TFOS DEWS III: Executive Summary

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TFOS DEWS III: Executive Summary

Victor L. Perez,[1] Wei Chen,[2] Jennifer P. Craig,[3] Murat Dogru,[4] Lyndon Jones,[5] Fiona Stapleton,[6] James S. Wolffsohn,[7] David A. Sullivan[8]

[1] Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, FL, USA
[2] Eye Hospital of Wenzhou Medical University, National Eye Clinic Research Center, China.
[3] Department of Ophthalmology, Aotearoa New Zealand National Eye Centre, The University of Auckland, Auckland, New Zealand
[4] Ichikawa General Hospital, Tokyo Dental College, Dept of Ophthalmology, Ichikawa, Chiba, Japan.
[5] Centre for Ocular Research & Education (CORE), School of Optometry and Vision Science, University of Waterloo, Waterloo, ON, Canada
[6] School of Optometry and Vision Science, UNSW Sydney, NSW, Australia
[7] School of Optometry, College of Health and Life Sciences, Aston University, Birmingham, UK
[8] Tear Film & Ocular Surface Society, Boston, USA

Abstract

This article presents an Executive Summary of the conclusions and recommendations of the TFOS DEWS III reports, published in the American Journal of Ophthalmology (AJO) in the Spring of 2025. Downloadable, pdf copies of the three comprehensive TFOS DEWS III reports are available on the AJO website (www.ajo.com).

1. Introduction

The Tear Film & Ocular Surface Society (TFOS; www.tearfilm.org) is a non-profit organization established in 2000 to promote international collaboration, research, and education in the field of the tear film and ocular surface. Among its most influential contributions are the TFOS Workshops, particularly those focused on dry eye disease (DED), a highly prevalent condition that affects hundreds of millions globally and remains a leading cause of visits to eye care providers. In more severe forms, DED can result in substantial discomfort, visual disturbance, and reduced quality of life.

The publication of the original TFOS Dry Eye Workshop (TFOS DEWS) report in 2007 marked a turning point in the standardization of DED understanding and management (1-7). A decade later, TFOS DEWS II (2017) expanded on these foundations with broader scientific input and a more comprehensive framework, stimulating widespread research activity (8-18). TFOS DEWS III, launched in 2023, represents the next step in this evolution—reflecting both the scientific

advancements since TFOS DEWS II publication and growing understanding of this complex field. Its objective was to update and refine the definition, classification, diagnostic approaches, and therapeutic strategies for DED. Their evolution was supported by a broad-spectrum Digest, developed to summarize recent progress in relevant related areas such as epidemiology, pathophysiology, tear film biology, pain mechanisms, sex, gender and hormone influences, iatrogenic causes, and clinical trial design.

This progression across TFOS DEWS, DEWS II, and now DEWS III reflects the natural development of a field that is still maturing. Compared to other subspecialties in ophthalmology, the ocular surface field is relatively young, making these periodic updates essential as new data emerge and clinical understanding deepens. TFOS DEWS III brought together 80 experts from 19 countries, who engaged in a transparent, evidence-based process to achieve global consensus on multiple aspects of DED (19). Steering committee members (Table 1) played an instrumental role in guiding the process and ensuring harmonization of information across all reports. Members of the three Subcommittees and the review panels that provided in-depth critique of the Diagnostic Methodology and Management & Therapy reports are listed in Table 2.

Table 1. TFOS DEWS III Steering Committee

Victor L. Perez (USA) – Chair
Lyndon Jones (Canada) - Vice-Chair
James S. Wolffsohn (UK) - Vice-Chair
David A Sullivan (USA) – Organizer
Wei Chen (China)
Jennifer P. Craig (New Zealand)
Murat Dogru (Japan)
Fiona Stapleton (Australia)

The TFOS DEWS III report was published in open access format as a Special Supplement in the American Journal of Ophthalmology (AJO) in the Spring of 2025 (19-22). Downloadable copies of the individual TFOS DEWS III reports are available on the AJO website (www.ajo.com).

This article is an Executive Summary of the full TFOS DEWS III report. The Diagnostic Methodology and Management and Therapy Reports are summarized along with the individual Digest sections. Additional details and all references can be obtained in the original documents (19-22).

Table 2. TFOS DEWS III members

Diagnostic Methodology Subcommittee
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Dimitri Azar (USA)
Ying Jie (China)

Clinical Trial Design
Penny Asbell (USA)

Charles Bosworth (USA)
Joseph Ciolino (USA)
Kenji Konomi (Japan)

2. Diagnostic Methodology Report (20)

The TFOS DEWS II Diagnostic Methodology report published in 2017 provided a standardized, practical, clinical process for diagnosing DED (16). This was based on the available evidence regarding tests with diagnostic potential and aligned with the definition of DED (9). The TFOS DEWS III: Diagnostic Methodology committee reviewed the previous definition, and minor amendments were made to reflect that the homeostasis of the ocular surface microenvironment, as well as that of the tear film, has potential to be disrupted in DED, and that any of the pathophysiological drivers could be present in an individual, was acknowledged. However, key aspects of the previous definition that include dry eye being recognized as a disease, being multifactorial and requiring presence of both symptoms (which can include discomfort and visual disturbance) and clinical signs remain. The TFOS DEWS III definition is thus as follows:

"Dry eye is a multifactorial, symptomatic disease characterized by a loss of homeostasis of the tear film and/or ocular surface, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities are etiological factors."

