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DISCOVERY
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Managing dry eye disease: A review of emerging and established treatments

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ABSTRACT

Dry eye syndrome (DES) is a widespread condition that impacts the ocular surface. It originates from multiple etiological factors and results in an imbalance in tear film homeostasis. A range of eye-related symptoms emerging from this disorder can significantly impair vision-related quality of life. If left untreated, it may lead to chronic conjunctivitis and keratitis and potentially cause epithelial defects and ulceration. This review describes the different treatment modalities available to clinicians treating patients with dry eye disease. A targeted search of PubMed and the National Library of Medicine, along with current guidelines and specialized manuals, identified a variety of FDA-approved pharmacological and device-based treatments for dry eye disorder, including artificial tears, cyclosporine A, lifitegrast, warming and humidity devices, scleral lenses, and intranasal neurostimulation. Furthermore, off-label treatments are gaining popularity due to their mechanism of restoring balance to the tear film. In conclusion, contributions to understanding the aetiopathogenesis of dry eye syndrome (DES) and advances in selecting new interventions using technology, as well as these interventions being evaluated in clinical trials, ensure better management of patients. Management options for dry eye syndrome are determined by the severity of the disease and vary from conservative to more advanced.

Keywords: Dry eye syndrome, ocular surface disease, meibomian gland dysfunction, aqueous tear-deficient dry eye, evaporative dry eye

1. INTRODUCTION

Dry eye syndrome (DES) is a complex ocular surface disease. It results from disturbances in tear film homeostasis with associated ocular manifestations. It is linked to an elevated osmolarity of the tear film and eye surface irritation. DES is

a relatively common chronic condition that impacts quality of life, with an estimated prevalence of 5-50% globally (Stapleton et al., 2017). In Poland, however, the prevalence is notably higher, reaching 63% (Ambroziak, 2018). Among specific subpopulations, such as contact lens wearers and peri-menopausal and postmenopausal women, the incidence is reported to be higher. The primary clinical symptoms reported by patients include non-specific redness, burning, stinging, foreign body sensation, itching, and photophobia, all of which significantly affect daily vision.

If not addressed, it can advance to chronic conjunctivitis and keratitis, potentially leading to epithelial damage and ulcer formation. Given its characteristics, it is referred to in the literature as dysfunctional tear syndrome (DTS), keratoconjunctivitis sicca (KCS), dry eye disease (DED), and ocular surface disorder (OSD). In 2007, an updated etiopathogenic classification of DES was released. The primary types of dry eye are aqueous tear-deficient dry eye (ADDE) and evaporative dry eye (EDE). ADDE arises from dysfunction or damage to the lacrimal glands, impairing their ability to produce adequate tear volume. This reduction in tear secretion leads to hyperosmolarity of the ocular surface, triggering a cascade of inflammatory responses.

Two subgroups of ADDE can be identified: Sjögren Syndrome Dry Eye (SSDE) and non-Sjögren Syndrome Dry Eye (NSSDE). SSDE is further classified into primary and secondary Sjögren syndrome, while NSSDE includes primary and secondary lacrimal gland deficiency, lacrimal duct obstruction, and reflex hyposecretion. Evaporative Dry Eye results from excessive water loss from the ocular surface with normal tear secretory function. Intrinsic and extrinsic causes of EDE were distinguished. Intrinsic factors involve meibomian gland dysfunction (MGD), low blinking rate, disruptions in eyelid opening, and the alignment or movement coordination between the eyelid and eyeball. Extrinsic factors may include vitamin A deficiency, contact lens wear, chronic use of topical anesthetics and preservatives, and conditions that impact the eye surface, such as allergic conjunctivitis.

These categories can trigger dry eye, though they are not mutually exclusive. It is acknowledged that a condition originating in one primary group can coexist with or even lead to issues that trigger dry eye through a different mechanism. This creates a vicious cycle of interactions that can worsen the severity of dry eye. Numerous internal and external factors can contribute to the development of dry eye disease. Internal factors include conditions originating within the body, such as autoimmunity, hormonal imbalances (low androgen levels and elevated estrogen levels), systemic diseases (e.g., diabetes mellitus, xerophthalmia), genetic disorders, nerve damage, and gut dysbiosis. Autoimmune diseases most notably associated with dry eye include Sjögren's syndrome, Graves' ophthalmopathy, and multiple sclerosis.

External factors include environmental influences (impurities, low humidity, high temperature), habits and behaviors, eye surgeries, and accessories – especially contact lenses. Factors that may contribute to the problem include smoking and overuse of electronics. DES's wide range of causes explains its widespread occurrence (Huang et al., 2022). Accurate diagnostic and monitoring techniques for patients are vital to providing the most appropriate treatment and improving patients' quality of life. Subjective questionaries, commonly self-administered by the patient, are used to evaluate symptoms and visual disturbance. The Ocular Surface Disease Index (OSDI) is the questionnaire most frequently employed in clinical trials for DED. It evaluates the frequency of symptoms, environmental triggers, and vision-related quality of life.

In addition to the OSDI, several other questionnaires are commonly used to assess DED and related symptoms, including the Dry Eye Questionnaire (DEQ-5), Impact of Dry Eye on Everyday Living (IDEEL), National Eye Institute's Visual Function Questionnaire (NEI VFQ-25), Dry Eye-Related Quality-of-Life Score (DEQS) and Computer-vision symptom scale (CVSS17). The definition of dry eye syndrome inherently includes tear film instability, which can be evaluated through various diagnostic tests. For this purpose, we have at our disposal several tests, including tear film breakup time (TBUT; the most commonly used in clinical practice), fluorescein breakup time (FBUT), non-invasive tear breakup time, thermography, osmolarity testing, and tear evaporation rate (Wolffsohn et al., 2017).

