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CLINICAL PERSPECTIVE

Improving Care for Patients with Dry Eye Symptoms: See What the Experts Say

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ABSTRACT

A panel of experts was invited to discuss the following questions: Why does the prevalence of dry eye disease (DED) appear to be increasing? Are you satisfied with the current definition and classification of DED—aqueous deficiency versus evaporative dry eye? Beyond the innate human factors (e.g., genetics), what external factors might contribute to DED? What areas related to DED need to be more fully understood? In examining a patient complaining of dry eye, what is your strategy (e.g., tests, questionnaire)? What is your strategy in unraveling the root cause of a patient's dry eye symptoms that may be shared by many anterior segment diseases? What are the two or three most common errors made by clinicians in diagnosing DED? Why do contact lens (CL) patients complain of dry eye while wearing lenses but not when not wearing lenses? What areas related to CL discomfort need to be more fully understood? What is your most effective strategy for minimizing CL discomfort? With current advances in biotechnology in dry eye diagnostics and management tools, do you think our clinicians are better prepared to diagnose and treat this chronic condition than they were 5 or 10 years ago? Do you foresee any of these new point-of-care tests becoming standard clinical tests in ocular surface evaluation? What treatments are effective for obstructed Meibomian glands secondary to lid margin keratinization? What level of DED would prevent you from recommending an elected ophthalmic surgery? What strategy do you use to help your patients comply with the recommended home therapies? How do you best manage patients whose severity of dry eye symptoms does not necessarily match clinical test results, especially in cases of ocular surface neuropathy? Where do you see dry eye diagnosis and treatment in 10 years or more?

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Key Words: dry eye disease, ocular surface disease, meibomian gland dysfunction, definitions, diagnosis, treatment, management, contact lens discomfort

During the past 10 years, there has been an enormous growth in our understanding of the diagnosis, treatment, and management of patients with dry eye (DE) symptoms. Significantly, we now understand that there is not one but rather a multitude of ocular surface diseases (OSDs) and conditions that can cause DE symptoms. Just as important, patient complaints about dryness do not necessarily indicate the presence of “dry eye.” As readers will learn below, the diversity of opinions expressed by our expert panel (see Appendix, available online

at <http://links.lww.com/OPX/A215>) suggest areas of potential clinical development that involve both general agreement and disagreement among the panelists, as well as suggestions for future research directions. Given the widespread clinical relevance of dry eye disease (DED), it will be important to remain current with the latest trends.

Why Does the Prevalence of DED Appear to Be Increasing?

[Reza Dana, MD, MPH, MSc]: There are several reasons. First, our population is aging, and age-specific prevalence rates consistently go up with age. Second, the prevalence of patients with “dry eye” symptoms is going up as more people are engaged in visual tasks such as computer use and smartphone use, which stress the ocular surface because staring decreases blinking and induces desiccation. Third, poor air quality and high pollution levels can exacerbate DED. Fourth, the prevalence of use of preserved topical medications

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is going up. Similarly, corneal surgery rates (LASIK [laser-assisted *in situ* keratomileusis], etc.) are far higher than they were 20 years ago, and thus, there are iatrogenic causes that promote DED.

[Todd Margolis, MD, PhD]: I do not believe that the prevalence of DED is increasing; on the contrary, DED is overdiagnosed. Only a small percentage of the population presenting with DE symptoms actually has a DE owing to insufficient tear production. Furthermore, DE attributed to exposure is a very different problem from DE attributed to aqueous insufficiency and should probably not be labeled a disease at all. All too often, ocular surface pain and disease attributed to inflammatory conditions is misdiagnosed as DED.

[Heiko Pult, PhD, MSc]: The criteria in the evaluation of DE have changed, making it difficult to compare previous and recent figures on the prevalence of DE. The prevalence of DE symptoms may have increased with greater awareness among patients because of promotion and availability of eye drops over the counter and more challenging visual tasks (e.g., computers, smartphones, etc.). Environmental conditions may have changed; for example, we may be exposed to much drier air than some years ago, especially in countries in which air conditioning was not common 20 years ago, but is now installed in almost every new car and in many shops and homes. Diet might have also changed over the past decade. Thus, it is difficult to state with confidence that the prevalence of DE is increasing.

Are You Satisfied with the Current Definition and Classification of DED—Aqueous Deficiency versus Evaporative DE?

