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TFOS DEWS II Report Executive Summary

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ABSTRACT

This article presents an Executive Summary of the conclusions and recommendations of the 10-chapter TFOS DEWS II report. The entire TFOS DEWS II report was published in the July 2017 issue of *The Ocular Surface*. A downloadable version of the document and additional material, including videos of diagnostic and management techniques, are available on the TFOS website: www.TearFilm.org.

1. Introduction

Dry eye disease (DED) affects hundreds of millions of people throughout the world and is one of the most frequent causes of patient visits to eye care practitioners. It is a symptomatic disease, characterized by a vicious cycle of tear film instability and hyperosmolarity, which leads to increased ocular surface inflammation, damage and neurosensory abnormalities. Moderate to severe DED is associated with significant pain, limitations in performing daily activities, reduced vitality, poor general health, and often depression.

To increase our understanding of DED, the Tear Film & Ocular Surface Society (TFOS), a non-profit organization, launched the TFOS Dry Eye Workshop II (TFOS DEWS II) in March 2015 [1]. This initiative reflected the TFOS mission, which is to advance the research, literacy, and educational aspects of the scientific field of the tear film and ocular surface. The goal of the TFOS DEWS II was to achieve a global consensus concerning multiple aspects of DED. More specifically, TFOS DEWS II sought to: 1) Update the definition and classification of DED; 2) Evaluate critically the epidemiology, pathophysiology, mechanism, and impact of this disorder; 3) Develop recommendations for the diagnosis, management and therapy of this disease; and 4) Recommend the design of clinical

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trials to assess future interventions for DED treatment.

The TFOS DEWS II involved the efforts of 150 clinical and basic science research experts from around the world, who utilized an evidence-based approach and a process of open communication, dialogue and transparency to increase our understanding of DED. This process required more than 2 years to complete.

The entire TFOS DEWS II report was published in the July 2017 issue of *The Ocular Surface*. A downloadable version of the document and additional material, including videos of diagnostic and management techniques, are available on the TFOS website: www.TearFilm.org. It is anticipated that translations of the report will be offered in many languages, including, but not limited to, Chinese, French, German, Italian, Japanese, Korean, Polish, Portuguese, Romanian, Spanish, Turkish and Vietnamese. These translations, when completed, will be available on the TFOS website.

An Executive Summary of the conclusions and recommendations of the TFOS DEWS II report is presented in this article. The material is abstracted from the reports of ten TFOS DEWS II Subcommittees, which were Definition and Classification; Epidemiology; Sex, Gender, and Hormones; Pathophysiology; Tear Film; Iatrogenic Dry Eye; Pain and Sensation; Diagnostic Methodology; Management and Therapy; and Clinical Trial Design. Additional details and all references can be obtained in the open access, online version.

2. Definition and classification [2]

The goals of the TFOS DEWS II Definition and Classification Subcommittee were to create an evidence-based definition and a contemporary classification system for DED. The new definition is as follows:

> "Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."

The terminology in this definition, including diction, word order, emphasis, and accepted meaning, was critical in creating an internationally accepted definition. The term "multifactorial disease" recognizes DED as a significant and complex, functional disorder that cannot be characterized by a single process, sign or symptom. The term "ocular surface" is defined as comprising the structures of the ocular surface and adnexa, including the tear film, lacrimal and meibomian glands, cornea, conjunctiva and eyelids. "Homeostasis" describes a state of dynamic equilibrium in the body with respect to its various functions, and to the chemical composition of the fluids and tissues. Disruption of homeostasis is considered to be the unifying characteristic that encompasses the myriad of signs of tear film and ocular surface imbalance that might be observed in DED. The term "symptoms" embraces a broad range of possible patient-reported experiences associated with DED including, but not limited to, discomfort and visual disturbance. The key elements contributing to the pathophysiological process, including tear film instability, hyperosmolarity, inflammation and damage, recognized as etiological triggers of the vicious circle, were deemed important, along with neurosensory abnormalities, which have featured increasingly in the recent literature, for inclusion in the definition.

In the classification of DED, the latest evidence supports a scheme based on its pathophysiology in which aqueous deficient dry eye (ADDE) and evaporative dry eye (EDE) exist as a continuum, such that elements of each need to be considered in diagnosis and management. This approach is not intended to override clinical assessment and judgment but to help guide clinical management and future research.

The Subcommittee's recommended classification of DED is shown in Fig. 1. The upper portion of the figure represents a clinical decision algorithm, beginning with the assessment of symptoms, and followed by review for signs of ocular surface disease. DED exhibits both symptoms and signs, and can be differentiated from other ocular surface disease with the use of triaging questions and ancillary testing. It is to this DED group that diagnostic subtyping, and conventional DED management strategies, apply. Symptomatic patients without demonstrable clinical signs do not fall into the DED group, but are differentiated into pre-clinical ocular surface disease or neuropathic pain (non-ocular surface disease). Conversely, asymptomatic patients exhibiting signs are differentiated into patients with poor corneal sensitivity, or those with prodromal signs, who may be at risk of developing manifest DED with time or provocation, for example following ophthalmic surgery or contact lens fitting. Finally, the option exists for patients without either signs or symptoms to be classified, according to the flow chart, as 'normal'.

The lower portion of Fig. 1 represents the etiological classification of DED, and highlights the two predominant and non-mutually exclusive categories; ADDE and EDE. Epidemiological and clinical evidence suggest that the preponderance of DED is evaporative in nature, which is reflected by devotion of a greater proportion of Fig. 1 to EDE than to ADDE. While it is possible that ADDE can occur without obvious signs of EDE and vice versa, as DED progresses, it is increasingly likely that characteristics of both ADDE and EDE will become evident. Further subclassification of ADDE and EDE is not detailed in Fig. 1, but is acknowledged to relate to a vast range of conditions, as described in the TFOS DEWS II Pathophysiology report. ADDE describes conditions affecting lacrimal gland function. EDE is recognized to include both lid-related (for example, meibomian gland dysfunction [MGD] and blink-related) and ocular surface-related (such as mucin and contact lens-related) causes.

3. Epidemiology [3]

The TFOS DEWS II Epidemiology report examines literature on the prevalence, incidence, risk factors, natural history, and morbidity and reviewed questionnaires used in epidemiological studies of DED. The report focuses on epidemiological studies published since the previous TFOS DEWS report in 2007. A meta-analysis of all published prevalence data was undertaken to estimate the impact of age (Table 1) and sex on symptoms and signs of DED. Global mapping of DED prevalence was undertaken using geospatial analysis. The report summarizes the available evidence on the epidemiology of DED and provides recommendations for future needs and opportunities.

DED epidemiology continues to be challenged by the failure for a standardized definition and diagnostic criteria to be used. Consequently, the report describes prevalence based on commonly used diagnostic criteria, including those based on symptoms, on self-report of a practitioner diagnosis, and on DED signs.

