular surface disease[54]

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In evaluating patients, clinicians must keep in mind that many patients are being seen on referral after being treated unsuccessfully or after a prolonged period of self-treatment. In addition to making the diagnosis, determining the cause of the patient's DED is important for identifying potentially modifiable triggering factors. Clinicians must also maintain an index of suspicion for the presence of more serious conditions that can masquerade as DED, such as sebaceous cell carcinoma or ocular cicatricial pemphigoid.

CASES FROM THE CLINIC

Management of Ocular Surface Disease Prior to Cataract Refractive Surgery

Stefano Barabino, MD, PhD

A 69-year-old female presenting with visual acuity 20/50 OD, 20/25 OS is diagnosed with cataract OD. She has no other vision or ocular complaints and is anxious to have surgery. What should the surgeon do?

Before scheduling a cataract procedure, surgeons should carefully evaluate patients to identify and treat existing DED. Dry eye disease is common in the cataract surgery patient population[56] and it can affect surgical outcomes and patient satisfaction. Dry eye disease can affect the accuracy of keratometry measurements used for intraocular lens power calculations.[57] In addition, cataract surgery can induce or exacerbate DED **(Figure 8)**.[58,59]

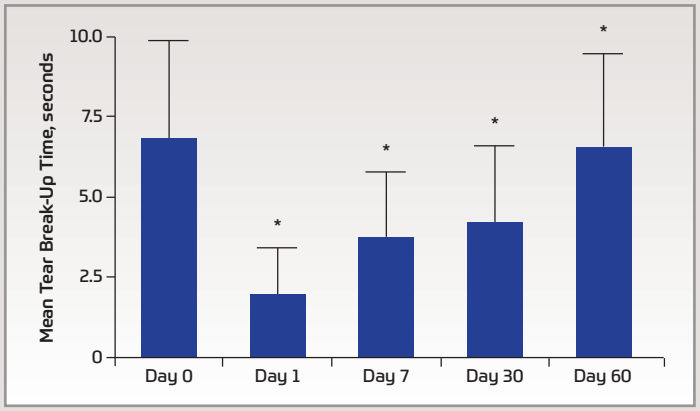

Figure 8. Mean tear break-up time before (day 0) and after phacoemulsification cataract surgery (n = 40)[59]

* *P* < .05 vs day 0

Because patients may not spontaneously report DED symptoms, they should be asked about burning, foreign body sensation, grittiness, or needing to close their eyes for symptom relief. Patients should also be asked about itching, the hallmark of allergic conjunctivitis. Allergic conjunctivitis and DED share common symptoms, but allergy can also be comorbid with and cause or exacerbate DED.

A simple and efficient approach to screening for DED in cataract surgery candidates should include a slit-lamp examination, with assessment of corneal and conjunctival staining using fluorescein and lissamine green. Instillation of fluorescein dye also allows for assessment of tear meniscus height and conjunctivochalasis, and lissamine green is useful for assessing the lid margins.

The ocular surface and the lid margins should be evaluated for evidence of inflammation, and the lid margin should also be examined for signs of MGD or chronic blepharitis, which is characterized by a change in the configuration of the lid margin from flat to convex **(Figure 9)**.

Confocal microscopy can also be used to evaluate the cornea for increased numbers of APCs, which will be present in DED.[60] Chronic contact lens wear is also associated with the increased presence of corneal APCs.[61]

Treatment with artificial tears after cataract surgery can mitigate signs and symptoms of DED, decrease inflammation as measured by HLA-DR expression, and improve visual function.[62] In patients with preexisting DED associated with inflammation, however, artificial tears alone may not be sufficient treatment for improving the ocular surface preoperatively or for postsurgical management.