Although not explicitly stated in the definition of DED, tear film volume plays a crucial role in ocular surface health. It is assessed using meniscometry, phenol red thread, and Schirmer tests. Key factors in the etiology of dry eye include damage to the ocular surface, associated inflammation, and any eyelid disorders that can be detected through various diagnostic tests. Diagnosis and monitoring of dry eye disease should consider its multifactorial nature to ensure the correct and effective application of the appropriate treatment.

2. METHODS

This review is based on relevant publications from a targeted search of PubMed and the National Library of Medicine, supplemented by existing guidelines and specialized reference materials. The search involved reviewing original articles, clinical studies, review

papers, and meta-analyses published between January 2011 and August 2024, using key terms such as dry eye syndrome, ocular surface disease, meibomian gland dysfunction, aqueous tear-deficient dry eye, and evaporative dry eye.

3. RESULT AND DISCUSSION

Current treatment methods for DES

Dry eye syndrome can significantly impact a patient's quality of visual life. Guidelines for treating dry eye recommend a comprehensive, multi-step approach, as illustrated in table 1 and elaborated upon in the subsequent sections of this article. Given the importance of lifestyle factors in the development and progression of the condition, it is imperative for practitioners to educate the patients on the condition, available treatment options, and possible outcomes. It is essential that lifestyle modifications, including diet adjustment, harmful environmental factors elimination, and discontinuation of medications that exacerbate DES, along with proper eye care instructions, form the foundation of successful treatment. Nutritional strategies that have shown beneficial effects on DES include omega-3 fatty acid and vitamin A supplementation.

Environmental strategies to manage dry eye syndrome include using portable humidifiers, avoiding exposure to cigarette smoke, limiting prolonged activities like television viewing or reading, taking regular breaks to rest the eyes, ensuring adequate sleep and hydration, reducing screen time on computers or other digital devices (Rouen and White, 2018). Individuals who frequently use computer stations should make ergonomic adjustments, such as lowering the screen to encourage a downward gaze. Such a position minimizes exposure of the ocular surface to air, which in turn minimizes tear film evaporation. For proper eye care, daily eyelid hygiene is recommended, which includes the application of warm compresses, the use of hypoallergenic cleansing agents, and gentle massage to facilitate the expression of meibomian gland secretions, thereby improving lipid layer stability and reducing tear film evaporation (Sheppard et al., 2023).

Table 1 Key Treatment Approaches for Dry Eye Management

Treatment Stage	Key Interventions and Considerations
Initial approach	Comprehensive, Multi-Step Treatment: - Educate patients about their condition. - Address contributing factors (systemic diseases, medications, poor nutrition, environmental factors). - Identify dry eye type: aqueous-deficient, evaporative, or mixed.
	Symptom Management: - Use artificial tears (drops/gels), enhanced with hyaluronic acid, dexpanthenol, or vitamin A. - Maintain eyelid hygiene with hypoallergenic products, warm compresses, and gentle massage. - Focus on meibomian gland dysfunction for evaporative dry eye.
Targeted Therapies	Advanced Interventions: - Tear Duct Plugs: Insert punctal plugs to retain moisture by blocking tear drainage. - Anti-Inflammatory Medications: Corticosteroids, cyclosporine A, lifitegrast to reduce inflammation and improve quality of life.
	Medical Procedures for Meibomian Glands: - Intense Pulsed Light (IPL): Reduces inflammation and improves meibum flow. - Thermal Pulsation Therapy: Devices like TearCare, Vectored Thermal Pulsation, and MiBo Thermoflo improve glandular secretions. - Meibomian Gland Probing: Mechanically unblocks glands with a stainless steel probe.
	Specialized Treatments: - Serum Drops: Derived from blood, rich in adhesion molecules, fibronectin, and

	vitamin A, used for corneal defects and disorders. - Contact Lenses: Soft and rigid lenses protect the ocular surface and shield it from dryness. - Amniotic Membrane Transplants: Promote tissue regeneration, reduce inflammation, and prevent corneal scarring.
Emerging Treatments	Off-Label and Experimental Therapies: - Amniotic membrane extract eye drops. - Stem cell therapy. - Mucin-like glycoproteins (lubricin, lacricin). - Thymosin beta 4. - Honey-based therapies (Royal Jelly, Manuka honey).

The treatment selection is based on the severity of the patient's symptoms and the extent of lesions observed on the ocular surface. As a first-line treatment for the symptoms of dry eye syndrome, preservative-free artificial tear preparations, topical or general cyclosporine are used, or tear point plugs are inserted. Artificial tears are lubricating eye drops or solutions designed to mimic the natural tear film to relieve dryness and eye irritation. They assist in hydrating the ocular surface, restoring the integrity of the tear film, and alleviating symptoms such as dryness, burning, or pruritus. Most artificial tear products are aqueous-based and contain viscosity-enhancing agents that improve lubrication and prolong the retention time on the ocular surface.

Additional ingredients may include osmotic agents, osmoprotectants, antioxidants, preservatives, and excipients like pH buffers and electrolytes. Aqueous-based artificial tears primarily address the muco-aqueous phase of the tear film but have been shown to alleviate symptoms of dry eye disease across all subtypes. Lipid-based formulations, which target the superficial tear lipid layer, are increasingly used to manage evaporative dry eye, particularly in cases related to meibomian gland dysfunction. These products may include nano-emulsion drops or liposomal sprays, which can be applied to closed eyelids and are often more convenient for patients with difficulty instilling traditional eye drops (Semp et al., 2023).

