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TFOS DEWS III Management and Therapy Report

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Title: **TFOS DEWS III Management and Therapy Report**

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1 Keywords

Artificial tears; dry eye disease; lifestyle advice; management; therapy; treatment; medication; pharmacological

2 Abbreviations

CMC	Carboxymethylcellulose
CsA	Cyclosporine
DED	Dry eye disease
DEWS	Dry eye workshops
FDA	Food and Drug Administration
HP-guar	Hydroxypropyl guar
HA	Hyaluronic acid
IL	Interleukin
IPL	Intense pulsed light
LASIK	Laser-assisted in situ keratomileusis
LLT	Lipid layer thickness
LLLT	Low-level light therapy
MGD	Meibomian gland dysfunction
MMP	Matrix metalloproteinase
NGF	Nerve growth factor
NIBUT	Non-invasive breakup time
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
OSDI	Ocular Surface Disease Index
PEG	Polyethylene glycol
PRGF	Plasma rich in growth factors
PRP	Platelet-rich plasma
PUFA	Polyunsaturated fatty acids
RCT	Randomized controlled trial
rhPRG4	Recombinant human proteoglycan 4
ROS	Reactive oxygen species
SANDE	Symptom Assessment iN Dry Eye (questionnaire)

SDP-4	Silk-derived protein
SPEED	Standard Patient Evaluation of Eye Dryness (questionnaire)
TBUT	Tear breakup time
TFOS	Tear Film & Ocular Surface Society
TMH	Tear meniscus height
TRPM8	Transient Receptor Potential cation channel subfamily M member 8
TTO	Tea tree oil
UCS	Umbilical cord serum

3 Abstract

This report provides an evidence-based review of current strategies to manage dry eye disease (DED). First-line management focuses on methods to replenish, conserve and stimulate the tear film, with an emphasis on ocular supplements, which remain the cornerstone of DED treatment. Meibomian gland dysfunction, a primary contributor to DED, is typically treated with warm compresses and a wide variety of in-office treatments, including device-driven technologies to warm the eyelids, intense pulsed light therapy, low-level light therapy and other new and emerging technologies. Lid hygiene treatments include lid wipes, anti-*Demodex* therapies, blepharoexfoliation and topical antibiotics.

DED caused by certain etiological drivers can benefit from anti-inflammatory therapies, including corticosteroids, T-cell immunomodulatory topical drugs and a wide variety of pharmacological agents, in addition to biologic tear substitutes such as autologous serum and platelet-rich plasma. Emerging therapies, such as neuromodulation via nasal neurostimulation and novel pharmacological treatments offer potential future options. Advanced options, including amniotic membrane grafts and complex surgical methods, provide options for severe or refractory cases. Lifestyle modifications, including optimized blinking, dietary supplementation and environmental adjustments, play a crucial role in long-term management. Patient education and adherence to treatment regimens remain essential for sustained symptom relief.

The TFOS DEWS III prescribing algorithm provides an evidence-based framework to offer guidance to clinicians in selecting relevant interventions based on disease etiology that aim to provide targeted management of the subtype of DED that an individual is experiencing.

Keywords: Artificial tears; dry eye disease; lifestyle advice; management; therapy; treatment; medication; pharmacological

4 Report aims

The aim of this report was to provide a contemporary overview of the available evidence on the management of patients with dry eye disease (DED). The subsequent aim was to provide an evidence-based algorithm to assist clinicians with when to use these therapies. The presenting signs and symptoms and diagnostic testing, informed by the Tear Film & Ocular Surface Society (TFOS) Dry Eye Workshop (DEWS) III subclassifications were considered in developing the algorithm [1]. The report was focused on evidence published since the previous TFOS DEWS II Management & Therapy Report [2].

A number of treatments listed overlap with other broad areas of management due to overlapping mechanisms of action (for example, some treatments may be anti-inflammatory or antimicrobial and also treat lid and lid abnormalities). The final aim was to outline whether there is evidence to support use of the listed management options to treat one or more of the updated subclassifications described in the TFOS DEWS III Diagnostic Methodology Report [1].

5 Lifestyle advice

Lifestyle factors play a critical role in both the development and management of DED, influencing not only ocular health but also overall happiness and quality of life [3,4]. Modern behaviors, including poor sleep [5-10], use of cosmetics [11], choice of elective ocular and peri-ocular procedures [12] and systemic medications [9,12] can exacerbate or create dry eye symptoms, leading to discomfort, visual disturbances, and reduced daily functioning.

Excessive digital device use is one of the most significant lifestyle contributors to DED [9,13,14]. Reduced blink rates and incomplete blinking while staring at screens can lead to tear film instability, increased evaporation, and ocular surface damage [14]. This chronic discomfort often leads to frustration, fatigue, and decreased productivity, negatively impacting mental well-being. Diet also plays a role in DED severity. Diets rich in omega-3 fatty acids, found in fish and

flaxseeds, can improve tear quality and reduce inflammation. Conversely, diets high in processed foods and low in essential nutrients can contribute to systemic inflammation, worsening ocular surface disease [9,15-18].

The cumulative burden of dry eye symptoms can extend beyond physical discomfort, affecting mood, social engagement, and overall quality of life [3,19]. Patients with chronic DED frequently report higher levels of anxiety and depression [20-24], likely due to persistent irritation and visual impairment interfering with daily activities [5,25].

Environmental conditions can affect the ocular surface and may lead to DED. These have been described comprehensively in the TFOS Lifestyle report on the topic [26], and include climate factors (sunlight, temperature, humidity, windspeed and vapors), pollutants and allergens. The conditions can affect the ocular surface directly, causing immediate sensation, or indirectly such as through ultraviolet radiation causing pterygia, the physical presence of which affects lid-globe congruity and leads to disruption of the tear film (see Section 11.1.4).

Specific lifestyle considerations to discuss include:

- Avoidance of factors that precipitate symptoms of DED: while this may not always be possible, it can be recommended for specific factors that are known to exacerbate DED, such as prolonged reading or avoidance of draughty environments [26].
- Control of the local environment: Humidifiers, including simple USB-driven desktop devices that enhance the humidity of the local air, improve tear-film stability and subjective comfort [27,28]. Humidifiers built into eyewear also have a similar effect [29].
- Physical protection: side panels offer protection of the eyes from windspeed and vapors, but this has only been investigated in conjunction with increasing humidity around the eyes [30]. Moisture retaining spectacles (see Section 6.2.2) protect the eye from evaporation [31] and pollutants, and

increase the humidity of the air adjacent to the face of the wearer, and are effective in improving the ocular surface [32] and tear film, and in reducing DED symptoms [33]. Ultraviolet light protection of the ocular surface in the form of soft contact lenses for a period of at least five years, did not visibly improve the ocular surface, although the tear film was not assessed [31].

By recognizing the profound connection between lifestyle, dry eye symptoms, and quality of life, clinicians can guide patients toward sustainable changes that foster long-term relief and improved happiness. A recent publication [34] demonstrated that laughter can have therapeutic effects on DED, with improvements in symptoms and signs outperforming those of topical 0.1% hyaluronic acid (HA). Addressing lifestyle factors through conscious modifications, such as screen breaks, improved nutrition, and sleep hygiene, can significantly alleviate symptoms, enhancing both ocular health and overall well-being. These lifestyle modifications should be considered for all subjects, regardless of the type of DED and the management options proposed to deal with their presenting signs and symptoms.

6 Tear insufficiency

6.1 Tear replenishment

6.1.1 Tear supplements and stabilisers

Tear supplements are agents that enhance and/or stabilise the tear film in cases of DED and remain a cornerstone of DED management for addressing tear insufficiency or dysfunction that can arise regardless of the underlying etiology [35].

While these products are available in some countries as non-prescription, „over-the-counter" drops, more recently, this group of supplements have been joined by agents that may only be available on prescription due to their regulatory approval. The goal of these therapies is to restore homeostasis of the tear film and ocular surface microenvironment, in many cases by stabilising the preocular tear film. This should minimize perpetuation of the cycle of tear film instability,

hyperosmolarity, inflammation and epithelial damage described as the „vicious circle of DED" [36-38].

These products have been designed to mimic the tear film components, but lack the biologically active components found in the natural tear film [39]. While it is possible to list the “active” ingredients that may be included in tear supplements and stabilisers, their efficacy may not be solely related to an individual ingredient, and what is considered “active” can be restricted by the regulatory body of a region. For example, in the US, non-prescription tear supplements must have only active ingredients from a short list in the Food and Drug Administration (FDA) monograph, despite possibly having important excipients. Some formulations, for example, may contain two active demulcents but also “inactive polymers”, all of which play distinct but important roles of lubrication, retention, and hydration. Thus, it is the overall formulation and composition and the way in which the components interact that impact their performance. Coupled with this is consideration of the presence or absence of preservatives and the delivery system.

As previously described [2,40-44], the composition of tear supplements is complex and may include:

- Viscosity-enhancing agents that can be aqueous-based formulations targeting aqueous deficient DED, such as carbomer 940, carboxymethylcellulose (CMC), dextran, hydroxypropyl guar (HP-guar), hydroxypropyl methylcellulose, polyvinyl alcohol, polyvinylpyrrolidone and polyethylene glycol (PEG).
- Lipomimetic formulations targeting evaporative DED, which reduce the surface tension of the tear film and permit a more even distribution of tears over the ocular surface [39]. Lipids incorporated (see Section 6.1.1.5) include phospholipids, triglycerides, saturated and unsaturated fatty acids, mineral oil, castor oil, coconut oil and lecithin [40-43,45,46]. Phospholipids can be neutral (zwitterionic), negatively (anionic) or positively (cationic) charged.

- A tear stabiliser (perfluorohexyloctane), which is a prescription drug in the US and a medical device in other regions [47-50].
- Hyaluronic acid (HA), an increasingly common constituent of tear supplements. As a naturally occurring glycosaminoglycan, it is found throughout the body, including within synovial fluid, the vitreous and aqueous humor. The high molecular weight formulation of HA has been reported in an animal model to be more effective than its lower molecular counterpart in treating DED [51], and to protect against corneal cell apoptosis and inflammation in vitro [52]. Further information is provided in Section 6.1.1.2.
- Preservatives, including benzalkonium chloride and ethylene diamine-tetraacetic acid, are used to protect against bacterial contamination of the drops. Preservatives such as benzalkonium chloride can result in toxic and pro-inflammatory effects, exacerbating dry eye signs and symptoms [53,54]. There has therefore been a move towards using preservative-free unit-dose formulations, less damaging preservatives such as stabilized oxychloro complex (Purite®) [55,56] or sodium perborate (GenAqua®; Alcon, Ft Worth, TX, USA; Dequest®) [57], or the use of multi-dose, preservative-free bottles that are specifically designed to prevent contamination with microorganisms [58]. Another preservative with a long history of use in tear supplements is polyquaternium-1 (Polyquad®; Alcon, Ft Worth, TX, USA) [57]. This is a bactericidal quaternary ammonium compound used in tear supplements at a typical concentration of 0.001%. At this concentration it has been shown to have no adverse effects on the cytokinetic movement, morphology, or mitotic activity of cultured human corneal epithelial cells after a 24-hour exposure period [59].
- Hypo-osmotic agents designed to counteract the hypertonicity of the tear film in DED [60].
- Osmoprotectants, that aim to optimize cellular health to enable the ocular surface to withstand the impacts of tear hyperosmolarity and inflammation [61-63]. Examples include L-carnitine, erythritol, trehalose (see Section 6.1.1.7), betaine, sorbitol and glycerin [43].

- Excipients:
    - buffers: (e.g. bicarbonate, phosphate, citrate, borate) to maintain the normal pH (7.4) of the tear film [2,53,58]
    - salts to regulate tonicity.

The following section reviews various tear supplement formulations, with a primary focus on new knowledge since the publication of the equivalent report for TFOS DEWS II [2].

6.1.1.1 Guar-based supplements

Hydroxypropyl guar (HP-guar) is a high molecular weight polymer with chemistry along the polymer backbone to generate a high viscosity gel when placed in the eye. The hydroxypropyl groups block the intermolecular hydrogen bonding so that the solubility of guar is increased and can bind preferentially to hydrophobic regions via the hydroxypropyl groups to damaged areas of the glycocalyx surface [64]. Borate is a buffer in Systane® (Alcon; Ft Worth, TX, USA) formulations and the borate ions bind with cis-diols of the HP-guar to form covalent bonds and crosslink the polymers to form viscoelastic gels [65]. The HP-guar viscosity-enhancing polymer in combination with demulcents forms a hydrated scaffold on the ocular surface to protect and resist desorption for long term protection [66]. The in-situ crosslinking generated with HP-guar and borate is unique in that it works with the ocular pH of the tear film [66]. The generated gel is facilitated by the physiological pH of the ocular surface tear film to help retain the demulcents on the ocular surface [67]. Clinical studies have demonstrated that the HP-guar based supplement, in combination with PEG and/or propylene glycol, significantly enhances tear film stability and provides prolonged lubrication [68]. It has also been shown to reduce tear osmolarity, corneal staining, and improve overall ocular surface health [69]. Additionally, this combination improves goblet cell density and promotes epithelial repair by creating a protective layer that prevents further damage to the ocular surface, supporting the renewal of surface epithelial cells [70].

6.1.1.2 Hyaluronic acid-containing supplements

Hyaluronic acid is a naturally occurring, anionic non-sulfated glycosaminoglycan found throughout the body's extracellular matrix, including as a major component of synovial fluid. The molecular weight of HA can be very large, often reaching several million Daltons. Its primary function is to contribute to cell proliferation and migration, and it is used in a variety of tear supplements to increase viscosity and provide enhanced lubrication. Hyaluronic acid exhibits non-Newtonian shear-thinning properties, where viscosity varies with shear rate [71,72]. These shear-thinning properties are also dependent upon molecular weight [73]. A study demonstrated that high molecular weight HA provided longer tear breakup time (TBUT) and lower lissamine green staining scores than either low molecular weight HA or diquafosol drops in a mouse model of DED [51].

A review of published literature on the safety and efficacy of tear supplements containing HA for DED management identified 53 eligible clinical trials, including eight placebo-controlled studies [74]. Studies used HA concentrations ranging from 0.1% to 0.4% over periods of four weeks to three months and, overall, demonstrated effectiveness in improving both signs and symptoms of DED without any serious side effects. Major knowledge gaps identified were the ideal drop frequency, and the optimal formulation and concentration of HA.

A literature review of 21 randomized trials compared HA to 17 other single ingredient DED treatments [75]. Most ocular surface and tear film measures showed no significant difference between treatment groups, suggesting either equivalence of treatments, or that the studies were underpowered, the drop frequency was not optimised (between one and eight drops were prescribed daily) or the concentration of HA used may have been too low to be therapeutically relevant.

A systematic review with meta-analysis of 18 studies comparing HA to non-HA-based tear supplements showed superiority of HA-containing tear supplements in improving ocular staining, as well as patient-reported symptoms [76]. Tear production measured by the Schirmer test and tear film stability measured by TBUT did not significantly differ between the treatments.

Efficacy and safety of tear supplements combining CMC with HA, to CMC alone, applied twice daily for 90 days were assessed in a large multicenter study [77]. Both participant-reported symptoms and clinician-measured ocular surface and tear film parameters improved significantly relative to baseline, albeit with minimal difference in outcomes between groups.

Hyaluronic acid can be modified in various ways, such as its molecular weight, viscosity, and hydrophobicity, to alter its properties. Cross-linking certain sections of the molecule may increase its resistance to degradation and enhance bioavailability [78].

6.1.1.3 Xanthan gum

Xanthan gum is a highly viscous polysaccharide molecule extracted from *Xanthomonas campestris* [79]. Its behavior has been likened to tears, including features such as decreasing viscosity with increasing shear rate, and similarities in temperature, biopolymer and salt concentrations, as well as pH [79]. These behaviors have enabled xanthan gum to be used as a vehicle in ophthalmic drugs to improve residence times on the ocular surface [80]. In DED, the effects of xanthan gum have been compared to CMC [79] and PEG/propylene glycol [81]. Xanthan gum has been evaluated *in vitro* and in rabbits in combination with other constituents with regard to its antioxidant and osmoprotective effects [82].

In a study that evaluated a 0.2% concentration of xanthan gum in 15 participants with DED, xanthan gum was found to significantly improve goblet cell parameters, conjunctival cytological features and corneal staining when used

four times a day for one month, compared to CMC, although a reduction in the Schirmer I test was also reported [79]. A Phase III, multicenter randomized controlled trial (RCT) involved 148 participants with DED who used 0.09% xanthan gum with 0.1% chondroitin sulfate, xanthan gum four times a day for 60 days compared to PEG/propylene glycol [81]. Efficacy was found to be similar between the two treatments, with both improving clinical signs such as Schirmer test score, TBUT and ocular comfort [81].

A prospective, multicentre clinical investigation was undertaken on a preservative-free ophthalmic solution containing xanthan gum 0.2% and desonide sodium phosphate 0.025% instilled three times a day in 30 participants with DED [83]. The study formulation was associated with a significant reduction in redness after one month of treatment compared to baseline. In addition, the solution significantly increased TBUT and promoted a significant reduction in corneal and conjunctival staining. It also reduced DED symptoms and exhibited a very good safety profile.

6.1.1.4 Polymer combinations

Multi-polymer formulations, including polymers with anti-inflammatory properties, such as xanthan gum and guar gum, have been reported to contribute to reducing inflammation and promoting epithelial healing [84,85].

One commonly used combination includes HP-guar and HA. A systemic review evaluating preclinical and clinical effects of this combination of polymers summarised their hydration, lubrication and moisture retention capabilities [86]. In an in-vivo corneal injury model, HP-guar+HA significantly accelerated corneal re-epithelialization, outperforming other HA-based eye drops [87].

Clinical trials highlighted that this combination of dual-polymer lubricating drops reduced the clinical signs & symptoms of DED, improved TBUT and exhibited improved retention time on the ocular surface [88,89]. In a retrospective study of post-cataract surgery patients, the dual-polymer formulation was associated with

reduced dry eye symptoms and corneal damage, especially when administered pre-operatively [90]. In healthy individuals, HP-guar+HA drops significantly enhanced tear film quality, increasing both TBUT and tear meniscus height (TMH) [91]. Additionally, in digital device users, the dual polymer composition significantly improved eye comfort and quality of life [92].

Clinical studies have demonstrated that tear supplements containing polymer combinations outperform single-polymer formulations in terms of DED symptom relief, tear film stability and patient satisfaction [77,93,94]. For example, an RCT comparing HA+CMC combination drops to a product containing CMC alone showed significantly greater improvement in Ocular Surface Disease Index (OSDI) scores and TBUT in the combination group [77]. Another study reported that tear supplements with PEG and propylene glycol, used three times a day for 90 days, significantly improved goblet cell density and corneal and conjunctival staining relative to baseline levels [70].

6.1.1.5 Lipid-containing supplements

Lipid-containing tear supplements, formulated as emulsions, are increasing in availability and popularity [40-43,45,46,95,96]. When comparing lipid-containing and non-lipid-containing formulations, lipid-containing tear supplements have been reported to be more effective at improving lipid layer appearance in both the short-term [46,97] and longer-term [98-100]. Additionally, lipomimetic tear supplements have been associated with greater subjective symptom relief and higher patient satisfaction among contact lens wearers, as well as improved clinical signs such as lid wiper epitheliopathy and corneal staining [45]. In head-to-head comparisons of lipid-containing tear supplements, a Phase IV, multicenter, randomized, double-masked study of 231 adults with evaporative DED compared two lipid-containing tear supplements when used four times a day for 35 days [101]. The drops were found to perform similarly in terms of TBUT and both were well-tolerated [101]. Large, multicentre clinical trials have demonstrated that a HP-guar phospholipid nanoemulsion resulted in significant improvements in TBUT and

reduced dry eye symptoms for up to eight hours in various sub-types of DED, significantly improving tear film stability, lipid layer thickness (LLT), and ocular comfort (aqueous deficient, evaporative & mixed) [102-104].

Preclinical studies showed superior hydration, retention and faster recovery, enhancing lubrication and tear film stability [105]. Clinical trials demonstrated significant improvements in tear film BUT, reducing dry eye symptoms that included burning, grittiness, and stinging [104]. A phospholipid nanoemulsion with HP-guar effectively targets key aspects of DED, offering both immediate and sustained symptom relief, improved ocular surface health, and enhanced tear film quality [102].

Table 1 provides data on peer-reviewed publications on various commercially available lipid-containing drops and the lipids that they contain.

Table 1: Examples of studies examining lipid containing supplements

Lipid component	Brand name (Manufacturer)	Published studies
Castor oil	Optive Plus (Allergan, Irvine, CA, USA)	Kaercher et al. 2014 [106] Karcenty et al. 2021 [107]
	Refresh Endura (Allergan, Irvine, CA, USA)	Di Pascuale et al. 2004 [108] Fogagnolo et al. 2016 [109]
	Refresh Optive Advanced (Allergan, Irvine, CA, USA)	Jerkins et al. 2020 [101]
Medium chain triglycerides	Liposic (Bausch + Lomb, Rochester, NY, USA)	Wang et al. 2010 [110] Chung et al. 2016 [111] Kim et al. 2017 [112]
	Artelac Lipid (Bausch + Lomb, Rochester, NY, USA)	Mihaltz et al. 2018 [113] Lim et al. 2020 [114]
Mineral oil	Cationorm (Santen, Japan)	Robert el al. 2016 [115] Lim et al. 2020 [114] Fogagnolo et al. 2020 [116] Makri et al. 2021 [117]
	Retaine (marketed as Cationorm outside of the USA)	Ousler et al. 2015 [118]
	Soothe (Bausch + Lomb, Rochester, NY, USA)	Fogagnolo et al. 2016 [109]
	Soothe XP (Bausch + Lomb, Rochester, NY, USA)	Korb et al. 2005 [119]
Mineral oil + phospholipids	Systane Balance (Alcon, Fort Worth, TX, USA)	Aguilar et al. 2014 [120] Guthrie et al. 2015 [45] Gokul et al. 2018 [121] Jerkins et al. 2020 [101]

	Systane Complete (Alcon, Fort Worth, TX, USA)	Silverstein et al., 2020 [102] Yeu et al., 2020 [103] Muntz et al. 2020 [46] Pucker et al. 2021 [122] Craig et al. 2021 [98] Antman et al. 2024 [123]
Omega-3 fatty acid (flaxseed oil)	Refresh Optive Mega-3 (Allergan, Irvine, CA, USA)	Deinema et al. 2017 [124] Fogt et al. 2019 [125] Downie et al. 2020 [126]
Liposomal spray	Tears Again (Optima, Hallbergmoos, Germany)	Turnbull et al. 2018 [127]
Phospholipids	Emustil (SIFI, San Antonio, Italy)	McCann et al. 2012 [128]
	Tears Again (Optima Medical, Switzerland)	Craig et al. 2010 [129] Rohit et al. 2017 [130] Essa et al. 2018 [99] Pult et al. 2021 [131]

6.1.1.6 Perfluorohexyloctane ophthalmic solution

Perfluorohexyloctane ophthalmic solution (Miebo®, Bausch + Lomb, Bridgewater, NJ, USA) is a single ingredient, water-free, preservative-free formulation. The active ingredient, perfluorohexyloctane, has amphiphilic properties and is comprised of a lipophobic fluorocarbon segment and a lipophilic hydrocarbon segment [48]. This formulation received marketing approval in the US in 2023 and has been available for several years in Europe, Australia and New Zealand (EvoTears® /NovaTears®), including variations with and without added omega-3 [132,133]. While the majority of tear supplements in this category are available without a prescription, this tear stabiliser is available only by prescription in some countries, due to the required regulatory approval pathway of the non-monograph active ingredient.

There are several proposed mechanisms of action for perfluorohexyloctane in the treatment of signs and symptoms of DED. The first is inhibition of tear evaporation through the formation of a monolayer at the interface of the tear film with the environment [48,134,135]. In support of this, *in vitro*, perfluorohexyloctane ophthalmic solution has been shown to outperform tear supplements and meibum extracted from a single healthy volunteer in terms of reducing the evaporation of saline [47], but this not been confirmed *in vivo* using devices that clinically determine rates of evaporation. *In vivo*, preclinical data has demonstrated that topical application of perfluorohexyloctane for seven days in healthy rabbits improved the lipid level grade as early as five minutes after a single instillation and following repeated doses from five to seven days, although there was no significant effect on the tear film evaporation rate, or on tear film volume or osmolarity in this healthy animal model [136]. When compared to a cationic nano-emulsion in patients with DED, the emulsion increased LLT and higher order aberrations immediately after application, while perfluorohexyloctane led to an increase in LLT over 12 weeks, with no change in higher order aberrations [137]. Improvements in both the lipid layer grade and tear film thickness were also observed in a four-week study in patients with DED and

meibomian gland dysfunction (MGD) [138]. Topical perfluorohexyloctane reduces the corneal surface temperature and increases the activity of corneal Transient Receptor Potential cation channel subfamily M member 8 (TRPM8) cold thermoreceptors. This response could lead to heightened reflex lacrimation and blinking, alleviation of the dry eye, and a decrease in discomfort and pain [139].

Efficacy and safety of perfluorohexyloctane were demonstrated in multiple clinical studies in participants with DED [140-144]. In a Phase II study, treatment with perfluorohexyloctane instilled either two or four times a day resulted in significant improvements over control (isotonic saline) in total corneal fluorescein staining and eye dryness, although four times daily dosing resulted in greater efficacy [140]. Two Phase III studies confirmed that perfluorohexyloctane dosed four times a day resulted in significant improvements over control (hypotonic saline) in both DED signs and symptoms as early as Day 15 (the first evaluation time point) and at Day 57, which was the primary endpoint [141,142]. Across the studies, the most common adverse event with perfluorohexyloctane was blurred vision (2.1% of participants), which was mild and transient [145]. Similar results have been reported in a Phase III study conducted in Chinese participants [144]. In randomized clinical trials in patients treated with perfluorohexyloctane, the most common event (reported in 2.5% of cases) was blurred vision [50]. Perfluorohexyloctane used topically was found to be non-toxic and non-bio-accumulative based on a rigorous program of non-clinical studies [146].

A Phase III, multicenter, single-arm, open-label study in participants with evaporative DED treated with perfluorohexyloctane ophthalmic solution (n = 208) four times a day for 52 weeks found the treatment to be safe, well-tolerated and efficacious in improving the signs and symptoms of DED [143]. Participants who were switched from saline (n=111) to perfluorohexyloctane experienced an improvement in DED signs and symptoms after four weeks, which was the first evaluation time point [143]. Efficacy of perfluorohexyloctane ophthalmic solution in reducing dry eye symptoms was observed in a multicenter, single-arm study at

five minutes and 60 minutes following a single instillation and also at day three, seven and 14 with four times daily dosing [49].

A systematic review published in 2023 reviewed six RCTs and reported a greater improvement in most variables recorded (OSDI, LLT, corneal staining, adverse events) in participants using perfluorohexyloctane ophthalmic solution compared to control drops [133]. However, TBUT was longer in the control group [133]. A recent meta-analysis concluded that perfluorohexyloctane is an effective and safe alternative for the treatment of evaporative DED secondary to MGD and can significantly reduce corneal staining and eye dryness symptoms [50].

6.1.1.7 Trehalose-containing supplements

Trehalose is a natural disaccharide consisting of two glucose molecules, and is reported to stabilize proteins and membranes, prevent denaturation and inhibit oxidative damage [147-149]. *In vitro*, trehalose has been shown to enhance autophagic flux when combined with HA-based eye drops [150], which contributes to osmoprotective effects, and the maintenance of epithelial cell homeostasis in DED [150]. This is important because autophagy degrades and recycles cellular components, allowing the cellular environment to adapt to a desiccated environment. In a desiccating model of DED, a combination of 3% trehalose and 0.15% HA in a preservative-free formulation (Thealoz® Duo; Laboratoires Thea, Clermont-Ferrand, France) showed goblet cell recovery and reduced inflammatory markers compared to a combination of 0.001% hydrocortisone and 0.2% HA [151].

In humans, trehalose-containing tear supplements have been reported to have an excellent safety profile [152]. The use of trehalose-containing tear supplements in DED has been described in a systematic review that included 10 RCTs [153]. When compared to controls, trehalose-containing tear supplements showed an improvement in terms of ocular comfort and markers of homeostasis (TBUT and corneal staining) and no adverse events were reported in any of the studies

analyzed [153]. Since publication of this systematic review, other studies have compared trehalose as a component of tear supplements relative to other formulations, most commonly in combination with HA. There is reported efficacy of this formulation in patients with DED [154], in peri-menopausal and post-menopausal women [155], and in patients post-cataract surgery [156].

6.1.1.8 Ectoine-containing supplements

Ectoine is a bacteria-derived extremolyte with the ability to protect proteins and biological membranes from damage caused by extreme environmental conditions and is considered a natural osmoprotectant [157]. A prospective study on 18 participants with DED using a preservative-free ectoine-containing eye spray used three times daily for approximately 2 weeks demonstrated a reduction in DED symptoms and increase in non-invasive TBUT [158]. A study investigated the impact of a topical ectoine-based drop on a desiccation mouse model compared to a vehicle control [159]. The ectoine treatment protected mice from corneal damage in a concentration-dependent manner, and ectoine at 1.0 and 2.0% significantly restored corneal regularity and reduced corneal staining. Expression of various pro-inflammatory cytokines and chemokines was significantly elevated in the corneas and conjunctivas of desiccation-exposed mice, whereas 1.0 and 2.0% ectoine suppressed these inflammatory mediators to near normal levels [159]. In a similar mouse model, topical 2% ectoine was shown to significantly reduce corneal damage, and enhance goblet cell density and mucin production compared with vehicle through restoring imbalanced interleukin (IL)-13/Interferon-gamma signaling in a murine dry eye model [160].

6.1.1.9 Antioxidant-containing supplements

Oral nutritional supplements containing antioxidants are often advocated for improved ocular health, particularly age-related macular degeneration [161]. The use of antioxidants as constituents in tear supplements has been studied in relation to cataracts [161], but less is known regarding their use to manage patients with DED.

Antioxidants are mainly associated either with lipophilic membranes or lipoproteins such as vitamin E and ubiquinols, or aqueous components such as ascorbate, glutathione and thioredoxin [162].

A study on alpha-lipoic acid, a naturally occurring antioxidant that can interact with both lipid and aqueous phases, in patients with diabetes and DED showed that a topical combination of alpha-lipoic acid and hydroxypropyl methylcellulose resulted in a greater improvement in corneal staining than with hydroxypropyl methylcellulose alone [162], while both groups displayed an improvement in TBUT [162].

The application of selenium to cells can increase selenoprotein expression, counteracting the effect of reactive oxygen species (ROS) by increasing the presence of antioxidant enzymes [163].

6.1.1.10 Vitamin-containing supplements (A; B12; C; D)

In DED, vitamins are typically studied as oral supplements rather than as components of topically applied tear supplements. See Section 12.2 for further details.

Vitamin A is perhaps the most well-studied vitamin in regard to DED, particularly as an oral supplement [16]. It has also been studied as a topical supplement. One RCT compared the efficacy of topical vitamin A (retinyl palmitate 0.05%) four times a day versus cyclosporine A (CsA) 0.05% twice a day, versus control in 150 participants with DED [164] alongside tear supplements. Both treatment groups improved in symptoms and signs, including TBUT, corneal staining, goblet cell density and impression cytology gradings [164]. However, as recently reviewed [11], one of the vitamin A metabolites, isotretinoin (13-cis retinoic acid) is detrimental to meibomian gland health [165,166]. This Vitamin A metabolite inhibits the proliferation and promotes the death of human meibomian gland epithelial cells

[165,166]. These effects may be the reason, at least in part, for the 13-cis retinoic acid–related induction of MGD [166,167].

Vitamin B12 is reported to have antioxidant and anti-inflammatory properties, and as such has been evaluated in 30 participants using a topical formulation with 0.3% HA in post-menopausal female participants with DED [168]. The HA 0.3% and vitamin B12 eye drops decreased dry eye symptoms and improved tear film stability and tear volume compared to baseline. A larger randomized comparative clinical trial is needed to establish if the combination has greater efficacy than HA alone. Similar symptom and sign results were found with a formulation of 0.15% HA, 0.5% PEG 8000 and vitamin B12 in participants with moderate or severe DED [169].