[Dr. Dana]: I am not sure that we can ever achieve a classification scheme that will be satisfactory for all settings that affect a complex chronic condition such as DED. Conceptually, I like the evaporative/meibomian gland dysfunction (MGD) versus aqueous-insufficient classification of DED, because it can be helpful clinically. There are patients with MGD who do not have aqueous insufficiency. However, it is rare to see patients with a “pure” form of aqueous insufficiency without concomitant MGD. Nearly all patients with moderate to severe tear insufficiency (e.g., Sjogren or graft-versus-host disease patients) have significant MGD. This means clinically that if a patient has “pure MGD” with significant lid inflammation, but normal or supranormal Schirmer, then the treatment of the lid disease must take precedence. Punctal occlusion or topical cyclosporine A would not be primary treatment strategies. However, if there is tear insufficiency, even with concomitant MGD, the treatment should take precedence with punctal plugs, anti-inflammatories, and so on. In patients with severe OSD, for example, corneal and conjunctival staining, regardless of the type of DED, we use topical and systemic (e.g., tetracycline) anti-inflammatories, plus methods to support the epithelium such as use of autologous serum tears.

[Dr. Margolis]: I am not satisfied with current DE definitions, and one reason I believe DED is overdiagnosed is that the profession tends to classify most patients who have DE symptoms as having DED. In fact, this is not the case; most patients with DE symptoms have an adequate tear supply. Therefore, we should not classify a patient who presents with DE symptoms as having DED but rather specifically categorize the problem. Some examples of

those who should not be classified as having DED include patients with MGD with normal tear film breakup time (TBUT) and Schirmer test. Another would be patients with infrequent or incomplete blink who may be symptom free if living in the tropics; thus, I would suggest that this does not merit the diagnosis of a “disease.” Another important example would include many contact lens (CL) wearers who frequently complain of DE while wearing their lenses but are, in most cases, symptom free upon removal. This is CL intolerance, not disease. A common treatment of DE is the use of punctal plugs; however, plugs worsen signs and symptoms in patients with MGD, probably by retaining inflammatory mediators on the ocular surface. Finally, about 25% of “DE patients” I see in my practice do not have primary DE but experience ocular surface irritation caused by topical medications (including preserved glaucoma medications, and preserved and nonpreserved artificial tears and ointment). This is medication toxicity and not DE. In summary, the profession should begin moving toward an etiology-based diagnosis founded on objective findings and not on patient symptoms. Clumping all patients together as having DED based on symptoms often leads to the wrong therapy.

[Nancy McNamara, OD, PhD]: I reserve the use of DE for those patients who are truly aqueous deficient. I do not believe the classification of evaporative dry eye (EDE) accurately conveys the underlying etiology of ocular conditions that lead to symptoms of dryness but are not attributed to reduced tear secretion. For example, there are many meibomitis patients who experience ocular dryness despite having a TBUT greater than 10 seconds. My preference would be to do away with the aqueous-deficient versus evaporative classification and provide patients with an explanation and diagnosis that more clearly depict the ocular surface condition that is causing their eyes to feel dry.

[Edoardo Villani, MD]: The etiological classification provided by DEWS 2007 is a good evidence-based starting point.¹ Several challenges remain. Tear hyperosmolarity and tear film instability are hypothesized to be the core mechanisms, but there are numerous (not necessarily fully understood) feedback processes and vicious cycles. Moreover, when we move from etiology and pathogenesis to clinical approach (intended to improve patient management), symptoms and lack of association with signs become a major concern. DEWS 2007 and Delphi Panel provide us with useful treatment recommendations, but they are based on a severity grading that appears unsuitable to drive a tailored and dynamic therapeutic approach.^{1,2}

Beyond the Innate Human Factors (e.g., Genetics), What External Factors (e.g., Environment, Medications) Might Contribute to DED?

[Charles McMonnies, DSc, MSc]: There has been considerable interest in environmental influences on tear function such as humidity, air conditioning, and air movement. However, it is seldom easy to determine to what extent other air qualities also contribute to DE symptoms. Air-conditioning systems can become contaminated by fungi, molds, and bacteria. Contaminants or by-products from local industrial activities might combine with city and traffic pollution as well as pollens and molds to reduce air quality. Finally, a lowered threshold for psychosomatic experiences might contribute to the perception of symptoms.

Stress, depression, anxiety, dissatisfaction with work demands, low support levels, poor interpersonal relations, and other aspects of the psychosocial work environment may increase perception of symptoms.

What Areas Related to DED Need to be More Fully Understood?

[Reiko Arita, MD, PhD]: Meibomian gland dysfunction accounts for most cases of DE.³ Therefore, understanding the pathogenesis of MGD and developing new treatment strategies are critical. We found that evaluation of ocular symptoms, lid margin abnormalities, and lost MG area (meiboscore) are reliable markers for diagnosis.⁴ Given that it is difficult to distinguish aqueous-deficient dry eye (ADDE) from EDE based on ocular symptoms alone, the subtype of DED should be diagnosed by taking into account not only corneal-conjunctival epithelial disorders, tear film stability (TBUT), and tear production (Schirmer test value), but also lid margin abnormalities, characteristics of meibum (meibomian lipids), and morphological evaluation of MGs by meibography. Understanding underlying pathogenesis should inform the direction of treatment, whether aqueous- or mucin-oriented therapy for ADDE or MG-oriented therapy for MGD.

