

Review Article

Dry Eye Treatment Paradigm – A Review

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Introduction

Dry Eye Disease (DED), or keratoconjunctivitis sicca, is a chronic condition which has become much more prevalent in recent years. DED is reported to affect up to 60% of people in certain populations, which is a significant increase from the studies of 2001 which indicated that only up to 20% of adults aged 45+ years' experience dry eye symptoms [1,2]. It is imperative that we acknowledge the importance of discussing DED because it is still a largely misunderstood diagnosis which continuously affects many people, with an estimated number of 16 million Americans [3]. DED is indeed the quiet ophthalmic pandemic. This article explores the currently known causes, symptoms, work-up and treatment of dry eye disease.

Causes of Dry Eye Disease

Dry eye disease is multifactorial and generally categorized into two subtypes: evaporative and non-evaporative. Evaporative DED is a result of deficient tear film lipid layers which leads to an increase in tear evaporation⁴. The non-evaporative subtype is a result of reduced aqueous production from lacrimal glands, leading to aqueous deficiency which may or may not be related to Sjogren's syndrome.

Although many factors may contribute to the development of evaporative dry eye disease, the leading cause in clinics is Meibomian Gland Disorder (MGD) [5]. Patients with MGD expe-

Abstract

Dry Eye Disease (DED) is a chronic condition which has become more prevalent in recent years. It is a multifactorial disease that causes affected individuals to experience symptoms such as ocular discomfort, transitional visual disturbances, a foreign body sensation or burning. Although several people are affected by this disease, it remains a largely misunderstood condition. Over-the-counter products and FDA-approved medication options are available on the market for dry eye disease. Several additional pipeline treatment options are currently being assessed in clinical trials. Treatment of DED involves a combination of behavioral modification and medical management. This article explores the currently known causes, symptoms, work-up and treatment of dry eye disease.

Keywords: Dry eye disease; DED treatment; Meibomian gland disorder

rience a reduction in meibum secretion or composition which increases tear film evaporation rate. This evaporation leads to complications such as inflammation, desiccation and apoptosis of ocular surface cells which contribute to the symptomatic presentation of DED [6]. Since sex hormones are known as key regulators of meibomian gland function, patients with androgen deficiency are more likely to suffer from evaporative dry eye disease due to MGD than unaffected people⁵. Additional risk factors for MGD and subsequent dry eye symptoms are advanced age, use of postmenopausal hormone therapy, anti-allergy drugs and smoking [7]. More than 80% of DED cases are due to either MGD or a mixed MGD/aqueous deficiency disorder and about 10% of cases are a due to aqueous deficiency alone [8].

Non-evaporative DED can be subdivided into Sjogren syndrome-related and non-Sjogren syndrome-related⁴. Sjogren syndrome, an autoimmune condition characterized by lymphocytic infiltration, causes permanent destruction of exocrine glands and results in symptoms of dry mouth and dry eye [9]. Aside from Sjogren's syndrome, several other systemic disorders have been linked to DED. A controlled study to observe the ocular abnormalities and their correlation with psoriatic patients was done in 2019 with 300 participants. Within the study, it was shown that dry eye disease was one of the most common

ocular issues within psoriatic patients, demonstrated by higher OSDI (ocular surface disease index) [10]. Additional systemic disorders that are linked to DED are rheumatoid arthritis, lupus and thyroid disease [11].

Dry eye symptoms have been noted to differ between different climate and humidity levels, with data confirming that moist environments are healthier for those experiencing dry eye symptoms [12]. A climatic and environmental correlational report from the Dry Eye Assessment and Management (DREAM) indicated that those in semiarid and subtropical desert climates reported increased corneal dryness compared to Mediterranean climates via fluorescein staining and DED signs. The report also indicates that areas with higher levels of wind, sunlight, and temperature appear to increase DED symptoms [12]. This information suggests that the development of dry eye disease may be correlated with environmental conditions or exposures and sheds light on the need for additional research.

In addition to the causes of DED listed above, other potential causes include topical medication with toxic preservatives, glaucoma drops, systemic medication, or ophthalmic surgeries (*ex: cataract surgery, keratoplasty, LASIK*). Prolonged use of computer devices, environmental pollutants, and skin diseases around the eyelid are also known as potential culprits [11]. Since there are many factors associated with an ability to cause symptoms of dry eye disease, it is imperative that we remain aware and educate patients so that they may avoid triggers as much as possible to preserve quality of life.

Symptoms

The Tear Film and Ocular Surface Society International Dry Eye Workshop II (TFOS DEWS II) described dry eye disease as a multifactorial etiological process the presence of key factors such as a dysfunctional tear film and ocular symptoms to confirm a diagnosis of DED [13]. Symptoms include ocular discomfort and transitional visual disturbances [14]. Complaints of visual disturbances may involve trouble driving at night, photophobia, and television-watching and reading discomfort [15]. Visual acuity itself may also be reduced due to the lack of properly distributed tear film [16]. Additional symptoms experienced by patients include a grittiness or foreign-body sensation, soreness, burning, and increased blinking. Other common symptoms include irritation, redness, and eye fatigue. Ocular pain is also a possibility followed by sensitivity to environmental conditions such as wind and temperature fluctuations [16]. Corneal neuropathic pain that is either sharp or dull can also be present due to extensive innervation in the region [17]. The great variety and the subjective nature of clinical presentations serve as additional components contributing to the challenge of treating DED. To combat this challenge, screening tools are available to help quantify symptoms upon initial evaluations and to measure treatment responses [18].