Ascorbic acid is the pure form of vitamin C and an antioxidative agent known to maintain free radical balance by scavenging ROS [170]. One study reported on the use of an eyedrop incorporating ascorbic acid and mesenchymal stem cell-derived exosomes, showing a decrease in ocular surface inflammation and reduced ocular surface damage *in vitro* and *in vivo* [171].

A systematic review and meta-analysis showed that serum levels of vitamin D were significantly lower in participants with DED, and correlated with OSDI scores, but no other DED parameter [172]. Very few studies have investigated the direct incorporation of vitamin D into topical lubricants. A small cohort of eight participants with obstructive MGD were treated with a topical eyelid application of an analog of vitamin D3 [173]. The clinical scores for plugging of the meibomian gland orifices, lid margin vascularity, TBUT, meibum grade, and meibomian gland area were significantly improved in the participants with MGD after the eight-week treatment period, compared with pretreatment values. Oral supplementation with vitamin D resulted in significant improvements in the production, stability and quality of tears by reducing ocular surface damage and inflammatory markers in the tears [172,174-176].

In conclusion, there is emerging evidence that antioxidants and vitamins may have a role in the management of patients with DED. However, prior to their widespread adoption in DED management, high quality evidence is needed on their safety and efficacy when used alone and in combination with other compounds.

6.1.1.11 Challenges in using tear supplements

Patients often face a trial-and-error approach to product selection, leading to significant costs and frustration [177]. A Cochrane systematic review of 43 RCTs looking at head-to-head comparisons of non-prescription tear supplements in 3497 people with DED [178], indicated that while tear supplements may be effective in providing symptomatic relief, the relative lack of published head-to-head studies resulted in uncertainty as to which tear supplements were most effective. Moreover, there was limited agreement between studies in terms of the diagnostic criteria used, the study design and the measurements taken [178]. The review, however, found that 0.2% polyacrylic acid-based tear supplements were more effective at treating DED symptoms than 1.4% polyvinyl alcohol-based tear supplements [178]; it was not possible to draw conclusions on other tear supplements due to conflicting findings across studies.

In a more recent systematic review, combination formulations were found to be more effective than products containing a single active ingredient [94]. The combination of CMC with HA was more effective than either in isolation, while HA and the lower molecular weight, sodium hyaluronate, appear to benefit from the addition of trehalose, and CMC is enhanced by the addition of glycerine. A PEG-based lubricant was found to be more effective than CMC+carmellose sodium and hydroxypropyl methylcellulose-based products [94].

A recent parallel-group study [179] consisting of 20 participants per arm with moderate DED compared five differing lubricants every 15 minutes for one-hour

post-insertion, with one eye acting as the control (no drops). These five commercially available lubricants were based on products containing 0.5% and 1% CMC, 0.1% HA+trehalose, 0.4% PEG 400+0.3% propylene glycol and 0.1% HA+0.4% PEG 400+0.3% propylene glycol. Over the course of the test period, there was no difference between products or between eyes (test vs control) for TMH or ocular redness at any time point. There was a significant increase in non-invasive breakup time (NIBUT) between eyes and at all time points over the hour, with no product demonstrating superiority. These results demonstrate that short-term increases in tear stability can be achieved promptly with varying lubricant formulations [179].

The dosage and duration of treatment required to observe an effect have also been debated. A systematic review of 64 RCTs found “good” evidence that symptoms of DED can improve within one month of four times daily use of lubricants [94]. In comparison, dry eye signs can take around four months to improve [98]. This is highly relevant to the clinical advice given to patients. Patients failing to see an improvement in symptoms following use of the lubricants for at least one month, should consider a different artificial tear product or an alternative management strategy. Approximately one quarter of patients may not benefit from a particular artificial tear [98]. This also has implications for study design, whereby shorter studies, less than four months in duration, are unlikely to demonstrate a clinical improvement in ocular surface and tear film parameters.

There are some practical considerations with respect to tear supplements. Different bottle types, each with their unique material strength and dispensing mechanism, may be challenging for patients with limited dexterity and pinch strength. An examination of the average force required to dispense a product was undertaken on 60 different bottles (57 lubricants and three dry eye medications) [180]. The average force varied depending on the bottle type, with multidose preservative free bottles requiring more force than all other bottle types. This suggests that hand and pinch strength should be considered when

choosing products for DED management, as the squeezability of a lubricant drop bottle may influence compliance with its administration. Storage of lubricants is a consideration, as some patients store their lubricants in the fridge to provide a “cool and refreshing feeling” upon administration. However, the complex formulation of many products could be adversely affected by refrigeration and factors such as viscosity may be impacted, resulting in adverse effects on comfort and vision upon application. Indeed, studies have shown that there are no demonstrable comfort benefits through adopting such a refrigeration approach [181,182].

In conclusion, careful consideration of the literature suggests that while there is a great number of tear supplements, most of which are readily available over-the-counter, there is little agreement as to whether one formulation works better than another in treating different subtypes of DED. However, the evidence would suggest that patients with lipid deficiency benefit most from lipid-containing supplements [98]. One month‟s compliant use of the lubricant four times daily is likely to determine if a particular artificial tear supplement will be effective for symptom relief. To observe an effect on signs, an artificial tear supplement would be expected to require more extended use, for around four months [98].

Research continues to explore novel polymer combinations and advanced delivery systems to further enhance the efficacy of tear supplements. Innovations such as nanotechnology-based carriers and biodegradable microspheres are being investigated to provide sustained release of lubricants and therapeutic agents, potentially offering even greater benefits for patients experiencing the effects of chronic and severe DED [96]. Future studies need to be more consistent in study design, including the selection of core outcome measures and there is a need for evidence-based, well run clinical studies comparing products over an adequate follow-up period, in well-defined groups of patients with DED.

6.2 Tear conservation devices

6.2.1 Contact lenses

Contact lenses can be a risk factor for DED due to their impact on the ocular surface [183], and therefore DED management may involve modifying the contact lens material, design, frequency of replacement or care system to mitigate this effect [184,185]. In contrast, they can also protect the ocular surface from the stress forces of the eyelids moving over a poorly lubricated cornea and reduce corneal desiccation, leading to improved corneal healing and a reduction in pain, possibly by shielding the nociceptors [186].

Hydrophilic bandage lens materials worn on an extended wear basis for one week decrease dry eye signs and symptoms in participants with MGD following cataract extraction and intraocular lens implantation [187,188]. Six weeks use of a bandage silicone hydrogel lens (replaced after three weeks of continuous wear) outperformed autologous serum in the management of participants with Sjögren disease over a three-month period [189]. Soft contact lenses can also be used to hold an amniotic membrane over the ocular surface (see Section 10.3) [190]. Soft contact lenses can also be used for improving drug delivery to the ocular surface [191,192], but this has not yet been developed into a commercial product for the management of DED.

Microbial keratitis is a risk factor when bandage contact lenses are worn overnight [193-195], and in wearers with severe DED this risk is exacerbated [186,196]. In such cases, topical non-preserved antibiotics are often added to the regime to reduce the risk of serious infection [186].

Scleral contact lenses have been used to treat patients with DED [197], providing the therapeutic benefit of enhancing both visual function and improving the health of the ocular surface. One retrospective study of 134 participants wearing scleral

lenses showed an improvement in OSDI scores in all but two participants from lens fit to follow-up, regardless of duration over which the lens had been worn [198]. Constructed from rigid, highly gas-permeable polymers, these lenses vault over the cornea and rest on the sclera [186,199,200]. This design creates a fluid reservoir between the posterior surface of the lens and the anterior surface of the corneal epithelium. This void can be filled with tear supplements or saline, creating a fluid reservoir, hence acting as a liquid bandage to not only provide ongoing moisture, but to also prevent evaporation at the ocular surface. They have been reported to be efficacious and well-tolerated in participants with severe DED [201]. In a retrospective report of scleral lenses when used in conjunction with plasma rich in growth factors (PRGF) eye drops in participants with a range of ocular surface diseases, the combination was found to be safe and effective in decreasing patient symptoms [202]. The rigid nature of the lens also offers protection against the microtrauma induced by the movement of the lid over the cornea. Additionally, the lens reduces evaporation of the tear film and the resulting increase in tear volume provides significant benefits. Improvement in visual acuity occurs due to the correction of the irregular astigmatism that is often present in these patients [186].

Several studies have reported an improvement in visual acuity in patients with DED due to various underlying conditions such as Stevens-Johnson syndrome, Sjögren disease, and ocular graft versus host disease [203-206]. Scleral contact lens use also improves ocular staining scores for both the cornea and conjunctiva, along with reduction in tear osmolarity levels [203,205,207]. Symptomatic improvement, reflected by improved OSDI scores, has also been accompanied by enhanced quality of life scores [203,205]. The fluid reservoir of the scleral contact lenses has been used as a modality for drug delivery. A study reported improvement in corneal neovascularization and visual acuity with concurrent instillation of bevacizumab to the reservoir [208] and another loaded the reservoir with CsA in nine participants with DED [209].

To fully realize the benefits of scleral contact lenses, it is essential to ensure optimal fitting parameters [200,210]. This is even more important in patients with DED, who also have compromised ocular surfaces. Proper edge alignment with good central and limbal vault while avoiding mid haptic vessel compression can help improve comfort with scleral contact lens use. A common challenge associated with scleral contact lens use is midday fogging, which occurs due to accumulation of debris within the tear reservoir [186,200,211,212]. Poor wettability of the lens can also be an issue, which can increase discomfort and hamper visual function. Nevertheless, scleral contact lens use is generally not linked to significant complications and effectively improve the symptoms and signs of DED [200,205,207,213,214]. However, to date there is sparse evidence in the form of robust studies to advocate the use of scleral lenses for the management of patients with DED, despite its relatively common use in clinical practice.

6.2.2 Moisture retaining spectacles

Moisture retaining spectacles enclose the space surrounding the eyes, thereby limiting periocular airflow, increasing periocular humidity and reducing the rate of tear film evaporation [32,33,215]. Sponge inserts can further increase chamber humidity in the periocular environment. For these to be effective, the frames need to be adjusted to the shape of the patient"s face, to minimize leaks.

In a study evaluating the short-term effects of moisture retaining spectacles on participants with DED (n = 30), ocular comfort, TMH, NIBUT, and LLT continuously increased over time, reaching maximum levels at 60 minutes before gradually decreasing. However, these values remained higher than the baseline compared to a group who received sterile saline drops [33]. In another study of 14 participants with DED, when exposed to a controlled wind exposure environment for 10 minutes, those wearing the moisture retaining spectacles had greater ocular comfort than those wearing conventional spectacles and those not wearing spectacles at all [31]. Tear evaporation rate and blink rate were also less,

and ocular surface measures (TBUT and fluorescein staining) after exposure were not different from baseline [31].

6.2.3 Punctal plugging

Punctal occlusion is recognized as an interventional treatment for moderate-to-severe aqueous deficient DED [2], with the aim of increasing ocular surface fluid retention by partially or totally blocking the tear drainage system. A Cochrane systematic review that included 18 RCTs of collagen or silicone punctal plugs did not find conclusive improvements in symptoms or signs of DED [216]. One trial found that the frequency of artificial tear application was lower in eyes with punctal plugs than those without. Variations in the type of punctal plug used, in the DED subtype and severity of recruited participants, and a lack of standardized trial methodology limited the evidence surrounding efficacy and safety [216]. The review also found that punctal plugs can be associated with adverse reactions such as epiphora and plug displacement and, more rarely, with inflammatory and infectious conditions such as canaliculitis, pyogenic granuloma and dacryocystitis [216].

In a prospective, longitudinal, single-center study, nonabsorbable punctal plugs were inserted bilaterally into the lower punctum of 30 patients with moderate DED. Three weeks after punctal occlusion, tear proteins including glutathione synthase and IL-1 were upregulated, while cholinergic receptor (neuronal) alpha-7 and lymphocyte cytosolic protein-1 were down-regulated [217].

An RCT that enrolled 50 participants with DED to receive either an intracanalicular injection of hydroxybutyl chitosan solution (Qisheng Biologic Agent Limited Company, Shanghai, China) or VisiPlug® treatment (Lacrimedics Inc, Dupont, WA, US) found both methods comparably alleviated symptoms and signs of DED relative to baseline after 12 weeks of treatment [218].

One study examined the microbiologic outcomes of removing silicone punctal plugs from dry-eye participants due to discomfort, mostly secondary to protrusion of the plug, with or without granulation [219]. Bacterial culture was positive in 42.2% of cases, with *Klebsiella* being the most frequently identified organism (18.5%). Susceptibility to vancomycin was demonstrated to be 100%, to third-generation cephalosporins was 88.5%, and to levofloxacin was 81.0% among the quinolones tested [219]. These findings, along with local knowledge of antimicrobial resistance patterns for ocular isolates, may help guide the selection of antibiotics for treating complications associated with silicone punctal plugs [220,221].

6.2.4 Newer plug designs and other technologies

A single-site, prospective, open-label study evaluated an intracanalicular plug made of cross-linked HA. Sixty-three participants with DED for whom tear supplements were not effective were included. The study found improvements in corneal staining, Schirmer test scores, TBUT and TMH relative to baseline, three months after fitting [78].

A prospective, multicenter, double-masked RCT was conducted with 157 participants to compare a novel crosslinked HA canalicular filler (LACRIFILL® Canalicular Gel; Nordic Pharma, Hoofddorp, The Netherlands) with a commercially available hydrogel canalicular plug [222]. The filler or plugs were inserted bilaterally in the inferior canaliculi. The filler was found to be non-inferior to plugs for the mean Schirmer test score change from baseline and for the proportion of participants achieving a clinically important improvement in OSDI. The study concluded that the crosslinked HA filler is a safe, well-tolerated, and effective method to treat DED by canalicular occlusion. Clinically and statistically significant improvements in signs and symptoms of DED were sustained through six months [222].

Other innovative technologies have been proposed to improve the efficacy of punctal plugs in treating DED. Drug-loaded hydrogel or organogel punctal plugs

using highly biocompatible HA derivatives or immunomodulators such as CsA have been tested *in vitro* and *in vivo* [223,224]. Whilst 3D printing has been used to create personalized punctal plugs with built-in drug delivery systems tailored to individual punctal morphology, no clinical studies have been published to date [225].

6.3 Tear restoration or stimulation

Tear deficiency due to reduced volume or altered composition can lead to DED. A lack of individual tear film constituents can be addressed through various approaches (Sections 6.3.1, 6.3.2 and 6.3.3), that restore or stimulate the production of the individual missing tear film elements. As discussed in Section 6.3.4, an emerging category of "neuromodulation" is based on increasing activity of the trigeminal nerve to stimulate tear production that includes several tear components.

6.3.1 Restoration or stimulation of lipid

The 2011 TFOS workshop on MGD demonstrated the significant impact that MGD has as an etiological driver of DED [167,226-229] prompting considerable research in optimising its management to enhance lipid delivery to the ocular surface.

6.3.1.1 Meibomian Gland Dysfunction: At-home treatments

6.3.1.1.1 Warm compresses

Warm compresses are employed in the treatment of MGD, with the objective of melting thickened meibum within the glands, facilitating gland expression via subsequent manual massage. The aim of warm compresses is to enhance tear film LLT and encourage improved gland function.

There has been a surge in options available for patient-applied („at-home") therapies, whereby the patient warms their eyelids with non-prescription over-

the-counter warm compresses, ranging from heated, moist towels, to commercially available products through to more technological electronic devices [230-243]. At-home therapies are readily accessible to consumers through online platforms and small manufacturers. However, not all available options have accompanying evidence regarding their safety and efficacy, or even a standardized approach to application [234,236,241].

Secretions from obstructed meibomian glands have higher melting points than those from normal glands [244]. Therefore, it is recommended to use heating temperatures between 40°C and 41.5°C and to ensure the heat is retained long enough to be effective [245]. The temperatures reached should not be so high as to risk burning the skin or other adverse effects on the eyelids and ocular surface [236].

Warm compresses can be classified into those that apply dry or wet heat, subdivided into those that are chemically heated, microwave heated or electronically powered, and it is recognized that they may not have equivalent efficacy [234,239]. One study compared dry heat and moist heat warm compresses and reported that, during the moist heat treatment, the eyelids may become wet, leading to a potentially counterproductive effect due to evaporative cooling [246].

Based on the limited available evidence, it is suggested that an appropriate heated device is used at least once a day for 10 minutes [239] or twice a day for five minutes [247], followed by gentle expression of the glands to help express the meibum. Towels heated to 45°C every two minutes have been found to be comparable in their delivery of heat to commercially available devices [241], but this is a time-intensive process, risking potential challenges with patient compliance over time.

Following the application of warm compresses, lid massage is required to express the meibum and help unblock the meibomian glands [241,248-250]. While massage of the lids and the globe chronically has been associated with corneal deformation and keratoconus, a prospective study reviewing corneal topography

following 30 minutes of eyelid warming and massage found no significant differences during the observation period [251].

The efficacy of several new products have been reported, with varying degrees of certainty with regards to supporting evidence [230,232,233,235,238,252-255]. Increasingly, the clinician plays a valuable role in guiding patients about the evidence supporting these products and to recommend suitable treatments tailored to their specific diagnosis.

One study investigated the impact of a warm compress containing menthol as a potential treatment for DED by examining its effects on the tear film in 20 healthy participants and 35 participants with DED [256]. Repeated application of menthol-containing warm compresses significantly increased tear meniscus volume and TBUT in both groups. The authors suggested that the repeated use of the warm compress containing menthol stimulated TRPM8 channels and could be a potential novel treatment for DED [256].

Previous reviews of clinical studies using warm compresses for the management of MGD have been published [230,234,236,241]. Table 2 highlights a variety of studies using different warm compress approaches and their significant findings.

A number of topics require further investigation and clarification, including:

- The general lack of studies on many commercially available warming masks;
- Lack of evidence as to how long a compress or mask should be applied;
- Lack of standardization as to the appropriate type and length of eyelid massage following mask use;
- Lack of evidence on the effect on corneal topography that extended time may have when wearing a „heavier" mask, as some patients may fall asleep with their mask on their eyes.

Table 2: Example of studies using warm compresses to treat MGD

Study	Type of participants	Treatment	Product comparison	Sample size	Duration	Randomized	Outcomes showing improvement	No significant differences from comparator
Leeungurasatien et al, 2020 [238]	Healthy	Wheat hot pack	Pottery hot pack	30 crossover	10 mins use and after 10 mins	Yes	-	Surface lid temperature Tissue blood flow
Travé-Huarte and Wolffsohn, 2021 [243]	DED (TFOS DEWS II criteria)	Water propelled, heating eye massager	No treatment	15	2 weeks	Yes	Symptoms	Osmolarity NIBUT TMH LLT corneal and conjunctival staining heart rate sleep pattern
Garcia-Marques et al, 2022 [235]	DED (TFOS DEWS II criteria)	MGDRx Eyebag in 18-31 year olds	MGDRx Eyebag in 61-90 year olds	30 younger; 30 older	2 weeks	No	NIBUT LLT	Symptoms Meibomian gland loss Meibum quality Gland obstruction

								Telangiectasia
Arazi et al, 2024 [254]	Meibomian gland disease	Spectacle mounted infrared warming device	None	10	2 weeks	No	-	Symptoms TBUT Schirmer
Wang et al, 2024 [257]	Mixed form DED	Disposable self-heating mask	Hot cotton towel	134	12 weeks	Yes, non-masked	Symptoms TBUT Corneal staining	Schirmer

LLT: lipid layer thickness; NIKBUT: non-invasive Keratograph breakup time; OSDI: Ocular Surface Disease Index; TBUT: tear breakup time; TMH: tear meniscus height

6.3.1.1.2 Essential fatty acids

Polyunsaturated fatty acids (PUFA) such as omega-3s can play a role in improving the signs and symptoms of DED in patients with MGD [258-263], although some studies have been unable to demonstrate any positive benefits of oral omega-3 intake on MGD parameters [264,265].

A prospective, randomized, double-masked, RCT enrolled 50 subjects with mild to moderate DED who exhibited signs of MGD [262]. Patients were divided into two groups: 24 patients in the omega-3 group and 26 patients in the placebo group. The omega-3 group received 600 mg of eicosapentaenoic acid and 1640 mg of docosahexaenoic acid, while the placebo group received 3000 mg of olive oil. The TBUT, corneal staining and OSDI scores improved significantly after four and eight weeks in both groups. After eight weeks, TBUT and MGD score in the omega-3 group was significantly improved to a greater degree than the placebo group [262].

A multicenter, randomized, investigator-masked study investigated the effectiveness of a re-esterified triglyceride form of omega-3 in 107 subjects with MGD, post cataract surgery [263]. Patients were randomly assigned to the omega-3 group or a control group. After 12 weeks, TBUT, corneal staining, Standard Patient Evaluation of Eye Dryness (SPEED) and OSDI scores were significantly improved in the omega-3 group compared with the control group. In addition, meibomian gland quality and expressibility were significantly improved in subjects with more severe MGD in the omega-3 group only [263].

6.3.1.1.3 Topical pharmacological treatments

The TFOS Meibomian Gland Disease Workshop concluded that the core mechanisms of gland obstruction were ductal hyperkeratinization and increased meibum viscosity, with consequent orifice plugging, ductal obstruction and dilation, and ultimately gland atrophy observed clinically as dropout [167].

6.3.1.1.3.1 Topical azithromycin

Application of topical azithromycin is also an option for the management of MGD, as it offers comparable results to oral antibiotics, such as doxycycline, without the systemic side effects (gastrointestinal disturbance being the most common) [266-268]. Further RCTs with large populations and different demographics are needed to assess the long-term effects of topical antibiotics such as azithromycin as a management option for MGD.

6.3.1.1.3.2 Topical selenium sulfide

Topical preparations of selenium sulfide are an effective treatment for hyperkeratotic conditions, tinea versicolor, seborrheic keratitis and other dermatologic conditions [269,270]. Selenium sulfide is thought to break down protein aggregates and may slow future deposition of keratin [271]. Selenium products have poor ability to cross epithelial boundaries. They must be applied topically at the site of intended action, where a redox reaction causes breakage of disulfide bonds and consequent protein disaggregation [272-274]. AZR-MD-001 (Azura Ophthalmics, Tel Aviv, Israel) containing selenium sulfide, was developed as a semi-solid ointment for ophthalmic use. A Phase II study of 245 participants with MGD treated with ointment to the eyelid margin twice weekly demonstrated efficacy after three months in improving both patient symptoms (by OSDI, visual analog scale and SPEED questionnaires) and clinical signs [271]. The number of meibomian glands yielding liquid secretion, meibum quality and TBUT improved after three months of treatment relative to vehicle, and this was sustained after six months of treatment [275]. Separate studies in 67 participants with MGD and contact lens discomfort reported improvements in the number of glands yielding liquid secretion, meibum quality, TBUT and contact lens wearing time [276,277]. These studies indicated that AZR-MD-001 is safe, well-tolerated and effective for the treatment of evaporative DED secondary to MGD with only two bed-time applications per week.

6.3.1.2 Meibomian Gland Dysfunction: In-office treatments

6.3.1.2.1 Device-driven technologies: Inner eyelid heating and massaging

The LipiFlow® Thermal Pulsation System (Johnson & Johnson Surgical Vision, Inc. Irvine, CA, USA) is an in-office vectored thermo-mechanical therapy that delivers localized heat and pressure to the meibomian glands, facilitating the flow of the meibum to contribute to the tear film lipid layer at the ocular surface in a single application [2]. This procedure requires topical anaesthesia prior to its use. It has been shown that a single procedure can increase meibomian gland secretions and reduce DED symptoms and that the effect can be sustained for at least six months [278,279]. In a study of 20 participants with evaporative DED secondary to MGD, a single 12-minute thermal pulsation procedure was shown to result in significant improvement in meibomian gland secretions and SPEED scores for up to three years [280].

A publication reviewed 11 articles on the value of LipiFlow in treating DED [281]. While LipiFlow has shown benefits relative to warm compress treatment, the three studies without direct industry support concluded that LipiFlow treatment was not significantly more effective than warm compress and eyelid hygiene regimens, when these latter regimens are undertaken appropriately [281]. A systematic review evaluating the outcomes reported from 13 trials with a total of 1155 randomized participants [282] found no evidence of a difference in meibomian gland expression, meibum quality, or TBUT when comparing LipiFlow with warm compresses. Another five trials found thermostatic devices (TearCare; iLux; MiBoFlo) achieved a mean of 4.59 points better on OSDI than LipiFlow at four weeks, although the evidence was of low certainty [282]. When comparing LipiFlow plus an eyelid hygiene with eyelid hygiene alone, there was no evidence of a difference in signs or symptoms at any evaluated time point [282].

Systane iLux® (TearFilm Innovations, Inc., Alcon, Fort Worth, TX, USA) is an eyelid thermal pulsation system consisting of a single-use patient interface device and a handheld, battery-powered instrument [283,284]. Its purpose is to maintain an eyelid temperature of 38-42°C to melt meibum, while simultaneously compressing and expressing the meibomian glands [283,284]. This treatment also requires topical anaesthesia prior to device application. No adverse events related to device use were reported in two clinical studies [283,284].

When iLux was compared with LipiFlow treatment, both treatments improved the signs and symptoms of MGD, including meibomian gland score, TBUT, and OSDI scores after four weeks of treatment, with no statistically significant difference between them [283]. Another randomized trial demonstrated that iLux improved clinical parameters, such as meibomian gland score, NIBUT and patient symptoms (by Impact of Dry Eye in Everyday Life - Symptom Bother scale), after 12 months following a single treatment [285].

A review of various in-office thermal treatments suggested that iLux could be a better treatment option for patients who prefer a single treatment over 6-12 months or are not compliant with time-intensive, at-home regimens [284]. However, while such in-office treatments provide rapid relief of symptoms that may last up to one year, there is a considerably higher cost than the at-home treatments [284]. A new generation device, ILux^2® is available, which has replaced the magnifier with a screen for meibomian gland imaging, hence it can be used both as a diagnostic tool and a therapeutic treatment option.

6.3.1.2.2 Device-driven technologies: External eyelid heating

The TearCare® System (Sight Sciences, Inc. Menlo Park, CA, USA) consists of four electrothermal devices (SmartLids®) that are adhesively affixed to the upper and lower eyelids [284,286-288]. These devices deliver regulated thermal energy across the eyelids at temperatures ranging from 41°C to 45°C for 15 minutes at a

single visit [288]. Meibomian gland expression is then manually performed after lid heating by the eyecare practitioner [284,286-288]. Application of this treatment itself does not require anesthesia and because the adhesives are placed on the outer lid, the person can blink normally and go about their daily activities (ie. reading, watching tv, etc) when being treated.

TearCare treatment demonstrated a significant improvement in TBUT (of nearly 12 secs by two weeks), corneal and conjunctival staining, and meibomian gland score compared to a daily warm compress regimen (n=12 in each group), that was maintained over six months [287]. No adverse events were reported. The study group underwent re-treatment at month seven, and the participants experienced additional benefits in both objective and subjective parameters [287].

A multicenter RCT was undertaken whereby participants with DED due to MGD received either a single TearCare treatment (n = 67) or a single LipiFlow treatment (n = 68) at baseline and were followed up for one month post-treatment [289]. Both groups demonstrated significant improvements in TBUT, meibomian gland secretion score and symptoms, with no significant differences for any result between the treatments. The results demonstrated that a single TearCare treatment significantly alleviates the signs and symptoms of DED in participants with MGD and was equivalent in its safety and effectiveness profile to a single LipiFlow treatment [289]. In a follow-up multicenter RCT, participants with MGD received either a single TearCare treatment (n = 115) or a single LipiFlow treatment (n = 120) and were followed for one month post-treatment [290]. In participants with more severe MGD, TearCare performed significantly better than LipiFlow in improving quality of vision and overall DED symptom frequency, as determined by OSDI and Symptom Assessment iN Dry Eye (SANDE) questionnaires [290].

In another study, TearCare-treated participants showed more significant improvements in TBUT and meibomian gland scores over a six-month period

than those treated with twice daily CsA (Restasis®; AbbVie; North Chicago, IL, USA) drops [291]. Symptoms improved similarly in both groups, and conjunctival and corneal staining, meibomian gland score and Schirmer test scores were also similar [291].

MiBoFlo Thermoflo® (MiBo Medical, Dallas, TX, USA) is a thermostatic device that consists of a silver-plated handheld probe that delivers thermoelectric heat to the outer eyelid, maintaining a temperature of 42°C for 10 minutes [292]. This procedure does not require anaesthesia. A retrospective case series involving 102 participants with MGD demonstrated that 6 months following three MiBoFlo treatments, with a two week interval between each, there was a 36% improvement in SPEED and a 35% improvement in OSDI questionnaire scores compared to baseline [293]. Objective parameters, such as corneal and conjunctival staining, TBUT, osmolarity and the number of glands secreting any liquid also improved significantly, and no device-related adverse events were reported [293].

In a prospective clinical trial involving 54 participants with MGD, MiBoFlo and LipiFlow similarly improved OSDI and meibomian gland secretions relative to baseline, but had no effect on non-invasive TBUT, corneal fluorescein staining or meibomian gland loss [292]. In a non-randomized case series, participants were either treated with MiBoFlo and manual expression or automated expression using LipiFlow [294]. Both treatments showed improved OSDI and SPEED questionnaire scores and corneal staining, lissamine green conjunctival staining and TBUT at the six-month follow-up visit. Manual therapy with MiBoFlo resulted in greater subjective and objective improvement scores than automated therapy with the LipiFlow device.

Latent heat using a goggle, marketed under the name Blephasteam® (Laboratoires Thea, Clermont-Ferrand, France), has been described previously in the TFOS DEWS II Management report [2] and others [295,296].

In a prospective study, 73 participants used the device twice a day for 21 days [297]. Participants found the device comfortable and were able to carry out certain activities (ie. watching TV, reading and using a computer) during the treatment session, with no adverse events reported. Symptoms, using a visual analog scale, decreased significantly. Schirmer score, osmolarity and TBUT showed no significant changes during the study period.

A three-month RCT examined participants with MGD who were randomized into three treatment groups (warm towel, EyeGeine® self-heating eye mask and Blephasteam) [298]. Participants using the Blephasteam device reported a significant improvement in symptoms compared to those using a warm towel, with the EyeGeine mask not significantly different to the warm towel. No significant changes were observed for Schirmer score, TBUT or number of occluded meibomian glands.

Treatment effectiveness according to MGD severity was evaluated using three treatment options (Blephasteam, a liposomal spray and a microwaveable eye-mask [127]. NIBUT and lipid layer grade improved after 10 minutes, independent of treatment type. The improvement in NIBUT was significant for the pronounced MGD group, with the mild and control groups failing to reach significance. More research is needed to evaluate efficacy across gland dropout severity groups with a variety of eyelid warming devices.

A prospective, case-controlled study compared hot compresses, Blephasteam and a sauna for 10 minutes at approximately 85˚ C, on the temperature of the eyelid using infrared thermography [253]. The study revealed that Blephasteam significantly increased the mean eyelid temperature from baseline and was more effective than hot compresses.

An open-label, randomized study evaluated a microwaveable eye mask (TheraPearl, Bausch + Lomb, Rochester, NY) and Blephasteam in a Norwegian

population with mild to moderate MGD [299]. Both treatments improved TBUT and OSDI but did not differ from each other after six months of daily use. Of note is that a decrease in compliance was observed using a daily diary for both treatments over the study period, which remains an issue with the management of patients with DED.

A review of the literature in 2021 resulted in 18 articles on warm, moist air eyelid warming devices [300]. For a single application, seven studies using Blephasteam and four studies using a steam-based research prototype found an increase in eyelid temperature, and improvements in LLT and TBUT.

Overall, the latent heat Blephasteam device appears to be a well-tolerated, safe device for elevating eyelid temperature to therapeutic levels and improving signs and symptoms in patients with MGD. However, there remains a paucity of RCTs comparing this latent heat device with other eyelid warming devices across the dry eye severity spectrum and evidence of moist versus dry heat benefits are still lacking.