[Dr. McMonnies]: Blink rate and completeness can be significant contributors to DED. For example, incomplete blinks can represent 10 to 22% of the total number of blinks and approximately double tear evaporation. Lower blink rates and increased interblink intervals can increase tear osmolarity and concentration of inflammatory mediators. Given the importance of incomplete blinks, there is a great need for developing better ways to improve and maintain adequate rates of blinking and blink completeness.

[Dr. McNamara]: There is a critical unmet need for new therapies to treat DED. An important yet often overlooked component of patients is altered innervation of the cornea and lacrimal gland. Loss of neuronal inputs upsets the complex reflex network connecting the ocular mucosal tissues (e.g., cornea, limbus, and conjunctiva) and tear-secreting machinery (e.g., lacrimal glands) that maintains ocular surface and glandular epithelial homeostasis. Furthermore, there is growing evidence that innervation is a negative modulator of inflammation and a positive regulator of progenitor cell-mediated regeneration. Despite the essential need for a functional nerve supply, current medications and therapeutic strategies do not address the important need to maintain or reinnervate ocular tissues and stimulate tear secretion in DE patients.

[Dr. Villani]: A major unmet need is the availability of validated biomarkers. In clinical practice, we would need them not only to clearly identify the pathogenic process affecting our patient but also to predict and assess the clinical response to treatment. In clinical research, biomarkers would be essential to enroll truly homogeneous groups, get valid surrogate end points, and help new drug development that offer to regulatory agencies, investors, and researchers the opportunity to perform more successful clinical trials.

In Examining a Patient Complaining of DE, What Is Your Strategy (e.g., Tests, Questionnaire)?

[Dr. Arita]: Clinical parameters for the diagnosis of DE disease are presented in Table 1.

These clinical examinations allow differentiation of ADDE from EDE and therefore inform selection of the most appropriate treatment (Fig. 1).

[Caroline Blackie, OD, PhD]: I approach all DE suspects with the following structure in mind:

Diagnose and treat the root cause: As MGD is the primary cause of all DE, I evaluate MG function and structure—using metrics—on every DE suspect. If necessary, I will also evaluate for lacrimal gland and goblet cell dysfunction.

Measure and manage the sequelae: Dry eye is a diagnosis of sequelae, not etiology, and the sequelae are varied: reduced vision, ocular surface damage, inflammation, tear film instability, increased osmolarity, and symptoms.¹ Each of these sequelae requires a different suite of clinical metrics. Each patient has a different presentation; thus, no one test or combination of tests will be appropriate for all. I tailor my testing and management to each specific presentation.

Educate patients about their roles in the disease: Dry eye patients frequently feel like victims with a disease that no one understands. They often are unaware that their lifestyles play a dramatic role in their disease process. Educating them appropriately empowers them to participate in their recovery process. Suhaimi et al.⁵ demonstrated that evaporative stress is not benign; rather, it causes obstructive MGD. This is a dramatic change in our understanding. Previously, we understood that MGD causes evaporative stress by degrading the protective lipid layer, and it does. We now know that exposing healthy eyes with normal MG function to evaporative stress leads to MGD. I help my patients to help themselves by educating them about how to avoid evaporative stress.

[Dr. McNamara]: In the Dry Eye Clinic at UC Berkeley, we ask every new patient to fill out the Ocular Surface Disease Index (OSDI).⁶ This questionnaire provides both a quantitative and a qualitative assessment of symptoms. In the clinical examination, we have adopted the ocular staining score developed by the Sjogren's International Collaborative Clinical Alliance. This ocular staining score is generated through the use of fluorescein dye to assess punctate epithelial erosion of the cornea and lissamine green to assess the bulbar conjunctiva.⁷ Examination of lids/lashes and manual expression of MGs is essential for assessment of blepharitis and meibomitis. Unanesthetized Schirmer of less than 5 mm provides a clear indication of aqueous deficiency. It is perhaps most

TABLE 1.
Clinical tests for diagnosing DED (courtesy of Reiko Arita)

Evaluation	Tools or devices
1. Questionnaire	OSDI, DEQS, etc.
2. Lid margin abnormalities	Slit lamp microscope
3. Epithelial disorders	Fluorescein—REPEAT—see below
4. TBUT	Fluorescein
5. Meibomian gland morphology	Meibography
6. Schirmer test	Schirmer strip
7. Meibum grade	Fingers or forceps

DEQS, Dry Eye–Related Quality-of-Life score.