Anti-inflammatory agents: corticosteroids, cyclosporin, lifitegrast

Corticosteroids in unpreserved eye drops have been shown to reduce ocular irritation symptoms, decrease corneal fluorescein staining, and improve filamentary keratitis when instilled over 2 to 4 weeks (Mohamed et al., 2022). Low-dose topical corticosteroid therapy can be applied intermittently for short durations to help suppress ocular surface inflammation. Prolonged use of steroids can lead to adverse effects, including cataract formation and elevated intraocular pressure. In systemic inflammatory diseases or autoimmune disorders, such as Sjögren's syndrome, short-term systemic corticosteroid therapy (e.g., 40 mg on alternate days) may be indicated to manage inflammation, provided it is administered under careful medical supervision.

Topical and systemic corticosteroids effectively relieve both the subjective symptoms and clinical signs of the disease; however, their administration requires careful monitoring and oversight by specialists to maintain safety and effectiveness (Akpek et al., 2019). Cyclosporine A (CsA) is a peptide derived from fungi, used primarily as an immunosuppressant that inhibits T-cell activation, reduces inflammatory cytokine production, and prevents apoptosis. When applied topically, cyclosporine A has been shown to enhance tear production, likely by promoting the local release of parasympathetic neurotransmitters. The FDA has approved 0.05% cyclosporine A eye drops for twice-daily use to treat ocular surface inflammation in dry eye syndrome (Mohamed et al., 2022). This treatment has improved Schirmer test scores, reduced corneal fluorescein staining, increased goblet cell density, and alleviated symptoms such as blurry vision and ocular dryness.

Treatment with topical CsA may induce patient long-term, treatment-free remission of symptoms and signs, implying a role of topical CsA as a disease-modifying agent in dry eye disease. However, this treatment has its drawbacks. The most common side effects are eye irritation and burning, which is often the primary reason patients discontinue use. Other potential side effects include conjunctival hyperemia, ocular discharge, epiphora, eye pain, foreign body sensation, pruritus, and visual disturbances such as blurred vision. The concurrent use of steroid eye drops may help mitigate some side effects of cyclosporine A (O'Neil et al., 2019). Lifitegrast is a lymphocyte function-associated antigen-1 (LFA-1) antagonist that works by blocking the interaction between LFA-1 (found on immune cells like T and B lymphocytes) and its ligand, ICAM-1, which is often overexpressed in dry eye disease.

By binding to LFA-1, lifitegrast reduces the release of inflammatory cytokines that contribute to the inflammatory cycle and worsen DED symptoms. Lifitegrast's high solubility in phosphate-buffered saline enables a 10% solution with osmolality near human tears (~300 mOsm/L), reducing the risk of local irritation (Haber et al., 2019). Based on the SONATA (Safety Of a 5.0% coNcentrATion of lifitegrAst ophthalmic solution) trials, which were the first research to examine the long-term safety of lifitegrast for treating DED, the investigators found that a 5% concentration of lifitegrast ophthalmic solution was safe and well tolerated for up to one year, with a safety profile like that observed in the 12-week trials.

This discovery was confirmed by a 2018 analysis of five clinical trials involving 2464 patients, which found that lifitegrast 5% (twice daily) was generally safe and well-tolerated for treating dry eye disease. Common side effects included instillation site irritation, pain, and dysgeusia, which were mainly mild to moderate. Discontinuation due to side effects occurred in 7.0% of lifitegrast patients compared to 2.6% in the placebo group. There were no serious ocular side effects, and nonocular serious events were rare and unrelated to the drug. Despite initial discomfort with the drops, patient comfort improved over time. Less common side effects of lifitegrast include blurred vision, conjunctival redness, eye irritation, headaches, increased tear production, eye discharge, discomfort, itching, and sinusitis.

Rare severe reactions reported during postmarketing surveillance include anaphylaxis, bronchospasm, respiratory distress, swelling of the pharynx or tongue, urticaria, eye swelling, and skin rash. While lifitegrast may have some effect on lymphocytes, studies found only minor changes in serum lymphocyte levels, and no cases of opportunistic infections were reported in clinical trials. Additionally, due to its low systemic absorption, no drug interactions have been identified or are expected (Donnenfeld et al., 2016).

Blood-derived products

Serum, a liquid blood component, closely resembles human tears in pH and osmolality and contains similar or higher levels of key growth factors, including epidermal growth factor (EGF), transforming growth factor b (TGF b), vitamin A, lysozyme, and fibronectin. Due to the rich content of epitheliotropic factors responsible for their therapeutic effects, autologous serum eye drops have demonstrated clinical efficacy not only in the management of dry eye disease but also in other ocular surface disorders, including neurotrophic keratopathy and persistent corneal epithelial defects. No universal guidelines have been established to prepare autologous serum eye drops, so research on these products may include formulations with serum concentrations ranging from 20% to 100%.

However, the challenges in producing autologous serum eye drops are consistent across different methods and include the need to collect material directly from the patient, the restrictive storage and transport requirements, and the high associated costs. Autologous serum eye drops (ASED) have shown benefits in treating DED and other ocular conditions, with several studies indicating improvements in symptoms and clinical measures. A Cochrane review found limited short-term benefits over artificial tears. In contrast, a systematic review and meta-analysis demonstrated better outcomes with ASED for subjective symptoms and objective tests like tear film breakup time. An American Academy of Ophthalmology report also highlighted significant improvements in severe DED and persistent corneal epithelial defects, though proper handling is crucial to avoid microbial contamination.

