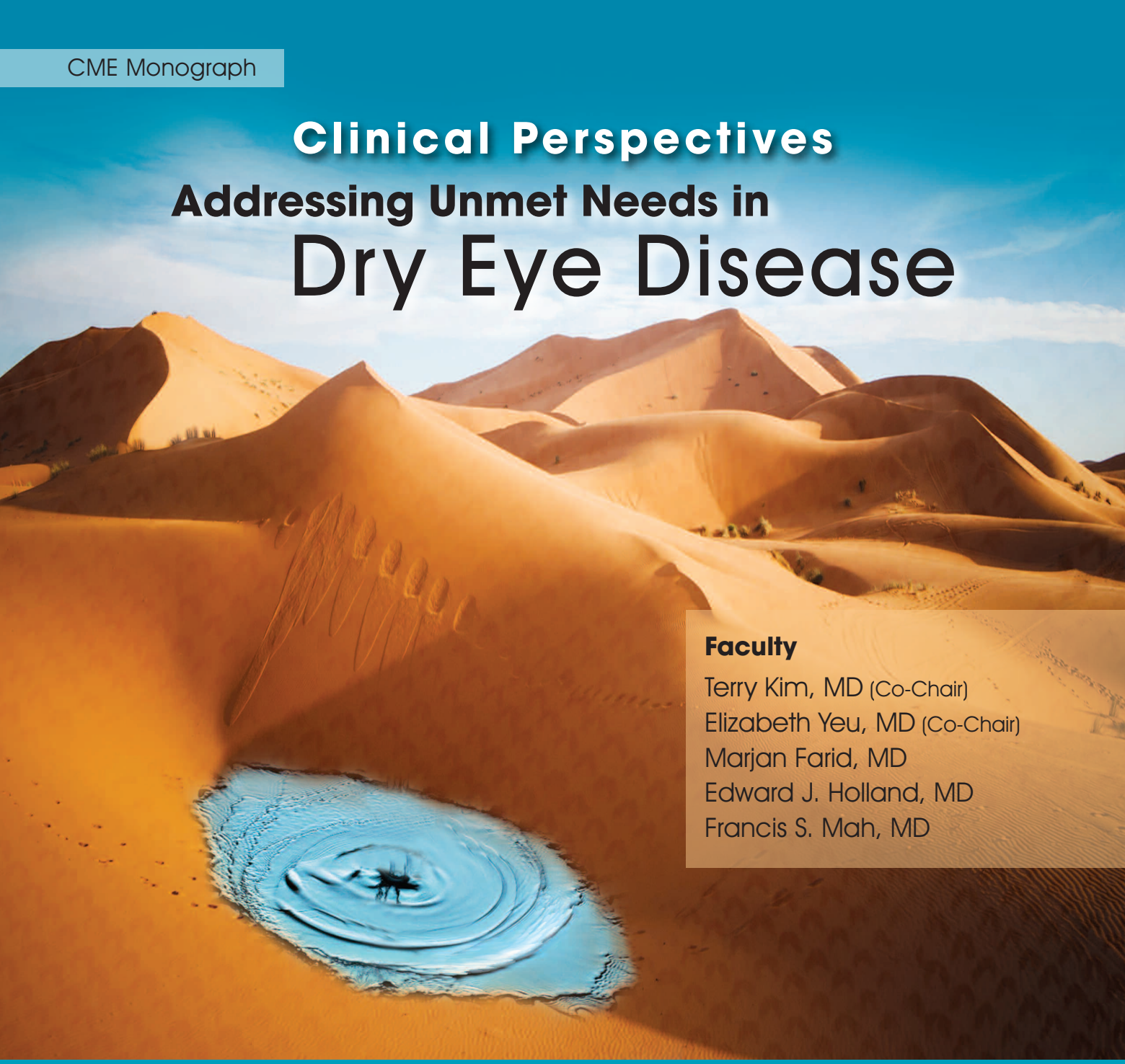
CME Monograph

Clinical Perspectives

Addressing Unmet Needs in

Dry Eye Disease



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Proceedings From a CME Symposium During AAO 2015

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Activity Description
Dry eye disease is a modern epidemic, with increased prevalence attributed to a better understanding of the role of inflammation in a host of diseases, including dry eye. Dry eye negatively impacts multiple aspects of quality of life for patients, including social, psychological, and occupational function, along with overall health and well-being. Early recognition of dry eye disease is important to enable intervention that can improve patient well-being and prevent disability. Despite the high prevalence, costs, and morbidity of dry eye disease, it is often an underrecognized, underdiagnosed, and undertreated condition. The purpose of this activity is to update ophthalmologists on advances in the understanding of dry eye disease pathophysiology as well as developments in the diagnosis and treatment of patients with dry eye.

Target Audience
This educational activity is intended for ophthalmologists.

Learning Objectives
Upon completion of this activity, participants will be better able to:
- Diagnose and evaluate dry eye disease using at least one objective test, regardless of symptom severity
- Describe the implications of inflammation in dry eye disease on diagnosis and treatment approaches
- Apply evidence-based approaches for the treatment of dry eye disease
- Describe clinically relevant results for emerging treatments of dry eye disease

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Introduction

Dry eye disease ("dry eye") is a prevalent condition that is important to recognize and treat because of its potential to affect daily functioning, quality of life, and outcomes of cataract and refractive surgery. In a series of articles, this activity reviews the epidemiology, classification, and pathophysiology of dry eye along with current and emerging approaches to diagnosis and treatment. Practical approaches to the evaluation and management of dry eye are highlighted using expert case-based discussions.