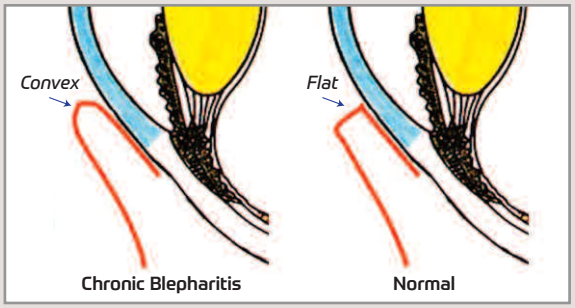

Figure 9. The convex shape of the lid margin in an eye with chronic blepharitis increases tear film evaporation

Images courtesy of Stefano Barabino, MD, PhD

Short-term treatment with a topical corticosteroid can rapidly improve the ocular surface. In a study randomizing patients to a tapering regimen of loteprednol etabonate, 0.5%, or normal saline, we found a significant reduction in ocular surface inflammation and symptoms after 2 weeks.[63] The treatment benefit persisted at 8 weeks, even though loteprednol was being administered just once daily every other day.

In conclusion, it is well worth the time it takes to evaluate patients for DED and other ocular surface conditions prior to cataract surgery. Existing ocular surface damage should be treated prior to surgery by using nonpreserved artificial tears, optimizing tear lipids, and addressing inflammation.

Evaluation and Management of a Patient With Mild Dry Eye Disease

Pr Marc Labetoulle, MD, PhD

A 62-year-old female presents on referral from her general ophthalmologist for DED that has been unresponsive to treatment with several types of artificial tears. She complains of eye stinging, burning, and sore eyes, mostly in the morning, along with itching and exacerbation of symptoms during allergy season. She is 12 years postmenopausal. Her medical history includes hyperparathyroidism, hair loss, knee osteoarthritis, stomach disorders, recurrent migraines, overactive bladder related to poliomyelitis at age 5 years, and allergy to Thuja trees and mold. Current medications include dietary supplements (L-cysteine, vitamin E, and copper), chondroitin sulfate, omeprazole, oxybutynin, and acetylsalicylic acid as needed.

Findings on examination are as follows: best-corrected visual acuity, 20/20 OU; refraction, -1.75 D -0.25 D @ 90° OD, -1.00 D -0.75 D @ 35° OS; OSDI score, 19.4/100; TBUT, 10 s OU; mild fluorescein staining of the cornea and conjunctiva along with lid wiper conjunctivitis; Schirmer I test without anesthesia, 10 mm/5 min OD, 9 mm/5 min OS; and tear osmolarity, 315/325 mOsm/L OD/OS. The patient has lid changes that may be related to MGD and periocular skin lesions that may be atopic dermatitis or seborrheic dermatitis **(Figure 10)**. She has no signs of keratoconus; findings suggesting Sjögren syndrome; or any loss of corneal light reflection, filaments, neovessels, corneal scarring, or conjunctival hyperemia.

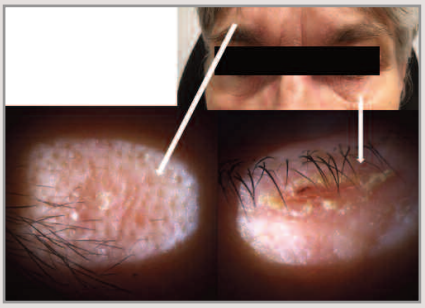

Figure 10. Skin abnormalities associated with DED include cutaneous scales and excoriation

Images courtesy of Pr Marc Labetoulle, MD, PhD

The patient is diagnosed with mild DED probably related to anterior blepharitis and exacerbated by allergy and use of the anticholinergic medication oxybutynin. Her complaint that her ocular symptoms are worse in the morning than in the evening is a clue to blepharitis.[64] The anterior blepharitis may be caused by her dermatitis.

Recommended treatment for this patient includes lid hygiene performed twice daily. In addition, she is told to use a nonpreserved ocular lubricant 4 times daily. A carbomer-, hydroxypropyl guar–, povidone-, or lipid-based product are all reasonable options. She is told to use a topical antihistamine eye drop at the time of allergy exacerbation and to return for follow-up in 3 to 6 months.

If the DED signs and symptoms are improved at follow-up, the patient will be advised to continue on the same regimen. A finding of no change suggests poor compliance with the treatment regimen and a need for counseling to reinforce the management recommendations. Worsening raises suspicion for Sjögren syndrome and the need for a more complete examination by an internist or rheumatologist. In addition, referral to a dermatologist for diagnosis and treatment of her skin condition is indicated.