6.3.1.2.3 Device-driven technologies: Various

6.3.1.2.3.1 Intense pulsed light (IPL)

The TFOS DEWS II Management & Therapy Report suggested that intense pulsed light (IPL) was a safe and effective way to treat MGD and DED [2]. It has been used in dermatology for many years to improve a variety of skin complaints and the exact mechanism of action in managing DED remains largely unknown. Potential mechanisms include thrombosis of abnormal blood vessels below the skin surrounding the eyes, heating the meibomian glands, activation of fibroblasts, decreasing bacterial load on the eyelids, regulation of anti-inflammatory agents and changes in the levels of ROS [301-304].

IPL, which involves the application of a series of non-coherent polychromatic light to the periorbital region, produces selective photothermolysis of the irradiated tissue, leading to ablation and reduction of telangiectatic blood vessels around the eyelid margin [305].

Since 2017, an increasing number of clinical trials have been conducted to assess the efficacy and safety of IPL. These trials have mostly been aimed at treatment of moderate to advanced MGD. IPL treatments have demonstrated reduced symptoms and signs of DED [306-309], improved optical quality [308], supporting an improved tear film lipid layer [309,310] and reduced dependence on the application of tear supplements [310].

A randomized trial involving 132 participants demonstrated that IPL was more effective for treating DED secondary to MGD than daily use of a traditional warm compress and eyelid gland massage [311]. An RCT of 45 participants assigned them to receive either the combination of IPL and meibomian gland expression or meibomian gland expression alone [312]. The results demonstrated that the combination therapy showed a benefit in lid margin abnormalities, LLT, TBUT and NIBUT, meibomian gland score and ocular surface fluorescein staining score at 24 and 32 weeks, as well as significant improvement in the SPEED score at 32 weeks [312]. Another clinical trial evaluated three sessions of IPL combined with meibomian gland expression compared to a sham, showing an improvement in meibomian gland yielding secretion score and TBUT at one, three and six months, but no difference at nine months [313]. Studies have suggested that IPL is more effective in patients with less severe meibomian gland atrophy [306"] if there is a lower baseline TBUT [314], and in younger patients [315].

Several systematic reviews have appraised the body of evidence for IPL in the management of DED. One included RCTs studying the effectiveness or safety of IPL for treating MGD [316]. Three RCTs included data from 114 adults (228 eyes), with follow-up periods ranging from 45 days to nine months. The authors

concluded that their review found a scarcity of RCT evidence relating to the effectiveness and safety of IPL as a treatment for MGD. In addition, due to a lack of comprehensive reporting of adverse events, the safety profile of IPL in this patient population was also unclear [316]. A systematic review provided data from 11 RCTs published between 2015 and 2021 on 759 participants [317]. The authors reported that IPL had a positive effect on tear stability (evaluated by TBUT and NIBUT) compared with baseline. However, the effect on DED symptoms (OSDI and SPEED) were less clear. Lei and colleagues included 1842 participants from 11 RCTs up to January 2022 [318]. Their results reported that IPL therapy was associated with significantly reduced OSDI and SPEED scores and that both TBUT and NIBUT significantly increased, but corneal fluorescein staining was unaffected [318]. The most recent systematic review published to date reported on studies up to March 2022, and included 13 studies on 931 participants [319]. The results demonstrated that TBUT and OSDI scores improved significantly post intervention, but that corneal fluorescein staining and SPEED scores showed no statistically significant difference from baseline. They concluded that current evidence indicates IPL as a possible adjunctive treatment in individuals with DED, but that further studies through more extensive trials are needed to validate this finding and elucidate its mechanism of action [319].

IPL treatment typically targets the skin below the lower eyelids and both temporal areas, excluding the upper eyelid [320]. In a prospective trial, 30 participants had standard IPL treatment, with half randomly assigned to receive additional IPL treatment on the upper eyelid [320]. While dry eye symptoms improved in both groups, participants who received additional upper eyelid treatment showed a greater improvement and patient satisfaction remained high [320].

In IPL treatment, the penetration depth and selective chromophore targeting can be adjusted using specific filters and fluences. In a study involving 40 participants [321], IPL treatment was randomly administered using more power in one eye (560 nm and 16 mJ/cm^2 versus 590 nm and 14 mJ/cm^2). There was no significant

difference in therapeutic efficacy and patient satisfaction, but less discomfort was reported by the group treated with the shorter wavelength and higher energy filter. Another prospective, randomized paired eye trial found a cut-off (590nm filter) and a notch (acne) filter both similarly improved ocular surface parameters, meibomian gland function, and subjective symptoms [322]. A comparison of an IPL device using three treatments of „optimal pulse technology" (with no pulse spike) compared to four treatments of „intense regulated pulsed light (regulated train pulses) found that while both devices improved signs and symptoms for three months, the former performed better in enhancing the meibomian gland function in the lower eyelids and in improving some tear film metrics [323]. However, it should be noted that this study lacked a control group, and the follow-up period was relatively short.

Studies have analyzed changes in cytokine levels following IPL treatment. One RCT involving 13 participants [324] found those treated with IPL combined with meibomian gland expression exhibited greater reductions in IL-6, IL-6R, IL-1b, IL-13, and CCL11/Eotaxin than those using warm compresses combined with meibomian gland expression. Both groups showed a significant decrease in all tear cytokine levels compared to baseline.

In addition to patients with MGD, studies have demonstrated that patients with blepharokeratoconjunctivitis [325], Sjögren disease [326], glaucoma-related DED [327], refractive surgery-induced DED [328], graft-versus-host disease [329] and neuropathic pain [330,331] can all benefit from IPL treatment.

In addition to treatment with IPL alone, various studies have reported positive responses from combination treatments for patients with DED. These include the use of IPL in combination with 0.05% CsA [332], diquafosol [333], doxycycline [334], blood extract eyedrops [330], thermal pulsation [335,336], heated eye masks [337,338], and microblepharoexfoliation [339].

Several companies now manufacture IPL instruments, and it is important to consult the user manual and individual company for any precautions inherent to each specific instrument. IPL is generally contraindicated in pregnant or breastfeeding women, those wearing a pacemaker or cardiac defibrillator, patients with diabetes, epilepsy or hemophilia, recent or planned radiation or chemotherapy, patients with a dark skin color (Fitzpatrick scale Type VI), previous history of sunlight allergy, recent exposure to tanning procedures (creams, tanning beds) and those using photosensitizing treatments such as doxycycline and tetracycline [340]. IPL should be avoided in young children and those with anterior uveitis or glaucomatocyclitic crises [341]. Caution should be taken with those with active skin infections or inflammation (eczema), tattoos, permanent eye makeup, cold sores, open lacerations or abrasions in the treatment zone. Cosmetics/creams should be removed prior to the procedure and moles/nevi in the treatment zone should be covered. Instrument-specific eye covers/shields/goggles should be used during the procedure for the patient and appropriate UV-filtering protective eyewear for the examiner. A sign or other identifier should be displayed outside the room to signal when the instrument is being used to avoid unintended light exposures for others as the light intensity is very bright. A report has shown preliminary positive outcomes of using IPL directly on the eyelids, under carefully controlled conditions, without a protective eye shield [342]. However, this remains to be investigated with other IPL instruments or protocols. This list of precautions is not exhaustive, and the literature is lacking a well-defined list of contraindications and precautions for IPL.

In conclusion, most studies investigating the use of IPL to treat patients with MGD-related DED have demonstrated improved symptoms and signs, although the degree of efficacy and its duration varied greatly depending on concomitant treatment, and the number of treatment sessions. In addition, there can be differences between instruments and the algorithms used. There is still a need for independent, large, randomized, controlled long-term studies to define the

most efficacious treatment regime and to predict which patients may benefit the most.

6.3.1.2.3.2 Low-level light therapy (LLLT: Red light)

Low-level light therapy (LLLT) is the application of low-power, high-fluence monochromatic or quasi-monochromatic light from light-emitting diodes through a wide array of wavelengths (e.g., red, yellow, blue). LLLT is believed to work via the process of photobiomodulation [343], which is a non-thermal biological process activated by specific wavelengths of light via photoacceptor molecules, to induce a cascade of physiological events.

In this process, the primary photoacceptor implicated is cytochrome c oxidase, an enzyme in the mitochondrial respiratory chain. When photons are absorbed by this enzyme, it undergoes redox changes, leading to enhanced mitochondrial activity. This results in increased production of adenosine triphosphate, the cell's primary energy currency [344,345]. Additionally, photobiomodulation induces the photodissociation of nitric oxide from cytochrome c oxidase, improving mitochondrial respiration by relieving inhibition caused by nitric oxide [346,347]. This process also generates ROS at controlled levels, which act as secondary messengers to activate signaling pathways [348]. Together, these mechanisms are believed to contribute to LLLT's therapeutic benefits, including accelerated tissue healing, pain relief, and anti-inflammatory effects. By carefully controlling parameters such as wavelength, intensity, and energy dose, photobiomodulation can precisely modulate cellular responses without causing harm to the tissue [343,346,348,349].

This type of photobiomodulation had its beginnings in dermatology and is now also demonstrating efficacy in lid diseases that contribute to DED and other inflammatory conditions of the ocular surface and periocular area. The limited studies that have investigated the efficacy of LLLT as a stand-alone treatment have used varying devices, light parameters and clinical protocols, although the

majority within the ophthalmology literature have employed the eye-light® (Espansione Group, Bologna, Italy) device [350-354]. One review suggested that, at the time, there was a lack of clear evidence demonstrating that LLLT alone is beneficial in the management of MGD [355].

A randomized clinical trial of LLLT twice a week for three weeks compared to a sham (n=20 in each group) showed better results with respect to fluorescein and lissamine green ocular surface staining, Schirmer test, and upper lid meibomian gland drop out scores, but not TBUT, lid swelling, lid telangiectasia, meibomian gland secretion, and expressibility scores [350]. Thirty participants with mild-to-moderate DED underwent three applications of LLLT for 15 mins with the eye-light® device at each visit over three weeks [354]. Treatment with LLLT resulted in significant differences in NIBUT, TMH, tear film LLT, OSDI score, Schirmer test score, meibum quality score and eyelid temperature.

A significant difference between LLLT and IPL is that LLLT can be applied directly to the eyelids, unlike IPL. Also, LLLT is unaffected by skin colour and can therefore be applied safely to all skin types. A randomized clinical trial comparing LLLT and IPL (n=20 in each group) found both treatments to be effective in alleviating ocular discomfort symptoms and safe, although LLLT resulted in a more significant improvement in symptoms and an increase in tear volume [351].

Several studies have combined the effect of IPL with LLLT using the eye-light® device in participants with MGD [356-360]. In a multicenter retrospective chart review, researchers evaluated the effects of combined IPL and LLLT therapy delivered with the eye-light® device on 460 eyes of participants who were unresponsive to other medical management for MGD [360]. Combined treatment was applied in intense short pulses on the area of the face near the eye. This was followed by longer exposure to low-level red light on the cheek and over the closed lids. Two to four treatments were applied one to two weeks apart. Following the combined treatment, mean OSDI scores were significantly lower. In

addition, a one-step or greater reduction in MGD grading was found in 70% of eyes, and 28% of eyes had a two-step or greater reduction and TBUT also improved. Prior to treatment, TBUT was ≤6 seconds in 86.7% of eyes, versus 33.9% of eyes after treatment [360].

More research is needed to fully understand the long-term efficacy of LLLT and optimal treatment protocols, and it is often considered most effective when combined with other treatments for DED. More work is needed to determine the relative contributions to the benefits of LLLT from photobiomodulation and from other possible mechanisms, such as the heat generated by the light-emitting diode array in the treatment device [355].

6.3.1.2.3.3 Plasma treatment

Plasma treatment for evaporative DED secondary to MGD involves plasma application directly onto both the upper and lower eyelids [361]. This technology produces mobile ions from atmospheric gas, to transform the superficial layers of the target tissue from a solid form to a gaseous state at low temperatures [362]. To date, little evidence is available on its efficacy for the management of DED. A single cohort study with 20 participants with MGD and no control group reported an improvement in symptoms relative to baseline (although no statistics were presented), but no sustained benefit in tear film stability or volume [361].

6.3.1.2.3.4 Quantum Molecular Resonance Electrotherapy

Quantum molecular resonance is a technique in which a low intensity high frequency electric current is administered to a specific biological tissue. In vitro studies have shown that electrical stimulation („electrotherapy") can increase cell migration and proliferation [363]. There are several studies of its use in participants with DED [364-369].

A case series in participants with mixed DED using the standard protocol of a 20-minute session per week for four weeks showed improvements in OSDI, NIBUT, corneal staining and meibomian gland parameters, in addition to a reduction in

matrix metalloproteinase-9 (MMP-9) levels [367]. In addition, it has also been found to be effective in the management of DED participants exhibiting MGD [364]. More recently it has been shown to be effective in treating patients with recalcitrant DED [365]. However, the follow-up for this study was limited at only two weeks post treatment. A double-blind RCT in an academic medical center for two years was conducted in which 40 participants (20 per arm) received treatment or placebo with the quantum molecular resonance device, once per week for four weeks [369]. The mean OSDI score significantly improved in the intervention group, whereas the control group showed no significant change. MGD scores and corneal staining significantly improved in the intervention group only. No significant difference was seen in TBUT, visual acuity, and Schirmer scores between the test and control groups.

More research is needed to understand the true value of this technique, with randomized trials conducted over extended periods of time.

6.3.1.2.3.5 Radiofrequency

Radiofrequency is an electromagnetic wave that uses an oscillatory field to charge particles within the target tissue, generating heat through friction between vibrating tissue particles [370]. A pilot study involving 10 participants with MGD compared LipiFlow with ThermaLid® radiofrequency (Pellevé wrinkle reduction system, Ellman International, UK) [370]. After three months of treatment, they had similar efficacy in improving meibomian gland expression, wax plugging score, SPEED, and OSDI scores. The Marx line score decreased after three months in the radiofrequency group, but neither group showed improvements in NIBUT, corneal staining, tear osmolarity, or Schirmer score. Additionally, a cohort study of 31 participants that combined radiofrequency with IPL and meibomian gland expression demonstrated significant improvements in the signs and symptoms of MGD, but there was no control group [371].

Currently, there is no strong evidence that supports the use of radiofrequency for the treatment of DED and more studies, especially RCTs with larger groups and for longer follow-up periods, are needed to better understand how this technology works and how it fits into the management of DED.

6.3.1.2.3.6 Thermo-mechanical skin treatment

Thermo-mechanical fractional skin treatment (Tixel, Novoxel, Israel) is a novel therapy approved by the FDA in 2021 for cosmetic use in the field of dermatology [372]. Periorbital treatment involves the application of a 400°C titanium-tipped handpiece comprising a matrix of 24 pyramid-shaped protrusions, that transiently contacts the skin for between five and 18 milliseconds, over an area of 0.3cm^2. Device application has been reported to reduce the appearance of periorbital rhytides (wrinkles), and signs of acne rosacea, hemangiomas and scarring, in addition to having the potential to facilitate transdermal drug delivery [372]. Its application as a non-ablative treatment in evaporative DED has been explored in studies with positive outcomes in terms of safety and efficacy although, to date, only in open-label studies [373,374]. A manufacturer-sponsored prospective, investigator-masked study of the Tixel thermo-mechanical treatment described comparable clinical outcomes to thermal pulsation therapy [375].

Of note, a recent industry-supported study reported statistically and clinically significant changes in spectacle refraction, with the most marked changes observed in participants with more severe DED [376]. On this basis, the authors caution users if the treatment is to be applied prior to biometric assessment for refractive surgery [376].

6.3.1.3 Lid margin treatments

6.3.1.3.1 Intraductal meibomian gland probing

Intraductal meibomian gland probing involves the introduction of a stainless-steel, non-sharp probe (76 µm in diameter and lengths of 1, 2, 4 or 6 mm) into

the obstructed meibomian gland to forcefully remove or dislodge the obstructed material and promote meibum secretion [377]. As the probe enters the orifice towards the central duct of the meibomian gland, an audible „pop" may be heard when resistance is encountered. Since the TFOS DEWS II Management and Therapy Report [2], more studies using this procedure for the treatment of MGD have been reported, including three RCTs, as well as retrospective and/or non-randomized studies.

A prospective study with 58 eyes from 30 MGD participants had intraductal meibomian probing undertaken using a modified technique, receiving one to four probing procedures during the study [378]. All participants were prescribed additional treatments, which included topical antibiotics, corticosteroids, tear supplements, warm compresses and eyelid massage. At three months post treatment, significant improvements in TBUT, conjunctival hyperemia, lid margin vascularization and OSDI scores were observed. However, it is difficult to differentiate the impact of the probing from the additional treatments.

A retrospective chart review of 108 consecutive participants with obstructive MGD, representing 11,776 glands, noted that 84% showed mechanical resistance [379]. However, the clinical relevance of this resistance and its relation to gland expressibility has yet to be fully elucidated.

A retrospective review of video recordings of meibography-guided intraductal probing using a 1 mm probe from 38 lower lids have addressed some of the concerns surrounding the invasive nature of this technique and its potential for damage to the delicate structure of the meibomian glands [380]. Recordings revealed that 99.9% of the glands (996/997) were successfully probed and 91.8% revealed the location of the probe. A different study used *in vivo* confocal microscopy to retrospectively study the duct microanatomy of meibomian glands, post probing [381]. Thirty-six glands from the upper lids of MGD participants (n=16) revealed an increase in basement membrane, duct wall (layers and thickness)

and lumen area compared to MGD controls (n= 4) who did not receive probing. The authors propose that the procedure stimulates an epithelial regenerative process, although further research is needed to understand the mechanism of action and which factors direct this process.

A review of the literature in 2020 resulted in 14 studies that were identified, with most (10/14) lacking a control group [382]. The intraductal probing procedure was found to be “safe”, with no major post-operative complications. However, bleeding (dot hemorrhages) of the eyelid and gland orifices were frequent, but self-limiting. Tear breakup time was the most common reported objective measure and showed improvement in most studies, except in the only randomized sham-control trial [383], which found no difference. Some studies had adjunctive therapies (antibiotics, steroids, IPL) potentially confounding the results for TBUT. Corneal staining was also reported (5/14 studies) as an outcome measure, but similarly to TBUT, adjunctive treatments were reported, making for unclear interpretation. The inventor of the procedure disagreed with the conclusions of this review and wrote a rebuttal letter on some of the conclusions reached [384].

Three RCTs have been published on intraductal gland probing in recent years. Intraductal probing in addition to conventional treatments (tear supplements, warm compresses, eyelid massage, lid hygiene, topical antibiotics, omega-3 supplements and oral azithromycin) showed better outcomes (OSDI score, Schirmer test, TBUT and Oxford grading) than conventional treatments alone over 90 days, except for meibum expressibility [385]. A study with 90 eyes from 45 obstructive MGD participants separated into three groups; an IPL group (three treatments at three week intervals); a group who received a single intraductal probing; and a group who received probing followed by IPL [386]. All groups showed improvement, however the probing-IPL group had better outcomes (SPEED score, TBUT, corneal staining, meibum grade) than either of the other two groups at relieving signs and symptoms. The only double masked RCT that

did not include an additive treatment revealed that intraductal probing had significant improvement for symptoms, but failed to show improvement in clinical signs over placebo [383].

In conclusion, intraductal meibomian gland probing appears, on the basis of relatively short-term outcomes, to be a procedure with self-limiting adverse events. Prospective RCTs are needed to obtain a better understanding of its mechanism of action in improving symptoms, signs, meibomian gland ductal integrity and meibum expressibility without concurrent treatments. Meibography-guided intraductal probing may provide an added value in the management of obstructive MGD, with larger scale studies and long-term evaluation of gland structural integrity.

6.3.1.3.2 Lid margin debridement

Meibomian gland blockage is primarily caused by the buildup of keratinized material around the eyelid margin and duct openings [167,227]. This buildup can obstruct the gland, preventing the release of meibum into the tear film. Debridement of the eyelid margin physically removes accumulated debris and keratinized cells from the surface of the lid margin, thereby encouraging improved outflow of meibum from the glands and into the tear film [387]. Two, one-month RCTs reported improvements in symptoms and meibomian gland secretion with debridement relative to control, untreated participants [387,388].

A novel, multi-modal thermal device (MGrx, OcuSci®, Inc, CA, USA) has been developed to facilitate thermal lid debridement, thermal lid massage, and thermal gland expression. A study was undertaken that included 37 adult participants with MGD and DED in an open-label treatment with the MGrx [389]. A statistically significant improvement in SPEED score, TBUT, and meibomian gland score for both eyes was noted after the treatment. No adverse reactions were noted in this small cohort. A subsequent RCT found a similar improvement in symptoms from conventional and MGrx treatment, but clinical signs were not improved [390].

A retrospective case series study reported that combining lid margin debridement with microblepharoexfoliation (BlephEx®; RySurg, Fort Worth, FL, USA) and meibomian gland expression resulted in improvements in clinical outcomes, subjective symptoms, meibomian gland function, and ocular surface MMP-9 levels [391]. However, there remains a lack of prospective studies with sham treatments and double masking.

6.3.2 Restoration or stimulation of aqueous

6.3.2.1 Topical secretagogues

6.3.2.1.1 Diquafosol tetrasodium

3% Diquafosol ophthalmic solution has a novel mechanism of action involving the stimulation of both aqueous and mucin secretion [392]. It is a P2Y2 purinergic receptor agonist that activates P2Y2 receptors on the ocular surface. Diquafosol stimulates both fluid secretion from the conjunctival epithelial cells and mucin secretion from the conjunctival goblet cells directly on the ocular surface, by an interaction with the P2Y2 receptors [392,393].

Multiple, long-term studies have been undertaken on this class of topical medication (Table 3). A meta-analysis of 14 RCTs indicated that, relative to participants treated with other topical drops, such as tear supplements or HA-based products, application of 3% diquafosol drops was associated with significantly better improvement at four weeks in terms of TBUT, Schirmer score, corneal fluorescein staining score and Rose Bengal conjunctival staining [394]. No discernible difference was apparent in terms of OSDI symptom score [394].

In a group of participants (n = 47) with MGD, one drop of tear supplements or one drop of diquafosol was applied randomly to the eyes of each patient [395]. Diquafosol significantly increased LLT and NIBUT for at least 90 mins, whereas

tear supplements had no such effect. These results suggest that diquafosol may be a potential treatment not only for aqueous-deficient DED but also for evaporative DED associated with MGD.

Table 3: Prospective interventional studies examining the efficacy and safety of Diquafosol

Study	Type of participants	Treatment	Product comparator	Sample size	Duration	Randomized	Outcomes showing improvement	No significant differences from comparator
Miyake and Yokoi, 2017 [396]	4 weeks post-cataract surgery	Diquas 3%	Artificial tears	433	1 month	Yes	TBUT Total symptom score	Corneal staining Conjunctival staining
Shimazaki et al, 2017 [397]	Computer users DED	Diquas 3%	Rebamipide	67	2 months	Yes	Satisfaction score	DEQS TBUT NIBUT Corneal staining
Cui et al, 2018 [398]	DED post-cataract surgery	Diquas 3%	0.15% HA	94	3 months	No	OSDI TBUT Goblet cell density	ST
Kaido et al, 2018 [399]	Short TBUT DED	Diquas 3%	Artificial tears	27	5 weeks	No	Corneal sensitivity TBUT	TMH
Jun et al, 2019 [400]	DED post-cataract surgery	Diquas 3% preservative free	a) Diquas 3% preserved b) 0.15% HA	117	3 months	No	TBUT MGD grade meibum quality	OSDI Corneal staining

Fukuoka & Arita, 2019 [395]	DED with MGD	Diquas 3%	Artificial tears	47	90 mins	Yes	NIBUT LLT	
Ji et al., 2019 [401]	DED	Diquas 3%	CsA 0.05%	18	1 month	No	Tear proteome	OSDI TBUT ST Corneal staining Conjunctival staining
Kim et al, 2021 [402]	DED post-cataract surgery	Diquas 3%	0.15% HA	56	15 weeks	Yes	LLT TBUT	OSDI ST
Eom & Kim, 2021 [403]	DED	Diquas 3%	CsA 0.1% or combination	279	3 months	No	TBUT	SANDE DEQS Corneal staining Conjunctival staining
Yamazaki et al, 2022 [404]	Post-Femto cataract surgery	Diquas 3%	Saline	20	2 weeks	Yes	TBUT	TMH DEQS ST Corneal staining
Jung et al, 2023 [405]	DED	Diquas 3%	CsA 0.1% CsA 0.05%	80	3 months	No	Tear proteome	SANDE TBUT Conjunctival staining
Wang et al, 2023 [406]	Femtosecond LASIK	Diquas 3% + 0.15% HA	0.15% HA	40	1 month	No	OSDI TBUT LLG Bulbar redness	NIBUT SRI

							Limbal redness	
Kaido & Arita, 2024 [407]	DED	High viscosity Diquas 3%	Conventional Diquas 3%	66	1 month	No	Questionnaire Corneal staining TBUT	
Arita et al, 2024 [408]	DED	High viscosity Diquas 3%	Conventional Diquas 3%	341	3 months	No	SPEED TBUT TMH Corneal staining ST	

CsA: cyclosporine; DED: dry eye disease; DEQS: Dry Eye-Related Quality-of-Life Score; Femto: femtosecond laser; HA: hyaluronic acid; LASIK: laser in-situ keratomileusis; LLG: lipid layer grade; LLT: lipid layer thickness; MGD: meibomian gland dysfunction; MMP-9: matrix metalloproteinase-9; NIBUT: non-invasive breakup time; OSDI: Ocular Surface Disease Index; SANDE: Symptom Assessment in Dry Eye questionnaire; SMILE: small incision lenticule extraction; SPEED: Standard Patient Evaluation of Eye Dryness; SRI: surface regularity index; ST: Schirmer test; TBUT: tear breakup time; TFLL: tear film lipid layer; TMH: tear meniscus height

6.3.2.2 Oral secretagogues

An early body of literature described the use of oral pilocarpine and cevimeline for the treatment of DED, specifically in patients with Sjögren-related DED [2]. Pilocarpine and cevimeline are both cholinergic agonists, which act as an acetylcholine-mimicking neurotransmitter and as a targeting-selector for muscarinic receptors M1 to M3.

Since the TFOS DEWS II Management and Therapy report [2], most of the studies on oral secretagogues have involved participants with Sjögren disease, due to the medication targeting the salivary glands. A placebo-controlled crossover study involving 5mg of pilocarpine, taken orally four times a day, reported improvements in OSDI score, along with increased NIBUT and fluorescein TBUT and Schirmer scores, and improved ocular surface staining and tear ferning test grades in patients with DED. However, there was a high percentage of drug-induced side effects [409].

Oral administration of secretagogues results in simultaneous stimulation of muscarinic receptors on other exocrine glands and can result in increased sweating, salivation, frequency of urination, flushing, paraesthesia and myalgia [409-412]. Other side effects not reported in published clinical trials but reported on national formularies (such as National Institute for Health and Care Research; NIHR) include diaphoresis, nausea, bradycardia, bronchospasm and diarrhoea, headaches and vision disorders.

6.3.3 Restoration or stimulation of mucin

A number of pharmacological agents seek to act by increasing tear mucins.

6.3.3.1 Diquafosol tetrasodium

As described previously (see Section 6.3.2.1.1), Diquafosol is reported to stimulate mucin production on the ocular surface [392,393].

6.3.3.2 Rebamipide

Rebamipide (2-(4-chlorobenzoylamino)-3-[2(1H)-quinolinon-4-yl]propionic acid; OPC-12759), a mucosal protective agent, has been used to treat gastritis and stomach ulcers via oral administration. Rebamipide has also been shown to stimulate COX2 and production of prostaglandins, scavenges oxygen radicals, suppress proinflammatory cytokines and functions as an anti-inflammatory drug in both acute and chronic mucosal inflammation [413]. Although this drug has been found to increase the number of goblet cells in the conjunctiva, the exact mechanism at the molecular level and the nature of the cellular receptor remain unknown [414].

Several clinical trials on the use of rebamipide have been reported (Table 4). In studies, 1% and 2% rebamipide DED groups had greater improvements than placebo in TBUT, corneal staining score and Schirmer scores, but not in OSDI score [415]. In a randomized, controlled, double-masked study, participants with digital eye strain treated with 2% rebamipide showed significantly reduced corneal staining and nasal bulbar conjunctival redness scores compared to those treated with topical 0.1% HA drops for four weeks, although improvements in OSDI, the 5-item Dry Eye Questionnaire, TBUT and conjunctival staining scores were similar across the two groups [416]. A systematic review of the use of rebamipide in the management patients with DED included seven papers [417]. It was noted that the majority of the studies were company sponsored. Rebamipide outperformed the control group for total corneal fluorescein staining, Schirmer test without anesthesia, TBUT and dry eye-related quality of life score. A more recent systematic review and meta-analysis produced similar findings [418].

Table 4: List of comparative trials for rebamipide

Study	Type of participants	Treatment	Product comparison	Sample size	Duration	Randomized	Outcomes showing improvement	No significant differences from comparator
Kinoshita et al, 2013 [419]	DED	Rebamipide 2% 4-6 times a day	0.1% HA 4-6 times a day	188	4 weeks	Yes	Conjunctival staining Some symptoms	Corneal staining Schirmer's test TBUT Some symptoms
Igarashi et al, 2015 [420]	DED after corneal refractive surgery	Rebamipide 2% qid	Artificial tears qid	60	4 weeks	Yes – no direct comparison	Schirmer score, TBUT Corneal staining Ocular scatter index Some symptoms	Some symptoms
Kobashi et al, 2017 [421]	DED after penetrating keratoplasty	Rebamipide	Diquafosol	40	4 weeks	Yes	-	TBUT Corneal staining Symptoms
Shimazaki et al, 2017 [397]	DED in computer users	Rebamipide 2% qid	Diquafosol 3% 6 times a day	79	8 weeks	Yes	-	Symptoms TBUT
Eom et al, 2023 [415]	DED	Rebamipide 1%	Placebo (vehicle)	220	12 weeks	Yes	Symptoms Corneal staining (wrt 2%)	TBUT Schirmer

		2% qid	qid					Corneal staining (wrt 1%)
Jain et al, 2023 [422]	DED	Rebamipide 2% qid	0.5% CMC-based lubricant qid	80	12 weeks	Yes	** Only category analysis was conduced	TBUT Schirmer Corneal and conjunctival staining
Lee & Han, 2024 [416]	DED in computer users	Rebamipide 2% qid	0.1% HA qid	56	4 weeks	Yes	Corneal staining	Symptoms TBUT Conjunctival staining

CMC: carboxymethylcellulose; DED: dry eye disease; HA: Hyaluronic acid; OSDI: Ocular Surface Disease Index; qid: four times a day; TBUT: tear breakup time; tid: three times a day

6.3.4 Neuromodulation / neurostimulation

Stimulation of tear film production is driven by environmental stimuli detected by sensory afferent nerves of the cornea and conjunctiva, as well as parasympathetic nerves found in the nasal cavity. Once activated, these sensory nerves relay this environmental information via action potentials through the trigeminal nerve, triggering an efferent parasympathetic response that orchestrates increased activity of the secretory glands of the lacrimal functional unit (lacrimal glands, meibomian glands and goblet cells) [36,423-426]. Neuromodulation as a treatment for DED is based on stimulating these sensory nerves to activate trigeminal nerve signaling, which leads to an increase in basal tear production that is not solely related to an increase in the aqueous component of the tears [423,425-430]. Such modulation can be accomplished through mechanical, electrical pressure/vibration or pharmacological means.

6.3.4.1 Device-driven neuromodulation

6.3.4.1.1 Nasal electrochemical stimulation

Neurostimulation through the nasal cavities has been achieved by transcutaneous electrical stimulation of the mucosa and anterior ethmoidal branch of the trigeminal nerve, which triggers nasolacrimal reflex tear production.

