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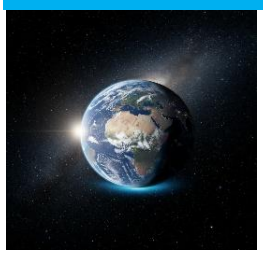

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BEYOND ARTIFICIAL TEARS: A NEW ERA IN DRY EYE DISEASE MANAGEMENT – A REVIEW ARTICLE

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ABSTRACT

Introduction: Dry eye disease (DED) is a prevalent and increasingly recognized disorder of the ocular surface that poses a significant clinical and public health challenge worldwide. Its complex and heterogeneous nature reflects the interplay of tear film instability, inflammation, epithelial dysfunction, and neurosensory abnormalities. The evolving understanding of DED pathophysiology has led to substantial changes in diagnostic criteria and therapeutic paradigms, shifting from purely symptomatic management toward mechanism-based and individualized approaches. Ongoing advances in molecular biology, immunology, and biomedical technology continue to reshape the therapeutic landscape of DED.

Purpose of the work: In light of the growing clinical burden and the evolving understanding of DED as a complex, multifactorial disorder of the ocular surface characterized by loss of tear film homeostasis, hyperosmolarity, inflammation, and neurosensory abnormalities—as defined by the Tear Film & Ocular Surface Society in the TFOS DEWS III report—the purpose of this study was to comprehensively review the current evidence regarding DED pathophysiology, risk factors, classification, diagnostic algorithms, and contemporary therapeutic strategies, with particular emphasis on mechanism-based and emerging treatments.

Materials and methods: A structured narrative review of the literature was conducted based on current international consensus documents (including TFOS DEWS III), randomized clinical trials, systematic reviews, and phase II–III studies evaluating pharmacological and non-pharmacological interventions for DED. A systematic search of PubMed, Scopus, Cochrane Library, and Web of Science was performed to identify studies published between 2015 and 2025. The analysis addressed molecular and cellular mechanisms underlying tear film instability; etiology and risk factors; contemporary etiology-based classification systems; validated diagnostic criteria; and therapeutic modalities, ranging from advanced topical drug delivery systems and immunomodulatory agents to biologic therapies, light-based procedures, neuromodulation, scleral lenses, and cryopreserved amniotic membrane devices.

Results: DED should be recognized as a heterogeneous, self-perpetuating inflammatory disorder driven by interrelated mechanisms involving tear film instability, immune activation, epithelial damage, and neurosensory remodeling. Contemporary management is evolving from symptomatic lubrication toward individualized, mechanism-oriented therapy targeting specific pathophysiological pathways. Advances in immunomodulation, secretagogue therapy, neuromodulation, biologics, regenerative approaches, and device-based interventions expand the therapeutic landscape, particularly for refractory disease. A deeper understanding of molecular and neurosensory mechanisms is essential to optimize precision treatment strategies and improve long-term clinical outcomes.

Keywords: dry eye disease (DED), tear film homeostasis, meibomian gland dysfunction (MGD), current concepts in dry eye disease, emerging therapies for dry eye disease, personalized therapy in dry eye disease.

1. INTRODUCTION

Dry eye disease (DED), according to the definition established by the Tear Film & Ocular Surface Society in the Dry Eye Workshop III (TFOS DEWS III), is a multifactorial, symptomatic disease characterized by loss of homeostasis of the tear film and/or ocular surface. The principal etiological factors include tear film instability and hyperosmolarity, ocular surface inflammation and damage, as well as neurosensory abnormalities. [1] Depending on the population studied, DED is estimated to affect between 5% and as many as 50% of individuals, occurring more frequently in women and older adults. Subjective symptoms, such as ocular dryness and burning sensation, the need for frequent blinking, and conjunctival hyperemia, significantly impair patients' quality of life, hindering social functioning and reducing occupational productivity. This burden translates into deterioration of mental well-being, higher levels of anxiety, and an increased risk of depression. DED also represents a substantial economic burden, generating annual costs in the United States estimated at approximately USD 3.84 billion, attributable to direct treatment expenses and indirect costs associated with reduced work productivity. [1–4] A comprehensive understanding of the mechanisms underlying DED, which contribute to the development of subjective symptoms, is essential for the development of targeted and individualized therapeutic strategies capable of providing meaningful symptomatic relief.

2. PATHOPHYSIOLOGY OF DRY EYE DISEASE

In the complex and multifactorial etiopathogenesis of dry eye disease (DED), a self-perpetuating "vicious cycle" constitutes the central pathophysiological mechanism, in which tear film instability and hyperosmolarity, inflammation, and neurosensory abnormalities play key roles.

The initiating event is tear film instability, manifested as either excessive evaporation or insufficient aqueous tear production. This leads to tear film hyperosmolarity (≥308 mOsm/L), which directly damages the corneal and conjunctival epithelium, induces oxidative stress, and activates inflammatory signaling pathways (including cGAS–STING and TLR-4). This results in the release of proinflammatory mediators, such as interleukin-1 (IL-1), IL-6, IL-17A, tumor

necrosis factor alpha (TNF-α), and prostaglandin E2 (PGE2), as well as matrix metalloproteinase-9 (MMP-9), all of which further damage the ocular surface and exacerbate tear film instability. [7–9]

Inflammation represents a universal and integral component of DED pathophysiology, although its severity varies depending on the disease subtype. In aqueous-deficient dry eye, inflammatory responses and protease activity are typically pronounced. In evaporative dry eye, most commonly caused by meibomian gland dysfunction (MGD), which accounts for approximately 33–50% of all DED cases, the inflammatory response may be attenuated, while dysfunction of the lipid layer plays a central role. MGD, characterized by gland obstruction and alterations in meibum composition (including increased phase transition temperature and lipid oxidation), leads to impairment of the evaporation barrier, thereby exacerbating hyperosmolarity and perpetuating the vicious cycle. [10–13, 18]

