Ophthalmol Ther (2025) 14:1411–1428
https://doi.org/10.1007/s40123-025-01161-8

REVIEW

Dry Eye Disease: From Causes to Patient Care and Clinical Collaboration—A Narrative Review

Pasquale Aragona · Stefano Barabino · Antonio Di Zazzo · Giuseppe Giannaccare · Edoardo Villani · Francesco Aiello · Elena Antoniazzi · Stefano Bonini · Emilia Cantera · Gianpaolo Carlini · Chiara Chierego · Rossella Colabelli · Romina Fasciani · Antonella Franch · Giovanna Gabbriellini · Caterina Maria Rita Gagliano · Andrea Leonardi · Angelo Macrì · Rita Mencucci · Luigi Mosca · Vincenzo Orfeo · Antonio Pinna · Augusto Pocobelli · Romolo Protti · Paolo Rama · Laura Rania · Miguel Rechichi · Pierangela Rubino · Andrea Russo · Vincenzo Scorcia · Leopoldo Spadea · Marco Trentadue · Salvatore Troisi · Piera Versura · Maurizio Rolando

Received: February 27, 2025 / Accepted: April 24, 2025 / Published online: May 28, 2025

ABSTRACT

Dry eye disease (DED) is a common condition of the ocular surface that affects tens of millions of people worldwide. It is often characterized by decreased tear production or increased evaporation, resulting in a wide range of signs and symptoms. This review provides a comprehensive analysis of the literature related to DED,

P. Aragona
Department of Biomedical Sciences, Ophthalmology Clinic, University of Messina, Messina, Italy

S. Barabino
Ocular Surface and Dry Eye Center, Ospedale L. Sacco, University of Milan, Milan, Italy

A. Di Zazzo (✉) · S. Bonini
Cornea Service, Department of Ophthalmology, University of Rome Campus Biomedico, Campus Bio-Medico University Hospital Foundation, Via Alvaro del Portillo 200, 00128 Rome, RM, Italy
e-mail: a.dizazzo@policlinicocampus.it

G. Giannaccare
Eye Clinic, Department of Surgical Sciences, University of Cagliari, Cagliari, Italy

E. Villani
Eye Clinic, San Giuseppe Hospital, IRCCS Multimedica, University of Milan, Milan, Italy

F. Aiello
Ophthalmology Unit, Department of Experimental Medicine, University of Rome Tor Vergata, Rome, Italy

E. Antoniazzi
IRCCS Policlinico San Matteo Foundation, Pavia, Italy

E. Cantera
Israelitic Hospital, Rome, Italy

G. Carlini
ASL Napoli 1 Centro, Naples, Italy

C. Chierego
Ophthalmic Unit, Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy

R. Colabelli · A. Pocobelli
UOC Oftalmologia-Banca degli Occhi, San Giovanni Addolorata Hospital, Rome, Italy

R. Fasciani · L. Mosca
Fondazione Policlinico Universitario A. Gemelli-IRCCS, Rome, Italy

A. Franch
Fondazione Banca Degli Occhi del Veneto Onlus, Department of Ophthalmology, SS Giovanni and Paolo Hospital, Venice, Italy

G. Gabbriellini
Ophthalmology Unit, Department of Surgical, Medical and Molecular Pathology and Critical Care Medicine, University of Pisa, Pisa, Italy

detailing causes, diagnostic tests, and medical management. Several mechanisms contribute to the maintenance of the physiological integrity of the ocular surface, and their dysfunction may result in noticeable symptoms. Accurate diagnosis is therefore essential, even when physiological function is only minimally impaired or no clear pathological signs are present. The review emphasizes the importance of addressing the underlying causes through a combination of treatment options, lifestyle changes, and enhanced communication between patients and healthcare providers to break the cycle of inflammation and tear instability. It aims to raise awareness among patients, healthcare professionals, and researchers regarding the diagnosis and treatment of DED, while also highlighting recent advancements and future challenges in its management.

Keywords: Dry eye disease; Inflammation; Hyperosmolarity; Ocular surface diseases; Quality of life; Patients; Symptoms; Therapy

C. M. R. Gagliano
Department of Medicine and Surgery, Kore University of Enna, Enna, Italy

C. M. R. Gagliano
"G.B. Morgagni" Foundation, Catania, Italy

A. Leonardi
Ophthalmology Unit, Department of Neuroscience, University of Padua, Padua, Italy

A. Macrì
IRCCS San Martino Polyclinic Hospital, Genoa, Italy

R. Mencucci
Eye Clinic, Department of Neuroscience, Psychology, Pharmacology and Child Health, University of Florence, Florence, Italy

V. Orfeo
Ophthalmology Unit, "Clinica Mediterranea", Naples, Italy

A. Pinna
Ophthalmology Unit, Department of Medicine, Surgery and Pharmacy, University of Sassari, Sassari, Italy

R. Protti
Ophthalmic Unit, San Biagio Hospital, Domodossola (VB), Italy

P. Rama
Department of Ophthalmology, IRCCS Policlinico San Matteo, Pavia, Italy

L. Rania
Department of Ophthalmology, Istituto per la Sicurezza Sociale, San Marino State Hospital, Cailungo, San Marino

M. Rechichi
Centro Polispecialistico Mediterraneo, Sellia Marina (CZ), Italy

P. Rubino
Ophthalmology Unit, Department of General and Specialized Surgery, University Hospital of Parma, Via Gramsci 14, 43126 Parma, Italy

A. Russo
Eye Clinic, Department of Neurological and Vision Sciences, University of Brescia, Piazzale Spedale Civili, 1, 25100 Brescia, Italy

V. Scorcia
Department of Ophthalmology, University "Magna Græcia" of Catanzaro, Viale Europa, 88100 Catanzaro, Italy

L. Spadea
Eye Clinic, Policlinico Umberto I, "Sapienza" University of Rome, Rome, Italy

M. Trentadue
Azienda Ospedaliera "Ospedale Consorziale Policlinico", Bari, Italy

S. Troisi
Eye Department, AOU "San Giovanni di Dio e Ruggi d'Aragona", Salerno, Italy

P. Versura
Ophthalmology Unit, Department of Experimental, Diagnostic and Specialty Medicine (DIMES), Alma Mater Studiorum University of Bologna, Sant'Orsola-Malpighi University Hospital of Bologna, Bologna, Italy

M. Rolando
Ocular Surface and Dry Eye Center, Vista Vision and ISPRE Ophthalmics, Genoa, Italy

Key Summary Points

Effective management of dry eye disease (DED) requires addressing key factors such as inflammation, tear film instability, and environmental or lifestyle contributors, emphasizing the need to target underlying chore mechanisms.

A combination of pharmacological treatments, lifestyle modifications, and personalized education is vital to breaking the cycle of inflammation and tear instability.

Therapeutic advances such as novel anti-inflammatory agents and tear-stabilizing technologies offer promising opportunities for more personalized and effective management of DED.

Healthcare providers play a critical role in educating patients about DED's chronic and fluctuating nature, promoting adherence to long-term care protocols and fostering active patient involvement.

Integrating expertise from ophthalmologists and other healthcare professionals enables tailored strategies that improve patient outcomes and quality of life.

INTRODUCTION

Dry eye disease (DED) is one of the most common ocular conditions worldwide, affecting tens of millions of people [1]. The prevalence of DED is higher in women than in men, although the differences become significant with increasing age, when the prevalence also increases [1]. This widespread condition not only affects visual function, but also significantly reduces the quality of life of those affected. The impact of DED goes beyond individual inconvenience, as it has a significant socio-economic impact, affecting productivity, healthcare costs, and the overall well-being of society [2]. DED is characterized by tear film instability, hyperosmolarity, and ocular surface inflammation resulting from a loss of homeostasis. Corneal nerve injury can cause neural plasticity and peripheral and central sensitization, resulting in neuropathic ocular pain (NOP) [3]. In the early stages, symptoms may be transient and reversible, often accompanied by subclinical inflammation that can go unnoticed. However, if the ocular surface cannot re-equilibrate, more severe disease can develop, marked by chronic inflammation, persistent epithelial changes, and vision impairment [4]. Therefore, if left untreated, DED can become an irreversible chronic condition driven by reduced tear flow, increased evaporation, and repeated nerve stimulation. This creates a self-perpetuating cycle of inflammation that leads to treatment-resistant disease and permanent ocular surface damage [5]. The heterogeneity of DED presentations and the variability in disease progression pose significant clinical challenges. Treatment strategies must focus on restoring and maintaining ocular surface homeostasis to break the vicious cycle of the disease [6].

This narrative review, conceived by the Italian Dry Eye Consensus Group [7], analyses the importance of addressing the causes of DED through combined treatments and improved communication between patients and healthcare professionals, and aims to raise awareness of the importance of diagnosing and managing DED.

