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IMPROVING DIAGNOSIS, TREATMENT,
AND MANAGEMENT OF
DRY EYE DISEASE
IN THE 21ST CENTURY

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FACULTY

Kelly K. Nichols, OD, MPH, PhD, FAAO (*Chair*)

Paul M. Karpecki, OD, FAAO

Blair Lonsberry, MS, OD, MEd, FAAO

Katherine M. Mastrota, MS, OD, FAAO, Dipl ABO

COPE approved for 2.0 credits for optometrists
COPE Course ID: 54992-AS
COPE Course Category: Treatment & Management of Ocular
Disease: Anterior Segment (AS)



Administrator

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CONTENT SOURCE

This continuing education (CE) activity captures content from an expert roundtable discussion held on March 24, 2017.

ACTIVITY DESCRIPTION

Dry eye disease (DED) is a common condition that is important to recognize and treat because of its potential to affect vision, ocular and contact lens wear comfort, ocular surgery outcomes, and quality of life. Dry eye disease, however, is also underdiagnosed and undertreated. The purpose of this activity is to present approaches that optometrists can easily adopt into daily practice to improve detection and management of DED.

TARGET AUDIENCE

This educational activity is intended for optometrists.

LEARNING OBJECTIVES

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

- Diagnose DED using at least 1 objective test regardless of symptom severity
- Describe the implications of inflammation in DED on diagnosis and treatment approaches
- Discuss the safety and efficacy of anti-inflammatory treatment for patients with dry eye
- Select appropriate dry eye treatment according to individual patient characteristics

ACCREDITATION STATEMENT

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Administrator: **MedEdicus**

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FACULTY

Kelly K. Nichols, OD, MPH, PhD, FAAO *(Chair)*

Dean

Professor, Department of Optometry and
Vision Science

University of Houston College of Optometry

University of Alabama at Birmingham

School of Optometry

Birmingham, Alabama

Paul M. Karpecki, OD, FAAO

Director, Cornea and External Disease

Kentucky Eye Institute

Gaddie Eye Centers

Lexington, Kentucky

Blair Lonsberry, MS, OD, MEd, FAAO

Professor of Optometry

Pacific University College of Optometry

Portland, Oregon

Katherine M. Mastrota, MS, OD, FAAO, Dipl ABO

Director of Optometry

New York Hotel Trades Council/Hotel Association
of New York City, Inc

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New York, New York

IMPROVING DIAGNOSIS, TREATMENT, AND MANAGEMENT OF

DRY EYE DISEASE

IN THE 21ST CENTURY

PREVALENCE

Dr Nichols: Findings from surveys and epidemiologic studies show that dry eye disease (DED) affects tens of millions of Americans and that its prevalence is higher in women than in men and increases with age.^{1,2} The prevalence of DED reported in various studies, however, depends on the recruited population and the criteria used to define DED. Most data on DED prevalence in the United States come from studies that were conducted 10 to 20 years ago and included adults aged 48 years and older.¹ Considering your recent experience, are you noticing any trends in the number or type of patients you are seeing with DED?

Dr Karpecki: Compared with when I started my dry eye clinic in 1997, I am not seeing any real difference in recent years in the proportions of patients who present with Sjögren syndrome–related or other forms of aqueous-deficient DED. The overall number of patients with DED seems to be increasing, however, and I believe this is partly because of increased awareness of the disease among patients and referring eye care practitioners and because of better diagnostic tests. When I started my DED clinic, new patients calling in for a first appointment could be seen within 1 to 2 weeks. Now there is a wait of up to 4 months.

Dr Nichols: Because Dr Karpecki has a dedicated dry eye clinic, many of the patients he sees are referrals who have already been diagnosed with DED. Dr Lonsberry and Dr Mastrota, have you noticed any trends in your primary care practices in the type or number of patients being diagnosed with DED?

Dr Lonsberry: I am seeing more younger patients with DED. This reflects the increased use of computers, smartphones, and other digital screen technologies and their association with DED.^{3,4} Many of these patients are in their 20s, but I have even seen some teenagers with DED related to digital screen use. These individuals generally present with contact lens–related complaints and most often report lens discomfort that develops by the middle of their day. They sometimes describe dryness, irritation, fluctuating vision, and increased use of drops for comfort.

Dr Mastrota: Our optometry service operates within a multidisciplinary health care delivery system, so we are cognizant of trends in the number of patients presenting with various medical comorbidities. The prevalence of DED related to a growing number of patients with conditions that are risk factors for DED is increasing. These risk factors include diabetes, asthma, allergies, and the use of a continuous positive airway pressure machine for sleep apnea.⁵⁻⁷

DEFINITION AND PATHOPHYSIOLOGY

Dr Nichols: The definition of DED from the first Dry Eye WorkShop (DEWS), sponsored by the Tear Film & Ocular Surface Society in 2007, reflected understanding that DED was a condition characterized by tear film instability and ocular surface damage and recognized the pathophysiologic roles of inflammation and tear film hyperosmolarity.⁸ A decade later, DEWS II developed an updated definition of DED that expands on previous understanding to include knowledge that neurosensory abnormalities can be part of the etiology and that disruption of tear film homeostasis is a key element. The DEWS II definition of dry eye states that it "is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."⁹

Considering the original definition and reflecting on the new definition, do you think that better understanding of the pathophysiology of DED has altered approaches to treatment?

Dr Mastrotta: I believe so, given that the first DEWS identified DED as an inflammatory disease and therefore brought the importance of addressing inflammation to the forefront, even though inflammation may not always be clinically evident.