Neurosensory abnormalities constitute another critical component in the course of DED. Chronic exposure to hyperosmolarity and inflammation results in corneal nerve damage, leading to structural remodeling, reduced nerve density, increased tortuosity, and the formation of microneuromas. These changes give rise to altered corneal sensitivity, which may manifest as hypoesthesia or hyperesthesia. Such alterations underlie both clinical symptoms and the well-recognized discordance between subjective complaints and objective signs of disease. Furthermore, impaired corneal innervation disrupts reflex tear secretion, thereby aggravating tear film deficiency. In severe cases, this may lead to the development of neuropathic corneal pain. [5, 15, 16]

Damage to the glycocalyx—the mucin-rich layer covering the corneal epithelium—caused by hyperosmolarity and inflammation further destabilizes the tear film. Environmental factors, including particulate matter (PM2.5) and air pollutants, also contribute to disease pathogenesis by inducing chronic inflammation and enhancing oxidative stress. Even factors such as gut dysbiosis, through activation of the immune system, may exacerbate ocular surface inflammation. [8, 17]

DED is a complex disorder characterized by a cyclical and self-perpetuating nature. A thorough understanding of the underlying interrelated mechanisms is essential for the development of targeted and effective therapeutic strategies.

3. ETIOLOGY OF DRY EYE DISEASE

Dry eye disease (DED) is a multifactorial condition, the development of which results from the interplay of numerous interrelated pathogenic mechanisms. These can be broadly categorized into non-modifiable factors, related to individual predispositions, and modifiable factors, which may be directly influenced.

Key non-modifiable factors include:

- **Sex and hormonal factors:** Women exhibit a significantly higher prevalence of DED, which is associated with sexual dimorphism in the structure and function of the lacrimal and meibomian glands, as well as a higher susceptibility to autoimmune diseases in the female population. Androgen deficiency represents an important risk

factor, whereas the roles of estrogens and progestogens remain inconclusive. [1, 8, 14]

- **Age:** The prevalence of DED increases with advancing age, correlating with the physiological involution of the lacrimal glands and a decline in their function. [1, 8, 14]
- **Genetic factors and ethnicity:** Genetic predisposition and Asian ethnicity are associated with an increased risk of developing DED. [8]
- **Systemic diseases:** Important predictors of DED include, among others, autoimmune diseases (Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus), endocrine disorders (androgen deficiency, thyroid diseases, polycystic ovary syndrome), dermatological conditions (psoriasis, rosacea), and chronic pain disorders (fibromyalgia, irritable bowel syndrome). [1, 8]

Modifiable factors include:

- **Exposure to medications and medical procedures (iatrogenic DED):**
  - **Topical medications:** Antiglaucoma eye drops, particularly those containing preservatives (e.g., benzalkonium chloride [BAK]), which damage the epithelium, corneal nerves, and meibomian glands. [8]
  - **Systemic medications:** Anticholinergic agents (including antihistamines), isotretinoin, certain antidepressants, and hormone therapy. [1, 8]
  - **Procedures:** Contact lens wear; ocular surgeries (including refractive procedures and cataract surgery); botulinum toxin injections; radiotherapy of the head and neck region; and bone marrow transplantation (with graft-versus-host disease [GVHD] as a potential complication). [8]
- **Environmental and lifestyle factors:**
  - **Environment:** Low ambient humidity, air conditioning, exposure to air pollution, and wind. [1, 8, 16]
  - **Lifestyle:** Prolonged use of digital screens, leading to reduced blink rate and incomplete blinking, as well as an inadequate diet characterized by low intake of omega-3 fatty acids and vitamins (A, D, B12). [1, 8, 16]
  - **Ocular factors:** Coexisting conditions such as meibomian gland dysfunction (MGD), anterior blepharitis, allergic conjunctivitis, and facial nerve palsy significantly increase the risk of developing DED. [1, 8]

The etiology of DED constitutes a complex network of mutually reinforcing determinants. Identification and, where possible, modification of key risk factors in an individual patient are essential for effective prevention and management of this condition.

4. DRY EYE DISEASE CLASSIFICATION

Studies conducted in recent years have demonstrated that the traditional classification of dry eye disease (DED) into aqueous-deficient (ADDE) and evaporative (EDE) subtypes is insufficient. TFOS DEWS III introduces a more detailed etiology-based classification aimed at

identifying specific underlying causes in individual patients and guiding targeted therapeutic strategies. [1] This framework encompasses three main categories:

1. **Tear film component deficiencies**
    a. **Lipid layer deficiency:** Primarily caused by meibomian gland dysfunction (MGD), leading to alterations in the composition and quality of the lipid layer, resulting in excessive tear evaporation. [1]
    b. **Aqueous layer deficiency:** Arises from impaired lacrimal gland function, leading to reduced tear volume. [1]
    c. **Mucin layer (glycocalyx) deficiency:** Refers to damage to the mucin layer covering the corneal and conjunctival epithelium, which is essential for tear film stability, ocular surface wettability, barrier function, and protection against injury and infection. [1, 17]
2. **Eyelid abnormalities**
    a. **Blinking and eyelid closure disorders:** Incomplete blinking or lagophthalmos (inability to fully close the eyelids) leads to increased tear film exposure and secondary instability. [1]
    b. **Lid margin dysfunction:** Includes anterior blepharitis (e.g., associated with Demodex infestation), meibomian gland dysfunction, and ocular rosacea. These abnormalities directly impair tear film distribution and composition. [1]
3. **Ocular surface abnormalities**
    a. **Anatomical alterations:** The presence of conditions such as pterygium, pinguecula, or conjunctivochalasis, which mechanically disrupt tear film distribution and stability. [1]
    b. **Neuronal dysfunction:** Includes neurotrophic keratitis (reduced corneal sensitivity) and neuropathic corneal pain (abnormal sensory processing), in which symptoms are disproportionate to clinical signs. [1]
    c. **Ocular surface cell damage:** Caused directly by external factors or secondary to inflammation and tear film hyperosmolarity. [1]
    d. **Primary inflammation and oxidative stress:** A generalized inflammatory state of the ocular surface that may constitute a primary driver of DED, independent of other deficiencies. [1]

