A REVIEW OF OPTOMETRY SPECIAL REPORT

DEWS II: REDEFINING DRY EYE

Evidence-based guidelines from TFOS on the latest clinical protocols. Here's what it says and why it matters.

With an introduction by J. Daniel Nelson, MD, TFOS DEWS II Chair, and a conclusion by the Clinical Editors.

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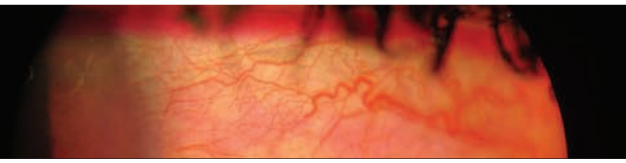


A DEFINITIVE DECADE FOR DRY EYE

An explosion of research followed the 2007 TFOS DEWS report. Ten years later, DEWS II puts it into perspective.

By J. Daniel Nelson, MD, *TFOS DEWS II Chair*

Having chaired the Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshop (DEWS) II steering committee over the last 2.5 years, I witnessed firsthand the magnitude of the task we chose to undertake: to modernize the eye care community's concepts and clinical practices surrounding this widespread yet poorly understood condition. The Workshop, comprised of 150 experts spanning 23 countries, reviewed thousands of published articles on dry eye disease (DED) to produce TFOS DEWS II, recently published in *Ocular Surface*. Coming a decade after the original TFOS DEWS report of 2007 and reflecting a body of scientific literature that had nearly doubled in that time alone, this new work—encompassing reports from 10 of the 12 TFOS subcommittees—updates the definition, classification and diagnostic methodology of dry eye disease; explores its causes, mechanisms and global impact; and offers an evidence-based consensus opinion on approaches to treatment.

The DEWS II definition of dry eye will move both research and clinical practice forward. It emphasizes that dry eye is indeed a *disease*—still a somewhat novel concept, even today—with multiple etiologies, but with the common aspect of a loss of tear film homeostasis due to tear film instability, hyperosmolarity, ocular surface inflammation and damage, or a combination of all three. Symptoms become the key element in the classification of dry eye.

The DEWS II classification is a significant step forward in our understanding of dry eye. It presents a patient-based approach that begins with the presence or absence of symptoms, and then is further divided into strata based on the presenting symptoms' correspondence (or lack thereof) with clinical signs, yielding four branches: the absence of symptoms with and without signs, and the presence of symptoms also with and without signs. Asymptomatic individuals without signs obviously do not have dry eye, while asymptomatic patients with signs may be at risk of developing symptoms following ocular procedures (e.g., refractive surgery) or other therapeutic interventions (e.g, systemic medications). Individuals with symptoms and signs are further separated into those with dry eye and those with other ocular surface diseases (e.g., allergy, ocular cicatricial pemphigoid). Individuals with symptoms and no signs may have neuropathic pain or a pre-clinical dry eye.

The Tear Film subcommittee report emphasizes that the tear film should be thought of in terms of a complex two-phase model with the lipid layer overlying a mucoaqueous phase, and that the entire tear film is involved in limiting evaporation.

The remaining subcommittee reports highlight several important areas, including the roles of sex, gender and hormones; epidemiology, with a notably global perspective; and pathophysiology of DED. The Pathophysiology report—the longest of the 10—emphasizes that the etiology is not linear, as in more conventional pathologies where an instigating event triggers a sequential cascade of processes that result in clinical manifestations, but rather a vicious, self-perpetuating circle. Tear hyperosmolarity is shown to be the hallmark of DED, functioning as both a catalyst and consequence of various steps along the circular process. There are many entrances into that circle that can result in DED signs and symptoms.

The Diagnostic Methodology report stresses the importance of using triaging questions to separate dry eye from other ocular surface diseases and then using tear break-up time (preferably noninvasive), osmolarity and ocular surface staining to identify a loss of tear film homeostasis.

TFOS DEWS II argues that management of dry eye should be aimed at restoring tear film homeostasis. Although the Management and Therapy report presents staged management and treatment recommendations, the heterogeneity of DED requires that clinicians manage and treat patients based on individual profiles, characteristics and responses.

The Iatrogenic report emphasizes that the clinician, as well as the patient, may be responsible for causing DED; with greater recognition of this, individual responsibility then becomes a factor in the overall approach toward hastening resolution.

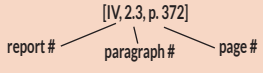
Finally, the Clinical Trial Design report provides guidelines on how to go about designing future studies that will have a better likelihood of getting therapeutic drugs and devices approved for clinical use in the decade ahead.

A key driver of our work was the goal of grounding the final TFOS DEWS II report in evidence-based medicine as a means of enabling broad adoption, free of influence or ambiguity. It is the fervent wish of all involved that this effort may translate into better clinical protocols that bring our patients sustained, long-term relief. ❍

GUIDE TO NOTATION

This supplement summarizes the 10 subcommittee reports that comprise TFOS DEWS II, published in the July 2017 *Ocular Surface*. The first page of each article lists the reports discussed therein. Readers interested in more detail are encouraged to seek out the full text. For easier exploring, key points cite the relevant source by report, paragraph and page number.

As you read the ensuing articles, look for TFOS DEWS II citations in this notation:



WHAT DOES "DRY EYE" MEAN TODAY?

There's a new answer. Here's what you need to know about dry eye's definition, classification and epidemiology.

By Michael Iannucci and Michael Riviello, *Associate Editors*

In light of three decades of increasing dry eye disease (DED) awareness, the TFOS DEWS II Definition and Classification subcommittee was tasked with constructing an updated, evidence-based definition and new classification system for DED. [I, abstract, p. 276] During a special session at this year's Association for Research in Vision and Ophthalmology (ARVO) meeting in Baltimore, Md., subcommittee co-chair Jennifer Craig, PhD, said the main goals of the definition update were "resolving the confusion between the diagnostic vs. pathophysiological features, acknowledging the multitude of etiological triggers that could lead to the perpetuated, vicious cycle we see of events in DED and recognizing the role of neurosensory abnormalities in DED."

Following a thorough review of today's collective understanding of DED, the subcommittee arrived at the following revised definition: [I, 4.3, p. 278]

Dry eye 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.

A major change in the new definition compared to the 2007 version is the addition of "a loss of homeostasis" as a disease characterization. [I, 4.3, p. 278] In the report, the subcommittee highlights a loss of tear film homeostasis as "the unifying characteristic that describes the fundamental process in the development of DED." [I, 5.4, p. 278] According to Definition and Classification subcommittee co-chair Kelly K. Nichols, OD, MPH, PhD, the term "loss of homeostasis" was a critical element added to the definition "to reflect our current knowledge of the importance of maintaining all aspects of tear film and ocular surface equilibrium. The terminology also keeps the door open to include any elements that are found to impact the delicate tear film homeostasis as we learn more in the future about dry eye etiology."

REPORTS COVERED
I. Definition and Classification
III. Epidemiology
VII. Iatrogenic

Another notable change is the generalization of ocular symptoms. While the 2007 DED definition specifically mentions discomfort and visual disturbance, the new definition remains more general, simply labeling DED as "accompanied by ocular symptoms." [I, 3, p. 277; I, 4.3, p. 278] This includes discomfort and visual disturbances while also accommodating the differences in symptoms reported across the world, said Dr. Craig.

In the 2007 definition, dry eye sequelae were described in terms of symptoms and tear film instability. [I, 3, p. 277] Increased tear film osmolarity and inflammation were also mentioned as factors that accompany DED. [I, 3, p. 277] However, the etiology of DED was not mentioned. [I, 3, p. 277] "It was still difficult to differentiate dry eye from other ocular diseases," Dr. Craig said. As a result, the subcommittee added "etiological factors that are important uniquely in dry eye" and made sure to "mention those as etiological factors and not […] as diagnostic criteria," Dr. Craig explained.