The FDA-approved a device for intranasal stimulation (TrueTear® Intranasal Tear Neurostimulator), but the product was discontinued in 2020 [425]. However, examination of the results from various studies examining the impact of this concept provides useful information on this potential method to manage DED. Two intranasal tips were inserted into each nasal cavity and, by means of a low-level electrical current, the tips vibrated while in contact with the intranasal tissue. An RCT comparing intranasal vs extranasal stimulation (control), found that three minutes after one intranasal stimulation session, aqueous production (measured via TMH and tear meniscus area) and conjunctival mucin-producing goblet cell density (via impression cytology) were increased compared to baseline, for both

DED and non-DED participants [431]. In a study with very similar methodology, following a three minute-treatment delivery, dryness and ocular discomfort scores were significantly reduced five minutes post-treatment [432]. Another RCT compared active and sham intranasal stimulation applied between four to eight times a day, for durations of between 30 seconds and three minutes in participants with DED [433]. Reviewed at days 0, seven, 14, 30 and 90, acute tear production (Schirmer test score) was significantly higher in the active stimulus group than sham, across all time points. The acute response to stimulation for the active group was highest at the early timepoints, around triple that of sham, but then declined to around twice the sham response by day 14 and remained consistent throughout the remainder of the study. At day 90, mean corneal and conjunctival staining scores showed some decrease from baseline, similarly in both active and sham groups, whilst the reported pain score was significantly decreased only in the active treatment group [433]. Nosebleeds, an electrical stinging sensation, nasal discomfort, headache, eyelid irritation, rhinorrhea (runny nose) and sensitive teeth were some of the events noted with the use of this device, most of them being transient in nature [432-434]. Improved Schirmer scores with intranasal stimulation versus external stimulation have also been noted following a three-minute treatment in participants with Sjögren disease, [435].

External therapy aims to stimulate the external branch of the anterior ethmoidal nerve. A multicenter, open-label, single-arm clinical trial of external nasal stimulation for 30 seconds, on each side of the nose, at least twice a day using a new, novel device (iTear® 100) on 101 participants found OSDI scores decreased from day 14 to 30. Schirmer scores increased from day 14 and remained elevated until the end of the study on day 180. There were no serious adverse events reported [436].

6.3.4.1.2 Transcutaneous electrical stimulation

High and low transcutaneous electrical nerve stimulation is a non-pharmacological therapy aimed at activating peripheral nerve pathways directly,

to block, change or correct pain perception. This therapy delivers alternating current via cutaneous electrodes placed proximal to the terminal cutaneous trigeminal nerve branches on the forehead and temple. The afferent electrical input arrives to the central nervous system, activating descending inhibitory systems to reduce hyperalgesia and releasing endogenous opioids [427,437]. Electrical stimulation is considered of potential benefit in modulating pain sensation in difficult-to-treat patients, such as those who exhibit “pain-without-stain”, neuropathic patients, photophobia and other chronic pain conditions that may be associated with ocular hyperalgesia [438-440].

An RCT in 45 participants comparing HA-containing tear supplements with or without transcutaneous electrical nerve stimulation found greater improvements in symptomatology, TBUT, Schirmer scores and corneal staining after four weeks of treatment with the stimulated group; no serious adverse events were recorded [441]. In another study of 27 participants, reduced OSDI scores and increased Schirmer scores were maintained after 12 months, and the improvements in TBUT and ocular staining score were still evident six months later [442].

6.3.4.2 Pharmacological neuromodulation

6.3.4.2.1 Acoltremon

Acoltremon (Alcon, Ft Worth, TX, USA) is a potent and highly selective TRPM8 agonist, and acoltremon ophthalmic solution 0.003% (formerly AR-15512) is under clinical evaluation for the treatment of the signs and symptoms of DED.

Members of the superfamily of transient receptor potential (TRP) channels are cation-permeable, plasma membrane ion channels that respond to a wide range of stimuli [443]. Expressed on corneal thermosensory neurons innervating the cornea and upper eyelids, TRPM8 ion channels are stimulated by small reductions in temperature and hyperosmolarity, such as occurs during evaporative cooling and corneal drying [423,443-445]. Stimulation of TRPM8, in turn,

activates the cold thermosensory neurons, leading to increased signalling through the trigeminal nerve and stimulation of basal tear production [445,446].

There has been one comparative clinical trial conducted with acoltremon [447]. In this RCT of 0.0014% and 0.003% AR-15512 compared to its vehicle, evidence of both symptom and sign efficacy was observed as follows: improved ocular discomfort score (at day 84) and also an improved global SANDE score (days 14, 28 and 84), increased tear production (unanesthetized Schirmer score and TMH, at days one and 14), reduced conjunctival redness (day 84) and improved ocular surface staining scores (days 14 and 84) with the 0.003% dosage. Mild adverse events were reported (instillation burning/stinging). There were no significant differences between active and vehicle groups for the co-primary endpoints, which were changes from baseline in ocular discomfort (ODS-VAS) and anesthetized Schirmer score at Day 28 [447].

6.3.4.2.2 Cryosim-3

Cryosim-3 (C3, 1-diisopropylphosphorylnonane) is a water soluble selective TRPM8 agonist. Topically applied to the upper eyelid surface, it may reduce discomfort by activating the TRPM8 receptor, which then elicits the sensation of cooling. In a randomized double-masked study comparing C3 (dissolved in 2mg/mL of distilled water) to vehicle, the intensity of symptoms decreased from five to 16 minutes after application, tear secretion increased at 20, 40 and 60 minutes and TBUT increased after 30 and 40 minutes with C3 compared to vehicle. An improvement in symptoms at two weeks after application was also reported [448]. A pilot study, where the participants were treated with C3 four times/day for one month, found similar results, with increased Schirmer scores and decreased ocular pain assessment survey scores at the end of the treatment period [449]. It is not currently in any active clinical trials as per publicly available information.

6.3.4.2.3 Varenicline

Varenicline (OC-01) is delivered in the form of an intranasal spray, with a therapeutic mechanism that targets nicotinic acetylcholine-receptors within the nasal cavity. Trigeminal nociceptors on the nasal mucosa and ocular surface form the start of the afferent arm that controls the production of tears. Nicotinic acetylcholine receptors on nasal nerve endings trigger an automatic reflex arc that causes endogenous tears to be secreted when triggered by pharmacologic nasal neural stimulation [426]. The nasal spray (Tyrvaya®; Oyster Point Pharma, NJ, USA) is FDA-approved to treat the signs and symptoms of DED. When the intranasal spray stimulates the receptor, it activates the trigeminal nerve pathway eliciting a lacrimation response.

In an effort to examine the effect of varenicline on conjunctival goblet cells, a phase 2, single-center, vehicle-controlled study examined 18 subjects with DED [450]. Subjects were randomized 2:1 to receive a 50µl dose of OC-01 0.06 mg or vehicle via a nasal spray in each nostril. OC-01 treatment decreased mean goblet cell area and perimeter, whereas the vehicle had no effect. This study demonstrated that a single administration of OC-01 in patients with DED reduced conjunctival goblet cell area and perimeter, suggesting goblet cell degranulation and associated release of lubricating mucin [450].

A randomized trial evaluating varenicline efficacy at different concentrations compared with a buffered saline found a dosage of 0.03 mg, administered twice a day resulted in a significant reduction in an eye dryness score by day 28 [451]. A second study from the same authors reported an effective increase in Schirmer score over a 12-week period, when using 0.03mg of varenicline [451]. Similar results have been found by other authors when using a 0.06mg concentration [452,453].

In Phase III clinical trials, varenicline OC-01 improved mean Schirmer scores and symptoms to a comparable or higher degree than lifitegrast, as reported in an

indirect comparison [454]. Varenicline was reported to be well tolerated and had an overall patient study completion rate of >93% [455]. However, almost all participants receiving OC-01 sneezed at least once during treatment (93.8% for OC-01 0.03 mg, 95.9% for OC-01 0.06 mg, and 28.3% for vehicle). Most sneezing (84.5% for OC-01 0.03 mg and 81.3% for OC-01 0.06 mg) occurred within the first minute after administration [456].

A systematic review and meta-analysis of the efficacy and safety of varenicline nasal spray for the management of DED versus placebo included three RCTs (n=1063 participants) [457]. There was a significant increase in mean Schirmer test result from baseline on day 28 and no significant difference between varenicline and placebo in the frequency of ocular adverse events. However, varenicline did have a significant effect on developing nasal cavity-related adverse events (cough and throat irritation). A more recent systematic review included eight studies [458]. Varenicline nasal spray achieved greater improvement than vehicle for eye dryness score, Schirmer test and total corneal fluorescein staining.

Table 5 details key contemporary clinical trials on varenicline.

Table 5: Comparative clinical trials of varenicline

Study	Type of participants	Treatment	Product comparison	Sample size	Duration	Randomized	Outcomes showing improvement	No significant differences from comparator
Dieckmann et al, 2022 [450]	DED	OC-01 0.06mg Once	Vehicle nasal spray	18	Single spray	No	Decreased conjunctival goblet cell area and perimeter	Meibomian gland area
Quiroz-Mercado et al, 2022 [452]	DED	OC-01 0.03 mg 0.06 mg bid	Vehicle nasal spray bid	123	12 weeks	Yes	Schirmer	-
Torkildsen et al, 2022 [459]	DED	OC-02 Simpinicline 0.11 mg, 0.55 mg, or 1.1 mg	Vehicle nasal spray	165	Single dose, 5 min post-use	Yes	Symptoms (0.55 & 1.1mg) Schirmer	-
Wirta et al, 2022 [451]	DED	Varenicline OC-01 0.006mg, 0.03mg, 0.06mg bid	Vehicle nasal spray bid	182	4 weeks	Yes	Symptoms (0.03mg) Schirmer test (0.03 and 0.06mg groups.	-
Wirta et al, 2022 [456]	DED	Varenicline OC-01 0.03mg	Vehicle nasal spray	758	4 weeks	Yes	Symptoms Schirmer	-

		0.06mg bid	bid					
Tian et al, 2024 [460]	DED	OC-01 0.6 mg/mL bid	Vehicle nasal spray bid	340	4 weeks	Yes	Symptoms Schirmer	Corneal fluorescein staining

bid: twice a day

7 Treatments for eyelid abnormalities

The eyelids are a critical part of the lacrimal functional unit and appropriate identification, and correction of lid margin abnormalities is an essential part of DED treatment. Since publication of the TFOS DEWS II Management & Therapy Report in 2017 [2], many studies have been published investigating newer treatment strategies for managing lid margin pathology.

These treatments can be grouped into the following broad categories:

1. **At-home treatments** include the use of warm compresses, relatively simple devices [232,235-237,239,241,242,256] and various eyelid wipes [231,461,462]. It should be remembered that warm compresses need to be followed up by lid massage for maximum efficacy.

2. **In-office procedures** include IPL [230], vectored thermal pulsation [282], low-level light therapy [351], microblepharoexfoliation [463], thermo-mechanical treatment [373,374], portable 445nm laser [464], various manual methods of heat-delivery to the lids and meibomian glands [240,285,289], intraductal probing [382,465] and manual meibomian gland expression [466].

3. **Pharmacological agents** such as lotilaner [467,468] and ivermectin-metronidazole gel [469]. These products target parasitic blepharitis and may improve patient symptoms and tear film and ocular surface parameters. Other pharmacological strategies for MGD management undergoing regulatory clinical trials include selenium sulfide [271] and azithromycin [470].

Evidence surrounding use of these therapies in the clinical setting are described according to disease presentation, below.

7.1 Blink and lid closure anomalies

Methods to optimise blinking, both frequency and completeness, are some of the simplest forms of management to recommend for managing DED, but perhaps one of the more difficult to execute. Web-based platforms and software programs exist to monitor blink rates when using digital devices and remind patients to blink appropriately [471].

7.1.1 Inadequate lid seal / lagophthalmos

Lagophthalmos refers to the inability to fully close the eyelids, while nocturnal lagophthalmos specifically describes this condition occurring only during sleep, meaning the eyes can close normally when awake but not while sleeping [472]. Inability to close the eyes is a major cause of non-responsive DED [473]. A Japanese survey evaluated the prevalence of nocturnal lagophthalmos and sleep quality in 2000 participants [6]. Participants were divided into two groups according to the presence or absence of DED symptoms. Sleep duration in those with DED was significantly shorter and sleep efficacy was worse compared with the non-DED group. Participants who self-reported nocturnal lagophthalmos were more prevalent in the DED group and the study concluded that nocturnal lagophthalmos was associated with worsened DED symptoms and poor sleep quality [6].

Conditions such as floppy eyelid syndrome, surgical cosmetic procedures and chemodenervation injections, lid deformities, Bell‟s palsy, age-related lid laxity, dermatochalasis, senile ectropion, trauma, Grave‟s disease and anatomical abnormalities can all lead to incomplete lid seal or lid closure [472,474]. Lid closure is a fundamental requirement to protect the eye from desiccation at night, especially since tear production is reduced during sleep [475]. Night-time application of ointment for incomplete eye closure is frequently recommended [476], but the benefits have not been formally evaluated.

Despite anecdotal reports, there are no studies on the impact of taping the eyelids at night to seal them closed. Patients‟ tolerability of such treatment may be expected to be limited due to risk of eyelid tissue reactions, the frequent need to navigate to the bathroom at night for older individuals and risk of lash loss upon tape removal. New lid seal products, which are hypoallergenic, latex-free, oxygen-permeable and don‟t stick to lashes have recently become available.

Sleep masks can help to an extent, in so far as they limit environmental conditions from exacerbating desiccative stress by limiting air movement [477]. Moisture goggles may be more useful than sleep masks in this regard since they provide a humid environment while limiting air movement, even when the eyes are not anatomically sealed shut (see Section 6.2.2).

Several studies have investigated the use of bandage soft contact lenses and, in particular, scleral lenses to manage chronic exposure [199,478-484]. As pointed out by Jacobs and colleagues [199], of the many papers reporting on the management of exposure, few mention contact lenses as an option, suggesting that they are a potentially overlooked management strategy.

Thyroid eye disease can also result in exposure due to exophthalmos and lid retraction [13,476,485-487]. A study of conservative management (lubrication with tear supplements, cool compresses, sleeping with the head elevated in bed, taping of the eyelids while sleeping and avoidance of smoking) concluded that mild cases had reduced symptoms and increased satisfaction at follow-up, while moderate cases also required additional topical steroids and severe cases required surgical intervention, but supporting data were not provided [486]. A study comparing participants before and six months after steroid pulse therapy followed by orbital radiotherapy showed improvements in proptosis, Clinical Activity Scores, and MGD, but not in other DED parameters [488].

A novel therapy involving an anti-IGF1R antibody (teprotumumab; Tepezza®; Amgen Therapeutics, Thousand Oaks, CA, USA) has shown promise for managing thyroid eye disease. This systemic treatment improves diplopia, proptosis, tear insufficiency and visual function [489,490]. However, side effects include hyperglycemia, diarrhea, hearing loss, and dryness of the skin and mucosa [491]. Given the high frequency of DED in thyroid eye disease and the benefits of reducing orbital inflammation, further studies are needed to balance the positive and negative impacts of anti-IGF therapy on DED and ocular surface health.

In thyroid eye disease participants with extreme exposure due to thyroid eye disease and its associated upper lid retraction, lateral tarsoconjunctival flap, blepharotomy or Botox injections may reduce ocular surface damage, although the procedures were not compared [492].

For severe lagophthalmos, such as that seen in facial paralysis through trauma or disease, surgical options include temporary or permanent tarsorrhaphy, upper eyelid weight placement in cases of lid retraction, and lateral canthoplasty, with or without a middle lamellar spacer for lower eyelid retraction, although comparative studies are lacking [493-495]. A novel method involves lipofilling of the upper eyelid with autologous fat, which avoids the risk of migration associated with loading the lid with weights. Upper eyelid lipofilling on 75 participants with unilateral facial palsy demonstrated immediate improvement in corneal discomfort and favourable aesthetic and functional results [496].

7.1.2 Partial blinking

Incomplete blinking and eyelid misalignment are prevalent regardless of eyelid morphology [497] and are associated with a 2.2 times increased risk of DED [498]. Individuals with incomplete blinking have higher OSDI scores, more significant meibomian gland dropout, more MGD signs, poorer tear film LLT and a shorter NIBUT [498]. In this study, blink frequency did not correlate with any ocular surface

parameters [498]. Along with tear film distribution, the muscle of Riolan contracts during complete blinking, exerting pressure on the meibomian glands and is believed to facilitate expression of meibum from the glands onto the ocular surface [167]. It is hypothesised that reduced meibum release from incomplete blinking has longer term impacts, including meibomian gland blockage and drop out, that perpetuates decreased lipid distribution at the ocular surface [498]. Studies have shown that intentional and repeated forceful blinks can enhance tear film LLT [499], and NIBUT, as well as improve dry eye symptomology and blink completeness [500].

Providing information on blink exercises and how to blink fully can reduce symptoms in patients with DED [500,501]. Additionally, techniques that promote more frequent blinking, such as animations for computer users, have been found to reduce dry eye symptoms [502,503].

7.2 Methods to reduce eyelid microbial load

Anterior blepharitis is a chronic eyelid inflammation located at the base of the eyelashes, its follicles (marginal blepharitis) and/or eyelid skin (blepharo-dermatitis) which is often characterised by redness, exanthema, sores, eschar, and swelling [35,504,505].

While the exact etiology is unknown, it is likely multifactorial, including chronic low-grade overcolonisation of the ocular surface with bacteria, infestations with parasites and inflammatory skin conditions such as seborrhea. Blepharitis can be categorized in several different ways. [504-506] Categorization can be based on the length of disease process (acute or chronic) or the causative agent, with anterior blepharitis being staphylococcal (bacterial), seborrheic or due to the presence of *Demodex* mites [504,505,507-510]. Treatment for anterior blepharitis depends on the underlying cause, but treatments typically attempt to reduce the microbial load of the eyelids.

While it is entirely possible to have microbial bioburden on the eyelid margin and remain asymptomatic [511], therapeutic benefits have been shown from lowering the eyelid margin bioburden, and several treatments for anterior blepharitis focus on this mechanism of action.

7.2.1 Anti-*Demodex* therapies

There appears to be a clear association between *Demodex* mite infestation and anterior blepharitis [36,512,513]. *Demodex* mites are also found on the eyelids of normal, healthy individuals, and *Demodex* infestation increases during aging and is higher in patients with DED, MGD, glaucoma and contact lens wear [510,512,514-518].

As noted previously [519], much remains to be described with respect to *Demodex* studies to allow for study comparisons, including standard nomenclature (cylindrical dandruff vs collarettes), the technique for mite retrieval from the lids (epilation vs lash rotation/manipulation), in addition to the technique used to identify the mites (in vivo vs ex vivo).

In symptomatic patients, *Demodex* infestation can be assumed to be the primary driver of the symptoms when patients present with cylindrical dandruff/collarettes on their eyelashes [518], which are considered the pathognomonic sign of *Demodex* infestation [515,518-520]. Since the life cycle of mites is about 14 to 23 days [513,521], treatment may need to be administered over several weeks to target the mites at all life-stages. Several treatment options exist, from over the counter at-home remedies to prescription drops, creams and systemic medications.

A consensus on best practice for diagnosis and treatment for demodicosis has been published [522], where an expert panel of eye care practitioners recommended at-home use of tea tree oil (TTO)-containing lid wipes as first line treatment. There was consensus on four to six weeks duration of treatment, on a twice daily basis, with a suggested patient recall of between two and six weeks

after treatment commencement to reassess and change to a second line of treatment if needed [522].

Care should be taken when treating for ocular *Demodex*, as the aim of the *Demodex* therapy should not necessarily be to completely eradicate the mites, but rather to decrease its numbers to restore the ecology of the lid margin to a commensal state of balance [509]. This concept appears reasonable, as *Demodex* has been suggested to play a role in mediating bacterial activity, as defence against other mite species [509]. A Delphi panel agreed that complete eradication of mites was not necessary [518]. With respect to what constitutes successful treatment of a patient with *Demodex* blepharitis, it has been suggested that no remaining itching of the lids, minimal to no lid erythema, reduced symptoms and decrease in collarettes would be reasonable outcomes to assess success [518].

While several studies have shown a link between the presence of *Demodex* mites and the presence of MGD and symptoms and signs of DED [523-528], to date there is no peer-reviewed evidence for *Demodex* directly causing DED or MGD. This concept requires further evidence to directly link the pathogenesis of MGD with the presence of mites.

7.2.1.1 Ivermectin

First derived from *Streptomyces avermitilis* in the 1970s, ivermectin is a broad-spectrum antiparasitic [529]. In its initial form, as an oral medication, ivermectin was shown to be safe, even at high doses [530], while reducing *Demodex* mite load and improving tear film stability [2,531,532]. Topical ivermectin has been proposed as a more efficient treatment that can be directly applied to the site of infestation [533]. It has been shown to be efficacious, but also quite uncomfortable for some participants [533-536].

Compared with eyelid hygiene using a TTO cleaning product alone (n=51), participants treated with topical ivermectin 1% cream applied to the upper and

lower eyelashes once weekly, and subsequently removed with an eyelid cleanser 15 minutes later, had significantly improved symptoms, ocular surface staining, eyelash debris, redness/swelling and telangiectasia [534].

In another study, 75 participants with ocular demodicosis applied topical ivermectin 1% cream to the lid margins of both eyes every night for three months [536]. Participants exhibited a significant reduction in all three ocular demodicosis characteristics, including the absolute numbers and proportion of lashes with cylindrical dandruff/collarettes, with visible *Demodex* tails and with follicle pouting. In addition, corneal fluorescein staining severity score improved significantly from baseline. Side effects were reported in two participants and included skin irritation and stinging upon application.

In a six year retrospective study reporting on 2157 participants (4314 eyes) with a diagnosis of *Demodex* blepharitis that were treated with topical ivermectin 1% once a day for two months [535], there were significantly less cylindrical dandruff/collarettes and conjunctival redness, as well as improved symptoms (OSDI score) post-treatment. All participants were followed for six months, and 312 participants (14.4%) underwent a second course of treatment following reoccurrence of cylindrical dandruff/collarettes. Fourteen participants (0.6%) reported ocular discomfort and irritation. Finally, ivermectin has also been combined with metronidazole for the treatment of *Demodex*, with a meta-analysis reporting that the combination reduces mite counts [537]

7.2.1.2 Lotilaner ophthalmic solution

Lotilaner ophthalmic solution 0.25% (XDEMVY®; Tarsus, Irvine, CA, USA) is the only FDA-approved treatment for the eradication of ocular *Demodex* mites. Lotilaner is a gamma-aminobutyric acid-gated chloride channel inhibitor selective for mites. Inhibition of these chloride channels causes paralysis in the target organism, leading to death [538]. Further, the lipophilic nature of the drop may promote its uptake in the oily sebum of the eyelash follicles where the mites

reside [538-540]. Dosing is twice a day for six weeks to account for the life cycle of the mites.

Efficacy (based on reduction in cylindrical dandruff/collarettes) and safety for lotilaner ophthalmic solution 0.25% was evaluated in 883 participants involved in two Phase III clinical trials (SATURN-1 and SATURN-2) [468,540]. In SATURN-1, at day 43, the proportion of patients achieving ≤2 collarettes was significantly higher in lotilaner-treated patients compared to vehicle (44% vs. 7.4%) [540]. The proportion of patients with ≤10 collarettes was 81.3% in the test group versus 23% in the control group. Similarly, in SATURN-2 the proportion of patients achieving ≤2 collarettes at day 43 was significantly higher in the lotilaner-treated group compared to the vehicle control group (56% vs. 12.5%) [468]. The proportion of eyes with ≤10 collarettes was 89.1% in the treated group versus 33.0% in the control group. Additionally, 96.4% of lotilaner-treated eyes had at least a one grade improvement in collarettes after six weeks of treatment. Demonstrating long term efficacy, a significantly higher proportion of patients treated with lotilaner ophthalmic solution 0.25%, had ≤2 collarettes and ≤10 collarettes throughout a one year extension study compared to those who received vehicle control [541].

Mite eradication was evaluated at Day 43 in the Phase 3 clinical trials. In the SATURN-1 study, complete mite eradication (0 mites / lash) was achieved in 67.9% of study patients vs. 17.6% of control patients [540]. In the SATURN-2 study, complete mite eradication was seen in 51.8% in the study group vs. 14.6% in the control group [468]. The most common adverse effect was instillation site stinging and burning, reported in 10% of participants, with <2% experiencing chalazion/ hordeolum and punctate keratitis at the one year follow-up [468,540,541].

The clinical relevance of reducing collarettes in asymptomatic participants remains to be addressed.

7.2.1.3 Okra (Abelmoschus esculentus)

Okra (*abelmoschus esculentus*) is rich in polysaccharides and other compounds with antibacterial and anti-inflammatory properties [542]. Due to the irritating nature of some TTO-impregnated lid wipes [543,544], coupled with the findings that TTO-derivatives can be toxic to the epithelium of both meibomian glands and corneal tissue [545,546], an alternative option is desirable for the management of *Demodex* blepharitis. A randomized study compared the anti-demodectic activity of an okra versus a TTO-based lid wipe for three months [547]. In both groups, the *Demodex* mite count reduced at 1 and 3 months, however the okra-based lid wipe outperformed the TTO-wipe for corneal staining at both time points. The okra-based lid wipe was well tolerated with no adverse events reported, making this a potential option for patients with ocular sensitivities, such as the pediatric and geriatric population. More research is warranted to evaluate the anti-demodectic activity of okra-based lid hygiene products over a longer time frame.

7.2.1.4 Tea tree oil

Tea tree oil or terpinen-4-ol is derived from the leaves of the Australian native plant *Melaleuca alternifolia* [2] and has traditionally been the most widely used topical antimicrobial treatment for *Demodex* blepharitis [509,518]. This essential oil is available in many forms, including impregnated wipes, foaming cleansers, and liquids and has been shown to exhibit antibacterial, antifungal and anti-inflammatory properties [548].

Studies have demonstrated that TTO reduces ocular *Demodex* load and effectively improves both the signs and symptoms of blepharitis at concentrations ranging from 2.5% to 50% [463,513,524,547,549-557]. Although TTO more effectively eradicates mites than other at-home treatment mainstays such as baby shampoo [555,556], safety and tolerability are concerns with higher concentrations of TTO or with long-term use [11,12,544]. A lower dose concentration of 2.5% terpinen-4-ol eye wipes were well tolerated in two reports [557,558].

While research has shown that high-concentration TTO products (>50%) are more effective for mite eradication than lower concentrations that result in variable mite eradication [559], >50% concentration is deemed unsafe for home use [513]. An *in vitro* study demonstrated that terpinen-4-ol is toxic to human meibomian gland epithelial cells at concentrations even 10- to 100-fold lower than those used to kill *Demodex* mites [545]. To that end, next-generation formulations are in development, with one formulation which encapsulates 5% terpinen-4-ol (T4O) in a nano-lipidic particle emulsion demonstrating a 100% kill rate within 137 minutes of exposure in an *in vitro* study [560].

7.2.2 Blepharoexfoliation

Motorised rotational electric toothbrush-like mechanical devices are available to aid with cleaning the lid margins and base of the eyelashes (a process termed microblepharoexfoliation or blepharoexfoliation). A single application with a foam cleanser reduced eyelid bacterial load and improved comfort and ocular surface signs in symptomatic contact lens wearers [561,562].

A one-month study of a prototype unpowered lid hygiene brush suggested improvement over simple cleansing with water, more so if it was used in conjunction with an ocular shampoo [563].

The benefits of microblepharoexfoliation have been explored in combination with TTO-based products for managing *Demodex* blepharitis. An RCT comparing terpinen-4-ol-containing lid wipes or a non-terpinen-4-ol sham twice daily for one month following microblepharoexfoliation reported reduced *Demodex* infestation levels, but there was no statistically meaningful improvements in other dry eye and blepharitis metrics observed between the groups [564]. An RCT comparing a nightly wash with TTO and a commercial lid scrub with or without prior microblepharoexfoliation found a similar reduction in *Demodex* folliculorum, with all three approaches after two and four weeks of treatment [550]. A longer RCT comparing the use of eyelid scrubs with 2% TTO shampoo twice a day for eight weeks with or without prior microblepharoexfoliation demonstrated additional

benefit of pre-treatment with microblepharoexfoliation in the reduction of symptoms and *Demodex* count [463]. Treatment effects may therefore take longer than one month to become apparent. Furthermore, a clear relationship between reduced Demodex counts and improved symptoms and signs of DED has not yet been established. In considering such chronic use of TTO-containing products, study outcomes recommend caution due to a potential for adverse ocular surface and adnexal effects [11].

A Delphi panel of 12 clinicians did not reach consensus on the necessity for mechanical intervention, such as microblepharoexfoliation for *Demodex* blepharitis. This type of intervention was still used by n=10 (83%) of the panel, but it was hoped that in future, with more effective therapeutic agents, that mechanical intervention might be negated [565]

7.2.3 Hypochlorous acid

Hypochlorous acid has broad antimicrobial activity [566] and is a powerful antibacterial agent [567]. At a concentration of 0.01%, it is as effective as 5% povidone iodine in reducing the bacterial load of the lid margins by over 90%, without altering the diversity of bacterial species on the skin of the lower lid [568,569]. At a concentration of 0.01%, *in vitro*, it could eliminate or diminish bacteria in biofilms, but was not found to disrupt biofilm structures and the susceptibility of tested staphylococcal blepharitis isolates varied by species [570]. Hypochlorous acid demonstrates a good ocular safety profile at a concentration of 0.01% [543,571] and may offer the highest degree of patient comfort among several eyelid cleansers [543].

Hypochlorous acid is commercially available mainly as a spray in concentrations ranging from 0.0085 to 0.2%. Further studies are warranted to determine if concentration is correlated to effectiveness for blepharitis management. Patient education is important as hypochlorous acid becomes unstable when exposed to light, air or extreme temperatures [572].

Hypochlorous acid solution applied to a wipe seems to be more effective than a HA-containing wipe for symptoms (OSDI) and ocular signs (tear film stability, TMH and meibomian gland expressibility) [461]. No difference was noted for Schirmer test, meibography, corneal staining or conjunctival redness after one month. Eyelid swabs were collected and cultured and revealed a significant reduction in bacterial load in both groups, although more pronounced with hypochlorous acid [461].

Delivered by ultrasonic atomization in a two week RCT, hypochlorous acid solution outperformed 0.9% saline lid scrubs in terms of improvements in DED signs [573], but outcomes may be confounded by the participants concurrently being prescribed warm compresses twice daily and topical 0.5% levofloxacin three times a day. Another study demonstrated that 0.01% hypochlorous acid shortened the survival time of *Demodex*, improved ocular parameters (Schirmer, TBUT, corneal/conjunctival staining) and reduced inflammation (MMP-9 and IL-2) [574].

7.2.4 Lid hygiene products

Since the TFOS DEWS II Management & Therapy Report [2], several clinical trials have been published on the use of lid hygiene products to treat anterior blepharitis. While these management options initially focused on wipes, patients now have options that include wipes, gels, foams, solutions, suspensions and sprays [575]. While this review demonstrates that comparative studies are rare, studies have typically shown effectiveness in decreasing both signs and symptoms of DED and to have less adverse changes on the ocular surface than when using a commonly used method of diluted baby shampoo (Sung et al, 2018) (Table 6).