It should be emphasized that, in clinical practice, DED frequently coexists with systemic conditions, such as autoimmune diseases (e.g., Sjögren's syndrome, rheumatoid arthritis), endocrine disorders (e.g., diabetes mellitus, thyroid diseases), and dermatological conditions (e.g., rosacea). These entities represent important modifiers of disease phenotype and course and should be taken into account when planning therapeutic management. [1]

5. DIAGNOSTIC ALGORITHM

The definition of dry eye disease (DED) emphasizes that the presence of subjective symptoms is an essential component required for diagnosis; however, it should be recognized

that their severity may be disproportionate to objective clinical findings. According to the TFOS DEWS III recommendations, the diagnosis of DED is based on the fulfillment of two criteria:

1. **Presence of symptoms, confirmed by a score of ≥4 points on the OSDI-6 (Ocular Surface Disease Index) questionnaire.**
2. **Presence of at least one of the following three signs of loss of tear film homeostasis:**
    a. **Tear film instability:** non-invasive tear break-up time (NIBUT) <10 s or fluorescein tear break-up time (TBUT) <5 s.
    b. **Tear film hyperosmolarity:** ≥308 mOsm/L in the eye with the higher value or an interocular difference >8 mOsm/L (TearLab thresholds).
    c. **Ocular surface staining:** >5 corneal fluorescein staining spots OR >9 conjunctival lissamine green staining spots OR lid margin staining with lissamine green (lid wiper epitheliopathy - LWE) with a length ≥2 mm and ≥25% of the lid width.

Diagnostic testing should be performed in sequence from least to most invasive to avoid inducing reflex tearing, which may confound subsequent measurements. In clinical practice, specific scenarios may be encountered, such as marked ocular surface staining in the absence of subjective symptoms (which may indicate neurotrophic keratitis), as well as the opposite situation, in which patients report severe symptoms that are not corroborated by objective findings (suggestive of neuropathic corneal pain). In such cases, a topical anesthetic challenge with proparacaine may be useful in the differential diagnosis, as it helps distinguish between peripheral and central sources of pain. [1] Examples of additional diagnostic tests used to identify specific DED subtypes are listed below:

1. **Assessment of tear film component deficiencies:**
    a. **Lipid layer:** Evaluation of meibum quality and expressibility; interferometry (lipid layer thickness <72 nm or abnormal patterns according to the Guillon scale); meibography (assessment of meibomian gland morphology and dropout). [1, 14]
    b. **Aqueous component:** Meniscometry (tear meniscus height <0.20 mm), phenol red thread test (<20 mm), Schirmer test. [1]
    c. **Mucin/glycocalyx component:** Conjunctival staining with lissamine green (>9 staining spots), conjunctival impression cytology (assessment of goblet cell density), tear ferning test (abnormal crystallization patterns). [1]
2. **Eyelid-related abnormalities:**
    a. **Blinking disorders and incomplete eyelid closure:** Assessment of blink rate and completeness, eyelid closure tests (e.g., Korb–Blackie Light Test), lagophthalmos. [1]
    b. **Lid margin status:** Anterior blepharitis (e.g., the presence of cylindrical dandruff in Demodex infestation), meibomian gland dysfunction (MGD)—including assessment of orifice obstruction, meibum consistency, and telangiectasia—as well as ocular rosacea. [1]

3. **Ocular surface abnormalities:**
    a. **Anatomical alterations:** Presence of pterygium, pinguecula, excessive folding and laxity of the bulbar conjunctiva (conjunctivochalasis), and lid-parallel conjunctival folds (LIPCOF). [1]
    b. **Neuronal dysfunction:** Esthesiometry (measurement of corneal sensitivity thresholds), in vivo confocal microscopy (assessment of corneal nerve density, length, and tortuosity; the presence of microneuromas is characteristic of neuropathy). [1]
    c. **Cellular damage:** Corneal, conjunctival, and lid margin staining using standardized grading scales (Oxford, NEI, Korb). [1]
d. **Primary inflammation/oxidative stress:** Imaging of conjunctival hyperemia, increased dendritic cell density using confocal microscopy; in the future, point-of-care tests for inflammatory biomarkers in tears (MMP-9, cytokines, neuropeptides). [1, 14]

6. TARGETED TOPICAL THERAPIES IN DRY EYE DISEASE

Contemporary pharmacological management of dry eye disease (DED) is evolving from purely symptomatic lubrication toward targeted therapies aimed at restoring ocular surface homeostasis. Traditional agents such as cyclosporine A (CsA) 0.05% ophthalmic emulsion (Restasis) constitute a cornerstone of anti-inflammatory treatment; however, their clinical utility may be limited by adverse effects, particularly ocular burning, frequently leading to treatment discontinuation. In response to these challenges, there has been rapid development of novel formulations and molecular entities designed not only to enhance therapeutic efficacy but also to improve tolerability and patient comfort. [3]

One of the principal limitations of topical DED therapy is the inherently low ocular bioavailability of conventional eye drops. Advanced drug delivery systems have been developed to address this issue. New-generation CsA formulations exemplify this evolution. Restasis 0.05%, approved by the U.S. Food and Drug Administration (FDA), utilizes a nanoemulsion platform which, owing to the small droplet size of the dispersed phase, enhances ocular surface adhesion, tissue penetration, and residence time compared with conventional formulations. Another FDA-approved CsA product, Cequa 0.09%, employs nanomicellar technology that significantly improves drug solubility and corneal penetration. A further innovation is the use of a water-free carrier based on semifluorinated alkanes (SFAs) in Vevye (CsA 0.1% solution). This vehicle enhances corneal diffusion and improves ocular surface spreading due to the exceptionally low surface tension generated by SFAs. [3, 7, 9, 19]