Despite several changes, the new definition still labels DED as a "multifactorial disease." [I, 4.3, p. 278] This first appeared in the 2007 definition and remains salient in recognizing "the multitude of factors that can be involved in dry eye," Dr. Craig said. [I, 3, p. 277]

A New Approach to Classification

The DED classification system also received a reboot to address some prevailing issues *(Figure 1)*. The structure of the previous system led many to believe that the aqueous deficient and evaporative categories could not overlap. [I, 6.2, p. 279] "Clinicians recognize that aqueous deficient and evaporative dry eye can occur together, often referred to as mixed DED, and the previous 2007 classification scheme did not make this clear. Importantly, the new classification allows for a patient to have components of both, on a sliding scale," says Dr. Nichols. "This now may require management of both in any one patient."

Also new to the classification system is accommodation for patients with discrepancies between signs and symptoms. The main path of the classification system includes patients who have both symptoms and signs. [I, 7.1, p. 280] This leads ODs to ask "triaging questions," which help in diagnosing other ocular surface conditions that may require management separate from DED. [I, 7.2, p. 280]

Not all dry eye patients present with both symptoms and signs, however, and the new classification takes this into consideration. Another path represents patients with symptoms but no signs, a possibility for those presenting with "a preclinical state in which the signs are too subtle to pick up," Dr. Craig said. [I, 7.3, p. 280; I, 7.4, p. 281] This situation could also come about if there is evidence of neuropathic pain. A path for patients with signs but no symptoms represents those "who may be picked up incidentally before ocular surgery, for instance, or it may be patients that have abnormal corneal sensation," said Dr. Craig. [I, 7.5, p. 281; I, 7.6, p. 281–282]

The final path is for patients with no symptoms and no signs. This leads to a "normal" diagnosis that requires no treatment, another new addition to the system. [I, Fig. 3, p. 281]

"Classification schemes should aid in appropriate diagnosis and subdiagnosis, and

therefore targeted management," Dr. Nichols says. "This new patient-centric approach to DED classification allows for a decision-tree to be used to guide the clinician in patient care of the DED patient."

Epidemiology

Ten years after the initial TFOS DEWS report, a vast swath of new literature exists to help practitioners better understand the epidemiology of DED. During this second review of the literature, the TFOS DEWS II Epidemiology subcommittee summarized the studies published in the past decade and performed meta-analyses to reveal disease prevalence stratified by sex and age. [III, abstract, p. 334; III, 1, p. 335-336] Additionally, the subcommittee summarized the available evidence on disease risk factors, natural history and morbidity. [III, 1, p. 335-336]

Key points of the Epidemiology report are as follows:

• ***DED definitions—and, thus, estimates—vary.*** The subcommittee evaluated the epidemiology of dry eye based on diagnostic criteria that include symptoms, signs or both, and on a prior diagnosis of DED made by an eye care practitioner, according to the report. [III, 7, p. 363] However, "there is considerable variation in terms of how the disease has been ascertained across these studies, and we broadly grouped the studies that were available into different diagnostic groups, including diagnostic criteria used in each of the studies of those with symptomatic disease, those that looked at signs only, those that looked at both symptoms and signs, and those looking at MGD," said Fiona Stapleton, MCOptom, PhD, lead author of the report, during the ARVO special session. She explained that the wide variation in symptomatic disease vs. signs-only disease that exists in the literature over the past decade—with more studies focusing on signs of DED than symptoms—complicated their task of assessing disease prevalence.

Perhaps, said Dr. Stapleton in a follow-up interview, the new TFOS DEWS II dry eye definition will help to inform future epidemiological studies. "The definition of a disease needs to be 'operationalized' or made specific for use in epidemiological studies," explains Dr. Stapleton, "so that in using a working diagnosis (e.g., Schirmer <5mm, corneal staining above a grade of 1, OSDI symptom score above 22), cases can be separated from non-cases."

"Further," adds Dr. Nichols, "our understanding of the factors that play a key role in the etiology—for example, those found in the DED definition—are largely explored through studies based in epidemiology."

• ***Regardless of definition, influencing factors remain constant.*** The subcommittee found sex, age and geographic location remain key factors for prevalence, regardless of diagnostic criteria used. [III, 4.2, p. 348-356] Prevalence increases linearly with age, for example, and females are more frequently affected, according to the report. [III, 3.2, p. 347; III, 4.2, p. 350] Prevalence appears higher in Asian than in Caucasian populations, though studies have not been conducted in all major geographic regions, the report says. [III, 4.2, p. 341; III, 4.4, p. 352]

Other factors that affect DED prevalence include diabetes and other systemic diseases, contact lens wear, environmental exposures, computer screen use and refractive surgery, the report says. [III, 4.2, p. 348-356]

In addition, "a meta-analysis of the published data to determine prevalence of dry eye stratified by age and sex shows a rate of change per decade between 8% and 10%; so, a high rate of change in symptomatic disease" was found, Dr. Stapleton said at ARVO.

• ***Sex matters, except in meibomian gland dysfunction (MGD).*** Looking at signs-based MGD stratified by sex and age, the report shows no female predilection in this group exists, explained Dr. Stapleton. In fact, "a different trend was observed for MGD than for other dry eye diagnostic criteria; males had a slightly higher prevalence for most age categories, although the differences were not statistically significant, except in the age 80+ group," according to the report. [III, 3.2, p. 347] However, the subcommittee notes only two studies reported age and sex data for MGD, possibly skewing the findings. "The effects of sex become more significant with age, and there does not appear to be the female preponderance in MGD as there is with other working diagnoses of dry eye disease, although this does require confirmation," Dr. Stapleton said at ARVO.

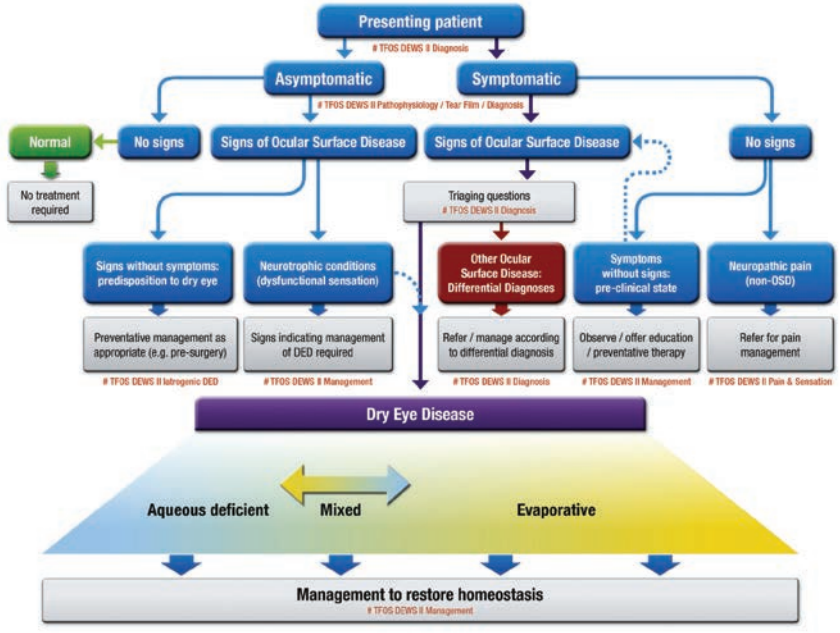


FIG. 1. CLASSIFICATION OF DRY EYE DISEASE. The upper portion represents a clinical decision algorithm, beginning with the assessment of symptoms and followed by review for signs of ocular surface disease. DED exhibits both symptoms and signs, and can be differentiated from other ocular surface disease with the use of triaging questions and ancillary testing. It is to this DED group that diagnostic subtyping, and conventional dry eye management strategies, apply. The lower portion of the figure represents the etiological classification of DED and highlights the two predominant and non-mutually exclusive categories: aqueous deficient dry eye (ADDE) and evaporative dry eye (EDE).