A 2022 randomized trial in Thailand confirmed the stability of key growth factors in ASED during storage and showed significant improvements in patients with severe DED. These drops are not considered first-line treatment and are typically used for patients with advanced and severe dry eye disease who have already exhausted other therapeutic options, such as artificial tears or various anti-inflammatory medications. They have proven more effective in cases of aqueous tear-deficient dry eye. However, their use is generally short-term because they are highly unstable due to the absence of preservatives, which creates a favorable environment for bacterial growth, making strict hygiene practices essential (Vazirani et al., 2023).

In addition to ASED, blood-derived products include eye-platelet-rich plasma (E-PRP) and plasma rich in growth factors (PRGF), which enhance the concentration of growth factors, cytokines, and cell adhesion molecules for therapeutic effects on the ocular surface. The growth factors in these products help stimulate the formation of new blood vessels, support cell repair, and activate immune cells (macrophages). These effects lead to improved visual acuity, increased tear production, and enhanced ocular surface health. E-PRP and PGRF are also devoid of leukocytes, typically found in serum-based preparations, and may contribute to elevated levels of pro-inflammatory cytokines, potentially exacerbating damage to the ocular surface (O'Neil et al., 2019).

Non-pharmacological therapeutic approaches

The next step in treating dry eye syndrome involves medical procedures and minor interventions, which are used alongside or following topical treatments to alleviate symptoms further and address changes to the ocular surface. These techniques utilize light, heat, or mechanical energy to enhance the function of dysfunctional meibomian glands.

Intense Pulsed Light

Intense Pulsed Light (IPL) systems are powerful light sources that emit a broad spectrum of non-coherent, polychromatic light, offering greater flexibility than laser systems, which use coherent light. This broad spectrum allows IPL devices to be adjusted for different skin types and therapeutic needs. Initially FDA-approved for treating telangiectasias, IPL was used off-label for managing evaporative dry eye disease (DED) due to meibomian gland dysfunction (MGD), particularly in patients with rosacea. In 2021, Lumenis received FDA approval for its IPL device, OptiLight™, making it the first FDA-approved IPL to treat dry eye disease. IPL targets capillaries to reduce inflammation, suppressing inflammatory mediators contributing to dry eye symptoms.

When combined with thermal pulsation therapy, IPL helps liquefy thickened meibum and address meibomian gland blockages, offering a gentler, more effective alternative to manual gland expression. IPL energy, absorbed by hemoglobin in abnormal blood vessels, heats and destroys these vessels, further reducing inflammation in the eyelids and meibomian glands. This combination therapy has improved clinical outcomes such as tear film breakup time (TBUT), ocular surface staining, and the Ocular Surface Disease Index (OSDI). Additionally, IPL helps eliminate Demodex mites in the meibomian and sebaceous glands, reducing bacterial load and inflammation and further alleviating MGD and DED symptoms (Suwal et al., 2020). IPL also stimulates a photochemical reaction that boosts ATP production, promoting fibroblast activity, collagen synthesis, and improved blood flow.

These effects contribute to IPL's success in both skin rejuvenation and treating MGD in dry eye patients. By improving eyelid skin elasticity, IPL helps prevent lid margin issues and incomplete blinks, which can reduce meibum secretion and tear evaporation, further breaking the inflammatory cycle in the dry eye. Combined with meibomian gland expression (MGX), IPL has proven to be an effective treatment for both MGD and DED. It stabilizes the tear film, reduces inflammation, and enhances meibum quality, leading to long-term symptom relief. Studies show IPL's effectiveness even in severe cases of MGD, as well as in patients with darker skin types, with minimal adverse effects. It has also been shown to provide rapid symptom relief in patients with Sjögren's disease. While IPL is generally safe, potential risks, such as burns or changes in skin pigmentation, should be discussed with patients before treatment.

Vectored Thermal Pulsation

The LipiFlow Thermal Pulsation System, cleared for use in 2011, treats meibomian gland dysfunction (MGD) by applying controlled heat and pressure to the eyelids. It includes a reusable console, cable, and a single-use device called the Activator, which features an eyelid warmer and an inflatable air bladder. Over 12 minutes, the device warms the meibomian glands (MGs) and uses intermittent pressure to massage and express the liquefied gland contents. The Activator's design was updated in 2021 with translucent bladders for better positioning without changing the heat or pressure mechanisms. Studies show that a single treatment significantly improves MG function and symptoms. The LipiFlow has proven safe and effective. A single 12-minute treatment improves MGD symptoms and signs, with benefits lasting up to 3 years.

While alternatives like warm compresses and eyelid hygiene offer similar results, they are less convenient and often lead to non-compliance. LipiFlow has been shown to be more effective than at-home treatments and comparable to other therapies, including thermal pulsation and pharmaceutical options. It is well-tolerated with minimal, transient side effects and no significant intraocular pressure or visual acuity concerns. LipiFlow is effective for preoperative MGD management in cataract and refractive surgery patients, improving tear film stability and preventing postoperative dry eye. It has also been used safely in glaucoma patients. However, further research is needed to explore combination therapies and confirm treatment duration with a randomized, placebo-controlled trial. Despite some limitations, LipiFlow remains a highly effective, low-risk option for MGD with long-lasting results (Blackie et al., 2024).

Meibomian Gland Probing

Meibomian Gland Probing (MGP), introduced in 2010, targets obstructed meibomian glands, often caused by periductal fibrosis in meibomian gland dysfunction. The procedure involves anesthetizing the nerves around the eye and applying lidocaine ointment and tetracaine. A 1-mm stainless steel probe is inserted into each gland's orifice, and resistance during probing indicates fibrosis. Audible

"firm pops" suggest a single obstruction, while "gritty" sounds indicate multiple blockages. Infrared meibography may be used for real-time visualization. A 2021 review of studies highlights Meibomian Gland Probing as a safe and effective treatment for obstructive MGD, particularly in patients resistant to standard therapies. Significant improvements were observed in subjective symptoms (e.g., SANDE, OSDI, SPEED scores) and objective signs (e.g., lid tenderness, tear breakup time, meibum quality, Schirmer test).