Dry Eye Disease: Prevalence and Impact

Edward J. Holland, MD

Dry eye is one of the most common ocular conditions. In population-based studies that used various disease definitions and considered different populations, the prevalence of dry eye ranged from approximately 8% to 34% (Table 1).[1] In an industry-sponsored online survey, 48% of American respondents reported regularly experiencing dry eye symptoms.[1,2]

Table 1. Prevalence of Dry Eye in Population-based Epidemiologic Studies[1]

Study	Age, years	Prevalence, %
Salisbury Eye Study	≥65	15
Beaver Dam	≥48	14
Women's Health Study	≥49	8
Blue Mountains (Australian)	≥50	17
Shihpai (Asian)	≥65	34
Sumatra (Asian)	≥21	27.5

Dry eye affects both sexes, but it occurs more commonly in women than in men.[1] In addition, the prevalence of dry eye increases with age.[3-5] The prevalence of moderate-to-severe dry eye has been suggested to lie at the lower end of the prevalence range reported in the population-based studies.[1] In a study of adults (mean age, 46 years; range, 26-72 years) with dry eye symptoms, disease severity was categorized as moderate or worse in 64% of subjects.[6]

Regardless of its severity, dry eye has a significant effect on daily functioning and quality of life. Mild-to-moderate dry eye affects numerous aspects of daily living, including success with contact lens wear, work performance, willingness to drive at night, and enjoyment of outdoor activities. The effect of severe dry eye has been ranked similarly to that of severe angina and dialysis.[7,8]

There is also growing recognition of how dry eye affects outcomes following laser vision correction and cataract refractive surgery. The tear film is the first refractive interface of the eye, and the anterior surface of the precorneal tear film has the greatest optical power of any ocular surface, providing approximately two-thirds of the eye's optical power when combined with the cornea.[9,10] In addition, irregularities in the tear film scatter light, leading to degradation in retinal image quality by up to 80%.[10] An unstable tear film, therefore, leads to blurred or fluctuating vision that may be incorrectly attributed to refractive error or cataract. The visual consequences of dry eye may also cause patients with cataracts to be unnecessarily excluded as candidates for a multifocal intraocular lens (IOL); moreover, dry eye can affect vision and image quality after surgery with implantation of a multifocal IOL or any type of IOL (Figure 1).

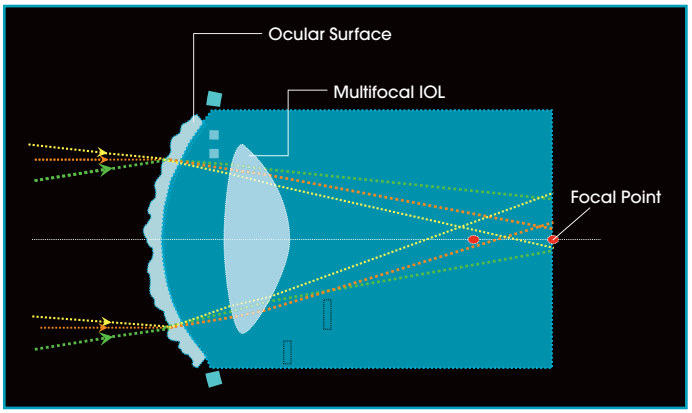


Figure 1. Disruption of the ocular surface induces distortion that is magnified by a multifocal IOL.

Image courtesy of Eric D. Donnenfeld, MD

Dry eye also affects the accuracy of measurements used in planning cataract and corneal refractive surgery, including keratometry, topography, and wavefront aberrometry.[11,12] The consequences of these errors include selecting the wrong type and/or power of monofocal IOL; planning for astigmatic correction when it is not needed or not planning for it when it is; positioning of a toric IOL on the wrong axis; and performing an unnecessary lens exchange or refractive enhancement procedure. Dry eye has also been reported as a factor underlying dissatisfaction in 15% of patients implanted with a multifocal IOL and 28% of patients following LASIK surgery.[13,14]

Furthermore, laser vision correction and cataract surgery by themselves can worsen dry eye secondary to neurotrophic changes arising from flap creation and corneal incisions.[15] Thus, patients with significant dry eye, as represented by corneal staining, should be treated to improve the condition of the ocular surface prior to undergoing surgery. Surgeons need to provide counseling so that patients understand that such an approach optimizes their outcome. Although patients eager to have their procedure may be disappointed and unhappy at first, in the long run, they are less likely to be dissatisfied with the surgery and the surgeon.

Targeting Better Diagnosis and Treatment

Despite its prevalence and consequences, dry eye is significantly underdiagnosed.[16] Various scenarios may explain this underdiagnosis of dry eye. Failure of clinicians to undertake a diagnostic evaluation unless a patient reports symptoms may be a contributing factor. Also, clinicians may have been reluctant to diagnose dry eye in the past, considering the limited effective treatment options available. Furthermore, while the term dry eye implies an aqueous-deficient disease process, meibomian gland

dysfunction (MGD) that leads to reduced tear film lipids and accelerated evaporation is considered the most common cause of dry eye.[17] Yet, only recently has the importance of MGD and careful lid examination as part of the diagnostic evaluation for dry eye received attention.

As highlighted by the results of a 2008 Gallup poll of dry eye sufferers, there is also a need for better treatment of dry eye.[18] In that survey of more than 750 patients, 97% found their dry eye condition frustrating; participants, on average, had tried 3 different brands of artificial tears, and 82% said they wished there was something more effective to treat their condition.

Fortunately, newer technologies have emerged that are improving the clinician's ability to properly diagnose dry eye at an earlier stage, and there are also new treatments on the horizon that should provide more options for effective management. These developments are important, considering the burden of dry eye and the fact that the condition may be a progressive disease that becomes increasingly more difficult to manage as its severity worsens.

Update on the Pathophysiology of Dry Eye Disease

Francis S. Mah, MD

A healthy tear film is essential for comfort, optimal vision, and integrity of the ocular surface.[19] A healthy tear film protects the ocular surface from environmental and infectious insults, and it provides the necessary trophic factors to maintain health and promote healing of the corneal and conjunctival epithelium.

The tear film comprises lipid, aqueous, and mucin components, and it contains a complex mixture of other substances, including antimicrobial proteins, growth factors and molecules that suppress inflammation, as well as electrolytes to maintain proper osmolarity. The lipid component of the tear film is provided by meibomian gland secretions and serves to restrict tear film evaporation to approximately 5% of the tear flow.[20]

The aqueous component of the tear film, as well as most tear proteins, comes from main and accessory lacrimal gland secretions. Mucins, which are soluble glycoproteins produced by conjunctival goblet cells, are essential for the viscosity and stability of the normal tear film. They may be thought of as "wetting agents" for the tear film because they promote its interaction with the conjunctival and corneal epithelial cells.[21]

In the healthy eye, tearing is controlled by a neuronal feedback loop linking the ocular surface and lacrimal glands via sensory and motor neurons—the so-called lacrimal functional unit (LFU) (Figure 2).[22] Multiple intrinsic and extrinsic factors can affect the structure and function of the LFU and the tear film. The consequence of these changes is tear film instability, which in turn drives reflex sensory stimulation to increase lacrimal tear secretion as a compensatory, homeostatic mechanism.