METHODS

A literature search was conducted using the PubMed database for studies and reviews published in English. Search criteria for publications included articles that focused on DED and addressed aetiopathogenesis, risk, chronicity and inflammation, diagnostic approach, pharmacological and non-pharmacological therapy, patient needs, compliance and quality of life, and the doctor–patient relationship. No restrictions were set for the date of publication. Articles considered most relevant and representative of a balanced view of the issue by the Italian Dry Eye Consensus Group were selected and included. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

NEW INSIGHTS INTO PATHOGENESIS

DED has traditionally been divided into two categories: evaporative dry eye (EDE), which is typically due to excessive evaporation of the tear film, and aqueous tear-deficient dry eye (ADDE), which is characterized by inefficiency or failure of the lacrimal glands to produce tears. However, these two categories are not mutually exclusive, and DED is often seen clinically as a combination of these subtypes [8]. Numerous extrinsic (e.g. environmental) and intrinsic (e.g. ageing and autoimmunity) factors contribute to the complexity of DED [9] (Fig. 1). The ocular surface, a highly exposed mucosa, is vulnerable to oxidative stress and environmental insults, which exacerbate tear evaporation and reduce tear clearance. This can lead to the accumulation of harmful agents in the tear film, making it toxic to the ocular surface [10]. The tear film, particularly its lipid layer, serves as a crucial barrier to water evaporation. Disruption of

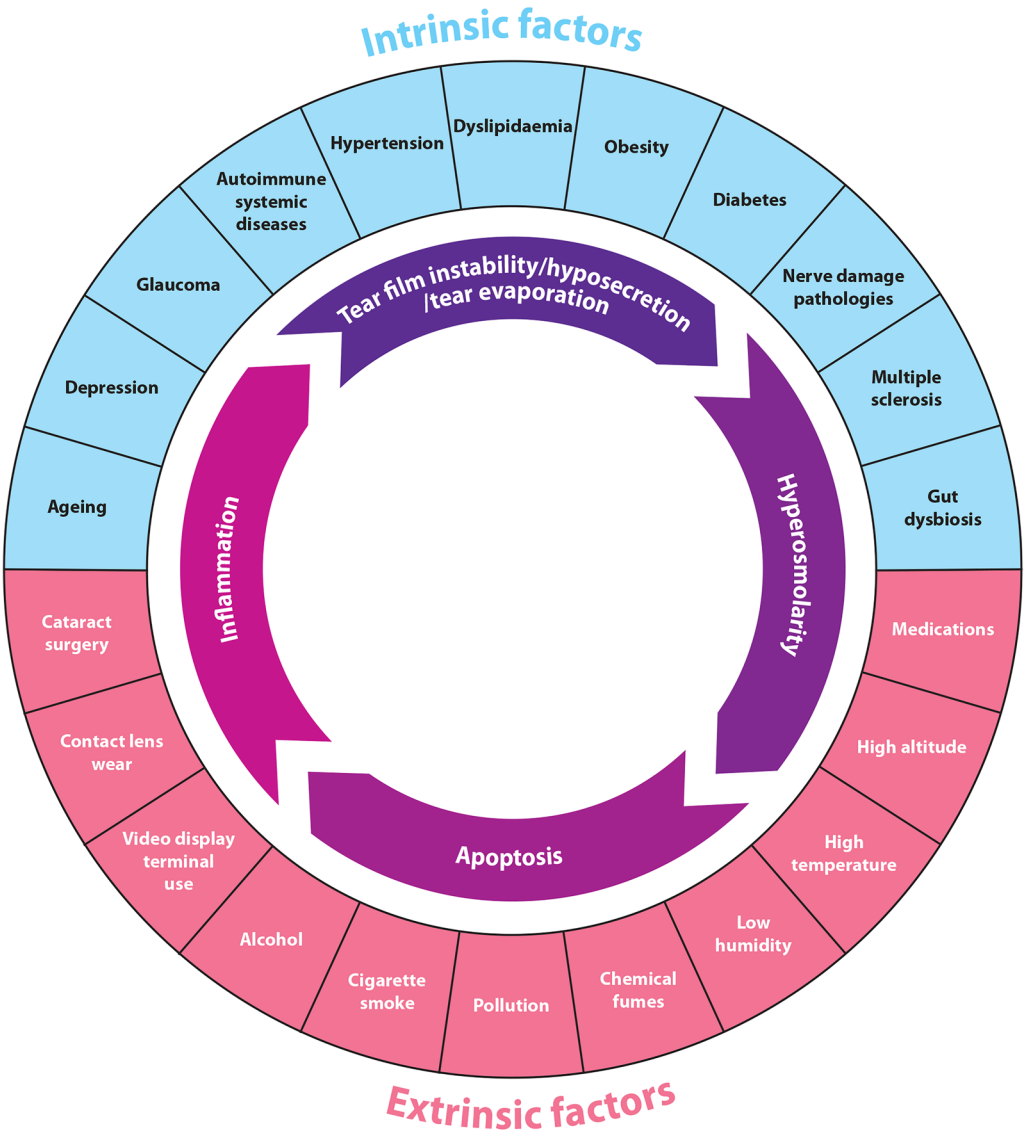


Fig. 1 Extrinsic and intrinsic factors that contribute to the vicious circle of dry eye disease (DED)

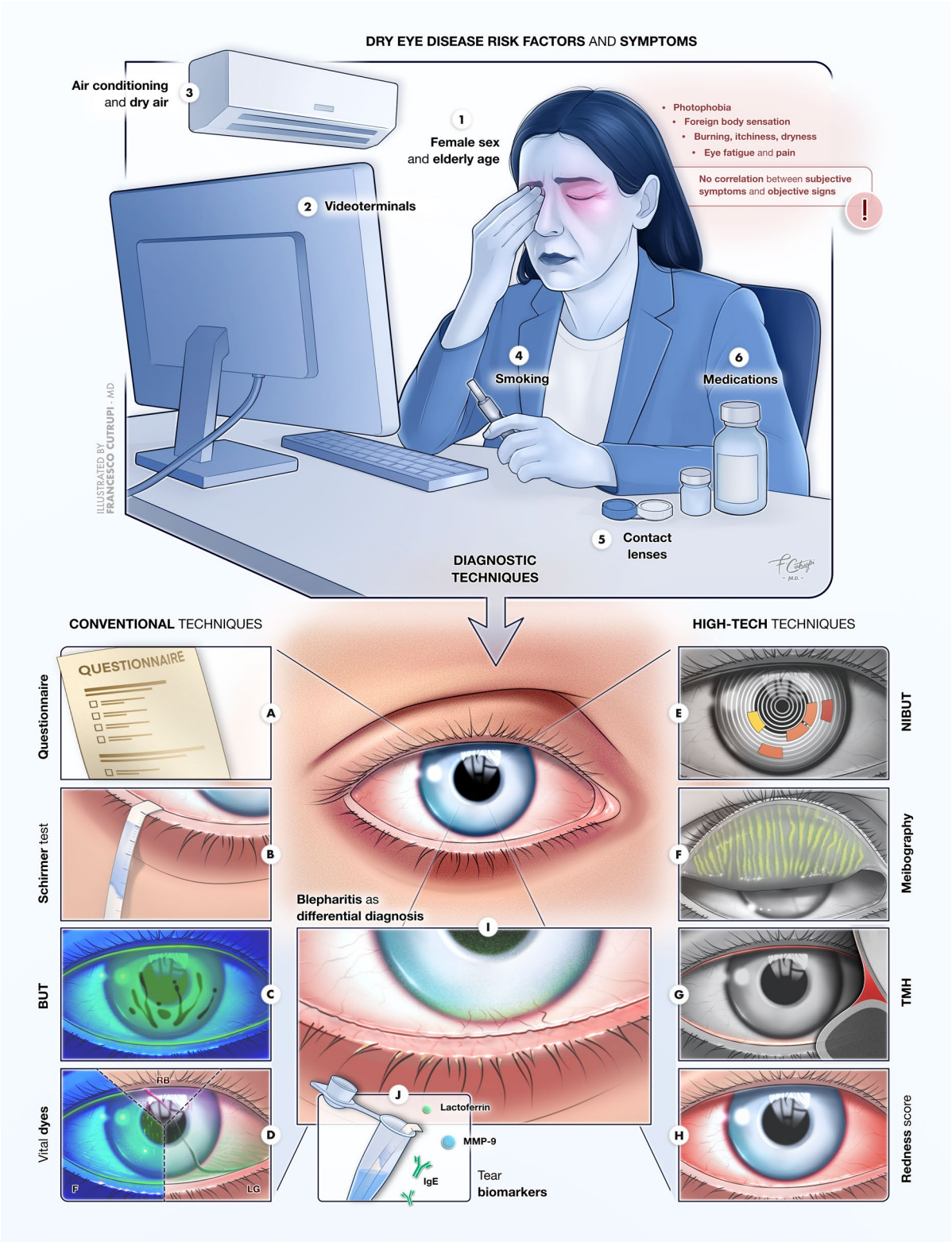
this layer exposes the tear film to air, increasing evaporation and leading to tear film thinning, instability, and tear break-up time (TBUT) [10].