MGP has proven effective in conditions like ocular rosacea and blepharitis, offering rapid symptom relief and improved tear film stability without significant adverse events. It is suitable as a first-line treatment or for refractory cases and may provide enhanced outcomes when combined with therapies like IPL or corticosteroids (Warren and Maskin, 2023). With sustained benefits and minimal complications, MGP is a promising option for managing meibomian gland dysfunction. However, patients may need retreatment after MGP due to advanced or recurrent MGD, harsh environments, or incomplete treatment. While symptoms like burning and stinging improve within 2–3 months, 25.9% of patients require reprobing.

MGP typically offers better long-term results than IPL, which has a higher retreatment rate and can provide significant symptom relief, even in complex cases. MGP targets the gland's natural orifice without damaging surrounding tissue and has no contraindications except for active infection. MGP is generally safe in the short term, with the most common complication being self-limited intraoperative bleeding. Some studies report no complications, and recent research confirms that the probes safely follow the glandular lumen (Magno et al., 2021). Overall, MGP has no significant postoperative complications. More research is needed to assess the efficacy of MGP thoroughly compared to other treatments for MGD, as current studies show mixed results and variability in outcomes.

The MiBo Thermoflo

The MiBo Thermoflo (MiBo Medical Group) is a device designed to treat dry eye disease caused by meibomian gland dysfunction by enhancing the liquefaction and secretion of meibum, thereby improving the tear film. The treatment involves applying ultrasound gel to a heated handheld probe, which is then gently massaged over the eyelids for 8-12 minutes, maintaining a constant temperature of 42°C. The manufacturer recommends three sessions, two weeks apart, with follow-up assessments to determine if additional treatments are necessary (O'Neil et al., 2019).

Preliminary data from a manufacturer-sponsored trial showed significant improvements in TBUT, osmolarity, SPEED, and OSDI scores four months after MiBoFlo treatment in 51 patients. However, a case study by found that the treatment did not raise the palpebral conjunctiva temperature above 40°C, which is necessary for effective meibum liquefaction. A 2021 study by Li Ang compared MiBoFlo and LipiFlow treatments for meibomian gland dysfunction in 54 Chinese patients. Both treatments significantly improved dry eye symptoms and meibomian gland function after 2 months, with no significant differences between the groups.

MiBoFlo showed more corneal staining (CFS) improvement, but there were no significant changes in tear film or meibomian gland loss. Both treatments were safe, though one LipiFlow patient had difficulty with the eye cup. Overall, both devices offer effective, non-invasive alternatives to pharmacological treatments for symptom relief, with MiBoFlo providing at least 2 months of sustained improvement in MGD symptoms (Li et al., 2022). There are limited reports on MiBoFlo's effectiveness, so a randomized, placebo-controlled trial is needed to further assess the device's efficacy and safety.

BlephEx

BlephEx® (Blephex LLC, USA) is an in-office, FDA-approved procedure that cleans and exfoliates the eyelid margins, targeting bacterial biofilm, excess bacteria, and toxins that cause symptoms like itching, redness, irritation, and dryness. Using a handheld medical-grade device, an eye care specialist gently exfoliates the base of the eyelashes, removing debris and bacterial buildup. This helps relieve blepharitis and dry eye syndrome symptoms and promotes healthier eyelids. A 2015 study by Connor et al. involving 20 patients showed positive effects of BlephEx™ on dry eye symptoms. Four weeks after treatment, significant improvements were seen in meibomian gland dysfunction, blepharitis grading (Efron Scale), TBUT, and OSDI scores. Additionally, in a subgroup of ten patients with positive MMP-9, all tested negative for MMP-9 after treatment.

However, the double-masked, randomized controlled trial by Siegel et al., (2024) assessed the effectiveness of the BlephEx™ device for treating blepharitis and found no significant benefit of the BlephEx™ device over a sham treatment. Both groups showed similar improvements in key outcomes, with the sham group even showing a greater reduction in OSDI scores, suggesting a placebo effect. While BlephEx™ reduced bacterial load, it did not significantly improve meibomian gland function or symptoms of chronic blepharitis.

The study concluded that simpler, cost-effective eyelid hygiene methods may be as effective as BlephEx™ (Siegel et al., 2024). Studies on BlephEx treatment, particularly regarding its effectiveness in eliminating Demodex mites as a contributing factor to dry eye disease, have yielded mixed results.

Found that a single BlephEx treatment followed by nightly OcuSoft Lid Scrub Plus reduced Demodex and symptoms after 2 to 4 weeks. Found that while terpinen-4-ol and sham scrubs reduced Demodex levels over 2 months, there were no significant changes in ocular symptoms. The sham group showed improved blepharitis signs and meibomian gland expression but worsened tear production (Valencia-Nieto et al., 2020). The limited number of studies on BlephEx™ for dry eye syndrome prevents conclusive evidence of its efficacy. While some studies suggest benefits like reduced bacterial load and improved meibomian gland function, more extensive trials are needed to confirm its effectiveness.

