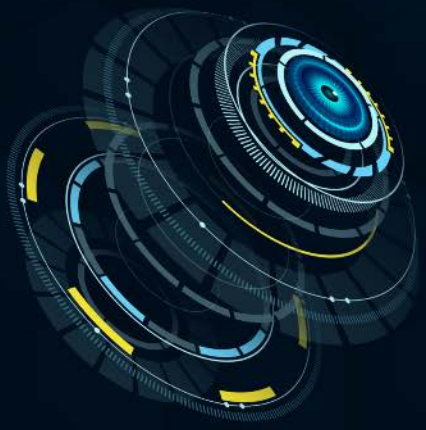

BEYOND DEWS II

An overview of the latest advances in dry eye disease management, treatment innovations, and insights into the condition's pathophysiology since the landmark TFOS DEWS II report.

BY QUILLAN M. AUSTRIA, MD, AND CHRISTOPHER E. STARR, MD

In 2017, the Tear Film and Ocular Surface Society (TFOS) published the TFOS Dry Eye Workshop II (DEWS II) in *The Ocular Surface*.[1-9] The objectives were to update the definition of dry eye disease (DED) established in DEWS I and critically review and integrate the substantial volume of literature on various aspects of DED, including risk factors, pathophysiology, management, and future therapies. Since the publication of DEWS II, the field of DED has grown considerably, with more than 8,000 studies added to the literature. This article highlights some of the significant advances since the publication of DEWS II and seeks to increase awareness of future interventions in DED treatment.

TEAR FILM HOMEOSTASIS

At the core of the DEWS II definition of DED is the disruption of tear film homeostasis.[1] Since 2017, clinicians' awareness and understanding of the crucial role and visual impact of the tear film and ocular surface on postoperative outcomes have grown. In 2019, the ASCRS Cornea Clinical Committee published its now widely adopted novel preoperative ocular surface disease (OSD) diagnostic and treatment algorithm. This tool can help busy cataract and refractive surgeons with diagnosing and managing perioperative OSD.[10]

The factors contributing to tear film disruption are extensive; they encompass individual characteristics, the physical environment, and daily lifestyle decisions. A significant lifestyle factor highlighted in DEWS II, one that is increasingly prevalent in daily life, is the digital environment. The TFOS lifestyle report on the impact of the digital environment on the ocular surface explores how technology affects DED and digital eye strain.[11] The digital environment is a crucial risk factor for DED. Studies have found that 78% to 97% of computer users experience poor tear film stability, leading to symptoms of DED.[12,13] Research has also indicated that the increased use of digital devices correlates with lower scores on the Schirmer test. Talens-Estarelles et al demonstrated that, the greater the number of years an individual has used a computer and the longer the duration of use is, the more likely they are to have lower Schirmer test scores.[14] This increased dryness is thought to result from a reduced blink rate and incomplete blinking, which increase the tear film's susceptibility to evaporative and aqueous deficiency disruptions.[15]

LIFESTYLE AND ENVIRONMENTAL FACTORS

The COVID-19 pandemic significantly altered people's lifestyles and introduced novel risk factors for DED, notably the use of face masks.[16] Mask-associated DED had been identified before the pandemic and is believed to be caused when an improperly fitted mask directs airflow around the eyes.[17] The widespread recommendation for mask usage during the pandemic led to an increase in the number of people presenting with first-time dry eye symptoms. A survey of 3,605 patients found that 18.3% experienced worsened dry eye symptoms while wearing masks.[18] A prospective cohort study of 203 participants assessed dry eye symptoms in groups categorized by mask-wearing duration. It found that those wearing masks for less than 3 hours per day had significantly fewer dry eye symptoms than those wearing masks for 3 to 6 hours daily ($P = .01$).[19]

DEWS II recommended a stepwise approach to DED management, starting with patient education, dietary modifications, and lubricating eye drops and advancing to prescription medications, punctal plugs, and more sophisticated forms of treatment.[9] Significant progress has been made in treatment methodologies since then.

NUTRITIONAL INTERVENTIONS AND GUT MICROBIOME

The evidence on omega-3 fatty acid supplementation has been mixed.[20] Shortly after DEWS II was published, the Dry Eye Assessment and Management (DREAM) study found that omega-3

supplementation did not yield better outcomes compared to controls.[21] Later, Downie et al conducted a Cochrane review of 34 studies involving 4,314 participants and concluded that there was low-certainty evidence that omega-3 supplements reduced dry eye symptoms compared to placebo but moderate-certainty evidence suggesting improvements in Schirmer scores and tear film breakup time.[22] These findings indicate that omega-3 fatty acids might improve the physical indicators of dry eye rather than the symptoms.

In contrast, another meta-analysis including 17 trials with 3,363 patients reported improvements in both the symptoms and signs of DED with omega-3 supplementation.[23] Moreover, the TFOS report on the digital environment and ocular surface identified oral omega-3 supplementation as a likely effective treatment for digital eye strain.[11] Although further research

EMERGING FDA-APPROVED TREATMENTS IN DED MANAGEMENT

Lacrifill (cross-linked hyaluronic acid derivative; Nordic Pharma).