While ADDE is often associated with autoimmune disorders [11], meibomian gland dysfunction (MGD) is the most common cause of EDE [12]. Tear hyperosmolarity also plays a critical role in the development and progression of DED. It occurs in the presence of poor aqueous tear flow, excessive tear evaporation, or a combination of these events, due to changes in tear composition and production [11]. Tear hyperosmolarity can also indirectly cause ocular surface damage by inducing an inflammatory response that leads to apoptosis of corneal and conjunctival epithelial cells [11]. Inflammatory cells, such as neutrophils, macrophages, natural killer cells, dendritic cells, and T cells, play crucial roles in maintaining immune defence at the ocular surface. These cells respond to various triggers and contribute to an inflammatory cascade, activating common signalling pathways like mitogen-activated protein kinase (MAPK), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and transforming growth factor-beta (TGF-β) [13]. In addition to immune cell activation, neuronal injury can trigger neurogenic inflammation, perpetuating chronic dry eye inflammation [14]. These factors—chronic immune cell activation, disrupted tear film, and nerve damage—contribute to a self-perpetuating cycle that exacerbates and sustains ocular surface damage [13]. Therefore, osmoprotectants, small organic molecules used in many cell types to restore cell volume and stabilize protein function to allow adaptation to hyperosmolarity, are often contained in tear substitutes to counteract the surface damage caused by a hyperosmolar tear film [15]. There is now a growing body of evidence supporting the efficacy of various osmoprotectants such as trehalose, erythritol, taurine, and L-carnitine [15].

Excessive external stimuli can elicit an adaptive immunological response called para-inflammation, which has intermediate characteristics between the homeostatic and inflammatory states. The physiological role of para-inflammation is to restore tissue homeostasis; however, if tissue malfunction persists, para-inflammation can turn from a beneficial and protective response to a detrimental and damaging process, inducing a continuous inflammatory state, leading to the chronicity of the disease [10, 16]. Furthermore, topical medications themselves may cause dry eye through the action of active principles and/or preservatives [17]. The risk of iatrogenic DED is also increased by taking five or more systemic drugs (polypharmacy) regardless of the type [18]. Other causes of dry eye may include the use of contact lenses, video display terminals, and eye surgery (e.g. corneal refractive surgery, cataract surgery, lid surgeries) [18]. In particular, more than half of patients presenting for cataract surgery have DED and MGD, even in the absence of frank symptoms. Therefore, as a routine approach to cataract surgery, preoperative assessment for the risk of developing or worsening DED should be encouraged in all patients [19].

DIAGNOSTIC CHALLENGES

The diagnosis of DED usually comprises a combination of subjective complaints assessed with various types of questionnaires and the detection of clinical signs detected with different techniques [20]. Subjective symptoms include photophobia, foreign body sensation, burning, itchiness, dryness, eye fatigue, and pain [21] (Fig. 2). One of the major challenges in the diagnosis of DED is the lack of correlation between the changes and severity of the clinical signs and the symptoms reported by the patient [22, 23]. In fact, some symptomatic patients have minimal ocular surface damage, while others show signs of DED without specific symptoms or no symptoms at all [22]. It is common to see patients with suspected DED and severe corneal neuralgia but no clinical signs. These patients are referred to as ‘pain without stain’ [24]. Therefore, it is essential to identify the general and local risk factors that may increase or predispose to the risk of ocular surface disease [21]. In many cases, detection and assessment of dry eye condition can be obtained quickly and without expensive equipment using a series of slit lamp-assisted tests performed during routine examinations [21]. Some of the conventional diagnostic


DRY EYE DISEASE RISK FACTORS AND SYMPTOMS
Air conditioning and dry air
3
1
Female sex and elderly age
2 Videoterminals
• Photophobia
• Foreign body sensation
• Burning, itchiness, dryness
• Eye fatigue and pain
No correlation between subjective symptoms and objective signs
4 Smoking
6 Medications
5 Contact lenses
ILLUSTRATED BY FRANCESCO CUTRUPI - MD
DIAGNOSTIC TECHNIQUES
CONVENTIONAL TECHNIQUES
HIGH-TECH TECHNIQUES
Questionnaire
QUESTIONNAIRE
A
Schirmer test
B
BUT
C
Vital dyes
RB
D
F
LG
Blepharitis as differential diagnosis
I
J
Lactoferrin
MMP-9
IgE
Tear biomarkers
E
NIBUT
F
Meibography
G
TMH
H
Redness score

◂**Fig. 2** Dry eye disease—risk factors, symptoms, and diagnostic approach. The upper portion of the illustration depicts the main risk factors of DED alongside its common symptoms. The lower portion focuses on diagnostic techniques, including low-tech (left column, boxes **A**–**D**) and high-tech methods (right column, boxes **E**–**H**). The illustration also highlights the importance of differential diagnosis with blepharitis (box **I**) and new diagnostic approaches such as tear fluid analysis for biomarkers (box **J**). *F* fluorescein, *RP* rose bengal, *LG* lissamine green, *BUT* break-up time, *NIBUT* non-invasive break-up time, *TMH* tear meniscus height, *IgE* immunoglobulin E, *MMP-9* matrix metalloproteinase-9

techniques for examination include Schirmer's test, slit lamp examination with TBUT measurement, and ocular surface staining with vital dyes [25, 26] (Fig. 2). In general, these low-tech assessments face challenges with invasiveness and subjectivity, which can affect their repeatability and reproducibility [27]. In recent years, new high-tech instruments have changed clinical practice by providing better assessments of tear film quality, tear volume, and meibomian gland function. These tests, which include non-invasive tear break-up time (NIBUT), tear meniscus height (TMH), infrared meibography, and redness score, have shown better performance in detecting changes over time due to treatment, and results are particularly superior to low-tech assessments when different tests are combined [27] (Fig. 2). In vivo confocal microscopy (IVCM) is an emerging technology that enables in vivo assessment of structural changes in various ocular surface diseases. In dry eye research, IVCM has been utilized to examine the cornea, bulbar and palpebral conjunctiva, meibomian glands, and lacrimal glands [28]. The tear film is a reservoir for potential biomarkers, which have to be rapidly quantifiable. Access to patients' tears allows rapid, objective tear-based diagnostics, and early detection of biomarkers, such as lactoferrin, total immunoglobulin E (IgE), and matrix metalloproteinase 9 (MMP-9), may lead to faster intervention and more targeted disease monitoring [26]. Despite the plethora of tear biomarkers for DED, none of them has a universal clinical value, and the levels of these biomarkers must be considered along with the clinical history and other ocular surface parameters for an accurate diagnosis [29].

Ideal DED diagnostic tests should be rapid, objective, reproducible, clinically impactful, and easy to use for efficient workflow [26]. In addition, many conditions, such as anterior blepharitis and *Demodex*-related blepharitis, can present with symptoms similar to those of DED; therefore, a differential diagnosis is essential to carefully distinguish DED from other potential causes [30]. Blepharitis is closely associated with DED, sharing various symptoms such as burning, irritation, photophobia, blurred vision, and red eyes. Clinical examination may reveal characteristic features of blepharitis, including scurf, telangiectatic vascular changes at the lid margin, inspissated meibomian glands, conjunctival hyperaemia, punctate keratopathy, and corneal vascularization and ulceration [31].

The classification of DED is based primarily on the severity of both symptoms and clinical signs. However, there is little consensus across Europe regarding precise definitions. In 2015, a group of Italian ocular surface experts proposed a multi-item flowchart to better define the diagnosis and determine appropriate treatments in patients with tear dysfunction [21]. In 2007, the International Dry Eye WorkShop (DEWS) introduced a severity grading scheme for DED, which was later confirmed in DEWS 2017 [8, 32]. In 2014, the ODISSEY Group published a tailored algorithm for severe DED [33]. Currently, it is unclear to what extent such an algorithm is followed in daily practice, as it only applies to severe dry eye. More recently, the work of the Italian Dry Eye Consensus Group has attempted to define practical algorithms for treatment recommendations that may be useful in a clinical setting for general ophthalmologists [34, 35], along with the definition of novel non-invasive screening tools [36] and an overview of eyelid-related issues [31, 37].