TearCare System

The TearCare® System (Sight Sciences, Menlo Park, CA) provides localized heat therapy for adult patients with evaporative dry eye disease caused by meibomian gland dysfunction and is used alongside manual expression of the glands. It uses a single-use kit with four electrothermal iLid™ devices that attach to the eyelids, allowing patients to blink during the treatment to help express meibum naturally. The iLid devices are connected to the TearCare controller, delivering regulated thermal energy (41°C–45°C) to melt meibum. After the thermal cycle, manual meibomian gland expression is performed to clear any remaining blockages. This combined approach targets meibomian gland dysfunction effectively (Badawi, 2018).

In a manufacturer-sponsored trial with 24 patients, TearCare® treatment followed by meibomian gland expression significantly improved tear breakup time by 11.7 seconds compared to a 0.3-second decrease in the warm compress group ($p<0.001$), with benefits sustained for six months. Significant improvements were also observed in corneal and conjunctival staining and subjective symptoms (SPEED, OSDI, SANDE scores). The treatment was well tolerated, with no reported adverse events (O'Neil et al., 2019). In a randomized trial comparing TearCare® (TC) to cyclosporine A (CsA) for treating dry eye disease, TC showed superior improvement in tear breakup time and meibomian gland function. TC also demonstrated comparable benefits in other measures, such as OSDI and conjunctival staining, with better tolerance than CsA.

After repeat TC treatment at month 7, TBUT improvement was sustained through month 13. TC's advantage is its non-reliance on patient adherence, providing durable results, making it an effective treatment for DED associated with meibomian gland dysfunction (Ayres et al., 2023). A 2022 randomized controlled trial by Gupta et al., (2022) found that the TearCare® System demonstrated comparable efficacy and safety to the LipiFlow Thermal Pulsation system for managing meibomian gland dysfunction associated with dry eye disease. Both treatments significantly improved tear breakup time and meibomian gland function, with sustained benefits for up to one month. TearCare provided superior symptomatic relief, with more patients reporting improved OSDI scores and reduced use of lubricating drops, though statistical superiority was not established.

Both treatments were well tolerated, with no serious adverse events. While TearCare showed promise in clearing gland obstructions and enhancing tear film stability, the study's limitations included subjective outcomes and a lack of long-term follow-up (Gupta et al., 2022). TearCare® effectively treats dry eye disease associated with meibomian gland dysfunction, improving tear breakup time, gland function, and symptoms with lasting benefits. It compares favorably to other treatments, especially in severe cases, with minimal side effects and no need for patient adherence. Long-term research is needed to confirm its full efficacy.

Intranasal tear neurostimulation (TrueTear®)

Intranasal tear neurostimulation (ITN, TrueTear®, Allergan, plc) is a novel dry eye disease treatment involving small electrical currents to the anterior ethmoidal nerve. This nerve acts as an alternative afferent pathway to the corneal sensory nerves. By stimulating this pathway, ITN activates the nasolacrimal reflex, enhancing the body's natural tear production system and relieving individuals with DED (Li et al., 2023). A meta-analysis of 15 clinical trials showed that ITN improves Schirmer II test results and meibomian gland structures in DED patients, with a proven safety profile. The TrueTear device, approved by the FDA in 2017, demonstrated significant improvements in various DED outcomes, although its high cost limits its accessibility.

Despite some variation in effectiveness measures, such as OSDI and Schirmer test scores, ITN resulted in notable short-term improvements in tear production. Long-term use showed sustained benefits, although the effects decreased after the initial increase. Most adverse events were mild, including nasal discomfort, burning, pain, nosebleeds, electrical discomfort, nasal congestion, facial

pain, and headaches. It is contraindicated in patients with cardiac pacemakers, implanted defibrillators, or other metallic/electronic implants in the head or neck, as well as those with hypersensitivity to the device's hydrogel coating or chronic nosebleeds (O'Neil et al., 2019). The results suggest that ITN is an effective and safe treatment for DED, although additional research is needed to overcome the current limitations.

Scleral lenses

Scleral lenses (SLs), traditionally used for corneal irregularities, are increasingly being considered for managing dry eye disease, as many patients report symptom relief. While their use is well-supported in cases with corneal irregularities, practitioners are now exploring SLs for DED even without such conditions (Chaudhary et al., 2023). Scleral contact lenses (ScCLs) are specialized lenses that sit on the sclera, creating a fluid-filled space over the cornea, which serves as a protective shield against dryness and injury. These lenses come in mini-scleral and large scleral varieties. They are used for correcting refractive errors, safeguarding the ocular surface, aiding in healing epithelial defects, and administering medications to the eye (Qiu et al., 2024).

Scleral contact lenses effectively treat DED, persistent epithelial defects (PEDs), exposure keratopathy, and neuropathic pain. They help alleviate symptoms by protecting the ocular surface, enhancing healing, and improving visual acuity and quality of life. ScCLs are especially useful in conditions like Sjögren's syndrome, Stevens-Johnson syndrome, and graft-versus-host disease. However, they do not stabilize the tear film or improve meibomian gland function, and prolonged use may lead to inflammation. Regular monitoring is essential, particularly for PED patients. Despite these drawbacks, ScCLs provide significant therapeutic benefits for severe ocular surface disorders, though additional research is needed to refine their use.

Scleral lenses offer significant advantages for managing dry eye syndrome, particularly for symptomatic soft contact lens users without corneal irregularities. These benefits include preventing tear film evaporation, avoiding lens dehydration, promoting corneal healing, and improving visual acuity and comfort by masking corneal irregularities. However, midday fogging, affecting 75% of SL wearers with dry eye disease, can cause vision issues due to debris buildup beneath the lens. Inadequate lens surface wettability may also lead to blurry vision, discomfort, and dryness, especially in patients with meibomian gland dysfunction. While SLs are increasingly used for DED patients without corneal irregularities, further research is needed to evaluate their effectiveness in early-to-moderate DED and establish their role in treatment protocols.