- **Type:** Temporary ocular canalicular occlusion device
- **Purpose:** Enhances tear film stability and provides relief for dry eye disease (DED) symptoms by temporarily occluding the canalicular system
- **FDA status:** Approved in 2024

Cyclosporine ophthalmic solution 0.1% (Vevye, Harrow)

- **Type:** Prescription medication
- **Purpose:** Increases tear production with less irritation owing to a water-free, preservative-free formulation
- **FDA status:** Approved in May 2023
- **Notable finding:** In phase 3 trials, 71.6% of participants experienced clinically meaningful benefits.[1-3]

Perfluorohexyloctane ophthalmic solution (Miebo, Bausch + Lomb)

- **Type:** First prescription eye drop for evaporative DED
- **Purpose:** Forms a protective layer to reduce tear evaporation
- **FDA status:** Approved in May 2023
- **Notable finding:** Clinical improvement in dry eye symptoms at 4 weeks, with significant improvement at 2 and 8 weeks.[4-6]

Lotilaner ophthalmic solution 0.25% (Xdemvy, Tarsus Pharmaceuticals)

- **Type:** Treatment for anterior blepharitis due to *Demodex* infestation
- **Purpose:** Targets mites residing in the meibomian glands and lash follicles
- **FDA status:** Approved in July 2023
- **Notable finding:** Significant mite eradication and symptom improvement in the Saturn-1 trial[7-10]

Loteprednol etabonate ophthalmic suspension 0.25% (Eysuvis, Alcon)

- **Type:** First eye drop indicated for the short-term treatment of DED flares
- **Purpose:** Addresses sudden exacerbations in previously stable DED patients
- **FDA status:** Approved in October 2020
- **Notable finding:** Provided rapid relief from DED flare symptoms[11]

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into omega-3 fatty acids for DED is needed, other supplements such as turmeric and vitamin D3 have shown benefits for these patients.[24]

Research is exploring the impact of nutrition on inflammatory mediators—recognized contributors to DED—via modifications in the gut microbiome. Investigations have shown alterations in the gut microbiome in patients with DED and Sjögren syndrome.[25] A noteworthy study found that patients with Sjögren syndrome who underwent fecal transplants, which significantly altered their microbiome, reported relief from dry eye symptoms at 3 months.[26] These findings are encouraging, but questions remain about the specific microbiome properties most advantageous for patients with DED and how to develop a safe, effective method for modifying gut flora.

PRESCRIPTION MEDICATIONS

Significant advances have been made in the second level of treatment proposed by DEWS II—prescription medication. Antiinflammatory modulators such as cyclosporine A (CsA) 0.05% (Restasis, Allergan/AbbVie) were observed to be a widely used treatment for DED in DEWS II.[9] Since then, a Cochrane review on the efficacy of CsA 0.05% for dry eye patients found the evidence to be inconclusive. Although treatment with CsA 0.05% led to an increase in the number of conjunctival mucosal cells, no improvements in mucus secretion or associated tear film parameters were found. The review also highlighted a potential increase in adverse events, particularly a burning sensation associated with the topical application of cyclosporine.[27] The conclusion was that more long-term studies are required.

Some limitations associated with CsA (both 0.05% and 0.09% [Cequa, Sun Ophthalmics]) emulsion might be mitigated by a new water-free and preservative-free CsA formulation dissolved in a semifluorinated alkane (Vevye, Harrow), which was recently approved by the FDA. Vevye contains CsA at a 0.1% concentration.[28] Due to its higher concentration and distinct vehicle, Vevye might offer increased bioavailability and cause less irritation to the ocular surface.[28] In a phase 2 clinical trial, treated patients experienced improvements in corneal staining and a faster onset of symptom improvement compared to those who received the 0.05% emulsion.[29] A subsequent phase 3 randomized clinical trial, ESSENCE-2, corroborated these results. ESSENCE-2 involved 834 participants, and 71.6% of those in the CsA group experienced clinically meaningful benefits from treatment.[30] Although the initial data are promising, further long-term efficacy studies are necessary. (For detailed information on recent FDA-approved treatments in DED management, see the sidebar.)

INNOVATIONS TARGETING EVAPORATIVE DED

Some strategies for managing DED focus on evaporative dry eye, caused primarily by meibomian gland dysfunction, which affects the tear film's lipid layer. The FDA recently approved the first prescription drop aimed at evaporative DED, perfluorohexyloctane (PFHO) ophthalmic solution (Miebo, Bausch + Lomb), a water- and preservative-free alkane liquid. The product targets excessive evaporation by forming a monolayer at the tear film air-liquid interface.[31] Preliminary studies suggest that PFHO can enhance the tear film's lipid layer by coating the eye for up to 6 hours.[32] Early clinical results support PFHO's use. The phase 3 randomized controlled GOBI trial of 597 patients showed a clinical improvement in dry eye symptoms at 4 weeks and a significant improvement at 2 and 8 weeks.[33] The MOJAVE trial, which included 620 patients, reported similar safety and efficacy outcomes.[34]

EMERGING TREATMENTS FOR ANTERIOR BLEPHARITIS AND DED FLARES

Anterior blepharitis, often triggered by *Demodex* infestation, can cause various symptoms. The FDA recently approved lotilaner ophthalmic solution 0.25% (Xdemvy, Tarsus Pharmaceuticals). Targeting *Demodex* blepharitis, the drug reaches the meibomian glands and lash follicles where mites reside.[35,36] Its effectiveness was demonstrated in the Saturn-1 trial, a randomized controlled study of 421 patients that showed significant mite eradication, collarette improvement, and complete cure at 43 days.[37] The Saturn-2 trial supported the drug's safety and efficacy, with more than 90% of participants tolerating the treatment and showing significant clinical improvement.[38]

The concept of a DED flare—a sudden exacerbation in a previously stable patient—emerged after publication of the DEWS II report.[39] The FDA approved the first eye drop for the short-term treatment of a DED flare, loteprednol etabonate ophthalmic suspension 0.25% (Eysuvis, Alcon), in 2020.

LOOKING AHEAD TO DEWS III

This article highlights just a few advances in DED research since the publication of TFOS DEWS II, including the subsequent TFOS OSD lifestyle report. The field is evolving rapidly. The TFOS DEWS III Workshop has begun, promising further insights in about 3 years. ■

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