While much new information has been published in the last 10 years, no population studies have reported on prevalence of DED for populations south of the equator. Much of the attention has focused on Asia and Europe. The prevalence of DED, with and without symptoms, ranged in prevalence from 5 to 50%. DED prevalence based on signs alone was generally higher and more variable, reaching up to 75% in some populations. Criteria for positive DED signs varied between studies and it was acknowledged that some signs may reflect secondary outcomes or may be related to normal aging. Very few studies were conducted in younger populations (less than 40 years of age) but indications are that DED is also prevalent in these populations. The evidence

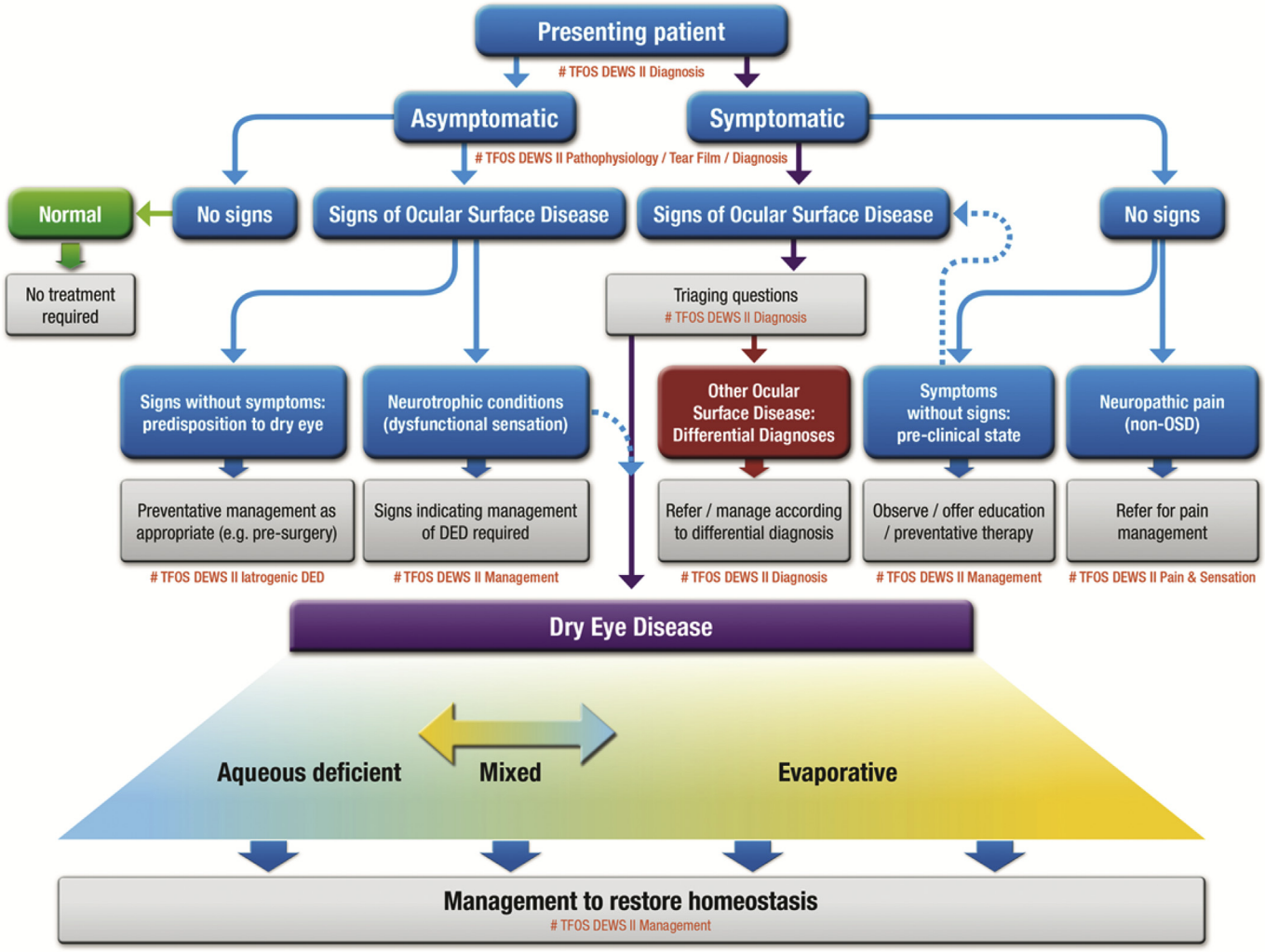

Fig. 1. DED classification scheme. Please see the original report for a complete description of this figure [2].

for Asian race as a risk factor for DED now appears mostly consistent.

The meta-analysis confirmed that symptomatic disease and signs of DED increase with age, however prevalence of signs showed a greater increase per decade than symptomatic disease. Higher rates of DED are reported in women than men, although the differences generally become significant only with increasing age.

Risk factors were categorised as consistent, probable, and inconclusive, in line with the previous TFOS DEWS report [4]. Age, sex, race, MGD, connective tissue disease, Sjögren syndrome, androgen deficiency, computer use, contact lens wear, estrogen replacement therapy, hematopoietic stem cell transplantation, certain environmental conditions (such as pollution, low humidity, and sick building syndrome) and medication use (for example, antihistamines, antidepressants, anxiolytics, and isotretinoin) were identified as consistent risk factors. Probable risk factors included diabetes, rosacea, viral infection, thyroid disease, psychiatric conditions, pterygium, low fatty acid intake, refractive surgery, allergic conjunctivitis, and additional medications (e.g. anti-cholinergic, diuretics, β-blockers). Inconclusive DED risks are Hispanic ethnicity, menopause, acne, sarcoidosis, smoking, alcohol, pregnancy, demodex infestation, botulinum toxin injection, multivitamins and oral contraceptives.

The economic burden on society and impact of DED on the individual, through its detrimental effect on vision, quality of life, and work productivity, as well as the psychological and physical impact of pain, are considerable. The most significant costs are indirect costs due to reduced work productivity. Questionnaires used to evaluate DED vary in their utility for epidemiological studies and further evidence for normative ranges and clinically significant changes are required.

Future research needs include better evaluation of the prevalence of DED of varying severity and in youth, the incidence of disease in different populations, and the impact of modifiable risk factors such as mobile device usage. Geographical mapping approaches will further allow the impact of climate, environment and socioeconomic factors on DED to be elucidated. There has been limited study of the natural history of both treated and untreated DED and this remains an important area for future research.

4. Sex, gender, and hormones [5]

One of the most compelling features of DED is that it occurs more frequently in women than in men. In fact, the female sex is a significant risk factor for the development of DED. That such a sex-related variation exists in the prevalence of an eye disease, or any other ocular function, should not be a surprise, as sex-related

Table 1
Regression analysis of prevalence data by age for each diagnostic subgroup.