As defined by members of the International Dry Eye WorkShop (DEWS), dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability, with potential damage to the ocular surface.[22] The definition also recognized that dry eye is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.

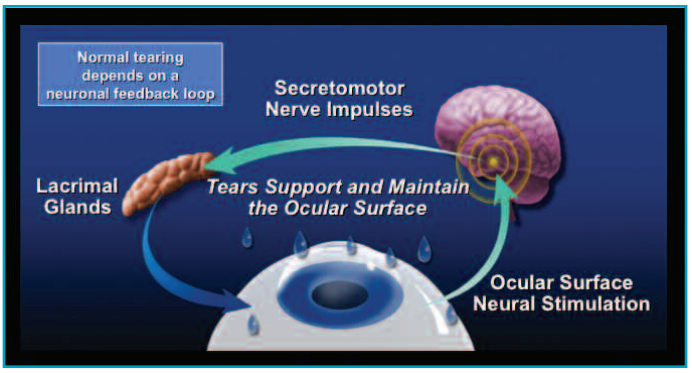


Figure 2. In the healthy eye, components of the ocular surface, lacrimal glands, and interconnecting innervation act as a functional unit regulating tear secretion to maintain integrity of the ocular surface.

Adapted from Stern ME, et al. *Cornea*. 1998;17(6):584-589.

The ocular surface inflammation develops secondarily as the reflex tear secretion becomes insufficient, and the inflammation acts to drive worsening of dry eye disease by damaging LFU components. As dry eye becomes chronic, there are reduced amounts of mucin, lipids, and aqueous humor in the tear film; decreased concentrations of necessary proteins and growth factors; and increased levels of electrolytes, proteases, and proinflammatory mediators.[23] Tear film osmolarity is increased and its viscosity is reduced. These changes compromise ocular surface lubrication and lead to tear film irregularities along with increased tear film breakup.

Inflammation in dry eye is associated with an upregulation of intercellular adhesion molecule-1 (ICAM-1) in the epithelial cells of conjunctival and accessory lacrimal tissues.[24] Binding to ICAM-1 by lymphocyte function-associated antigen-1 (LFA-1), a cell surface protein found on leukocytes, drives immunological synapses, resulting in activation of T-cells and their migration to target tissues (Figure 3). The T-cells multiply and release inflammatory cytokines that amplify ICAM-1 expression and the entire immuno-inflammatory pathway.

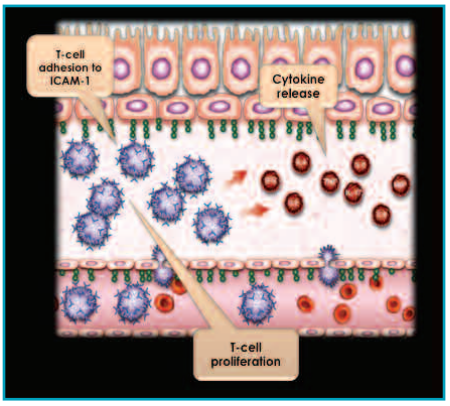


Figure 3. Interaction between LFA-1, a cell surface protein found on leukocytes, and ICAM-1, which is expressed in corneal and conjunctival tissues, is central to the formation of immunological synapses.

Image courtesy of Francis S. Mah, MD

Types of Dry Eye Disease

An etiopathogenic classification of dry eye divides the disease into 2 main types: aqueous tear deficient and evaporative.[22] Aqueous tear-deficient dry eye is further divided into Sjögren syndrome and non-Sjögren syndrome dry eye, of which the latter is more common. An age-related increase in pathology of the lacrimal gland ducts leading to obstruction, and ultimately lacrimal gland dysfunction, is 1 cause for non-Sjögren syndrome

dry eye.[1] An age-related decline in androgen levels may also be involved, and that concept is supported by clinical evidence that androgen receptor blockade leads to dry eye symptoms.[22]

Sjögren syndrome is caused by autoimmune destruction of the lacrimal glands. Salivary glands and other organs are also affected by this exocrinopathy that occurs predominantly in women.[1,25]

Evaporative dry eye is more common than aqueous-deficient disease, and MGD is considered the leading cause of evaporative dry eye.[17,26] Meibomian gland dysfunction is caused primarily by obstruction of the meibomian gland terminal ducts, with thickened opaque meibum containing keratinized cell material. Hyperkeratinization of the ductal epithelium and increased meibum viscosity contribute to the obstruction that ultimately may lead to intraglandular cystic dilation, meibocyte atrophy, and meibomian gland dropout.

By compromising the quality and quantity of the tear film's lipid layer, MGD leads to increased tear evaporation, even with normal aqueous tear production, and results in increased tear electrolyte concentrations. The electrolyte changes are responsible for pathologic changes in goblet cell density and corneal epithelial glycogen levels. Increased electrolyte concentration in the tear film also increases levels of polar lipids in the lipid layer, causing rupture of the tear film.

Clinical Implications

Understanding the pathophysiology of dry eye provides a foundation for a rational approach to evaluation and treatment. The diagnostic evaluation must consider the presence of aqueous-deficient disease and evaporative disease as well as inflammation. Then, optimal management of dry eye should aim to restore an environment that will promote ocular surface healing and support its ongoing health. Such a strategy necessitates eliminating the underlying cause, whenever possible, and targeting inflammation.

Update on Diagnosis and Treatment of Dry Eye Disease: Current and Emerging Approaches

Marjan Farid, MD

Evidence-based guidelines for the diagnosis and treatment of dry eye disease are available from several groups, including DEWS, the American Academy of Ophthalmology (AAO) Preferred Practice Patterns, and the International Workshop on MGD.[21,27,28] Information continues to emerge, new diagnostic systems have been introduced, and new therapies are in development. As such, an update of the DEWS report is in development.[29]

Current techniques for diagnosing dry eye include traditional tests and newer point-of-care modalities. The traditional tests, which provide some clues as to the type of dry eye and severity, include tear breakup time (TBUT), ocular surface staining with vital dyes (lissamine and fluorescein), the Schirmer test, and slit-lamp biomicroscopic evaluation of the ocular surface and lid margin. Newer point-of-care tests that include tear film osmolarity, tear film matrix metalloproteinase-9 (MMP-9) assay, lipid layer interferometry, and meibography provide more objective diagnostic information than the traditional tests and, therefore, a scientific basis for treatment decisions.