Adapted and reprinted from Ocular Surface (2017) 276–283, Craig JP, Nichols KK, Nichols JJ, et al. TFOS DEWS II definition and classification report, p. 281, © 2017, with permission from Elsevier.

• ***Kids and adults under 40 might be at risk for DED.*** "Most studies—again, using signs-based disease—showed an increased prevalence with age; however, symptoms were certainly high in the studies that looked at younger age groups," said Dr. Stapleton at ARVO. Limited studies have been carried out in youth, and there remains a need for studies in populations under 40 years of age, according to the report. [III, 7, p. 363] "The high symptom reporting in youths described by clinicians requires further exploration," Dr. Stapleton mentioned in her talk.

Elaborating, Dr. Stapleton says, "there were two studies, both in Southeast Asia, which suggested high rates of symptomatic DED in children and young adults. The vast majority of studies have included only individuals older than 40, so the rate of dry eye in youth represents a significant unanswered question and the impact of digital device use in this population requires further study."

• ***Geographical mapping reveals regional variations.*** The subcommittee looked at prevalence data from a novel geographical perspective. This approach will facilitate future exploration of climate, socioeconomic and environmental factors. [III, 3.2, p. 342, 347]

Despite these advances, many epidemiological questions remain unanswered. While consistent risk factors were confirmed, more hypothesis-driven studies are needed to evaluate digital device use, genetics and environment. [III, 5.1, 5.2, p. 357; III, 7, p. 363] In addition, little in the way of incidence studies exist, and more populations need to be studied. "The natural history is still unknown, and this is a key area to understand the disease prognosis," concludes Dr. Stapleton. ❍

IATROGENIC DRY EYE: WHEN A TREATMENT BECOMES A TRIGGER

The Iatrogenic subcommittee defines this form as "dry eye induced unintentionally by medical treatment from a physician or a health-related professional," Subcommittee Chair José Alvaro Gomes, MD, said during the ARVO session. [VII, 1, p. 516–517] To gain a better understanding of contemporary iatrogenic causes, the subcommittee developed an iatrogenic dry eye classification system of the following categories: ophthalmic surgery, pharmaceuticals, contact lenses (CLs), non-surgical ophthalmic procedures and non-ophthalmic conditions. [VII, 3, p. 517]

Findings in ophthalmic surgery-induced dry eye are among the most notable of the report. The authors took a comprehensive look at literature on refractive surgery, keratoprosthesis, cataract surgery, lid surgery and more. [VII, 4.4.1, p. 524; VII, 4.4.2, p. 525; VII, 4.4.3, p. 525–526; VII, 4.4.4, p. 526–528] Post-refractive surgery links to dry eye include the effect of a neurotrophic component on the lacrimal functional unit, as well as ocular rosacea's tendency to reduce tear break-up time. [VII, 4.4.1, p. 524] In keratoprosthesis, post-procedure reorganization of the nerves surfaced as a possible culprit, Dr. Gomes said. Literature on cataract surgery showed topical anesthetics and desiccation, possible light toxicity from the operating microscope, nerve transection, elevation of inflammatory factors, goblet cell loss and MGD as potential dry eye contributors. [VII, 4.4.2, p. 525] Also, a close interaction of the eyelid, tear film and ocular surface showed some prevalence in lid surgery-related dry eye. [VII, 4.4.3, p. 525–526]

Drug-induced dry eye can be related to either topical or systemic medications. [VII, 3, p. 517] For topical drugs (*Table 1*), the subcommittee found that the concentration of preservatives in glaucoma medications, specifically benzalkonium chloride, has the potential to cause inflammation and proptosis. [VII, 4.2.3, p. 521] "We know also that these patients sometimes don't use one—they use two or three medications, and this causes a potential effect of toxicity and dry eye," Dr. Gomes said. Of the top 100 best-selling systemic drugs in the United States in 2009, 22 proved to possibly cause dry eye secondary to decreased tear production, altered nerve input and reflex secretion, inflammatory effects on secretory glands or direct irritation effects through secretion into the tears, according to the report. [VII, 4.1.1, p. 517]

Factors involved in CL-induced dry eye include biophysical changes to the tear film such as a thinner lipid layer and increased tear evaporation, and ocular responses such as alterations to Langerhans cells, conjunctival goblet cell density and lid wiper epitheliopathy. [VII, 4.3.2, p. 524] Recall that existing DED can be exacerbated by lens wear and lenses can induce a dry eye state. Paul Karpecki, OD, who co-chaired the TFOS contact lens session and served on the TFOS DEWS II Diagnostic Methodology committee, noted studies by Villani and Arita showing that contact lenses can cause structural changes to the meibomian glands but said "it is up to the clinician to monitor for these and intervene before functional changes ensue."

Environmental circumstances such as computer use in an office setting also seemed to be a contributing factor to dry eye. [VII, 4.3.2, p. 524] In each instance, careful exploration of symptoms and signs are warranted to detect early stages of DED, Dr. Karpecki noted.

Some nonsurgical ophthalmic procedures that show dry eye prevalence include botulinum toxin treatment, corneal collagen crosslinking, positive pressure noninvasive ventilation, radiation treatment and cosmetic procedures such as eye makeup, tattooing and piercing. [VII, 4.5.1, p. 528; VII, 4.5.2, p. 529; VII, 4.5.3, p. 529; VII, 4.5.4.1, p. 530; VII, 4.5.4.2, p. 530]

Table 1. Topical Drugs Considered to Cause or Aggravate DED

- *Agents used to treat glaucoma*
  - Beta-blocking agents: betaxolol, carteolol, levobunolol, metipranolol, timolol
  - Adrenergic agonist drugs: apraclonidine, brimonidine, dipivefrin
  - Carbonic anhydrase inhibitors: brinzolamide, dorzolamide
  - Cholinergic agents: pilocarpine, ecothiopate
  - Prostaglandins: bimatoprost, latanoprost, travoprost, unoprostone
- *Agents used to treat allergies:* emedastine, olopatadine
- *Antiviral agents:* aciclovir, idoxuridine, trifluridine
- *Decongestants:* naphazoline, tetryzoline
- *Miotics:* dapiprazole
- *Mydriatics and cyclopegics:* cyclopentolate, tropicamide, hydroxyamphetamine
- *Preservatives:* benzalkonium chloride
- *Topical and local anesthetics:* cocaine, proxymetacaine, tetracaine
- *Topical ocular NSAIDs:* bromfenac, diclofenac, ketorolac, nepafenac

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NEW INSIGHTS ON HOW DRY EYE HAPPENS

Hyperosmolarity, inflammation and tear instability create a vicious circle that, once begun, is difficult to escape.

By Rebecca Hepp, *Managing Editor*

Research on dry eye has flourished over the last decade. While the original TFOS DEWS report included a section on research, it spanned just 14 pages with 216 references. TFOS DEWS II cites over 5,000 references in total and breaks the topic down into several research-specific subsections, such as pathophysiology; sex, gender and hormones; the tear film; and pain and sensation.

DEWS II provides unparalleled access to the global expert consensus on today's understanding of the disease and the ocular structures it affects. Here's a look at how they can impact your clinical acumen when treating patients with dry eye.