Evaluation and Management of a Patient With Severe Dry Eye Disease

Elisabeth M. Messmer, MD, FEBO

A 63-year-old white female presents with a 20+-year history of dry eye and dry mouth. She has seen many ophthalmologists in the past, has used multiple artificial tear products, and is desperate for relief of her symptoms. Her ocular complaints, which are bilateral, include severe dryness, foreign body sensation, and photophobia for more than 10 years, although her symptoms worsened after cataract surgery. She states that she is unable to keep her eyes open and she also feels her visual acuity has worsened.

She has experienced difficulty swallowing, parotid gland swelling, and intermittent arthralgias, and was diagnosed with primary Sjögren syndrome after testing positive for Sjögren-specific antibody A and Sjögren-specific antibody B. Findings on examination and diagnostic testing are best-corrected visual acuity, 20/50 OD, 20/40 OS; normal intraocular pressure; lid margin thickening with telangiectasias; obstructed meibomian glands with thickened secretions; a foamy tear film **(Figure 11)**; 2+ conjunctival injection; 3+ staining of the cornea and conjunctiva; filiform keratitis; TBUT, immediate; Schirmer test without anesthesia, 1 mm/5 min and 2 mm/5 min OD/OS; and tear film osmolarity, 343 mOsm/L OU. The MMP-9 test was positive, and the anterior chamber is deep without evidence of inflammation.

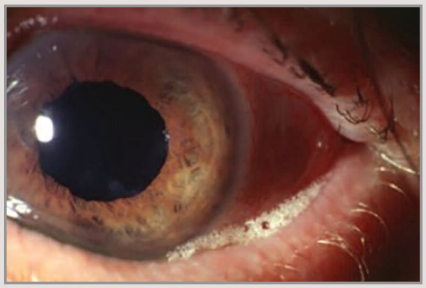

Figure 11. Meibomitis with severe meibomian gland dysfunction and foamy tear film in a patient with Sjögren syndrome

Image courtesy of Elisabeth M. Messmer, MD, FEBO

This patient has severe aqueous-deficient dry eye and marked inflammation associated with primary Sjögren syndrome and MGD. She requires aggressive multimodal treatment and was started on frequent use of artificial tears, including a nonpreserved hyaluronic acid product and a lipid-based product for daytime use, along with a gel at bedtime. In addition, she was educated on lid hygiene and started on topical cyclosporine cationic emulsion, 0.1%, at bedtime, oral omega-3 fatty acids, and a short course of topical corticosteroid therapy using a nonpreserved product that is tapered over 4 weeks.

The patient returned 6 weeks later and reported her eyes felt better. Clinical examination showed improvement in her MGD and resolution of filiform lesions, but she still had pronounced keratitis. She was maintained on her existing treatment with the addition of punctal plugs. Three months later, her symptoms were further improved, she had significant reduction in ocular surface staining, and her tear osmolarity was reduced to 318 mOsm/L. The MMP-9 test was not repeated.

In 2015, Foulks and colleagues published clinical guidelines for the management of dry eye associated with Sjögren syndrome.[65] As outlined in this paper, options for further treatment, had the patient not improved, include oral pilocarpine or cevimeline to stimulate lacrimal and salivary gland secretion and autologous serum drops. Mucolytic therapy with compounded topical N-acetylcysteine, 10%, is a good option for treating filiform keratopathy. Alternatively, the corneal filaments can be removed surgically, followed by bandage contact lens wear. Due to the risk of corneal infection, treatment with a nonpreserved topical antibiotic should be started as prophylaxis.

Sjögren syndrome is a multisystem disease that can involve the lymph nodes, lungs, and kidneys, and it is associated with an increased risk of B-cell lymphoma.[66] Any patient with Sjögren syndrome should be referred to a rheumatologist who may initiate systemic immunosuppressive therapy. In addition, these patients need to be under the care of a dentist because severe dry mouth leads to complications that can include difficulty swallowing, dental caries, and oral infections.[67]

Dr Messmer: Doxycycline 40 mg is commercially available in Germany, but is indicated only for the treatment of rosacea. For patients with DED, we have to use the 100-mg dosage form.

