REVIEW ARTICLE

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Dry Eye

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DRY EYE IS A COMMON DISORDER OF THE OCULAR SURFACE THAT AFFECTS millions of people worldwide, with varying severity. At a minimum, dry eye causes discomfort, but it can also cause disabling pain and fluctuating vision, substantially affecting vision-related quality of life by limiting such activities as driving and reading, as well as recreation.[1] Dry eye also influences productivity in the workplace by making it more difficult to use a computer or read for extended periods, decreasing tolerance for certain environments, and reducing work time.[1] In the United States, the wide prevalence of dry eye imposes a substantial economic burden (an estimated $3.8 billion in health care expenditures annually).[2] Each year, the societal costs (i.e., reduced productivity and indirect costs) associated with this chronic condition amount to approximately $55 billion in the United States.[2]

Dry eye disease is an umbrella term covering a host of symptoms and signs associated with compromised ocular lubrication — that is, reduced quality or quantity of tears on the ocular surface. However, this monolithic approach to dry eye has not served science or patients well. Dry eye has many causes, which often overlap and interact. It frequently occurs with other conditions, is a consequence of environmental triggers, or is caused by medications, including over-the-counter drugs such as antihistamines. The condition can be caused or exacerbated by ocular surgery, computer use, contact-lens use, or low-humidity conditions. Diagnosis, at least initially, often relies on subjective symptoms, with variable presentation and few objective signs that can be assessed in the primary care setting. However, by thinking in terms of the subtypes of dry eye, classified on the basis of risk factors and pathophysiological features, clinicians will be better equipped to diagnose and treat cases.

As the population ages, the prevalence of dry eye is likely to increase, yet the condition is often underrecognized and undertreated. This review describes current knowledge of the causes and treatment of dry eye, ongoing research, and future directions for advancing knowledge and treatment of the condition.

DESCRIPTION OF THE EYE

The external aspect of the eye consists of the ocular surface (cornea, conjunctiva, and tear film) and the ocular adnexa (eyelids, lacrimal system, orbit, and connecting muscles and nerves). The cornea is a transparent, dome-shaped structure, 500 μm thick, that makes up the central external portion of the eye, much like a crystal on a wristwatch. Along with the tear film, the cornea provides the major refractive power of the eye, bending light rays to bring images into focus on the retina. Corneal tissue is a highly organized, avascular structure nourished by tears anteriorly and the aqueous humor posteriorly.