Dr Karpecki: The first DEWS definition and report promoted understanding that DED has a multifactorial etiology and that the various triggers cause tear film hyperosmolarity or instability that leads to ocular surface damage and, subsequently, inflammation (Figure 1).⁹ This has been further clarified and enhanced in the new DEWS II definition.⁹

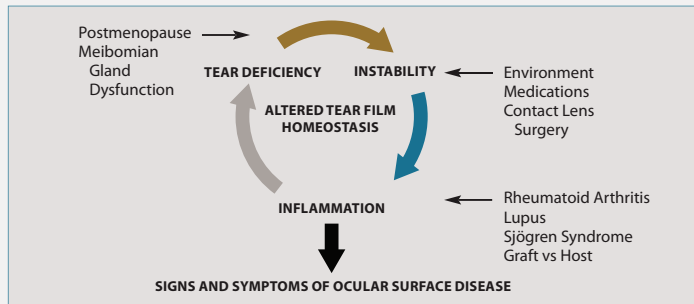


Figure 1. Dry eye disease triggers include multiple endogenous and exogenous factors that affect tear film homeostasis by causing tear deficiency (quality and/or quantity), tear film instability, or inflammation

Image courtesy of Mark S. Milner, MD

Both DEWS and DEWS II reinforced the idea that inflammation, subsequent to or following a hyperosmolar state, is a primary component of the DED pathophysiologic pathway. Therefore, although treatment with artificial tears is helpful for patient comfort, DEWS and DEWS II underscore that effective management for DED must also address the causative factors and the inflammation.^{8,9}

DRY EYE DISEASE DIAGNOSIS

Symptom Assessment

Dr Nichols: I think everyone would agree regarding the importance of eliciting symptoms of DED, which can be done with structured questionnaires or informal questioning. Dr Karpecki, how do you identify symptoms?

Dr Karpecki: In our general practice, we administer either the Standard Patient Evaluation of Eye Dryness (SPEED) Questionnaire (Figure 2)¹⁰ or Dry Eye Questionnaire 5 (Figure 3)¹¹ to all patients as an initial screening tool. Patients whose responses indicate they may have DED and those who present on referral to our dry eye clinic are each administered a more extensive questionnaire that tries to identify all contributing factors. As an informal screening question, however, I think simply asking about the use of drops or the feeling of the need to use drops can be helpful.

Dr Nichols: That is a very good idea because I find that many patients with DED have already bought drops to self-treat before talking to a clinician about their symptoms. In addition, patients who are already using an over-the-counter drop may represent a subset who can be more readily transitioned to other therapies that can provide better results.

I think another useful way to screen for DED is to ask patients if their eyes ever feel uncomfortable. When developing the Dry Eye Questionnaire 5, Begley and colleagues found that asking about the frequency of feeling eye dryness discriminated patients with keratoconjunctivitis sicca from those without the condition.¹² Not everyone identifies with the feeling of dryness, but I think “uncomfortable” or “discomfort” are terms most people can relate to.

SPEED™ QUESTIONNAIRE

Name: _____ Date: ____/____/____

Sex: M F (Circle) DOB: ____/____/____

For the Standardized Patient Evaluation of Eye Dryness (SPEED) Questionnaire, please answer the following questions by checking the box that best represents your answer. Select only one answer per question.

1. Report the type of SYMPTOMS you experience and when they occur:

Symptoms	At this visit		Within past 72 hours		Within past 3 months	
	Yes	No	Yes	No	Yes	No
Dryness, Grittiness, or Scratchiness						
Soreness or Irritation						
Burning or Watering						
Eye Fatigue						

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

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

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

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

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

0 = No Problems 1 = Tolerable - not perfect, but not uncomfortable 2 = Uncomfortable - irritating, but does not interfere with my day 3 = Botherome - irritating and interferes with my day 4 = Intolerable - unable to perform my daily tasks

4. Do you use eye drops for lubrication? YES NO If yes, how often?

Cornea. 2013 Sep;32(9):1204-10
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13-ADV-123 A

For office use only
Total SPEED score (Frequency + Severity) = ____/28

Figure 2. The Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire can be useful as a screening tool for dry eye disease¹⁰

DEQ 5

1. Questions about **EYE DISCOMFORT:**

a. During a typical day in the past month, **how often** did your eyes feel discomfort?

0 Never
1 Rarely
2 Sometimes
3 Frequently
4 Constantly

b. When your eyes felt discomfort, **how intense was this feeling of discomfort** at the end of the day, within 2 hours of going to bed?

Never have it	Not at All Intense					Very Intense
0	1	2	3	4		5

2. Questions about **EYE DRYNESS:**

a. During a typical day in the past month, how often did your eyes feel dry?

0 Never
1 Rarely
2 Sometimes
3 Frequently
4 Constantly

b. When your eyes felt dry, **how intense was this feeling of dryness** at the end of the day, within 2 hours of going to bed?

Never have it	Not at All Intense					Very Intense
0	1	2	3	4		5

3. Question about **WATERY EYES:**

During a typical day in the past month, **how often** did your eyes look or feel excessively watery?

0 Never
1 Rarely
2 Sometimes
3 Frequently
4 Constantly

Score: 1a + 1b + 2a + 2b + 3 = Total
+ + + + =

Figure 3. The Dry Eye Questionnaire 5. A total score > 6 suggests dry eye; testing to rule out Sjögren syndrome may be indicated if the total score is > 12.¹¹

Reprinted from *Contact Lens & Anterior Eye*, Chalmers RL, Begley CG, Caffery B, Validation of the 5-Item Dry Eye Questionnaire (DEQ-5): discrimination across self-assessed severity and aqueous tear deficient dry eye diagnoses, 55-60, Copyright 2010, with permission from Elsevier.

Dr Mastrotta: For research-based examinations, I ask patients to complete the Ocular Surface Disease Index, SPEED, or the University of North Carolina Dry Eye Management Scale.^{10,13,14} But in daily practice, I find it helpful to simply ask patients, “On a scale of 1 to 10, with 10 being unbearable, how much does the feeling of your eyes bother you?” This approach is something that is easily understood, and the answer also provides a metric that can be followed for change over time.

Clinical Examination

Dr Nichols: We know from a number of studies that there can be discordance between DED signs and symptoms.¹⁵⁻¹⁷ In a recent study in which I participated, only 57% of 263 patients who had been diagnosed with DED on the basis of objective signs reported symptoms consistent with DED.¹⁶ What do you include in a basic clinical examination for DED?

Dr Mastrotta: In the examination, as well as through a thorough history, I try to identify conditions that are risk factors for DED or that can produce overlapping symptoms, so that I can make a proper diagnosis and decide on appropriate management (**Table 1**). I evaluate the conjunctiva, including lid eversion, and I look for such things as conjunctivochalasis, scleral show, concretions, and staining of the palpebral, superior, and inferior conjunctiva. Changes of the conjunctiva, such as superior bulbar conjunctival staining, or the presence of concretions in the palpebral conjunctiva are highly suggestive to me of ocular surface pathology.