Diagnostic subgroup	N of studies	Slope estimate (per decade of age)	Std error of slope estimate	p-value (H_0: slope = 0)	R^2
1. Symptoms or OSDI ≥ 23	8	3.43	0.57	0.001	0.858
2. Self-report of a clinician diagnosis of dry eye	8	2.01	0.73	0.034	0.556
3. WHS Criteria	8	−0.44	0.57	0.475[a]	0.088
[b]4. Schirmer	5	10.55	1.78	0.010	0.921
[b]5. Tear break up time	5	9.71	1.20	0.004	0.956
[b]6. Corneal staining	5	7.63	1.67	0.020	0.875
[b]7. MGD	5	5.23	1.44	0.036	0.815

OSDI - Ocular Surface Disease Index; WHS - Women's Health Study; MGD - meibomian gland dysfunction. Please see the original report for a complete description of this figure [3].
[a] Indicates that there is no change in prevalence by age for the WHS criteria.
[b] Regression analyses are based on estimates of prevalence from age 40–49 and beyond (i.e., missing values for prevalence for ages 15–18, 19–29, and 30–39).

differences are present in almost every cell, tissue and organ system of the body. Indeed, since 1945, more than 575,000 scientific reports have been published which address the basic and/or clinical impact of sex on human physiology and pathophysiology.

The TFOS DEWS II Sex, Gender, and Hormones report details numerous sex-related differences that have been identified in the eye. Many of these differences have been attributed to the effects of sex steroids (e.g. androgens and estrogens), hypothalamic-pituitary hormones, glucocorticoids, insulin, insulin-like growth factor 1 and thyroid hormones. For example, androgens are extremely important in the regulation of the ocular surface and adnexa. They appear to mediate many of the sex-related differences in these tissues. Androgen deficiency, in turn, predisposes to lacrimal gland dysfunction, serves as a risk factor for MGD, and is associated with the development of both ADDE and EDE. In contrast to androgens, the role of estrogens at the ocular surface is less well defined, with effects that appear to be sex-, tissue-, and dose-specific.

In addition, sex-related differences may arise from the sex chromosome complement, including differences in parent-of-origin effects, X chromosome gene dosage (e.g. X-inactivation) and genes in the non-recombining region of the Y chromosome, as well as from sex-specific autosomal factors and epigenetics (e.g. microRNAs, DNA methylation and acetylation, histone modifications).

It is important to note that the word “sex” is used for a reason. Although “sex” and “gender” are often used interchangeably, they have distinct meanings. As stated in a 2001 report by the Institute of Medicine [6], “sex” refers to the classification of living things, generally as male or female, according to their reproductive organs and functions assigned by chromosomal complement. “Gender” refers to a person's self-representation as a man or woman, or how social institutions respond to that person based on the individual's gender presentation. Gender is rooted in biology, but is shaped by environment and experience. In other words, sex distinguishes males and females based on their biological characteristics. Gender, in turn, reflects socially constructed characteristics such as behaviors and expectations related to being a man, masculine, or being a woman, feminine. Furthermore, gender is dynamic, context-related and operates on a spectrum.

In effect, both sex and gender affect health and disease, as well as patients' perceptions about their health. Gender also affects individuals' access to and interactions with the health care system. Many health disparities are associated with gender. Disparities arise from a range of influences that are biological, behavioral/perceptual, cultural, and societal. Therefore, both sex and gender—terms that are distinguishable, but intertwined, should be considered, as they both have pronounced effects on health and on health disparities. Gender and biological sex affect DED risk, presentation of the disease, immune responses, pain, care-seeking behaviors, service utilization, and a myriad of other facets of eye health.

Overall, sex, gender and hormones play a major role in the regulation of ocular surface and adnexal tissues, and in the difference in DED prevalence between women and men.

5. Pathophysiology [7]

On the basis of peer-reviewed literature, the TFOS DEWS II Pathophysiology Subcommittee concluded that the core mechanism of DED is evaporation-induced tear hyperosmolarity, which is the hallmark of the disease. It damages the ocular surface both directly and by initiating inflammation. The cycle of events, described as the Vicious Circle of DED, is shown at the center of Fig. 2.

Two forms of DED are recognized, ADDE and EDE. In ADDE, tear hyperosmolarity results when lacrimal secretion is reduced, in conditions of normal evaporation from the eye. In EDE, tear hyperosmolarity is caused by excessive evaporation from the exposed tear film in the presence of a normally functioning lacrimal gland. Since tear osmolarity is a function of tear evaporation in either ADDE or EDE, tear hyperosmolarity arises due to evaporation from the ocular surface and, in that sense, all forms of DED are evaporative. In other words, EDE is more accurately considered a hyper-evaporative state.

In DED, tear hyperosmolarity is considered to be the trigger for a cascade of signaling events within surface epithelial cells, which leads to the release of inflammatory mediators and proteases. Such mediators, together with the tear hyperosmolarity itself, are understood to cause goblet cell and epithelial cell loss and damage to the epithelial glycocalyx. Inflammatory mediators from activated T-cells, recruited to the ocular surface, reinforce damage. The net result is the characteristic punctate epitheliopathy of DED and a tear film instability which leads at some point to early tear film breakup. This breakup exacerbates and amplifies tear hyperosmolarity and completes the vicious circle events that lead to ocular surface damage. Ultimately this is thought to lead to self-perpetuation of the disease.

Tear film instability can be initiated without the prior occurrence of tear hyperosmolarity, by conditions that affect the ocular surface, including xerophthalmia, ocular allergy, topical preservative use and contact lens wear. In this case, early tear film breakup is hypothesized to be the primary basis for tear film hyperosmolarity initially experienced locally at the site of breakup, and with increasing severity, at some point becoming detectable in tear meniscus samples. This represents an ocular surface–related form of EDE. In MGD-related EDE tear hyperosmolarity results from a tear film lipid layer deficiency. In ADDE the onset of early breakup during the evolution of the disease, may add a secondary evaporative element to the DED.