Among the most notable SFA-based formulations developed in recent years is perfluorohexyloctane (NOV03/MIEBO), which acts by forming a barrier on the ocular surface that substitutes for the dysfunctional lipid layer and effectively reduces tear evaporation. Its efficacy in DED associated with meibomian gland dysfunction (MGD) has been demonstrated in phase III randomized clinical trials (*GOBI, MOJAVE*), which showed significant improvements in corneal fluorescein staining (CFS) and patient-reported dryness scores assessed using the visual analog scale (VAS). Long-term data from the 52-week *KALAHARI* study confirmed sustained efficacy alongside a favorable safety profile. [21–23]

Controlled drug-release systems represent another promising strategy with the potential to revolutionize dosing regimens and improve treatment adherence. These include solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and mucus-penetrating nanoparticles (MPNs). An example of MPN technology is loteprednol etabonate formulated with poloxamer 407 (KPI-121), approved by the FDA in 2020 for short-term treatment of DED exacerbations. In preclinical work by Liu et al. (2014), phenylboronic acid-modified cationic nanoparticles enabled maintenance of therapeutic CsA concentrations with once-weekly administration. Additional approaches include drug-eluting contact lenses, intracanalicular inserts, nanoplates, and punctal plugs designed for sustained drug delivery. Drug-loaded contact lenses enhance bioavailability through prolonged corneal contact while simultaneously reducing tear evaporation. Biodegradable punctal plugs may provide controlled drug release for up to 30 days, thereby facilitating adherence. [9, 19]

Advances in understanding DED pathogenesis have led to identification of novel therapeutic targets and the development of specialized molecular agents. Lifitegrast (Xiidra), a next-generation immunomodulator and LFA-1 antagonist approved by the FDA in 2016, inhibits the LFA-1/ICAM-1 interaction, thereby suppressing both afferent and efferent phases of T-cell–mediated inflammation. Compared with CsA formulations, lifitegrast demonstrates a relatively rapid onset of action (with clinical improvement observed within approximately two weeks) and established long-term safety, although adverse events such as dysgeusia and local irritation are relatively common. [3, 19, 24, 40]

Among secretagogues that stimulate endogenous tear film production, diquafosol (a P2Y2 receptor agonist) and rebamipide (a mucin secretagogue) are approved in Japan and South Korea. These agents promote aqueous secretion (diquafosol) and mucin production (both diquafosol and rebamipide) from conjunctival goblet cells, while rebamipide additionally stabilizes the mucin layer of the tear film, directly addressing deficiencies in its key components. [9, 16, 18, 25]

Cenegermin, a recombinant human nerve growth factor (rhNGF) approved for the treatment of neurotrophic keratitis (NK) as Oxervate 0.002%, has also generated interest. It promotes survival, differentiation, and regeneration of corneal sensory neurons, thereby indirectly and directly supporting epithelial healing. In the REPARO trial, cenegermin significantly accelerated healing of persistent epithelial defects (PEDs). Preliminary data suggest potential benefits in severe DED; however, further investigation is required. [2, 16]

Tiwanisiran, a small interfering RNA (siRNA) targeting the TRPV1 receptor involved in nociceptive signaling, is currently in phase III clinical development. Its mechanism involves reduction of pain and discomfort through suppression of TRPV1 expression. [9, 17] Isunakinra (EBI-005), also in advanced clinical evaluation, directly inhibits pro-inflammatory signaling via interleukin-1 (IL-1) receptor antagonism. [9, 24, 26]

An emerging therapeutic direction involves neuromodulation. Agents such as acoltremon and cryosim-3 are TRPM8 receptor agonists. TRPM8, activated by cold stimuli and menthol, induces a cooling sensation, modulates neural signaling, and enhances tear secretion. Based on phase III *COMET-2* and *COMET-3* trials, 0.003% acoltremon ophthalmic solution was approved by the FDA in May 2025 in the United States. These studies demonstrated both safety and efficacy in increasing tear production (Schirmer test) and improving symptoms assessed using the SANDE questionnaire. [16, 26, 27]

Lacritin, a tear glycoprotein secreted by the lacrimal gland, represents a molecule at the interface of secretagogues and endogenous ocular surface proteins. It stimulates tear secretion and is significantly reduced in patients with Sjögren's syndrome, implicating its role in aqueous-deficient DED. In 2023, Tauber et al. published the first clinical trial evaluating topical lacritin in humans (204 patients with Sjögren's syndrome). Despite an excellent safety profile, efficacy findings were mixed. Improvements were observed in burning/watering symptoms and inferior corneal fluorescein staining; however, overall dryness scores assessed by VAS and total CFS did not differ significantly from placebo. [3, 9, 16, 29]

Lubricin, another ocular surface glycoprotein, reduces friction between the eyelid and ocular surface and limits bacterial adhesion. In phase II studies, lubricin demonstrated superiority over sodium hyaluronate in reducing patient-reported symptoms and improving objective parameters such as CFS, tear film break-up time (TFBUT), and SANDE scores, with good tolerability. [3, 9, 16, 28]

Thymosin β4, a naturally occurring peptide with anti-inflammatory and epithelial regenerative properties, has also been investigated. In small phase III trials, synthetic 0.1% thymosin β4 (RGN-259) demonstrated significant superiority over placebo in neurotrophic keratitis. Between 2015 and 2021, three large phase III trials (*ARISE-1*, *ARISE-2*, *ARISE-3*) evaluated its efficacy in DED. Although *ARISE-1* and *ARISE-2* reported improvements in symptoms and OSDI scores, *ARISE-3* failed to meet its primary endpoints. [30–33]