Workup

The workup for DED begins with a symptomatic investigation. Focused questions are asked to determine which diagnostic tests or treatments should be utilized and many providers use established questionnaires. Examples of questionnaires that aim to assess dry eye symptoms are:

Dry Eye Questionnaire [19]

5-Item Dry Eye Questionnaire [20]

Dry-Eye Related Quality-of-Life Score (DEQS) [21]

Impact of Dry Eye on Everyday Life (IDEEL) [22]

McMonnies' Questionnaire (MQ) [23]

Ocular Comfort Index (OCT and OCI-C) [24]

Ocular Surface Disease Index (OSDI) [25]

Symptom Assessment in Dry Eye (SANDE) [26]

Several other questionnaires have been designed for regular contact lens wearers such as the Contact Lens Dry Eye Questionnaire (CLDEQ) and the 8-Item Contact Lens Dry Eye Questionnaire (CLDEQ-8) [27]. From the listed examples, OSDI and DEQ-5 are the most used due to long-term use in the field and quick nature of the form, respectively. Both questionnaires focus on visual disturbances and function.

The TFOS DEWS II considers "tear film instability" a prerequisite for diagnosing DED [13]. Tear film instability can be tested through the following measures: tear film breakup time, fluorescein breakup time, Non-invasive tear Breakup Time (NIBUT), thermography, osmolarity variability, and tear evaporation rate. The most frequently used test for this measure is the tear film breakup time due to its simplicity and time-effectiveness. However, there can be variability between measurement of this test among clinicians. NIBUT has recently been recommended as a more objective measure although there is still a potential for subjectivity [24].

Additional factors that can be measured in DED are tear volume, ocular surface changes and eyelid characteristics. Tear volume is best measured with the non-invasive meniscometry for the purpose of DED sub-classification, and the Schirmer test is best if the patient has suspected aqueous deficiency (*i.e.* Sjögren syndrome). Ocular surface damage can be analyzed with staining, impression cytology, Lid Parallel Conjunctival Folds (LIPCOF), *in vivo* confocal imaging, and ocular surface sensitivity [18]. Ocular surface inflammation, a non-specific yet key pathophysiologic component of DED, can be tested through slit-lamp examination of ocular and/or conjunctival redness. Matrix metalloproteinases via MMP-9 tear assay may also be measured, as well as cytokines and chemokines. Characteristics of the eyelid can be assessed visually by detecting blepharitis, blink rate, and blink completeness. Lipid thickness measurement and meibography should be assessed as well.

The diagnosis of DED can be made if at least 6 points on the DEQ-5 or at least 13 points on the OSDI are met in addition to having at least one positive homeostasis marker test (NIBUT, osmolarity, and ocular surface staining). Symptoms recognized in these two questionnaires and alterations in the three homeostasis markers should prompt next steps in testing, treatment, and/or referral. In treatment-resistant/chronic symptoms or lack of observable signs, neuropathic pain should be taken into consideration [18].

In addition to questionnaires, devices such as Lipiscan® Meibomian Imager or the TearScience® LipiView® II Ocular Surface Interferometer may be used to assess DED.

Treatment Workflow

Behavior Modifications

Studies have shown that symptoms of dry eye disease are increased by extended visual tasking such as computer, television, and cellular phone screen time as well as prolonged reading and driving [28]. Reduced blinking has also been associated

with symptoms of dry eye disease since blinking is known to help distribute tear fluid over the ocular surface [8]. The blinking rate is significantly reduced from 15.5 blinks/minute to 5.3 blinks/minute when individuals are engaged in visual tasking, which further exacerbates the exposure to dry eye triggers. Counseling patients regarding the need to reduce screen time and consciously maintain adequate blinking while performing visual tasks could be very useful for symptom relief.

Additional modifiable factors include cigarette smoking, dry heating air, and air conditioning. Patients may benefit from eliminating direct high airflow fans and opting to use humidifiers [11]. A randomized trial of desktop humidifiers for dry eye relief in computer users showed that even a modest increase in relative humidity can potentially improve tear-film stability [29]. Cigarette smoking has displayed a significant association with the presence of dry eye symptoms with deteriorating effects on the ocular surface. Patients exhibiting dry eye symptoms may benefit from smoking cessation [30].

Removing known offenders such as benzalkonium chloride, which serves as preservative in many topical ophthalmic medications may also be of benefit [31]. Many patients are encouraged to use preservative free preparations of ophthalmic medications to reduce risk of ocular surface abnormalities. Reducing use of mascara and makeup applied to the lid margin has been shown to be helpful. Tattooing the eyelid margin has been shown to reduce meibomian gland function in a recent study therefore patients should be cautioned against this procedure.

Topical – Over-the-Counter (OTC) Remedies

The therapeutic aim for the treatment of dry eye disease includes restoration of natural tear film, protection of the ocular surface and comfort [32]. Artificial tears have been used as a mainstay of therapy, displaying up to a 25% improvement in dry eye symptoms [33]. Several brands are commercially available for purchase over-the-counter, such as Systane, Refresh, TheraTears, Similasan, iVIZIA, and Optase.

iVizia

iVizia is a newer over-the-counter eye lubricant which is available in both eye drop and eye gel formulations. The active ingredient of iVizia is povidone but the formulation also contains hyaluronic acid and trehalose which have shown a synergistic effect of increasing tear film thickness for up to 240 minutes. The product is packaged in a preservative-free bottle that is large which potentially contributes to an ease-of-use for patients.