Pathophysiology

While the original TFOS DEWS report of 2007 did not include a separate pathophysiology section, the TFOS DEWS II report dedicates 75 pages to fully exploring the current understanding of the mechanisms of action behind DED. With 1,220 references, this section provides a comprehensive look at the mechanisms involved in the creation and perpetuation of DED.

The bottom line: "DED is initiated by desiccating stress and perpetuated by a vicious circle of ocular surface inflammation." [VI, 3, p. 442]

"The concept of the vicious circle has been reinforced over the past 10 years with evaporation, influenced by the environment, being the source of tear hyperosmolarity," Anthony Bron, FRCOph, lead author of the Pathophysiology section, explained during a special session at this year's ARVO meeting.

REPORTS COVERED

- **II.** Sex, Gender and Hormones
- **IV.** Tear Film
- **V.** Pain and Sensation
- **VI.** Pathophysiology

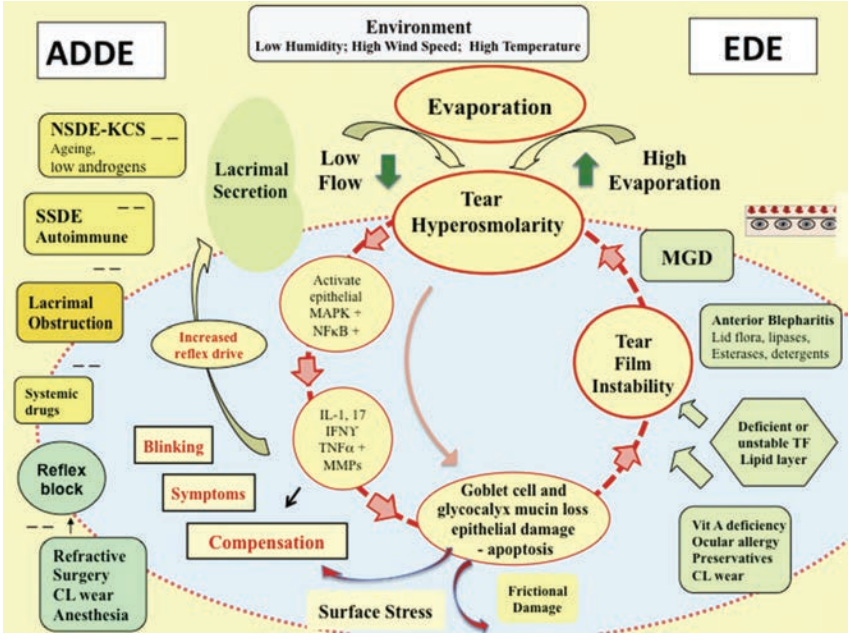

FIG. 1. THE VICIOUS CIRCLE OF DRY EYE DISEASE. The core mechanism of DED is tear hyperosmolarity, the hallmark of the disease. It damages the ocular surface both directly and by initiating inflammation. The cycle of events is shown at the center of the figure.

Two forms of DED are recognized, ADDE and EDE. In ADDE, hyperosmolarity results when lacrimal secretion is reduced, in conditions of normal evaporation. In EDE, tear hyperosmolarity is caused by excessive evaporation from the exposed tear film in the presence of a normally functioning lacrimal gland. Since tear osmolarity can only arise as a result of tear evaporation in both ADDE and EDE, hyperosmolarity is due to evaporation from the ocular surface and, in that sense, all forms of DED are evaporative. EDE is a hyper-evaporative state.

In DED, hyperosmolarity is considered to set up a cascade of signaling events in surface epithelial cells that leads to the release of inflammatory mediators and proteases. Such mediators, together with the hyperosmolarity itself, are conceived to cause goblet and epithelial cell loss and damage to the epithelial glycocalyx. Damage is reinforced by inflammatory mediators from activated T-cells, recruited to the ocular surface. The net result is the characteristic punctate epitheliopathy of DED and tear film instability, which leads to early tear film break-up. This exacerbates and amplifies hyperosmolarity and completes the vicious circle events that produce ocular surface damage. Ultimately, this is thought to lead to self-perpetuation of the disease.

Adapted and reprinted from Ocular Surface (2017) 441–515, Bron AJ, de Paiva CS, Chauhan SK, et al. TFOS DEWS II pathophysiology report, p. 460, © 2017, with permission from Elsevier.

"We know that hyperosmolarity causes pain directly, induces inflammatory signaling, epithelial cell death, MMP production, glycocalyx changes and it amplifies the process of mitosis, whereby the release of extracellular DNA activates a multicomponent inflammatory response of the ocular surface," said Dr. Bron.

This general thesis was just the starting point, however. The subcommittee further described the mechanics that maintain the tear film and what happens when homeostasis is lost—namely, exposure of the ocular surface to damaging desiccation. [VI, 3, p. 442]

The central mechanism at play, they summarize, is evaporative water loss leading to hyperosmolar tissue damage. [VI, abstract, p. 441] This central mechanism initiates changes that lead to evaporative dry eye (EDE)—"where tear hyperosmolarity is the result of an excessive evaporation from the tear film in the presence of normal lacrimal function"—and aqueous-deficient dry eye (ADDE)—"where hyperosmolarity results from a reduced lacrimal secretion in the presence of a normal rate of tear evaporation." [VI, 5.1, p. 455] From here, the vicious circle takes over, perpetuating ocular surface issues that exacerbate signs and symptoms and often morphs the condition into a hybrid form of dry eye *(Figure 1)*.

Because of this complex interplay between various forms of DED, the subcommittee recommends retaining the terms EDE and ADDE "to describe the initiating basis of a dry eye, but it should be recognized that with progression any form of DED may take on additional evaporative features." [VI, 5.1, p. 456]

Also, while studying what is known about the mechanisms of dry eye, the researchers realized that not all patients who show corneal staining have DED, and conversely, those with staining might have conditions other than dry eye.

"A portion of normal corneas show a little staining, so no staining is not the default in the normal eye," Dr. Bron said at ARVO. This provides more support for the inclusion of the normal eye in the updated classification system.

The lengthy review also highlighted areas lacking proper research, and Dr. Bron boiled down the subcommittee's biggest findings and recommendations: "We need new methods to measure the tear evaporation and osmolarity at the tissue level. We should recognize that the absence of corneal staining is not the normal default, and that hybrid dry eye states are very prominent."

Sex, Gender and Hormones

With 994 references, this report provides a comprehensive look at a body of literature that spans centuries, focused on the role sex, gender and hormones play in regulating the ocular surface and disease prevalence and progression. All three are integral and affect a patient's health, disease risk, diagnosis and progression, and even perceptions about health, the authors assert. [II, 1, p. 285]

"Our eye health is affected by various hormones," says Juan Ding, OD, PhD, a coauthor of the report. "When we treat dry eye disease, it is helpful to keep in mind that the patient's overall well-being may be a reason for their dry eye, and that we are not just treating the eye, but are actually treating the person by taking into consideration potential systemic causes of dry eye disease."

"Does sex matter? Yes, every self has a sex," said David A. Sullivan, PhD, the TFOS DEWS II report organizer, during the ARVO special session. "It's an important basic human variable, especially considering that the occurrence, frequency and severity of diseases may vary between males and females."

For starters, women in the United States are as much as 70% more likely to be diagnosed with DED than men, and the literature suggests women experience a greater impact of DED on visual quality indicators and on tasks requiring sustained visual attention. [II, 2.2.1, p. 286; II, 2.2.2, p. 287]

The research also shows a significant sex-related difference in ocular structures, including the lacrimal glands, meibomian glands, cornea, conjunctiva, nasolacrimal duct and tear film—all of which the subcommittee members speculate may contribute to the increased prevalence of DED in women. [II, 2.3, p. 288]

"There is a huge body of evidence to support that female sex is a risk factor for dry eye," says Sruthi Srinivasan, PhD, BS Optom, a coauthor of the report. "Are we being proactive about this in our practice? This report should make clinicians and researchers think about using different dry eye diagnostic tests and management techniques and strategies while examining men vs. women."