Another mechanistically distinct compound is SKQ1 (Visomitin), a mitochondria-targeted antioxidant that neutralizes reactive oxygen species (ROS) and inhibits NF-κB signaling, which is a central mediator of the inflammatory response. Currently, Russia remains the only country where this agent is approved for clinical use in DED. A multicenter phase III study conducted there demonstrated significant improvements in TBUT, CFS, and symptoms compared with placebo. *VISTA-1* and *VISTA-2* (phase II/III), conducted outside Russia, suggested improvements in CFS and best-corrected visual acuity (BCVA); however, the available data derive from press releases and have not yet been published in peer-reviewed scientific journals. [4, 9, 16, 34, 35]

There are also several compounds currently at earlier stages of investigation, including ferulic acid and naringenin. Ferulic acid is an antioxidant with potential antibacterial properties. In preclinical studies conducted in animal models, its combination with kaempferol improved tear production and supported corneal epithelial regeneration. In vitro models have additionally demonstrated anti-inflammatory properties of ferulic acid, including a reduction in the expression of all analyzed pro-inflammatory cytokines, such as IL-1β, IL-6, and IL-8. [16, 36] Naringenin is a flavonoid compound that, similarly to ferulic acid, exhibits antioxidant and anti-inflammatory properties. A formulation with enhanced solubility, achieved using dipotassium glycyrrhizinate micelles, was evaluated in a murine model of DED induced by benzalkonium chloride. The developed formulation proved more effective in reducing DED manifestations compared with a standard naringenin solution and, in selected analyzed parameters, also outperformed commercially available eye drops containing 0.1% sodium hyaluronate. [16, 37] It should be emphasized, however, that at the present stage there are no registered clinical trials evaluating the efficacy of ferulic acid or naringenin in the treatment of DED in humans.

Therapies based on blood-derived products and stem cells represent some of the most advanced and personalized approaches to the treatment of severe, refractory forms of DED. The first clinical study in humans employing allogeneic eye drops containing umbilical cord–derived mesenchymal stem cells (UC-MSCs) demonstrated significant changes in clinical

parameters. A two-week course of therapy resulted in a statistically significant improvement in tear production as measured by the Schirmer test, as well as a reduction in meibomian gland obstruction. The therapeutic effect was more pronounced and sustained in patients with non-Sjögren DED. Proteomic analysis of tear samples and biomarker assessment indicated that the mechanism of action is based on immunomodulation, particularly through inhibition of the pathological CCL20/IL-23 – Th17 – IL-17A axis. [2, 20]

Traditional blood-derived products, such as autologous serum eye drops, remain important therapies with established efficacy in severe DED, providing a mixture of growth factors and proteins that support ocular surface regeneration. Meta-analyses indicate their superiority over artificial tears with respect to improvements in OSDI scores, tear break-up time (TBUT), and rose bengal staining. Platelet-rich plasma (PRP), plasma rich in growth factors (PRGF), and platelet lysates may contain even higher concentrations of growth factors than autologous serum eye drops and have demonstrated comparable clinical efficacy in patient studies. However, significant limitations to their broader implementation include the lack of standardization of preparation protocols, frequently high treatment costs, logistical challenges related to product storage, and the absence of formal regulatory approval for these therapeutic modalities. A potential response to some of these limitations is the relatively novel "finger-prick" procedure, which involves the self-administration of freshly obtained autologous whole blood from a fingertip puncture directly into the conjunctival sac. This method offers several advantages: it is inexpensive, readily accessible, eliminates the need for storage, and allows for immediate treatment tailored to the patient's current needs. In a clinical study involving 60 patients, the finger-prick procedure resulted in a statistically significant improvement in OSDI scores compared with the control group. Nevertheless, further adequately powered and well-designed studies are required to evaluate the efficacy and long-term benefits of this approach. [16, 38, 39]

Biological tear substitutes also include amniotic membrane extract eye drops (AMEED). A unique component isolated from the amniotic membrane is the HC-HA/PTX3 complex, which—together with numerous growth factors and protease inhibitors—exerts anti-inflammatory and anti-scarring effects and accelerates corneal epithelial healing by promoting cellular proliferation and differentiation. [74] In a multicenter retrospective study, Yeu et al. (2019) analyzed 4- and 12-week DED treatment with AMEED administered twice daily in 16 and 38 patients, respectively. Baseline disease severity was comparable in both groups. A statistically significant reduction in patient-reported ocular dryness, assessed using the VAS, was observed and continued through week 12: 81% of patients achieved at least a 30% decrease in symptom severity, and 67% achieved a reduction of at least 40%. Significant positive changes were also noted in corneal fluorescein staining and conjunctival lissamine green staining; by week 12, 95% of patients demonstrated at least a 50% reduction in corneal epithelial damage. Visual acuity remained stable or exhibited a slight but statistically significant increase. [75] To conclusively confirm the efficacy of AMEED, prospective, randomized controlled trials involving larger patient populations and longer follow-up periods are required.

7. BEYOND EYE DROPS: DEVICE-BASED AND PROCEDURAL THERAPIES

Dry eye disease (DED) is a chronic, multifactorial disorder of the ocular surface characterized by loss of tear film homeostasis. While topical eye drops (artificial tears and anti-inflammatory agents) constitute the mainstay of treatment, a broad range of non-

pharmacological interventions has gained increasing importance, offering targeted therapeutic approaches, particularly in cases associated with meibomian gland dysfunction (MGD) and those refractory to standard therapy.