Quality of life (QoL) for patients with DED is significantly reduced by symptoms and altered visual function [38]. In diagnosing DED, most questionnaires ask about their impact on QoL, and reliable assessment of these parameters would be of great value in monitoring QoL over time and evaluating the effect of treatment in clinical practice [38]. Questionnaires

are valuable tools in both clinical research and practice for DED, providing consistent information on various aspects of the disease. They help assess objective clinical findings, such as tear film and ocular surface damage, as well as subjective symptoms [38]. The absence or delay of diagnosis is associated with poorer health-related mental health QoL in people with severe DED [39]. Undiagnosed DED may impose a greater burden on sufferers than diagnosed cases, as it leads to uncertainty, limited treatment prospects, and a lack of recognition due to the absence of clear clinical signs. This underscores the value of questionnaires in assessing both objective clinical findings, such as tear film and ocular surface damage, and subjective symptoms [39]. In addition, though effective medications for DED are available, achieving optimal symptom alleviation remains a challenge, as side effects can impact medication adherence [40].

TAILORED MANAGEMENT

The lack of a single clinical assessment method and the wide variety of symptoms make both diagnosis and treatment of DED difficult. For these reasons, it is crucial to educate patients about the chronic nature of DED, emphasizing that treatment is typically lifelong and may take time to show significant improvement [7]. Treatment of DED involves a stepwise approach according to the severity of the disease [41], and adapting lifestyle habits is essential in managing DED (Fig. 3). Patients should be encouraged to avoid aggravating factors such as cigarette smoke, dry heating air, air conditioning, prolonged reading, excessive screen time, and extended contact lens use [41]. Additionally, dietary changes, including increasing oral intake of essential fatty acids, can help alleviate symptoms. Proper lid hygiene is also crucial for maintaining eye health and managing the condition effectively [41]. Eyelid changes leading to lid margin disease, such as blepharitis or MGD, can lead to ocular surface system failure, potentially resulting in severe DED, requiring the establishment of appropriate supportive therapy [31, 37]. As MGD leads to a reduction in the thickness of the lipid layer, it may be beneficial to replace the lipids with lubricating eye drops or sprays containing lipids. A number of studies have shown an improvement in the signs and symptoms of dry eye with the use of lipid-based drops [41].

Artificial tears are the cornerstone of treatment for all stages of DED, aimed at both relieving symptoms and preventing their onset (Fig. 3). They should be applied consistently throughout the day, rather than on an as-needed basis, to prevent symptom exacerbation [6]. Various hydrophilic polymers, such as hyaluronic acid (HA), are commonly used in these formulations to enhance tear film stability. Newer generations combine HA with osmoprotectants and anti-inflammatory agents for a multi-action approach to therapy [6]. However, artificial tears containing preservatives like benzalkonium chloride should be avoided in cases of ocular surface disorders, as they may further irritate the eyes [42].

Effective management of inflammation, which is often present in a subclinical form, is critical for the improvement of DED symptoms and the disruption of the harmful cycle of surface damage and inflammation. Treatment options for controlling this inflammation include topical corticosteroids and cyclosporine A, oral antibiotics (macrolides, such as the immunosuppressant tacrolimus, and tetracyclines), along with essential fatty acids and *N*-acetyl-aspartyl-glutamic acid (NAAGA) [41, 43] (Fig. 3). While secretagogues and biological tear substitutes such as serum are sometimes considered in the management of DED and have been used to treat patients with severe ocular surface lesions unresponsive to conventional treatments [44], their use raises concerns regarding efficacy and safety due to the limited evidence and controlled trials available to support their effectiveness [45]. Furthermore, non-pharmacological therapies also offer valuable options for patients (Fig. 3). Punctal plugs, which use small collagen or silicone plugs to temporarily block the tear ducts, are effective in patients with severe ADDE, blocking tear drainage and increasing tear retention on the ocular surface [20]. However, concomitant anti-inflammatory treatment is indicated during this

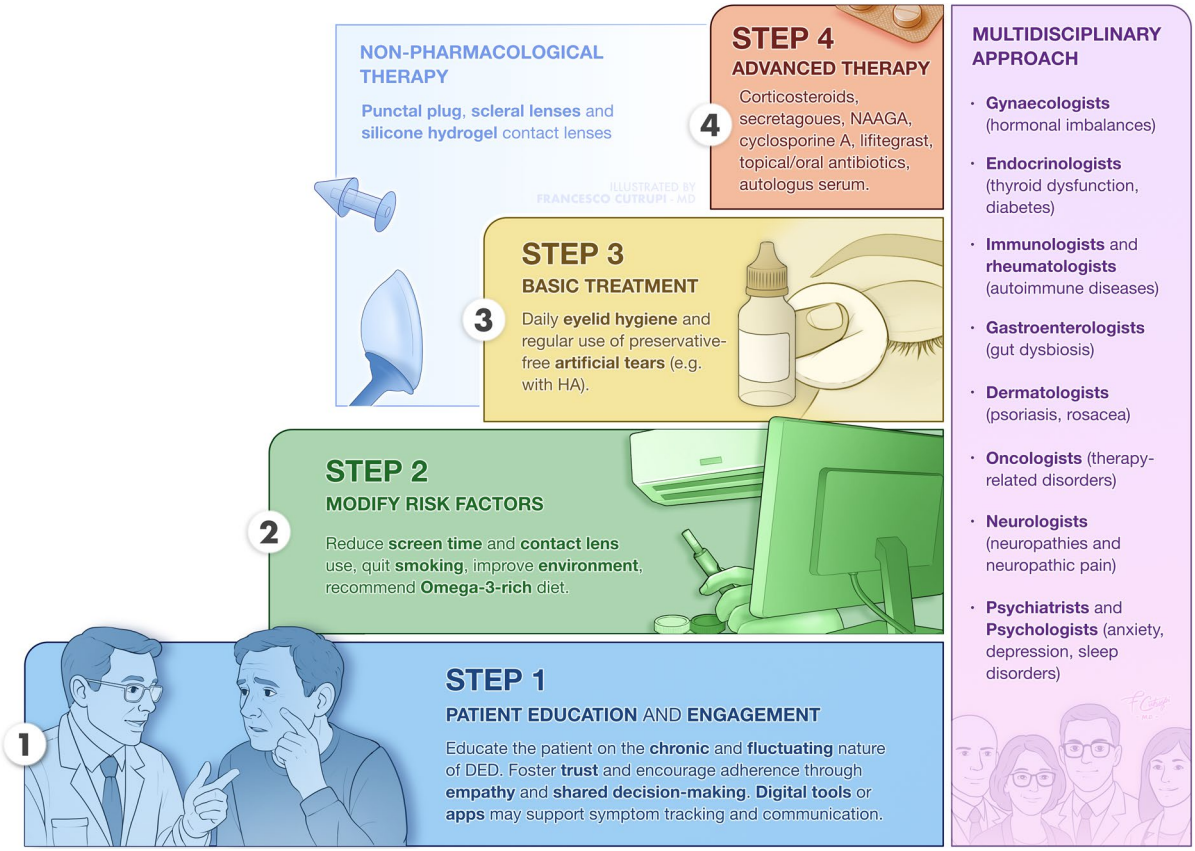


Fig. 3 Stepwise therapeutic approach for dry eye disease. This illustration outlines a stepwise approach to the treatment of DED, beginning with patient education and lifestyle modification, progressing through basic therapy with eyelid hygiene and artificial tears, and advancing to pharmacologic and non-pharmacologic interventions according to severity. A multidisciplinary approach is always essential to address systemic and psychological comorbidities and ensure comprehensive care. *HA* hyaluronic acid, *NAAGA* *N*-acetyl-aspartyl-glutamic acid

procedure, as delayed tear drainage leads to the persistence of toxic and inflammatory factors on the ocular surface [20]. On the other hand, scleral lenses and silicone hydrogel contact lenses provide mechanical support and protection and have been suggested as a possible treatment for DED [6]. Recently, a stepped management algorithm has been developed to provide a stepwise approach to the implementation of the different management and therapeutic options according to the severity of the disease [41]. The subtype of DED, the presence of inflammation, and the presence of external and behavioural factors that may contribute to DED are important features to consider [46]. ED treatment should be personalized based on disease characteristics, patient factors, and environmental influences to ensure optimal management. The consequences of managing DED include the ability to perform activities of daily living, emotional well-being, and the ability to work or drive, which also affect the productivity of patients at work [47, 48]. In addition, for some patients, the severity of the condition and its chronic nature are also associated with a high level of mood swings, anxiety, and depression [49]. Thus, patient education and counselling to emphasize the need for compliance are key factors in the successful management of DED, as is the development of new treatments aimed at reducing the disabling symptoms of the disease. Consequently, to ensure long-term relief and prevent chronicity of the disease, it is important not only to prescribe the appropriate treatment, giving clear

instructions, but also to monitor its effects over time [38]. Moreover, to improve patient satisfaction, co-operation and adherence, it is important for clinicians to demonstrate disease awareness and empathy, and to understand the patient's condition not only in terms of objective ocular parameters, but also in terms of their personal experience [7]. Experts in the consensus group emphasize the importance of empathy, dialogue, and communication in the management of patients with DED. In addition, they suggest a therapeutic alliance based on three main components: shared goals, agreed interventions, and a therapist–patient bond [50]. For this task, apps could improve doctor–patient communication by asking patients questions about their symptoms, adherence, and disease characteristics over time [7]. In addition, some DED patients may benefit from mental health interventions given the association between DED and depression/anxiety.