Amniotic membrane

The amniotic membrane (AM) is a thin, avascular tissue supporting the ocular surface. It contains growth factors that aid healing, reduce inflammation, and prevent scarring. Amniotic membrane transplantation (AMT) has been used to treat various ocular conditions, including chemical burns, corneal ulcers, and immune-mediated diseases like Stevens-Johnson Syndrome. AMT can be performed using different techniques, such as inlay, onlay, or combinatorial methods, with both sutured and sutureless options. Cryopreserved amniotic membrane has enhanced the preservation of growth factors and extracellular matrices, making it more effective for long-term use (Chen et al., 2021).

There are currently two commercially available forms of AM: Cryopreserved at −80°C, such as PROKERA™ (Bio-Tissue, Inc., Miami, FL), and sterilized dehydrated AM stored at room temperature, like AmbioDisk™ (Katena Products, Inc., Denville, NJ) (O'Neil et al., 2019). The PROKERA device, a self-retained cryopreserved AM, has been particularly effective in managing moderate-to-severe dry eye disease. Studies have shown significant improvements in symptoms like tear film breakup time, corneal staining, corneal nerve density, enhanced visual acuity, and reduced discomfort. Additionally, PROKERA has provided temporary relief for autoimmune-related DED and neuropathic corneal pain, showing effectiveness in cases of DED resistant to standard treatments. However, some patients have experienced mild discomfort, resulting in early removal in some instances (Mead et al., 2020).

The future of dry eye syndrome treatment

The future of dry eye syndrome treatment is focused on advanced, personalized approaches, including regenerative therapies like stem cells and amniotic membrane-derived products, targeted biologics, and anti-inflammatory drugs. Improved diagnostic tools will enable more precise treatments, while combination therapies and better drug delivery systems are expected to enhance effectiveness and patient outcomes. These innovations should provide longer-lasting relief and more individualized care for patients suffering from dry eye syndrome.

Amniotic membrane extract eye drops

Amniotic membrane extract (AME) and its ophthalmic derivative AMEED can potentially treat various eye conditions, including corneal injuries, chemical burns, and limbal stem cell deficiency (LSCD). When combined with umbilical cord blood, AMEED can enhance its anti-inflammatory effects, promoting healing by reducing inflammation and encouraging cell growth. The preparation methods for AME vary, influencing the concentration of key bioactive components like HGF. AMEED has been shown to speed up corneal healing and alleviate inflammation in conditions such as persistent epithelial defects and corneal abrasions.

It is also effective when used alongside amniotic membrane transplantation, extending the benefits of treatment (Murri et al., 2018). Though several companies produce AME products, they are not FDA-regulated, and their manufacturing processes differ, raising concerns about preservation and consistency. More research, including clinical trials, is needed to confirm AMEED's effectiveness, compare it with other treatments, and standardize production methods. Despite these issues, AMEED provides a non-invasive alternative to surgery and could significantly improve healing in ocular surface diseases.

Stem cell

Due to their regenerative properties, stem cells are being explored as a potential treatment for dry eye disease, particularly in cases of lacrimal gland hyposecretion caused by autoimmune disorders like Sjögren's syndrome (SS). Animal studies have shown promising outcomes, such as increased tear production, reduced inflammation, and the restoration of lacrimal gland structure. Preliminary human trials, including the AMASS study, have reported improvements in clinical outcomes, including reductions in OSDI scores, better tear film stability, increased tear production (Schirmer test), and improved staining scores.

These improvements were most notable around four weeks after treatment and continued for up to a year (Mittal et al., 2021). Minor side effects, such as pain and discomfort, were noted, but no serious adverse events occurred, indicating that the treatment was safe and practical. However, the observation of similar benefits with vehicle solutions containing anti-inflammatory agents indicates the results may have been influenced by placebo effects or other unconnected factors. Despite these encouraging findings, further large-scale studies are needed to refine treatment protocols, confirm long-term effectiveness, and deepen our understanding of the mechanisms behind stem cell therapy for DED (Møller-Hansen, 2023).

A mucin-like glycoprotein group

Lacritin, a lacrimal and ocular surface cell glycoprotein, boosts tear production and epithelial growth. It enhances MUC16 production, basal tear secretion, and corneal repair. Animal studies show sustained tear production increases after topical application, lasting up to a week post- treatment (Samudre et al., 2011). In dry eye disease, tears contain various forms of lacritin, including C-terminal fragments, monomers, and larger inactive multimers formed through tissue transglutaminase cross-linking, which impairs their ability to bind syndecan-1. Elevated tissue transglutaminase activity in dry eye conditions likely contributes to a reduction in the active lacritin monomer. Proteomic analyses reveal a significant lacritin deficiency in different types of dry eye, with a significantly pronounced absence in Sjögren's syndrome (Dias-Teixeira et al., 2020).

A clinical trial (NCT03226444) evaluated the safety and efficacy of Lacripep™, a synthetic peptide designed to mimic lacritin's active helix, for treating dry eye in patients with primary Sjögren's syndrome. The treatment was well-tolerated, with mild irritation reported in less than 3% of participants and no serious side effects. Although primary outcomes, such as corneal fluorescein staining (CFS) and Eye Dryness Scores, showed no significant changes overall, a post hoc analysis found notable improvements in severe DES cases. Benefits included reduced inferior CFS, decreased burning and stinging, and enhanced conjunctival staining at certain time points. The trial also highlighted a bell-shaped dose response, with lower doses perhaps being more effective, reinforcing the need to further optimize both dosing and timing (Tauber et al., 2023). Lubricin (PRG4) is a mucin-like glycoprotein produced by the healthy ocular surface, but its expression is reduced by inflammatory cytokines, such as those involved in dry eye disease.