Hence DED remains a specific symptomatic subset of ocular surface disease and differential diagnosis is important to rule out conditions that can mimic DED. The key risk factors for DED, particularly those that are modifiable and might influence the guidance given to a patient, are discussed in the report, drawing on the evidence described in the TFOS DEWS III Digest (22). Evidence published since TFOS DEWS II demonstrated that the screening questionnaires recommended in 2017 do not offer comparable measures of symptoms. In standardizing a diagnosis, therefore, it was deemed appropriate that only a single questionnaire be recommended for symptom screening purposes when confirming the presence of symptoms described in the DED definition. The shortened form of the Ocular Surface Disease Index, the OSDI-6 was selected as a rapid, valid and sensitive measure of dry eye symptomology for screening purposes.

In terms of clinical signs, existing criteria require a minimum of one of a limited number of signs to be present to make a diagnosis of DED and subsequent research has confirmed that this current approach is robust. Furthermore, since TFOS DEWS II it has been demonstrated that assessment of ocular surface staining (comprising fluorescein staining of the cornea and quantification of conjunctival and lid margin staining, ideally with lissamine green dye), combined with *either* non-invasive tear breakup time *or* osmolarity, is sufficient to reliably confirm the presence or absence of dry eye disease (Figure 3). Breakup time measured after applying fluorescein is not the preferred measure of tear film stability due to its invasive nature.

(Figure 3). Breakup time measured after applying fluorescein is not the preferred measure of tear film stability due to its invasive nature. Where fluorescein is used, the tear film stability cut-off time for dry eye should be reduced from 10 s to 5 s. The potential for describing a severity rating was explored, but due to the recognized weak association between signs and symptoms, and even between different clinical signs, it was not possible at this time to generate an evidence-based weighting system to quantify overall severity.

Most DED is acknowledged to be (hyper)evaporative in nature, driven by a range of different etiologies. Clinical tests can help differentiate DED into these etiological subtypes that can be broadly described as tear film component deficiencies, eyelid anomalies and ocular surface abnormalities. These have been differentiated in TFOS DEWS III to support better informed DED management than was possible with the former aqueous deficient and "evaporative" DED subtypes only. Tests are further subdivided according to complexity into those that could form part of routine testing and those that are currently more advanced. Threshold values for differentiating dry eye from normal are provided where these could be confirmed in the literature. These dry eye subtypes (Figure 1), alongside the broad need for lifestyle risk factors and, where present, systemic drivers to be managed, are revisited in the TFOS DEWS III Management and Therapy report where evidence-based treatment options are linked to the various subtypes according to their established effect(s) on the etiological drivers. A table is provided to aid clinician selection of treatments according to the latest evidence and to highlight current gaps in knowledge to drive future research.

Finally, the report addresses possible causes and appropriate management of patients who present with only symptoms or only ocular surface signs, but not both, as these fall outside the definition of DED. The report concludes with a discussion surrounding the potential for future advances including applications of artificial intelligence, tear biomarker testing and concerns regarding sustainability, as well as identifying the need for a Delphi panel to address less comprehensively researched areas where the field awaits sufficient high quality evidence to inform critical elements of clinical practice.