7.1 Light-Based Therapies

The dominant group of noninvasive procedures comprises therapies utilizing light energy. Intense pulsed light (IPL) therapy is one of the more extensively investigated treatment modalities for DED. Its mechanism of action is based on the principle of selective photothermolysis, whereby broad-spectrum light (500–1200 nm) is absorbed by chromophores, primarily hemoglobin within eyelid telangiectasias. This results in a localized increase in intravascular temperature, reaching up to 80–90°C, and subsequent coagulation of pathological capillaries, thereby reducing the source of inflammatory mediators reaching the meibomian glands. Additionally, the thermal effect warms and liquefies inspissated meibum, restoring gland patency and inducing eradication of Demodex spp. [10–13, 46] The most consistently documented effect of IPL is the improvement of tear film stability, reflected by prolonged tear break-up time in numerous studies. [10, 41–43] Other parameters demonstrating significant benefit include OSDI scores as well as meibomian gland function and morphology assessed by meibography. [10, 12, 44, 45] The combination of manual meibomian gland expression (MGX) with IPL appears to be optimal, as it enables mechanical evacuation of heat-liquefied meibum, thereby potentiating the therapeutic effects of both modalities, as supported by clinical data. [10, 12, 47] The therapeutic effect of IPL tends to diminish after approximately 6 months; therefore, maintenance sessions every 6–12 months are required for sustained disease control. [10] The safety profile is favorable, with predominantly mild adverse effects, including procedural discomfort, erythema, edema, and, in rare cases, skin hyperpigmentation. [11, 12, 45] Particular caution is warranted in patients with Fitzpatrick skin phototypes V–VI. [10, 45] However, universal protocols defining the optimal number of sessions and irradiation parameters (duration and energy dose) for IPL remain lacking.

Low-level light therapy (LLLT), also referred to as photobiomodulation (PBM), exerts its effects through non-thermal mechanisms at the cellular level using low-energy light. [48] Light in the red and near-infrared spectrum (600–1100 nm) is absorbed by cytochrome c oxidase within mitochondria, leading to increased ATP production, activation of signaling pathways that stimulate cell proliferation and migration, and modulation of inflammation and oxidative stress, thereby supporting cellular repair processes. [48, 49] A clinical study by Park et al. (2022) demonstrated that LLLT alone improved corneal fluorescein staining (CFS), Schirmer test results, and upper eyelid meibomian gland morphology assessed by meibography. [50] Portable LLLT devices in the form of masks have also been developed for safe home use. In a study evaluating their efficacy, significant improvements were observed in non-invasive keratograph break-up time (NIKBUT) and tear meniscus height (TMH). [51]

The combination of IPL and LLLT within a single therapeutic session has gained popularity, aiming to achieve synergistic effects between the thermal action of IPL on blood vessels and meibum and the photobiomodulatory effects of LLLT in promoting tissue repair and modulating inflammation. [42–44, 52, 76] Studies investigating this combined approach indicate sustained improvement in OSDI scores and non-invasive break-up time (NIBUT), persisting for up to 12–15 months. [42, 52] However, a comparative analysis by Marques et al. (2022) did not demonstrate clear superiority of combined therapy over IPL alone, except for additional benefits in Schirmer test outcomes. [53] As with IPL, standardized treatment protocols for LLLT have yet to be established.

7.2 Thermal and Mechanical Meibomian Gland Interventions

Direct restoration of meibomian gland patency represents a key strategy in the management of DED associated with MGD. In addition to manual gland expression (MGX), meibomian gland probing (MGP)—mechanical dilation of gland ducts using a fine probe—is employed in more challenging cases. This procedure provides immediate relief of eyelid pain and may potentially induce glandular regeneration. [3] Clinical studies confirm the efficacy of MGP in reducing patient-reported symptoms and improving both the quality and quantity of expressed meibum. [54]

Many advanced systems used in the management of MGD are based on controlled heat delivery to the eyelids, sometimes combined with mechanical massage. LipiFlow is one such device, simultaneously heating the inner eyelid surface while applying pulsatile pressure externally, thereby effectively evacuating meibomian gland contents. [2, 3] Clinical studies have demonstrated superior efficacy of LipiFlow compared with conventional warm compress therapy in improving OSDI scores and meibomian gland function. [2]

TearCare represents a less invasive alternative, utilizing controlled external eyelid heating to liquefy meibum, followed by manual gland expression performed by a clinician. In comparative studies, both LipiFlow and TearCare demonstrated statistically significant improvements in evaluated parameters, with a slight advantage observed for TearCare. [55] In another study comparing TearCare with topical 0.05% cyclosporine A (CsA), eyelid heating achieved superior outcomes in TBUT and meibomian gland function relative to pharmacological treatment. [56]

Similarly, iLux delivers heat to both the inner and outer eyelid surfaces. Its efficacy in improving TBUT, meibomian gland function, and OSDI scores is comparable to that of LipiFlow. [57]

Another device utilizing thermal liquefaction of meibum is Mibo Thermoflo, which consists of a handheld heated probe applied externally with ultrasound gel for 8–12 minutes, followed by manual gland expression (MGX). [3] In a retrospective study involving 102 patients, Gomez et al. (2022) reported statistically significant improvements in all assessed parameters following Mibo Thermoflo treatment, with effects persisting at 6 months. SPEED and OSDI scores decreased by 35% relative to baseline values. [58] In a separate study conducted in China involving 54 patients, Mibo Thermoflo was compared with LipiFlow, and no statistically significant differences were identified, indicating comparable efficacy of both systems in the treatment of MGD. [59]

Thermal liquefaction of meibum is not limited to in-office systems but is also achievable with home-use devices. Various technologies have been developed, including electrically powered goggles delivering warm, humid air around the eyelids (e.g., Blephasteam). More affordable and simpler alternatives include heated eyelid masks, some of which are electronic devices, while others rely on microwave-heated inserts (e.g., EyeBag) or oxygen-activated heat-generating inserts producing temperatures of approximately 40–45°C (e.g., EyeGiene). [62]

In a comparative study of EyeBag and EyeGiene, both methods demonstrated similar efficacy in reducing DED symptoms, although eyelid temperature elevation was significantly greater in the EyeBag group. [62] A randomized, placebo-controlled trial published in 2024 by

Wang et al., involving 144 patients, compared heated eyelid masks with traditional warm compress therapy. After 4 weeks, statistically significant differences favoring the mask-treated group were observed in OSDI and CFS. At 12 weeks, the advantage of heated masks was more pronounced, with significant differences in OSDI, CFS, TBUT, and meibum quality and expressibility. [61]