Its primary function is to reduce friction between the cornea, conjunctiva, and eyelid, and it is thought to be a key component of the ocular surface glycocalyx, helping to prevent epithelial dysfunction and damage (O'Neil et al., 2019). Lubricin degradation by inflammatory cytokines exacerbates inflammation and mechanical stress in dry eye disease. Exogenous lubricin shows therapeutic promise by alleviating friction and inflammation (Schmidt et al., 2013). Recombinant human PRG4 (rhPRG4) can regulate inflammatory pathways, such as NF-κB, and reduce MMP-9 activity as central to its therapeutic effects. Beyond DED, rhPRG4 may have broader

applications in managing other inflammatory conditions, including those affecting joints and cartilage. Additional research is necessary to explore its therapeutic capabilities fully (Menon et al., 2021).

Thymosin beta 4

Thymosin beta 4 (Tβ4) is a key tissue repair and regeneration protein. It enhances cell migration, stem cell recruitment, protease activity, and regulatory gene expression while reducing inflammation, microbial growth, scar formation, and apoptosis. Tβ4 supports dermal repair, regulates actin polymerization for cell movement, and stabilizes epithelial sheets. Tβ4 also helps reduce oxidative damage and supports the healing of the cornea by promoting epithelial cell movement, partly through factors like laminin-332. While it's been widely studied in other body parts, its specific role in eye repair and corneal healing is still not completely understood. Tβ4 helps the body respond to trauma by reducing inflammation, such as by lowering the activity of inflammatory pathways like NF-κB (Sosne and Kleinman, 2015).

Because Tβ4 has such wide-ranging effects, it shows great potential as a treatment for various inflammatory and traumatic conditions, not just in the skin but also in the eyes, heart, and nervous system. A 2015 study showed no significant differences between the 0.1% Tβ4 ophthalmic solution and the placebo regarding the primary outcomes, such as inferior corneal staining and ocular discomfort. However, further analysis showed that the Tβ4 group had notable superior and central corneal staining improvements. Both groups experienced more ocular discomfort after environmental exposure, but the increase was less noticeable in the Tβ4 group. Overall, the treatment was well-tolerated, with mild side effects occurring more often in the placebo group than in the Tβ4 group, and no serious safety concerns were reported (Sosne and Ousler, 2015).

Natural compounds

Royal jelly (RJ) is a highly nutritious substance produced by worker honeybees and is known for its health benefits, often referred to as a "superfood". It is secreted by the hypopharyngeal and mandibular glands of bees. RJ contains royalactin, a vital component that enables a larva to develop into a queen bee, playing a role in the queen's extended life expectancy. Beyond its importance in beekeeping, royal jelly is also used in human health for its numerous potential benefits, such as antibacterial, antitumor, anti-inflammatory, and immune-enhancing effects. It is highly regarded in traditional and contemporary medicine for its ability to manage various chronic health issues (Pasupuleti et al., 2017). Royal jelly is considered the most effective bee product for improving tear secretion and supporting mitochondrial health in these glands.

Researchers found that three specific fatty acids in royal jelly—10HDAA, 8HOA, and 3,10DDA—when combined with acetylcholine (ACh), may help in the treatment of dry eye. RJ seems to enhance the effects of Ach, an important neurotransmitter involved in stimulating tear production in the lacrimal glands, by protecting it from being broken down and helping it reach its target sites more effectively (Yamaga et al., 2021). Clinical trials and reviews confirm RJ's beneficial effects on DED symptoms with minimal side effects. However, RJ may cause allergic reactions in sensitive individuals and is not advised for children under ten or pregnant women due to its estrogen-like properties.

Manuka honey, derived from the nectar of the Manuka bush found in New Zealand and southeast Australia, contains methylglyoxal as its key active ingredient and is rich in carbohydrates like maltose, glucose, and fructose. Renowned for its exceptional antioxidant and anti-inflammatory properties, it surpasses other honeys in promoting heart health, aiding digestion, detoxifying the body, healing wounds, supporting respiratory health, and enhancing metabolism. These unique benefits also make it valuable for sports nutrition, athlete recovery, and potentially dry eye treatment (Grzebisz and Grzebisz, 2016). Recent discoveries showed that honey-based treatments, such as Manuka honey and Royal Jelly, effectively improved symptoms of dry eye disease.

Patients who used these treatments had better tear production, with noticeable improvements in tear breakup time and lower Ocular Surface Disease Index scores. However, there were no significant differences between honey treatments and the control group in some measures, like corneal staining. The positive effects are probably attributed to honey's antioxidant and anti-inflammatory properties, as well as Royal Jelly's ability to promote tear production. While minor side effects, like temporary discomfort, were observed, no serious adverse effects were observed (Prinz et al., 2023). Additional research will be required to determine which type of honey treatment is most appropriate for DED.

4. CONCLUSIONS

The proposed treatment plan serves as a framework for addressing dry eye but allows for flexibility and overlap among various methods. Treatment should be tailored to each patient, considering the severity of their condition based on symptoms and clinical observations. In conclusion, with knowledge about the causes of dry eye syndrome expanding, the management will be directed to address the underlying causes of dry eye disease rather than just temporarily alleviating symptoms. However, advances in technology and ongoing clinical studies have made greater options available to patients. The objective progression of the disease and the subjective symptoms reported by the patient should be weighed when choosing a treatment approach. The severity of dry eye syndrome determines the strategic choice of treatment methods, ranging from mild interventions to more advanced therapies.

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Author's Contributions

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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