Dr Rocha: Even 20 mg daily can be effective, but the 20-mg product can be more expensive than the 100-mg product, and the choice will depend on what is covered by the patient's prescription drug plan. We have found the 40-mg dose a happy medium because it seems to work well, does not cause many side effects, and is often quite affordable.

Dr Barabino: Omega-3 fatty acids also have anti-inflammatory activity. I was an investigator in a randomized controlled trial of patients with mild-to-moderate DED that found significant reduction in conjunctival HLA-DR expression after 3 months of oral treatment with omega-3/omega-6 fatty acids compared with placebo control.[68]

TAKE-HOME POINTS

Dry eye disease is a disease of the lacrimal functional unit, and its immunoinflammatory pathway of pathogenesis has led to the development of new diagnostic tools and targeted therapies.

Evaluation for and monitoring of DED may include new diagnostic tools and should consider the presence of inflammation, tear film hyperosmolarity, meibomian gland abnormalities, and nerve dysfunction, along with the potential for disparity between signs and symptoms.

Treatment for DED should consider the type of disease, its severity, and the need for anti-inflammatory treatment.

Newer treatments for DED include a novel anti-inflammatory medication that inhibits T-cell activity and a novel formulation of topical cyclosporine.

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FOR INSTANT PROCESSING, COMPLETE THE CME POST TEST ONLINE
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CME POST TEST QUESTIONS

To obtain *AMA PRA Category 1 Credit*™ for this activity, complete the CME Post Test by writing the best answer to each question in the Answer Box located on the Activity Evaluation/Credit Request form on the following page. Alternatively, you can complete the CME Post Test online at **https://tinyurl.com/NovelApproachesDryEye**.

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

1. The highest prevalence rates of DED have been reported in studies of populations from which continent?
   A. Asia
   B. Australia
   C. Europe
   D. North America

2. Which of the following tear film osmolarity findings is NOT associated with DED?
   A. < 308 mOsm/L
   B. > 308 mOsm/L
   C. Intereye variability
   D. Intraeye variability

3. Lipid layer interferometry is useful for:
   A. Determining readiness for cataract surgery
   B. Determining response to topical cyclosporine in a patient with Sjögren syndrome
   C. Diagnosing inflammation related to DED
   D. Diagnosing MGD

4. Dry eye disease symptoms of hot burning pain and sensitivity to wind and light suggest the presence of:
   A. Allergy comorbidity
   B. MGD
   C. Mucin deficiency
   D. Neuropathic pain

5. The MMP-9 assay:
   A. Is a point-of-care test for diagnosing MGD
   B. Is a point-of-care test for diagnosing Sjögren syndrome
   C. Provides a qualitative measurement of MMP-9 concentration in the tear film
   D. Rules out a diagnosis of DED if the test is negative

6. Which of the following findings identify severe DED according to criteria from the ODISSEY European Consensus Group?
   A. OSDI ≥ 33 or CFS (Oxford Scale) ≥ 3
   B. OSDI ≥ 33 and CFS (Oxford Scale) ≥ 3
   C. OSDI ≥ 33 and CFS (Oxford Scale) ≥ 4
   D. OSDI ≥ 33 or CFS (Oxford Scale) ≥ 4

7. In premarketing clinical trials, lifitegrast provided significant relief of the symptom of eye dryness by:
   A. 14 days
   B. 28 days
   C. 3 months
   D. 6 months

8. The cationic emulsion formulation of cyclosporine:
   A. Contains 0.01% of the active ingredient
   B. Prolongs ocular surface residence time because of the positively charged droplets
   C. Is approved for the treatment of signs and symptoms of DED
   D. Showed evidence of improving ocular surface inflammation by day 14 in the pivotal trial

9. Tavilermide and a TRPM8 agonist are investigational treatments for DED that act on:
   A. Meibum secretion
   B. Goblet cells to stimulate mucin
   C. T-cell activation
   D. The neural component