While most literature focuses on the biological differences between sexes, some highlights the role gender plays as well.

"Sex is not the same as gender," Dr. Sullivan emphasized at ARVO. "Sex is distinguished as males and females based on biological characteristics, and gender is first linked to socially constructed characteristics such as roles, behaviors and expectations related to being male or female."

"The literature abounds with examples of gender-based health disparities in access to care, care-seeking behavior (particularly in women in developed countries), communication with health care providers, service utilization and health outcomes around the world," according to the report—and all of these may apply with DED. [II, 4.1, p. 314]

Current research makes clear the importance of sex, gender and hormones on a patient's health and health care experience; still, the study authors also identified a number of shortcomings within the literature and recommend researchers work to remove barriers, including ethical, financial, sociological and scientific considerations. [II, 2.1.1, p. 286]

The Tear Film

Perhaps the most important factor in the study of dry eye is the tear film, as "DED is characterized by loss of tear volume, more rapid break-up of the tear film and increased evaporation of tears from the ocular surface." [IV, 1, p. 369]

Understanding the rapid break-up of the tear film demands a firm knowledge of the structure itself—not an easy task. While most researchers are comfortable with the many components of the tear film, such as lipids, proteins, mucins and electrolytes, how they all interact is still under investigation. The TFOS DEWS II Tear Film subcommittee emphasized that holding firm to the three-layer model of the tear film "has generally limited novel perspectives that might lead to a clearer understanding of the dynamics,

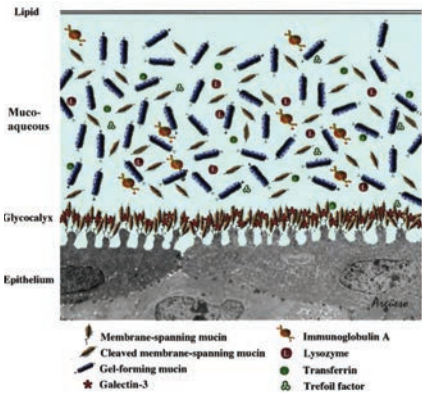

FIG. 2. The tear film structure showing the mucins and galectin of the glycocalyx, soluble mucins and proteins in the mucoaqueous layer and the surface lipid layer.

Reprinted from Ocular Surface (2017) 369-406, Willcox MDP, Argüeso P, Georgiev GA, et al. TFOS DEWS II tear film report, p. 383, © 2017, with permission from Elsevier.

structure and function of the tear film and the changes that occur to cause dry eye." [IV, 1, p. 369] Instead, researchers and clinicians should see the tear film for what it is: "a dynamic functional unit with different compartments." [IV, 1, p. 369–70] The committee described a lipid layer covering and integrated with a complex mixture of aqueous, mucins and proteins, all of which work together to maintain tear film and ocular surface homeostasis *(Figure 2)*.

A closer look at the lipid layer specifically helped to highlight both its importance and the long research road ahead to understand it fully. For one thing, the lipid layer lowers the tear surface tension, sustaining the tear film's high area-to-volume aspect ratio, the report states. [IV, 3.3, p. 378] "The tear film lipid layer was clearly important in stabilizing the tear film, as degradation increases the surface tension; but interestingly, supplementation to delipidated tears with meibum lipids does not seem to be able to restore the lost surface tension," explained Mark Willcox, PhD, lead author of the Tear Film subcommittee report, during the ARVO special session. This suggests normal surface tension may rely on not just lipids, but possibly proteins and glycoproteins from the mucoaqueous layer, the report says. [IV, 3.3, p. 378]

In addition, despite varying hypotheses to explain tear evaporation suppression—with the lipid layer variously credited with some, all or none of the effect—the researchers finally concluded that "all tear film key constituents may contribute to increased evaporative resistance." [IV, 3.1, p. 376–377]

So far, it's clear tear film osmolarity increases in DED, and changes to proteins and mucins can be used as biomarkers, but more research is still needed to fully understand the mechanisms at play within the tear film.

"Still, the most useful, from a clinical perspective, methods for diagnosing dry eye in the clinic are measuring osmolarity and stability of the tear film," Dr. Willcox said in a correspondence. "These, coupled with Schirmer I, questionnaires such as the Ocular Surface Dryness Index and examining the meibomian glands, facilitate a good diagnosis."

To aid in further studies, the report authors recommend researchers be meticulous with terminology to avoid confusion and misrepresentation.

For example, the assumption that tear osmolarity is approximately 302mOsm/L is often acceptable, but technically that number is the value only for tears from the lower tear meniscus. [IV, 1, p. 370] It may represent the overall osmolarity of the ocular surface, but no evidence supports that hypothesis yet. A more careful approach to terminology could lead to more precise data and better findings.

"Newer methods that measure aspects of the tear film, such as changes in the concentration of proteins, lipids and mucins, are being developed, but are not at the stage of clinical testing," Dr. Willcox continued. "It is probable that future testing will incorporate changes in, for example, a range of proteins and this should improve the specificity and sensitivity of tests." ❍

SPOTLIGHT ON PAIN AND SENSATION

"We insist on the concept that dry eye symptoms and sensations are a form of pain," said lead author Carlos Belmonte, MD, PhD, during the ARVO special session. Moving forward with this concept in mind, the Pain and Sensation subcommittee took a closer look not only at the neurons that innervate the ocular surface but how they respond to "mechanical forces, noxious chemicals and to low temperatures and the change in osmolarity," said Dr. Belmonte.

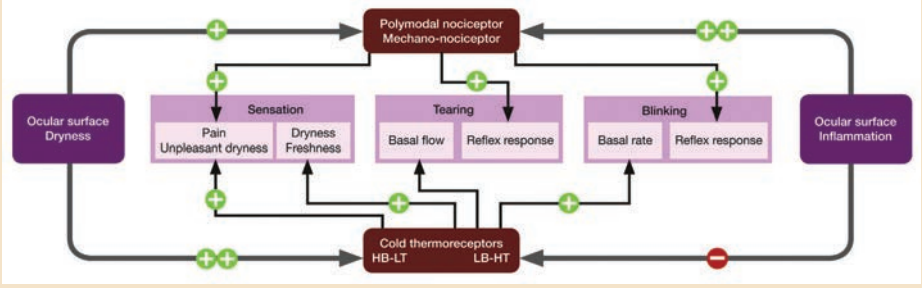

FIG. 3. How ocular inflammation or ocular surface dryness provoke variable increases (+) or decreases (-) of nerve impulse activity in polymodal- and mechano-nociceptors and in cold thermoreceptors of the high background, low threshold (HB-LT) and low background, high threshold (LB-HT) types. Together these changes evoke conscious sensations of different quality, as well as changes in tear flow and in spontaneous and reflex blinking.

Adapted and reprinted from Ocular Surface (2017) 407–440, Bron AJ, de Paiva CS, Chauhan SK, et al. TFOS DEWS II pain and sensation report, p. 423, © 2017, with permission from Elsevier.