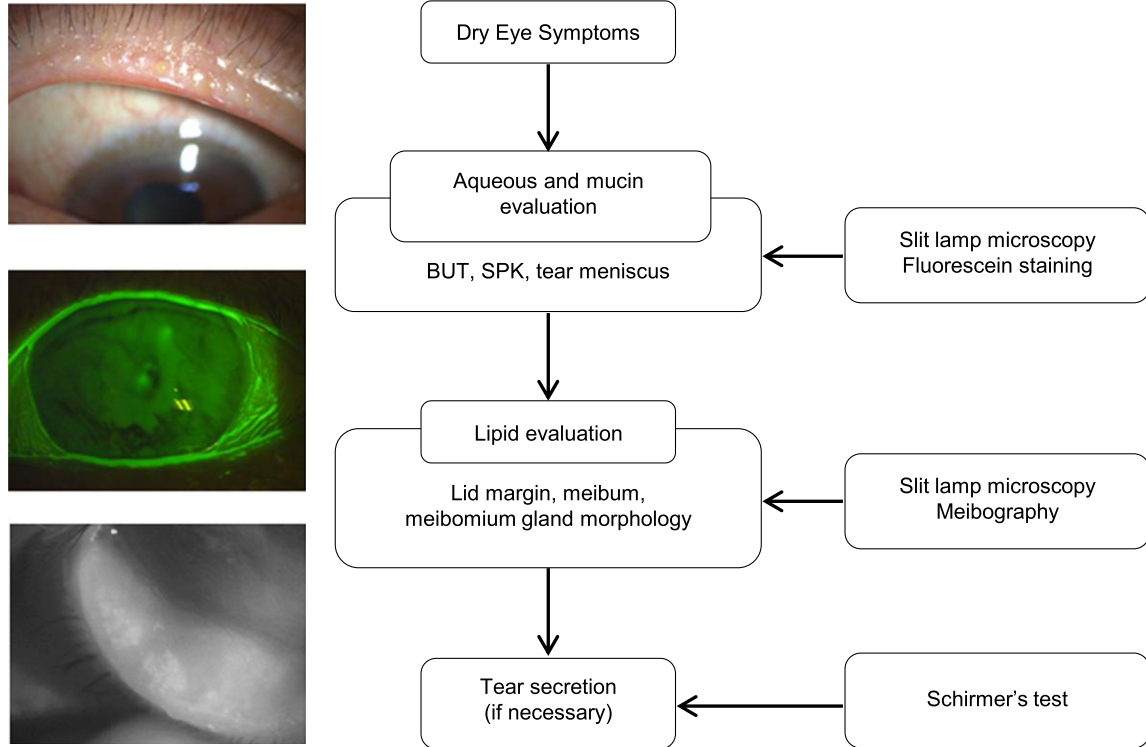


FIGURE 1.

Flowchart of clinical tests that allow differentiation of ADDE from EDE (courtesy of Reiko Arita). A color version of this figure is available online at www.optvissci.com.

important to dedicate 10 to 15 minutes at the beginning of every examination to thoroughly review the patient’s disease history. This conversation must include a detailed discussion of how long, how often, and when and where they experience ocular dryness. It is important to know which treatments they have already tried, for how long, as well as what appears to help and what appears to make the condition worse. Finally, there are many systemic conditions that can cause OSD, and dryness is often a presenting symptom (e.g., Sjogren syndrome). Therefore, it is important to look beyond the ocular surface and consider the whole clinical picture when assessing a patient with DE symptoms.

[Dr. Pult]: We differentiate among three DE types: ADDE, EDE, and a combination of both. It starts with DE screening, a combination of questionnaire and one tear film test (osmolality or tear film stability), and one ocular DE sign (lid-wiper epitheliopathy or lid-parallel conjunctival folds). The clinician then needs to investigate tear film volume, the lipid layer, lids, and function and morphology of MGs.

[Dr. Villani]: The first step is to reassure patients by acknowledging their symptoms that negatively impact their quality of life. Good communication results in a deeper understanding of medical history and symptoms, and a greater chance of establishing a therapeutic alliance. My open questions are followed by a standardized questionnaire for symptoms (OSDI). My clinical examination includes inspections and a proper sequence of tests. Inspections assess the patient’s attitude, posture, hands, skin, and face, followed by ocular examinations (eyelids, eyelid margin, tarsal conjunctiva, fornix, bulbar conjunctiva, cornea, and anterior chamber). I usually adopt the “practical sequence of tests” suggested by DEWS 2007,^{1,8} enriched with corneal sensitivity evaluation, lissamine green ocular surface staining, and imaging techniques.

What Is Your Strategy in Unraveling the Root Cause of a Patient’s DE Symptoms That May Be Shared by Many Anterior Segment Diseases?

[Dr. Margolis]: When I encounter a very symptomatic patient who exhibits no clinical signs, I anesthetize the ocular surface to determine if OSD is the source of discomfort. If discomfort persists, I consider neuralgia or centralized pain in the diagnosis.