MULTIDISCIPLINARY APPROACH IN THE MANAGEMENT OF DED

DED is often linked to various comorbidities, many of which are treated by primary care clinicians or other specialists, such as rheumatologists, gynaecologists, endocrinologists, and gastroenterologists [51]. Given this common overlap, it is essential that practitioners across different specialties develop a clear understanding of DED and its potential connections to the conditions they treat. Therefore, a multidisciplinary approach involving ophthalmologists and other specialists is recommended to ensure effective diagnosis, management, and improved outcomes for patients with DED and its associated conditions (Fig. 3).

Gynaecologists

Some studies have suggested that changes in oestrogen levels alter the ocular surface balance and affect dry eye symptoms in female patients. In female patients with DED, the oestrogen peak is associated with symptoms of impaired tear production [52]. Evidence suggests that longer duration and greater quantity of hormonal contraception use is significantly associated with a greater chance of DED [53]. Despite these associations, however, the evidence remains inconclusive, as studies have produced conflicting results, making it difficult to establish a definitive connection between hormone therapy and DED [54]. Research has also indicated a possible link between hormone replacement therapy (HRT) and DED, suggesting that women who use HRT, particularly oestrogen alone, may be at increased risk of DED. Therefore, gynaecologists should warn women taking or considering HRT about this potential complication [55]. Additionally, women with polycystic ovarian syndrome (PCOS) have been shown to suffer from more severe DED symptoms, further suggesting that hormonal imbalances may play a significant role in the progression and severity of the disease [56].

Endocrinologists

Hormonal imbalances, either physiological (menopause, ageing) or pathological, should be considered in the diagnosis and treatment planning of DED. Thyroid disorders have been implicated in the development of DED. Thyroid eye disease, thyroid-associated ophthalmopathy, thyroid-associated orbitopathy, and Graves' ophthalmopathy refer to an immune-mediated inflammatory condition that causes expansion of the extraocular muscles and fat in the orbit [57]. In particular, changes in the tear film and ocular surface are common in patients with thyroid-associated ophthalmopathy, while patients with active thyroid eye disease have evidence of severe MGD [57].

In severe cases, exposure keratopathy can complicate the course of thyroid eye disease. It results from inadequate lid closure due to axial proptosis (exophthalmos), a hallmark of Graves' disease, leading to dryness and corneal damage, particularly in the inferior region [58]. Effective diagnosis and treatment require a multidisciplinary team, including ophthalmologists, internists, radiologists, and head and neck surgeons [58]. Smoking cessation and euthyroid status help to prevent further exacerbations and reduce

the duration of active disease. The first and only US Food and Drug Administration (FDA)-approved prescription treatment for thyroid eye disease, teprotumumab, has been shown in clinical trials to reduce signs and symptoms in treated patients [59, 60]. For milder cases of corneal exposure, daily lubricant use and nightly patching are usually prescribed with success; for more severe cases, partial tarsorrhaphy or orbital decompression may be required [58]. Additionally, patients with diabetes mellitus show a high incidence of DED, further highlighting the connection between systemic conditions and dry eye symptoms [61].

Immunologists/Rheumatologists

Consultation with an immunologist or rheumatologist may be necessary when immune factors are suspected in the development of DED. In patients with immune system disorders, approximately 10–95% of cases are accompanied by dry eye [62]. Under normal conditions, the eye's intrinsic immune mechanisms are responsible for maintaining homeostasis of the microenvironment. When the immune system targets the eye, particularly in autoimmune diseases, the ocular immune response is over-stimulated by relevant immunoregulatory molecules. The result is an imbalance in the immunoregulatory mechanisms, leading to chronic ocular surface inflammation and DED [62]. For example, Sjögren's syndrome is a common autoimmune disease characterized by chronic inflammation, resulting in 'sicca' symptoms such as dry eyes and mouth that affect patients' QoL [63]. In addition, ocular manifestations are commonly seen in patients with systemic lupus erythematosus and rheumatoid arthritis [64, 65]. DED is the most common ocular manifestation in rheumatoid arthritis, and keratoconjunctivitis sicca is commonly seen in systemic lupus erythematosus [66]. Systemic sclerosis (SSc), a rare chronic connective tissue disease, also commonly presents with DED [66]. Other associated disorders include polyarteritis nodosa, Wegener's granulomatosis, primary biliary cholangitis (PBC), and mixed connective tissue disease [67].

Gastroenterologists

Alterations in the intestinal microbiome may be involved in the pathogenesis and/or maintenance of several ocular surface diseases, especially those in which inflammatory, neural, and/or hormonal factors are implicated [68, 69]. Many studies have reported imbalanced gut microbiota in patients with Sjögren's syndrome compared to controls [70, 71], and people with DED without autoimmune aetiology have shown changes in gut microbiome composition intermediate between Sjögren's syndrome and controls [71]. In addition, there may be a link between irritable bowel syndrome and DED, further suggesting that disturbances in gut health may have an impact on eye conditions, and that DED symptoms may be a source of further complications for patients with irritable bowel syndrome [72]. Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, is linked to lacrimal gland dysfunction and ocular inflammation and serves as an independent risk factor for DED and corneal surface damage [73].

Dermatologists

People with dry skin often have dry eyes, and there is some statistical association between dry skin and DED [74]. Some evidence also suggests that patients with psoriasis have an increased risk of DED. However, the relationship between the two conditions remains unclear [75]. In addition, ocular rosacea is an underdiagnosed form of rosacea that can occur with or without the typical skin signs, and one of the most common symptoms is dryness [76]. Ocular rosacea is often associated with ocular conditions such as blepharitis and meibomitis, which can lead to MGD and subsequent atrophy [77], 30.

Oncologists

Modern cancer therapies are associated with ocular surface side effects that can cause severe

discomfort and even vision loss. The rapid detection of these adverse events is critical, as early intervention can aid in managing these conditions to prevent loss of vision and reduce the negative impact on QoL [78]. In particular, the use of aromatase inhibitors for breast cancer [79] or treatment with paclitaxel [80] can lead to DED. In addition, radiotherapy has many ophthalmic applications, and different studies have found a positive correlation between the incidence of DED and total radiation dose in patients with head and neck cancer [81, 82]. A recent study has also found a link between the presence of ovarian cancer and the development of DED [83].

Neurologists

Several neurological alterations including stroke, paralysis, migraine, myasthenia gravis, diabetic neuropathy, and neurotrophic keratitis are associated with tear film abnormalities and DED due to potential impairment of sensory and/or motor ocular innervation [84–86]. Therefore, neurologists should consider referring patients to an ophthalmologist for regular ocular surface evaluation. Neuropathic ocular pain, which is associated with injury to the corneal nerves, the terminal endings of the ophthalmic division of the trigeminal somatosensory system, can occur independently of dry eye, but it can also be a component of DED [87].

Psychiatrists

Some dry eye symptoms may be related to a mental health condition. Depression and anxiety are the most likely comorbidities and were found to be significantly correlated with the symptoms, but not signs, of DED [88]. Depression and anxiety may be both causes and effects of DED [88], along with the typical association of DED with sleep disturbance [89]. In some cases, depression can be a manifestation of the Sjögren's syndrome [90]. In addition, the use of antidepressants and tranquillizers can also worsen the signs and symptoms of DED [91]. The ocular discomfort and fatigue associated with DED can be distressing for patients, limiting their ability to work and causing mood changes [88]. This suggests that appropriate medical management of psychological symptoms by a psychologist, in addition to DED therapy, may be beneficial for some patients with new-onset depression or anxiety symptoms following a diagnosis of DED.

Paediatricians

The prevalence of DED in paediatric patients is likely underestimated due to limited epidemiological data. Diagnosis is particularly challenging due to symptom identification difficulties, the lack of validated diagnostic criteria, and the absence of paediatric-specific tests [92]. Certain rare congenital disorders, including Riley–Day syndrome, ectodermal dysplasia syndromes, and epidermolysis bullosa, as well as autoimmune diseases, can contribute to reduced tear production and paediatric DED [93].