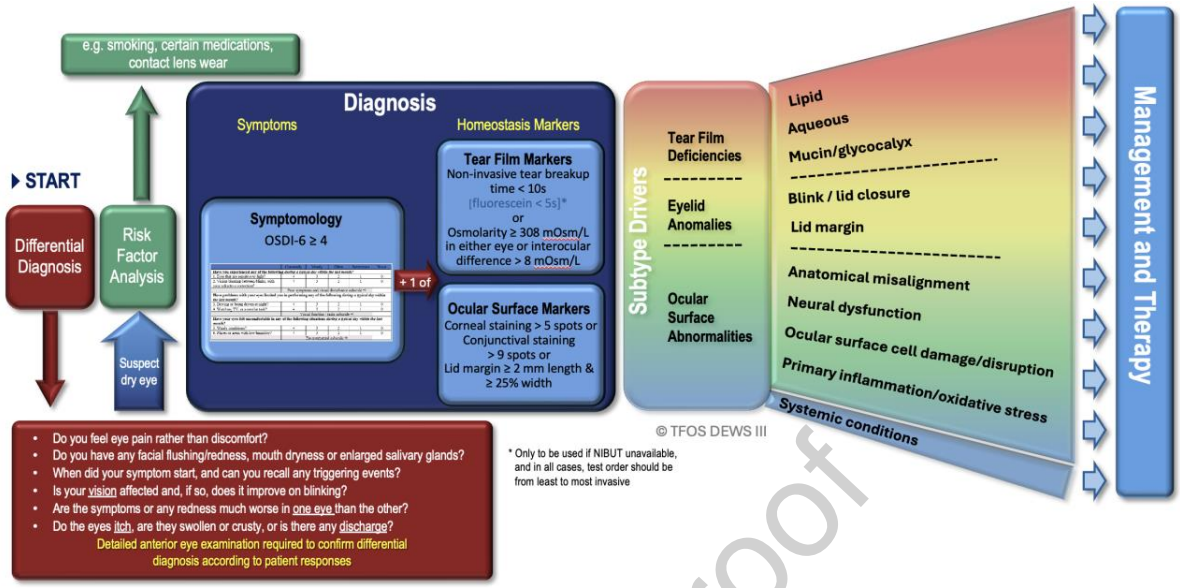


Figure 1: Diagnosis and subtyping of DED to inform restoration of tear film and ocular surface homeostasis through appropriate management and therapy. The diagnosis involves establishing both symptoms (an OSDI-6 summed score of ≥4) and at least one key sign of a loss of homeostasis. This sign could be: a non-invasive tear breakup time <10s, hyperosmolarity (≥308 mOsm/L) or a difference in osmolarity between the eyes of >8 mOsm/L), and/or ocular surface staining (corneal fluorescein staining of > 5 punctate spots; lissamine green conjunctiva staining >9 punctate spots and/or lissamine green lid margin staining of ≥2 mm length & ≥25 % width). The differential diagnosis questions highlight cases where a more detailed ocular surface examination is needed to exclude other causes. In a patient with a positive OSDI-6 screening of dry eye symptoms, but with no ocular surface staining, only non-invasive tear breakup time or osmolarity needs to be measured to confirm the presence or absence of dry eye disease.

3. Management and Therapy Report (21)

The TFOS DEWS II Management and Therapy report provided a comprehensive review of the evidence regarding the available management and therapy options at that time (17). The aim was to offer guidance regarding the most appropriate treatment options for varying levels of DED severity and subtypes. However, while evidence of the effectiveness of various pharmaceutical agents and devices compared to a placebo existed, few studies directly compared treatments across a range of DED severities and subtypes. Therefore, a staged approach was proposed, based on the clinical expert opinion surrounding the management strategies used at the time. A subsequent TFOS survey confirmed this general approach, and identified how clinical practice varied between regions and across professions (23, 24).

The TFOS DEWS III Management & Therapy report provides a contemporary overview of the available evidence on the management of patients with DED. The research evidence since publication of the previous report has been categorized based on the primary mechanisms of action, although some treatments have been shown to contribute to reducing the impact of multiple etiological drivers. Lifestyle impacts on the ocular surface have been extensively described in a recent set of TFOS reports, leading to the recommendation to offer patient advice according to relevant lifestyle factors across all dry eye subtypes (25-35). Tear supplementation and stabilization of the tear film remain the mainstay of DED treatments and the actions of a wide range of compounds have been explored in randomized controlled trials. Tear conservation devices include contact lenses, moisture-retaining spectacles and punctal plugs. There have been a number of pharmaceuticals and devices marketed to restore or stimulate each of the lipid, aqueous and mucin components of the tear film, along with tear neurostimulation, which is effected via the sensory afferent nerves of the cornea and conjunctiva, as well as parasympathetic nerves located in the nasal cavity.

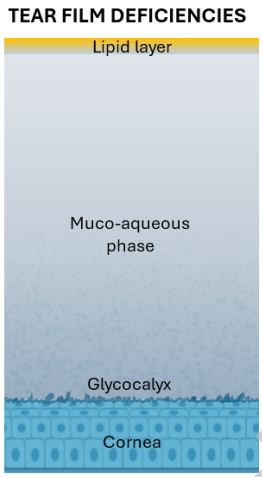
Treatment of eyelid abnormalities includes management and therapy of blink and lid closure anomalies, along with methods to reduce eyelid microbial load and manage meibomian gland dysfunction. Topical anti-inflammatory pharmacological therapies include corticosteroids and T-cell immunomodulatory drugs, and a range of pharmacological compounds that are under development. An increasing range of heat-based, light-based and electrotherapeutic devices, for application to the eyelid, show promise in managing MGD. Evidence surrounding the use of oral antimicrobial agents, including tetracycline and its analogues, as well as macrolide antibiotics, is discussed. Epithelial promoters or ocular surface regeneration agents with evidence of effectiveness in treating DED are described. These include biological supplements such as blood-derived products, as well as lubricin, amniotic membrane and amniotic membrane extract drops, along with other products in development.

Surgical treatments for ocular surface abnormalities that affect anatomical alignment of the lid and globe, and management of lid anomalies, are highlighted. Further sections highlight DED management through nutritional modifications and alternative therapies, such as macronutrients, micronutrients and natural products or interventions, along with prevention and treatment of surgical iatrogenic DED, in particular that arising secondarily to cataract and refractive surgery.