Lid hygiene products are available with and without antimicrobials. Antimicrobials can include TTO, terpinen-4-ol (T40), capryloyl glycine, okra (*Abelmoschus esculentus*), hypochlorous acid, linalool and aloe vera, which have recently been

reviewed [12]. That review also highlighted the need for more research with respect to cross product comparisons, uniform lid cleansing technique, understanding the impact of lid hygiene on patient lifestyle (compliance depending on the duration of treatment or symptomology, cost, ease of use, comfort, etc), and difficulty in product comparisons due to legislative reporting of ingredients, that may vary geographically [12]. Another consideration is the differences amongst eyecare professionals with respect to lid hygiene recommendations. Patient applied anti-*Demodex* lid cleansing wipes were recommended by more practitioners than in-office anti-*Demodex* treatment (by 1.55 times), on an international survey of 1,139 ECPs [576]. A recent online survey of 261 eyecare professionals investigated the management of *Demodex* blepharitis from India and Australasia [577]. Significant differences were noted amongst practitioners from the two regions with respect to the diagnostic approach (perceived prevalence, slit lamp magnification to identify mites) and in the treatment option (TTO for Australasia versus standard lid hygiene, which included warm compresses, for India), duration of treatment (longer for Australasia) and frequency of treatment (India: twice a day vs Australasia: once a day) [577]. These differences in practice patterns may be influenced by legislative restrictions, accessibility of products geographically, cost and other factors, but further highlights the importance of using an evidence-based approach for the management of all forms of blepharitis. An expanded summary on the use of warm compresses to treat MGD and their efficacy can be found in a publication on a novel, water propelled heating eye mask [243].

Table 6. Studies investigating the use of various lid hygiene methods to manage anterior blepharitis

Study	Type of participants	Treatment	Product comparison	Sample size	Duration	Randomized	Outcomes showing improvement	No significant differences from comparator
Peral et al, 2016 [578]	Pre-surgical candidates	Caprylol glycine lid wipe	None	45	5 days	N/A	Reduction of microbial load	N/A
Stroman et al, 2017 [568]	Blepharitis	0.01% Hypochlorous acid	None	36 (71 eyes)	20 min	N/A	Decreased number of bacterial isolates, especially staphylococcal	N/A
Sung et al, 2018 [462]	Anterior blepharitis	Eyelid cleanser (foam) bid	Diluted baby shampoo solution bid	43 Contralateral	4 weeks	Yes	Some symptoms LLT Inferior LWE Cylindrical collarettes MMP-9 expression Worsened MG capping and MUC5AC expression in baby shampoo group	Some symptoms Superior LWE Lash crusting Trichiasis
Eom et al, 2020 [579]	Anterior blepharitis and obstructive MGD undergoing	Eyelid hygiene group bid	None	69	10 days (from 3 days before surgery) and	Yes	Symptoms Anterior blepharitis MG expressibility at 1 week Debris & redness/swelling	MG secretion MG area Telangiectasia Corneal and conjunctival

	cataract surgery				assessed again at 4 weeks		at 1 week TBUT at 4 weeks	fluorescein staining
Liu & Gong, 2021 [547]	Demodex blepharitis	Okra-based cleanser	Tea tree oil	52	3 months	Yes	Demodex survival time OSDI Demodex count	OSDI Demodex count TBUT Meibum quality Meibomian gland expressibility
Zarei-Ghanavati et al, 2021 [580]	MGD	Tea Tree Oil shampoo	Regular eyelid shampoo	40 contralateral	4 and 12 weeks	Yes	Symptoms Plugging and capping of MG orifices Foamy tears Meibomian gland expressibility TBUT Telangiectasia	Meibum quality, Conjunctival hyperemia, Corneal and conjunctival staining Schirmer Trichiasis and distichiasis
Arici et al, 2022 [549]	Seborrheic blepharitis	Lid wipes (T4O+sodium hyaluronate) bid	Baby shampoo bid	48	8 weeks treatment and 4-week post follow-up	Yes	Some symptoms	Some symptoms NIBUT TBUT Schirmer

								Fluorescein corneal and conjunctival staining Demodex count MG area
Runda et al, 2022 [581]	MGD	Lid wipes bid + (antibiotics qid/bid and lubricants qid) + systemic antibiotic bid in severe MGD	wet towel + lid massage bid + (antibiotics qid/bid and lubricants qid) + systemic antibiotic bid in severe MGD	50	3 months	Yes		Symptoms NIBUT LLT Tear meniscus height Osmolarity Eyelash contamination Telangiectasia MG area, blockage and secretion
Aghaei et al, 2023 [582]	Anterior blepharitis	Gel (TTO 2%) bid	Topical erythromycin ointment at night + fluorometho	61	45 days	Yes	Symptoms (day 45) Eyelash debris, Erythema Edema (day 45)	-

			lone 0.01% eyedrops tid Heated compress bid Baby shampoo bid					

bid: twice a day; DED: Dry Eye Disease; LLT: Lipid Layer Thickness;, LW: Lid Wipes; LWE: Lid Wiper Epitheliopathy; MG: Meibomian Gland; MGD: Meibomian Gland Dysfunction; MMP-9: Matrix Metalloproteinase 9; MUC5AC: Mucin-5AC gene; NIBUT: Non-invasive breakup time; OSDI: Ocular Surface Disease Index; qid: four times a day; SANDE: Symptom Assessment iN Dry Eye questionnaire; SPEED: Standard Patient Evaluation of Eye Dryness Questionnaire; TBUT: Fluorescein Breakup Time; TTO: Tea Tree Oil; T4O: Terpinen-4-ol; WC: Warm Compress.

7.2.5 Low-level light therapy (LLLT: Blue light)

While low-level light therapy with red and near-infrared light is understood to operate via photobiomodulation (see Section 6.3.1.2.3.2), the same clinical device with blue light offers different properties.

Blue light, particularly in the wavelength range of 410-430 nm, has inherent antimicrobial properties due to the generation of ROS on interaction with microbial cells, which can damage cellular components such as deoxyribonucleic acid, proteins, and lipids, leading to bacterial cell death [583,584]. Blue light can influence the expression of specific genes involved in bacterial metabolism and stress responses. For instance, in osteosarcoma cells, blue light application has been shown to induce apoptosis by increasing ROS levels and regulating pathways such as SOCS3 and PTEN/PI3K/AKT [585]. While this study focuses on cancer cells, similar mechanisms may be at play in bacterial cells, where ROS generation leads to cellular damage and death.

Blue light application can alter the composition of the microbiome. In a study on mice with ligature-induced periodontitis, blue light irradiation significantly changed the oral microbiome composition. It decreased the α-diversity and the number of observed features and altered the relative abundances of specific bacterial phyla and genera [583]. This suggests that blue light can selectively affect different bacterial populations, potentially reducing pathogenic bacteria while allowing beneficial bacteria to thrive. Blue light also has direct antimicrobial action. It can directly kill bacteria without the need for a photosensitizer. This has been demonstrated in various studies, including those targeting Helicobacter pylori, where blue light reduced bacterial load in an in vitro study [586]. Finally, when combined with a photosensitizer, blue light can enhance the production of ROS, leading to more effective bacterial killing. This approach, known as antimicrobial photodynamic therapy (aPDT), has been used to target dental biofilm bacteria and other microbial infections [587].

Patients who may benefit from blue LLLT are patients with bacterial overload on their lid margins and eyelashes. By reducing this biofilm via the antimicrobial properties of blue light LLLT, the speed of resolution of blepharitis can theoretically be enhanced. Further well controlled studies are required to optimize the appropriate clinical protocols to reduce bacterial biofilm on the lid.

7.2.6 Manuka honey

Natural honey has long been renowned for its anti-inflammatory and antimicrobial qualities, which are due to its low pH, high osmolarity, as well as hydrogen peroxide content and methylglyoxal [588]. For ocular application, attention is focused on a specific type of honey, New Zealand native Mānuka honey (*Leptospermum scoparium*), which has a higher concentration of methylglyoxal compared to other honeys [589,590]. When complexed with α-cyclodextrin, the antimicrobial effects of Manuka honey can be further augmented [591,592]. The cyclical structure of α-cyclodextrin is made up of six glucopyranose units, featuring a hydrophobic cavity that accommodates lipophilic molecules. This enables the formation of water-soluble inclusion complexes, which improves the stability and solubility of hydrophobic drugs [593]. Results of one study demonstrate that the *in vitro* antiparasitic efficacy of cyclodextrin-complexed Manuka honey was comparable to 50% TTO [594].

In another study, 53 participants with blepharitis applied a topical methylglyoxal Manuka honey eye cream, complexed with α-cyclodextrin in a microemulsion, to the closed eyelids of one eye overnight for three months [595]. Significant reductions in SANDE and SPEED symptom scores were observed in treated eyes from one month, along with clinical improvements in NIBUT, LLT and inferior lid wiper epitheliopathy at three months. After the three-month treatment period, there was also a significant decrease in ocular *Demodex, Corynebacterium macginleyi, Propionibacterium acnes*, and *Staphylococcus epidermidis* loads in treated eyes. In the first two weeks, five participants (9%)

experienced temporary ocular stinging and discomfort due to accidental application of the product too close to the eyelash margin or using an excessive amount of eye cream, likely causing the product to migrate onto the ocular surface. Otherwise, no major adverse events were reported, and visual acuity remained unchanged throughout the 90 days [595]. Further RCTs are needed to firmly establish the efficacy and safety of Manuka honey therapy, given the propensity for ocular surface irritation due to the low pH.

7.2.7 Topical antibiotics

An increased bacterial load on the eyelids has been found in patients presenting with both MGD and blepharitis [167,596,597], providing a basis for antibiotic therapy in the management of these conditions. While the use of oral antibiotics has shown promise in the management of MGD (see Sections 9.1 and 9.2), the use of topical antibiotics to manage lid conditions has been less well studied. Topical antimicrobial agents such as erythromycin, vancomycin, azithromycin, chlorhexidine, hypochlorous acid (see Section 7.2.3), melaleuca alternifolia leaf oil or TTO (see Section 7.2.1.4) can be used to reduce the bioburden along the eyelid margin, with varying degrees of antibacterial activity [596,598].

Antibiotic resistance is an ongoing clinical concern in eyecare, as treatment outcomes may be affected. The Antibiotic Resistance Monitoring in Ocular micRoorganisms (ARMOR) surveillance study periodically reports the minimum inhibitory concentrations of numerous ocular antibiotics on conjunctival isolates [599]. An increase in antibiotic resistance with age was found, especially amongst staphylococci. Methicillin-resistant staphylococci showed multidrug resistance (>74%) over methicillin-susceptible isolates [599].

Topical azithromycin is a macrolide antibiotic that is particularly effective against gram-negative microorganisms [600] and also possesses anti-inflammatory properties [601,602]. Azithromycin was used for 14 days to reduce the bacterial load

in patients presenting with blepharitis and MGD, with significant improvements in lid vascularity, lid plugging, and meibum grade with no adverse events even at two weeks post-treatment (on day 28) [603]. To address the long-term effectiveness of azithromycin, a prospective observational cohort study on MGD patients revealed improved signs (TBUT, MGD grading) and symptoms (sensitivity to light, grittiness, burning sensation, blurred vision) after twice a day treatment for two weeks, followed by once a day for another two weeks [604]. At a one-year follow-up, patients filled out a survey and reported a reduction in symptoms, a reduction in self-care treatments (lid hygiene, artificial tear use), and a positive impact on their quality of life (reading, night driving, computer use, etc).

Another small-scale study compared topical azithromycin (15 mg/g ophthalmic solution used twice a day for three days and then once daily for a total of one month) to oral azithromycin (500 mg on day one, followed by 250 mg for four additional days, for a total of three cycles of treatment with five day intervals) [605]. Patient symptoms, eyelid margin signs, TBUT, corneal/conjunctival staining score, Schirmer test score, and conjunctival brush cytology were evaluated at baseline, one and five weeks. Both topical azithromycin and oral azithromycin were found to be effective in improving clinical signs and symptoms, however, topical treatment was superior in improving the cytology findings and TBUT. Similarly, a randomized trial compared topical azithromycin (15 mg/g applied one drop twice daily for two days and then once daily for 26 days) to doxycycline (100 mg twice daily for six weeks) [266]. Both treatments improved signs and symptoms of ocular surface disease, with no significant difference between the groups, although, there was a higher frequency of systemic side effects with doxycycline.

8 Anti-inflammatory pharmacological therapies

8.1 Corticosteroids

Corticosteroids have long been recognized as therapeutics to treat both inflammation and pain, both relevant targets in the treatment of some forms of DED. The TFOS DEWS II Management & Therapy Report reviewed the significant body of published research on the use of several different corticosteroid preparations in improving both symptoms and signs of dry eye [2]. The report also noted the potential for complications from the long-term use of corticosteroids. These complications were noted even following the use of fluorometholone and loteprednol (see Section 8.1.1), which are both considered to carry a lower risk of ocular complications such as increases in intraocular pressure and cataract. The TFOS DEWS II Management & Therapy Report included topical corticosteroids in Step 2 of the staged management and treatment recommendations, with caution noted for their "limited duration" use [2]. Patients prescribed topical steroids require regular review by an eye care practitioner.

A number of studies on the use of corticosteroids to manage DED have been published since the TFOS DEWS II Management & Therapy Report [2], including a Cochrane systematic review of 22 RCTs that included 4169 participants around the world [606-608]. The report cited a high risk of bias associated with selective results-reporting among the included studies, but concluded that the use of topical corticosteroids likely provided a small to moderate degree of symptom relief beyond that of lubricants, a modest effect on lowering corneal staining scores, a slight increase in TBUT, but little effect on tear osmolarity [608].

Subtyping of the DED present may also be important for appropriate patient selection when considering prescribing topical steroids. This could avoid mild downstream inflammation being treated with steroids (as a „quick fix") instead of

the source dysfunction being sought and addressed as a more appropriate, longer term management.

8.1.1 Loteprednol etabonate 0.25%

Loteprednol etabonate ophthalmic suspension 0.25% (Eyesuvis®; Alcon, Ft Worth, TX, USA) is an ester-based topical ophthalmic corticosteroid designed to be quickly metabolized into inactive metabolites by cellular esterase in ocular tissues, leading to an improved safety profile relative to ketone-based corticosteroids and reducing the potential side effects typically associated with topical corticosteroid use, while maintaining potent anti-inflammatory properties [609-613].

Eyesuvis is currently the only FDA-approved prescription corticosteroid therapy for the short-term (up to two weeks) treatment of “dry eye flares”. DED is a chronic disease, but it has also been long noted that many patients report an episodic rather than a continuous pattern of symptoms [614,615]. The TFOS DEWS II Definition and Classification report described intermittent symptoms that occur early in the development of DED [616]. Even later in the course of DED, episodic symptoms may be triggered by environmental stresses (e.g. dry or windy environments, contact lens wear, environmental allergens), ocular surgeries, medicamentosa including topical preservative agents and other causes [617]. A number of reports, including a meta-analysis of 22 studies, concluded there was good evidence for the existence of episodic “flares” in DED, and identified common triggers and confirmed the presence of inflammatory cytokines in the tears of patients with DED exposed to such triggers [618-621].

Drug delivery to the ocular surface is limited by many factors, including washout by tear flow, lymphatic and blood circulation and the challenges of drug penetration through the hydrophilic mucin layer of the tear film [622]. For molecules to move through the mucin layer they must be small, hydrophilic and carry a

neutral charge to avoid adhesion [623]. Development of mucin-penetrating particle technology is ongoing [624,625]. Such particles can offer improved physical and chemical stability over polymeric nanoparticles, and preparations can be shelf-stable in a ready-to-use form as aqueous suspensions [626].

Delivery of 3.6x higher concentrations of mucus-penetrating loteprednol-loaded particles to the cornea compared with traditional formulations in rabbits has also been reported [627]. This body of preclinical work led to the development program for Eyesuvis for the treatment of episodic DED that involved 2800 participants [628]. Since the drug‟s approval, several studies have reported on both the efficacy and safety of Eyesuvis in the treatment of acute DED flares [622,629,630]. Currently, its scope for use is unclear in the treatment of a chronic condition such as DED, particularly when precise criteria for resolution of a DED flare has not been defined, nor has a number of treatable flares per year suitable for treatment with Eyesuvis been defined. Complicating the situation further are the many more accessible topical steroid alternatives, although not specifically approved for the management of DED, and their recognized side-effects with long-term use.

8.1.2 Medicated tear supplements

Medicated tear supplements refers to when the primary component is the lubricating polymer, with the addition of an active pharmacological ingredient at a low concentration as an ancillary agent. The potential benefits of medicated tear supplements include more targeted therapy, for example, in the case of the inclusion of a corticosteroid, which can target the inflammatory pathway. A randomized study of 38 individuals with DED compared 0.2% HA with 0.001% hydrocortisone to 0.15% HA and 3% trehalose, both used four times daily for three months [631]. Both groups improved, with the greater improvement noted in TBUT and LLT in the medicated tear supplements group [631]. In a retrospective study of 155 participants with DED, the same formulation (0.2% HA and 0.001% hydrocortisone, Idroflog®, Alfa Intes, Italy) relative to non-steroid containing tear

supplements, resulted in improved TBUT over a 45-day period, particularly in those post-cataract surgery [632].

One consideration with this management option relates to the length of use by the patients and thus the risk of side effects, including the risk of elevated intraocular pressure when using an artificial tear that includes a corticosteroid. However, in the study that compared the known-dose steroid combination with a control drop over a three-month period, no difference in intraocular pressure was noted [631].

8.2 T-cell immunomodulatory topical drugs

8.2.1 Cyclosporine A

Cyclosporine A (CsA) is an immunomodulator [633,634] and since the approval of Restasis (CsA 0.05%) by the FDA in 2002 a number of products with differing formulations have been licenced in regions around the world for use in patients with DED [635]. Cyclosporine A is a calcineurin inhibitor that exerts immunomodulatory effects by blocking T cell infiltration, activation, and the subsequent release of inflammatory cytokines [634,636-639].

While over 600 peer reviewed articles have been published on the use of CsA in the management of DED since the publication of the TFOS DEWS II Management and Therapy report [2], only around 60 were RCTs, with a focus on improving formulations to deliver more rapid effect and superiority relative to other DED treatments. A recent systematic review and meta-analysis identified 583 RCTs in which various formulations of CsA were used to treat DED [640]. Thirty trials found significantly better efficacy with CsA, irrespective of dose or concentration, and the effect of CsA was comparable to tear supplements, to vehicle, and to fluorometholone 0.1%, tacrolimus 0.03% or diquafosol 3% in 13 trials.

The high molecular weight and hydrophobicity of CsA, combined with the continual flushing of the ocular surface though the blink action and tears, has made drug delivery of current formulations challenging [635]. Most marketed formulations are emulsions or nano-emulsions containing oils and surfactants such as cetalkonium chloride, polysorbate 80, Octoxinol-40.

Pooled data from two studies examining a 0.1% cationic CsA emulsion (Ikervis®, Santen, Japan) compared to its vehicle in participants with moderate to severe DED, suggested a reduction in corneal staining and symptoms after six months of use, but not in a population with Sjögren disease [641]. A systematic review of current commercial formulations of CsA suggested some were better than others at improving various signs and symptoms [642].

A 0.05% CsA nano-emulsion formulation (Cycloome®, Shenyang Xingqi, China) uses Ailic-Tech® technology to create a transparent microemulsion that minimizes ocular intolerance reactions. The Phase III study showed that the treated group displayed a significant improvement in ocular surface test results from day seven [643]. In another study, it improved Schirmer scores, corneal goblet cell density, and reduced dendritic cell density more effectively than 0.1% fluorometholone after three and six months [644]. This formulation also showed significant improvement in OSDI, TBUT, corneal fluorescein staining and corneal sensitivity following various forms of refractive surgery [645-647].

A water-free version was shown to significantly reduce corneal staining compared to a vehicle control, but there were no differences in symptoms compared to the semi-fluorinated alkane treatment arm [648-651]. A water-free semi-fluorinated alkane-based 0.1% CsA formulation has been approved in the US (Vevye™; Harrow, Nashville, TN, USA) and in the European Union (Vevizye®; Laboratoires Thea, Clermont-Ferrand, France), comprising a solution of CsA in a

perfluorobutylpentane vehicle. The spreading and residence properties of the product are believed to lead to higher local bioavailability compared to other CsA-containing emulsions at 0.05% and 0.1%, and animal studies suggest that perfluorobutylpentane improves lipid layer grading, which may play a role in reducing tear evaporation [136,652,653]. The product was investigated in four RCTs and an open-label, long term safety study involving more than 1500 participants with DED [648-651,654]. The initial Phase II study showed an early onset of effect and significantly higher improvements in ocular surface staining endpoints compared to the active comparator, a 0.05% CsA emulsion [651]. The subsequent three Phase III studies in predominantly aqueous deficient DED met the primary endpoint, reducing total corneal fluorescein staining at four weeks compared to vehicle; responder analyses showed that the magnitude of improvement was clinically meaningful in >50% of participants by week 2. Conjunctival staining improved significantly in all three studies compared to the vehicle. While symptoms improved in all trials from baseline, superiority over vehicle could not be demonstrated consistently in the studies [648-650]. The incidence of adverse events was comparable between active and vehicle groups in all studies; the most frequent ocular AEs were instillation site reactions, which occurred in <10% of participants, which is lower than has been reported with other pharmacological DED treatments [649,650,655].

A micellar nano-particulate CsA formulation of 0.09% CsA (OTX-101; CEQUA®; Sun Pharmaceutical Industries, Cranbury, NJ, USA) showed efficacy relative to its vehicle in participants with aqueous deficient DED [656-659] and demonstrated safety over a 12 week study period [650]. A 0.05% CsA nano-emulsion (Cyporin N®; Taejoon Pharma, Seoul, Republic of Korea) improved tear stability and Schirmer test results over the course of a 12 week trial compared to HA 0.15% tear supplements, but symptoms in the mild-to-moderate DED participants were not improved in either treatment group (n=15 in each) [660]. The 0.05% nano-emulsion (Cyporin N) performed better than a 0.05% emulsion (Restasis) (in

conjunctival staining score) or diquafosol 3% (in tear film stability and volume) over a 12 week study in participants with DED and Sjögren disease [661,662]. Another study found a 0.08% nano-emulsion (TJO-087; Taejoon Pharma, Seoul, Republic of Korea) to be equivalent in efficacy to a 0.05% emulsion of CsA (Restasis) over a 32-week follow-up period [663]. A small study (n=24) compared a CsA emulsion versus a nanoemulsion. To relieve discomfort, participants in both groups received fluorometholone concomitantly during the first four weeks. Both treatments showed improvements in signs and symptoms compared to baseline at week four to 12 [664].

A systematic review identified 11 previous RCTs on the use of CsA for the management of DED compared to tear supplements [665]. Pooled results of the 1,085 participants recruited showed that CsA improved TBUT, fluorescein staining score, and patient-reported symptoms on OSDI (by approximately five points) more than tear supplements; although more adverse events, none of which were considered serious, were reported with CsA than with tear supplements [665]. However, most studies were only of between two- and four months duration and the longest was only 12 months, so long-term treatment effects are not yet known. In addition, some studies observed no benefit of the CsA emulsion over tear supplements containing HA (0.1%, 0.15% and 0.3%) over a 12-week evaluation period [666]. Further studies since this review found no benefit of CsA over 0.15% HA tear supplements [655], while a 0.05% CsA nano-emulsion (Cycloome®, Shenyang Xingqi, China) exhibited improved OSDI scores compared with its vehicle [643] and 0.05% CsA nano-emulsion (Cyporin N) was more effective than 0.15% HA and warm compress use by participants with obstructive MGD [667]. In a prospective three group comparison of 0.15% HA, 0.05% CsA (Cyporin N) and 3% diquafosol sodium in the treatment of young adults with moderate-to-severe DED, corneal staining, OSDI symptoms, Schirmer test, TMH and TBUT showed similar improvements in all groups,

whereas the decrease in inflammatory markers after 12-weeks was greater with CsA than in the group prescribed HA [668].

The data on whether an artificial tear enhances the effect of CsA in reducing inflammatory markers, corneal staining and symptoms is equivocal [655,665,669,670]. In other combinations, CsA (0.1%) combined with loteprednol (0.2%) compared with CsA (0.05%) alone showed no benefits over a four-week follow-up, except in higher order aberrations, but how and when these were assessed is not made clear in the publication [671]. Topical CsA 0.1% in combination with diquafosol tetrasodium 3% improved TBUT compared to CsA alone, but did not improve symptoms or corneal and conjunctival staining scores [672].

In an RCT, increasing the concentration of CsA (from 0.05 to 0.09%) improved symptoms, corneal staining, tear production and tear film osmolarity over three months, but had no effect on conjunctival morphology and tear film stability, and increased reported adverse events, including discomfort using the drops [673]. Low doses of CsA (0.01 and 0.02% with 3% trehalose) have little effect in participants with severe DED compared to a placebo [674].

In a study of 62 severe DED participants in whom corneal staining had been dramatically improved after either six or 12-months of CsA 0.1% use [675], the estimated time to relapse after CsA withdrawal was 32-weeks for those who initially received 12-months of treatment, versus 25-weeks in those having received six-months of treatment [676].

Another relevant area in which CsA has been investigated is in the management of patients with MGD. In a retrospective analysis, 53 patients with MGD were enrolled in a three-month study in which treatment with topical 0.05% CsA in conjunction with a topical, preservative free HA-based lubricant (experimental group, n=74 eyes) and use of a HA lubricant only (control group, n=32 eyes)

were compared [677]. The experimental group showed a statistically significant improvement in OSDI score, TBUT, Schirmer score and lid margin telangiectasia. Additionally, mean change from baseline in OSDI, TBUT, Schirmer score, corneal staining score, lid margin telangiectasia and conjunctival injection showed a greater improvement in the experimental group than in the control group after three months [677].

A prospective study included 64 patients with DED and MGD who were randomly assigned to one of three groups: Group 1 (n=24; 0.1% HA-based eye drops + conventional 0.05% CsA), Group 2 (n=21; 0.1% HA-based eye drops nano-emulsion 0.05% CsA), and Group 3 (n=19; 0.1% HA-based eye drops only; control) [678]. Subjects were evaluated after four, eight and 12 weeks of treatment. In Group 3 (control), lid margin telangiectasia, corneal staining and conjunctival injection improved after eight weeks and TBUT after 12 weeks. In Group 1 (conventional CsA), lid margin telangiectasia, meibomian gland secretion and TBUT improved significantly after four weeks, whereas corneal staining, conjunctival injection Schirmer score and LLT improved significantly after eight weeks and OSDI after 12 weeks. In Group 2 (nano-CsA), lid margin telangiectasia, meibomian gland secretion, corneal staining, conjunctival injection, TBUT and OSDI significantly improved after four weeks, and Schirmer score after eight weeks. The LLT was significantly higher than in the other two groups after four weeks. These results demonstrated that both CsA formulations were superior to an ocular lubricant alone and that the nano-CsA formulation resulted in improvements in various signs and symptoms of DED in subjects with MGD faster than in the conventional CsA group [678].

In a prospective, randomized, single-blinded, three-month, controlled clinical study, 51 patients with obstructive MGD were randomly assigned to one of two groups. The CsA group received a 0.05% CsA topical nanoemulsion twice daily, 0.15% HA-based lubricants four times daily, and 10 minutes of twice daily warm

compress application [667]. The control group used the 0.15% HA-based lubricant six times daily and twice daily warm compresses for 10 minutes at a time. At the three-month evaluation, the CsA group showed significantly greater improvements in TBUT, eyelid debris, eyelid redness/swelling, and lower meibomian gland secretion score [667].

8.2.2 Lifitegrast

Lifitegrast ophthalmic solution 5% (Xiidra®; Bausch + Lomb, Bridgewater, NJ, USA) is a lymphocyte function-associated antigen-1 (LFA-1) antagonist which binds to the integrin LFA-1, a cell surface protein found on leukocytes and blocks the interaction of LFA-1 with its ligand intercellular adhesion molecule-1. This inhibits any further downstream inflammatory cascade mediated by the migration and proliferation of lymphocytes and cytokine production [679]. Two large scale studies (OPUS 1 and OPUS 2) established an improvement in the signs and symptoms of DED with lifitegrast 5% solution [680,681]. The subsequent OPUS 3, a Phase III, randomized, multicenter study, evaluated the change in eye dryness score from baseline to day 84 as the primary efficacy end point [682]. A significant improvement was noted in the treated group compared with those who received placebo within 14 days of initiation of lifitegrast and persisted throughout the study period.

A post-hoc analysis reviewing the pooled data of 1429 participants from two RCTs (OPUS 2 and OPUS 3) found that concurrent improvement in both signs and symptoms was more likely to be observed in participants with moderate-to-severe DED (inferior corneal staining of >1.5 and eye dryness scores of >60) [683]. This provides added insight into the contrast between the results of OPUS 1, which reported an improvement in signs but not the symptoms, and OPUS 2, which reported an improvement in symptoms but not signs, as each study enrolled a patient population with differing severity of DED. Similarly, in a meta-analysis of 3197 participants with DED receiving lifitegrast, an improvement was

noted in the symptoms (ocular discomfort score, eye dryness score, eye discomfort score, OSDI) and signs (total corneal staining scores, nasal lissamine staining score, TBUT) [684]. Pooled analysis of the safety of lifitegrast evaluated across five RCTs with 2464 participants estimated a discontinuation rate of 7% due to treatment-emergent adverse events. Overall, the drug was considered safe and well-tolerated in participants with DED [685].

A reduction in the dependency on concurrent tear supplements has also been noted with lifitegrast [686]. A RCT investigating participants with MGD found that lifitegrast treatment, as compared to thermal pulsation therapy, led to a greater improvement from baseline to day 42 in eye dryness, corneal staining, and eyelid redness [687]. In two prospective studies in participants with DED undergoing cataract surgery, treatment with lifitegrast improved signs and symptoms of DED and resulted in improvements in biometry accuracy and postoperative refractive outcomes [688,689]. Real-world data regarding lifitegrast use has reported improvement in ocular symptoms and signs, which persisted 12-months after use [690].

Reports describe patient dissatisfaction, particularly with respect to instillation site irritation (burning) and dysgeusia (metallic or salty taste post insertion that may last four to five hrs) [684,685,691,692]. A systematic review and meta-analysis reported that dysgeusia occurred in 16% of subjects, a rate which was 36 times higher in patients applying the drug compared with patients using a placebo [684].

8.2.3 Tacrolimus

Tacrolimus (FK-506) is a macrolide immunomodulatory agent, with a similar mechanism of action to CsA, but delivered in ointment rather than drop form, and with 10-to-100-fold greater potency [693]. A six-month study involving the direct comparison of topical 0.03% tacrolimus and 0.05% CsA (n=30 participants per study arm) showed both significantly improved patient symptoms and ocular

surface staining, reducing the frequency of tear supplements use compared to placebo-controlled eyes [694]. However, no significant difference in efficacy between the two treatments was evident in participants with severe DED due to Sjögren disease over the study period. A small RCT (n=20) demonstrated the effectiveness of one month application of 0.03% tacrolimus ointment for refractory cases of posterior blepharitis [695].

The main issue with the use of tacrolimus has been the lack of commercially available topical ophthalmic formulations in many parts of the world, although they are now becoming available in some countries. Some studies have described off-label use of a topical skin preparation of tacrolimus, demonstrating significant efficacy in resistant blepharitis and in individuals with Sjögren disease [694,695].

8.3 Pharmacological compounds under development

8.3.1 Carbonized nanogels

Carbonized nanogels developed via the pyrolysis of lysine hydrochloride are topical nanogels designed to offer longer retention rates over the ocular surface. *In vivo* rabbit studies have reported similar therapeutic effectiveness of a 10-fold lower dose of carbonized nanogels as 0.05% CsA [696]. This increased ocular bioavailability indicates the potential for a longer dosing interval and lower dose concentration. The nanogels exert free radical scavenging properties and improve ocular surface health via their antioxidant and anti-inflammatory properties [696].

8.3.2 Fenofibrate

Fenofibrate is a synthetic peroxisome proliferator-activated receptor α-agonist, which exerts an anti-inflammatory effect not only on the cornea and conjunctiva

but also within the lacrimal gland. Fenofibrate activates the peroxisome proliferator-activated receptor α-agonist, resulting in inhibition of Th1 and Th-17-mediated inflammation [697-699]. It also promotes T-regulatory cells and reduces IL-17 and INF-γ levels [697-699]. In other studies, fenofibrate has been reported to decrease lacrimal gland inflammation, increase aqueous tear secretion, and reduce corneal fluorescein staining in non-obese diabetic mice, as well as to partially reverse the negative lacrimal gland sequelae in a high-fat diet experimental mouse model [697,700].