Historically, and even often today, the trigger for initiating the diagnostic evaluation for dry eye has been patient complaints of disease-related symptoms, which include burning, redness, foreign body sensation, or ocular fatigue. Considering data showing that 40% to 50% of patients with dry eye have tear film abnormalities in the absence of classic symptoms, this reactive approach of evaluating only symptomatic patients risks leaving a large proportion of patients with dry eye undiagnosed.[30,31]

It is important for clinicians to recognize the potential for lack of correlation between signs and symptoms of dry eye and to be proactive in their diagnostic efforts. In particular, evaluation for dry eye should be considered in all patients presenting for cataract or refractive surgery. Training technicians to ask a few screening questions and empowering them to undertake diagnostic testing when appropriate, on the basis of a patient's responses, can improve the detection of dry eye. This approach also improves workflow efficiency, considering that 2 of the newer diagnostic tests—tear film osmolarity and MMP-9—need to be done before the eye is exposed to any medication, vital dyes, bright lights, or direct contact.

Tear film osmolarity testing analyzes a 50-nL tear sample. A result of >308 mOsms/L in either eye or a >10 mOsms/L intereye difference is considered diagnostic for dry eye.[32,33] The actual osmolarity level is an indication of disease severity, and therefore helps guide treatment decisions based on the available guidelines.[32,33] Tear film osmolarity is also useful for monitoring response to treatment. This test does not, however, help determine disease etiology because elevated osmolarity can be a feature of both aqueous-deficient and evaporative dry eye. In addition, tear film osmolarity values are subject to fluctuation and may overlap between normal eyes and those of patients with dry eye.[34] Tear film osmolarity values, therefore, need to be evaluated within the context of symptoms and other signs of dry eye.

MMP-9 testing determines if there is an elevated level of this inflammatory marker in the tear film. A positive result (MMP-9 concentration ≥40 ng/mL) is identified by the appearance of a red line in the result window.[35] A future version of this test may display the actual MMP-9 concentration. Anecdotally, a red line that develops relatively quickly (users should allow 10 minutes for the analysis to complete), is darker in hue, or is thicker in width using the currently available test suggests a higher concentration of MMP-9 and, hence, more severe inflammation.

A positive MMP-9 test is not specific for dry eye and should be considered in the context of other findings. When accompanied by other evidence of dry eye, a positive MMP-9 test should be a trigger for initiating appropriate anti-inflammatory treatment. Response to treatment for dry eye can be evaluated by repeating the MMP-9 test after 1 month.

Lipid layer interferometry assesses the thickness of the tear film lipid layer. Because of the potential for dilution or alteration of baseline tear lipid status, patients should avoid using any drops in their eyes or any cosmetics or personal care products around the eyes on the day of testing. The same device used for interferometry also features high-resolution infrared meibography. The meibography images allow assessment of meibomian gland architecture and atrophy, enable correlation between gland structure and function, and are a useful educational tool to use when counseling patients about their disease. Another available multifunctional platform for meibography also provides topography and measurements of the tear meniscus, ocular redness, TBUT, and tear breakup location.

In-office questionnaires, such as OSDI (Ocular Surface Disease Index) and SPEED (Standard Patient Evaluation of Eye Dryness), are very useful in the evaluation of patients for dry eye. In addition, there is a newer, in-office blood test for diagnosing Sjögren syndrome that may detect this autoimmune condition earlier than the standard test and thereby allow timely referral of patients to a rheumatologist's care. Two additional assays measure lactoferrin/immunoglobulin E and lysozyme, but generally have value only for clinical research.

Treatment

The modalities used for treating dry eye are based on various strategies and include agents acting to lubricate the ocular surface, reduce inflammation, or target relief of obstructed meibomian glands, along with nutritional supplements, autologous serum, and other adjunctive measures (Table 2).

Table 2. Treatments for Dry Eye

Lubricants
- Emulsions
- Gels
- Ointments
- Sustained release

Nutrition
- Essential fatty acids

Anti-inflammatory agents
- Topical cyclosporine
- Topical corticosteroids
- Oral doxycycline, minocycline

Autologous serum

Lid margin disease management
- Manual
- Mechanical
- Intense pulsed light

Adjuncts
- Punctal occlusion
- Contact lenses
- Environmental (external milieu) and systemic medication modifications

Ocular lubricants are a mainstay in managing all dry eye, and these products are available in a variety of formulations. Lipid-containing products should be considered in managing MGD. Thicker gels and ointments can provide more durable benefit, but may be particularly reserved appropriate for nighttime use because of their persistence and potential to cause blur. A hydroxypropyl cellulose gel insert that is placed into the inferior fornix can provide sustained lubrication for up to 24 hours.

Ocular lubricants are often used as a first-line agent for managing dry eye, but their effect is palliative rather than therapeutic. More aggressive intervention should be considered for any patient who remains symptomatic while using artificial tears 2 to 3 times a day.

Treatment directed at lid margin disease has traditionally involved the use of warm compresses and digital lid massage. Newer approaches include various commercially available lid scrubs as well as in-office techniques and technologies for opening clogged meibomian glands. Comprising the latter options are devices that apply heat alone or, combined with mechanical pulsation, use of intense pulsed light with manual gland expression and invasive orifice penetration with intraductal probing.[28,36-40]

There are also several anti-inflammatory agents used in the management of dry eye. Approved in December 2002, topical cyclosporine A 0.05% emulsion is the only medication in this category with a specific indication for dry eye. By inhibiting T-cell activity, cyclosporine decreases levels of inflammatory cytokines, and it has been demonstrated in clinical trials to increase tear volume, increase goblet cells, decrease corneal staining, and minimize artificial tear use compared with artificial tears as the control.[41] Treatment benefit with topical cyclosporine may not be realized for a few months, depending on the end point, but accrues with ongoing use.[41] Burning and stinging were the most common side effects associated with topical cyclosporine in the pivotal trials.[41] These side effects dissipate as the condition of the ocular surface improves with continued treatment, but they may cause some patients to prematurely stop using topical cyclosporine.