These evidence-based treatment approaches are linked to the etiologic subtypes, categorized as tear component deficiencies (Figure 2), eyelid anomalies (Figure 3) and ocular surface abnormalities (Figure 4) as identified in the TFOS DEWS III Diagnostic Methodology report (21). The resulting algorithms are designed to allow clinicians to employ appropriate clinical tests to identify the (often multiple) etiological drivers of DED in an individual patient and then to select treatments which have been shown in robust clinical studies to have a mechanism of action that addresses the specific driver. Multiple treatments in combination are often required to

address the multiple pathogenic drivers of DED. Sustained clinical improvement often necessitates comprehensive patient education on lifestyle factors and adherence to the prescribed management plan. Each algorithm is accompanied by a table summarizing the current high-quality evidence supporting each of the interventions. The algorithms also highlight areas for which there is currently limited evidence and where future research is needed.

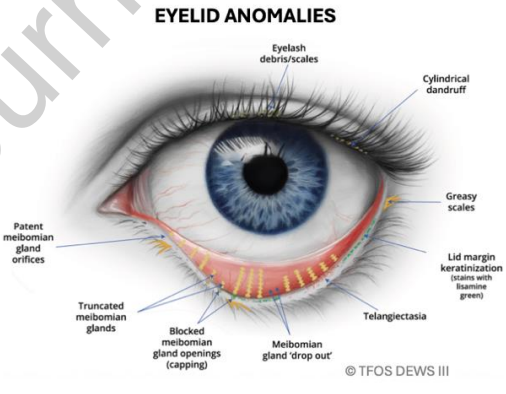
ETIOLOGIC DRIVER TESTS
Lipid
Tear film lipid layer thickness / interferometry
Meibomian gland expressibility
Meibum quality
Aqueous
Tear meniscus height
Meniscometry / Schirmer⁺ / phenol red thread test⁺
Mucin / glycocalyx
Lissamine green / rose bengal staining
Conjunctival impression cytology



EVIDENCE-BASED INTERVENTIONS
Lipid
Tear supplementation / stabilization (lipomimetics)
Tear conservation devices (moisture-retaining spectacles)
Pharmacological tear stimulation / restoration
Device tear stimulation / restoration
Blink therapies
Topical lid hygiene
Aqueous
Oral nutrition (Omega 3)
Tear supplementation / stabilization
Tear conservation devices
Pharmacological / device tear stimulation / restoration
Topical anti-inflammatories
Ocular surface regenerators
Surgical options
Mucin / glycocalyx
Tear supplementation / stabilization (HP guar)
Topical anti-inflammatories
Pharmacological tear stimulation
Device tear stimulation (neurostimulation)

Figure 2. Diagnostic tests and evidence-based interventions to manage the etiologic drivers associated with tear film deficiency-related subtypes of dry eye disease. Full details are provided in the TFOS DEWS III Management & Therapy report (22).

ETIOLOGIC DRIVER TESTS
Blinking / lid closure
Incomplete blinking
Anterior blepharitis
Eyelid biomicroscopy - greasy (seborrheic) or flaky (staphylococcal)
Eyelash base - cylindrical dandruff - *Demodex*
Meibomian gland dysfunction
Pouting, missing, displaced gland orifices
Meibomian gland expressibility
Meibography – truncated, dilated glands, 'drop out'
Telangiectasia
Lid margin keratinization



EVIDENCE-BASED INTERVENTIONS
Blinking / lid closure
Blink exercises
Anterior blepharitis
Topical lid hygiene
Oral antibiotics
Meibomian gland dysfunction
Oral nutrition (vitamin D3)
Tear supplementation / stabilization (lipid-based, androgen)
Pharmacological tear stimulation / restoration (topical azithromycin, selenium sulfide)
Device tear stimulation / restoration (internal and external lid heating; IPL; LLLT; QMR; radio-frequency
Lid margin debridement for significant keratinization
Oral antibiotics

Figure 3. Diagnostic tests and evidence-based interventions to manage the etiologic drivers associated with eyelid-related subtypes of dry eye disease. Full details are provided in the TFOS DEWS III Management & Therapy report (22).