DE Diagnosis Is Frequently Missed by Clinicians. What Are the Two or Three Most Common Errors Made by Clinicians in Diagnosing DED?

[Dr. Arita]: The two most common errors made by clinicians in diagnosing DED are as follows: (1) Overlooking lid margin abnormalities. Tear film conditions or epithelial disorders are readily observed, but the condition of the eyelids, orifices of MGs, and meibum as well as MG morphology may be overlooked in the clinic. (2) Misunderstanding the method for measurement of TBUT. There are important points that should be accounted for by clinicians during assessment of TBUT (Table 2).

[Dr. Blackie]: Failure to embrace metrics. Clinically meaningful MG function is defined as oil released from an orifice during deliberate blinking.⁹ This cannot be reliably estimated using digital or Q-tip pressure any more than intraocular pressure can be evaluated digitally. Metrics are the key. Early changes in MG function can be detected well in advance of any DE sequelae but not without use of quality metrics. Another error is failure to recognize that DE is a diagnosis of sequelae and not etiology. When we focus on managing sequelae only, we can become

TABLE 2.

Important points that clinicians should take into account during tear breakup assessment (courtesy of Reiko Arita)

Error	What happens:
Lifting up eyelid	Miss precise tear function (incorrect evaluation)
Touching eyelid	Inducing meibum secretion (overestimation of tear film stability)
Overloading with fluorescein	Masking of epithelial disorders Altered TBUT value

trapped in a cycle of failure. For success to be possible, we need to treat the root causes and measure and manage sequelae.

[Dr. Dana]: Dry eye disease (just like many other chronic “syndromal” conditions such as lupus or fibromyalgia) is both underdiagnosed and overdiagnosed. Many other conditions such as allergy, floppy eyelid syndrome, or lid appositional problems are called DE just as there are DED patients who are misdiagnosed as having “pink eye.” Several principal reasons may explain why DED is often underappreciated. First, clinicians should listen to patients—their stories and their descriptions of long-standing symptoms, what exacerbates these symptoms, and what ameliorates them. This will make it much easier to distinguish true DED from ocular atopy or possibly overlap syndromes. Second, clinicians should refrain from relying on one “magic” diagnostic test: whether it is the Schirmer test, MMP-9 (InflammaDry), or tear osmolarity, or symptoms alone. Many of these tests are unreliable or nonspecific. Dry eye disease is a syndrome consisting of both patient symptoms of dryness and incontrovertible objective signs of ocular surface epitheliopathy. Third, clinicians should look at the whole patient and not go directly to the slit lamp. How old are they? Do they have signs of rheumatoid arthritis? Are they blinking normally (lid excursion and blink frequency)? Do they have a dry mouth? Is there sign of facial rosacea?

Why Do CL Patients Complain of DE while Wearing Lenses but Not when Not Wearing Lenses? Does This Really Indicate an Absence of DED, or Does CL Wear Lower the Threshold for a Patient Experiencing DE Symptoms?

[Dr. Blackie]: Remember that DE is a diagnosis of sequelae. The presence of DE means that the ocular surface is evidencing signs of desiccating stress. It can be transient or chronic. A CL is a tear film stressor and will compromise even the most robust of tear films by immediately destabilizing the tear film and placing the ocular surface under evaporative stress. This results in two phenomena: first, the tear film destabilizes and, second, chronic exposure to evaporative stress will accelerate the progression of MGD.^{5,10}

[Dr. Dana]: To the contrary, CLs in most patients exacerbate true dryness—it is not a matter of making the patients more prone to becoming symptomatic; CLs actually do make the eye drier. In fact, bandage CLs can, at least in the short term, mask symptoms of DED by protecting the surface epithelium from the microtrauma of blinking. However, CLs, especially high-water

content soft lenses, can desiccate the eye surface and induce epithelial disease. Why? First, CLs induce a state of relative “hypesthesia” leading to lower blink rates, which can induce relative desiccation. Second, high-water CLs can act as a “sponge” on the surface and reduce precorneal tear volume. Third, CLs appear to affect corneal nerve density and thus indirectly affect the epitheliotrophic support of the nerves. Fourth, soft CLs can act as reservoirs of various chemical species (e.g., from cleaning solutions) that can be epithelial-toxic and thus lower the threshold for the epithelium demonstrating stress from desiccation.

[Dr. McMonnies]: Contact lens wear is a provocative test for tear function. Even marginal tear deficiency may significantly reduce CL performance. Healthy tear function before lens wear is often impaired by the presence of a CL, which causes symptoms of dryness by disrupting normal tear physiology through thinning and breakup of tear film, interrupting its reformation over the lens front surface, and rupturing the lipid layer with consequent increases in tear film evaporation. At the end of lens wear, the lens anterior surface may be less lubricious because of lens drying and soiling so that lid-wiper friction during blink-related movements over the lens is exaggerated. Lens awareness can be a trigger for both early and late replacement of lenses.⁸ Initial very comfortable wear can lead to a habit of delaying lens replacement or other forms of noncompliance. Unfortunately, the inflammatory responses associated with the habit of wearing lenses until they are too uncomfortable or other forms of noncompliance appear likely to contribute to greater inflammatory responses and reduced comfort.