There are various causes of ADDE. It may result from blocking the sensory drive to the lacrimal gland that is essential to maintain tear film homeostasis. Bilateral topical anesthesia can cause both a

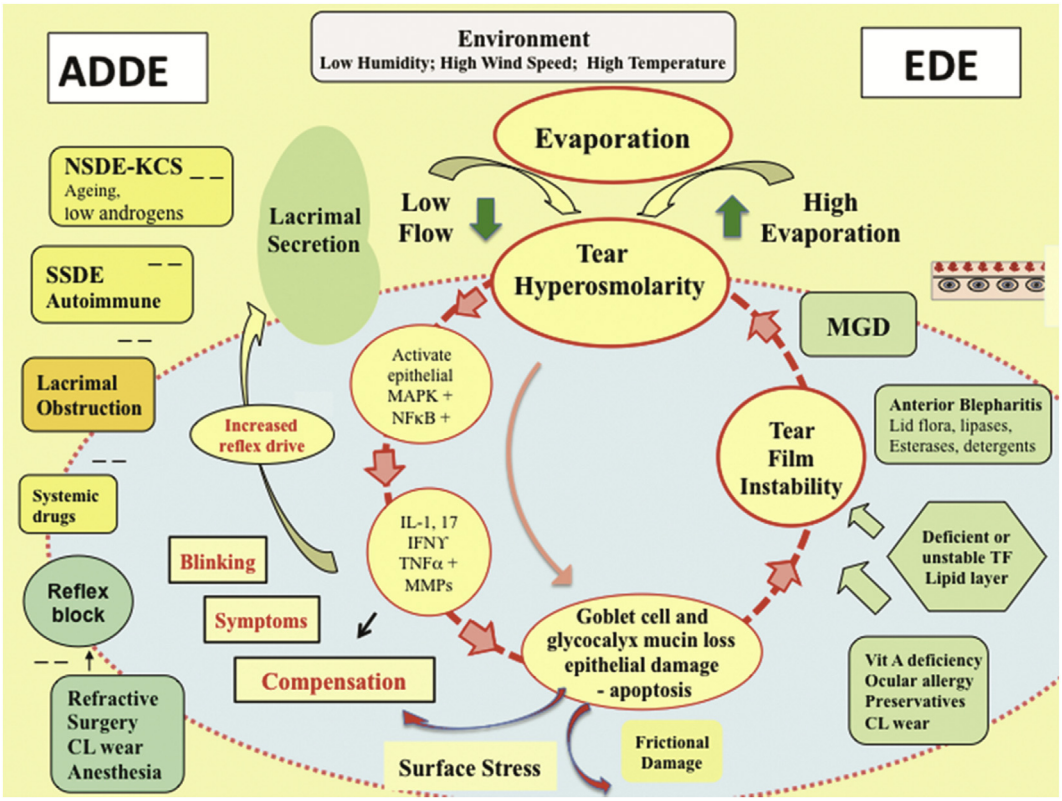

Fig. 2. Pathophysiology of DED. Please see the original report for a complete description of this figure [7].

reduction in tear secretion and blink rate. DED due to a block in reflex tearing can be caused by chronic abuse of topical anesthetics, trigeminal nerve damage and refractive surgery including LASIK surgery. The delivery of aqueous tears to the tear sac can also be reduced by obstruction to the lacrimal ducts, which might occur in any form of cicatricial conjunctival disease, such as trachoma, ocular cicatricial pemphigoid, erythema multiforme, graft-versus-host-disease and chemical burns. A number of drugs in systemic use, such as antihistamines, β-blockers, antispasmodics, diuretics and some psychotropic drugs, can cause a reduction in lacrimal secretion and are risk factors for DED [3,8]. Also, tear secretion rate falls in later life.

In the Western world the most common cause of ADDE is inflammatory infiltration of the lacrimal gland, encountered most severely in the DED associated with autoimmune disorders such as Sjögren syndrome (SSDE) and, with lesser severity, in non-Sjögren syndrome (NSDE). Inflammation causes both acinar and ductal epithelial cell dysfunction and/or destruction and a potentially reversible neurosecretory block. Circulating antibodies to the muscarinic (M3) receptor may also cause a receptor block. Low tissue androgen levels may predispose to lacrimal gland inflammation.

Epithelial injury and defective glycocalyx, loss of tear volume and of goblet cell mucin, lead to increased frictional damage and friction-related symptoms. The tear hyperosmolarity and epithelial injury caused by DED stimulates corneal nerve endings, leading to symptoms of discomfort, increased blink rate and potentially, to a compensatory, reflex increase in lacrimal tear secretion. This compensatory secretion is more likely in EDE, where lacrimal gland function is potentially normal.

A schematic diagram to show the etiology and mechanism of MGD, which is the major cause of EDE, is shown in Fig. 3. Although many mechanistic aspects are not yet understood, the figure attempts to summarize the current view. The upper part of the figure illustrates the etiology of the two forms of MGD that result in low delivery of meibum, cicatricial and non-cicatricial MGD.

With age, there is an increase in meibomian gland dropout, particularly after the age of 50 years, which correlates with the appearance of primary MGD. A fall in bioavailable androgens may contribute to these events. In youth, treatment of acne vulgaris with *cis*-retinoic acid may induce gland atrophy and MGD, while in an older age group, androgen receptor insensitivity or blockade may induce signs of MGD. The anti-glaucoma drugs pilocarpine and timolol also have direct effects on human meibomian gland epithelial cells that may influence their morphology, survival and/or proliferative capacity, and possibly promote MGD. Polychlorinated biphenyls may cause a systemic disorder that includes MGD-like features. Certain skin disorders, such as acne rosacea, atopic dermatitis, seborrheic dermatitis and psoriasis are associated with non-cicatricial MGD, while cicatricial conjunctival diseases such as trachoma, erythema multiforme and pemphigoid, lead to cicatricial MGD.

A key event in non-cicatricial MGD is hyperkeratinization of the terminal ducts, leading to duct obstruction, duct dilatation and disuse atrophy of the glands. Later, obliteration of the gland orifices may occur. Obstruction may be exacerbated by changes in oil composition that increase meibum viscosity. The degree to which inflammatory changes are found around affected glands varies in different reports, but signs of inflammation are common at the lid margin. Inflammatory mediators and lipids may be released into tears and onto the ocular surface to cause epithelial damage. In cicatricial MGD, submucosal conjunctival scarring drags the meibomian orifices, terminal ducts and mucocutaneous junction posteriorly, across the posterior lid border and onto the