Compared with cyclosporine, topical corticosteroids provide a faster onset of benefit. Their use over a longer term, however, is generally limited by treatment-related side effects that include intraocular pressure (IOP) elevation, cataract, and risk for infection. Thus, corticosteroid treatment for dry eye may be best used as rescue treatment, pulsed dosing during symptom exacerbation, and as an adjunct when initiating cyclosporine to hasten reduction of inflammation and improve cyclosporine tolerability.[42]

Oral tetracyclines are also used in the management of dry eye because of their anti-inflammatory properties. In addition, at higher doses, oral tetracyclines have antibacterial effects, resulting in a reduction of bacterial lid flora and bacteria-produced exocytotoxins and lipolytic enzymes that cause breakdown of meibomian lipids.[28] According to their activity profile, tetracyclines may be particularly helpful for patients with concomitant rosacea or recurrent staphylococcal marginal keratitis.

Typically, oral doxycycline for the treatment of MGD is administered in doses of 50 to 100 mg twice daily, and it may be prescribed in a pulse regimen of 2 months on with 6 months off. One study found that in patients with chronic MGD, doxycycline 20 mg twice daily was as effective as 200 mg twice daily for improving TBUT, Schirmer test scores, and symptoms, but the lower dose was better tolerated.[43] Side effects of oral tetracyclines include gastrointestinal upset, photosensitivity, and risk for vaginal yeast infections in women.

Lifitegrast is a first-in-kind investigational anti-inflammatory treatment for dry eye. It acts as an integrin inhibitor, preventing binding of LFA-1 to ICAM-1, thereby interfering with T-cell recruitment and activation and the release of inflammatory cytokines.[44] It was investigated in 3 double-masked phase 3 studies, OPUS-1, OPUS-2, and OPUS-3, that randomized patients to treatment with lifitegrast 5.0% or placebo for 84 days.[45-47]

In OPUS-1, lifitegrast met its coprimary end point, demonstrating statistically significant superiority to placebo for reducing the sign of inferior corneal staining ($P=.0007$); in secondary end point analyses, reduction of superior cornea ($P=.0392$), total cornea ($P=.0148$), nasal conjunctival ($P=.0039$), and total conjunctival staining ($P=.00086$) were also significantly greater with lifitegrast than with placebo (Figure 4).[45] However, lifitegrast did not meet the symptom coprimary end point (visual-related OSDI function subscale score) ($P=.7894$).[45]

In OPUS-2, which required patients to meet a minimum symptom severity score for enrollment, lifitegrast-treated patients had a significantly greater improvement in eye dryness score (symptom coprimary end point) ($P<.0001$) and other symptom-related secondary end points (ocular discomfort [$P=.0005$] and eye discomfort [$P<.0001$]) compared with placebo (Figure 5).[46] Lifitegrast did not meet the coprimary end point investigating superiority for reducing the sign of inferior corneal staining ($P=.6186$).[46] OPUS-3 results, not yet published, corroborated the efficacy of lifitegrast for significantly improving symptoms, as measured by the eye dryness score as well as other symptoms, and the effect was seen rapidly by day 14.[47]

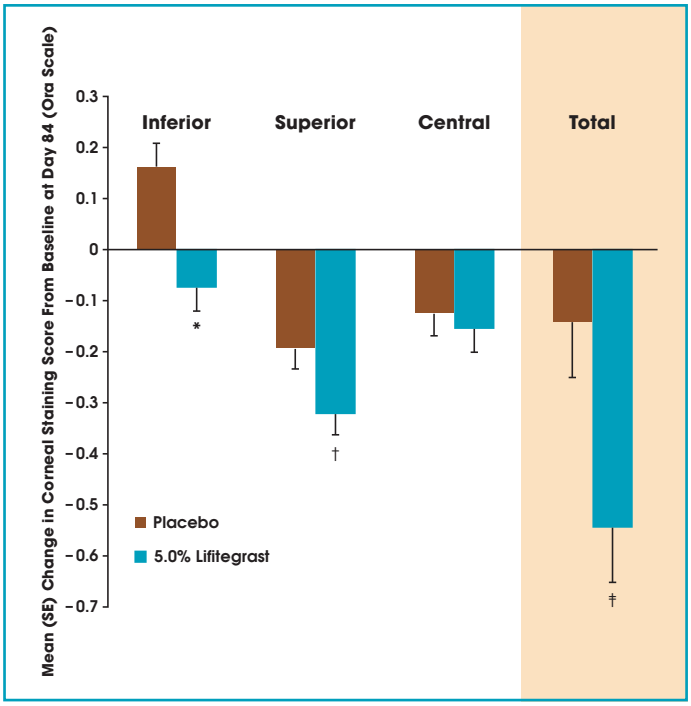


Figure 4. Change from baseline to day 84 in corneal fluorescein staining scores in the placebo and lifitegrast groups in OPUS-1.

Abbreviation: SE, standard error.

* $P = .0007$
† $P = .0392$
‡ $P = .0148$

Adapted from Sheppard JD, et al.[45]

In the clinical trials, the most frequently reported ocular adverse effects associated with lifitegrast treatment were mostly transient and mild, occurred primarily with the first dose, and included instillation site burning, reduced visual acuity, and dysgeusia.[45-47] There were no serious ocular adverse events.

Other promising and novel therapies are also in clinical development and should improve our capability to effectively manage dry eye (Table 3).[48,49] In the meantime, clinicians need to think about a paradigm shift in their approach to dry eye diagnosis and management. Keeping in mind that dry eye is a progressive, inflammatory disease that is easier to treat when management is initiated at an earlier stage, a diagnostic evaluation should be undertaken regardless of symptoms and using conventional and newer modalities to determine the type of dry eye along with the presence of inflammation in order to guide appropriate treatment.

Table 3. Investigational Approaches for Management of Dry Eye[48,49]

Anti-inflammatory agents
- Novel cyclosporine formulations
- Novel corticosteroid formulations (dexamethasone intracanalicular depot, loteprednol etabonate mucus penetrating particle technology)
- Cis-urocanic acid (Janus N-terminal kinase signaling inhibitor)
- Integrin inhibitor

Artificial tears
- Hyaluronic acid and F6H8 based

Other
- MIM-D3 (tropomyosin receptor kinase A receptor agonist/nerve growth factor mimetic)
- SkQ1 (antioxidant reactive oxygen species scavenger)
- RGN-259 (thymosin beta-4 antagonist)
- Intranasal neurostimulatory device