Corneal sensory neurons are broken down into three categories: polymodal nociceptors, specific mechano-nociceptors and cold thermoreceptor neurons. While polymodal nociceptors respond to chemical, mechanical and thermal stimuli and become sensitized by inflammation, mechano-nociceptors only respond to mechanical forces. [V, 8, p. 430] The most important neurons in the pathology of dry eye, researchers suspect, are cold thermoreceptors, which discharge continuously with normal eye surface temperature and increase or decrease the firing frequency based on cooling or warming, respectively. These neurons also seem to be sensitive to changes in osmolarity, leading the authors to suggest that "cold-sensitive fibers contribute to the reflex control of basal tear production and blinking." [V, 8, p. 430]

The inflammation in DED caused by reduced tear secretions may sensitize polymodal nociceptors and mechano-nociceptors, while depressing cold thermoreceptor activity, they found. [V, 8, p. 430] But at the same time, the literature shows sensitization of nociceptor fibers is minor in DED, while a prominent and abnormal increase in cold thermoreceptor nerve activity occurs that parallels the morphological changes in corneal innervation. [V, 8, p. 430]

But knowing the science behind pain pathways can only take you so far in your clinical practice, because "the complex pain and discomfort experience suffered by dry eye patients is very variable," Dr. Belmonte said. The subcommittee recommends clinicians rely on pain questionnaires to help characterize their patients' discomfort, in addition to tear component testing and *in vivo* confocal microscopy to better view the nerve endings affected by DED. More studies are needed in this emerging area of dry eye disease, they conclude.

MODERNIZE YOUR METHODS OF DRY EYE CARE

Put your new understanding of ocular surface dynamics into action with these updated guidelines.

By **Bill Kekevian**, *Senior Editor*

The heterogeneity of the dry eye population—diverse in both physical characteristics and clinical presentation—adds much complexity to the task of determining the etiology and devising an appropriate treatment plan. The TFOS DEWS II Diagnostic Methodology subcommittee report embraces the idea that evaluating for dryness requires flexibility in approach to accommodate such a varied patient base.

The 2007 DEWS report identified a set of key elements deemed necessary for diagnosis, including symptoms of discomfort, visual disturbance, tear film instability, increased osmolarity and inflammation of the ocular surface. Those elements were expected to be present, at least subclinically, and the aim was to use those clinical findings to narrow the diagnosis into one of two subcategories: evaporative or aqueous deficient. The 2017 DEWS II Diagnostic Methodology recommendations are more nuanced and fluid.

In parallel with this diagnostic refinement, treatment advancements have allowed eye care practitioners to now choose from a wider range of treatment options than 10 years ago. The DEWS II Management and Therapy subcommittee report offers a staged approach to therapy and updated recommendations on treatment methods available for tear insufficiency and lid abnormalities, as well as the ascendant role of anti-inflammatory drugs and lifestyle changes.

REPORTS COVERED

VIII. Diagnostic Methodology
IX. Management and Therapy
X. Clinical Trial Design

Diagnostics

The primary change to the Diagnostic Methodology protocols between the 2007 and 2017 reports is the new publication's specification of a diagnostic process (*Figure 1*) rather than circumscribing the approach with a set of mandatory requirements, according to Leslie O'Dell, OD, a member of the TFOS Public Awareness and Education committee. For example, the 2017 report blurs the previously strict division between evaporative dry eye and aqueous deficient dry eye. Instead, it embraces the concept of an evaporative/aqueous deficiency spectrum, which clinicians have long recognized anecdotally.

According to James Wolffsohn, FCOptom, PhD, associate pro-vice chancellor and professor of optometry at the Aston University School of Life and Health Sciences in Birmingham, UK, and chair of the Diagnostic Methodology subcommittee, viewing the two DED categories as discrete conditions does not capture the true spectrum of the condition resulting from the many factors that influence DED.

The report itself advocates a more holistic, patient-centric approach, noting that "any indication that specific signs must be present" to diagnose dry eye "has been removed and an emphasis has been placed on the homeostasis of the tear film. Loss of homeostasis implies the body has lost the ability to maintain equilibrium, resulting in a hyperosmolar, unstable tear film with associated sequelae," such as increased osmolarity, inflammation, neuropathy and reduced function, according to the report. "Hence, diagnosis requires knowledge of what is considered normal, even though this may vary with patient demographics." [VIII, 3, p. 545]

Among its many areas of guidance, the report advises practitioners to:

• ***Ask the right questions.*** The DEWS II Diagnostic Methodology report asserts that the first step in a dry eye workup should include gathering a comprehensive patient history via one of the available patient questionnaires (*Table 1*) to quantify their experience of their condition in a systematic fashion, giving the clinician early signals to pursue. [VIII, 6.2.1, p. 549]

Table 1. Selected Patient Questionnaires for Eliciting Symptoms of Visual Disturbance

- Ocular Surface Disease Index (OSDI)
- Dry Eye Questionnaire (DEQ-5)
- Impact of Dry Eye on Everyday Living (IDEEL)
- National Eye Institute's Visual Function Questionnaire (NEI VFQ-25)
- Dry Eye-related Quality-of-Life Score (DEQS)
- Computer-vision Symptom Scale (CVSS-17)

The report reviews all surveys; while each can be a valuable tool, the text states that "the consensus view of the committee was to use the OSDI, due to its strong establishment in the field, or the DEQ-5, due to its short length and discriminative ability." [VIII, 6.1.1, p. 549] Dr. O'Dell says this recommendation is likely to change how she practices. "For me, the questionnaires are the biggest change," she says, noting in particular the recommendation to use the DEQ-5, which she previously did not employ. Dr. O'Dell hopes to use it to better diagnose Sjögren's syndrome, which can make a big impact. "Patients who have Sjögren's are 44 times more likely to develop lymphoma," she says.

In addition to questionnaires, the report emphasizes the importance of conducting a patient risk factor analysis by asking about their medications, contact lens wear and tobacco use, among other factors. [VIII, Fig. 5, p. 361]

• ***Identify homeostasis markers.*** Once symptom screening identifies a dry eye suspect, evaluate homeostasis markers. DEWS II encourages doctors to pick at least one from these three categories: tear break-up time (TBUT), hyperosmolarity and ocular

surface staining. [VIII, 6.3, p. 551] TBUT is best measured noninvasively, the report indicates, since "fluorescein reduces the stability of the tear film and therefore the measurement may not be an accurate reflection of its status." [VIII, 6.3.1.2, p. 551] However, the sensitivity and specificity of fluorescein TBUT for patients with Sjögren's are moderate: 72.2% and 61.6%, respectively. [VIII, 6.3.1.2, p. 581]

Every office has the ability to perform a conventional fluorescein TBUT. Noninvasive TBUT measurements can be performed with a number of devices, including corneal topographers, the Keratograph (Oculus), CA-800 (Topcon), the HD Analyzer (Visiometrics) and interferometers. "Although noninvasive testing is preferred, more sensitive and recommended," says Paul Karpecki, OD, a TFOS Diagnostic Methodology committee member, "the committee noted that clinicians who do not yet have access to these technologies can default to standard fluorescein TBUT tests to achieve this element of diagnostic testing."