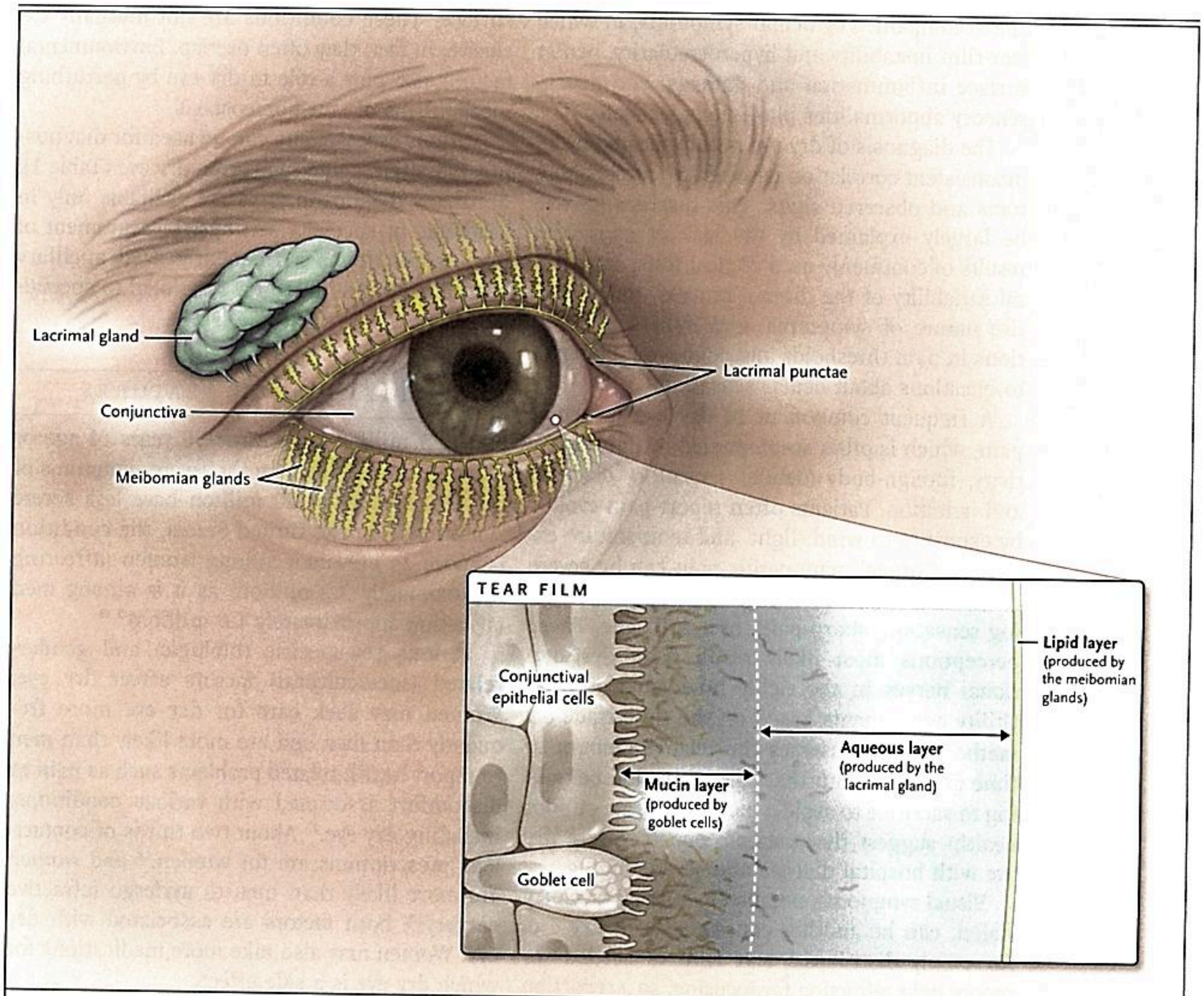

Figure 1. Structures Involved in the Production of Tear Film.
The three main components of tear film are the mucin layer, the aqueous layer, and the lipid layer.

The tear film that coats the eye consists primarily of aqueous, lipid, and mucin components (Fig. 1). The lacrimal glands produce the aqueous portion, which is enriched with a complex mixture of electrolytes, enzymes, antibodies, vitamins, antimicrobial proteins, and other substances. The lipids are produced by the meibomian glands, which are modified sebaceous glands along the eyelid margin. This hydrophobic lipid layer retards evaporation of the tear film and helps prevent tears from spilling onto the cheeks. Mucins (i.e., gelatinous glycoproteins) are produced by conjunctival goblet cells. In healthy eyes, this mucous component provides an even, slippery tear coating, minimizing friction and protecting the cornea during blinking. A neural feedback loop maintains ocular surface lubrication, with ocular sensation through corneal innervation driving basal tear production by the lacrimal gland.

SYMPTOMS AND SIGNS OF DRY EYE

The 2017 report of the Tear Film and Ocular Surface Society International Dry Eye Workshop II (TFOS DEWS II) defines dry eye as "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."[3]

The diagnosis of dry eye is complicated by an inconsistent correlation between reported symptoms and observed signs. This discrepancy can be largely explained by the lack of consistent results of commonly used clinical tests, the natural variability of the disease process, the subjective nature of symptoms, and individual variations in pain thresholds and cognitive responses to questions about ocular sensation.[4]

A frequent component of dry eye is ocular pain, which is often accompanied by light sensitivity, foreign-body (debris) sensation, dryness, and irritation. Patients often report pain evoked by exposure to wind, light, and temperature extremes. Corneal neuropathic pain can be severe and can be characterized as a burning or stinging sensation, sharp pain, or a dull ache. These perceptions most likely result from dysfunctional nerves in the richly innervated cornea.[5] Utility assessments based on the time trade-off method (which assesses the relative amount of time in good health that patients would be willing to sacrifice to avoid a particular state of poor health) suggest that patients equate severe dry eye with hospital dialysis and severe angina.[6,7]

Visual symptoms, notably fluctuating or blurry vision, can be another consequence of dry eye. An evenly distributed tear film is needed for proper light refraction for focusing, so a reduction in the quantity or quality of tears (e.g., increased osmolarity) can affect visual acuity. Clinicians are often frustrated when trying to help patients with blurry vision due to dry eye because tests may be normal at the time of examination.[8]

A TFOS DEWS II subcommittee recently updated a dry eye classification scheme based on cause, vision effects, mechanism, and disease severity.[9] It is important for clinicians to consider the evaporative dry eye and aqueous-deficient dry eye forms as they diagnose, treat, and monitor dry eye, since risk factors, causes, and treatment vary according to the form and subtype (Fig. 2).

Aqueous-deficient dry eye is characterized by decreased secretion of tears from the lacrimal glands, whereas evaporative dry eye results from increased evaporation of tear fluid from the eye surface. These conditions are not mutually exclusive; in fact, they often overlap. Environmental factors also play a role in dry eye by perturbing mechanisms of tear homeostasis.

Various assessments can be used for diagnosing, classifying, and managing dry eye (Table 1), but many diagnostic tools are available only in academic or specialty settings. Measurement of tear osmolarity is a frequently used ancillary clinical test[13] but is largely restricted to specialist practice.