What Areas Related to CL Discomfort Need to Be More Fully Understood?

[Dr. Pult]: The interaction between the upper lid and the CL surface should be considered, especially lid-wiper epitheliopathy. From a tribological viewpoint, with high blink speed, it is not the CL surface but the viscosity of the tear film that may impact lid wiper. Yet, coefficient of friction of CL material may matter in low velocity, possibly at the starting and reversal points of blinks and in eye movements. It would be of interest to investigate the impact of the CL on tear film viscosity—cornea as well as upper and lower lid wipers.

[Dr. Villani]: We need to improve our knowledge of etiology and pathogenic processes triggered by CL wear. Moreover, we need to understand and demonstrate the associations between discomfort and factors such as lens features, ocular surface changes, and tear film characteristics. This is essential to orient our therapeutic approach, often limited to relatively blind attempts to modify factors interacting in the “ocular surface + CL” system.

Minimizing CL Discomfort Can Be a Challenging Task. What Is Your Most Effective Strategy?

[Dr. Blackie]: The most effective way to reduce CL discomfort would be to proactively enhance and maintain the robustness of the tear film and to educate the patient about the impact of ongoing lid margin and MG health maintenance. This introduces a model of prevention whereby all CL wearers should:

- be screened for MGD and have MG function and structure evaluated and quantified during every CL evaluation.

- have their blink profiles evaluated and quantified during every CL evaluation.
- be educated about the necessity of ongoing eyelid margin and MG health maintenance, including the importance of optimal blinking.

About 100 years ago, the dental profession began to recognize the importance of dental hygiene and, in so doing, embraced a culture of prevention. Using this strategy, we have a tremendous opportunity in eye care to promote a culture of prevention with regard to ocular surface health.

[Dr. Pult]: Any coexisting ocular disease needs to be addressed first, followed by fitting CLs having the lowest interaction with the lid wiper, with reduced movement and low coefficient of friction, and using appropriate lens-care solutions (peroxides) or avoiding any lens-care solutions, as one can do with daily disposable lenses.

With Current Advances in Biotechnology in DE Diagnostics (e.g., InflammaDry, Osmometer, Sjo Test) and Management Tools (e.g., LipiFlow, BlephEx), Do You Think Our Clinicians Are Better Prepared to Diagnose and Treat This Chronic Condition than They Were 5 or 10 Years Ago? Do You Foresee Any of These New Point-of-Care Tests Becoming Standard Clinical Tests in Ocular Surface Evaluation?

[Dr. Arita]: The tear film is composed of an aqueous layer (aqueous plus mucin) and a lipid layer. Noninvasive meibography allows us to observe the morphology of MGs,¹¹ and LipiView has allowed evaluation of the function of the lipid layer.¹² For evaluation of the aqueous layer, Schirmer test provides a measure of tear production, and strip meniscometry allows estimation of tear volume at the ocular surface.¹³ However, quantitative analysis of mucin is still not available in the clinic. Eye drops that stimulate the production of mucin in tears, including diquafosol sodium and rebamipide, are now commercially available.^{14,15} Measurement of mucin is required to evaluate the clinical efficacy of such eye drops.

[Dr. Margolis]: The best tools for unraveling root causes of DE symptoms are a thorough history and a careful examination of the ocular surface aided by the use of topical fluorescein and lissamine green dyes. I have not found most of these new technologies to be of much added diagnostic value. The jury is still out on how the Sjo test will change our practices because Sjogren syndrome patients are a very small percentage of patients complaining of DE, and it is not clear in population-based studies what the increased capture of Sjogren patients might be with this test. In regard to LipiFlow and BlephEx, it would be great to have any data showing long-term benefit. I am still waiting for any study to demonstrate that treating MGD with any of our current therapies prevents MG loss over time.

What Treatments Are Effective for Obstructed MGs Secondary to Lid Margin Keratinization?

[Dr. Blackie]: A simple in-office procedure for debriding and scaling the lid margin and line of Marx (surface cells of the mucocutaneous junction) has been developed that greatly assists in cleaning up the lid margin and removing any loose tissue that may be either blocking the flow of meibum out of a gland or obstructing its path from the orifice

to the tear film. This technique is performed using a golf club spud from a foreign body removal kit.¹⁶

What Level of DED Would Prevent You from Recommending an Elected Ophthalmic Surgery? In Your Opinion, Is It Critical to Treat OSD before These Surgeries?