Table 1. Risk Factors for Dry Eye^{1,4-8,18}

Allergy and Atopy

- Ask about rhinitis, sinus headaches, history of eczema, or other rashes

Contact Lens Wear

Environmental Issues

- Ask about exposure to wind, low humidity, or smoke

Medications

- Ask about use of topical antihistamines, systemic antihistamines, diuretics, or medications with anticholinergic activity

Prior Cataract, Cornea, or Keratorefractive Surgery

Prolonged Computer Use

Rosacea

Sjögren Syndrome

- Ask about dry mouth, dental cavities, oral ulcers, fatigue, joint pain, and presence of other systemic autoimmune diseases

In addition, I assess the lids and lid margins because we know that the vast majority of patients with DED have meibomian gland dysfunction (MGD). According to a study by Lemp and colleagues, 86% of patients with DED had some component of MGD.¹⁹ I perform meibomian gland expression and look for signs of specific causes of lid margin disease, such as rosacea, *Demodex* overpopulation, or any type of dermatitis. In addition, I look for lid contour changes—ectropion or entropion—and abnormalities of the puncta. I also look for changes in eyelash color, shape, length, density, or position. Lash ptosis (**Figure 4**) is a common finding in patients with floppy eyelid syndrome, a condition that is associated with chronic conjunctivitis and ocular surface disease.²⁰

In the examination, I also observe the frequency and completeness of the patient’s blink, and at the slit lamp, I check the tear film for meniscus height and for homogenous tear spreading.

Dr Lonsberry: Before I administer any drops, I measure tear film osmolarity and carefully evaluate the tear prism, making sure not to shine the slit lamp beam into the pupil and thereby potentially eliciting reflex tearing. I assess the lower lid tear prism for quantity and quality of tears. If no tear prism is present, the patient is likely not producing a significant amount of tears, and if the tear prism has a “junky” appearance, then it is likely that the tear film quality is

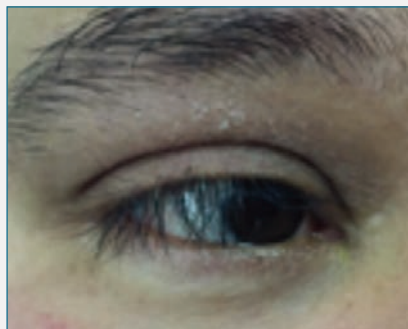


Figure 4. Obvious lash ptosis in a patient with floppy eyelid syndrome (FES). Ocular surface-related complaints are common in patients with FES.

Image courtesy of Katherine M. Mastrotta, MS, OD

poor. I also do fluorescein staining routinely, and I encourage the use of sodium fluorescein rather than products that contain benoxinate because the anesthetic itself can cause staining and interfere with the ability to accurately check tear break-up time (TBUT). After assessing the tear prism, I assess the lids and lid margins and scan the rest of the eye. At that time, I instill the sodium fluorescein to check for staining of the cornea and conjunctiva and assess TBUT.

Dr Karpecki: In my dry eye clinic, by the time I see patients in the examination lane, they have already completed symptom questionnaires, the tear film osmolarity test, meibography, and, often, noninvasive TBUT. Then, I do a careful evaluation at the slit lamp that includes examination of the lashes and lids with meibomian gland expression, assessment of corneal and conjunctival staining using fluorescein and lissamine green, and determination of tear meniscus height and TBUT.

Instrument-Based Diagnostic Testing Tear Film Osmolarity

Dr Nichols: Dr Karpecki and Dr Lonsberry mentioned tear film osmolarity. I am aware that in some practices, tear film osmolarity or some other instrument-based diagnostic test is done routinely to screen for DED as an early detection measure, an attractive practice from the standpoint of prevention. Do you think this approach is becoming more widespread, or is cost a barrier, considering there is no reimbursement if the patient does not have DED?

Dr Lonsberry: Notably, there seems to be a high prevalence of DED in Alaska, a situation probably explained by environmental factors. In the private office in which I practice, tear film osmolarity is measured in anyone who reports DED symptoms, either as a presenting complaint or upon questioning.

Dr Karpecki: I think there is a trend for using tear film osmolarity as a screening tool, although another strategy, which is followed by 1 practice that refers patients to our dry eye clinic, is to use it more selectively according to results of a screening questionnaire. At that practice, all patients complete a validated questionnaire, and only those whose score indicates a positive response undergo further evaluation with tear film osmolarity measurement, meibomian gland expression, and a slit-lamp examination for other signs of DED. I think this is a good model for justifying additional testing and evaluation, but I also think it may be ideal to do osmolarity testing regardless of symptoms because of the discordance between signs and symptoms.

Relying on fluorescein corneal staining as an objective sign of DED is problematic because patients may already have more advanced disease by the time they show corneal epithelial damage.²¹ Tear film osmolarity enables diagnosis of DED at an earlier stage. Studies show that osmolarity distinguishes patients with DED from those without DED, and differentiates between patients with mild/moderate DED and those with severe DED.^{22,23} There appears to be a linear relationship between osmolarity and DED severity (**Figure 5**); an osmolarity value > 308 mOsm/L has been reported to offer good sensitivity as a cutoff for differentiating people with mild/moderate DED from normal controls.^{22,23}

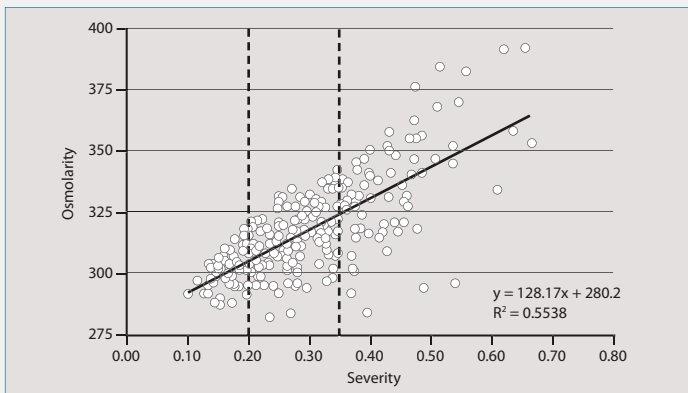


Figure 5. In a study including data from 299 subjects aged 18 to 82 years recruited from the general patient population, the relationship between osmolarity and dry eye disease severity was generally linear throughout the dynamic range. Values for severity of dry eye are based on a composite score using clinical measurements and scaled between 0 (representing the least evidence of disease) and 1 (representing the most evidence of dry eye).²³ Normal, mild/moderate, and severe groups are demarcated by the vertical dashed lines at 0.20 and 0.35.