Optase

The Optase company provides another source of preservative-free OTC products for the relief of dry eye symptoms. The Optase Hylo Relief Dry Eye Drops contain hyaluronic acid and glycerin, delivered in a multi-use drop bottle for mild to moderate dry eye symptoms. The MGD Advanced Dry Eye Drops contain sacha inchi seed oil, trehalose and hyaluronic acid, marketed to strengthen and replenish tear film. The Optase Dry Eye Intense Drops are advertised to improve symptoms of moderate to severe dry eye. Optase Hylo Night ointment uniquely contains vitamin A which is expected to improve the tear film and protect the surface of the eye [34].

Refresh

The active ingredients of Refresh products differ from those

in the Systane family and include different combinations of carboxymethylcellulose sodium, glycerin and polysorbate 80. The Refresh Classic, however, includes different ingredients than the rest of the family and instead includes polyvinyl alcohol and povidone. The same applies to Refresh P.M. and Refresh Lacri-Lube, which both include mineral oil and white petrolatum. Many of the Refresh products boast the use of HydroCell technology which is marketed to help prevent further irritation. Refresh Plus is a subset of the Refresh family of which studies have displayed an improvement in tear ferning patterns for at least three hours [35].

Systane

Systane Lubricating Eye drops have displayed the ability to effectively relieve symptoms of moderate dry eye disease [36]. The inactive ingredients vary slightly and give each product its unique characteristics. For example, Systane Ultra contains sorbitol which minimizes blurring or haze upon installation and Systane Balance contains a lipid emulsion which protects the ocular surface and replenishes tear film lipids [32].

TheraTears

Like Refresh products, TheraTears utilize sodium carboxymethylcellulose as an active ingredient. TheraTears advertises the ability of its preservative to turn into pure oxygen and water on eye contact. In addition to eye drop products, the TheraTears brand has formulated an ocular nutraceutical and a lid hygiene product which have displayed a significant relief in dry eye symptoms and signs when used in combination with TheraTears eye drops [37].

FDA Approved Prescription and Branded Therapy for Dry Eye Disease

Prescription and branded topical therapy may be indicated for patients who fail to respond to artificial tear replacement, behavioral adjustments, and environmental changes. Restasis, Cequa, Xiidra, Eysuvis, Tyrvaya, Miebo, Vevye and Xdemvy are currently available, as well as the first generic use of cyclosporine which was approved in February 2022.

Cyclosporine A (Restasis, Cequa)

Restasis and Cequa are both FDA-approved for dry eye disease and contain the same active ingredient—cyclosporine A. Cyclosporine A is a calcineurin inhibitor immunosuppressant which is indicated to increase tear production and has been shown to protect human conjunctival epithelial cells from apoptosis [38]. Restasis is available as a 0.05% emulsion of cyclosporine. Although they have differences in the strength of formulation, a major difference between the products involves drug delivery. Restasis has been FDA-approved to treat dry eye disease since 2003 and is available as Restasis single-use vials or a Restasis Multidose bottle if a single bottle is preferred by the patient. Cequa, FDA-approved since 2018, is unique in that it is available as 0.09% strength and is a clear and aqueous nanomicellar formulation which has been shown to provide a greater bioavailability than the oil-based Restasis. The recent FDA approval of generic cyclosporine is a generic version of the Restasis single use vials, enabling access to a lower cost generic product.

Lifitegrast (Xiidra)

Xiidra has been approved to treat dry eye disease since 2016. The active ingredient, lifitegrast, works by binding to lympho-

cyte function-associated antigen-1 and blocking the interaction with intercellular adhesion molecule-1 (ICAM-1), inhibiting T-cell activation and possibly inflammatory cytokines [39]. Xiidra therefore markets the ability to improve dry eye symptoms by reducing a source of inflammation which may cause dry eye disease. A pooled analysis revealed that it appears to be well tolerated, improving comfort within three minutes of installation [40].

Loteprednol Etabonate (Eysuvis)

Eysuvis 0.25% ophthalmic suspension is a corticosteroid indicated for the short-term (up to two weeks) treatment of the signs and symptoms of dry eye disease. It is the only FDA-approved short-term prescription eye drop that quickly treats dry eye symptom flare-ups at the source. It is dosed twice daily at 12-hour intervals. Eysuvis has been proven to relieve a myriad of acute symptoms of dry eye disease such as redness, scratchiness, tearing and vision fluctuation.

Varenicline (Tyrvaya)

As of 2021, the FDA has approved the use of Tyrvaya for the treatment of dry eye disease. The active ingredient, varenicline, is formulated as a nasal spray to be used in each nostril twice daily. Varenicline is a cholinergic agonist, and it is proposed that binding at the nicotinic receptor activates the trigeminal parasympathetic pathway which then leads to an increase of basal tear film. Pervaya is the first and only approved nasal spray for the treatment of dry eye disease, providing additional drug delivery options for patients. This may be a preferred treatment modality especially in those patients that are unable to use eye drops due to systemic conditions like arthritis, or in patients who are already using a multitude of drops for other conditions like glaucoma.

Perfluorohexyloctane (Miebo)

Miebo, formerly known as NOV03, is a proprietary, water-free, and preservative-free eye drop based on patented EyeSol technology from Novaliq (GmbH, Heidelberg, Germany). Novaliq has a business alliance with Bausch + Lomb to develop, manufacture and commercialize Miebo in USA and Canada. As of May 2023, it has become the first and only FDA-approved treatment for dry eye disease that directly targets tear evaporation. Miebo uses perfluorohexyloctane (PFHO), an amphiphilic, clear, colorless liquid with low surface tension. PFHO's primary mechanism of action involves the inhibition of tear film evaporation. PFHO spreads across the ocular surface to form an anti-evaporative layer on the tear film surface that prevents evaporation of the aqueous layer underneath. In addition, as a semi-fluorinated alkane, PFHO is expected to lubricate the ocular surface and reduce surface friction⁴¹.