8.3.3 Ferulic acid

Ferulic acid, an antioxidant derived from angelica root, has been studied in rabbit models and *in vitro* cell culture. The molecule reduces pro-inflammatory cytokines such as TNF-α, IL-6 and IL-8 and improves tear volume and ocular surface staining compared with a buffer saline control [701].

8.3.4 Lacritin

Lacritin is a glycoprotein, found naturally in tears, that is selectively reduced in DED [702,703]. Topical lacritin can mediate a therapeutic effect in Aire mice by improving tear secretion and corneal staining scores and also reducing T cell infiltration in the lacrimal glands [704]. Lacripep™ (TearSolutions, Charlottesville, VA, USA) is a synthetic 19-amino acid peptide fragment of lacritin with preserved biologic activity of the full lacritin monomer. A first-in-human study carried out in 204 participants with Sjögren disease demonstrated good safety and tolerability for both the 22 μM and 44 μM concentrations [705]. However, the primary efficacy endpoints of improvement in total corneal staining score and eye dryness score were not met by the end of the study period (28 days). Participants with greater severity of disease at baseline demonstrated a better response, indicating the need for consideration of patient DED severity and subtype, and dose titration to determine the optimal dosing regimens in future studies.

8.3.5 Naringenin

Naringenin is a naturally occurring flavonoid, found in various fruits, particularly tomatoes and citrus fruits such as grapefruits and oranges. It has been widely studied for its antioxidant, anti-inflammatory, anti-neoplastic and neuroprotective properties [706]. In a mouse model of DED, naringenin has been shown to improve the ocular surface quality with increased tear volume and reduced corneal and conjunctival staining in animal models [707].

8.3.6 Repository corticotropin injection

Acthar® Gel (repository corticotropin injection; Mallinckrodt Pharmaceuticals, Bridgewater, NJ, USA) is a naturally sourced complex mixture of adrenocorticotropic hormone analogs and other pituitary peptides that is believed to have both steroidogenic and non-steroidogenic immunomodulatory effects via activation of melanocortin receptors in various cells throughout the body [708].

In an attempt to address an unmet need for effective therapies to treat patients with refractory DED, adults with moderate or severe-acute DED received 80 units of subcutaneous repository corticotropin injection twice weekly for 12 weeks [709]. Fifteen subjects received at least 1 dose of repository corticotropin injection and 12 subjects completed the study. Compared to baseline (day 1), reduced corneal staining was observed at day 14 and day 84 after repository corticotropin injection treatment. Mean SANDE scores progressively declined from 62.0 at baseline to 46.9 at day 84. Schirmer test scores showed no significant changes throughout the study. These results suggest that repository corticotropin injection may be an effective treatment for moderate and severe DED, however, further, larger, masked clinical studies are required to confirm this.

8.3.7 Reproxalap

Reactive aldehyde species are involved in proinflammatory signaling and are elevated in DED. Reproxalap (Aldeyra Therapeutics; Lexington, MA, USA), a

small molecule that binds reactive aldehyde species, inhibits inflammation by competing with malondialdehyde and 4-hydroxy-2-nonenal for their biological targets. The binding of reproxalap to these reactive species, prevents reactive aldehyde species from interacting with amino and thiol groups on receptors and kinases [710-712]. This disrupts upstream proinflammatory signaling cascades involving nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), inflammasomes, and other mediators, thus reducing Th1 and Th2-mediated inflammation [710-712]. Additionally, reproxalap prevents reactive aldehyde species and phosphatidylethanolamine interaction in the tear lipidome, thereby preventing tear lipid modification [712-714]. In a Phase IIa trial, 51 participants were randomized to receive three formulations of reproxalap (0.1%, 0.5% ophthalmic solution, and 0.5% lipid ophthalmic solution) in a parallel-group design [712]. A similar response rate was noted across all three formulations with a reduction of symptom and lissamine green overall staining scores from baseline in participants with DED [712]. In the subsequent Phase IIb multicentre trial, 0.1% and 0.25% concentrations of reproxalap were compared to a vehicle control, and 300 participants randomized to each of these groups were assessed over a period of 12 weeks [715]. A dose-dependent response from baseline was noted, with reproxalap performing superiorly to the vehicle with respect to improving both symptoms and signs of DED. Based on these results, the study determined that the 0.25% concentration would be used for the subsequent Phase III trials. The drug was found to be safe and tolerable.

8.3.8 Topical porphyrin

The potential benefits of porphyrin, a topical, experimental, synthetically derived antioxidant, have been explored in animal ocular surface disease models and *in vitro* cell cultures [716,717]. An improvement in corneal fluorescein staining scores was observed with topical porphyrin in both mouse and rabbit models [716,717].

8.3.9 Visomitin

Oxidative stress mediated via ROS is believed to play an important role in the pathogenesis of DED [718]. SkQ1 is a small molecule and the active ingredient of Visomitin (Mitotech LLC, Moscow, Russian Federation) [719]. SkQ1 targets and neutralizes ROS within mitochondria, which are otherwise inaccessible to natural antioxidants. In a randomized, double-masked, placebo-controlled clinical study, 240 participants with DED were assigned topical Visomitin or placebo for administration three times daily for six weeks [720]. A significant improvement was noted in TBUT at the two-, four-, and six-week time points and in central and total corneal fluorescein staining score at six weeks [720]. In a Phase II, single-center, randomized, placebo-controlled study with 91 participants with mild-to-moderate DED, SkQ1 demonstrated efficacy in treating dry eye signs, with statistically significant improvements in corneal fluorescein staining, conjunctival lissamine green staining, lid margin redness, ocular discomfort, dryness and grittiness compared to placebo [721]. However, the primary efficacy endpoints were not met, with no difference between SkQ1 and placebo for corneal staining in the inferior region at day 29 nor in the mean score for the worst dry eye symptom over the seven days preceding the day 29 visit. The drug was shown to be safe and well-tolerated.

9 Oral antimicrobial agents

Oral tetracyclines (tetracycline, minocycline, or doxycycline) or macrolides (erythromycin and azithromycin) have been used to alleviate symptoms and improve ocular surface and tear film parameters in participants with DED. Beneficial effects include anti-inflammatory effects, reduced ocular surface bacterial load and improved meibum quality.

9.1 Tetracycline and analogues

Tetracyclines are broad-spectrum antibiotics with activity against a wide range of microorganisms, including gram-positive and gram-negative bacteria, chlamydiae, mycoplasmas, rickettsiae, and protozoan parasites. Tetracyclines penetrate bacterial cells by passive diffusion and inhibit bacterial growth by interfering with protein synthesis by inhibiting the 30S ribosomal subunit. They hinder the binding of the aminoacyl-tRNA to the acceptor site on the mRNA-ribosome complex [722].

A decrease in bacteria-producing lipolytic exoenzymes [723,724] and inhibition of lipase production [725] with resultant decrease in meibomian lipid breakdown products, may contribute to improvement in clinical parameters in evaporative DED. These agents also have anti-inflammatory properties. They impair the activity of collagenase, phospholipase A2, and several MMP types, and decrease the production of inflammatory mediators such as IL-1 and TNF-alpha in a wide range of tissues, including in the corneal epithelium [726,727].

Tetracycline and its analogues have been used to treat disorders that are associated with ocular surface and tear film abnormalities such as those associated with rosacea [728], MGD [729,730] and various forms of anterior blepharitis [730,731]. Although there are many published papers in the field [731], thus far, only two studies have a robust study design with placebo control and double masking. A parallel group RCT compared oral doxycycline (40 mg once a day) with placebo in 70 participants with anterior blepharitis and facial rosacea over three months (NCT00560703). There was little to no effect of the doxycycline on subjective dry eye symptoms and bulbar conjunctival hyperemia at 12 weeks. Tear production measured by the Schirmer test, and tear stability measured by TBUT, showed statistically significant improvement from baseline, although the clinical relevance of these changes remain uncertain. A three-arm RCT

investigated the effect of high dose (200 mg twice a day) and low dose (20 mg twice a day) oral doxycycline versus placebo during a one month of treatment period [732]. The study enrolled 50 participants with chronic MGD in each treatment arm (150 participants total). The results suggested that oral doxycycline could impart a modest improvement in patient reported symptoms, more so in the higher dose doxycycline group compared to placebo at one month, but the group difference was not statistically significant.

The optimal dosing of oral tetracyclines for the treatment of DED has not been well established. In general, treatment with 50 or 100 mg doxycycline once or twice a day for a period of several weeks to several months is well tolerated. Doxycycline (40 mg daily) is the only tetracycline approved by the FDA in the treatment of acne rosacea for up to 16 weeks. Of note, long term doxycycline treatment at this level does not lead to development of antibiotic resistance, likely because this antibiotic is bacteriostatic rather than bactericidal [733,734].

Tetracyclines are contraindicated during pregnancy and in children under 8 years old due to their potential adverse effects on dental and bone development. These antibiotics can bind to calcium ions, leading to permanent yellow-brown discoloration of teeth and enamel hypoplasia when administered during tooth development. Additionally, tetracyclines can slow down skeletal growth in young children [735,736]. In addition to side effects such as gastrointestinal symptoms and photosensitivity, safety issues such as an increased risk of breast cancer with long-term antibiotic therapy have been raised [737,738]. A large scale study did not substantiate these findings [739]. Nonetheless, there is currently no conclusive evidence and additional larger-scale prospective studies are needed to define any risks with longer-term tetracycline use.

9.2 Macrolide antibiotics

Macrolides are bacteriostatic antibiotics that inhibit bacterial protein biosynthesis, by binding reversibly to the P site on the 50S subunit of the bacterial ribosome [740]. Macrolides are actively concentrated within leukocytes and thus are transported into the site of infection. The two main macrolides used in the treatment of ocular surface diseases are azithromycin and erythromycin. Orally administered macrolides are better tolerated than tetracyclines and do not have the photosensitivity side effect. The cession of the treatment prior to an in-office procedure to manage DED utilizing light energy, such as IPL, is not necessary.

A pre-clinical study of five days dosing on immortalized human meibomian gland cells found azithromycin, but not doxycycline, minocycline, or tetracycline significantly increased the cellular accumulation of cholesterol, cholesterol esters, phospholipids, and lysosomes [741].

A RCT with a crossover design enrolled 115 consecutive participants to compare oral treatment with doxycycline (4 g for 30 days; 100 mg twice a day for seven days and then 100 mg/day for a further 21 days) or azithromycin (1.25 g for five days; 500 mg on the first day and then 250 mg/day for an additional four days) [742]. Therapy was switched or conservative management maintained according to signs and symptoms. Both antibiotics were effective and safe for treating participants with persistent MGD over the nine month study, although azithromycin required a reduced dose and shorter course of therapy (five days vs. four weeks) [742].

A systematic review and meta-analysis compared oral azithromycin to oral doxycycline for the management of MGD [743]. The review suggested that oral azithromycin may be more effective in reducing signs of MGD than oral doxycycline. Azithromycin also demonstrated a better safety profile, with fewer gastrointestinal adverse events. It concluded that further research is needed to

determine the optimal antibiotic treatment for MGD. The risks of azithromycin therapy should also be noted, in particular serious side effects including cardiac arrhythmias, pancreatitis, and vertigo.

Since the use of tetracycline and its analogues is contraindicated in children aged less than eight years because of dental enamel abnormalities [735,736], oral erythromycin may offer a reasonable alternative to tetracycline for managing childhood blepharokeratoconjunctivitis [744,745]. Erythromycin 5 mg/Kg/day is the oral dose typically prescribed, for a period of several weeks to several months.

Two reviews suggested that participants with posterior blepharitis or MGD-related ocular surface disease may experience short-term benefits of antibiotics for the duration of the treatment [730,731]. However, evidence for lasting improvement after cessation of treatment is lacking. In addition, there is mounting evidence regarding in-office procedures to improve MGD-related DED, without the known systemic side effects and inconvenience for the patient. Given the unclear long-term benefits, common gastrointestinal side effects, and potential serious systemic problems such as malignancies, the existing literature is insufficient to conclude that antibiotics are particularly useful in long-term MGD management, and these are rarely considered first line options.

10 Ocular surface promotors/regenerators

10.1 Biologics

10.1.1 Blood-based treatments

Blood-based eye drops represent an emerging treatment for DED and come in a wide variety of options (Figure 1). The application of blood-based eye drops increases the concentration of active growth factors and mediators that mimic the function of natural tears.

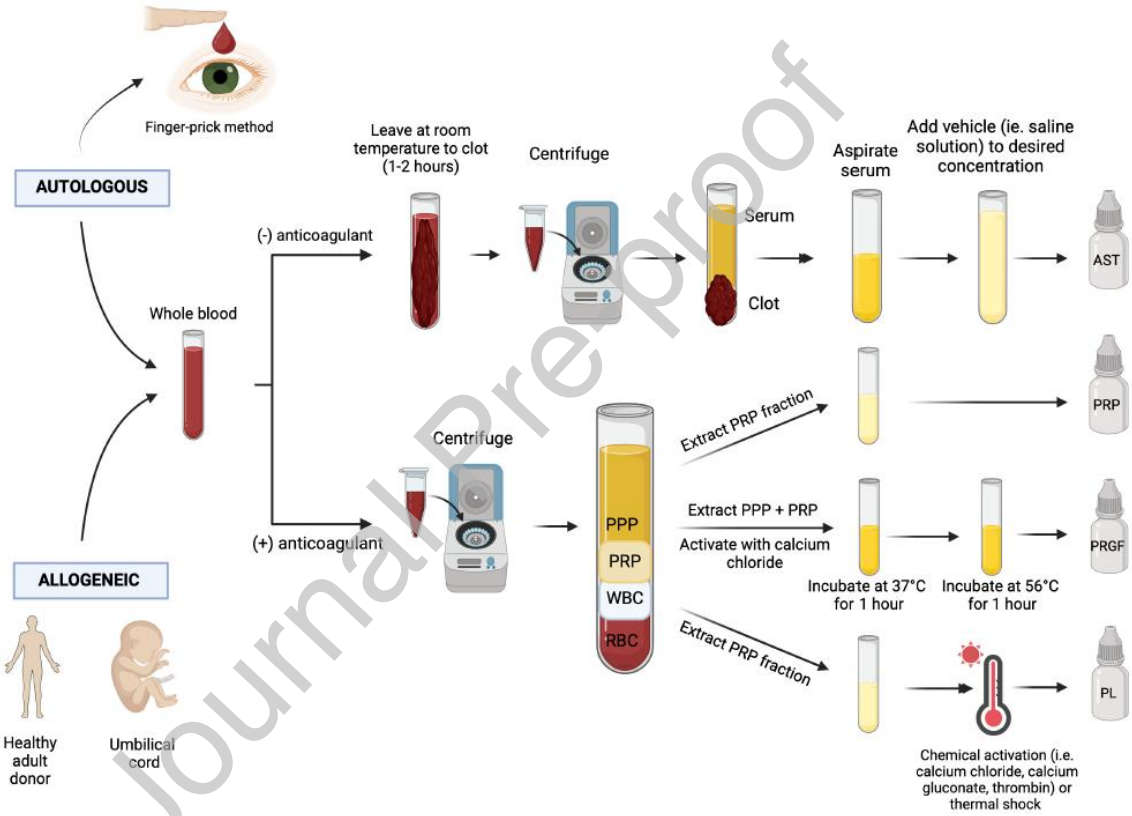

Figure 1: *Processing pathways for autologous and allogeneic blood-derived eye drops. Autologous tears are derived from the patient's own blood either via the Finger-Prick Method (direct application to the eye) or through whole blood processing. Allogeneic tears are obtained from either healthy adult donors or umbilical cord serum (UCS) and are processed exclusively from whole blood. Whole blood undergoes either centrifugation without anticoagulant to produce serum tears, or centrifugation with anticoagulant to separate into platelet-poor plasma (PPP), platelet-rich plasma (PRP), white blood cells (WBC), and red blood cells (RBC). PRP-derived eye drops are further classified into PRP drops (direct extraction), PRGF (Plasma Rich in Growth Factors) drops (PPP + PRP activated with calcium chloride and incubated at 56°C for one hour), and PL (Platelet Lysate) drops (PRP chemically activated using calcium chloride, calcium gluconate, thrombin, or subjected to thermal shock). Modified from Tovar and Sabater [746].*

10.1.2 Autologous serum tears

Natural tears are a complex mixture of water, electrolytes, lipids and mucins, but also vitamins, enzymes and over 1500 proteins [747], cytokines/chemokines, growth factors and neuromediators [748-750]. Importantly, and as previously reported in TFOS DEWS II Management and Therapy report [2], serum has been reported to contain growth factors such as epidermal growth factor, nerve growth factor (NGF), transforming growth factor-alpha, keratocyte growth factor, insulin growth factor-1 and others [751], as well as vitamins A and E and fibronectin [752], which are all believed to prevent apoptosis and facilitate epithelial cell growth and differentiation [753,754].

The TFOS DEWS II Management and Therapy Report [2] reviewed the published literature on serum tears, citing 14 clinical studies and included the use of serum tears in Step 3 of the staged treatment algorithm. The report cited the lack of a universally accepted methodology for the preparation of autologous serum, patient access issues and contamination concerns as factors that had limited more widespread adoption by clinicians.

Thus far, only a few RCTs have been performed evaluating the efficacy of serum tears for the treatment of DED. This is perhaps because of the cost of such trials and the lack of a commercial producer of serum tears. Historically, clinicians have either prepared serum tears in their offices, sometimes under non-sterile conditions, or had them prepared in compounding pharmacies or at blood donation locations, creating a lack of standardization in methodology [2].

A Cochrane review identified 29 studies but found only five that satisfied the criteria for inclusion, citing high heterogeneity and a lack of quantitative reporting for many outcome metrics [755]. The report concluded that there might be some short-term benefit in reducing symptoms with autologous serum tears compared with tear supplements, but additional RCTs were required to define the effects

with greater certainty. A more recent meta-analysis of seven RCTs reported better efficacy compared with tear supplements for both patient symptoms and multiple signs of ocular surface disease [756]. An American Academy of Ophthalmology Preferred Practice assessment report reviewed 10 studies and found eight to be high quality, demonstrating improved symptoms and at least one objective clinical sign of dry eye with the use of serum tears [757]. A task force report from the European League Against Rheumatism (EULAR) provided an algorithm for treating ocular dryness, and recommended the use of autologous serum tears in patients whose symptoms were uncontrolled after ocular lubricants and CsA [758]. A report of Preferred Practice Patterns in India concluded that there was sufficient evidence to recommend the use of autologous serum tears in patients with DED, but emphasized the need for standardization of preparation methods [759].

While it is not possible to prepare and distribute serum tears in the same manner as a topical pharmacological medication, it is worth noting that providers are now preparing autologous serum tears under sterile conditions using standardized centrifugation and dilution methods, and distributing them to patients, shipped under refrigeration. Since the last TFOS Management and Therapy report [2] there have been very few RCTs comparing the efficacy of autologous serum tears to current FDA-approved topical pharmacological drugs. One study reported a statistically significant reduction in OSDI scores with 20% serum tears relative to CsA 0.05% eyedrops [760].

10.1.3 Allogeneic serum tears

An alternative to autologous serum tears is the use of allogeneic serum eye drops from healthy donors. Allogeneic serum eye drops may have an advantage in patient-specific conditions such as poor venous access, fear of needles, logistical problems, cognitive decline, advanced age, limited mobility, systemic diseases and blood dyscrasias [761]. In a prospective, randomized crossover trial

of severe dry eye participants, a group was randomized to either receive autologous serum drops for one month, followed by a one-month washout, before receiving allogeneic serum drops for one month and the other group was treated with the serum preparations in reverse order. There was no difference in OSDI score at the end of the trial, with comparable efficacy and tolerability [762]. In a randomized clinical trial of 63 severe dry eye participants comparing autologous versus allogeneic serum drops and umbilical cord serum (UCS) drops there was a significant improvement in dry eye signs, such as Schirmer, TBUT and fluorescein and lissamine green staining measurements and symptoms [763]. However, there were no noticeable differences between the treatments. Allogeneic serum eye drops seem to be a safe and efficacious alternative for certain populations of dry eye patients with limited access to autologous preparations.

In summary, there is evidence from RCTs and other high quality meta-analyses and reviews demonstrating the efficacy and rapid onset of improvement of patient symptoms and signs to treat DED for both autologous and allogeneic preparations. However, further RCTs, in addition to comprehensive guidelines for the preparation of these products, are required for more thorough assessments of their efficacy and potential adoption in treatment of patients with severe DED.

10.1.4 Platelet derived preparations

These preparations differ from autologous serum tears in that they are diluted in plasma, which contains clotting proteins and biologically active agents derived from platelets, such as epidermal growth factor, transforming growth factor-beta, platelet-derived growth factor, NGF and insulin-like growth factor. Although many platelet-rich formulations have been described, normally these involve isolating and concentrating platelets within differing volumes of plasma, and the platelets are then activated to release growth factors.

A systematic review and meta-analysis of platelet-based eye drop therapies for DED included 19 prospective studies of different formulations, such as platelet-rich plasma (PRP) and PRGF, compared outcomes with either tear supplements or autologous serum tears, observing both signs and symptoms of DED before and after treatment [764]. Of the ten comparative studies included, six were randomized and four were non-randomized studies. Three were prospective and six were retrospective. In terms of symptom changes after platelet-based therapies, there were significant changes in the pooled standardized mean difference and also in the overall effect size. Dry eye clinical signs, tear quality, tear quantity and corneal staining demonstrated statistically significant changes in the pooled standardized mean difference and overall effect size. However, this paper demonstrated a significant improvement in dry eye symptoms and signs with PRP only when these were compared to tear supplements. The study did not demonstrate significant differences for dry eye parameters between PRP and autologous serum.

10.1.5 Platelet Rich Plasma (PRP)

This formulation is prepared from a plasma fraction that is extracted and then centrifuged, to obtain a layer of PRP, using sodium citrate as an anticoagulant. The product is aspirated and diluted for administration from sterilized bottles with eyedrop applicators.

An interventional case series of 368 participants with moderate-to-severe DED that used PRP eye drops six times a day for six weeks reported that 87.5% of participants showed a statistically significant improvement in symptoms, as measured by OSDI, and 76.1% demonstrated a reduction in corneal staining from baseline [765].

An RCT was undertaken in which monthly lacrimal gland injections of autologous PRP with topical HA drops (n=15) was compared to HA eye drops only (n=15) for

participants with Sjögren disease [766]. At 90 days, every patient in the treatment group demonstrated significantly improved signs, such as a reduction in corneal staining, an increase in mean Schirmer test value, and an increase in TBUT. Improved symptoms in OSDI scores were also noted, and no adverse effects were observed. Although limited by the small sample size of 30 participants, this study suggests that lacrimal gland injections of PRP may be an effective intervention for severe Sjögren disease [766].

A prospective, randomized, masked intervention study on 44 participants with aqueous deficient DED treated with PRP eye drops compared results with 39 participants treated with tear supplements for 30 days [767]. PRP treatment resulted in a significant reduction in symptoms, hyperemia, osmolarity and corneal and conjunctival staining, as well as an increase in visual acuity, tear production and caliciform cell density at 15 and 30 days of treatment, relative to control.

In a systematic review of 38 papers evaluating PRP treatments for DED [768], most clinical studies reported improved patient signs and symptoms with an increasing variety of human platelet products, PRP eye drops, human platelet lysate and platelet gels. Due to variations in production methods and study designs, as well as inconsistent terminology, it was suggested that characterization of platelet products is needed for proper evaluation across studies.

A prospective RCT randomly assigned 38 participants with primary Sjögren disease to use either autologous serum or PRP eye drops for 12 weeks [769]. Corneal and conjunctival staining scores and TBUT significantly improved at 4 and 12 weeks in both groups, with no significant difference between the groups being observed. Schirmer and OSDI scores, conjunctival metaplasia grade and goblet cell density grade did not significantly change in either group. These results demonstrate that both autologous serum and PRP eye drops are equally

effective in the management of Sjögren disease. The authors concluded that as the preparation time of PRP is shorter than that of autologous serum, that PRP could be considered a useful alternative treatment for patients with Sjögren disease [769].

10.1.6 Plasma Rich in Growth Factors (PRGF)

PRGF is formulated from blood placed in tubes that contain sodium citrate anticoagulant and are spun in a centrifuge to isolate and aspirate the PRP, free of leukocytes. The platelets are then activated to release growth factors by the addition of calcium chloride. The resulting eye drops are rich in biologically active mediators such as growth factors, neurotrophic agents, vitamin A and fibronectin and do not contain high levels of pro-inflammatory molecules. Although similar in preparation to PRP, PRGF is considered a subtype of PRP that is high in growth factors, devoid of leukocytes and lacking proinflammatory activity [770].

A longitudinal, retrospective, comparative, descriptive study of 77 eyes of 42 patients with DED following laser in-situ keratomileusis (LASIK) surgery was undertaken to evaluate the efficacy of 1-4 treatment cycles (1 cycle = 6 weeks) of PRGF treatment (38 eyes) compared to a control group (39 eyes) who used ocular lubricants four times per day [771]. The control group only showed a significant change before and after treatment for TBUT values. There was a statistically significant improvement in visual acuity, TBUT, OSDI score, reports of frequency and severity of DED symptoms and Schirmer test scores after PRGF treatment and no adverse events were reported. These results suggest that PRGF eye drops are effective for the improvement of dry eye symptoms and signs in patients undergoing LASIK surgery in comparison to conventional dry eye therapy [771].

In a retrospective, multicentre interventional case series of participants that used PRGF eyedrops for the management of different ocular surface disease for the

first time, 61 participants suffered from DED [772]. In this subgroup, corneal epitheliopathy, measured with standardized corneal fluorescein staining scales, and symptoms measured by the SANDE questionnaire, were significantly improved at three months after treatment. At the final visit, 74.3% of participants showed an improvement in corneal staining from baseline. Only one participant described an ocular surface burning sensation as a side effect.

An observational, longitudinal study compared the efficacy of PRGF in 59 participants, when added to standard treatment protocols for DED, such as tear supplements, lid hygiene, and anti-inflammatory therapies compared to standard treatment alone in 43 participants, after three months of treatment [773]. Symptoms, as measured by the OSDI and SANDE questionnaires, and ocular redness and TBUT were significantly improved. However, no significant difference between groups was found in corneal staining.

A retrospective study involved 83 participants with DED who received PRGF eye drops in addition to standard DED treatment over a three-month period [774]. Significant improvements from baseline in OSDI symptoms and Schirmer test score were noted. The group treated with PRGF demonstrated improved subbasal nerve plexus metrics as determined by *in vivo* confocal microscopy when compared to standard DED treatment alone.

10.1.7 Autologous serum versus PRP or PRGF

Few studies have directly compared outcomes in participants treated with autologous serum versus PRP. One three month, non-randomized trial compared the outcomes of 22 participants with primary Sjögren disease treated with either 100% autologous serum or 100% PRP [775]. Signs and symptoms were reduced in both groups, and significantly greater improvement in visual acuity and OSDI was observed in the autologous serum group. No significant differences were observed in corneal staining, TBUT or Schirmer test. A network meta-analysis

reviewed 39 studies involving both pharmacological and blood product therapies for DED, with >50% being RCTs [776]. The authors concluded that treatment with platelet lysate or PRP improved OSDI and corneal staining more than autologous serum, but described all pairwise comparisons as “low certainty of evidence” because of study limitations, inconsistency, and imprecision.

A single-centre, randomised, double-masked clinical trial was conducted on 96 subjects with moderate-to-severe DED that compared four-week treatments of PRP drops and autologous serum [777]. After four weeks of treatment, there was no significant difference in OSDI scores, TBUT, ocular surface staining, Schirmer score, meibum quality or expressibility between groups [777].

The use of serum tears in 40 participants with persistent corneal epithelial defects, despite the use of amniotic membrane grafting, was reported and showed enhanced healing and better vision recovery relative to artificial tear use [778].

10.1.8 Umbilical cord serum (UCS) eye drops

Allogeneic UCS eye drops, prepared from cord samples collected from donors during the birthing process, contain higher concentrations of epidermal growth factor, transforming growth factor-β, NGF, and substance P than autologous serum drops [779]. UCS can provide growth factors that facilitate proliferation, migration, and differentiation of the ocular surface epithelium [780]. These components can be stable for up to one month at 4°C and three months at -20°C [779]. An advantage of UCS over other hematopoietic blood products is that a considerable amount of serum can be collected from the umbilical vein at one time, instead of performing multiple phlebotomies. Another advantage is cost saving, as unlike the case of autologous serum, regulatory bodies do not require cord donors to undergo additional infection screen as this would already be completed as part of the banking requirements of a cord blood bank [781].

A prospective, interventional non-controlled case series, including 20 participants, observed that UCS use was associated with increased corneal epithelial nerve density, and an improvement in nerve morphology and corneal sensitivity [782]. A prospective, two-month, controlled case series compared UCS with autologous serum tears for Sjögren and non-Sjögren-associated DED [783]. Both treatments increased the TBUT similarly, but UCS resulted in a significantly larger decrease in ocular surface staining scores and symptoms than did autologous serum tears. However, a more recent RCT comparing autologous serum tears, allogeneic serum tears and UCS on a total of 63 participants over three months showed similar clinical benefits for improvements in TBUT, ocular surface staining scores and symptoms scores between the three serum types [763].

10.1.9 Whole blood autologous tears

The use of whole blood by using a “finger-prick” protocol to deliver autologous whole blood drops as a treatment for DED has emerged as an innovative option. This technique involves collecting a small drop of the patient‟s blood through a simple finger-prick method and using the autologous whole blood to treat dry eye signs and symptoms [784-789].

A multicentre RCT compared thirty participants who were treated with the finger-prick autologous blood four times a day in addition to their conventional medical dry eye therapy, with a group of 30 participants with conventional dry eye treatment alone [787]. The addition of autologous blood eye drops via a finger-prick significantly decreased OSDI scores as compared to conventional therapy-alone. No adverse effects were noted. A prospective, interventional case series of sixteen participants suffering from DED were treated with a drop of their own blood via the finger-prick method and demonstrated an improvement in corneal staining, TBUT, visual acuity and ocular comfort index [788]. After four weeks of cessation of the therapy, corneal staining grade and symptoms worsened.

This technique appears to be patient-friendly and cost effective, does not require product refrigeration, and is readily available. However, it may be limited by the patient‟s willingness or ability to perform the finger-prick process multiple times a day.

10.2 Lubricin

Lubricin is a natural, mucinous surface-active, 277 kDa glycoprotein synthesized and secreted by chondrocytes and synoviocytes that plays an important role in mammalian cartilage integrity [790]. Lubricin coats the cartilage surface, providing boundary lubrication and preventing cell and protein adhesion to reduce the shear stress and cartilage degradation on articular surfaces. Thus far, two forms of recombinant human lubricin with relevance to DED have been produced. Full-length recombinant human proteoglycan (rhPRG4) [791] at 0.015% concentration applied twice daily over a two week period was superior to 0.18% HA-containing tear supplements, in improving signs and symptoms of DED as well as corneal staining score in a small scale RCT [792]. *In vitro*, rhPRG4 has been shown to reduce inflammation-induced cytokine production and NF-κB activity in corneal epithelial cells, as well as to bind MMP-9 and inhibit its activity [793].

Another form of recombinant human lubricin (ECF843), produced from the same cell line as rhPRG4, but manufactured using a different process, was assessed in a dry eye clinical trial, but failed to improve signs or symptoms of dry eye relative to vehicle. Significant differences in the molecular structure and function of ECF843 and rhPRG4 may account for the disparate dry eye clinical trial results [793]. Further *in vivo* studies are required to determine the effectivity of lubricin in the management of DED.