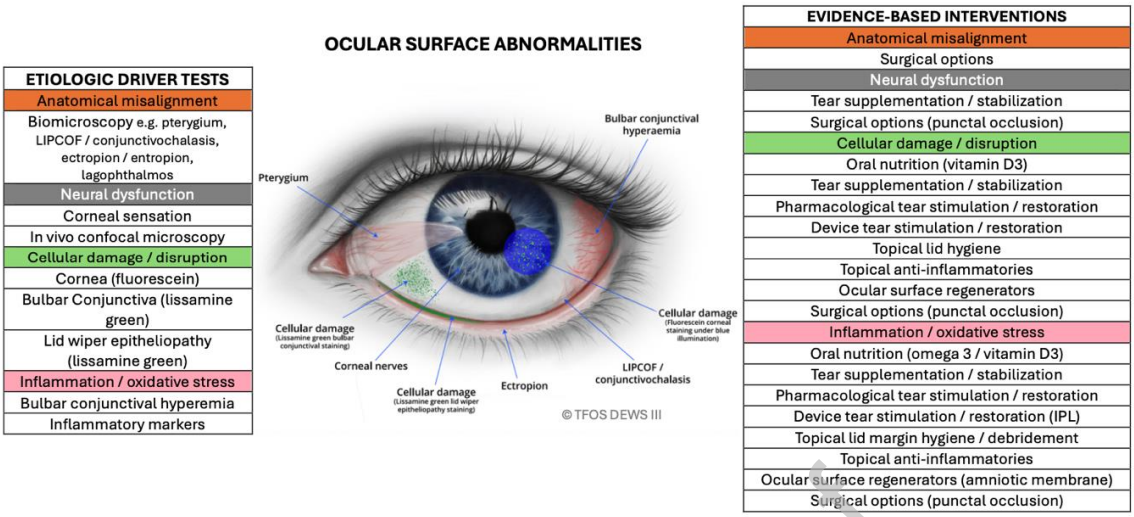


Figure 4. Diagnostic tests and evidence-based interventions to manage the etiologic drivers associated with ocular surface-related subtypes of dry eye disease. Full details are provided in the TFOS DEWS III Management & Therapy report (22).

4. TFOS Digest Report (22)

4.1. Sex, gender, and hormones

The TFOS DEWS II report on Sex, Gender, and Hormones (11) addressed numerous sex- and gender-related differences that significantly influence the ocular surface in health and dry eye disease (DED). Many of these differences appeared to be due to the effects of hormones, sex chromosomes, sex-specific autosomal factors, epigenetics, care-seeking behavior and service utilization. The purpose of this section is to highlight some of the relevant research since the publication of that report.

During the past eight years, studies have continued to demonstrate a significant sexual dimorphism in the structure and/or function of the lacrimal gland, meibomian gland, cornea and eyelid. These differences, which are attributed in part to androgen effects, may contribute to the increased prevalence of certain subtypes of DED in females. Additional research has linked insulin-like growth factor and insulin to the health of the ocular surface and tear film, progesterone to the suppression of ocular pain, and thyroid eye disease to DED.

In contrast, although both "sex" (which biologically distinguishes males from females) and "gender" (which refers to a person’s self-representation as a man or woman) affect DED risk, there is limited information on the impact of gender-affirming hormone therapy on the eye. Overall, investigations have shown that sex, gender and hormones play a major role in the control of ocular surface and adnexal tissues and the tear film, and in the difference in DED prevalence between men and women.

4.2. Epidemiology

Extending beyond the evidence reported in the TFOS DEWS II Epidemiology report (10), the epidemiology section of TFOS DEWS III considered the prevalence of DED in studies that have described disease rates by age and sex (20). Eight major diagnostic groups were identified and prevalence varied with different diagnostic criteria such that not all disease was found to increase with age or show a female predominance. Broadly, studies using the Women's Health Study criteria, show DED increases with age and is more common in women. A clinical diagnosis of DED showed a female preponderance, but not an age-related effect. Symptoms and signs were more common in women with higher rates in younger and older adults. Classification as any or severe MGD was observed to be age-related, with older males more likely to have MGD than females. These findings may not be unexpected given the multifactorial nature of DED, the specificity of ocular symptom measurements and differences in the etiology of different subtypes of DED. There is some evidence for DED increasing in prevalence over time.