Cyclosporine (Vevye)

Vevye was FDA approved in 2023 for the treatment of both the signs and symptoms of dry eye disease. This product was acquired by Harrow, a leading US eyecare pharmaceutical company. It is a topical anti-inflammatory and immunomodulating ophthalmic drug combination of EyeSol and 0.1% cyclosporine indicated for the treatment of the signs and symptoms of dry eye disease. The EyeSol water-free moiety increases the cyclosporine contact time on the ocular surface, resulting in a high bioavailability [42].

Lotilaner (Xdemvy)

Xdemvy is a topical ophthalmic formulation of lotilaner developed by Tarsus Pharmaceuticals. It has been FDA-approved for the treatment of Demodex blepharitis and proven safe and effective when compared with the vehicle control [43]. It works by selectively inhibiting the Demodex-specific GABA-CL channels.

SYSTEMIC MEDICATIONS

While there are several potential causes of dry eye disease, meibomian gland dysfunction or posterior blepharitis is a common cause. Inadequate responses to topical therapy may warrant a trial of oral antibiotics such as doxycycline and azithromycin. While they have both displayed effectiveness and safety, azithromycin may be considered superior because the treatment period is five days versus the 4 weeks of treatment required using doxycycline [44]. Baseline measurements of corneal and conjunctival staining are remeasured at the three-month mark to document patient improvement. The benefits regarding the use of estrogen replacement therapy in postmenopausal women has remained inconclusive. It is important that we consider the possible impact of hormonal replacement therapy, especially if DED symptoms remain refractory to conventional treatment. Postmenopausal women, for example, may benefit from collaboration between an ophthalmologist and endocrinologist when managing DED symptoms.

Individuals seeking to relieve dry eye disease symptoms may encounter inconclusive information regarding the benefits of omega-3 supplements. A study published in 2005 evaluated 32,000 women and found that a higher dietary intake of omega-3 fatty acids was associated with a decreased incidence of dry eye disease in women [45]. However, there have also been studies dismissing the benefit of omega-3 fatty acids, such as the DREAM study which showed that patients who discontinued omega-3 supplements did not have significantly worse outcomes compared to those who continued to use the supplements [46]. Despite the inconsistencies regarding efficacy of omega-3 supplements, it is proposed that oral consumption of omega-3 is associated with a decrease in the rate of tear evaporation and improvement in dry eye symptoms [47].

Tear Plugs, Thermal Pulsation, Scleral Lenses and Intense Pulsed Light Therapy

Punctal plugs which are made of collagen or silicone, are tiny devices that are placed in the tear punctum and canalicular plugs are placed deeper [48]. The plug stops tears from escaping the ocular surface. This helps keep the eye's surface moist and comfortable. Absorbable, from one week to 6 months, and nonabsorbable plugs usually made of silicone, may last many years. Plugs are used in later phases of dry eye management or for more advanced dry eye disease due to systemic illnesses or offending medications.

Thermal pulsation devices are thought to emulsify the sebum which has been trapped in the meibomian glands. Most treatments last for 8 to 10 minutes and are performed in the office under the physician's supervision. There are several devices on the market like LipiScan Thermal Pulsation System, Ocusoft's Thermal 1-One Touch, TearScience® LipiFlow® Thermal Pulsation System, TearCare from Sight Sciences, Systane iLux by Alcon, Mibo ThermoFlo by Mibo Group, and ExpressTears by LuNovu.

Treatment of MGD is often only one component of the causes of DED and should be used in conjunction with other treatments. Thermal pulsation is considered early in DED management if the patient shows signs and symptoms of MGD and active rosacea conjunctivitis. Intense Pulsed Light (IPL) has entered the workflow of dry eye disease mainly for patients with rosacea and meibomian gland dysfunction [49]. Following IPL, erythema and inflammation are reduced and the outflow of meibum is increased thereby stabilizing the tear film. While many patients may benefit from this treatment, it is only indicated for Fitzpatrick skin types I-III and sometimes IV [50]. Patients with darker skin tones (Fitzpatrick Types V-VI) are not good candidates for intense pulsed light due to a risk of hypopigmentation and scarring [51].

Scleral lenses are large diameter, gas permeable contact lenses, which cover the entire corneal surface and are typically fitted in three sizes measuring small to large. The back lens surface is also a tear reservoir that provides a source of continuous hydration for the corneal surface.

Pipeline Treatments for Dry Eye

AR-15512 (Alcon)

Cold thermoreceptors on the cornea and conjunctiva may be an important target in treating Dry Eye symptoms. This unique class of corneo-conjunctival sensory neurons is susceptible to dynamic temperature reductions [52]. These neurons fire nerve impulses in bursts at the average temperature of the cornea or conjunctiva (34–35°C) and increase the rate of impulse activity when the temperature drops [53]. The impulses stabilize gradually at the new baseline temperature. Therefore, these thermoreceptors can sense the magnitude and rate of temperature reductions at the ocular surface [54–56]. These receptors' unique and specific properties are mainly attributed to a membrane ion channel known as TRPM8, which is widely expressed in corneo-conjunctival trigeminal neurons [52,57].

AR 15512 will stimulate cold thermoreceptors on the ocular surface as an ophthalmic solution, directly leading to increased nerve impulses sent to higher brain centers. The stimulation at these brain centers will cause the activation of neural fibers that activate lacrimal gland secretion, causing an increase in tear production. The estimated Phase III study completion date is October 2023.