10. Preoperative evaluation of a patient who presents for cataract surgery identifies 2+ cornea fluorescein staining that is determined to be secondary to MGD. An MMP-9 assay is positive. What treatment would you recommend if trying to satisfy the patient's request to have the surgery as soon as possible?
    A. Artificial tears and punctal plugs
    B. Eyelid warming and lid margin massage
    C. Topical corticosteroid treatment
    D. Topical cyclosporine

ACTIVITY EVALUATION/CREDIT REQUEST

Original Release: August 1, 2017
Expiration: August 31, 2018

Novel Approaches in the Management of Dry Eye Disease: Expert Case Discussions

To receive *AMA PRA Category 1 Credit™*, you must complete this **Evaluation** form and the **Post Test**. Record your answers to the **Post Test** in the **Answer Box** located below. Scan this completed page and return via e-mail to cme@nyee.edu or fax it to 212-353-5703. Your comments help us to determine the extent to which this educational activity has met its stated objectives, assess future educational needs, and create timely and pertinent future activities. Please provide all the requested information below. This ensures that your certificate is filled out correctly and is e-mailed to the proper address. It also enables us to contact you about future CME activities. Please print clearly or type. Illegible submissions cannot be processed.

PARTICIPANT INFORMATION (*Please Print*) ❑ Home ❑ Office

Last Name _____ First Name _____

Specialty _____ Degree ❑ MD ❑ DO ❑ OD ❑ PharmD ❑ RPh ❑ NP ❑ RN ❑ PA ❑ Other _____

Institution _____

Street Address _____

City _____ State _____ ZIP Code _____ Country _____

E-mail _____ Phone _____ Fax _____

Please note: We do not sell or share e-mail addresses. *They are used strictly for conducting post-activity follow-up surveys to assess the impact of this educational activity on your practice.*

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❑ Yes ❑ No I and/or my family member have a financial relationship with **New York Eye and Ear Infirmary of Mount Sinai** and/or refer Medicare/Medicaid patients to it.

❑ I certify that I have participated in the entire activity and claim 1.5 *AMA PRA Category 1 Credits™*.

Signature Required _____ **Date Completed** _____

OUTCOMES MEASUREMENT

❑ Yes ❑ No **Did you perceive any commercial bias in any part of this activity? IMPORTANT! If you answered "Yes," we urge you to be specific about where the bias occurred so we can address the perceived bias with the contributor and/or in the subject matter in future activities.**

_____

Circle the number that best reflects your opinion on the degree to which the following learning objectives were met:
5 = Strongly Agree 4 = Agree 3 = Neutral 2 = Disagree 1 = Strongly Disagree

Upon completion of this activity, I am better able to:

• Diagnose and monitor DED with appropriate assessment tools and techniques	5	4	3	2	1
• Describe the implications of inflammation in DED for diagnosis and management	5	4	3	2	1
• Apply evidence-based approaches for the treatment of DED	5	4	3	2	1
• Describe clinically relevant results for new and emerging treatments for DED	5	4	3	2	1

1. Please list one or more things, if any, you learned from participating in this educational activity that you did not already know. _____

_____

2. As a result of the knowledge gained in this educational activity, how likely are you to implement changes in your practice?
4 = definitely will implement changes 3 = likely will implement changes 2 = likely will not implement any changes 1 = definitely will not make any changes

4 3 2 1

Please describe the change(s) you plan to make: _____

_____

3. Related to what you learned in this activity, what barriers to implementing these changes or achieving better patient outcomes do you face?

_____

_____

4. Number of patients I see per week with dry eye disease (DED) ❑ 1–10 ❑ 11–20 ❑ 21–40 ❑ 41–60 ❑ More than 60

5. Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced for you through participation in this activity. ❑ Patient Care ❑ Practice-Based Learning and Improvement ❑ Professionalism ❑ Medical Knowledge ❑ Interpersonal and Communication Skills ❑ Systems-Based Practice

6. What other topics would you like to see covered in future CME programs? _____

_____

ADDITIONAL COMMENTS _____

_____

_____

POST TEST ANSWER BOX

1	2	3	4	5	6	7	8	9	10