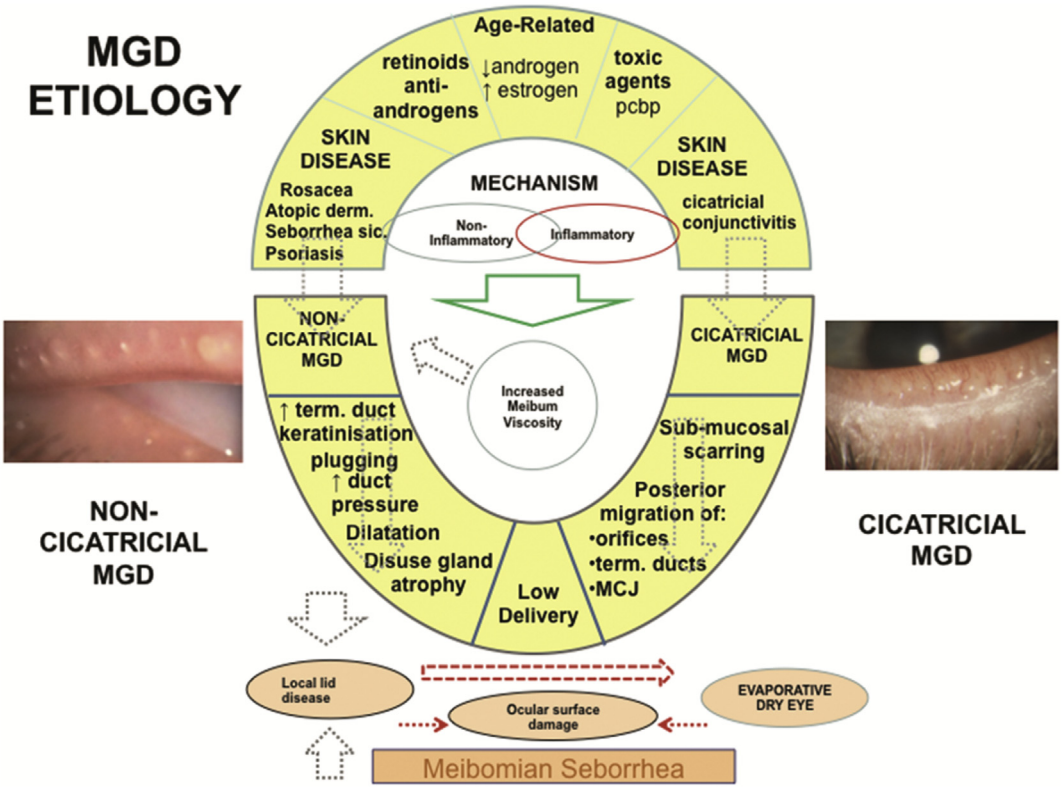

Fig. 3. Pathophysiology of MGD. Please see the original report for a complete description of this figure [7].

tarsal plate, where the narrowed and displaced ducts can no longer deliver meibum effectively to the tear film lipid layer. Low meibum delivery and changes in oil composition can lead to tear film instability, increased tear evaporation and ultimately to EDE. In low delivery MGD, symptoms may arise from the local lid disease itself, from lid disease with ocular surface damage and from EDE.

6. Tear film [8]

The TFOS DEWS II Tear Film Subcommittee recommended a two-phase model of the tear film, which has a lipid layer overlying a muco-aqueous phase. Wax and cholesteryl esters (non-polar lipids) make up the majority of the tear lipid layer and these are spread onto the muco-aqueous layer by an underlying layer of polar lipids, including (O-acyl)-ω-hydroxy fatty acids and possibly phospholipids. The role of the tear film lipid layer alone in preventing evaporation and breakup of tears on the eye is controversial. It is likely that interactions of the whole tear film, including lipids, mucins, proteins and salts, prevent evaporation and collapse, but further work is needed to confirm this together with the relative roles of the various components.

Several studies have attempted to correlate changes in tear lipid biochemistry with DED, but no definitive linkage has yet been made. In contrast, tear osmolarity received considerable attention as the hallmark of DED, increasing with the severity of DED.

The muco-aqueous layer overlies the apical epithelial cells and their carbohydrate-rich glycocalyx. Changes in the amount of mucin or the glycosylation of different components have been reported in tears collected from DED patients. The muco-aqueous layer contains at least four major mucins, and over 1500 different proteins and peptides. Tear proteins have been reported to differ in tears from DED subjects, but no definitive set of proteins or their degrees of change are yet validated to aid diagnosis. This is an area that should receive increased attention.

Changes to the tear film clearly occur in DED. However, the lack of unified clinical parameters in tear film studies and the relatively limited understanding of the structure of the tear film has hampered comprehension of how these changes occur and their significance in the pathophysiology of DED. Improvements in the ability to characterize the biochemistry of the tear film may lead to the identification of new markers that can be used to diagnose, potentially predict, and even treat DED. A holistic approach to understanding tear film structure and function will undoubtedly lead to better treatments for patients with this disease.

7. Pain and sensation [9]

As noted by the TFOS DEWS II Pain & Sensation Subcommittee, pain can be differentiated into nociceptive and neuropathic types. Nociceptive pain occurs in response to actual or threatened damage to tissues. However, neuropathic pain occurs due to a lesion within the somatosensory nervous system and is commonly referred to as pathologic pain or pain without biological value.

Pain associated with DED is transmitted via the peripheral axons of trigeminal ganglion (TG) neurons innervating the cornea and conjunctiva. Within the corneal stroma, they form a subepithelial nerve plexus whose ascending branches ramify extensively to terminate within the surface epithelial layers. Functionally, sensory nerves belong to polymodal nociceptor neurons, pure mechano-nociceptor neurons and cold thermoreceptor neurons. Polymodal nociceptors are normally silent and respond to chemical,

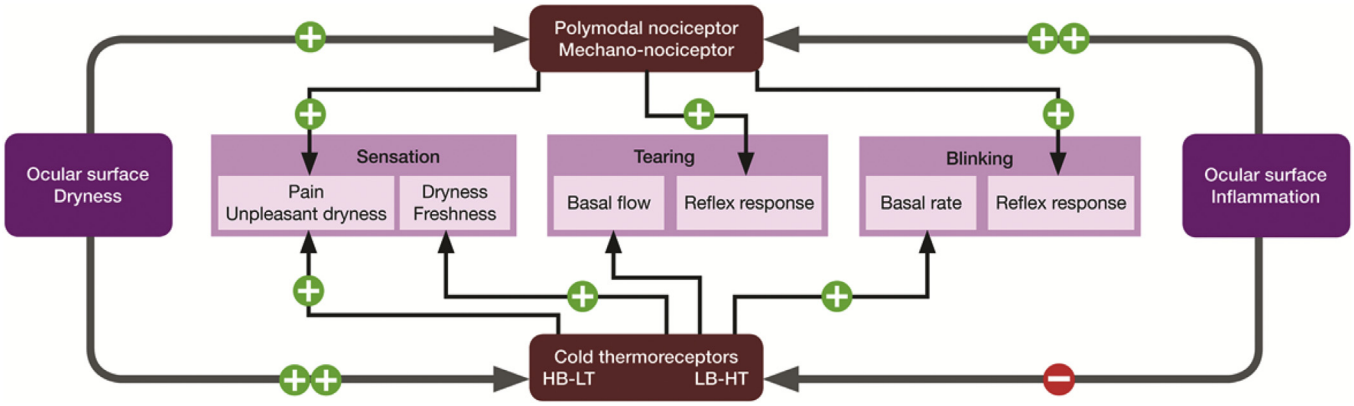

Fig. 4. Diagram summarizing how ocular inflammation of various etiologies or ocular surface drying in DED, provoke variable increases (+) or decreases (−) of nerve impulse activity in polymodal- and mechano-nociceptors and in cold thermoreceptors of the high background, low threshold (HB-LT) and low background, high threshold (LB-HT) types. Together these changes elicit conscious sensations of different quality, as well as changes in tear flow and in spontaneous and reflex blinking.

mechanical, and thermal stimuli. The inflammatory mediators released during injury sensitize them. The transient receptor potential cation channel subfamily V member 1 (TRPV1) is important for sensory transduction and sensitization of polymodal nociceptors. Pure mechano-nociceptors are also silent at rest and respond only to mechanical forces perhaps through piezo2 and other non-identified transducing channels. Cold thermoreceptors continuously discharge nerve impulses at the normal eye surface temperature, respectively augmenting or decreasing the basal firing frequency with cooling or warming. TRPM8 is their main cold transducing channel and is also sensitive to osmolarity increases. Inter-blink tear evaporation causes discrete cooling of the ocular surface and tear osmolarity rises, thereby augmenting basal activity of cold thermoreceptors. This is consistent with the hypothesis that cold-sensitive fibers contribute to the reflex control of basal tear production and blinking.