Surface Ophthalmic Products

Surface Ophthalmics Inc. has created several unique, preservative-free unit eye drops to treat various forms of Dry Eye Disease. These products are expected to launch between 2025 and 2027. The foundation of their eye drop formulation is centered around three active ingredients: betamethasone, mycophenolate and chondroitin sulfate (Klarity). Betamethasone is a corticosteroid also used to treat chronic symptoms of DED by decreasing inflammation yet with a low incidence of intraocular pressure spikes. Mycophenolate is an immunomodulator that reduces guanosine nucleotides in T and B lymphocytes, inhibiting their proliferation and thus suppressing the inflammatory process. Additionally, mycophenolate has also been seen to upregulate mucin production in the eye, which enhances the spread of the tear film over the corneal epithelium utilizing surface tension [11,58]. Finally, chondroitin sulfate reduces cellular oxidative stress and edema, increases ocular surface contact time and its natural properties also function as lubrication for the eye.

SURF-100 combines Klarity, mycophenolate sodium and low-concentration betamethasone. The company's data comparing their MPA drop against other active drugs has demonstrated statistically significant non-inferiority and potentially superior outcomes compared to lifitegrast 5% ophthalmic solution and cyclosporine 0.05% ophthalmic emulsion in reducing DED symptoms.

SURF-200 combines a low dose of betamethasone with the Klarity vehicle. It is designed to be pulsed dosed to treat acute dry eye flares. Klarity is currently available as an over-the-counter artificial tear eye drop that uses chondroitin sulfate.

AZR-MD-001 (Azura Ophthalmic Ltd.)

Meibomian Gland Dysfunction (MGD) is a common precursor that could lead to Dry Eye Disease. AZR-MD-001 is an ophthalmic solution aimed at being the first FDA-approved medication for treating meibomian gland dysfunction. The active ingredient in this ophthalmic ointment is Selenium Sulfide (SeS₂), which is believed to have a multi-modal mechanism of action. The phase 2b trial demonstrated the efficacy of Selenium sulfide to break down the bonds between abnormal keratin proteins to soften the occluded gland. It also prevents future blockages of the meibomian glands and increases the quantity and quality of meibum produced by decreasing future keratin production [59].

Reproxalap (Aldeyra)

Reactive Aldehyde Species (RASP) are molecules that facilitate inflammation. These pro-inflammatory mediators are increased in the tears of patients with dry eye disease. Reproxalap 0.25% is a topical Reactive Aldehyde Species (RASP) inhibitor that acts early in the inflammatory cascade. Notably, this novel treatment is not cataratogenic and does not raise IOP. Aldeyra Therapeutics Achieved Primary Endpoint in Phase 3 TRANQUILITY-2 Trial in Dry Eye Disease. Reproxalap was statistically superior to vehicle for each of the two prespecified primary endpoints, Schirmer test ($p=0.0001$) and ≥ 10 mm Schirmer test responder proportions ($p<0.0001$) after a single day of dosing. It demonstrated broad activity across a variety of symptoms and signs in patients with dry eye disease [60]. This data has been submitted to the FDA.

OTX-DED (Dexamethasone Intracanalicular Insert by Ocular Therapeutix)

Ocular Therapeutix aims to resolve unmet needs in Dry Eye therapy by eliminating the potential for drop overuse or misuse by patients. Their OTX-DED program is a physician-administered, resorbable, preservative-free, hydrogel-based insert placed into the canaliculus and releases dexamethasone to the ocular surface for 2-3 weeks. It is being evaluated for the short-term treatment of signs and symptoms of DED. The drug mechanism of action combines two common strategies: It decreases inflammation by using a sustained and tapered delivery of dexamethasone and aids in tear conservation by punctal occlusion.

This program has currently finished Phase II. The data concluded a statistically significant improvement in bulbar conjunctival hyperemia and eye dryness scores when patients used OTX-DED relative to vehicle hydrogel [61].

OTX-CSI (Ocular Therapeutix)

OTX-CSI is another drug being produced by Ocular Therapeutix. It is a sustained-release, biodegradable, preservative-free cyclosporine insert designed to provide effective therapy for up

to 12 weeks. OTX-CSI combines two common DED treatment modalities into a single therapy, using punctal occlusion and cyclosporine to treat DED. This drug contains 0.36 mg of cyclosporine in a Polyethylene Glycol (PEG) hydrogel rod, and it is inserted into the canaliculus, where it slowly releases cyclosporine.

The program's Phase I concluded that OTX-CSI was observed to have a favorable safety profile and was well-tolerated. There were no adverse effects of eye irritation, stinging, blurred vision, or burning over 16 weeks. Phase II tested the safety, tolerability, and efficacy of OTX-CSI for treating individuals with Dry Eye Disease. At week 12, there was minimal separation between the active drug group and control groups for the primary endpoint of increased tear product measured by Schirmer test score [62].

Serum Tears

Autologous serum tears have been used in the management of various eye disorders, including dry eye disease. Serum eye drops have been shown to provide lubrication and promote epithelial healing [63]. Studies have shown that treatment with serum tears may be effective for severe dry eye or persistent epithelial defect, but additional research is still needed to determine the long-term effectiveness of this approach [64,65].

New Treatment Paradigm for Dry Eye Disease

This new treatment proposal approaches the disease in 5 main phases and can be used in all causes and types of dry eye disease in treatment of naive patients:

Phase 1 - Behavior Modification such as reducing screen time on devices or consciously blinking during extended screen time is suggested. Branded preservative free tear drops, over the counter, two to four times a day are also recommended. Eysuvis four times a day should be started immediately if acute signs and symptoms are present such as 2+ ocular injection, more than 4+ superficial punctate keratopathy or less than 7 seconds tear break up time. Omega 3 supplementation is recommended early.