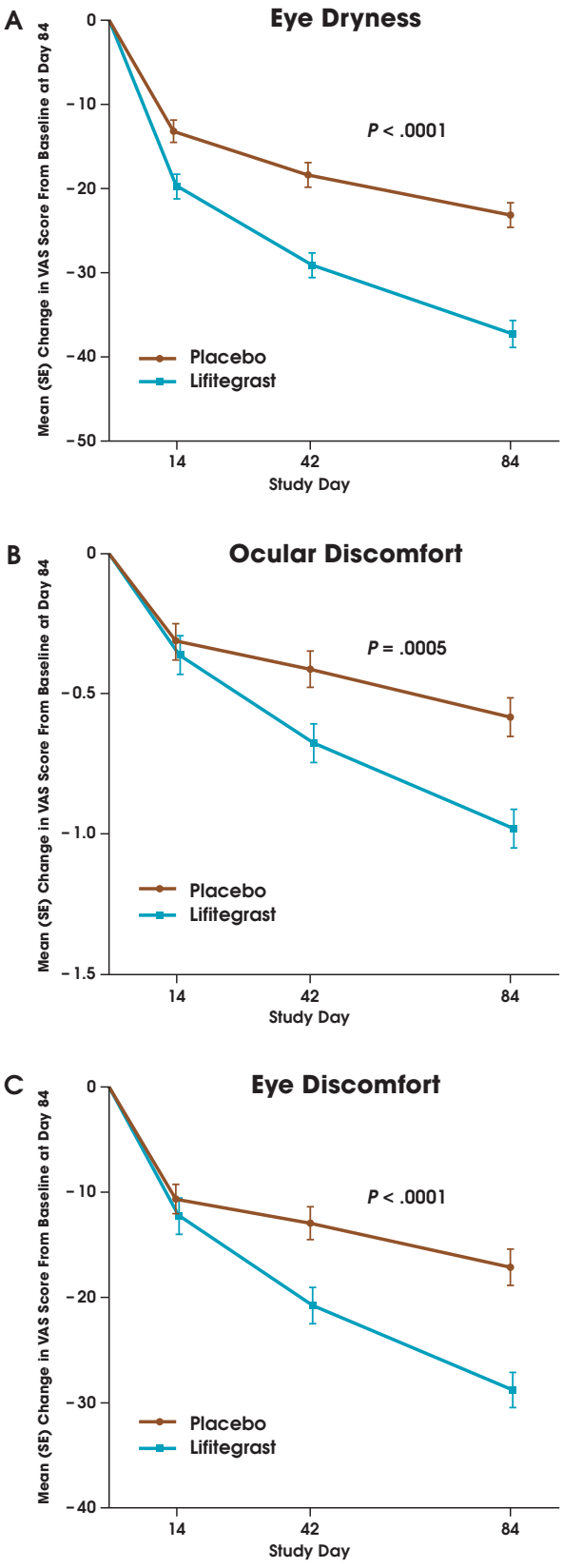


Figure 5. Change from baseline to day 84 in symptom scores in the placebo and lifitegrast groups in OPUS-2. Eye dryness was a coprimary end point.

Abbreviations: SE, standard error, VAS; visual analogue scale.

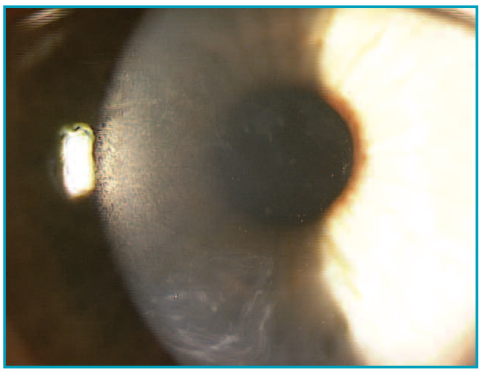
Adapted from Tauber J, et al.[46]

Case 1

From the Files of Elizabeth Yeu, MD

A 57-year-old morbidly obese woman presents with "blurred vision" that she says improves with significant blinking. She has no pain, irritation, or foreign body sensation. She is taking 12 medications, including metoprolol, valsartan, oxycodone, gabapentin, and fluoxetine. On examination, she has trace punctate epithelial keratopathy (PEK); normal meibum expression; TBUT 0 seconds; tear osmolarity 318/321 mOsms/L OD/OS; and negative MMP-9. The corneal examination shows epithelial basement membrane dystrophy (EBMD) (Figure 6A), and the topography image is consistent with that diagnosis (Figure 6B).

A



B

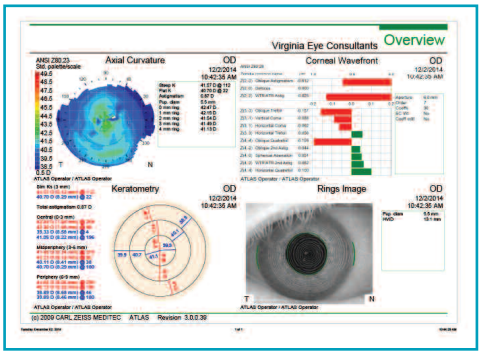


Figure 6. EBMD seen on slit-lamp image (A) leads to smudgy and irregular mires on the topographic image (B).

Images courtesy of Elizabeth Yeu, MD

Dr Yeu: The axial map and the Placido disk images of topography can be very insightful for diagnosing ocular surface disease. Irregular astigmatism, steep or flat islands, and/or missing spots on the axial map can be indicative of an epithelial irregularity induced by dry eye or, in this case, EBMD.

What would you select first to treat this patient?

Dr Holland: First, I would determine if the EBMD is within the visual axis. If it is, and because the patient's chief complaint relates to her vision, I would treat the EBMD first by performing superficial keratectomy. Her elevated tear osmolarity and abnormal TBUT indicate MGD, and I therefore would also recommend artificial tears and initiate an omega-3 fatty acid supplement.

If, however, impaired healing is expected on the basis of the patient's MGD severity and comorbidities, I would optimize the ocular surface before keratectomy. I would consider adding topical azithromycin and/or low-dose oral doxycycline 50 mg/d. With advanced untreated MGD, the patient could be at risk for slow healing of her epithelium and developing haze and scarring, with loss of best corrected visual acuity (BCVA) after the keratectomy.

Dr Farid: I agree with that approach, and I would also use autologous serum.[50] In my experience, autologous serum can provide additional nutritional/trophic support in cases in which corneal pathology reveals an unstable epithelium.

In EBMD, however, the wave pattern in the basement membrane may shift over time. Therefore, if the patient is willing to wait, she can be observed to see if her vision improves without intervention.