The TG neurons from the ocular surface project primarily into two spatially discrete regions within the trigeminal brain stem nuclear complex: the transition region between caudal Vi and Vc (ViVc transition) and at the Vc/upper cervical cord junction (VcC1 region). Evidence suggests that the VcC1 region plays a dominant role in sensory-discriminative aspects of ocular pain. ViVc transition neurons are excited by bright light and are activated by changes in the moisture status of the ocular surface. Ocular neurons at the ViVc transition project to brain regions that control lacrimation (superior salivatory nucleus) and blinking (facial motor nucleus) as well as to the sensory thalamus. Thus, it is suggested that ocular neurons at the ViVc transition play a significant role in maintaining ocular surface homeostasis.

The secretory activity of the main lacrimal gland is regulated by autonomic sympathetic and parasympathetic nerves whose activity is regulated by reflex influences from sensory neurons supplying the ocular surface. Parasympathetic innervation is more extensive. Very little is known about the neural control of accessory lacrimal glands, but it appears to be similar to the main lacrimal gland. While nerves are present around the meibomian glands, there are no studies examining the role of sensory or autonomic nerves and their neurotransmitters in regulating the holocrine secretion of the meibomian gland. Activation of sensory nerves supplying the rat cornea evokes goblet cell mucous secretion; however efferent nerve type(s) involved in this reflex response remain to be established. Several non-neural processes regulate the release of mucins from stratified squamous cells, but to date no regulatory role for nerves or neurotransmitters has been identified.

In addition to regulation of tear production, ocular surface nerves mediating sensations contribute to blinking behavior (Fig. 4). It has been suggested that spontaneous blinking is maintained, at least in part by the continuous nerve impulse firing of eye surface cold thermoreceptors, an effect likely mediated by the connections of TG neurons with brainstem Vi/Vc neurons which in turn project to the motor neurons of the facial nerve (Cranial nerve VII). Nociceptor sensory input, projecting to neurons at the VcC1 region, initiates reflex blinking through their projections to ViVc transition neurons, and sets blink amplitude and peak velocity of corneal reflex blinks.

In DED, reduced tear secretion leaves the corneal epithelium exposed to adverse environmental conditions and often leads to variable levels of inflammation and to peripheral nerve terminal damage. Inflammation causes sensitization of polymodal nociceptors and mechano-nociceptors, while it depresses cold thermoreceptor activity. However, in experimental DED the sensitization of nociceptor fibers is discrete and the most prominent nerve disturbance is the sustained, abnormal increase in cold thermoreceptor nerve activity that occurs in parallel with morphological changes in corneal innervation. This suggests that dryness-induced nerve damage dominates over inflammation, causing abnormal activity primarily in cold terminals. In parallel with these changes in peripheral nerve activity, brainstem ocular neurons at both ViVc and VcC1 regions display enhanced responsiveness.

8. Iatrogenic dry eye [10]

As reported by the TFOS DEWS II Iatrogenic Dry Eye Subcommittee, DED can be caused by a variety of iatrogenic interventions, including topical and systemic drugs, the use of contact lenses, and ophthalmic surgical and non-surgical procedures.

Topical medications that cause DED (Table 2) interact with the ocular surface by exerting allergic, toxic and immuno-inflammatory effects. Preservatives, such as benzalkonium chloride, may cause or aggravate DED through their toxic and proinflammatory effects, as well as detergent tensioactive properties. Moreover, a great variety of systemic drugs, such as vasodilators, sulfonylureas, anxiolytics, antidepressants, antihistamines, and those listed in Table 3, may also induce DED secondary to decreased tear production, altered

Table 2
Examples of topical treatments that may induce or worsen DED.

Compounds	Examples
Adrenergic agonists	Apraclonidine, Brimonidine, Dipivefrin
Anti-allergics	Emedastine, Olopatadine
Anti-virals	Aciclovir, Idoxuridine, Trifluridine
β−blockers	Betaxolol, Carteolol, Levobunolol, Metipranolol, Timolol
Carbonic anhydrase inhibitors	Brinzolamide, Dorzolamide
Cholinergic agonists	Pilocarpine, Ecothiopate
Decongestants	Naphazoline, Tetryzoline
Miotics	Dapiprazole
Mydriatics & cyclopegics	Cyclopentolate, Tropicamide, Hydroxyamfetamine
Prostaglandins	Bimatoprost, Latanoprost, Travoprost, Unoprostone
Topical and local anesthetics	Cocaine, Proxymetacaine, Tetracaine
Topical ocular non-steroidal anti-inflammatory drugs	Bromfenac, Diclofenac, Ketorolac, Nepafenac

Table 3
Known or suspected systemic medications causing, contributing to, or aggravating DED.

Category	Subcategory
Analgesic	Antirheumatic
	Cannabinoid
	Opioid
Anesthesia	
Anticholinergic (antimuscarinic)	Antiarrythmic/Bronchodilating
	Antihistamine
	Antidepressant
	Anti-Parkinson's
	Antipsychotic
	Antispasmodic
	Decongestant
Antihypertensive	Adrenergic blocking
	Na^+Cl^- Co-transporter (diuretic)
Antileprosy	
Antimalarial	
Antineoplastic	
Anxiolytic/hypnotic	
Chelator/Calcium Regulator	
Depressant	
Herbal and Vitamins	
Hormonal	Antiandrogen/Estrogen replacement
Neurotoxin	
Sedative	

nerve input and reflex secretion, inflammatory effects on secretory glands, or direct irritation effect through secretion into the tears.

DED in contact lens wearers has been identified as an ongoing issue for many patients. The use of contact lenses can either induce or be associated with DED. Biophysical changes to the tear film in contact lens wearers with DED include a thinner, patchy lipid layer; tear film instability; lower basal tear turnover rate; and decreased tear meniscus volume.

Surgical procedures such as corneal refractive surgery and keratoplasty may cause or aggravate DED through mechanisms intrinsic to the procedure (i.e. corneal nerve transection) or even by the use of postoperative topical drugs. Cataract surgery, lid surgeries, botulinum toxin application and cosmetic procedures are also considered risk factors for iatrogenic DED, which can be the cause of patient dissatisfaction, visual disturbance and poor surgical outcomes.