10.3 Amniotic membrane and amniotic membrane extract drops

Severe DED can lead to significant central or diffuse, coarse or confluent epithelial micro-erosions of the cornea. These erosions may then coalesce and form epithelial defects, with increased risk of infection or ulceration and subsequent loss of vision. Amniotic membrane grafts can be considered to enhance the healing of the corneal epithelium and decrease ocular surface inflammation. PROKERA® SLIM (Bio-TissueDoral, FL, USA) is a human amniotic membrane contained within a single plastic ring that permits the device to be inserted onto the ocular surface like a scleral contact lens. The membrane typically dissolves within three to five days, although the membrane does not have to be dissolved for it to be removed. Thus far, no RCTs have been published on its use. Two multicenter, retrospective chart review studies reported results in participants with severe DED, refractory to various other treatments, including autologous serum tears and CsA 0.05%, who received cryopreserved amniotic membrane [794,795]. After a treatment period of two to seven days, two-thirds to three-quarters of the participants reported significant improvement in symptoms as well as demonstrating an improved ocular surface staining score at three months. About 10% of participants required repeat treatment to complete healing during the three-month follow-up period. Ocular discomfort was reported in both studies, albeit without the mention of severity or frequency. A cost effectiveness decision tree model found the societal (direct and indirect) cost of cryopreserved amniotic membrane was less than that of topical CsA A 0.05% over a year (cost/utility: $18,275/0.78 vs. $20,740/0.74). If examining direct costs only, topical CsA was the least expensive option over a one year timeframe ($4,112 vs. $10,300) [796].

A dried, gamma ray-sterilized amniotic membrane applied using a bandage contact lens is another in-office, sutureless and painless treatment that can be used for treatment of severe DED. A retrospective review of 56 eyes in 52

participants demonstrated improvement of corneal epithelial erosions after one to two weeks of treatment [797]. The amniotic membrane is semi-transparent, and many participants report blurred vision, whether it is cryopreserved or dehydrated. A large diameter (17mm) dehydrated amniotic membrane with a 6 mm central aperture, (Omnigen® VIEW, NuVision Biotherapies, Nottingham, UK) under an 18mm, 74% water content soft bandage contact lens (OmniLenz®, NuVision Biotherapies, Nottingham, UK) can be used to overcome vision-related issues. A prospective study included 35 participants diagnosed with moderate-to-severe DED treated with this membrane bilaterally for 8-10 days, who demonstrated a 31% improvement in patient symptoms and 42% decrease in ocular surface staining score [190]. A further RCT in participants with moderate-to-severe DED showed two applications for one week in total significantly and rapidly improved dry eye symptoms as well as ocular surface signs for at least three months as well as enhancing corneal nerve health while reducing activated/mature corneal inflammatory cell numbers [798].

A study reviewed the ability of amniotic membrane extract drops to treat ocular surface disease in 12 studies [799]. In a review of 296 eyes of 205 participants, 59% of eyes were treated for DED, 23% for an epithelial defect, and the rest (18%) for other corneal wound healing disorders. Three main types of preparations were described, lyophilized, homogenized, and fresh amniotic membrane extract drops. All studies showed various grades of improvement in both signs and symptoms, the incidence of ocular side effects was 2.3% and it was concluded that overall, the available literature suggests that amniotic membrane extract drops are a valuable tool in the treatment of ocular surface disorders [799].

10.4 Cenegermin 0.002%

Nerve growth factor was first discovered in the 1950s and has since been shown to be essential to corneal and conjunctival trophism, sensitivity and healing [800-802]. Cenegermin-bkbj ophthalmic solution 0.002% (Oxervate®; 20 µg/mL; Dompé farmaceutici, Milan, Italy) is an ophthalmic solution containing a recombinant form of human NGF [803]. Currently, it is FDA-approved for the treatment of neurotrophic keratitis [804], however owing to the agent‟s mechanism of action, it is being investigated for its ability to treat DED [805].

Cenegermin-bkbj was studied in two RCTs on participants with Stage two (moderate) or three (severe) neurotrophic keratitis [806,807] with 65 to 72% achieving complete corneal healing after eight weeks, compared to 17 to 33% of the vehicle control groups [806,807]. The most common adverse reaction was instillation-site pain, which was reported in approximately 16% of participants. Consistent with these findings, another study demonstrated the safety and efficacy of topically-applied human NGF (at 20 µg/mL or at 4 µg/mL concentrations) in 40 consecutive participants with moderate-to-severe DED dosed two times per day for 28 days [805]. However, because there was no control group, it was concluded that the improvement of symptoms and signs after topical recombinant human NGF treatment may have been due, at least in part, to a placebo effect.

10.5 RGN-259 0.1%

RGN-259 0.1% (RegeneRx Biopharmaceuticals; Glen Echo, MD, USA) contains a synthetic copy of the naturally occurring molecule thymosin beta 4 (Tβ4) [808]. In a dry eye mouse model, topical RGN-259 increased corneal epithelial cell migration, promoted mucin and goblet cell recovery and reduced inflammation [809].

In a Phase III study, a topical ophthalmic solution was applied five times per day in participants with Stages two and three neurotrophic keratitis, resulting in an increased proportion achieving complete healing, a faster rate of healing, reduction in lesion size and severity, and improved comfort measurements, with the drug being safe and well tolerated [808].

10.6 Silk-derived protein (SDP-4)

Tear film mucins enhance ocular surface wetting properties due to their amphiphilic chemistry, while also providing natural bioactivity that works towards maintaining a healthy ocular surface [810]. Silk-derived protein (SDP-4) is a naturally derived protein from the Bombyx mori silkworm cocoon [811]. Similar to mucin, it improves wetting of the ocular surface and acts as a replacement for demulcents and surfactants that may elicit higher toxicity profiles [812].

In vitro studies have demonstrated silk fibroin‟s ability to modulate pro-inflammatory signaling through inhibition of the NF-kB pathway [813-815]. Aqueous silk fibroin protein also was successfully used to treat ocular surface disease in a murine animal model of DED, improving clinical outcomes by increasing tear production, decreasing corneal irregularity, inhibiting epithelial cell detachment, and increasing goblet cell density through reduced inflammatory cytokine gene expression and secretion of intercellular adhesion molecule-1, MMP-2 and MMP-9 [816].

In the first known in-human clinical trial using SDP-4, participants with moderate-to-severe DED were dosed twice daily for up to 84-days in a double-masked, randomized, parallel-group, and serial cohort design [817]. Participants who received eye drops containing 1% SDP-4 had significantly increased TBUT from baseline, which was significantly greater than that observed in the vehicle control

group. Patient symptoms were also reduced, but similarly to the control. More than 90% of participants found the formulation comfortable.

10.7 Topical insulin

Expression of insulin receptors has previously been detected on the ocular surface [818] as well as in the lacrimal gland [819,820]. In addition, insulin-like growth factor has been detected in tears [821,822].

The potential benefits of topical insulin treatment to ocular surface issues were first reported in 2013 in a small-scale retrospective review of diabetic participants undergoing vitreoretinal surgery [823]. Topically applied insulin drops accelerated the healing of corneal epithelial defects created during surgery, improving visualization of the fundus intraoperatively, when compared to conventional treatment.

A single clinical trial involving 160 diabetic participants with DED compared topical insulin treatment to tear supplements, applied four times daily, over a four-week period of treatment [824]. A significant proportion of participants in both treatment arms showed improvement in their dry eye symptoms compared to baseline (66% and 63%, in the topical insulin and artificial tear groups respectively) but there was no significant difference between the two groups. This study failed to show any improvements in physician-measured tear film and ocular surface parameters.

11 Treatments for anatomical surface abnormalities

11.1 Ocular surface anatomical irregularities

Ocular surface abnormalities that impact ocular surface topography can contribute to and exacerbate DED by virtue of creating an irregular surface, over

which tear spreading and the creation and maintenance of a structured tear film may be impaired.

11.1.1 Conjunctivochalasis

Conjunctivochalasis is characterized by loose, redundant, non-edematous inferior bulbar conjunctiva located between the globe and the eyelid. This age-related ocular condition is often overlooked despite its significant impact on quality of life [825,826]. Similarly to the milder form of conjunctival folds (described as lid parallel conjunctival folds; see Section 11.1.2), conjunctivochalasis is commonly associated with DED, with a reported prevalence as high as 54% among individuals with DED [827].

While the exact etiology of conjunctivochalasis is not known, risk factors and associated conditions include age, female sex, contact lens wear, DED, hyperopia, the presence of pinguecula, ultraviolet exposure and eyelid disorders [826]. The underlying mechanism linking conjunctivochalasis to dry eye symptoms may involve its effect on lowering TMH [828,829]. Additionally, epiphora is a common symptom, particularly when conjunctivochalasis is located medially, and this can often be alleviated through surgical correction [830,831]. Participants with nasal conjunctivochalasis have worse dry eye symptoms [832] and signs (lower Schirmer scores, more meibomian gland dropout and eyelid vascularity) than those with conjunctivochalasis temporally or those without [825].

Conjunctivochalasis has been closely associated with MGD and meibomian gland drop-out, suggesting that lipid deficiency may play an indirect role through a lack of lubrication, resulting in increased friction and „dragging" of the conjunctival tissue over the ocular surface [833]. An alternative hypothesis is that conjunctivochalasis affects blink completeness, which drives meibomian gland drop out and subsequent lipid deficiency. In a study of 39 participants who underwent conjunctival tissue excision for conjunctivochalasis, OSDI, TBUT,

corneal staining and tear meniscus area were reported to be improved three-months post-operatively [834].

Management of conjunctivochalasis includes ocular lubrication through administration of topical lubricants, anti-inflammatory agents, ointment at night and various surgical techniques (see Section 14.4.1) such as cauterization, excision, scleral fixation of the conjunctiva, conjunctival ligation, laser conjunctivoplasty, radiowave electrosurgery and plasma-based conjunctivoplasty [835-839]. Two publications have proposed the use of radiofrequency to manage conjunctivochalasis [839,840] and two other publications have shown that HA-based tear supplements can be helpful in the management of symptoms secondary to conjunctivochalasis [632,841].

11.1.2 Lid Parallel Conjunctival Folds

Lid parallel conjunctival folds are characterized by folds in the inferonasal and inferotemporal quadrants of the bulbar conjunctiva, parallel to the lower lid margin [842]. In a systematic review of 26 studies, both lid parallel conjunctival folds and conjunctivochalasis were found to be significantly associated with dry eye symptoms in both contact lens wearers and non-lens wearers [838].

Treatment of DED secondary to lid parallel conjunctival folds primarily consists of regular lubrication [838].

11.1.3 Pingueculum

A pinguecula describes a fibrofatty, degenerative change in the bulbar conjunctiva, nasally and/or temporally, within the palpebral aperture [843]. Its etiology is thought to be similar to that of pterygium formation, being related to UV exposure [843], and its physical presence similarly can alter lid/globe alignment affecting tear spreading and function. As with pterygium, surgical excision of pinguecula has been found to reduce both the signs and the symptoms of DED

[844]. However, the high-quality evidence for this remains to be confirmed (see Section 14.4.2).

11.1.4 Pterygium

A pterygium is a progressive, wing-shaped fibrovascular growth of the nasal and/or temporal conjunctiva that extends over time onto the cornea [845]. It is one of the most commonly observed ocular conditions, with a global average prevalence of 10.2% [846]. It is predominantly associated with high levels of ultraviolet light exposure [845]. Pterygium presence is a recognized risk factor for developing DED [13], resulting in 63.6% of participants with primary or recurrent pterygia reporting dry eye symptoms [847], that include irritation, dryness, lacrimation and foreign body sensation [845]. Tear breakup time is shorter in eyes with pterygium [848], and significant differences in meibomian gland scores, lid margin abnormalities and meiboscores have also been reported relative to a control group without pterygium [848,849]. Physical presence of a pterygium thus disrupts the normal function of the tear film and surgical excision of the pterygium (see Section 14.4.2) often offers a means of reducing dry eye symptoms [850].

12 Nutritional modifications and alternative therapies

Growing interest exists in the potential role of dietary modification and supplementation and that of alternative therapies in the management of DED. The TFOS Lifestyle Report: Impact of Nutrition on the Ocular Surface discusses nutritional impacts on DED [16] and other reviews also explore these factors in detail [18,851,852].

12.1 Macronutrients

PUFA such as omega-3s can play a critical role in improving clinical symptoms associated with inflammatory disorders of the ocular surface, including DED (see

Figure 2). Derivates of omega-3 fatty acid metabolism, such as resolvins (D1 and E1) and protectins, have been shown to resolve acute inflammation of the ocular surface by inhibiting leukocyte infiltration and enhancing macrophage activity, resulting in improved corneal epithelial integrity and tear production [16,853-856]. The therapeutic role of neuroprotectin D1, derived from docosahexaenoic acid, in suppressing ocular surface inflammation and neuroprotection has been extensively studied [857,858]. The pathogenic disruption of corneal nerves due to various underlying aetiologies can result in loss of corneal epithelial integrity, delayed wound healing and ulceration [859]. A study demonstrated an association between omega-3 PUFA intake and improved corneal neuronal parameters, therefore supplementing these essential fatty acids may be beneficial for ocular surface health [860].

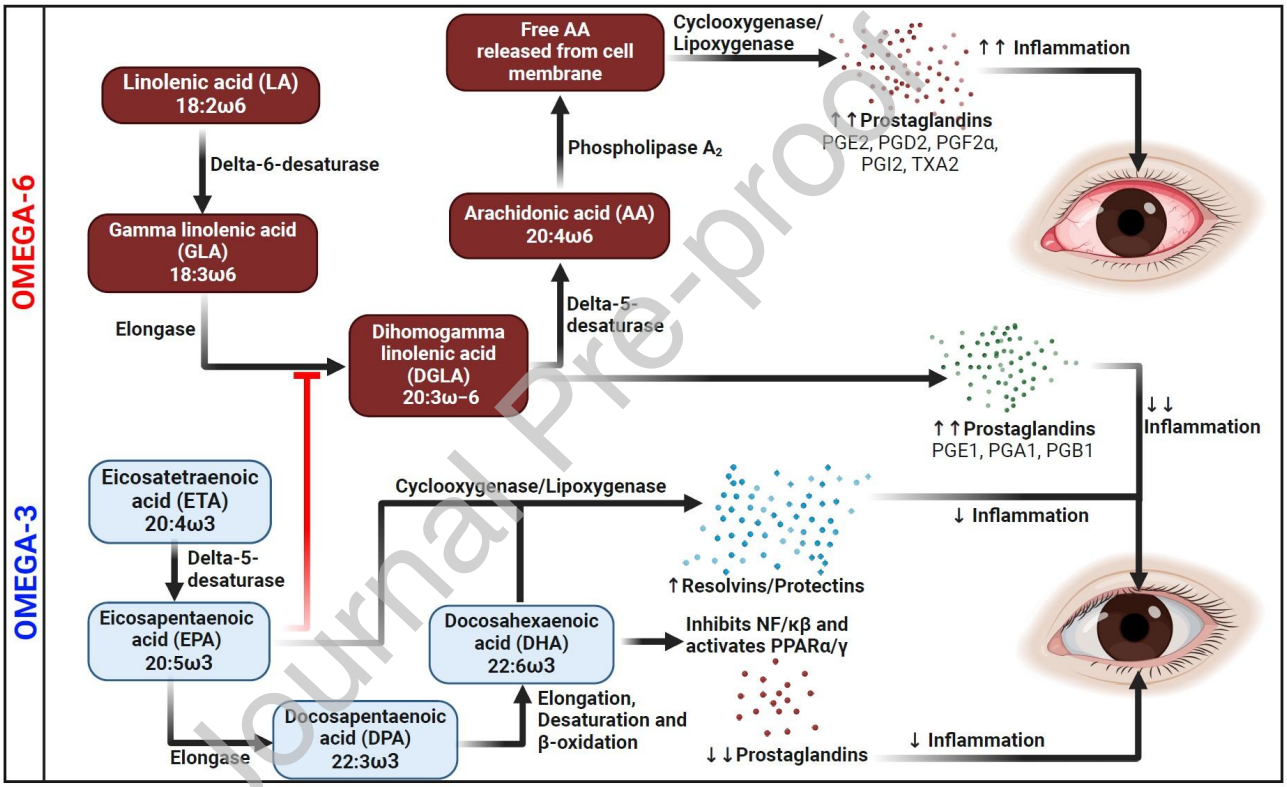

Figure 2: *Key metabolic pathways for omega-6 and omega-3 fatty acids. The conversion of short-chain to long-chain omega-3 and omega-6 fatty acids occurs through two independent metabolic pathways that share, and compete for, the same series of enzymes. Broadly speaking, the omega-6 pathway results in the production of inflammatory mediators; through a series of steps, linolenic acid is converted arachadonic acid, which is further metabolized to bioactive metabolites that include a range of prostaglandins. The omega-6 pathway also leads to generation of some anti-inflammatory mediators, in particular PGE1, although predominantly generates pro-inflammatory mediators. In the omega-3 pathway, alpha-linolenic acid is converted to long-chain fatty acids that include eicosapentaenoic (EPA) and docosahexaenoic acid (DHA), subsequently leading to the generation of various anti-inflammatory mediators, including families of resolvins and protectins; these are relevant in the context of dry eye as they can modulate physiological processes that include epithelial cell survival, recovery from oxidative stress and wound healing. Diets with a high-omega-6 to omega-3 ratio are considered pro-inflammatory, which increase the likelihood of signs and symptoms of DED, due to a bias towards the production of pro-inflammatory mediators. The red line 'inhibits" that pathway. Created in BioRender by Rohan Bir Singh MD (2025) https://BioRender.com/ n49o832.*

As highlighted in a Cochrane systematic review, the potential role of PUFAs in the treatment of DED remains uncertain [861].

The DREAM study found benefits among patients with DED who were randomly assigned to receive supplements containing 3000 mg of n-3 fatty acids or 5000 mg olive oil placebo for 12 months, but did not demonstrate significantly better outcomes with the n-3 fatty acids than those receiving the placebo [862,863], and thus called into question the benefits of PUFAs in the management of DED. Since the LTα genotype affects the inflammatory response to omega-3 PUFA, this should be considered as a potential confounding factor for treatment outcomes and may explain some of the differences reported between studies [864].

In a multi-center clinical trial, dietary supplementation with omega-3 PUFAs (2400 mg/day) resulted in significant improvement in DED symptoms, Schirmer score, TBUT, tear osmolarity and goblet cell density, compared to the placebo-treated control group [865]. Furthermore, a meta-analysis of 19 RCTs assessing the therapeutic efficacy of omega-3 PUFA for DED indicated significant improvement in dry eye symptoms and signs with its dietary supplementation, [866]. Additionally, a large cross-sectional study including women aged 45–84 years showed a reduced risk of DED in those with higher omega-3 fatty acid intake, and higher omega-6 compared to omega-3 PUFA consumption resulted in an increased risk of DED [867]. The same authors showed that regular tuna consumption (a rich source of omega-3) significantly reduced the risk of DED [867]. These findings point towards the importance of omega-3 PUFA in maintaining ocular health and preventing DED, although the evidence is not uncontroversial [862].

Other vegetable oils and seeds, such as extra virgin olive oil and flaxseed oil, have been shown to play a role in maintenance of ocular surface health [124,126,868-871]. Oral administration of flaxseed oil (rich in α-linolenic acid) for 180 days improved the signs and symptoms of DED compared to baseline values [871]. In contrast, oils from palm, corn, and soybean have a high concentration of omega-

6 compared to omega-3 fatty acids, which can potentially promote chronic inflammation and adverse effects on the ocular surface [872]. The ingestion of trans fatty acids from hydrogenated vegetable oils have been associated with systemic inflammation, which may further adversely impact ocular surface health [873]. A recent systematic review has discussed efficacy and the potential use of topical omega-3 PUFA, although there is still only a small number of studies and a limited availability of such products currently [874].

In conclusion, the overall evidence would suggest a beneficial effect of the use of oral supplements of omega-3 PUFA, however, the optimal source, dosage and/or ratio of omega-3 to omega-6 requires further investigation.

12.2 Micronutrients

Micronutrients such as vitamins (see Section 6.1.1.10) and minerals play a critical role in maintaining ocular surface health [15,17,851].

Vitamin A is essential for maintaining immune function as well as integrity of the ocular surface epithelium [875,876]. Deficiency in vitamin A can lead to severe ocular conditions such as xerophthalmia and corneal perforation, making it a significant cause of childhood blindness in developing countries [877]. In developed countries, gastric bypass surgery (often undertaken for weight loss) and alcoholism are common causes of vitamin A deficiency in adults [877]. In addition, it can occur due to restrictive diets in both adults and children [878-880].

Oral vitamin A supplementation might help in DED if there is a deficiency, but its role in the management of patients with non-vitamin A deficient DED remains unclear [15]. Short-term oral vitamin A supplementation improved the quality, but not quantity, of tears in patients with DED [881]. It was suggested that future studies should involve larger patient samples and longer periods of vitamin A supplementation. Administration of topical vitamin A drops have shown more consistent improvements in tear film stability and ocular surface health in patients

with DED [15,164]. Combination therapy with vitamin A and CsA might be beneficial in patients with MGD-driven DED, with a study showing greater improvements in TMH, OSDI score, Schirmer test and TBUT compared to CsA in association with 0.1% HA topical drops alone when used for 12-weeks [882].

Vitamin B12 is crucial for deoxyribonucleic acid synthesis and nerve function, with deficiency linked to an increased risk of DED [20]. In a study conducted in 30 post-menopausal women, application of eye drops containing vitamin B12, 0.3% HA, P-plus, sodium chloride, potassium chloride, calcium chloride, magnesium chloride, and stabilized complex oxychloride over a period of one-month resulted in significant improvement in ocular surface disease parameters and dry eye symptoms from baseline [168]. In another study, participants with Sjögren disease (with severe DED) treated with a combination of vitamin B12 and topical HA-containing drops showed significant improvement in Schirmer test score, OSDI, TBUT and tear fluorescein clearance test [883].

Vitamin D is another critical micronutrient that plays an essential role in calcium homeostasis, immune regulation, and cell proliferation and differentiation [884]. A meta-analysis of 14 observational studies showed that serum 25-hydroxy calcitriol was significantly lower in participants with DED [172]. Moreover, a randomized clinical trial including 100 Vitamin D deficient participants reported significant improvement in Schirmer test scores, TBUT and osmolarity on supplementing the diet with oral Vitamin D for eight weeks [885].

Minerals like selenium, zinc, and copper also play significant roles in ocular surface health, with selenium particularly noted for its antioxidant properties [886]. Selenium is essential for generation of selenoprotein P in the lacrimal glands and present in tears [887]. Studies have shown significantly lower levels of selenoprotein P in participants with DED, which may be associated with oxidative damage at the ocular surface [887].

12.3 Natural products and interventions

12.3.1 Acupuncture

The therapeutic effects of acupuncture are believed to occur via several mechanisms, including reduced expression of proinflammatory cytokines in chronic inflammatory conditions such as DED [888-891]. Acupuncture is also considered to increase systemic blood flow, reduce pain sensation, and modulate the sympathetic system [892-894]. Several studies have shown statistically significant improvements in symptoms and the ocular surface of participants with DED who underwent acupuncture treatment [895-901]. However, these findings were not replicated in all studies [902,903].

A prospective, randomized, double-masked clinical trial that included a sham acupuncture control group showed that two consecutive daily sessions of acupuncture improved dry eye symptoms [888]. The study suggested that acupuncture for DED may primarily modulate pain intensity or threshold rather than enhancing lacrimal gland function, as no improvements in tear flow, TBUT or ocular surface staining were observed. A systematic review and meta-analysis of acupuncture combined with tear supplements in managing DED was undertaken [904]. The review of sixteen studies including 1383 participants concluded that this integrative treatment was safe and effective when assessing objective indicators of DED.

In a randomized parallel group study, it was found that acupuncture over eight sessions improved conjunctival redness significantly compared to participants who used only an artificial lubricant [905].

12.3.2 Herbs and spices

Herbs, typically referring to the leaves and stems of soft-stemmed plants grown in temperate climates, have shown potential therapeutic effects on eye health.

Cassiae semen *(Leguminosae)*, which contains the vital compound emodin, plays a significant role in the linoleic acid peroxidation system due to its antioxidant properties. An RCT showed that antioxidant supplements containing anthocyanosides, astaxanthin, vitamins A, C, and E, and several herbal extracts, including Cassiae semen and Ophiopogonis japonicus can enhance tear production and tear film stability by reducing ROS [906].

Another herb, Lycii Fructus, contains the antioxidants zeaxanthin and lutein and anti-inflammatory polysaccharide [907]. It also contains lycium barbarum (goji berry), which has anti-inflammatory, and anti-apoptotic effects. Lycii Fructus has been reported to improve DED in rats by increasing tear volume and TBUT and reducing corneal and conjunctival fluorescein staining [908].

Curcumin is a polyphenol that is isolated from the plant Curcuma-Longa, and is known for its anti-oxidative properties by scavenging reactive nitrogen and oxygen species, and has anti-inflammatory properties [909,910]. *In-vitro* studies have shown the therapeutic effect of curcumin against hyperosmolarity-induced IL-1β upregulation in corneal epithelial cells through p38 mitogen-activated protein kinase (MAPK)/NF-κB pathways [911].

Achyranthis radix contains several anti-inflammatory molecules such as saponins and phytoecdysones [912]. In a pre-clinical study, topical treatment with Achyranthis radix improved corneal surface irregularities, reduced corneal epitheliopathy and increased conjunctival goblet cell density [701]. Herbal extracts ferulic acid (from Angelicae sinensis Radix) and Kaempferol (found in Ginkgo biloba and propolis) have been shown to downregulate pro-inflammatory cytokines (IL-1B, IL-6, IL-8, and TNF-α) in human corneal epithelial cells [913].

Topically applied esculetin, extracted from the Chinese herb "Qinpi," has been shown to inactivate the ERK1/2 pathway, associated with chronic ocular surface

inflammation. This action was demonstrated to enhance the anti-inflammatory function of CsA in a rabbit dry eye model [914].

Although preliminary evidence appears favorable, well-designed clinical trials are necessary to assess the possible benefit of dietary herbs and spices in ocular surface disease.

12.3.3 Hydration

Adequate hydration is essential for optimal bodily functions, including those of the ocular surface. While there is limited direct evidence linking hydration status to ocular surface health, studies have shown that plasma osmolality, a marker of systemic levels of hydration is directly correlated with osmolarity of the tear film [915,916]. Patients with DED often exhibit higher plasma osmolality, suggesting that dehydration may impair lacrimal gland function and increase tear osmolarity [917]. Interestingly, a cross-sectional study including 51,551 individuals in the Netherlands showed that higher water intake was observed in individuals with DED [918]. Evidence from clinical trials investigating the effect of water intake on ocular surface parameters is currently lacking.

12.3.4 Lactoferrin

Lactoferrin, an iron-binding glycoprotein, is produced by mucosal epithelial cells, and has well established anti-inflammatory, antioxidant and antimicrobial functions [919]. Previous studies have highlighted a significant correlation between low tear lactoferrin levels and DED [920-922]. Oral administration of lactoferrin maintains tear secretion in a restraint and desiccating-stress-induced mouse model of DED. This effect is postulated to be mediated through gut microbiota modulation [923].

The hyperosmolar environment in DED triggers inflammatory and oxidative cascades, resulting in impaired epithelial proliferation and differentiation [924]. The use of lactoferrin in treating DED is based on its ability to interrupt the vicious

cycle, particularly by addressing underlying inflammation and oxidative stress. Lactoferrin, through its iron-chelating properties, provides oxygen-free radical and hydroxyl scavenging activities [718,925,926]. These actions inhibit the pro-inflammatory and tissue-damaging effects of ROS. Additionally, lactoferrin is understood to mitigate excessive inflammation by inhibiting classical complement activation and downregulating inflammatory mediators.

12.3.5 Manuka honey

As noted in Section 7.2.6, Manuka honey has antibacterial, antifungal, antiviral, anti-inflammatory, and antioxidative properties [927]. Several clinical trials have highlighted the anti-inflammatory and therapeutic effects of topical Manuka honey in natural or compounded form for managing patients with DED [928,929], MGD [930,931], anterior and posterior blepharitis [591,595,932], and contact lens related dry eye [933]. A meta-analysis of five studies (including 323 participants) assessing the application of honey and its derivatives in the treatment of DED, showed a significant improvement in patient symptoms as measured by OSDI, along with improvements in Schirmer test and corneal fluorescein staining scores [929].

The therapeutic effects on ocular surface disease of honey as a dietary supplement has been less thoroughly explored. A double-masked RCT assessing oral royal jelly (a gelatinous substance produced by honey bees to feed the queen bees and their young) in participants with DED found significant improvements in TBUT and Schirmer test scores, particularly in participants with lower baseline scores [934]. However, no clear improvement in dry eye symptoms was observed.

12.3.6 Nutritional supplements

Data from two prospective, randomized clinical trials evaluating a dietary supplement (blink™ NutriTears®; Bausch + Lomb, Rochester, NY) containing lutein, zeaxanthin, curcumin, and vitamin D demonstrated significant improvements in tear volume and stability, as well as a reduction in level of

MMP-9 inflammatory biomarkers within the tear film [175,935]. These findings suggest it may be possible to achieve clinically meaningful benefits in the management of DED through ingesting a dietary supplement.

13 Prevention and treatment of surgical iatrogenic dry eye disease

Cataract surgery and refractive surgery can cause or exacerbate existing DED [12,936-938], resulting in an increase in dry eye symptoms and reduced satisfaction with surgical results [939,940]. Optimization of the ocular surface before and after cataract and refractive surgery has been demonstrated to reduce symptoms and improve clinical and refractive outcomes.

13.1 Dry eye disease and cataract surgery

There is consensus that the ocular surface should be optimized prior to cataract surgery [938] to decrease the rate of postoperative refractive errors [941,942], fluctuating vision, and new or worsening ocular surface related symptomatology [943]. Several prospective RCTs have been performed assessing preoperative treatment of MGD using different therapeutic interventions, including vectored thermal pulsation [940,944-946], IPL [947], and low-level light therapy [351]. Overall, these studies demonstrated improvement in the subjective symptoms and objective signs of MGD in the treatment group as compared to controls.

A prospective, randomized, open-label, crossover, multicenter study evaluated the effect of vectored thermal pulsation in participants undergoing cataract surgery with implantation of an extended depth of focus IOL [944]. Interestingly, at three months postoperatively, the group that underwent preoperative vectored thermal pulsation had a significantly lower incidence of being adversely affected by halos, but had a higher incidence of being adversely impacted by multiple or double images compared to the control group [944]. Postoperative application of thermal pulsation to the control group which had not received this treatment

preoperatively resulted in significant improvement in visual acuity and total meibomian gland score [944].

Prophylactic low-level light therapy one week before and after surgery in 73 healthy participants was compared to 80 controls in a prospective, randomized, interventional, controlled, double-masked clinical trial [351]. The researchers found significantly lower OSDI scores and higher non-invasive tear film stability values in the treated group one month after surgery [351]. Future studies on prophylactic treatment would benefit from longer follow-up.

Two studies have evaluated the benefits of applying lid hygiene either preoperatively alone [948], or with application both before and after cataract surgery [579]. Participants reported improved subjective and objective indicators of MGD. Another study examined participants with persistent post-cataract surgery DED lasting more than one month [949]. Lid hygiene with tear supplements, topical steroid drops, and ocular shampoo with TTO, compared to a similar mixture without TTO, resulted in significantly greater patient improvements in TBUT, OSDI, tear osmolarity and number of residual Demodex. There was no significant difference between the two groups in pre- and post-Schirmer test results.

13.2 Dry eye disease and refractive surgery

Dry eye symptoms in the early period post corneal refractive surgery are common and typically improve over 6-12 months [938,950,951]. However, a small subset of participants fail to respond to conventional therapy and develop refractory DED.

Studies have demonstrated the benefit of treating participants with refractory DED post-laser vision correction with modalities such as IPL [328,952], thermal pulsation [953], and warm compresses [954]. IPL was used in two prospectively designed studies involving participants who had undergone refractive surgery in the previous 10 years and had been suffering from LASIK-induced refractory

DED despite conventional treatment for at least one year [328,952]. In the first study, 42 eyes were treated with two IPL sessions, two weeks apart, resulting in statistically significant improvement at day 14 after the second treatment in the NIBUT, and at day 28 in NIBUT, OSDI, tear film lipid layer, meibomian gland quality and expressibility compared to a (non-randomized) control group (n=30 eyes) [952]. The second study was a prospective, randomized study of 50 participants comparing two IPL sessions to two IPL sessions plus a once-a-day heated eye mask in participants with refractory post-LASIK DED (experiencing moderate to severe DE following LASIK for over a year), with both groups using 0.1% HA drops on a daily basis. There was an improvement in both subjective and objective dry eye parameters in both groups, with a more pronounced effect in the group combining IPL with the heated eye mask [328], demonstrating the benefit of combining in-office procedures with at-home treatments. However, both studies examined only short-term effects (over 28 days).