EPIDEMIOLOGIC FEATURES

Nearly 5 million Americans 50 years of age or older report seeking care for severe symptoms of dry eye, and about 20 million have less severe symptoms.[1] In the United States, the condition is twice as prevalent among women (affecting approximately 3.2 million) as it is among men (affecting approximately 1.6 million).[1,16]

Various sex-specific (biologic) and gender-related (sociocultural) factors affect dry eye. Women may seek care for dry eye more frequently than men and are more likely than men to report health-related problems such as pain or discomfort associated with various conditions, including dry eye.[17] About two thirds of contact-lens prescriptions are for women,[18] and women are more likely than men to undergo refractive surgery[19]; both factors are associated with dry eye. Women may also take more medications for which dry eye is a side effect.

A study involving 3930 female monozygotic and dizygotic twins showed a heritability rate of approximately 30% for symptoms of dry eye and of 40% for a clinical diagnosis of dry eye.[20] Genetic factors appear to account for 25 to 80% of various signs and symptoms, such as eyelid inflammation, increased tear osmolarity, and reduced blinking rate. Environmental influences may account for the remaining signs and symptoms.

CAUSES AND RISK FACTORS

Ocular-surface inflammation is a key component of dry eye.[21] Ocular disease, infection, or immune-mediated conditions can cause chronic inflammation, and environmental exposures (e.g., wind and airborne particulates) can exacerbate it.[22] Many cellular and molecular compo-