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As another benefit, tear film osmolarity can help differentiate DED from conditions that can cause similar symptoms. For example, a patient may report ocular discomfort or fluctuating vision, but then is found to have a tear film osmolarity of 287 mOsm/L in both eyes. Because the osmolarity is in the normal range and within 8 mOsm/L between eyes, I know I should be looking for some condition other than DED as the cause of the patient's complaints.

Interferometry and Meibomian Gland Imaging

Dr Lonsberry: Lipid layer interferometry and meibomian gland imaging are also done for patients with DED symptoms (**Figure 6**). The information obtained from meibography is not only useful for making the diagnosis of MGD, but is valuable for helping affected patients understand their disease and the importance of treatment. Furthermore, the meibography findings help guide treatment for MGD because the approach will be different for a patient who has mild disease characterized by gland obstruction from that for a patient with advanced MGD who has extensive gland atrophy.

Dr Karpecki: I think screening with meibography also allows identification of patients with MGD who might otherwise be missed even with meibomian gland expression, and it is useful for documenting change over time and as a teaching tool. Showing patients their meibography images often leads to compliance and selection of effective treatment options, such as thermal pulsation in-office and hydrating compresses at home. Those who at first do not want to proceed with treatment may change their minds at their next visit, 6 or 12 months later, if repeat imaging clearly reveals worsening of their condition, with increased gland atrophy.

Matrix Metalloproteinase-9 Assay

Dr Nichols: In your opinions, what is the role of the matrix metalloproteinase-9 (MMP-9) assay in diagnosing and managing the effectiveness of treatment in DED?

Dr Karpecki: I do not think the assay helps with early diagnosis because patients who have a positive MMP-9 test are likely to already have moderate-to-severe DED.¹⁶ Furthermore, a negative result does not mean inflammation is absent, but only that the MMP-9 concentration in the tear film has not reached the test cutoff, which is ≥ 40 ng/mL.²⁴ The MMP-9 assay is useful, however, for helping me decide how aggressive I should be with anti-inflammatory treatment and when to or when not to consider punctal occlusion. Moreover, it

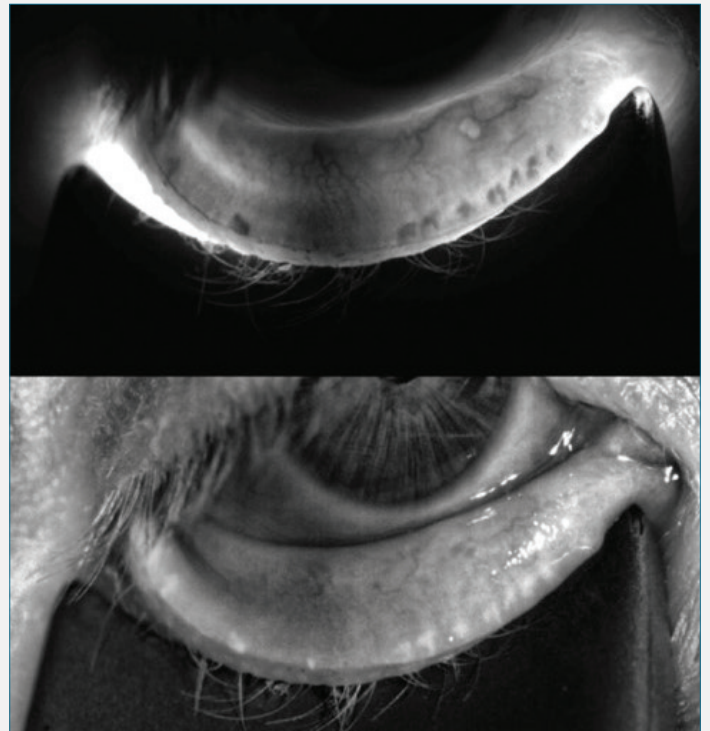


Figure 6. Meibography in a patient with Sjögren syndrome shows advanced meibomian gland atrophy and dropout

Images courtesy of Paul M. Karpecki, OD

helps me differentiate DED from other conditions that are associated with significant inflammation when the patient has a normal osmolarity test.

Dr Mastrotta: I find it very useful to use a 20 diopter lens when reading the MMP-9 results. I find magnification allows identification of a faint, pale pink positive result that otherwise can be easily missed.

Dr Nichols: It is important to remember that a patient might be improving and still have a positive MMP-9 test. Maintaining a treatment course and effective patient communication is paramount.

DRY EYE DISEASE MANAGEMENT

Basic Principles

Dr Nichols: What do you think are some general principles of DED management?

Dr Mastrotta: It is important to identify factors that are triggering or exacerbating DED and to address those that are modifiable. I also consider optimizing lifestyle and general health issues for all patients. In this regard, I encourage a proper diet, smoking avoidance, drinking enough water, and getting enough sleep.

Dr Lonsberry: Artificial tears to provide ocular lubrication are essential for all patients with DED.²⁵ I think it is important to "prescribe" a specific product because otherwise patients are likely to choose the least expensive option or something that is not appropriate, such as a vasoconstrictor to treat red eye. Many good artificial tears are on the market, but, in general, I recommend a lipid-based formulation. I think a lipid-based artificial tear works best for stabilizing the lipid-deficient tear film in people with MGD, and we know that most patients with DED have some component of MGD.¹⁹

Lid Hygiene

Dr Nichols: Lid hygiene with eyelid warming and cleansing is considered a mainstay of management for MGD.²⁶ There are a variety

of techniques for lid hygiene, but in my experience, it is often done suboptimally by patients, if not abandoned completely. What do you recommend for lid hygiene, and how do you promote compliance?