CONCLUSIONS

In conclusion, the effective management of DED requires an understanding of its complex pathogenesis, including dysfunctional parainflammation and tear film instability, as well as lifestyle and environmental factors. This complexity makes patient care a collaborative effort that goes beyond symptom management. A multifaceted approach that combines pharmacological treatments, lifestyle modifications, and personalized patient education is essential in breaking the cycle of inflammation and tear instability that perpetuates the disease. The role of healthcare providers is not only to treat but also to educate patients about the chronic and often fluctuating nature of DED. By promoting understanding and adherence to care plans, they encourage active patient participation, leading to better outcomes, fewer exacerbations, and improved QoL. Advancements in diagnostics and a multidisciplinary approach that integrates the expertise of ophthalmologists with that of other healthcare professionals are essential in creating tailored strategies for each patient. Emerging therapies,

such as novel anti-inflammatory agents and tear-stabilizing technologies, show promise in addressing DED's unique and individualized challenges. These evolving tools and strategies underscore the potential for a more personalized and effective approach to managing DED, paving the way for better patient experiences and outcomes.

Medical Writing/Editorial Assistance. Simona Citro, PhD, provided professional medical writing services for this manuscript, on behalf of Springer Healthcare. This medical writing assistance was funded by Thea Pharma Inc.

Author Contributions. Pasquale Aragona, Stefano Barabino, Antonio Di Zazzo, Giuseppe Giannaccare, Edoardo Villani, Francesco Aiello, Elena Antoniazzi, Stefano Bonini, Emilia Cantera, Gianpaolo Carlini, Chiara Chierego, Rossella Colabelli, Romina Fasciani, Antonella Franch, Giovanna Gabbriellini, Caterina Maria Rita Gagliano, Andrea Leonardi, Angelo Macrì, Rita Mencucci, Luigi Mosca, Vincenzo Orfeo, Antonio Pinna, Augusto Pocobelli, Romolo Protti, Paolo Rama, Laura Rania, Miguel Rechichi, Pierangela Rubino, Andrea Russo, Vincenzo Scorcia, Leopoldo Spadea, Marco Trentadue, Salvatore Troisi, Piera Versura, and Maurizio Rolando helped develop the concept and design for this manuscript, provided critical review of the manuscript drafts with suggestions for substantial revisions of the intellectual content, and reviewed and agreed on the final version for submission. All named authors agree to take responsibility and be accountable for the contents of the article and share responsibility to resolve any questions raised about the accuracy or integrity of the published work.

Funding. Sponsorship for this study was funded by Thea Pharma Inc. The journal's Rapid Service Fee was funded by Thea Pharma Inc.

Declarations

Conflict of Interest. Antonio Pinna received honoraria from Thea Pharma Inc. and Bausch & Lomb for educational activity related to the topics of this manuscript. Andrea Leonardi is a consultant for Alcon, FAES Farma, FIDIA, Santen Pharmaceutical Co. Ltd., Laboratoires Théa, SIFI, URSA-pharma. Pasquale Aragona, Stefano Barabino, Antonio Di Zazzo, Giuseppe Giannaccare, Edoardo Villani, Francesco Aiello, Elena Antoniazzi, Stefano Bonini, Emilia Cantera, Gianpaolo Carlini, Chiara Chierego, Rossella Colabelli, Romina Fasciani, Antonella Franch, Giovanna Gabbriellini, Caterina Maria Rita Gagliano, Angelo Macrì, Rita Mencucci, Luigi Mosca, Vincenzo Orfeo, Augusto Pocobelli, Romolo Protti, Paolo Rama, Laura Rania, Miguel Rechichi, Pierangela Rubino, Andrea Russo, Vincenzo Scorcia, Leopoldo Spadea, Marco Trentadue, Salvatore Troisi, Piera Versura, and Maurizio Rolando have nothing to disclose.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

REFERENCES

1. Stapleton F, et al. TFOS DEWS II epidemiology report. Ocul Surf. 2017;15(3):334–65. https://doi.org/10.1016/J.JTOS.2017.05.003.

2. Rouen PA, White ML. Dry eye disease: prevalence, assessment, and management. Home Healthc Now. 2018;36(2):74–83. https://doi.org/10.1097/NHH.0000000000000652.

3. Kalangara J, Kuruvilla M, Sarantopoulos KD. Treatment of ocular pain not responsive to traditional dry eye disease treatments. Dry Eye Dis. 2023. https://doi.org/10.1016/B978-0-323-82753-9.00013-8.

4. Barabino S, et al. Updated definition and classification of dry eye disease: renewed proposals using the nominal group and Delphi techniques. London: SAGE Publications; 2021. https://doi.org/10.1177/11206721209605 86.

5. Rolando M, Zierhut M, Barabino S. Should we reconsider the classification of patients with dry eye disease? Ocul Immunol Inflamm. 2021;29(3):521–3. https://doi.org/10.1080/09273948.2019.1682618.

6. Aragona P, Giannaccare G, Mencucci R, Rubino P, Cantera E, Rolando M. Modern approach to the treatment of dry eye, a complex multifactorial disease: a P.I.C.A.S.S.O. board review. Br J Ophthalmol. 2021;105(4):446–53. https://doi.org/10.1136/BJOPHTHALMOL-2019-315747.

7. Aragona P, et al. The management of dry eye disease: Proceedings of Italian dry eye consensus group using the Delphi method. J Clin Med. 2022;11(21):6437. https://doi.org/10.3390/JCM11216437.

8. Craig JP, et al. TFOS DEWS II definition and classification report. Ocul Surf. 2017;15(3):276–83. https://doi.org/10.1016/J.JTOS.2017.05.008.

9. Bron AJ, et al. TFOS DEWS II pathophysiology report. Ocul Surf. 2017;15(3):438–510. https://doi.org/10.1016/J.JTOS.2017.05.011.

10. Rolando M, Barabino S, Giannaccare G, Aragona P. Dealing with the persistent pathogenic issues of dry eye disease: the importance of external and internal stimuli and tissue responses. J Clin Med. 2023. https://doi.org/10.3390/JCM12062205.

11. Harrell CR, Feulner L, Djonov V, Pavlovic D, Volarevic V. The molecular mechanisms responsible for tear hyperosmolarity-induced pathological changes in the eyes of dry eye disease patients. Cells. 2023. https://doi.org/10.3390/CELLS12232755.

12. 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(3):1397. https://doi.org/10.1007/S40123-023-00669-1.

13. Chu L, Wang C, Zhou H. Inflammation mechanism and anti-inflammatory therapy of dry eye. Front Med (Lausanne). 2024;11:1307682. https://doi.org/10.3389/FMED.2024.1307682/BIBTEX.

14. Asiedu K. Role of ocular surface neurobiology in neuronal-mediated inflammation in dry eye disease. Neuropeptides. 2022. https://doi.org/10.1016/J.NPEP.2022.102266.

15. Baudouin C, et al. Role of hyperosmolarity in the pathogenesis and management of dry eye disease: proceedings of the OCEAN group meeting. Ocul Surf. 2013;11(4):246–58. https://doi.org/10.1016/J.JTOS.2013.07.003.

16. Rolando M, Barabino S. The subtle role of parainflammation in modulating the progression of dry eye disease. Ocul Immunol Inflamm. 2021;29(4):811–6. https://doi.org/10.1080/09273948.2021.1906908.

17. Fraunfelder FT, Sciubba JJ, Mathers WD. The role of medications in causing dry eye. J Ophthalmol. 2012. https://doi.org/10.1155/2012/285851.

18. Gomes JAP, et al. TFOS DEWS II iatrogenic report. Ocul Surf. 2017;15(3):511–38. https://doi.org/10.1016/J.JTOS.2017.05.004.

19. Giannaccare G, Barabino S, Di Zazzo A, Villani E. Preventing and managing iatrogenic dry eye disease during the entire surgical pathway: a study focusing on patients undergoing cataract surgery. J Clin Med. 2024. https://doi.org/10.3390/JCM13030748.

20. E. M. Messmer, "The pathophysiology, diagnosis, and treatment of dry eye disease," *Dtsch Arztebl Int*, vol. 112, no. 5, Jan. 2015, https://doi.org/10.3238/ARZTEBL.2015.0071.

21. Rolando M, Cantera E, Mencucci R, Rubino P, Aragona P. The correct diagnosis and therapeutic management of tear dysfunction: recommendations of the P.I.C.A.S.S.O. board. Int Ophthalmol. 2018;38(2):875–95. https://doi.org/10.1007/S10792-017-0524-4.