Dr Yeu: Even if it is not centrally located, EBMD can cause blurry and fluctuating vision, and it can also exacerbate dry eye. It can also mimic other symptoms of dry eye, including foreign body sensation and dull/sharp pain. The symptoms may be mitigated by medical management, but the definitive treatment for EBMD is a superficial keratectomy, with possible phototherapeutic keratectomy, particularly if recurrent erosions are present.

Case 2

From the Files of Terry Kim, MD

A 75-year-old white female complains of worsening vision, particularly when reading or watching television. She was previously diagnosed with dry eye and has been using artificial tears and topical cyclosporine for several years. The examination findings are the following: tear osmolarity 305/317 mOsms/L OD/OS; positive MMP-9 OU; BCVA 20/50 OD; 20/40 OS; 1+ telangiectasia at the lid margin; no meibum on expression; 1-2+ central PEK OU; and 3+ nuclear sclerotic cataract OU.

Dr Kim: What is your interpretation of the osmolarity results and what are your thoughts about the inability to express meibum?

Dr Farid: The osmolarity is abnormal because of the >10 mOsms/L intereye difference. The absence of meibum could be due to severe stasis or gland atrophy. Applying sustained pressure can help to differentiate between the 2 causes because even if there is severe stasis, it is usually possible to express some meibum if there are some functioning glands. Meibography can also be extremely valuable in looking for gland atrophy.

Dr Yeu: Would you proceed to surgery?

Dr Kim: No, because we know that existing ocular surface disease can affect cataract surgery outcomes in multiple ways, including reduced reliability of IOL power calculations. A recent study showed that tear film hyperosmolarity was associated with increased variability of the keratometry measurements used for determining spherical IOL power and toric IOL planning.[12]

Dr Kim: What are possible explanations for the MMP-9 test remaining positive after long-term treatment with topical cyclosporine?

Dr Mah: It may be due to poor compliance with the medication. The patient in this case, however, has MGD that was not being specifically addressed by cyclosporine.

Dr Kim: This was my patient, and at her initial visit, she appeared to be a candidate for toric IOL surgery based on keratometry showing cylinder of -1.90 D at 10° (Figure 7). She was started on treatment for MGD, and biometry 2 months later showed cylinder of -0.89 D at 172°. She underwent implantation of a non-toric aspheric IOL and did very well (Figure 7).

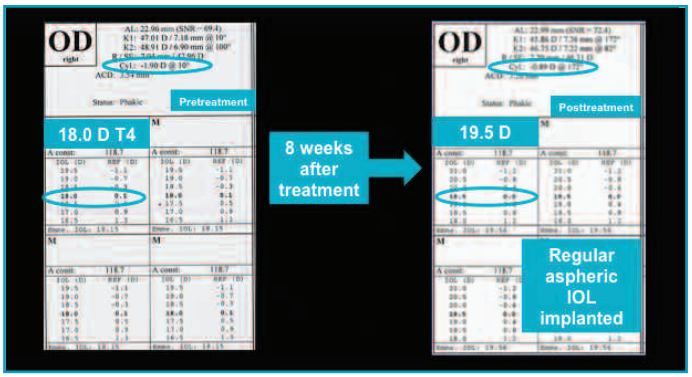


Figure 7. Results from biometry before and after treatment for MGD. Note the marked change in IOL power as well as the change from a toric IOL to an aspheric non-toric monofocal IOL based on the reduction of cylinder after treatment.

Images courtesy of Terry Kim, MD

Case 3

From the Files of Terry Kim, MD

A 74-year-old man is significantly dissatisfied after bilateral cataract surgery with multifocal IOL implantation performed by another surgeon. Distance uncorrected visual acuity is 20/40. He says he has to limit nighttime driving because of his vision and that he cannot see in low-lighting conditions.

Examination shows 3+ inferior/central PEK; well-centered IOLs with no posterior capsule opacification; normal macular OCT; tear osmolarity 324/336 mOsms/L OD/OS; positive MMP-9 OU; moderate-severe corneal staining; TBUT 6 seconds; inspissated meibomian glands; and dropout of mires and cylinder on topography (Figure 8).

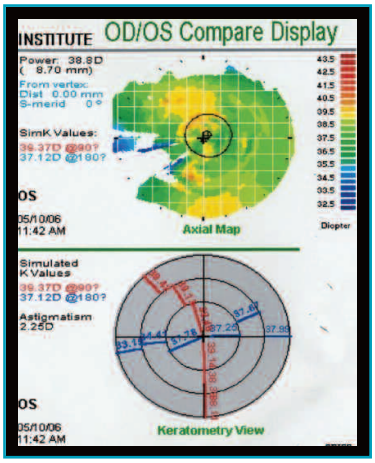


Figure 8. Note the pattern of irregular astigmatism as well as the area of dropout in the 8-o'clock region on the topography map (top), indicating an abnormal ocular surface.

Image courtesy of Terry Kim, MD

Dr Yeu: How would you treat this patient?

Dr Holland: This patient has mixed aqueous-deficient and evaporative/MGD dry eye. I would be very aggressive with regard to treatment because he is so unhappy with his current situation. In my clinical experience, the response to cyclosporine may be less optimal in older individuals, which may be explained by age-related atrophy of the lacrimal glands. Therefore, I would start this patient on a corticosteroid as anti-inflammatory treatment and would choose loteprednol because of its reduced potential to elevate IOP.[51] I would also start him on an omega-3 fatty acid supplement, doxycycline, and topical azithromycin as well as consider thermal pulsation treatment of the lid margin.

Dr Yeu: In-office treatments targeting the meibomian gland would also be helpful in this patient, and perhaps a self-retaining amniotic membrane, which has been shown to improve the ocular surface in moderate-to-severe dry eye.[52]

Dr Holland: It is most likely that this patient had significant dry eye before his cataract surgery which was not diagnosed because he did not present with symptomatic complaints. Once patients develop corneal staining, they have had long-standing dry eye and may have neurotrophic changes that explain their lack of symptoms of pain and discomfort. In addition, visual effects of dry eye can be masked by the presence of cataract. Once the cataract is removed, vision problems related to dry eye can emerge. This is not an uncommon scenario.

Dr Yeu: What type of patient counseling is necessary in this situation?

Dr Mah: Such patients should be told about the need to address the ocular surface before moving ahead with surgery. I will tell them that, with treatment for their ocular surface disease, they may start seeing better even before the procedure and will see much better after the cataract surgery than if they did not have treatment to improve their ocular surface. Because the surgery can exacerbate dry eye, I also counsel them about the need for continuing their prescribed management postoperatively.