[Dr. Blackie]: Any measurable level of tear film compromise or other DE sequelae is a reason to delay elective ophthalmic surgery. It is critical to treat the root cause and manage any sequelae of DE before elective ophthalmic surgery.

[Dr. McMonnies]: Apart from reducing symptoms and signs of DE, prophylactic and post-LASIK blink exercises to reduce incomplete blink rates and associated overexposure of the ocular surface may also contribute to more accurate refractive outcomes through faster wound healing.

Compliance with Home Therapy (i.e., Warm Compresses, Eyelid Margin Massage, and Cleaning) Is Often Difficult for Patients. What Strategy Do You Use to Help Your Patients Comply with the Recommended Home Therapies?

[Dr. Blackie]: Education is the key. Patients comply with dental hygiene because they know how important it is. When they do not comply, they understand that it is not the fault of the dentist. I show my patients their data relative to the norm and use these data to explain why I might be concerned.

[Dr. Pult]: Make it fun for the patient! Heat and relaxing are reasons why people love visiting a spa. So let us tell our patients that it is a 10-minute home-wellness timeout with relaxing and enjoyable heat for your eyes and your face. If you recommend lid massage and lid cleaning, explain to the patients that it is like daily tooth hygiene, and do not make it too complicated. Then, invite the patient to regular DE follow-ups in which you can always address the topic.

It Is Well Known That the Severity of a Patient's DE Symptoms Does Not Necessarily Match Clinical Test Results, Especially in Cases of Ocular Surface Neuropathy. How Do You Best Manage These Patients?

[Dr. Blackie]: With any disease process, symptoms are highly subjective and complex and should not be used as the sole indicator of treatment success, particularly in chronic disease, as there is a high likelihood of dysfunctional pain syndrome or neuropathic pain. Rosenthal and Borsook^{17,18} have written extensively on this topic. In severe cases, ocular surface neuropathy may also exist. The primary noxious stimulus for inducing symptoms of discomfort is desiccating stress experienced when the tear film can no longer protect the ocular surface. To assess whether symptoms can be successfully abated with comprehensive rehabilitation of the tear film and ocular surface, desiccating stress can be temporarily removed. This can be achieved using a moisture goggle to create 100% periocular humidity. We refer to this as “the goggle test.”¹⁹ The results are very effective for predicting how a patient's symptoms will improve with comprehensive rehabilitation of the

tear film and ocular surface. Also, experience while wearing moisture goggles is very educational for the patient. The goggle test reinforces to the patient and the practitioner that symptoms alone are not sufficient to guide management and treatment. We are not treating symptoms; we are treating the tear film and the ocular surface. Symptom control may or may not be possible depending on the patient and the severity and chronicity of their condition.

[Dr. McNamara]: The disconnect between a patient's symptoms of dryness and what we see clinically is likely to stem primarily from damage to sensory nerves innervating the cornea. Although we are in the beginning stages of understanding the specific cellular events that alter the communication between corneal nerves and the ocular mucosal epithelium in DE disease, it is likely driven by inflammation. We find that steroids help to temporarily alleviate symptoms, but they do not provide a long-term fix. There is a recent trend in my laboratory and others to gain a better understanding of the underlying disease process and to develop novel therapeutics that promote nerve regeneration and aqueous tear secretion. While we continue to pursue promising candidates, I believe that the most important approach with patients is to validate their symptoms. The discomfort they experience is real, but they are often told their eyes are fine and yet their symptoms continue to negatively impact their quality of life. Aggressive lubrication with chilled, preservative-free artificial tears can be helpful, as well as daily warm compresses and digital massage of the eyelid margin to address any associated MGD. There are some clinicians who implement the use of topical NSAIDs (nonsteroidal anti-inflammatory drugs) (e.g., Prolensa) for pain relief in such patients.

Where Do You See DE Diagnosis and Treatment in 10 Years or More (Please Think "Outside the Box," e.g., Stem Cell Transplantation, Genetic Modification, Artificial Tear/Drugs with Long Retention Time, MG Transplants)?

[Dr. Arita]: The aim of treatment of DED appears to be to ameliorate DE by manipulating the tear film. Eye drops that stimulate mucin secretion or tear fluid production are currently available, but stimulation of lipid production is not yet possible. The development of treatment or management strategies for MGD is essential. Further development or improvement of diagnostic methods such as meibography should also lead to establishment of a diagnostic strategy for MGD. Such advances will allow us to provide patients with phase-dependent care, including treatment of MGD or other MG-related conditions. Additionally, a novel point of view in DED is "Compensation theory." The existence of homeostasis in the tear film has been suggested, but the role of components of the tear film in such homeostasis has not been evaluated. As far as we investigated, tear fluid secretion (as reflected by Schirmer test value) was closely related to the severity of MG abnormality (as reflected by the meiboscore, which indicates MG loss), suggesting that tear fluid secretion increases as a compensatory response to the loss of tear film stability caused by deficiency of the oily layer (Arita et al., *Ophthalmology*, in press). The increase in tear secretion in patients with MGD might also serve to reduce friction between the eyelid and the cornea caused by