Dr Lonsberry: For eyelid warming, I recommend patients use one of the commercially available products that I know will stay at an adequately high temperature for at least 5 to 6 minutes. A study by Lacroix and colleagues evaluating heat retention of 5 commercially available eyelid warming masks and a washcloth warmed with hot tap water found the temperature of the commercial masks exceeded 40°C within 2 minutes after heating and stayed at that level for 5 minutes.²⁷ The temperature of the washcloth fell below 40°C after 3 minutes.

Dr Karpecki: I also recommend a moist-heat hydrating compress for at-home MGD treatment. For at-home lid hygiene, I recommend patients buy one of the commercially available lid cleansers and apply it while they are in the shower because some of the products require rinsing. I tell patients that after they wash their hands, hair, and body, they should use the product to cleanse their eyelids. None of the products I recommend are very expensive, so there is not much of a financial barrier to using them; this helps with compliance.

Something that I have found works well for encouraging compliance with lid hygiene, especially with asymptomatic patients, stems from the idea that a picture is worth a thousand words. I show patients images of their meibomian glands, either from the slit lamp or meibography, and tell them I see something that concerns me. I use that phrase because it seems to engage patients immediately. Then, I tell them that the consequences of leaving the problem untreated include contact lens intolerance, loss of eyelashes, and progression of disease that can eventually lead to scarring or permanent damage.

Maintaining compliance with lid hygiene long term can be a challenge. To address this problem, I tell patients to pay attention to how their eyes feel immediately after they use the moist hydrating mask, even the very first time. The effect can be remarkable, and reminding patients about it periodically seems to be good motivation for encouraging compliance.

Dr Mastrotta: To promote compliance, I find it is important that patients understand the rationale for lid hygiene and then associate it with some activity that is part of their daily routine. I explain to patients that the lids and lashes harbor environmental debris, allergens, and bacteria that can make the eyes uncomfortable, appear red, and cause contact lens discomfort. I suggest to patients that just as they wash their body, head, and beard when they take a shower, they would benefit from cleaning their lids and lashes. Commercial eye makeup removers may be used in combination with prescription and over-the-counter products specifically designed for lid hygiene.

Nutritional Supplements

Dr Nichols: Dr Mastrotta spoke about paying attention to proper diet. Is there a role for nutritional supplements in DED management?

Dr Lonsberry: I recommend taking an omega-3 fatty acid supplement because omega-3 fatty acids have anti-inflammatory activity, which is important for all patients with DED, and they improve the quality of the meibum, which is important for patients with MGD.^{28,29} A meta-analysis of randomized controlled studies published in 2014 found that omega-3 fatty acid supplementation improved TBUT and Schirmer scores in patients with DED.³⁰ Results from more recent studies also show objective and subjective benefits of omega-3 fatty acid supplementation in patients with DED or MGD.^{28,31} In a study of patients with MGD, Epitropoulos and colleagues found significant benefits vs control (omega-6 fatty acid supplement) for improving tear osmolarity and corneal staining within 6 weeks and a trend for improving TBUT.²⁸ By 12 weeks, there were statistically significant differences between the groups, favoring

omega-3 fatty acid supplementation for improving TBUT, Ocular Surface Disease Index scores, and MMP-9 positivity.

As with artificial tears, there are a lot of omega fatty acid supplements on the market, and, again, I recommend a specific omega-3 supplement to my patients because I have confidence in the product quality.

Dr Karpecki: I have found that products containing the omega-6 fatty acid gamma linolenic acid (GLA) in addition to the omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid are very effective. Gamma linolenic acid is converted to dihomo-linolenic acid, which is a precursor of the anti-inflammatory eicosanoid prostaglandin E1.³² Numerous clinical studies demonstrate benefits of treatment with oral omega-6 fatty acids alone or in combination with omega-3 fatty acids in patients with various forms of DED, including keratoconjunctivitis sicca and DED associated with MGD, photorefractive keratectomy, or contact lens wear.³²⁻³⁸

Dr Mastrotta: I also gravitate toward recommending a particular nutritional supplement that contains a proprietary blend of the omega-6 fatty acid GLA and the 2 omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid because of studies showing that GLA improved symptoms, reduced inflammation, and increased tear production in patients with DED.³³⁻³⁵

Dr Nichols: Are there any safety concerns associated with omega fatty acids?

Dr Lonsberry: There is the potential for increased anticoagulation when an omega-3 fatty acid supplement is taken with warfarin.³⁹ Therefore, I ask patients if they are on an anticoagulant, and I tell those who are to speak to the clinician who prescribed that medication before they start the omega-3 fatty acid.

Results of a case-cohort study raised concern that omega-3 fatty acids could increase prostate cancer risk.⁴⁰ The study, however, did not establish causation with omega-3 fatty acid intake. Instead, it found that men whose blood level of long-chain omega-3 fatty acids was in the highest quartile had an increased risk of developing prostate cancer compared with the reference group in the lowest quartile. Authors of a recent systematic review concluded there is insufficient evidence to show a relationship between intake of fish-derived omega-3 fatty acids and risk of prostate cancer.⁴¹

Addressing Inflammation

Dr Nichols: We now have 3 topical options for addressing DED-associated inflammation: corticosteroids, cyclosporine, and lifitegrast. Unlike cyclosporine and lifitegrast, corticosteroids do not have a specific indication for the treatment of DED. Cyclosporine is indicated to increase tear production in patients whose tear production is presumed to be suppressed because of ocular inflammation associated with keratoconjunctivitis sicca.⁴² It was first approved in 2003, but in 2016, a multidose, preservative-free version became available.⁴³ Its bottle features a proprietary dispensing tip that maintains sterility of the contents (**Figure 7**).



Figure 7. A multidose bottle of cyclosporine A, 0.05%, features a unidirectional valve and air filter technology that eliminates the need for a preservative

Image courtesy of Elizabeth Yeu, MD

Lifitegrast is a lymphocyte function-associated antigen-1 antagonist that acts to prevent T-cell activation, cytokine release, and migration and extravasation of new T cells into inflamed ocular surface tissues by interfering with lymphocyte function-associated antigen-1 binding to intercellular adhesion molecule 1.⁴⁴ It was approved by

the US Food and Drug Administration in June 2016 for the treatment of the signs and symptoms of DED.⁴⁵

How are you using these different medications?