Dr Farid: This case highlights the need for a paradigm shift in approaching dry eye diagnosis. Although today, patient complaints are still the driving factor for evaluation, symptoms may actually be absent in patients with more severe disease. If cataract surgeons are not proactive about looking for dry eye preoperatively, these patients will be missed and are likely to be unhappy with their postoperative vision.

Key Learning Points

- Dry eye is a common and commonly underdiagnosed progressive disease affecting vision, quality of life, and outcomes of cataract or refractive surgery.
- Clinicians must be proactive in their approach to diagnosing dry eye because it may be asymptomatic or present with symptoms that are not classic, such as fluctuating and/or blurred vision.
- Diagnosis should include lid margin evaluation, given that MGD is a leading cause of dry eye.
- New, objective point-of-care tests are a useful adjunct for diagnosing dry eye and guiding management.
- Multiple triggers for dry eye act to affect tear film quality and/or quantity, ultimately resulting in ocular surface damage and immune-based inflammation.
- Management of dry eye should consider the type of disease (aqueous deficient and/or evaporative) and include stabilizing the tear film and addressing inflammation.
- Dry eye and its related inflammation should be treated before proceeding with cataract or corneal refractive surgery.
- Lifitegrast is an investigational topical treatment for dry eye with an anti-inflammatory mechanism that has demonstrated efficacy for improving the signs and symptoms of dry eye.
- Other emerging treatments based on novel formulations of current modalities or new mechanisms of action hold promise for further improving patient care.

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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 **http://www.tinyurl.com/DryEyeCME**.

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

1. The most common cause of evaporative dry eye is:
   A. Age-related lacrimal gland obstruction
   B. Decreased estrogen in postmenopausal women
   C. Meibomian gland dysfunction
   D. Sjögren syndrome

2. According to published studies, what percentage of patients with dry eye may lack classic symptoms?
   A. 20% to 30%
   B. 30% to 40%
   C. 40% to 50%
   D. 50% to 60%

3. Inflammation in dry eye is associated with increased expression of the _____ molecule in conjunctival and lacrimal tissues.
   A. ICAM-1
   B. Rho kinase
   C. Tumor necrosis factor-alpha
   D. Vascular endothelial growth factor

4. The tear film MMP-9 assay is:
   A. Specific for diagnosing dry eye
   B. More sensitive than the standard antibody test for diagnosing Sjögren syndrome
   C. Positive if the level of MMP-9 in the tear film is >10 ng/mL
   D. Useful for diagnosis of dry eye and monitoring response to treatment

5. Elevated tear osmolarity (>308 mOsms/L):
   A. Has been associated with variability of keratometry measurements
   B. Indicates the presence of inflammation
   C. Is specific for aqueous-deficient dry eye
   D. Is specific for evaporative dry eye

6. Which of the following is not an in-office approach for relieving meibomian gland obstruction?
   A. Intense pulsed light treatment with manual gland expression
   B. Invasive orifice penetration with intraductal probing
   C. Radiofrequency microneedling with manual gland expression
   D. Warming with mechanical pulsation

7. What is the mechanism of action of lifitegrast?
   A. Directly stimulates mucin secretion by conjunctival goblet cells
   B. Directly stimulates lacrimal gland function
   C. Limits T-cell–mediated inflammation by preventing LFA-1 and ICAM-1 binding
   D. Promotes ocular surface repair by inhibiting T-cell migration and proliferation

8. Results of the OPUS-3 study investigating topical lifitegrast 0.05%:
   A. Confirmed results from OPUS-1, showing lifitegrast was significantly superior to placebo for improving inferior corneal staining
   B. Confirmed results from OPUS-1, showing lifitegrast was significantly superior to placebo for improving the visual-related OSDI function subscale score
   C. Confirmed results from OPUS-2, showing lifitegrast was significantly superior to placebo for improving eye dryness score
   D. Demonstrated a reduction of corneal staining within 14 days of treatment

9. A patient presents with complaints of mild ocular discomfort and itching. An evaluation for dry eye shows limited corneal staining, mildly altered meibum on lid expression, no meibomian gland dropout on meibography, negative MMP-9, and tear osmolarity 314 mOsms/L OD, 312 mOsms/L OS. Which of the following treatment regimens might be considered appropriate for this patient?
   A. Lid hygiene, artificial tears, and oral doxycycline 100 mg twice daily
   B. Lid hygiene, artificial tears, and oral omega-3 fatty acid supplementation
   C. Lid hygiene, artificial tears, and a pulsed topical corticosteroid
   D. Lid hygiene, topical corticosteroid (2 weeks), and topical cyclosporine

10. A patient with dry eye with elevated tear film osmolarity and a positive MMP-9 test is eager to have cataract surgery as soon as possible. Which treatment strategy would you recommend?
    A. Artificial tear ointment with oral doxycycline 200 mg twice daily
    B. Preservative-free artificial tears with punctal occlusion
    C. Topical cyclosporine A with artificial tears
    D. Topical corticosteroid with artificial tears

Activity Evaluation/Credit Request

Original Release: March 1, 2016
Last Review: January 29, 2016
Expiration: March 31, 2017

Clinical Perspectives: Addressing Unmet Needs in Dry Eye Disease

Proceedings from a CME Symposium During AAO 2015

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. Mail or Fax this completed page to **New York Eye and Ear Infirmary of Mount Sinai**–ICME, 310 East 14th Street, New York, NY 10003 (Fax: 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 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.*

Learner Disclosure: To ensure compliance with the US Centers for Medicare and Medicaid Services regarding gifts to physicians, **New York Eye and Ear Infirmary of Mount Sinai** Institute for CME requires that you disclose whether or not you have any financial, referral, and/or other relationship with our institution. **CME certificates cannot be awarded unless you answer this question.** For additional information, please call NYEE ICME at 212-979-4383. Thank you.

❑ 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 evaluate dry eye disease using at least one objective test, regardless of symptom severity	5	4	3	2	1
• Describe the implications of inflammation in dry eye disease on diagnosis and treatment approaches	5	4	3	2	1
• Apply evidence-based approaches for the treatment of dry eye disease	5	4	3	2	1
• Describe clinically relevant results for emerging treatments of dry eye disease	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. 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

5. 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