22. Bartlett JD, Keith MS, Sudharshan L, Snedecor SJ. Associations between signs and symptoms of dry eye disease: a systematic review. Clin Ophthalmol. 2015;9:1719. https://doi.org/10.2147/OPTH.S89700.

23. McMonnies CW. Why the symptoms and objective signs of dry eye disease may not correlate. J Optom. 2021;14(1):3–10. https://doi.org/10.1016/J.OPTOM.2020.10.002.

24. Rosenthal P, Baran I, Jacobs DS. Corneal pain without stain: is it real? Ocul Surf. 2009;7(1):28–40. https://doi.org/10.1016/S1542-0124(12)70290-2.

25. Aquavella JV, Santiago E, Zavislan JM. Advances in dry eye. Expert Rev Ophthalmol. 2023;18(4):231–4. https://doi.org/10.1080/17469899.2023.2258285.

26. Chester T, Garg SS, Johnston J, Ayers B, Gupta P. How can we best diagnose severity levels of dry eye disease: current perspectives. Clin Ophthalmol. 2023;17:1587. https://doi.org/10.2147/OPTH.S388289.

27. Fogagnolo P, et al. High-tech parameters for the evaluation of signs and symptoms of dry eye disease: identification of clinical cut-offs and agreement with low-tech tests. Ophthalmol Ther. 2024;13(11):2999. https://doi.org/10.1007/S40123-024-01034-6.

28. Wu Y, et al. Advances in dry eye disease examination techniques. Front Med (Lausanne). 2022;8:826530. https://doi.org/10.3389/FMED.2021.826530.

29. Chiva A. Tear biomarkers in dry eye disease. Eur Ophthalmic Rev. 2019;13(1):21. https://doi.org/10.17925/EOR.2019.13.1.21.

30. Wolffsohn JS, et al. TFOS DEWS II diagnostic methodology report. Ocul Surf. 2017;15(3):539–74. https://doi.org/10.1016/J.JTOS.2017.05.001.

31. Di Zazzo A, Giannaccare G, Villani E, Barabino S. Uncommon blepharitis. J Clin Med. 2024. https://doi.org/10.3390/JCM13030710.

32. Lemp MA, et al. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf. 2007;5(2):75–92. https://doi.org/10.1016/S1542-0124(12)70081-2.

33. Baudouin C, et al. Diagnosing the severity of dry eye: a clear and practical algorithm. Br J Ophthalmol. 2014;98(9):1168–76. https://doi.org/10.1136/BJOPHTHALMOL-2013-304619.

34. Aragona P, Giannaccare G, Rolando M. Special issue 'Managing dry eye disease over time: an Italian consensus conference.' J Clin Med. 2022;11(9):2507. https://doi.org/10.3390/JCM11092507.

35. Di Zazzo A, et al. One soul and several faces of evaporative dry eye disease. J Clin Med. 2024;13(5):1220. https://doi.org/10.3390/JCM13051220.

36. Vaccaro S, et al. A novel noninvasive screening tool for dry eye disease. Diagnostics. 2024;14(12):1209. https://doi.org/10.3390/DIAGNOSTICS14121209.

37. Di Zazzo A, Villani E, Barabino S, Giannaccare G. How eyelid changes may impact on tears. J Clin Med. 2024;13(22):6927. https://doi.org/10.3390/JCM13226927.

38. Barabino S, Labetoulle M, Rolando M, Messmer EM. Understanding symptoms and quality of life in patients with dry eye syndrome. Ocul Surf. 2016;14(3):365–76. https://doi.org/10.1016/J.JTOS.2016.04.005.

39. Morthen MK, Magno MS, Utheim TP, Snieder H, Hammond CJ, Vehof J. The physical and mental burden of dry eye disease: a large population-based study investigating the relationship with health-related quality of life and its determinants. Ocul Surf. 2021;21:107–17. https://doi.org/10.1016/J.JTOS.2021.05.006.

40. Ozdemir S, Yeo SWJ, Lee JJ, Bhaskar A, Finkelstein E, Tong L. Patient medication preferences for managing dry eye disease: the importance of medication side effects. Patient. 2022;15(6):679–90. https://doi.org/10.1007/S40271-022-00586-8/FIGURES/3.

41. Jones L, et al. TFOS DEWS II management and therapy report. Ocul Surf. 2017;15(3):575–628. https://doi.org/10.1016/J.JTOS.2017.05.006.

42. Walsh K, Jones L. The use of preservatives in dry eye drops. Clin Ophthalmol. 2019;13:1409. https://doi.org/10.2147/OPTH.S211611.

43. El Fekih L, Khairallah M, BenAmor H, Mahmoud A, Chiambaretta F, Messaoud R. Successful management of dry eye disease with a new eye drop formulation combining hyaluronic acid, trehalose, and N-acetyl-aspartyl-glutamic acid (NAAGA). J Fr Ophtalmol. 2024. https://doi.org/10.1016/J.JFO.2024.104169.

44. Samarkanova D, et al. Clinical evaluation of allogeneic eye drops from cord blood platelet lysate. Blood Transfus. 2021;19(4):347–56. https://doi.org/10.2450/2020.0130-20.

45. Jongkhajornpong P, et al. Short-term efficacy and safety of biological tear substitutes and topical secretagogues for dry eye disease: a systematic review and network meta-analysis. Cornea. 2022;41(9):1137–49. https://doi.org/10.1097/ICO.0000000000002943.

46. Matossian C, Crowley M, Periman L, Sorkin S. Personalized management of dry eye disease: beyond artificial tears. Clin Ophthalmol. 2022;16:3911–8. https://doi.org/10.2147/OPTH.S384819.

47. McDonald M, Patel DA, Keith MS, Snedecor SJ. Economic and humanistic burden of dry eye disease in Europe, North America, and Asia: a systematic literature review. Ocul Surf. 2016;14(2):144–67. https://doi.org/10.1016/J.JTOS.2015.11.002.

48. Shigeyasu C, Yamada M, Kawashima M, Suwaki K, Uchino M, Hiratsuka Y, Yokoi N, et al. Quality of life measures and health utility values among dry eye subgroups. Health Qual Life Outcomes. 2018. https://doi.org/10.1186/s12955-018-0999-3.

49. Kitazawa M, et al. The relationship of dry eye disease with depression and anxiety: a naturalistic observational study. Transl Vis Sci Technol. 2018;7(6):35–35. https://doi.org/10.1167/TVST.7.6.35.

50. Villani E, Barabino S, Giannaccare G, Di Zazzo A, Aragona P, Rolando M. From symptoms to satisfaction: optimizing patient-centered care in dry eye disease. J Clin Med. 2025;14(1):196. https://doi.org/10.3390/JCM14010196.

51. Verjee MA, Brissette AR, Starr CE. Dry Eye disease: early recognition with guidance on management and treatment for primary care family physicians. Ophthalmol Ther. 2020;9(4):877–88. https://doi.org/10.1007/S40123-020-00308-Z.

52. Matossian C, McDonald M, Donaldson KE, Nichols KK, Maciver S, Gupta PK. Dry eye disease: consideration for women's health. J Womens Health. 2019;28(4):502. https://doi.org/10.1089/JWH.2018.7041.

53. He B, Iovieno A, Etminan M, Kezouh A, Yeung SN. Effects of hormonal contraceptives on dry eye disease: a population-based study. Eye (London). 2022;36(3):634–8. https://doi.org/10.1038/S41433-021-01517-X.

54. Kemdinum Idu F, Osita Emina M, Oyem Ubaru C. Tear secretion and tear stability of women on hormonal contraceptives. J Optom. 2013;6(1):45. https://doi.org/10.1016/J.OPTOM.2012.08.006.

55. Schaumberg DA, Buring JE, Sullivan DA, RezaDana MR. Hormone replacement therapy and dry eye syndrome. JAMA. 2001;286(17):2114–9. https://doi.org/10.1001/JAMA.286.17.2114.

56. Bonini S, Mantelli F, Moretti C, Lambiase A, Bonini S, Micera A. Itchy-dry eye associated with polycystic ovary syndrome. Am J Ophthalmol. 2007;143(5):763-771.e2. https://doi.org/10.1016/J.AJO.2007.01.030.

57. Gorimanipalli B, Khamar P, Sethu S, Shetty R. Hormones and dry eye disease. Indian J Ophthalmol. 2023;71(4):1276–84. https://doi.org/10.4103/IJO.IJO_2887_22.

58. Rodriguez-Garcia A, Ruiz-Lozano RE, Barcelo-Canton RH, Marines-Sanchez HM, Homar Paez-Garza J. The etiologic and pathogenic spectrum of exposure keratopathy: diagnostic and therapeutic implications. Surv Ophthalmol. 2025. https://doi.org/10.1016/J.SURVOPHTHAL.2025.03.001.