A review by Magno et al. (2022) reported that devices delivering warm, humid air were associated with improvements in TBUT, lipid layer thickness (LLT), ocular surface staining, and subjective symptom scores (VAS, SANDE, OSDI). Long-term evaluations (2 weeks to 3 months) consistently demonstrated sustained improvement in subjective symptoms; however, objective parameters such as TBUT yielded inconsistent findings. [60]

An adjunctive procedure to the previously described techniques may involve mechanical debridement of the eyelid margins using the BlephEx device, which employs a disposable, rapidly rotating micro-sponge to remove accumulated biofilm, keratinized epithelium, and residual debris in an office-based setting. Ballesteros-Sanchez et al. (2023) conducted a systematic review of randomized controlled trials evaluating eyelid debridement in DED using BlephEx or a “Golf Club Spud” instrument. In all four studies involving BlephEx, statistically significant benefits were observed in the treatment group compared with controls, including improvements in OSDI, TBUT, or both, depending on the study. [63]

Similarly, NuLids is a home-use device designed to clean the eyelid margin and facilitate meibomian gland orifice patency. Preliminary results suggest its efficacy. Schanzlin et al. (2020) evaluated a 30-day self-administered NuLids therapy in 37 patients with DED, MGD, and blepharitis, reporting statistically significant improvements in all assessed parameters, including OSDI, TBUT, and meibum quality and expressibility. [64] However, larger randomized controlled trials are required to confirm its clinical effectiveness.

7.3 Tear Secretion Stimulation Technologies

In the management of dry eye disease associated with aqueous tear deficiency, attempts have been made to enhance tear secretion through activation of the nasolacrimal reflex by stimulating trigeminal nerve endings. The first device based on this mechanism was TrueTear, approved by the FDA in 2017. TrueTear consisted of two elongated probes which, when applied to the intranasal mucosa, stimulated the nasolacrimal reflex via electrical impulses. Although clinical studies demonstrated a significant increase in tear production as measured by the Schirmer test following TrueTear therapy, the device was discontinued in 2020 due to lack of commercial success. [2,3]

Other products with a similar mechanism of action remain available. One such example is iTear, a device designed to stimulate the external branch of the anterior ethmoidal nerve using an oscillating tip applied to the skin over the nasal ala. Ji et al. (2020) conducted a study involving 101 patients with aqueous-deficient dry eye in which participants used iTear twice daily for 30 seconds over a 30-day period. A significant increase in Schirmer test scores was observed on days 0, 14, and 30 immediately following stimulation, along with a reduction in symptoms assessed by the OSDI after completion of therapy. [65] iTear received FDA approval in 2020. [19]

Pharmacological stimulation of the nasolacrimal reflex represents another therapeutic approach. Tyrvaya, approved by the FDA in 2021, is an intranasal spray containing varenicline, a partial nicotinic acetylcholine receptor agonist. Similar to TrueTear, Tyrvaya stimulates

trigeminal nerve endings within the nasal mucosa, thereby enhancing tear production via activation of the lacrimal functional unit. Ballesteros-Sanchez et al. (2024) conducted a review of randomized controlled trials evaluating the efficacy of intranasal varenicline in DED. The analysis included eight studies comprising a total of 1,081 patients. In seven of these studies, the varenicline-treated groups demonstrated a statistically significant improvement in Schirmer test results compared with placebo. Furthermore, six studies reported a significant reduction in patient-reported symptom severity measured using the VAS. One study additionally demonstrated that varenicline induces rapid goblet cell degranulation, thereby enriching the mucin layer of the tear film. [5,66]

Simpinicline is another nicotinic receptor agonist with a mechanism of action analogous to that of varenicline, although it has been less extensively investigated. In the phase II clinical trial *The PEARL*, conducted in 165 patients, the efficacy of simpinicline was assessed immediately after administration at three different doses compared with placebo. Improvements in Schirmer test scores and reductions in ocular dryness symptoms measured using the VAS were greater in the simpinicline groups and exhibited a dose-dependent effect. Between 41.5% and 58.5% of participants reported adverse events, the majority of which were mild to moderate in severity (e.g., cough, throat irritation, ocular pruritus, and keratitis). [67]

7.4 Scleral Lenses and Ocular Surface Protection Strategies

In particularly refractory cases of DED and in patients with concomitant ocular surface disease (OSD), rigid scleral lenses (SL) may provide therapeutic benefit. These large-diameter, rigid gas-permeable lenses rest on the sclera and create a stable fluid reservoir over the cornea, thereby protecting the ocular surface and ensuring continuous hydration. Numerous studies have demonstrated the efficacy of this therapeutic modality in patients in whom DED constitutes a component of severe ocular surface disorders, such as graft-versus-host disease (GvHD). Magro et al. (2017) reported a statistically significant improvement in OSDI scores and corneal staining assessed using the Oxford scale after two months of SL wear in 60 patients with GvHD. In a large survey study by Bligdon et al. (2021) involving 306 patients with GvHD, 94% of current SL users reported improvement in dryness symptoms or foreign body sensation. La Porta Weber et al. (2016), in a prospective case series of 25 patients with various OSDs (including Stevens–Johnson syndrome, Sjögren syndrome, and GvHD), observed significant improvements in tear osmolarity, van Bijsterveld score, and OSDI after 12 months of SL use. A retrospective review by Asghari et al. (2022) of 43 patients with OSD confirmed significant improvement in OSDI at six months. [68]

Scientific evidence supporting the use of scleral lenses in isolated DES, however, remains limited. Fadel et al. (2024) evaluated 20 soft contact lens wearers presenting with DED symptoms. After one month of SL wear, statistically significant improvement was observed in the Contact Lens Dry Eye Questionnaire-8 (CLDEQ-8) as well as in subjective assessments of end-of-day comfort and dryness compared with baseline soft lens use. Forty-five percent of participants expressed willingness to continue SL therapy. A similar study by Wong et al. (2024) involving 18 non–contact lens wearers with DED demonstrated significant improvements in the same parameters after one month of SL use compared with baseline. Forty-four percent of participants opted to continue SL wear. [68]