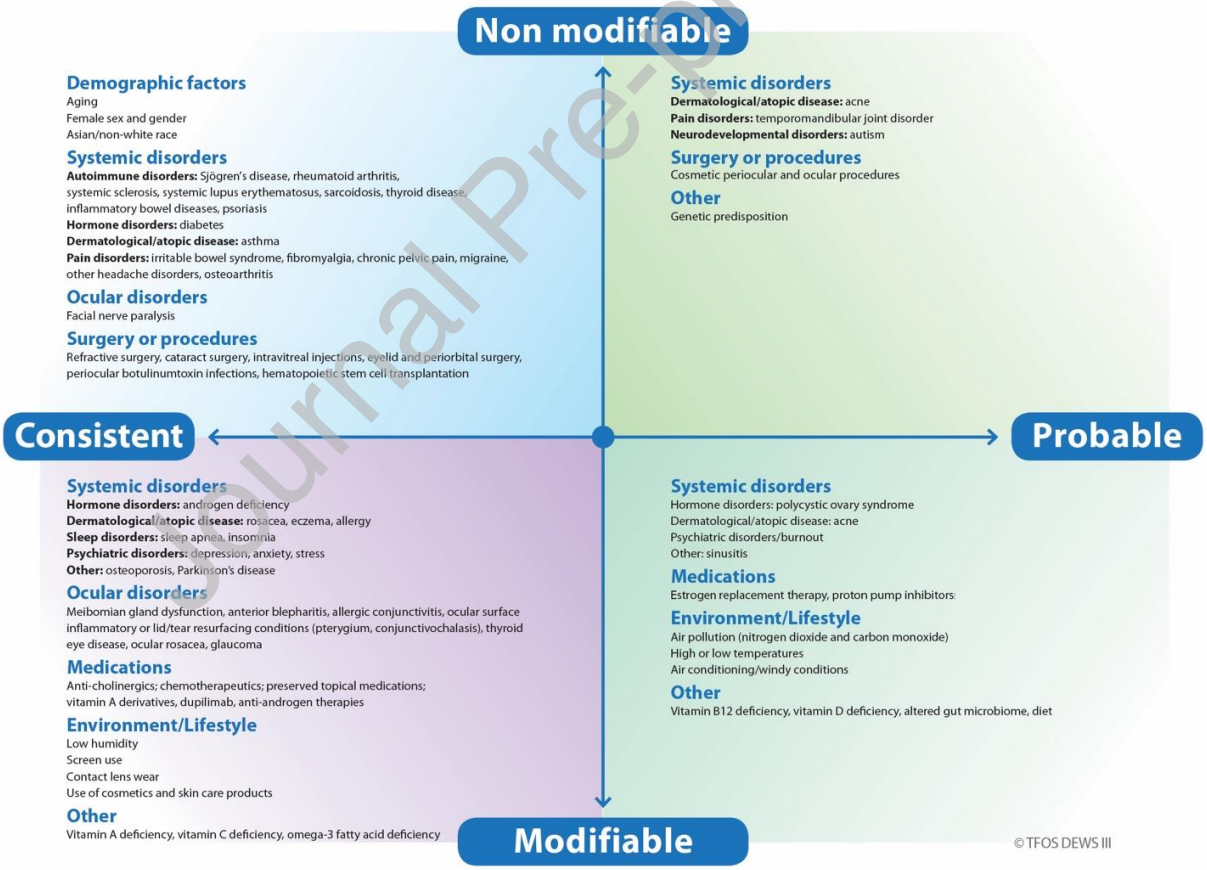


Figure 5. Risk factors for DED categorized by certainty according to current evidence and modifiability.

Studies reporting rates of DED in those under the age of 20 years are limited. Rates are lower than for adults for clinically diagnosed DED and any or significant MGD. High rates of symptom reporting are evident in those under 20 years, however, although it is recognised that symptom report alone is not specific for DED. Given this, appropriate triaging for other conditions and hypothesis-driven and appropriately powered studies to explore risk factors in children would be valuable. Most studies reporting symptoms did not report signs, although they may be present.

Evidence for risk factors for DED are reported and new risk factors related to environment, climate and lifestyle are included (Figure 5). Given the differences in prevalence and age/sex associations with different diagnostic criteria for DED, disaggregating risk factors for appropriately diagnosed DED and MGD, where possible, in future would be useful.

4.3. Pathophysiology

Since publication of the TFOS DEWS II Pathophysiology report (12), research has solidified distinctions between and within the aqueous deficient and evaporative forms of dry eye (22). Evaporative forms show a muted increase in inflammatory mediators in the tear film, with initiating triggers including phenotypic alterations in corneal epithelial cells that lead to a compromised glycocalyx, keratinization of the meibomian glands and reduced blink function during screen use that leads to desiccating stress. ADDE subsets are more closely associated with inflammatory ingress into the lacrimal gland driven by androgen deficiency or autoimmunity, causing a cascade of protease release, cytokine expression, inflammatory cell recruitment, dendritic cell maturation, and an adaptive T-cell mediated response. Physical stresses of hyperosmolarity and friction are compounded by mitochondrial stress, advanced glycation end products in the lacrimal gland, dysregulated or self-reactive immune cells, cellular stresses from cytokines, proteases, extracellular DNA and NETs, exogenous toxins, DAMPs, gut dysbiosis, and neurogenic inflammation. As disease severity increases, the evidence suggests a progressive accumulation of these mechanisms.

A particular focus of research has centered on the downstream effects of hyperosmolarity, that include the upregulation of IFN-γ, NLRP3 driven oxidative stress, TLR-4 activation and DAMPs in evaporative pathophysiology (22). In ADDE, protease activity of MMP-9, cathepsin S, plasmin, and neutrophil elastase are observed in excess of anti-proteases such as cystatin C and thrombospondin-1 that are not generally observed in non-autoimmune DED and in healthy controls. A common pathway shared between both evaporative forms and ADDE is an impaired glycocalyx. When competent, the glycocalyx has recently been shown to regulate immune cells, transduce extracellular environments to intracellular signaling pathways, and actively inhibit proteases such as MMP-9, which would further implicate the catabolism or downregulation of the glycocalyx as an initiating event in DED pathogenesis. Finally, understanding of the

meibomian gland is improving, including the regulatory roles of hypoxia, PPAR-γ, Soat1, APOE, and the potential to reverse gland atrophy, such as in Fgfr2 knockout mice.