Dr Lonsberry: If I want something that acts rapidly for controlling inflammation, I prescribe a short course of a corticosteroid. Patients who are already on cyclosporine are kept on that medication if they are doing well. Otherwise, I am mostly prescribing liftegrast when first starting treatment for inflammation. Because liftegrast is new, I want to gain experience using it to see how it works in routine practice. In addition, liftegrast seems to provide rapid symptom relief, which is important to patients. In 2 of the 3 phase 3 clinical trials of liftegrast (OPUS-2 and OPUS-3), patients using liftegrast had greater symptom improvement than did placebo-treated controls by day 14, as measured by the eye dryness score (**Figure 8**).^{46,47}

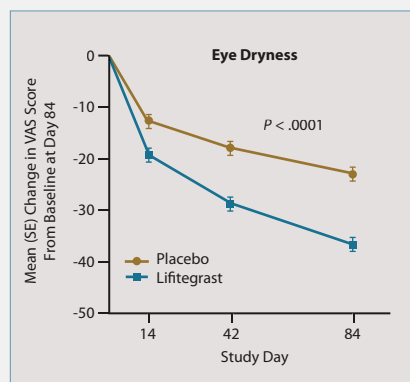


Figure 8. Change in eye dryness score from baseline to days 14, 42, and 84 in the placebo and liftegrast groups in OPUS-2⁴⁶

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

Reprinted from *Ophthalmology*, 122, Tauber J, Karpecki P, Latkany R, et al, Liftegrast ophthalmic solution 5.0% versus placebo for treatment of dry eye disease: results of the randomized phase III OPUS-2 study, 2423-2431, Copyright 2015, with permission requested from Elsevier.

Liftegrast also demonstrated activity for quickly reducing inflammatory ocular surface changes in the third pivotal trial (OPUS-1), as evidenced by significantly greater improvement from baseline to day 14 in total and nasal conjunctival lissamine staining scores compared with placebo.⁴⁸

Dr Karpecki: In addition to being rapid acting, corticosteroids have been shown to have a role as short-term therapy to alleviate burning and stinging that can occur when starting cyclosporine.⁴⁹ In my experience, liftegrast can also cause stinging early on, but I may not prescribe a corticosteroid when starting patients on liftegrast and instead wait to start the corticosteroid only if patients experience bothersome symptoms. I counsel all patients starting on cyclosporine or liftegrast about the potential for irritation, burning, and stinging so they know what to expect and will not stop treatment prematurely.

Dr Nichols: It has been reported previously, and as we discussed, that not all patients with DED have obvious signs of inflammation. In the past, many practitioners would wait to start cyclosporine until patients had more severe DED. What are your thoughts on getting practitioners to initiate treatment for DED earlier?

Dr Lonsberry: I think many clinicians use cyclosporine with moderate-to-severe DED because those are the patients who were enrolled in the clinical trials.⁵⁰ Those patients, however, may already have permanent damage to the tissues that secrete tear components, thus limiting the potential for treatment benefit.

So when educating colleagues about treating inflammation in patients with DED, my first message is that cyclosporine or liftegrast should be started before the patient has developed more advanced disease because either agent is likely to be more effective earlier than later. When practitioners see that earlier treatment is more likely to be successful, they will be more comfortable with early initiation.

Dr Nichols: Are there safety concerns with these anti-inflammatory therapies?

Dr Lonsberry: According to many years of clinical experience with cyclosporine and what has been published in the literature, cyclosporine does not appear to be associated with any serious side effects, even with longer use.⁵¹⁻⁵³ We do not have enough experience to talk definitively about the long-term safety of liftegrast. The agent was safe and well tolerated in the premarketing clinical trials, in which the most common treatment-emergent side effects were instillation site irritation, dysgeusia, and reduced visual acuity, all of which tend to disappear with ongoing use.⁴⁶⁻⁴⁸ This safety profile is consistent with my personal experience.

Dr Karpecki: I do not think there is concern about systemic side effects with topical cyclosporine or liftegrast because there is minimal to no systemic absorption of either of these medications.^{50,54}

Dr Nichols: What are the safety concerns with corticosteroids?

Dr Karpecki: Intraocular pressure (IOP) elevation is the most common concern with use of topical corticosteroids, so it is important to bring the patient back after 3 to 4 weeks to check IOP. Corticosteroid use also increases susceptibility to infection, but the risk is fairly low. The risk for IOP elevation and cataract increases with longer-term corticosteroid use; therefore, despite their potent anti-inflammatory activity and effective management of DED, corticosteroids should rarely be used as chronic treatment for DED.

Dr Mastropa: Some patients are afraid to use a topical corticosteroid because they are concerned about safety. I tell these patients that the homeostasis of their ocular surface environment has been compromised and thus is not effective in maintaining eye comfort. Application of a topical corticosteroid will “re-set” the ocular surface system into a place of calmness. Once the system is normalized, we can switch to another treatment that can be used safely long term. I find this counseling is useful for helping patients overcome their steroid phobia so they are comfortable using corticosteroids in a pulse therapy approach.

CASE ILLUSTRATION From the Files of Blair Lonsberry, MS, OD, MEEd

A 48-year-old woman presents with interest in LASIK (laser in situ keratomileusis) because of contact lens discomfort. She is a -2.00 D myope OU in contact lens monovision and wears a monthly disposable lens in her dominant right eye, with correction for distance.

Findings on examination are TBUT, instantaneous OD, 10 seconds OS; Schirmer score, 1 mm OD, completely wets the strip OS; and superficial punctate keratitis, OD only. She is taking a fish oil supplement.

Dr Nichols: Dr Lonsberry, what were your initial thoughts about the differential diagnosis and further workup?

Dr Lonsberry: I conducted a more comprehensive evaluation for DED in this patient because she was interested in LASIK. On the basis of the dramatic differences between the eyes in the findings from my examination, I immediately considered that the DED in the right eye was contact lens related.

I informed her that LASIK can worsen dry eye, and I proposed switching to a daily disposable lens to see if she could tolerate contact lens wear. She was adamant, however, about wanting surgery and not having to wear a contact lens anymore.

Dr Nichols: How did you manage the patient?