Barriers to SL use include limited availability and high cost, particularly in the case of advanced personalized systems such as PROSE (Prosthetic Replacement of the Ocular Surface Ecosystem) developed by BostonSight. Only a limited number of centers provide such specialized fitting services. Adverse effects must also be considered, the most common being

reduced visual clarity due to lens fogging, referred to as midday fogging (MDF). This phenomenon results from debris accumulation within the post-lens tear reservoir and insufficient surface wettability, particularly in patients with meibomian gland dysfunction (MGD). MDF occurs especially frequently in patients with DED, affecting up to 75% of users. These limitations render SL a last-resort therapeutic option reserved for severe, treatment-refractory DED, particularly when associated with other forms of OSD. [3,16,68]

Moisture chamber glasses represent another strategy aimed at reducing tear film evaporation. These devices are designed to create a semi-sealed periocular environment that limits airflow and minimizes exposure to environmental factors exacerbating DED symptoms. Certain models are additionally equipped with lateral reservoirs that promote continuous water evaporation, thereby increasing humidity within the chamber. [69,70]

Shen et al. (2016) evaluated moisture chamber glasses fitted with saline-soaked sponges in a cohort of 30 DED patients randomized into study and control groups. Measurements were performed at 15, 30, 45, 60, 75, and 90 minutes following intervention. Significant improvements were observed in ocular comfort (VAS), TMH, NIBUT, and LLT compared with controls. These parameters increased up to 60 minutes, followed by a slight decline while remaining above baseline values. No significant changes were observed in the control group. [69]

Ogawa et al. (2017) investigated the effect of moisture chamber glasses under controlled wind exposure conditions. Fourteen participants underwent 10-minute wind exposure in three configurations: without glasses, with conventional glasses, and with moisture chamber glasses equipped with humidity-enhancing reservoirs. Mean humidity inside the chamber was 58.8%, compared with 43.6% ambient humidity. No significant humidity differences were observed when conventional glasses were worn. Wind exposure without protective eyewear or with conventional glasses resulted in a significant increase in tear evaporation rate (TEROS), blink frequency, reduced TBUT, and exacerbation of dryness symptoms. These variables did not reach statistical significance during the use of moisture chamber glasses, suggesting a protective effect against environmental irritants such as wind and particulate matter. [70]

7.5 Amniotic Membrane Dressings

In patients with treatment-refractory DED, amniotic membrane (AM) dressings may represent a promising therapeutic option. Historically, AM was sutured to the ocular surface and used, among other indications, in the management of corneal epithelial defects as a biological scaffold supporting epithelial regeneration. Advances in processing and preservation techniques have enabled the development of cryopreserved AM devices that self-retain on the ocular surface, can be applied in an outpatient setting, and do not require suturing in the operating room. The first and, to date, only FDA-approved product in this category is PROKERA (BioTissue). [71,72] Amniotic membranes exhibit anti-inflammatory and anti-angiogenic properties and inhibit scar formation. They are rich in growth factors, including nerve growth factor (NGF), thereby promoting corneal nerve regeneration. Due to their structural properties, they sequester inflammatory cells, absorb reactive oxygen species, and inhibit matrix metalloproteinase activity. AM functions as a protective biological dressing, reducing tear evaporation and shielding the ocular surface from environmental stress while simultaneously serving as a scaffold facilitating epithelial migration and corneal repair. [71,73]

In a multicenter retrospective review, McDonald et al. (2018) analyzed 97 eyes of 84 patients with severe, refractory DED treated with cryopreserved PROKERA. The follow-up

period was three months, and the mean retention time of the membrane was 5.4 days. Patients were assessed using the DEWS severity scale, which incorporates both subjective and objective parameters of DED. Improvement in ocular surface status was observed in 88% of patients, and overall DEWS scores decreased significantly at all evaluated time points—after one week, one month, and three months. The only reported adverse effect was discomfort associated with membrane wear. [73]

8. CONCLUSIONS

Dry eye disease (DED) should be regarded as a complex, multifactorial disorder rather than a simple deficiency of tear volume amenable to symptomatic lubrication alone. Contemporary evidence supports its characterization as a dynamic and self-perpetuating process involving tear film instability, hyperosmolar stress, immune activation, epithelial barrier disruption, neurosensory alterations, and frequently meibomian gland dysfunction. The marked heterogeneity of pathogenic mechanisms underlies the variability in clinical phenotypes and explains the often-observed discordance between signs and symptoms.

The transition from a simplistic aqueous-deficiency versus evaporative classification toward an etiology-driven and mechanism-based framework marks a fundamental shift in clinical thinking. Modern diagnostic algorithms now serve not only to confirm the presence of DED but also to identify the dominant pathogenic components driving disease in individual patients. Such stratification is essential for rational, targeted therapeutic selection.

Over the past decade, therapeutic strategies have evolved substantially. Advances in ocular drug delivery systems, novel immunomodulatory and secretagogue agents, neuromodulatory compounds, biologic therapies, and regenerative approaches have expanded treatment possibilities beyond artificial tears. In parallel, device-based and procedural interventions—including light-based therapies, thermal pulsation systems, neurosensory stimulation technologies, and scleral lenses—offer phenotype-specific solutions, particularly in evaporative and refractory forms of the disease. Collectively, these innovations reflect a paradigm shift from temporary symptom relief toward restoration of ocular surface homeostasis.

Despite this progress, challenges remain, including the need for standardized treatment protocols, robust long-term outcome data, and validated biomarkers to guide precision medicine approaches. Future developments should focus on deeper phenotyping and integration of molecular insights into clinical practice, with the ultimate aim of achieving durable disease control and meaningful improvement in patients' quality of life.

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