4.4. Tear film

The TFOS DEWS III Digest section on the Tear Film (22) examined new research published since the release of the TFOS DEWS II Tear Film Report (13). It highlights new evidence on the reproducibility of clinical measures of tear film stability and the correlations between symptoms and tear film or ocular surface characteristics. It also explores changes in tear film lipids, proteins, and mucins, and their relationship to DED. Additionally, the Digest includes a synopsis of research investigating the expression of microRNAs in tears and their potential as biomarkers for DED. Translational models that attempt to replicate DED are examined, particularly those that can potentially be used to study the relative contribution of tear film components to DED. This section concludes with proposed directions for future research, emphasizing the need to better align models with human tear film components, and to further investigate whether changes in inflammatory components, the ocular microbiome and microRNAs play roles in DED pathogenesis and/or serve as biomarkers.

4.5. Pain and sensation

Ocular pain perception and sensation is a complex process that can be influenced by the structural integrity of corneal nerves, the functional capacity of neurons, and activity of the central and peripheral nervous systems. Normal corneal nerve structure may be altered by trauma, surgery, systemic disease, natural aging, and incomplete or improper neural regeneration. The resulting alterations are pleomorphic, but most commonly manifest as reduced nerve fiber density and increased nerve tortuosity. These aberrant corneal nerve structures have been closely associated with altered sensation, increased ocular pain, and symptoms typical of DED. Altered ocular sensation may also result from functional abnormalities in corneal nerves including abnormal growth factor activity and increased expression of sodium channels. These changes in neuronal activity can disrupt normal sensory signaling, dysregulate protective mechanisms such as blinking and tearing, and provoke symptoms of DED.

In some individuals, ocular pain can also be driven by generalized dysfunction of peripheral and central nervous systems, with studies supporting activation of the primary somatosensory, insular, and anterior mid-cingulate cortices in individuals with chronic ocular pain, which may be mitigated with certain therapies. Corneal sensitivity testing is a useful tool for evaluation of somatosensory disturbance, but results can vary significantly between etiologies of ocular pain and testing methodologies. Investigation of ocular pain and sensation is ongoing, and future developments may include the elucidation of specific pathways controlling corneal nerve development and regeneration, exploration of neuroimmune crosstalk in DED, greater

implementation of artificial intelligence networks in processing large bodies of data, more sophisticated assessments of peripheral and central nerve function, and targeted treatments to address dysfunction in an individual patient.

4.6. Iatrogenic dry eye

Iatrogenic dry eye disease is a common ocular surface condition caused or exacerbated by medical and ophthalmic treatments and procedures. Iatrogenic DED can be sub-classified into 5 categories: drug-related (topical or systemic), contact lens-associated, surgical interventions, non-surgical procedures, and systemic conditions.

Preserved topical medications, particularly regularly applied anti-glaucoma agents containing benzalkonium chloride, can result in DED through multiple mechanisms including preservative toxicity, tear film destabilization, and corneal nerve impairment, ultimately leading to chronic inflammation and tear hyposecretion. Systemic medications can also exacerbate DED through different mechanisms, including anticholinergic effects (antihistamines, antidepressants) or glandular atrophy (isotretinoin).

Contact lens-associated DED involves complex interactions between the contact lens, the lens materials and ocular surface and is characterized by tear film stratification, increased tear evaporation and mechanical trauma.

Ophthalmic surgical procedures, such as refractive corneal surgery, corneal collagen crosslinking (CXL) and botulinum toxin (BTX) may induce DED. Refractive corneal surgical procedures often cause injury to the corneal nerves, decreasing corneal sensation and decreasing blinking and reflex tearing. CXL can also impair corneal nerve function and result in tear film instability. BTX reduces tear secretion via acetylcholine inhibition and meibomian gland dysfunction.

In non-ophthalmic conditions, radiotherapy, bariatric surgery, and graft-versus-host disease (GVHD) induce DED through distinct pathways. GVHD leads to severe DED due to immune-mediated lacrimal gland fibrosis and inflammation. Radiotherapy can damage lacrimal glands, corneal epithelium, and meibomian glands. Post-bariatric surgery, DED may be induced through nutrient malabsorption, post-surgical metabolic changes and chronic inflammation.

Clinical management of iatrogenic dry eye emphasizes multimodal strategies: identification and substitution of causative medication, preservative-free formulations, surgical optimization, and personalized lubrication regimens incorporating autologous serum derivatives as appropriate. Addressing iatrogenic DED requires multidisciplinary collaboration, integrating basic research findings and clinical practice to improve patient quality of life and treatment safety. Future

research should prioritize understanding pathological mechanisms and disease epidemiology, developing standardized diagnostic and treatment protocols, and exploring novel innovative therapies.

4.7. Clinical trial design

The development of novel therapies for DED has historically been a significant challenge, with relatively few treatments evaluated in clinical development achieving market approval. This challenge is not unique to DED, however, and has been experienced across a range of indications where research and development success rates as low as 10% have been observed. In contrast, Phase 3 success rates as high as 80% have been observed when drug developers pay increased attention to disease heterogeneity, exposure and drug activity at the intended site of action.