Doctors may also rely on tear film osmolarity testing, which the Diagnostic Methodology report identifies as having "the highest correlation to disease severity of clinical DED tests, and has been frequently reported as the single best metric (if only one test was used) to diagnose and classify DED." [VIII, 6.5.1.1, p. 554]

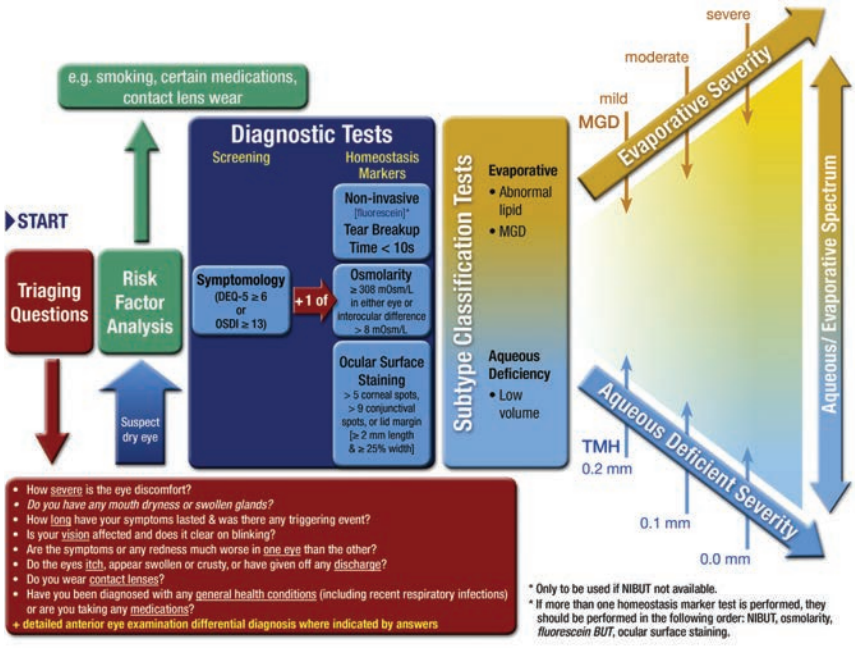

FIG. 1. DED DIAGNOSTIC TEST BATTERY. The screening DEQ-5 or OSDI confirms that a patient might have DED and triggers the diagnostic tests of noninvasive break-up time, osmolarity and ocular surface staining with fluorescein and lissamine green. On initial diagnosis, it is important to exclude conditions that can mimic DED with the aid of the triaging questions and to assess the risk factors which may inform management options. Marked symptoms in the absence of clinically observable signs suggest there may be an element of neuropathic pain.

DED is a subset of OSD; signs alone may still warrant management to prevent DED manifestation and to optimize the optical corneal surface, such as prior to refractive surgery or contact lens wear. MGD lipid thickness/dynamics and tear volume assessment and their severity inform the subtype classification of DED (as predominantly evaporative or predominantly aqueous deficient) which helps inform the management of DED.

***Mild MGD* is indicated by a secretion grade 4-7, an expressibility grade of 1 and an amorphous/color fringes lipid pattern. *Moderate MGD* is indicated by meibomian gland orifice plugging, lid margin vascularity, a secretion grade 8-12, an expressibility grade of 2 and a meshwork or wave (flow) lipid pattern. *Severe MGD* is indicated by lid margin meibomian gland orifice drop-out or displacement, a secretion grade 13, an expressibility grade of 3 and an absent, globular or abnormal colored fringes lipid pattern.**

Adapted and reprinted from Ocular Surface (2017) 544–579, Wolffsohn JS, Arita R, Chalmers, R, et al. TFOS DEWS II diagnostic methodology report, p. 561, © 2017, with permission from Elsevier.

The report also advocates both corneal fluorescein and conjunctival staining to evaluate DED, with a preference for lissamine green over rose bengal, as it is easier to obtain and less toxic, improving patient tolerance. Because staining shows the best correlation to disease severity in severe cases, the report recommends relying on it alone only for severe cases, and looking to the other two options to detect mild and moderate DED. [VIII, 6.5.1.1, p. 554]

• ***Recognize clinical subtypes.*** While the subclassifications of evaporative and aqueous deficient dry eye remain in the new classification scheme, the lines between them are now less distinct. Validated by the Diagnostic Methodology report "is what we've been seeing—there are a large number of patients in the mixed category, so it's not just 'aqueous deficient' or just 'evaporative' anymore," Dr. O'Dell says. "Newer, more sensitive tests show if patients are predominantly evaporative or predominantly aqueous deficient. My charting is now going to change to say 'mixed DED, predominately aqueous.'"

• ***Consider the differentials.*** Finally, the DEWS II Diagnostic Methodology report discusses the importance of differential diagnosis and recommends triaging questions and procedures to exclude other conditions that may mimic some signs and symptoms of dry eye.

"Because we understand how signs and symptoms do not correlate and that symptoms of dry eye disease can be consistent with numerous other ocular conditions, the committee felt that the addition of this section was vital, which was not present in DEWS I," Dr. Karpecki says. "For example, there is significant overlap between symptoms of itching and dryness in patients with DED and allergic conjunctivitis. Diagnostic differentiators include tests like osmolarity, corneal staining and even meibomian gland expression. But we also emphasize looking for clinical findings, including systemic ones such as rhinitis, which would indicate allergic conjunctivitis and not dry eye."

Other conditions that have potential symptoms of dryness, grittiness, burning, stinging and/or redness include conjunctivitis (e.g., allergic, bacterial, GPC and viral, as well as atopic keratoconjunctivitis), infectious diseases (e.g., chlamydia, herpes simplex/zoster), corneal abnormalities (e.g., abrasion, corneal erosion, foreign body and mucous plaques), filamentary and other

Table 2. DEWS II Staged Management & Treatment Recommendations

STEP 1:

- Education regarding the condition, its management, treatment and prognosis
- Modification of local environment
- Education regarding potential dietary modifications (including oral essential fatty acid supplementation)
- Identification and potential modification/elimination of offending systemic and topical medications
- Ocular lubricants of various types (if MGD is present, consider lipid-containing supplements)
- Lid hygiene and warm compresses of various types

STEP 2:

If above options are inadequate, consider:

- Non-preserved ocular lubricants to minimize preservative-induced toxicity
- Tea tree oil for *Demodex* (if present)
- Tear conservation
- Punctal occlusion
- Moisture chamber spectacles/goggles
- Overnight treatments (such as ointment or moisture chamber devices)
- In-office, physical heating and expression of the meibomian glands (including device-assisted therapies, such as LipiFlow, TearScience)
- In-office intense pulsed-light therapy for MGD
- Prescription drugs to manage DED
- Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present)
- Topical corticosteroid (limited duration)
- Topical secretagogues
- Topical non-glucocorticoid immunomodulatory drugs (such as cyclosporine)
- Topical LFA-1 antagonist drugs (such as lifitegrast)
- Oral macrolide or tetracycline antibiotics

STEP 3:

If above options are inadequate, consider:

- Oral secretagogues
- Autologous/allogeneic serum eye drops
- Therapeutic contact lens options
- Soft bandage lenses
- Rigid scleral lenses

STEP 4:

If above options are inadequate, consider:

- Topical corticosteroid for longer duration
- Amniotic membrane grafts
- Surgical punctal occlusion
- Other surgical approaches (e.g., tarsorrhaphy, salivary gland transplantation)

Adapted and reprinted from Ocular Surface (2017) 580–634, Jones L, Downie LE, Korb D, et al. TFOS DEWS II management and therapy report, p. 615, © 2017, with permission from Elsevier.

keratitides (e.g., interstitial) and keratopathies (e.g., neurotrophic and pseudophakic bullous), rheumatological conditions, visual asthenopia and other ocular conditions that mimic dry eye disease (e.g., epithelial basement membrane dystrophy, Salzmann's nodular degeneration, conjunctivochalasis). [VIII, 9, p. 564-568]

Therapeutics

"If you look at the original DEWS from a decade ago, there were fewer options available and we didn't have as much latitude" in devising a treatment regimen, says Lyndon Jones, BSc, PhD, Treatment and Management subcommittee chair and director of the Centre for Contact Lens Research at the University of Waterloo in Ontario, Canada. Another key departure, he notes: there was almost no mention of evaporative dry eye in the previous report. "It was almost all focused on aqueous deficient dry eye because that was the level of understanding at the time." The 2011 TFOS International Workshop on Meibomian Gland Dysfunction report "made us much more aware of having poor lipid delivery to the tear film and ocular surface," he observes. In its wake, attention shifted to better understanding this vector of dry eye development.