59. Douglas RS, et al. Teprotumumab for the treatment of active thyroid eye disease. N Engl J Med. 2020;382(4):341–52. https://doi.org/10.1056/NEJMOA1910434/SUPPL_FILE/NEJMOA1910434_DATA-SHARING.PDF.

60. Smith TJ, et al. Teprotumumab for thyroid-associated ophthalmopathy. N Engl J Med. 2017;376(18):1748–61. https://doi.org/10.1056/NEJMOA1614949/SUPPL_FILE/NEJMOA1614949_DISCLOSURES.PDF.

61. De Freitas GR, Ferraz GAM, Gehlen M, Skare TL. Dry eyes in patients with diabetes mellitus. Prim Care Diabetes. 2021;15(1):184–6. https://doi.org/10.1016/J.PCD.2020.01.011.

62. Shan H, Liu W, Li Y, Pang K. The autoimmune rheumatic disease related dry eye and its association with retinopathy. Biomolecules. 2023;13(5):724. https://doi.org/10.3390/BIOM13050724.

63. Jonsson R, Vogelsang P, Volchenkov R, Espinosa A, Wahren-Herlenius M, Appel S. The complexity of Sjögren's syndrome: novel aspects on pathogenesis. Immunol Lett. 2011;141(1):1–9. https://doi.org/10.1016/J.IMLET.2011.06.007.

64. Kemeny-Beke A, Szodoray P. Ocular manifestations of rheumatic diseases. Int Ophthalmol. 2020;40(2):503–10. https://doi.org/10.1007/S10792-019-01183-9/FIGURES/3.

65. El-Shereef RR, Mohamed AS, Hamdy L. Ocular manifestation of systemic lupus erythematosus. Rheumatol Int. 2013;33(6):1637–42. https://doi.org/10.1007/S00296-011-2296-X.

66. Ziaragkali S, Kotsalidou A, Trakos N. Dry eye disease in routine rheumatology practice. Mediterr J Rheumatol. 2018;29(3):127. https://doi.org/10.31138/MJR.29.3.127.

67. Taylor S, Pacheco P, Lightman S. Dry eyes in rheumatic disease. Curr Rheumatol Rev. 2011;7(1):3–14. https://doi.org/10.2174/157339711794474602.

68. Labetoulle M, et al. How gut microbiota may impact ocular surface homeostasis and related disorders. Prog Retin Eye Res. 2024. https://doi.org/10.1016/J.PRETEYERES.2024.101250.

69. Markoulli M, et al. TFOS lifestyle: impact of nutrition on the ocular surface. Ocul Surf. 2023;29:226–71. https://doi.org/10.1016/J.JTOS.2023.04.003.

70. Yang L, Xiang Z, Zou J, Zhang Y, Ni Y, Yang J. Comprehensive analysis of the relationships between

the gut microbiota and fecal metabolome in individuals with primary Sjogren's syndrome by 16S rRNA sequencing and LC–MS-based metabolomics. Front Immunol. 2022. https://doi.org/10.3389/FIMMU.2022.874021.

71. Mendez R, et al. Gut microbial dysbiosis in individuals with Sjögren's syndrome. Microb Cell Fact. 2020. https://doi.org/10.1186/S12934-020-01348-7.

72. Asproudis I, et al. Irritable bowel syndrome might be associated with dry eye disease. Ann Gastroenterol Q Publ Hellenic Soc Gastroenterol. 2016;29(4):487. https://doi.org/10.20524/AOG.2016.0064.

73. Ko YT, et al. Inflammatory bowel disease and the associated risk of dry eye and ocular surface injury: a nationwide matched cohort study. BMC Ophthalmol. 2023;23(1):415. https://doi.org/10.1186/S12886-023-03165-Z.

74. Petricek I, Tomic M. Dry eye and dry skin—is there a connection? Investig Ophthalmol Vis Sci. 2015;56(7):4442–4442.

75. Wu PC, Ma SH, Huang YY, Chang JY, Chang YT, Dai YX. Psoriasis and dry eye disease: a systematic review and meta-analysis. Dermatology. 2022;238(5):876–85. https://doi.org/10.1159/000522167.

76. Sobolewska B, Schaller M, Zierhut M. Rosacea and dry eye disease. Ocul Immunol Inflamm. 2022;30(3):570–9. https://doi.org/10.1080/09273948.2021.2025251.

77. Palamar M, Degirmenci C, Ertam I, Yagci A. Evaluation of dry eye and meibomian gland dysfunction with meibography in patients with rosacea. Cornea. 2015;34(5):497–9. https://doi.org/10.1097/ICO.0000000000000393.

78. Boucher R, et al. Ocular surface toxicities associated with modern anticancer therapies. Surv Ophthalmol. 2024;69(2):198–210. https://doi.org/10.1016/J.SURVOPHTHAL.2023.10.002.

79. Machairoudia G, et al. Prevalence and risk factors of dry eye disease in patients treated with aromatase inhibitors for breast cancer. Clin Exp Optom. 2024;107(4):415–9. https://doi.org/10.1080/08164622.2023.2239247.

80. Chiang JCB, et al. A cross-sectional study of ocular surface discomfort and corneal nerve dysfunction after paclitaxel treatment for cancer. Sci Rep. 2021;11(1):1–10. https://doi.org/10.1038/s41598-021-81398-y.

81. Soni M, Walia S, Jain P. Dry eye disease in head and neck cancer patients undergoing radiotherapy. Indian J Ophthalmol. 2023;71(4):1556. https://doi.org/10.4103/IJO.IJO_2673_22.

82. Nuzzi R, et al. Ocular complications after radiation therapy: an observational study. Clin Ophthalmol. 2020;14:3153–66. https://doi.org/10.2147/OPTH.S263291.

83. Lee CY, Yang SF, Chang YL, Huang JY, Chang CK. The association between ovarian cancer and the incidence of newly developed dry eye disease: a nationwide population-based study. Life. 2024;14(4):530. https://doi.org/10.3390/LIFE14040530.

84. Versura P, Giannaccare G, Pellegrini M, Sebastiani S, Campos EC. Neurotrophic keratitis: current challenges and future prospects. Eye Brain. 2018;10:37–45. https://doi.org/10.2147/EB.S117261.

85. Misra SL, et al. Peripheral neuropathy and tear film dysfunction in type 1 diabetes mellitus. J Diabetes Res. 2014. https://doi.org/10.1155/2014/848659.

86. Wang TJ, Wang IJ, Hu CC, Lin HC. Comorbidities of dry eye disease: a nationwide population-based study. Acta Ophthalmol. 2012;90(7):663–8. https://doi.org/10.1111/J.1755-3768.2010.01993.X.

87. Moshirfar M, Benstead EE, Sorrentino PM, Tripathy K. Ocular neuropathic pain. StatPearls, 2023. [Online]. https://www.ncbi.nlm.nih.gov/books/NBK542282/. Accessed 26 Mar 2025.

88. Basilious A, Xu CY, Malvankar-Mehta MS. Dry eye disease and psychiatric disorders: a systematic review and meta-analysis. Eur J Ophthalmol. 2022;32(4):1872–89. https://doi.org/10.1177/11206721211060963/ASSET/IMAGES/LARGE/10.1177_11206721211060963-FIG10.JPEG.

89. Rolando M, Arnaldi D, Minervino A, Aragona P, Barabino S. Dry eye in mind: Exploring the relationship between sleep and ocular surface diseases. Eur J Ophthalmol. 2024;34(4):1128–34. https://doi.org/10.1177/11206721231222063.

90. El-Ouakhoumi A, Joulal H, Yousfi J, Benjilali L, Zahlane M, Essaadouni L. Refractory depressive disorder as the first manifestation of adolescent Sjögren's syndrome, successfully treated with rituximab. Eur J Case Rep Intern Med. 2024;11(7):004621. https://doi.org/10.12890/2024_004621.

91. Rakofsky JJ, Rakofsky SI, Dunlop BW. Dry those crying eyes: the role of depression and antidepressants in dry eye disease. J Clin Psychopharmacol.

2021;41(3):295–303. https://doi.org/10.1097/JCP.0000000000001382.

92. Pediatric Dry Eye—American Academy of Ophthalmology. [Online]. https://www.aao.org/education/disease-review/pediatric-dry-eye. Accessed 26 Mar 2025.

93. Stapleton F, Velez FG, Lau C, Wolffsohn JS. Dry eye disease in the young: a narrative review. Ocul Surf. 2024;31:11–20. https://doi.org/10.1016/J.JTOS.2023.12.001.