Phase 2 - Re-evaluate after 3 weeks on the phase one regimen. If clinical signs and symptoms are still present, topical cyclosporine or lifitegrast solutions are added twice a day. The patient may continue preservative free tears throughout the day. Eysuvis should be discontinued. Temporary plugs should be trialed into the lower lids. Thermal pulsation should be offered particularly if the patient has MGD. The patient should be encouraged to use home remedies like hot compresses and combine lid hygiene with tea-tree oil pads.

Phase 3 - If the patient fails phases one and two or is still showing signs and symptoms of DES, we then move to lubricating gel, doxycycline, or metronidazole orally, IPL and extended punctal plugs. The IPL therapy should be focused on the lower lid and upper cheek area. Extended plugs are first placed in the lower lids and after two weeks of little to no improvement the upper lids may be plugged. Typically, after no less than 6 weeks, systemic medications such as doxycycline or metronidazole should be considered. Doxycycline can be prescribed as a loading dose of 100mg twice daily for two weeks then lowered to 50 to 100 mg daily.

Phase 4 - Serum tears can be compounded using the patient's own serum. They are buffered with Refresh tears and patients are instructed to use them at least three times a day. In addition, they are given consideration as well as topical vitamin A therapy.

Summary

As the prevalence of dry eye disease continues to increase in modern times, we as eye care clinicians are faced with a myriad of options and burden of effective management. DED reportedly affects up to 60% of people in certain populations [1]. We have presented the various types of management approaches with a treatment flow pattern that are simple and effective. The five-phase approach allows the clinician to effectively manage the various aspects of the disease and tailor disease management approaches according to the signs and clinical progress of their individual patient populations.

References

1. Donaldson K, Parkhurst G, Saenz B, Whitley W, Williamson B, Hovanesian J. Call to action: treating dry eye disease and setting the foundation for successful surgery. *J Cataract Refract Surg.* 2022; 48: 623-629.
2. Brewitt H, Sistani F. Dry eye disease: the scale of the problem. *Surv Ophthalmol.* 2001; 45: S199-202.
3. Farrand KF, Fridman M, Stillman IO, Schaumberg DA. Prevalence of Diagnosed Dry Eye Disease in the United States Among Adults Aged 18 Years and Older. *Am J Ophthalmol.* 2017; 182: 90-98.
4. Findlay Q, Reid K. Dry eye disease: when to treat and when to refer. *Aust Prescr.* 2018; 41: 160-163.
5. Wang LX, Deng YP. Androgen and meibomian gland dysfunction: from basic molecular biology to clinical applications. *Int J Ophthalmol.* 2021; 14: 915-922.
6. Sheppard JD, Nichols KK. Dry Eye Disease Associated with Meibomian Gland Dysfunction: Focus on Tear Film Characteristics and the Therapeutic Landscape. *Ophthalmol Ther.* 2023; 12: 1397-1418.
7. Machalinska A, Zakrzewska A, Safranow K, Wiszniewska B, Machalinski B. Risk Factors and Symptoms of Meibomian Gland Loss in a Healthy Population. *J Ophthalmol.* 2016; 2016: 7526120.
8. Messmer EM. The pathophysiology, diagnosis, and treatment of dry eye disease. *Dtsch Arztebl Int.* 2015; 112: 71-81; quiz 82.
9. Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjogren syndrome. *Arch Intern Med.* 2004; 164: 1275-84.
10. Ghalamkarpour F, Baradaran-Rafii A, Sadoughi MM, et al. Ocular findings in patients with psoriasis: is it related to the side effects of treatment or to psoriasis itself? A case-control study. *J Dermatol Treat.* 2020; 31: 27-32.
11. Golden MI, Meyer JJ, Patel BC. Dry Eye Syndrome. *StatPearls.* 2023.
12. Berg EJ, Ying GS, Maguire MG, et al. Climatic and Environmental Correlates of Dry Eye Disease Severity: A Report from the Dry Eye Assessment and Management (DREAM) Study. *Transl Vis Sci Technol.* 2020; 9: 25.
13. Craig JP, Nelson JD, Azar DT, Belmonte C, Bron AJ, Chauhan SK, et al. TFOS DEWS II Report Executive Summary. *Ocul Surf.* 2017; 15: 802-812.
14. Zemanova M. Dry Eye Disease. A Review. *Cesk Slov Oftalmol. Winter.* 2021; 77: 107-119.
15. Zeev MS, Miller DD, Ltkany R. Diagnosis of dry eye disease and emerging technologies. *Clin Ophthalmol.* 2014; 8: 581-90.
16. Clayton JA. Dry Eye. *N Engl J Med.* 2018; 379: e19.