As a guiding principle for DED treatment, the mantra DEWS II offers is *return to homeostasis*. "The goal is to screen for and identify dry eye disease, subclassify and target treatment appropriately" to restore homeostasis, notes Dr. Jones. Adds Dr. Karpecki, "it is critically important to follow-up to improve patient outcomes."

The data pertaining to interventions have been exhaustively researched over the last decade. "The most significant challenge we had as a group was the enormous explosion of studies in our areas to consider compared to the TFOS DEWS original report," says Dr. Jones. "The original management and therapy report had 185 references, and this one has more than a thousand."

The 2017 Management and Therapy report presents a hierarchy of treatment modalities, but moved away from a 'grade' system used in 2007 and into a 'step' approach (*Table 2*) because, Dr. Jones says, grades suggest that the patient needs to exhibit changes before being moved to a new class of treatments. Doctors should consider earlier detection and treatment for optimal patient outcomes, and also should consider it acceptable to combine treatment approaches found across subclassifications (i.e., aqueous deficient and evaporative DED).

"The more severe the DED is, the more likely you are to climb the management steps," explains Dr. Jones of the treatment/management steps listed, which range in order of severity from 1 to 4. "Don't be concerned about using Step 1 items and adding something from Step 2," he advises. "They can be used concurrently."

Key areas to address clinically include:

• ***Tear insufficiency.*** Aqueous deficient patients are typically treated using one of three methods: tear replacement, conservation or stimulation. A plethora of replacement options are reviewed in the DEWS II report; however, it reads, "these products do not target the underlying pathophysiology of DED." [IX, 2.1, p 583] Nonetheless, the report provides updates on the research into the myriad palliative therapies such as osmotic agents. An alternative therapy often used in more moderate to severe DED is autologous serum, considered a tear replacement with potential restorative effects. Tear conservation via punctal occlusion techniques, when combined with other treatment methods, can provide symptomatic improvement, but the evidence remains limited. Finally, the section on stimulation techniques includes a look at lipid stimulators, such as insulin-like growth factor 1, and the new category of nasal neurostimulation.

• ***Lid abnormalities and hygiene.*** Blepharitis, bacterial overcolonization, *Demodex* infestation, MGD and incomplete blinks can all predispose a patient to dry eye. As the Management and Therapy report describes,

with "no universally accepted guidelines for lid cleansing" available, patients may feel confused. [IX, 3.1.1, p. 593] However, a whole marketplace of remedies, including warm compress systems and physical treatments, attempt to combat the deleterious effects of lid abnormalities. [IX, 3.1.1, p. 593] Since compliance is typically low with warm compresses [IX, 3.2.2, p. 594], a cottage industry of at-home devices has emerged, such as moist heat eye masks. Additionally, treatments such a meibomian gland expression, intense pulsed-light therapy and LipiFlow (TearScience) all seek to better serve these patients.

- ***The role of anti-inflammatories.*** While anti-inflammatory agents such as corticosteroids are effective for short-term use, two in particular are expressly designed and tested for dry eye: Xiidra (lifitegrast, Shire) and Restasis (cyclosporine, Allergan). While these agents are effective, they must be used appropriately as part of a treatment plan that addresses all aspects of DED. For instance, Dr. O'Dell says, "in a patient whose presentation is predominantly evaporative in nature, there might also be inflammation present on the surface triggering hyperosmolarity." Such a patient would benefit from an anti-inflammatory agent to improve the ocular surface status combined with meibomian and eyelid interventions that seek to restore proper function, she notes. Tear osmolarity, as a biomarker of DED, can help gauge the response to anti-inflammatory treatment.

Dr. Jones concurs on the wisdom of using anti-inflammatory and lid hygiene therapies together. The Management and Therapy report offers that precise recommendation. Dr. Karpecki, who served on the Diagnostic Methodology committee, feels the management recommendations for patients with an evaporative dry eye component include managing lid hygiene, inflammation, meibomian gland obstruction and the tear film in concert.

An Eye to the Future

The TFOS DEWS II publication is a definitive advance in the understanding of DED, like the original 2007 DEWS before it and the TFOS MGD International Workshop, which itself brought to the forefront a greater understanding of evaporative dry eye and the role of lipids in the disease process.

As investigators look to the future, Dr. Jones suggests greater attention to biomarker research could reveal the next breakthrough in understanding and taming this complex, multifactorial disease. "What's happening on a cellular level of a damaged ocular surface—that's really interesting," he says about the frontiers ahead.

While the research world prepares for that radical shift, clinicians can begin to institute a sea change of their own. "I think optometrists should get onto the concept of preventative care, as dentists do," explains Dr. Jones. "Practitioners generally are not very good at trying to talk to patients about the ocular equivalent of flossing your teeth. If patients were managed earlier and we talked about ocular surface hygiene and moved toward managing homeostasis, maybe we could prevent some from progressing to the more intractable stages of dry eye."

The report's tenth and final report, Clinical Trial Design, aims to raise the bar. "What really shocked us was how little high-level evidence there is to support many of the things we do or we prescribe on a day-to-day basis," Dr. Jones noted at the DEWS II ARVO session. The recommendations the Clinical Trial Design report puts forth are targeted at eliminating what the authors refer to as "vagaries of dry eye disease" that were previously complicating clinical trials. [X, 3.1, p. 636] They endorse a prospective, randomized, doubled-masked, placebo- or vehicle-controlled, parallel-group approach. [X, 3.1, p. 636] With an evidence-based foundation for the eye care community's current protocols and greater rigor brought to study design, the future looks bright. ❍

FIVE WAYS TO APPLY TFOS DEWS II TO YOUR PRACTICE TODAY

By Kelly K. Nichols, OD, MPH, PhD, *co-chair of the Definition and Classification committee and Dean of the UAB School of Optometry*
and Paul M. Karpecki, OD, *TFOS Diagnostic Methodology committee member and Clinical Director of Advanced Ocular Surface Disease, Kentucky Eye Institute*

Have you ever had the feeling you were right on the edge of a defining moment? A game-changer? It does not happen often, but we sit up and pay attention when it does. Recently, we have seen a flood of efforts in the arena of dry eye disease—clinicians starting dry eye-specific clinics, patients asking for treatments, and lectures and workshops focused on dry eye, to name just a few. But what if you are starting from scratch—how can you get there? We can show you how.

"The TFOS DEWS II report is the singular most informative dry eye document from the last 10 years—it sums up everything we currently know and the direction we need to go," says Dr. Karpecki. Adds Dr. Nichols, "this report is less about the sheer volume of the information and more about the knowledge and forward-looking statements—it is what we do with this document as clinicians and scientists that will really make a difference."

For the last 2.5 years, we have both been part of this amazing process, and our collective advice in summarizing the reports is as follows:

1. Ask the right questions. Whether you or your staff administer a dry eye survey, the DEQ, OSDI or ask triaging questions, consistency in symptom assessment will aid screening and diagnosis.

2. Use screening tests. Every practice can perform two of the three recommended screening tests: TBUT, osmolarity and corneal staining. Make the most of your screening process.

3. Determine predominant subtype (aqueous deficient, evaporative). The right dry eye subclassification will guide treatment—and, don't forget, both can occur simultaneously.

4. Target your management plan. With many options, combined therapy targeting both subtypes will be most effective.

5. Manage expectations. You and your patient are in this for the long haul. An ounce of prevention may avoid a lifetime of suffering, and optometrists are poised to take charge.

At *Review of Optometry*, we are honored to have presented this DEWS II summary to you. Use it well and your dry eye patients will thank you.

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