Future directions to address iatrogenic DED include more in depth epidemiological studies about the risk factors, development of less toxic medications and preservatives, as well as new techniques for less invasive eye surgeries. Novel research into detecting early DED prior to ocular surgery, determining the benefits of prophylactic treatment, as well as efforts to establish appropriate therapeutics, and improving attempts to regulate and oversee medications, preservatives and procedures should be considered.

9. Diagnostic methodology [11]

The TFOS DEWS II Diagnostic Methodology Subcommittee examined the research evidence for tests to quantify patient symptoms, visual disturbance, tear film stability, osmolarity, tear volume, ocular surface damage, inflammation of the ocular surface and eyelid signs (such as MGD), and recommended the key diagnostic tests and techniques. While many tests have been suggested to be diagnostic of DED, their sensitivity and specificity is highly dependent on the inclusion criteria and severity of the DED group and the population examined. The Subcommittee made the following recommendations to represent the best available evidence to diagnose and subtype DED in a clinical setting. The selection principles were: diagnostic ability; minimal-invasiveness; objectivity; and clinical applicability.

The recommended tests for the diagnosis of DED and assessment of its severity are presented in Fig. 5 Prior to diagnosis, it is important to exclude conditions that can mimic DED with a number of triaging questions (Fig. 5). Such conditions and their differentiating features are outlined in the report. Following this, the Dry Eye Questionnaire-5 (DEQ-5) or Ocular Surface Disease Index (OSDI) should be completed to indicate whether a patient might have DED, and a positive symptom score on either of these questionnaires should then trigger a more detailed examination for clinical signs of DED. The presence of any one of three specified signs; reduced non-invasive break-up time; elevated or a large interocular disparity in osmolarity; or ocular surface staining (of the cornea, conjunctiva or lid margin) in either eye, is considered representative of disrupted homeostasis, confirming the diagnosis of DED. If a patient has DED symptoms and their practitioner does not have access to all these tests, a diagnosis is still possible, based on a positive result for any one of the markers, but may require referral for confirmation if the available homeostasis markers are negative. Guidance on how, and in which order, to conduct these tests are provided within the report and videos are available on the TFOS website (www.tearfilm.org).

Having confirmed that the condition is DED on the basis of a positive symptom score and one or more positive homeostatic marker results, further subtype classification tests such as meibography, lipid interferometry and tear volume measurement should be conducted to determine: 1) where the DED falls on the spectrum between ADDE and EDE, and 2) the severity of DED, in order to guide treatment.

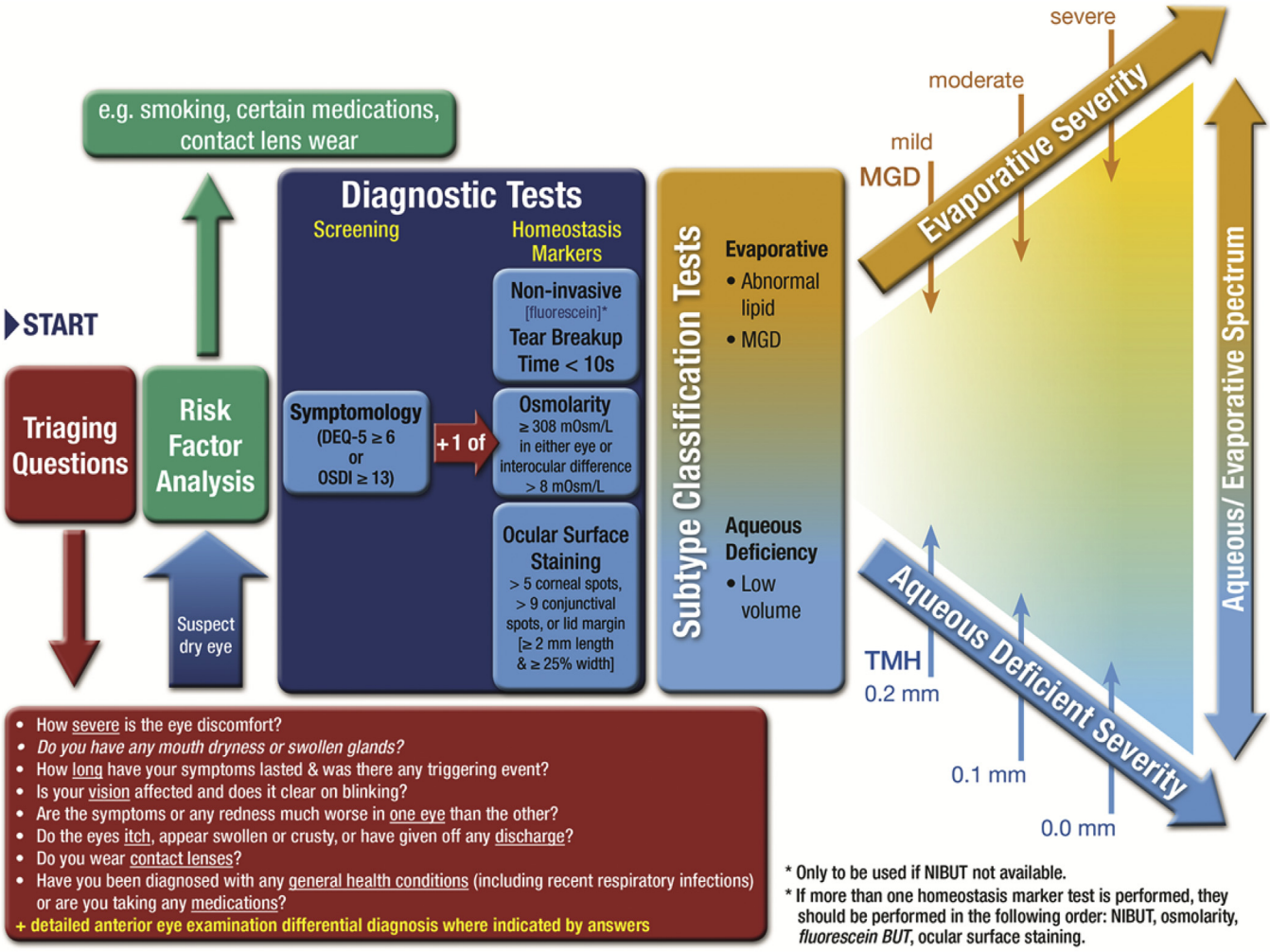

Fig. 5. Recommended diagnostic approach for DED. Please see the original report for a complete description of this figure [11].