17. Goyal S, Hamrah P. Understanding Neuropathic Corneal Pain--Gaps and Current Therapeutic Approaches. *Semin Ophthalmol*. 2016; 31: 59-70.
18. Wolffsohn JS, Arita R, Chalmers R, Djalilian A, Dogru M, Dumbleton K, et al. TFOS DEWS II Diagnostic Methodology report. *Ocul Surf*. 2017; 15: 539-574.
19. Begley CG, Chalmers RL, Mitchell GL, Nichols KK, Caffery B, Simpson T, et al. Characterization of ocular surface symptoms from optometric practices in North America. *Cornea*. 2001; 20: 610-8.
20. Chalmers RL, Begley CG, Caffery B. Validation of the 5-Item Dry Eye Questionnaire (DEQ-5): Discrimination across self-assessed severity and aqueous tear deficient dry eye diagnoses. *Cont Lens Anterior Eye*. 2010; 33: 55-60.
21. Sakane Y, Yamaguchi M, Yokoi N, Uchino M, Dogru M, Oishi T, et al. Development and validation of the Dry Eye-Related Quality-of-Life Score questionnaire. *JAMA Ophthalmol*. 2013; 131: 1331-8.
22. Abetz L, Rajagopalan K, Mertzanis P, Begley C, Barnes R, Chalmers R, et al. Development and validation of the impact of dry eye on everyday life (IDEEL) questionnaire, a patient-reported outcomes (PRO) measure for the assessment of the burden of dry eye on patients. *Health Qual Life Outcomes*. 2011; 9: 111.
23. McMonnies CW, Ho A. Responses to a dry eye questionnaire from a normal population. *J Am Optom Assoc*. 1987; 58: 588-91.
24. Johnson ME, Murphy PJ. Measurement of ocular surface irritation on a linear interval scale with the ocular comfort index. *Invest Ophthalmol Vis Sci*. 2007; 48: 4451-8.
25. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol*. 2000; 118: 615-21.
26. Schaumberg DA, Gulati A, Mathers WD, Clinch T, Lemp MA, Nelson JD, et al. Development and validation of a short global dry eye symptom index. *Ocul Surf*. 2007; 5: 50-7.
27. Chalmers RL, Begley CG, Moody K, Hickson-Curran SB. Contact Lens Dry Eye Questionnaire-8 (CLDEQ-8) and opinion of contact lens performance. *Optom Vis Sci*. 2012; 89: 1435-42.
28. Iyer JV, Lee SY, Tong L. The dry eye disease activity log study. *Scientific World Journal*. 2012; 2012: 589875.
29. Wang MTM, Chan E, Ea L, Kam C, Lu Y, Misra SL, et al. Randomized Trial of Desktop Humidifier for Dry Eye Relief in Computer Users. *Optom Vis Sci*. 2017; 94: 1052-1057.
30. Bhutia P, Sen S, Nath T, Shamshad MA. The effect of smoking on ocular surface and tear film based on clinical examination and optical coherence tomography. *Indian J Ophthalmol*. 2021; 69: 1693-1696.
31. Albdaya NA, Binyousef FH, Alrashid MH, et al. Prevalence of Dry Eye Disease and Its Association with the Frequent Usage of Eye Cosmetics Among Women. *Cureus*. 2022; 14: e27142.
32. Benelli U. Systane lubricant eye drops in the management of ocular dryness. *Clin Ophthalmol*. 2011; 5: 783-90.
33. Doughty MJ, Glavin S. Efficacy of different dry eye treatments with artificial tears or ocular lubricants: a systematic review. *Ophthalmic Physiol Opt*. 2009; 29: 573-83.
34. Company O. Hylo Night Eye Ointment. 2023.
35. Alanazi SA, Badawood YS, Aldawood MA, El-Hiti GA, Masmali AM. Effect of Refresh Plus((R)) preservative-free lubricant eye-drops on tear ferning patterns in dry eye and normal eye subjects. *Clin Ophthalmol*. 2019; 13: 1011-1017.
36. Versura P, Profazio V, Campos EC. One month use of Systane improves ocular surface parameters in subjects with moderate symptoms of ocular dryness. *Clin Ophthalmol*. 2008; 2: 629-35.
37. Ngo W, Srinivasan S, Houtman D, Jones L. The relief of dry eye signs and symptoms using a combination of lubricants, lid hygiene and ocular nutraceuticals. *J Optom*. 2017; 10: 26-33.
38. Periman LM, Mah FS, Karpecki PM. A Review of the Mechanism of Action of Cyclosporine A: The Role of Cyclosporine A in Dry Eye Disease and Recent Formulation Developments. *Clin Ophthalmol*. 2020; 14: 4187-4200.
39. Abidi A, Shukla P, Ahmad A. Lifitegrast: A novel drug for treatment of dry eye disease. *J Pharmacol Pharmacother*. 2016; 7: 194-198.
40. Nichols KK, Donnenfeld ED, Karpecki PM, Hovanesian JA, Raychaudhuri A, Shojaei A, et al. Safety and tolerability of lifitegrast ophthalmic solution 5.0%: Pooled analysis of five randomized controlled trials in dry eye disease. *Eur J Ophthalmol*. 2019; 29: 394-401.
41. Tauber J, Wirta DL, Sall K, Majmudar PA, Willen D, Krosser S, et al. A Randomized Clinical Study (SEECASE) to Assess Efficacy, Safety, and Tolerability of NOV03 for Treatment of Dry Eye Disease. *Cornea*. 2021; 40: 1132-1140.
42. Akpek EK, Wirta DL, Downing JE, Tauber J, Sheppard JD, Ciolino JB, et al. Efficacy and Safety of a Water-Free Topical Cyclosporine, 0.1%, Solution for the Treatment of Moderate to Severe Dry Eye Disease: The ESSENCE-2 Randomized Clinical Trial. *JAMA Ophthalmol*. 2023; 141: 459-466.
43. Yeu E, Wirta DL, Karpecki P, Baba SN, Holdbrook M, Saturn ISG. Lotilaner Ophthalmic Solution, 0.25%, for the Treatment of Demodex Blepharitis: Results of a Prospective, Randomized, Vehicle-Controlled, Double-Masked, Pivotal Trial (Saturn-1). *Cornea*. 2023; 42: 435-443.
44. De Benedetti G, Vaiano AS. Oral azithromycin and oral doxycycline for the treatment of Meibomian gland dysfunction: A 9-month comparative case series. *Indian J Ophthalmol*. 2019; 67: 464-471.
45. Miljanovic B, Trivedi KA, Dana MR, Gilbard JP, Buring JE, Schaumberg DA. Relation between dietary n-3 and n-6 fatty acids and clinically diagnosed dry eye syndrome in women. *Am J Clin Nutr*. 2005; 82: 887-93.
46. Hussain M, Shtein RM, Pistilli M, Maguire MG, Oydanich M, Asbell PA, et al. The Dry Eye Assessment and Management (DREAM) extension study - A randomized clinical trial of withdrawal of supplementation with omega-3 fatty acid in patients with dry eye disease. *Ocul Surf*. 2020; 18: 47-55.
47. Kangari H, Eftekhari MH, Sardari S, Hashemi H, Salamzadeh J, Ghassemi-Broumand M, et al. Short-term consumption of oral omega-3 and dry eye syndrome. *Ophthalmology*. 2013; 120: 2191-6.
48. Best AL, Labetoulle M, Legrand M, M'Garrech M, Barreau E, Rousseau A. Punctal and canalicular plugs: Indications, efficacy and safety. *J Fr Ophthalmol*. 2019; 42: e95-e104.
49. Vegunta S, Patel D, Shen JF. Combination Therapy of Intense Pulsed Light Therapy and Meibomian Gland Expression (IPL/MGX) Can Improve Dry Eye Symptoms and Meibomian Gland Function in Patients with Refractory Dry Eye: A Retrospective Analysis. *Cornea*. 2016; 35: 318-22.
50. Toyos R, McGill W, Briscoe D. Intense pulsed light treatment for dry eye disease due to meibomian gland dysfunction; a 3-year retrospective study. *Photomed Laser Surg*. 2015; 33: 41-6.