A retrospective study examined the effect of vectored thermal pulsation in 109 eyes of 57 participants post-laser vision correction with refractory dry eye symptoms who failed conventional therapy [953]. There was a significant improvement in the SPEED II score when reassessed at one month and six to eight months after a single treatment. Along with the subjective improvement, objective findings of an increase in TBUT, improved meibomian gland patency and decreased corneal staining were also observed [953]. In a separate study, the low-cost intervention of performing lid warming with a heated eye mask for 20 minutes was employed in 37 participants with persistent DED at least two years post-laser vision correction in a prospective study [954]. In this open-label, non-controlled trial, a significant increase in LLT and TBUT was observed, but these parameters were assessed only five minutes following lid warming.
A masked clinical trial randomized 61 healthy participants undergoing laser vision correction to receive either IPL treatment for three sessions total: pre-surgery, postop week one and postop week three or sham treatment [955]. The IPL group demonstrated an improvement in OSDI score, NIBUT, TMH, and meibography at

the three-month follow-up visit, while the control group showed a worsening of TMH compared to baseline. However, at the six-month follow-up visit, the OSDI differences faded, but the objective tear parameters (NIBUT, TMH and meibography) were still significantly different between the IPL and control (sham) groups. The authors reported IPL to be safe and effective in the perioperative period, but the question of cost/benefit ratio in these asymptomatic and healthy individuals undergoing refractive surgery was raised. Another prospective interventional study of LASIK participants with pre-existing MGD compared vectored thermal pulsation therapy one week prior to LASIK (n=32) to untreated controls (n=26); OSDI and TBUT were significantly improved relative to preoperative baseline at three-months in the treatment group and the effects were confirmed when the control group was subsequently treated [956].

In summary, proactive management of patients with DED, especially those with evaporative DED, undergoing cataract and refractive surgery improves gland function before surgery, results in a better patient experience [944,955] and improves visual performance after surgery [957], lending support to this being recommended as standard of care in the future.

14 Surgical management

14.1 Permanent punctal occlusion

Permanent closure of the lacrimal drainage pathway can be achieved using several techniques, the most common of which is punctal cauterization. The principle is similar to punctal occlusion with punctal or intracanalicular plugs and works by conserving the volume of tears within the conjunctival cul-de-sac [958]. See Section 6.2.3 for further details.

Punctal cautery is generally reserved for participants who are symptomatically improved with temporary plugs but are unable to retain or tolerate longer-term plugs [959]. In a retrospective review of punctal cauterization in 80 participants, a

significant reduction in the proportion of participants with moderate-to-severe DED was noted. The overall rate of recanalization was 21% and this rate was higher with the ongoing, regular use of topical steroids [959,960]. Requirement for recauterization has been reported to be the lowest in patients with chronic cicatricial disorders, possibly due to contributory fibrosis associated with the underlying disease [959]. In 65 participants with cicatricial disorders, the recanalization rate was only 11% after punctal cautery and participants responded well to repeat cautery where required [961]. The most common ocular indication for punctal cauterization in the study was graft-versus-host disease (n=36), followed by primary keratoconjunctivitis sicca (n=15) [959]. The study concluded that punctal cauterization effectively treats severe ocular surface disease in participants who frequently lose punctal plugs, with 54% reporting a significant improvement in symptoms and reduced corneal staining severity [959]. The procedure was able to be easily performed in a clinical setting with minimal complications.

Another study involving 23 participants with moderate-to-severe DED who received permanent inferior punctal occlusion via cautery reported improved TBUT, OSDI scores and corneal staining, along with increased corneal sub-basal nerve density, three months after treatment [962].

Combined canalicular ablation and punctal suturing was assessed for efficacy in 11 eyes of seven participants with severe DED [963]. This surgical punctal occlusion approach demonstrated a low recanalization rate, leading to significant objective and subjective improvements in DED signs and symptoms after one year [963].

A systematic review analyzed the efficacy in treating DED using permanent punctal occlusion by thermal or surgical methods [964]. Among nine selected single-arm studies, five used thermal punctal cauterization, and four used surgical occlusion techniques. At the final follow-up, Schirmer I and TBUT

improvements were similar for both forms of punctal occlusion. Across the studies, punctal recanalization was reported to occur between 0 and 38.7 % of patients following thermal cauterization and between 5 and 9% who underwent surgical techniques [964]. Disposable thermal cautery tips inserted into the punctum resulted in lower recanalization rates than radiofrequency monopolar cautery. The authors concluded that thermal or surgical punctal occlusion can improve tear volume in DED with similar recanalization rates [964]. However, there is insufficient high-quality evidence, and RCTs are needed to more definitely prove the efficacy of punctal cautery in treating DED.

14.2 Tarsorrhaphy

Tarsorrhaphy is a surgical technique that involves suturing the lateral aspect of the eyelids together, to narrow the palpebral fissure height. This can help protect the cornea and improve the ocular surface environment by reducing the area of the evaporating ocular surface exposure. Based on whether the suture is directly placed on the lids, or after creating a raw area by removal or incision of the lid margin, the tarsorrhaphy can be temporary or permanent, respectively. A tarsorrhaphy is more commonly indicated for the management of neurotrophic keratopathy, lagophthalmos, and ocular surface disorders such as Stevens-Johnson syndrome [965-967]. It can be considered in severe DED when topical therapy has failed to improve corneal epithelial health or if the patient has experienced recurrent epithelial breakdown. Literature on the efficacy of a tarsorrhaphy is limited in the context of DED.

14.3 Surgical management of lid abnormalities

14.3.1 Botulinum toxin injection

Botulinum toxin, produced by *Clostridium botulinum*, functions at the neuromuscular junction by inhibiting acetylcholine release [968]. In ophthalmology, botulinum toxin is widely used for various indications, including first-line treatment for blepharospasm and hemifacial spasm [969,970]. It is also employed to induce

ptosis for corneal protection in cases of persistent epithelial defects or ulcers [971,972], manage eyelid retraction in thyroid eye disease [973], and treat entropion [974,975]. Additionally, it has been used for managing refractory filamentary keratitis [976] and has gained traction as a therapeutic option for DED [40,977-979].

Research has shown that botulinum toxin injections into the medial lower eyelid can improve DED signs and symptoms, including increased TBUT, improved Schirmer test score, MMP-9 levels, corneal fluorescein staining and enhanced OSDI scores. These benefits have been demonstrated in multiple randomized trials [980,981] and several other studies [843,982]. Additionally, a study reported that botulinum toxin significantly improved post-LASIK dry eye symptoms with fewer complications compared to punctal plugs and conventional topical treatments [977].

Essential blepharospasm is a focal cranial dystonia affecting the eyelid and forehead muscles. Studies report that 40–60% of patients with essential blepharospasm experience dry eye symptoms and reduced Schirmer test scores [970,983-985]. Additionally, tear fluid analysis reveals elevated pro-inflammatory cytokine levels in essential blepharospasm patients with DED, compared to those with DED alone [986]. Botulinum toxin injection for patients with essential blepharospasm induces temporary pharmacologic denervation of the orbicularis oculi muscle. Several case-control studies have demonstrated that botulinum toxin injections improves dry eye symptoms and enhances tear film homeostasis, evidenced by increased TMH, TBUT, tear clearance time, and LLT [978,982,986-989]. However, these effects last for only three months [990]. Conversely, botulinum toxin injections administered too close to the lacrimal gland may impair tear production [979,985,991]. A randomized trial reported that approximately 19% of patients developed dry eye symptoms following botulinum toxin injections [992].

14.3.2 Dermatochalasis

Dermatochalasis refers to the presence of loose and redundant eyelid skin, commonly associated with aging. It has been suggested that 46–51% of patients with dermatochalasis experience dry eye symptoms, while 55–86% report

subjective improvement following upper eyelid blepharoplasty [993-995]. However, objective measures of tear function, such as tear osmolarity, Schirmer test score, TBUT, and conjunctival staining score, have failed to show significant improvement postoperatively. Additionally, resecting the orbicularis oculi (Müller muscle-conjunctival resection) for ptosis repair in conjunction with blepharoplasty mostly does not appear to influence outcomes [993,995,996], although one study showed increased dry eye signs and symptoms after combined blepharoplasty and ptosis repair, but not after blepharoplasty surgery alone [997]. The disparity between symptoms and signs improvement following surgery warrants further investigation.

14.3.3 Entropion and ectropion

Entropion and ectropion lead to ocular surface exposure, resulting in symptoms of DED, with entropion often causing concurrent trichiasis [998]. Paralytic lower lid ectropion and upper eyelid retraction can occur due to facial nerve palsy, attributed to reduced orbicularis oculi function secondary to paralysis of the greater superficial petrosal nerve [999]. Other contributing factors for entropion and ectropion include trauma (chemical; mechanical; surgical), tumors, facial surgery, and age-related lid laxity [1000].

Surgical intervention is the primary management approach for both entropion and ectropion, involving techniques such as canthal tendon tightening and removal of cicatricial or mechanical causes of eyelid malposition [1001-1005]. Studies have demonstrated that entropion correction improved vision, punctate keratopathy and TBUT, although Schirmer test results remained unchanged [1006]. Another study found that tarsorrhaphy was effective for entropion correction and supported epithelial healing in patients with severe DED [967].

A comparative study evaluated four procedural combinations for lower lid entropion repair, pairing one method to address horizontal laxity with another for vertical laxity. Horizontal laxity procedures included lateral tarsal strip and Bick"s

procedure, while vertical laxity procedures consisted of everting sutures and lower lid retractor plication. Results indicated that Bick"s procedure had a lower recurrence rate and fewer complications compared to lateral tarsal strip [1007]. For moderate to severe entropion, mucous membrane grafting has been utilized in both primary and recurrent cases [1008]. A study assessing labial mucous membrane grafts for cicatricial entropion reported complete symptom resolution in 83% of patients, with an 11% recurrence rate [1009].

14.3.4 Lagophthalmos

Lagophthalmos is the incomplete or defective closure of the eyelids, resulting in corneal exposure. Persistent or severe cases may necessitate surgical intervention, with options including upper eyelid weight implantation, lid springs, lid reconstruction, or partial/complete tarsorrhaphy [472,1010,1011]. Upper eyelid weights leverage gravity to facilitate passive eye closure. Traditionally, gold weights have been widely used due to their favorable safety profile and high density. However, more recent studies suggest that platinum chains may offer superior outcomes, as they require fewer revisions, have a lower risk of extrusion, and provide improved cosmesis due to their higher density, allowing for a slimmer design [1012,1013].

When corneal exposure persists despite upper eyelid surgery, lower eyelid elevation can be achieved through various techniques. One study reported that auricular cartilage grafts, used in both the upper and lower eyelids, resulted in successful eyelid closure in 80% of patients with mild-to-moderate lagophthalmos [1014]. Additionally, hard palate mucosa has been utilized to elevate the lower eyelid and improve ocular surface protection [1015]. The lateral tarsal strip technique, which tightens and repositions the lower eyelid, has been shown to enhance eyelid-globe apposition, reducing corneal exposure and epiphora in patients with paralytic ectropion [1016].

14.4 Surgical management of anatomical surface abnormalities

14.4.1 Conjunctivochalasis

In severe cases of conjunctivochalasis that are unresponsive to ocular lubricants, topical CsA, or punctal occlusion, surgical resection of excess conjunctival tissue may be considered [1017]. Various techniques have been reported to reduce excessive conjunctival folds, including electrocoagulation or thermal cauterization [1018,1019], conjunctival ligation [1020], simple fixation to the sclera [1021], argon laser conjunctivoplasty [1022], surgical excision [1023,1024] and more recently high-frequency radio-wave electrosurgery [839,1025,1026]. Studies have reported symptom improvement in over 75% of patients across all techniques. However, thermal cauterization and surgical excision have been associated with postoperative complications such as diplopia, symblepharon, and subconjunctival hemorrhage due to excessive cauterization and suturing [835,1027]. In contrast, high-frequency radio-wave electrosurgery has demonstrated effective resolution of redundant conjunctiva while promoting enhanced healing, likely due to its lower energy causing less thermal damage, reduced risk of scarring, and avoidance of sutures [835].

14.4.2 Pterygium and pinguecula

Pterygium and pinguecula are common ocular surface disorders, both characterized by abnormal overgrowth of conjunctival and limbal tissue. The key distinction is that pterygium extends over the cornea, potentially leading to visual impairment [1028]. These conditions can disrupt tear film stability, leading to uneven tear distribution and increased evaporation, thereby exacerbating dry eye symptoms and altering tear osmolarity [1029-1031]. Currently, surgery remains the most effective treatment. Some studies suggest that surgical intervention offers long term benefits by helping restore normal ocular surface anatomy and tear film function [843,850].

Various surgical techniques have been explored. Recent meta-analyses of comparative studies found that limbal-conjunctival autograft yields the best long-term ocular surface outcomes by reducing inflammation and promoting healing [1032,1033]. However, concerns exist regarding potential corneal damage from harvesting limbal and conjunctival tissue. Amniotic membrane transplantation offers an alternative that preserves the limbus and provides early post-surgical advantages [1032]. Both limbal-conjunctival autograft and amniotic membrane transplantation demonstrate lower recurrence rates compared to simple pterygium excision [1034].

Adjuvant therapies that have been used include CsA, mitomycin-C, 5-fluorouracil, beta-irradiation and large- and small-molecule antivascular endothelial growth factor (VEGF) agents, each with their own side-effect profile [1035,1036].

14.5 Salivary gland transplantation

Salivary gland transposition provides an option for improving ocular surface lubrication by supplementing the tear film with salivary secretions [1037]. The lacrimal and salivary glands have similar structural composition and autonomic innervation [1038]. The surgery may be useful in eyes with severe DED due to congenital or acquired alacrimia, facial nerve palsy, chronic cicatricial disorders such as Stevens-Johnson syndrome or chemical injuries. The transposed glands can be sourced from the major salivary glands, i.e. the parotid gland and the submandibular gland, or the minor salivary glands. A meticulous examination of these glands is crucial for optimal outcomes [1038]. Autologous transplantation should be avoided in pathologies where both the lacrimal and the salivary glands are targeted such as in patients with Sjögren disease, graft-versus-host disease, and radiotherapy [1039-1041]. In such cases, allogeneic salivary glands may be transplanted following human leukocyte antigen-typing [1038,1039].

Parotid gland transplantation is not routinely carried out in humans in view of its side effect profile, which include gustatory reflex secretion and the serous nature

of its secretions [1038]. Submandibular gland transplantation involves autologous microvascular submandibular gland transplantation into the temporal fossa, with duct placement via a subcuticular route into the conjunctival fornix [1038]. Several studies have reported an improvement of at least 15mm in Schirmer, improved TBUT and corneal staining scores and best corrected visual acuity [1038,1042,1043]. Although the tear volume increases substantially, it can lead to corneal edema due to the hypo-osmolarity of the new tear film, necessitating graft explantation [1043,1044]. The improvement in tear production is only sustained in about half the patients with Steven-Johnson syndrome due to atrophic and degenerative changes that occur in the transplanted glands over time [1045]. Other reported adverse effects include graft necrosis, infection, fistula formation, duct obstruction, stenosis, and sialolithiasis [1038].

Transplantation of the minor salivary glands is a simpler procedure that does not require an oral surgeon [1046]. The technique involves transplanting minor salivary glands into the upper or lower conjunctival fornix [1047-1049]. In patients with severe DED and entropion, the minor salivary glands, together with a labial mucous membrane graft, can be transplanted in a full-thickness opening created in the upper tarsus, improving both eyelid malpositioning and ocular surface lubrication [1050]. Improvement in surface staining scores, TBUT and visual acuity has been observed in several series, along with reduced dependency on topical tear supplements [1051-1053]. Postoperative complications include graft necrosis, infection, ptosis, and donor site granuloma formation [1038,1051]. In a comparative series between submandibular and minor salivary gland transplantation, the former demonstrated better outcomes for severe DED, while the latter offered some improvement but was more successful in less severe DED [1054].

14.6 Reinnervation of the lacrimal gland

A novel surgical procedure to reinnervate the denervated lacrimal gland in neurodeprivative DED due to facial nerve palsy has been recently described in a

small number of patients (n=10), reporting a high level of patient satisfaction, improved Schirmer test scores and reduced dependency on tear supplements at one year after surgery [1055]. Favourable long-term outcomes in this same patient cohort (n=9) have been reported after a mean follow-up time of 87 ± 15 (range 60 – 108) months, with improvements in subjective satisfaction, Schirmer test, TBUT and corneal fluorescein staining [1056].

15 Prescribing algorithm

Current understanding of the pathogenesis of ocular surface disease recognizes both the heterogeneity of patients‟ signs and symptoms and the multiple pathogenic drivers of those signs and symptoms. Simple division of patients into “subgroups” of DED (e.g aqueous deficient or evaporative dry eye) fails to account for the understanding that multiple drivers of signs and symptoms exist that may be present simultaneously, which may wax and wane over time and with treatment compliance. Staging or grading systems that attempt to group patients into discrete categories (e.g. mild, moderate and severe; stages 1,2,3 or 4; aqueous deficient or evaporative dry eye, etc.) are a suboptimal architecture for DED and can result in decision making that omits effective therapeutic interventions because of categorization that fails to describe the complexity and the changing nature of the multiple pathogenic drivers that result in signs and symptoms of DED.

By referring to the information in the TFOS DEWS III Diagnostic Methodology Report [1] the most likely clinically relevant drivers of a patient‟s dry eye can be identified. By reviewing the information from this Management and Therapy Report, clinicians can evaluate the evidence that supports the many therapeutic options available and match these to the clinically relevant driver of symptoms and/or signs present in any given patient. Multiple treatments used together are the likely and most appropriate management strategy, considering that DED has

multiple pathogenic drivers. The mapping of the treatment to the pathogenic driver is provided in Figures 3, 4 and 5.

Treatments for which there are high quality studies performed in humans to support their use are indicated with a checkmark (✓ if compared with a placebo and ☑ if compared with another treatment). A "?" indicates only some of the studies referred to in this report confirmed this mechanism of action and resulted in a positive response to the therapy applied.

For cross-referencing purposes, the three tables are presented in composite form, as Supplementary Information.

Insert Figs 3, 4 and 5

16 Summary and conclusions

The TFOS DEWS III Management and Therapy Report provides a comprehensive, evidence-based framework for optimally managing DED. The report outlines a treatment approach based on the etiological drivers of the disease in an individual. First-line management includes ocular lifestyle modifications, tear film supplements and environmental adjustments to stabilize the tear film. Meibomian gland dysfunction, a major contributor to evaporative DED, is addressed through warm compresses, lid massage, in-office heating devices, IPL, LLLT and emerging topical drugs. For patients with primary inflammatory or immune-mediated components, anti-inflammatory therapies such as corticosteroids, CsA, and lifitegrast should be considered, along with biologic tear substitutes, including autologous serum and PRP. Lid hygiene practices, including anti-*Demodex* treatments and blepharoexfoliation, further enhance management of lid disease. Novel pharmacological and neuromodulatory therapies have shown promise for tear production enhancement.

For refractory or severe cases, advanced interventions include amniotic membrane grafts and various surgical options. Emerging approaches continue to expand therapeutic possibilities. A prescribing algorithm has been developed to aid clinicians in selecting appropriate interventions based on the patient‟s disease etiologies.

In conclusion, the management of DED requires a personalized, multifaceted approach that considers the underlying causes and patient-specific factors. While tear supplements remain a cornerstone of therapy, growing evidence supports the importance of optimizing meibomian gland function and implementing lifestyle modifications. As novel therapies emerge, future research should focus on refining treatment algorithms and identifying biomarkers to guide targeted therapy. The TFOS DEWS III approach of identifying the etiological drivers of an individual patient‟s DED and matching this with the evidence-identified mechanism of action of treatment and therapies should enhance patient outcomes and quality of life.

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Declaration of Interest / Disclosure forms

According to Dr Sullivan, we are awaiting confirmation from the journal as to the required format that these should take. Please advise and these will uploaded as requested.

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

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

CATEGORIES	SECTION	EXAMPLES	LIPIDS	AQUEOUS	MUCIN / GLYCOCALYX
Lifestyle Advice	5	Modifiable risk factors	To be considered in all cases of dry eye disease		
Oral Nutrition	12	Omega 3 Vitamins Natural products		✓ Omega 3	
Tear Supplementation / Stabilization	6.1	Artificial tears Lubricants	✓ Lipomimetics	✓ Artificial tears	
Tear Conservation Devices	6.2	Punctal plugs Moisture retaining spectacles Contact lens options	☑ Moisture retaining spectacles	☑ Moisture retaining spectacles ? Punctal plugs; scleral contact lenses	
Pharmacological Tear Stimulation / Restoration	6.3	Secretagogues Neuromodulation	☑ Topical secretagogues	✓ Pharmacological neuromodulation ☑ Topical secretagogues	# secretagogues
Device Tear Stimulation / Restoration	6.3	Heating and massage devices Intense pulsed light therapy Low level light therapy	✓ Internal and external device lid heating; IPL; LLLT ☑ IPL ? Warm compress	✓ Neurostimulation ✓☑ LLLT	✓ Neurostimulation
Blink Therapies	7.1	Blink exercises	✓		
Topical Lid Hygiene (e.g. reducing bacterial load)	7.2	Wipes / gel / foam Antimicrobials Blepharoexfoliation	✓		
Topical Anti-Inflammatories	8	Corticosteroids T-cell immunomodulators	✓ Cyclosporine A	✓	✓
Ocular Surface Promotors / Regenerators	10.1	Serum Blood-derived products		✓ Biologics	
Surgical Options	11, 14	Tissue excision Punctal occlusion Lid surgery / tarsorrhaphy		✓	

IPL = intense pulsed light therapy; LLLT = low level light therapy.
Note: Treatments are listed in no particular order and selection for an individual patient between the options identified should be based on shared decision-making with the patient. Refer to the associated text for more details
Blank cells indicate where sufficient evidence is not currently available.
Treatments are named when differences exist within a treatment category.
Pharmacological is defined as having a direct biological effect (Fura 2006).
* Substitute invasive tests with non-invasive tests where possible.

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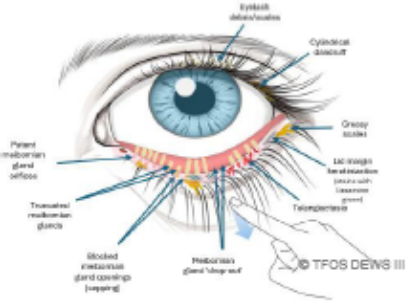
#	Preclinical evidence only
✓	RCT effective vs placebo
☑	RCT effective vs comparator
?	Conflicting evidence

Figure 3. Guide to dry eye subclassification following diagnosis of dry eye disease according to the TFOS DEWS III diagnostic criteria (symptoms plus clinical signs of tear film instability, hyperosmolarity and/or ocular surface staining). The figure highlights tear film deficiency-related subtypes of dry eye disease. The top section provides a checklist of identification tests relevant to the individual etiological drivers (left), a schematic representation of the tear film structure (centre) and a checklist of evidence-based interventions aligned to the etiological drivers (right). The lower section offers more detail in the form of an evidence-based treatment algorithm aligned to identified tear film-related drivers of dry eye disease. Dry eye subtypes are not mutually exclusive and concurrent management targeting identified deficiencies is appropriate to restore tear film and ocular surface homeostasis.

Fura, A. 2006. 'Role of pharmacologically active metabolites in drug discovery and development', *Drug Discov Today*, 11: 133-42.

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

EYELID ANOMALIES



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

CATEGORIES	SECTION	EXAMPLES	BLINKING / LID CLOSURE	LID MARGIN	
				ANTERIOR BLEPHARITIS	MEIBOMIAN GLAND DYSFUNCTION
Lifestyle Advice	5	Modifiable risk factors	To be considered in all cases of dry eye disease		
Oral Nutrition	12	Omega 3 Vitamins Natural products			✓ Omega 3 ? vitamin D3
Tear Supplementation / Stabilization	6.1	Artificial tears Lubricants			✓ Lipomimetics;
Tear Conservation Devices	6.2	Punctal plugs Moisture retaining spectacles Contact lens options	? Moisture retaining spectacles		
Pharmacological Tear Stimulation / Restoration	6.3	Secretagogues Neuromodulation			✓ Topical azithromycin; Selenium sulfide
Device Tear Stimulation / Restoration	6.3	Heating and massage devices Intense pulsed light therapy Low level light therapy			✓ Internal and external device lid heating; IPL; LLLT; QMR
Lid Margin Debridement	6.3.1.3.2	Debridement			☑ when significant keratinization
Blink Therapies	7.1	Blink exercises	✓		
Topical Lid Hygiene (e.g. reducing bacterial load)	7.2	Wipes / gel / foam Topical antimicrobials Blepharoexfoliation		✓	
Topical Anti-inflammatories	8.2	Corticosteroids T-cell immunomodulators			✓ Cyclosporine A
Oral Antibiotics	9	Tetracyclines and analogues Macrolides		✓	✓
Surgical Options	11, 14	Tissue excision Punctal occlusion Lid surgery	✓		

IPL = intense pulsed light therapy; LLLT = low level light therapy; QMR = quantum molecular resonance electrotherapy © TFOS DEWS

Note: The treatments are not listed in any particular order and selection for an individual patient between the options identified should be based on shared decision-making with the patient. RR the associated text for more details

Blank cells indicate where sufficient evidence is not currently available.

Treatments are named when differences exist within a treatment category

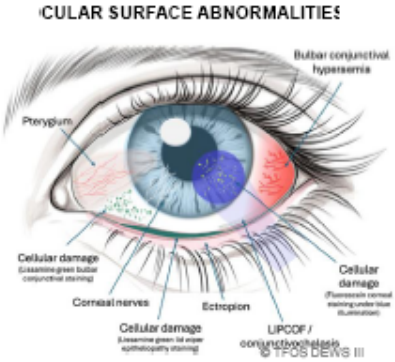
Pharmacological is defined as having a direct biological effect (Fura 2006).

✓	RCT effective vs placebo
☑	RCT effective vs comparator
?	Conflicting evidence

Figure 4. Guide to dry eye subclassification following diagnosis of dry eye disease according to the TFOS DEWS III diagnostic criteria (symptoms plus clinical signs of tear film instability, hyperosmolarity and/or ocular surface staining). The figure highlights eyelid-related subtypes of dry eye disease. The top section provides a checklist of identification tests relevant to the individual etiological drivers (left), a schematic representation of eyelid-related dry eye disease drivers (centre) and a checklist of evidence-based interventions aligned to the etiological drivers (right). The lower section offers more detail in the form of an evidence-based treatment algorithm aligned to identified eyelid-related drivers of dry eye disease. Dry eye subtypes are not mutually exclusive and concurrent management targeting identified deficiencies is appropriate to restore tear film and ocular surface homeostasis.

Fura, A. 2006. 'Role of pharmacologically active metabolites in drug discovery and development', *Drug Discov Today*, 11: 133-42.

ETIOLOGIC DRIVER TESTS
Anatomical misalignment
Biomicroscopy e.g. pterygium, LIPCOF / conjunctivochalasis, ectropion / entropion, lagophthalmos
Neural dysfunction
Corneal sensation
In vivo confocal microscopy
Cellular damage / disruption
Cornea (fluorescein)
Bulbar Conjunctiva (lissamine green)
Lid wiper epitheliopathy (lissamine green)
Inflammation / oxidative stress
Bulbar conjunctival hyperemia
Inflammatory markers



EVIDENCE-BASED INTERVENTIONS
Anatomical misalignment
Surgical options
Neural dysfunction
Tear supplementation / stabilization
Surgical options (punctal occlusion)
Cellular damage / disruption
Oral nutrition (vitamin D3)
Tear supplementation / stabilization
Pharmacological tear stimulation / restoration
Device tear stimulation / restoration
Topical lid hygiene
Topical anti-inflammatories
Ocular surface regenerators
Surgical options (punctal occlusion)
Inflammation / oxidative stress
Oral nutrition (omega 3 / vitamin D3)
Tear supplementation / stabilization
Pharmacological tear stimulation / restoration
Device tear stimulation / restoration (IPL)
Topical lid margin hygiene / debridement
Topical anti-inflammatories
Ocular surface regenerators (amniotic membrane)
Surgical options (punctal occlusion)

CATEGORIES	SECTION	EXAMPLES	ANATOMICAL MISALIGNMENT	NEURAL DYSFUNCTION	CELLULAR DAMAGE / DISRUPTION	INFLAMMATION / OXIDATIVE STRESS	
						PRIMARY	SECONDARY
Lifestyle Advice	5	Modifiable risk factors	To be considered in all cases of dry eye disease				
Oral Nutrition	12	Omega 3 Vitamins Natural products			✓ Vitamin D3		✓ Omega 3, vitamin D3
Tear Supplementation / Stabilization	6.1	Artificial tears Lubricants		✓ Vit A/B12/ ascorbic acid	✓ Hyaluronic acid, trehalose, xanthan, perfluorohexyloctane & HP-guar		✓ Hyaluronic acid, selenoprotein P, xanthan & HP-guar, serum
Pharmacological Tear Stimulation / Restoration	6.3	Secretagogues Neuromodulation			✓ Oral secretagogues ☑ topical secretagogues, pharmacological neuromodulation		✓ pharmacological neuromodulation
Device Tear Stimulation / Restoration	6.3	Heating and massage devices Intense pulsed light therapy Low level light therapy			✓ LLLT; QMR; neurostimulation ? IPL; probing ? external device lid heating; topical secretagogues		☑ IPL
Lid Margin Debridement	6.3.1.3.2	Debridement					?
Topical Lid Hygiene (e.g. reducing bacterial load)	7.2	Wipes / gel / foam Antimicrobials Blepharoexfoliation			?		?
Topical Anti-Inflammatories	8	Corticosteroids T-cell immunomodulators			✓	✓	
Ocular Surface Promotors / Regenerators	10	Amniotic membrane Insulin Biologics		? Biologics	✓☑ Lubricin ✓ Biologics	✓ Amniotic membrane	
Surgical Options	11, 14	Tissue excision Punctal occlusion Lid surgery / tarsorrhaphy	✓	? Punctal occlusion	? Punctal occlusion		? Punctal occlusion

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IPL = intense pulsed light therapy; LLLT = low level light therapy; QMR = quantum molecular resonance electrotherapy
Note: Treatments are listed in no particular order and selection for an individual patient from the options identified should be based on shared decision-making with the patient. Refer to the associated text for more details.
Blank cells indicate where sufficient evidence is not currently available.
Treatments are named when differences exist within a treatment category.
Pharmacological is defined as having a direct biological effect (Fura 2006).
Primary inflammation is considered to be that linked to underlying systemic disease, whereas secondary inflammation, a sequela of dry eye disease.

✓	RCT effective vs placebo
☑	RCT effective vs comparator
?	Conflicting evidence

Figure 6. Guide to dry eye subclassification following diagnosis of dry eye disease according to the TFOS DEWS III diagnostic criteria (symptoms plus clinical signs of tear film instability, hyperosmolarity and/or ocular surface staining). The figure highlights ocular surface-related subtypes of dry eye disease. The top section shows a checklist of identification tests relevant to the individual etiological drivers (left), a schematic representation of ocular surface disease drivers (centre) and a checklist of evidence-based interventions aligned to the etiological drivers (right). The lower section offers more detail in the form of an evidence-based treatment algorithm aligned to identified ocular surface-related drivers of dry eye disease. Dry eye subtypes are not mutually exclusive and concurrent management targeting identified deficiencies is appropriate to restore tear film and ocular surface homeostasis.

Fura, A. 2006. 'Role of pharmacologically active metabolites in drug discovery and development', *Drug Discov Today*, 11: 133-42.