10. Management and therapy [12]

The management of DED is complicated, due to its multifactorial etiology. Expanding upon the simple belief that "diagnosis precedes therapy" means that clinicians must make their best efforts to identify the degree to which EDE, ADDE and/or other ocular surface conditions are contributing to the patient's presentation. This aspect of determining the major causative factors behind the DED is critical to appropriate management.

The ultimate aim of DED management is to restore the homeostasis of the ocular surface and tear film, through breaking the vicious cycle of the disease. While certain treatments may be specifically indicated for one particular aspect of an individual patient's condition, a number of therapies might be appropriately recommended in order to treat the multiple aspects of a patient's presentation with DED. While aiming to identify and treat the primary source of the disease, the management of DED typically involves ongoing management to address chronic sequelae, rather than short-term treatment.

The presented management algorithm is not proposed as a rigid sequential approach to be followed linearly. Instead, it should be viewed as an organizational tool to help guide initiation of treatment with those interventions most likely to benefit most patients with DED, and progressing to more advanced and specific treatments aimed at particular aspects of the DED pathophysiology. Ongoing scientific evidence, as well as risk versus benefit and cost considerations, will also contribute to decisions made in choosing between multiple treatment options.

Management algorithms are often constructed to recommend a sequence of treatments according to the stage of disease, but this construction is complicated in DED, as the disease often varies from patient to patient, both in severity and in character. Table 4 lists a series of management and treatment options that have all been shown to result in alleviation of presenting DED [12]. Should patients not respond to a given level of management, or should they present with more severe DED, the next level of management is recommended and in some cases the previous therapy may be continued in addition to any new therapies. In general, management approaches begin with conventional, low-risk and easily accessible patient-applied therapies such as over-the-counter

Table 4
Recommendations for the staged management and treatment of DED.[a,b,c]

Step 1:
- Education regarding the condition, its management, treatment and prognosis
- Modification of local environment
- Education regarding potential dietary modifications (including oral essential fatty acid supplementation)
- Identification and potential modification/elimination of offending systemic and topical medications
- Ocular lubricants of various types (if MGD is present, then consider lipid-containing supplements)
- Lid hygiene and warm compresses of various types

Step 2:
If above options are inadequate consider:
- Non-preserved ocular lubricants to minimize preservative-induced toxicity
- Tea tree oil treatment for Demodex (if present)
- Tear conservation
  - Punctal occlusion
  - Moisture chamber spectacles/goggles
- Overnight treatments (such as ointment or moisture chamber devices)
- In-office, physical heating and expression of the meibomian glands (including device-assisted therapies, such as LipiFlow)
- In-office intense pulsed light therapy for MGD
- Prescription drugs to manage DED[d]
  - Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present)
  - Topical corticosteroid (limited-duration)
  - Topical secretagogues
  - Topical non-glucocorticoid immunomodulatory drugs (such as cyclosporine)
  - Topical LFA-1 antagonist drugs (such as lifitegrast)
  - Oral macrolide or tetracycline antibiotics

Step 3:
If above options are inadequate consider:
- Oral secretagogues
- Autologous/allogeneic serum eye drops
- Therapeutic contact lens options
  - Soft bandage lenses
  - Rigid scleral lenses

Step 4:
If above options are inadequate consider:
- Topical corticosteroid for longer duration
- Amniotic membrane grafts
- Surgical punctal occlusion
- Other surgical approaches (eg tarsorrhaphy, salivary gland transplantation)

MGD – meibomian gland dysfunction; DED – dry eye disease; This Table was reproduced from Ref. [12].
[a] Potential variations within the disease spectrum are acknowledged to exist between patients and the management options listed above are not intended to be exclusive. The severity and etiology of the DED state will dictate the range and number of management options selected from one or more steps.
[b] One or more options concurrently within each category can be considered within that step of the dry eye disease state. Options within a category are not ranked according to importance and may be equally valid.
[c] It should be noted that the evidence available to support the various management options differs and will inevitably be lower for newer management options. Thus, each treatment option should be considered in accordance with the level of evidence available at the time management is instigated.
[d] The use of prescription drugs needs to be considered in the context of the individual patient presentation, and the relative level of evidence supporting their use for that specific indication, as this group of agents differs widely in mechanism of action.

lubricants for early stage disease, and progress to more advanced therapies for more severe forms of DED. However, it must be understood that there is significant heterogeneity in the DED patient population. The approach cannot be overly formulaic and these recommendations may be modified and overlapped as required by practitioners based on an individual patient profile.

The expected treatment trial duration before concluding failure to improve is related both to the individual's response and to the therapy being considered. Most commonly, treatment effects are observed within one to three months, although some therapies (e.g. cyclosporine A) may take longer.

Overall, the treatment of DED remains something of an art, not easily lending itself to a rigid, evidence-based algorithm that accommodates all patients with DED symptoms or signs. All eye care providers who treat patients with DED must exercise their clinical skills to judge the significance of each of the varied pathogenic processes that may manifest similar subjective complaints and similar signs of ocular surface dysfunction.

11. Clinical trial design [13]

In order to improve the quality of clinical trials, to optimize resources, and to increase the opportunity for novel therapeutics to reach patients with DED, the TFOS DEWS II Clinical Trials Subcommittee made the following recommendations.

First, that studies be conducted consistent with Good Clinical Practice (GCP). While this may be a daunting task, clinical trialists should consult colleagues and drug development experts who are familiar with this system of controls. This includes appropriate protections for the study subjects. GCP also requires compliance with appropriate regulatory requirements in the jurisdiction of study conduct, and may require additional regulatory filings if the investigational shipment is prepared and sent from another state or country.

The Consolidated Standards of Reporting Trials (ConSORT) statement is useful to review prior to planning and starting a study. Next, the Subcommittee recommended that the design, treatments, and sample size be consistent with the investigational treatment,

the objectives of the study, and the phase of development. For example, a crossover or paired-comparison design may be appropriate for a comfort study in normal volunteers, but not for a long-lasting treatment with potential for systemic or contralateral effects. Also, the dose of a drug or biologic should not only be less than that which was toxic or not tolerated in nonclinical or previous clinical studies, but must be sufficient, in dose and frequency, to deliver therapeutic concentrations at the intended site of action. The duration of treatment, at least for a pivotal study, should also be consistent with the mechanism of action and time course of effect. For pivotal studies, sample size is key to the potential validity of the study.

Outcome measures are critical to determine the efficacy of the treatment and, if possible, should include minimally invasive objective metrics that align with the expected mechanism of action of the treatment. Exploration of new ways to evaluate DED, such as biomarkers, may lead to improvement in DED clinical trial design and increased clarity on the efficacy of new treatments.

Dedication

This TFOS DEWS II report is dedicated to the late Professor Juha Holopainen (Helsinki Eye Lab and Department of Ophthalmology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland), who served on the Steering Committee and Tear Film Subcommittee, in recognition of his outstanding scientific contributions to the field of the ocular surface and tear film.

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Fig. 6. TFOS DEWS II™ report.

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