Dr Lonsberry: The patient needed to have her DED treated before undergoing LASIK because a stable tear film is necessary for getting accurate keratometry, topography, and aberrometry measurements, which are used for planning the surgical procedure.^{55,56} I switched the contact lens to a daily disposable product, instructed her on lid hygiene with a warm hydrating mask and digital massage,

recommended frequent use of an ocular lubricant during the day, and started a short course of a corticosteroid, using fluorometholone, 0.1%, suspension 3 times daily for 4 weeks. I chose fluorometholone because it has less propensity to increase IOP compared with other steroids.⁵⁷ Yet, I think it is effective for treating ocular surface conditions, and it was an inexpensive option for my patient. The refractive surgeon added cyclosporine, 0.05%, emulsion twice daily to be started after she had been on the corticosteroid for 2 weeks.

The patient returned after 2 months. In her right eye, TBUT improved to 5 to 6 seconds, superficial punctate keratitis had resolved, and the Schirmer score improved slightly to 2 to 3 mm.

Dr Nichols: The first step that optometrists tend to take to resolve ocular surface issues in a contact lens wearer is to change something related to the contact lens or the care solutions. It is important, however, to think more broadly and to consider management for DED. What are your thoughts on this issue?

Dr Mastrotta: In a monocular contact lens-wearing patient, I would certainly consider limbal stem cell deficiency (LSCD) as a cause for ocular surface disease in the contact lens-wearing eye. Limbal stem cells can be exhausted for a number of reasons, with ocular surface stress related to long-term contact lens wear being one of them.^{58,59} Symptoms of LSCD include foreign body sensation, contact lens intolerance, and photophobia. Early signs of LSCD include lack of corneal luster and corneal epithelium staining, especially in a whorl-like pattern.^{58,59} My first recommendation to this patient would be to discontinue contact lens wear until the cornea appears normal. It may take months for corneal equilibrium to be established.

Dr Karpecki: I agree that optometrists usually first think about changing the lenses and/or care products and overlook specific management for DED. A 2-pronged approach is needed. First, the patient has to be using the best lenses and solutions. Second, it is important to treat the ocular surface disease.

The unilaterality of the findings in this patient is interesting. It implicates contact lens wear, considering that DED is typically a bilateral condition, and it is consistent with evidence that contact lens wear affects meibomian gland structure and function.⁶⁰ If this patient was wearing a contact lens in both eyes, I probably would have done more of a workup to look for another underlying cause that could explain the unilateral presentation, especially if tear film osmolarity was normal. Other potential considerations are giant papillary conjunctivitis, conjunctivochalasis, concretions, or superior limbic keratoconjunctivitis in the affected eye.

My workup for DED is also more extensive for patients who are anticipating surgery, either a cataract or refractive procedure. In addition, I tend to be more aggressive with my management of those patients because they and their surgeon generally want the procedure to be done soon. For patients interested in LASIK, I also want to make sure their DED responds well to therapy. If it does not, they are probably not good surgical candidates because LASIK may exacerbate preexisting dry eye.⁶¹

In terms of my general approach to treating DED, I have moved away from a step-up strategy because I think it wastes time and takes too many visits to find a regimen that works. What I am doing now for patients with MGD, who really represent most patients with DED, is to initiate treatment with a multimodal approach that addresses the multifactorial nature of the disease (**see Sidebar: Multimodal Management of Dry Eye Disease**).



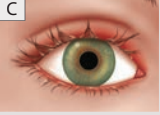
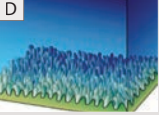
I have different protocols for patients with DED that is neurotrophic, purely aqueous deficient, or related to contact lens wear, but I find that punctal plugs are particularly helpful for all these patients. Although punctal plugs should not be thought of as a last resort, they should not be inserted until the inflammation is controlled.

Multimodal Management of Dry Eye Disease

Paul M. Karpecki, OD

My current approach for managing meibomian gland dysfunction (MGD) targets what I consider are the 4 components of MGD: meibomian gland obstruction, inflammation, biofilm abnormality, and tear film abnormality (**Table**). I recognize that all 4 of these issues may not be present in all patients, but I believe they coexist often enough that it makes sense to address each one routinely. It is important to reiterate that MGD is present in most patients with dry eye disease (DED).

Table. Components of a Multimodal Approach to Management of Meibomian Gland Dysfunction

A	B	C	D
			
OBSTRUCTION	BACTERIAL BIOFILM	INFLAMMATION	TEAR FILM INSUFFICIENCY
<ul style="list-style-type: none"> • Blinking exercises • Moist heat compress • Lid debridements • Thermal pulsation • Manual expression 	<ul style="list-style-type: none"> • Mechanical • Hypochlorous acid • Cotton swab wash • Surfactant cleansers 	<ul style="list-style-type: none"> • Cyclosporine • Lifitegrast • Corticosteroids • Omega fatty acids • Oral doxycycline • Topical azithromycin • Oral macrolides 	<ul style="list-style-type: none"> • Artificial tears • Environment change • Increase hydration • Punctal occlusion • Neurostimulation

A. © 1994 American Academy of Ophthalmology

B. Sebastian Kaulitzki/Hemera/Thinkstock

C. BSIP SA/Alamy Stock Photo

D. Republished from Association for Research in Vision and Ophthalmology, from

A new, specular reflection-based, precorneal tear film stability measurement technique in a rabbit model: viscoelastic increases tear film stability, Nankivil D, Gonzalez A, Arrieta E, et al, 55, 2014; permission request submitted through Copyright Clearance Center, Inc.

The aggressiveness of my treatment for each component is based on the severity of the disease. For early mild MGD, I treat with warm hydrating compresses for obstruction; either topical cyclosporine or lifitegrast, plus an oral omega fatty acid supplement for inflammation; lid scrubs to address the biofilm and help with gland obstruction; and a lipid-based artificial tear to stabilize the tear film. Because in my experience patients with DED do better when inflammation is treated both from the inside out and from the outside in, I like combining a topical medication with an oral intervention.

For patients with more advanced MGD, such as those with rosacea who have significant loss of meibomian glands, I am more aggressive with my treatment because I am aiming to preserve function of the remaining glands. To treat obstruction, I would add in-office thermal pulsation and eyelid debridement to the at-home warm hydrating compresses. Again, treating inflammation both topically and systemically, I would prescribe a short course of a topical corticosteroid, such as loteprednol, 0.5%, with lifitegrast or cyclosporine plus oral doxycycline or azithromycin. Once the inflammation is controlled, patients can be transitioned to an oral omega fatty acid with topical lifitegrast or cyclosporine. To remove the biofilm, I treat the lids with the rotating micro-sponge device, and I typically recommend topical hypochlorous acid for at least the first month. For the tear film, I have found that it is useful to use the most hypo-osmolar product in these patients rather than a lipid-based artificial tear because they tend to have a very elevated tear film osmolarity.