51. Cote S, Zhang AC, Ahmadzai V, Maleken A, Li C, Oppedisano J, et al. Intense pulsed light (IPL) therapy for the treatment of meibomian gland dysfunction. *Cochrane Database Syst Rev.* 2020; 3: CD013559.
52. Belmonte C, Gallar J. Cold thermoreceptors, unexpected players in tear production and ocular dryness sensations. *Invest Ophthalmol Vis Sci.* 2011; 52: 3888-92.
53. Hensel H. Thermoreception and temperature regulation. *Monogr Physiol Soc.* 1981; 38: 1-321.
54. Gallar J, Pozo MA, Tuckett RP, Belmonte C. Response of sensory units with unmyelinated fibres to mechanical, thermal and chemical stimulation of the cat's cornea. *J Physiol.* 1993; 468: 609-22.
55. Carr RW, Pianova S, Fernandez J, Fallon JB, Belmonte C, Brock JA. Effects of heating and cooling on nerve terminal impulses recorded from cold-sensitive receptors in the guinea-pig cornea. *J Gen Physiol.* 2003; 121: 427-39.
56. Parra A, Madrid R, Echevarria D, del Olmo S, Morenilla-Palao C, Acosta MC, et al. Ocular surface wetness is regulated by TRPM8-dependent cold thermoreceptors of the cornea. *Nat Med.* 2010; 16: 1396-9.
57. Viana F, de la Pena E, Belmonte C. Specificity of cold thermotransduction is determined by differential ionic channel expression. *Nat Neurosci.* 2002; 5: 254-60.
58. O'Neil EC, Henderson M, Massaro-Giordano M, Bunya VY. Advances in dry eye disease treatment. *Curr Opin Ophthalmol.* 2019; 30: 166-178.
59. Laura Elizabeth Downey SLW, Jacqueline Tan, Fiona Stapleton, Charles Bosworth. A multicenter, double-masked, vehicle-controlled, randomized, parallel group clinical trial of AZR-MD-001 (AZR) in individuals with meibomian gland dysfunction. *Invest Ophthalmol Vis Sci.* 2021; 62: 1334.
60. Clark D, Sheppard J, Brady TC. A Randomized Double-Masked Phase 2a Trial to Evaluate Activity and Safety of Topical Ocular Reproxalap, a Novel RASP Inhibitor, in Dry Eye Disease. *J Ocul Pharmacol Ther.* 2021; 37: 193-199.
61. Nijm L, Tauber J, Evans DG, Gillick B, Gurses-Ozden R, Goldstein M. Efficacy and Safety of OTX-DED Dexamethasone Intracanalicular Insert in Subjects with Dry Eye Disease: A Multicenter, Randomized, Vehicle-Controlled Phase 3 Study. *Investigative Ophthalmology & Visual Science.* 2022; 63: 1558-A0283.
62. Christie WC, Segal BA, Evans D. Phase 1/2 Trial Evaluating a Novel, Hydrogel-based Cyclosporine Intracanalicular Insert in Subjects with Dry Eye Disease. *American Academy of Ophthalmology Annual Meeting.* New Orleans, LA. 2021.
63. Vazirani J, Sridhar U, Gokhale N, Doddigarla VR, Sharma S, Basu S. Autologous serum eye drops in dry eye disease: Preferred practice pattern guidelines. *Indian J Ophthalmol.* 2023; 71: 1357-1363.
64. Shtein RM, Shen JF, Kuo AN, Hammersmith KM, Li JY, Weikert MP. Autologous Serum-Based Eye Drops for Treatment of Ocular Surface Disease: A Report by the American Academy of Ophthalmology. *Ophthalmology.* 2020; 127: 128-133.
65. Cui D, Li G, Akpek EK. Autologous serum eye drops for ocular surface disorders. *Curr Opin Allergy Clin Immunol.* 2021; 21: 493-499.
66. Gorimanipalli B, Khamar P, Sethu S, Shetty R. Hormones and dry eye disease. *Indian J Ophthalmol.* 2023; 71: 1276-1284.