deficiency of the oily layer of the tear film. Tear secretion in patients with MGD thus may increase to reduce ocular discomfort in response to tear film instability. Thus, we propose that treatment of tear diseases should focus on improvement of the balance between tear film components. The common aim of present and future DE treatments should be to maintain or recover homeostasis of the tear film. Further studies are necessary to establish the operation of this compensatory mechanism and to provide additional insight into tear film homeostasis, including blinking, tear osmolarity, condition of the mucin layer, and presence of inflammatory factors.

[Dr. Dana]: I do not think that stem cells, gene therapy, or exotic and unconventional surgeries will play very important roles in the management of a highly prevalent condition like DED, which affects tens of millions of people. It is simply not feasible either operationally or fiscally to support these approaches for a condition that affects one out of seven to eight adults in the United States alone. Personally, I think that the wave of the future in DED treatment will be molecular targeting of key pathophysiologic steps in DED. Most likely, for reasons of efficacy and safety, protein-based biologic therapies will lead the way. Just as biologic approaches have revolutionized the approach toward many conditions (e.g., anti-vascular endothelial growth factor in retinal diseases, anti-CD20 and anti-tumor necrosis factor in autoimmune disorders), I envision an era when biologic approaches that either inhibit inflammatory pathways or agonize (promote) trophic or immunoregulatory factors will provide more efficacious treatments for OSD.

[Dr. Margolis]: I see the field developing medications to treat ocular pain and discomfort.

[Dr. McMonnies]: The need to explain what are described as DE symptoms when signs of tear dysfunction DE are absent may lead to a wider appreciation of how factors unrelated to tear function can contribute to what are currently classified as "dry eye" problems. Any of these factors may exacerbate symptoms when tear function is present. Why can some people wear soiled unwet CLs without apparent problems? Can it be explained by stronger motivation to avoid wearing spectacles? Perhaps adaptation to lens wear has allowed the lid wiper to become keratinized with associated increased threshold for lens awareness, as can occur for the cornea. Ocular surface health can only be diagnosed provisionally based on an examination limited to a single instillation of sodium fluorescein. Evidence of abnormality might sometimes be detected by also using other vital stains, or a second instillation of fluorescein with observation made after allowing time for stain to develop. Alternatively, abnormal ocular surface status might also be indicated by reduced conjunctival or corneal sensitivity, hyperemia, an impaired epithelial barrier function, corneal or conjunctival edema, or reduced goblet cell density. Abnormality might be indicated by other signs of DE from hyperosmolarity to MGD, as well as by symptoms. It is hoped that, over the next 10 years, there will be significant improvements in our ability to determine ocular surface health.

[Dr. McNamara]: Dry eye is multifactorial; thus, in addition to exploring targeted therapeutics that address the underlying immune response, we need to broaden our approach by considering therapies that directly address changes occurring on the ocular surface. For example, chronic inflammation alters the activity of corneal stem cells, leading to pathological keratinization of the

ocular surface. I foresee a real opportunity to restore the normal programming of corneal stem cells through the application of genes that maintain corneal homeostasis through direct interaction with the corneal epithelium.²⁰ The combination of rapid tear turnover, blinking, reflex tearing, and corneal epithelial barrier function presents significant challenges in drug delivery. There has been some progress in developing ocular devices that resemble scleral lenses, such as the PROSE from the Boston foundation that can provide a depot to enhance drug delivery in patients with severe OSD.²¹ More recently, the exciting development of polymeric nanoparticles as drug carriers has gained attention. With this approach, existing or novel drugs can be fused to thermo-responsive, elastin-like polypeptide-based nanoparticles as a way to enhance the therapeutic index of topical treatments. Inevitably, success in the management of patients with OSD will come from a multifaceted approach that addresses the primary components of DE, including inflammation, loss of corneal nerves, and abnormal stem cell activity.

[Dr. Pult]: We may have implants or CL materials secreting natural tears and anti-inflammatory ingredients linked to our smartphones or body sensors like special watches or wristbands. Tear glands might be treated by stem cells or medications to regenerate, if we are able to investigate the real core mechanism of DE.

[Dr. Villani]: If we find valid biomarkers and improved algorithms for clinical classification, and if we get better instruments to develop drugs and artificial tears dedicated to specific subtypes of DE, then we will have won a great victory for our patients.

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APPENDIX

An appendix, which lists the members of the expert panel, their affiliations, and their declarations of commercial relationships and potential conflicts of interest, is available online at <http://links.lww.com/OPXA/A215>.

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