Implementation of this multipronged approach combined with having access to better diagnostics and new therapies has been a real game-changer in my practice. According to findings from our surveys, 10 to 15 years ago approximately 50% of patients were satisfied or very satisfied with treatment, whereas today, the satisfaction rate with this multimodal approach is more than 90%.

TAKE-HOME POINTS

Dry eye disease is a common condition that affects vision, ocular surgery outcomes, and quality of life.

Optometrists should be proactive about diagnosing DED early and should educate their staff about DED because they, too, can help with patient recognition and care.

A diagnostic evaluation for DED should include, as a minimum, investigation of symptoms and risk factors, lid and lid margin examination, ocular surface staining, and assessment of tear film stability.

Newer diagnostic modalities, such as tear film osmolarity, meibography, and the MMP-9 assay, can help to identify, subclassify, and determine the severity of DED, but are not necessary for diagnosis.

Treatment for DED should provide ocular surface lubrication and address lid/lid margin disease and inflammation.

Initiation of anti-inflammatory treatment for early/mild DED is important for interrupting the pathophysiologic pathway and preventing permanent tissue damage.

A variety of topical and oral treatments can be used to control inflammation in DED; selection of a specific agent may take disease severity into account.

Management of DED should also include identification and management of modifiable contributing factors.

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CE POST TEST QUESTIONS

To obtain COPE CE Credit for this activity, read the material in its entirety and consult referenced sources as necessary. We offer instant certificate processing and support Green CE. Please take this post test and evaluation online by going to <http://tinyurl.com/dryeyeCE>. Upon passing, you will receive your certificate immediately. You must score 70% or higher to receive credit for this activity, and may take the test up to 2 times.

- Which of the following is NOT associated with increased prevalence of DED?
 - Allergy
 - Diabetes
 - Male sex
 - Smartphone use
- According to the updated definition of DED from DEWS II, which is a newly mentioned etiologic factor?
 - Meibomian gland dysfunction
 - Neurosensory abnormalities
 - Pollution
 - Sjögren syndrome
- All of the following may be useful as a simple screening tool for DED, EXCEPT:
 - Asking, "Do your eyes ever feel uncomfortable?"
 - Dry Eye Questionnaire 5 (DEQ-5)
 - Short Form-36 (SF-36)
 - Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire
- In a study including 263 patients diagnosed with DED on the basis of objective signs, what percentage of patients reported symptoms consistent with DED?
 - 43%
 - 57%
 - 75%
 - 86%
- At a minimum, a diagnostic evaluation for DED should include all the following, EXCEPT:
 - Meibomian gland expression
 - Ocular surface staining
 - Query about symptoms
 - Tear film osmolarity
- Which of the following diagnostic tests is useful for identifying early/mild DED?
 - Fluorescein corneal staining
 - Lactoferrin
 - MMP-9
 - Tear film osmolarity
- The cutoff for identifying early DED with the tear film osmolarity test is:
 - > 290 mOsm/L
 - > 300 mOsm/L
 - > 308 mOsm/L
 - > 315 mOsm/L
- The cutoff for a positive MMP-9 assay is:
 - ≥ 10 ng/mL
 - ≥ 20 ng/mL
 - ≥ 30 ng/mL
 - ≥ 40 ng/mL
- A multimodal approach to treating DED considers all the following as a component of the disease, EXCEPT:
 - Bacterial infection
 - Inflammation
 - Meibomian gland obstruction
 - Tear film insufficiency
- In a study by Lemp and colleagues, what percentage of patients with DED had some component of MGD?
 - 33%
 - 50%
 - 86%
 - 92%
- Which oral medication has the potential for an adverse drug interaction with omega-3 fatty acid supplements?
 - Azithromycin
 - Doxycycline
 - Tamsulosin
 - Warfarin
- In a 12-week study of patients with MGD, Eitropoulos and colleagues reported oral omega-3 supplementation had statistically significant benefits vs control for improving all the following, EXCEPT:
 - MMP-9 positivity
 - Ocular Surface Disease Index score
 - Schirmer score
 - TBUT
- In phase 3 clinical trials, patients treated with topical lifitegrast achieved greater symptom improvement in eye dryness severity score than placebo-treated controls by treatment day _____.
 - 7
 - 14
 - 21
 - 28
- What pharmacologic property do azithromycin, lifitegrast, doxycycline, and omega-3 fatty acid supplements share in common?
 - Antibacterial activity
 - Anti-*Demodex* activity
 - Anti-inflammatory activity
 - Mucin secretagogue activity
- Which of the following treatments would you choose to achieve rapid control of ocular surface inflammation in a patient who is eager to have cataract surgery?
 - Oral omega fatty acid supplement
 - Topical corticosteroid
 - Topical cyclosporine
 - Punctal plugs
- Which of the following omega fatty acids taken as oral supplementation has not been shown to have benefit as a treatment for DED?
 - Eicosapentaenoic acid
 - Docosahexaenoic acid
 - Gamma linolenic acid
 - Oleic acid
- In premarketing clinical trials investigating topical lifitegrast, which of the following was NOT among the 3 most common treatment-emergent adverse events?
 - Conjunctival hyperemia
 - Dysgeusia
 - Instillation site irritation
 - Reduced visual acuity
- A proven effective strategy for mitigating stinging and burning when initiating topical cyclosporine is to begin treatment with:
 - A topical corticosteroid
 - Instillation every other day
 - Instillation once daily at bedtime
 - Punctal plug placement
- Systemic absorption from topically administered cyclosporine:
 - Is beneficial for patients whose DED is related to a systemic autoimmune disorder
 - Is minimal to absent
 - Is a concern only for patients with impaired renal function or hypertension
 - Occurs only when there is significant ocular surface damage
- Which is the most common side effect occurring with short-term topical corticosteroid treatment?
 - Cataract development
 - Endophthalmitis
 - Herpes simplex virus reactivation
 - IOP elevation



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