While prior TFOS DEWS reports focused on challenges hampering the design and success of trials in DED, this report focused on how recommendations from the TFOS DEWS II report (18) translated into innovations in trial design and how flexibility in application of the FDA draft guidance improved success rates for bringing novel treatments to patients. Trial design innovations have included better matching of treatment mechanism of action to patient sub-populations, more stringent control on concomitant treatments, inclusion of mechanistic biomarkers and identification and design control over sources of trial error (e.g., repeat baseline measurements to minimize endpoint regression). Flexibility exercised by the US FDA includes allowance of post-hoc analyses, utilization of secondary endpoints to demonstrate efficacy for a product under review, and flexibility in defining “replication” of a sign and/or symptoms across studies.

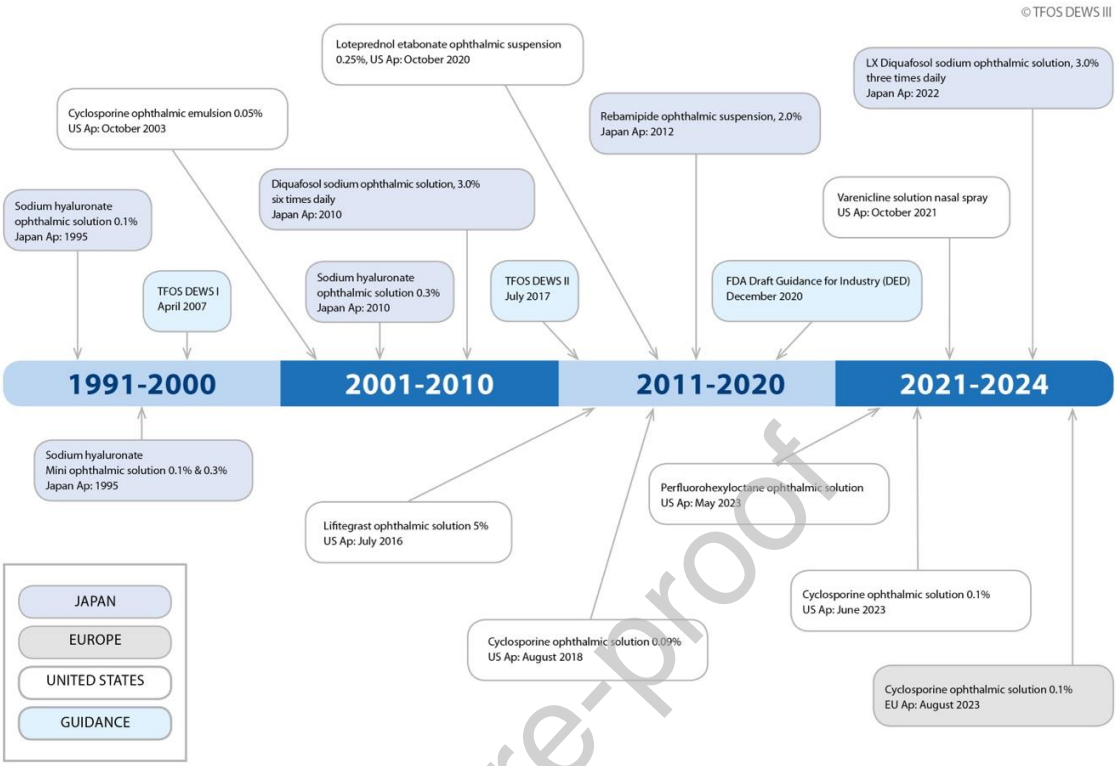


Figure 6. DED treatments achieving regulatory approval in the US, EU and Japan (1991-2025)

While prior TFOS DEWS reports focused on challenges hampering the design and success of trials in DED, this report focused on how recommendations from the TFOS DEWS II report (18) translated into innovations in trial design and how flexibility in application of the FDA draft guidance improved success rates for bringing novel treatments to patients. Trial design innovations have included better matching of treatment mechanism of action to patient sub-populations, more stringent control on concomitant treatments, inclusion of mechanistic biomarkers and identification and design control over sources of trial error (e.g., repeat baseline measurements to minimize endpoint regression). Flexibility exercised by the US FDA includes allowance of post-hoc analyses, utilization of secondary endpoints to demonstrate efficacy for a product under review, and flexibility in defining "replication" of a sign and/or symptoms across studies.

Conditions including ADDE, MGD and Contact Lens Discomfort represent ocular surface disease heterogeneity that has been accounted for in more recent DED trial designs by matching the mechanism of action of a proposed therapy to a potentially responsive population in which the treatment is likely to demonstrate efficacy. As trials in the various subpopulations result in

drug approvals, clinicians are encouraged to incorporate the latest evidence into their practices to ensure that the newer market entrants are used optimally in their intended populations and rely less on historically approved and labeled indications.

5. Dedication

TFOS dedicates this TFOS DEWS III report to the late Claes H. Dohlman, Gary N. Foulks, Michael A. Lemp and Juan Murube del Castillo for their pioneering efforts and outstanding achievements in tear film and ocular surface research.

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