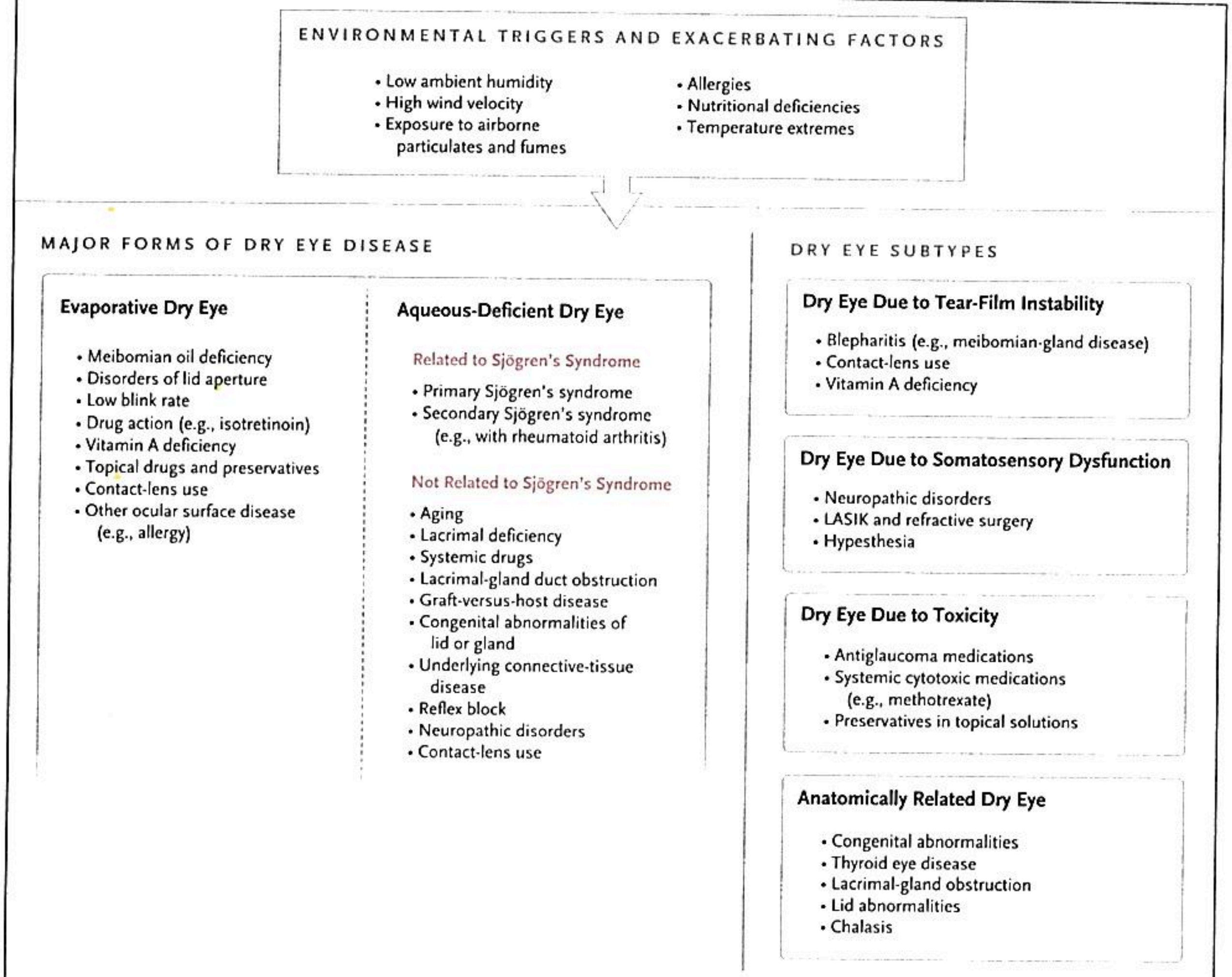

Figure 2. Two Major Forms of Dry Eye Disease and Four Examples of Dry Eye Subtypes.
Environmental factors and medical conditions can exacerbate dry eye. Manifestations of the dry eye forms may overlap.

nents contribute to the pathogenesis of dry eye, including inflammatory cytokines, metalloproteinases, and chemokines and their receptors, leading to immune-cell activation and associated inflammation.[23] The reduced tear secretion that is characteristic of aqueous-deficient dry eye results in tear-film hyperosmolarity associated with an inflammatory cascade involving mitogen-activated protein (MAP) kinase and nuclear factor κB signaling pathways[24,25] that produce various proinflammatory cytokines (e.g., interleukin-1α, interleukin-1β, tumor necrosis factor α [TNF-α]) and matrix metalloproteinase 9 (MMP9).[26] The result is a vicious cycle perpetuating dry eye and exacerbating its sequelae. Research also suggests that an abundance of extracellular DNA and neutrophil extracellular traps in the tear fluid of people with dry eye is caused by a nuclease deficiency and leads to ocular surface inflammation.[27,28] Hyperosmolar stress exacerbates this process.[29]

DISEASES OF THE IMMUNE SYSTEM

Autoimmune diseases, including rheumatoid arthritis and systemic lupus erythematosus, can cause dry eye. Furthermore, treatments for these diseases, including methotrexate and cyclophosphamide, can also cause or exacerbate dry eye.

Table 1. Examples of Assessments for Diagnosing and Evaluating Dry Eye Disease.*

Assessment Tool	Evaluation
Corneal and conjunctival vital dye staining	Assessment of damage to ocular surface[10]
Meibomian-gland grading	Classification of meibomian-gland dysfunction on the basis of anatomical changes, pathophysiological changes, or disease severity (e.g., plugging of the glands and quality of glandular secretions and meibum)[11]
Schirmer test (with or without anesthesia)	Assessment of tear volume, measured as moisture absorbed onto paper strips placed inside lower eyelids of both eyes for 5 min
Questionnaires	Patient-reported outcome measures assessing severity of dry eye symptoms, effects on vision-related quality of life, and visual functioning:
	Dry Eye Questionnaire Dry Eye Questionnaire 5 Ocular Surface Disease Index National Eye Institute Visual Functioning Questionnaire 25 Impact of Dry Eye on Everyday Life McMonnies questionnaire Symptom Assessment in Dry Eye Standard Patient Evaluation of Eye Dryness questionnaire Vision-Targeted Health-Related Quality of Life questionnaire (NIH Toolbox) Visual-analogue scale
Tear-film stability	Assessment of tear-film breakup time, measured by instilling sodium fluorescein vital dye onto the eye and measuring the time required for dry spots to appear on the corneal surface after blinking (short breakup time is a sign of poor tear-film quality) or by other optical methods[12]
Tear osmolarity	Measurement of solutes in tear fluid (increased levels are seen in dry eye)[13]
Tear-film interferometry	Assessment of balance between the lipid and aqueous layers of the tear film (to distinguish clinical subtypes of dry eye)[14]
InflammaDry immunoassay	Measurement of MMP9 levels in the tear film (levels >40 ng/ml indicate ocular surface inflammation)[15]

* MMP9 denotes matrix metalloproteinase 9, and NIH National Institutes of Health.

Dry eye is also known as keratoconjunctivitis sicca, a term coined by Swedish ophthalmologist Henrik S.C. Sjögren, for whom Sjögren's syndrome is named. Sjögren's syndrome is characterized by dry eye and dry mouth and sometimes has multiple extraglandular manifestations.[30] Although few patients with dry eye have Sjögren's syndrome, women account for 90% of cases of the syndrome. Primary Sjögren's syndrome is associated with aqueous-deficient dry eye, although it can also be manifested by other signs of dry eye, such as meibomian gland changes. In Sjögren's syndrome, an autoimmune-mediated exocrinopathy leads to T-cell infiltration of the lacrimal glands, reducing tear production. In conjunction with the action of circulating antibodies against glandular receptors, local release of proinflammatory cytokines causes neurosecretory block. Patients with Sjögren's syndrome who have high levels of corneal staining may paradoxically report fewer symptoms than patients without Sjögren's syndrome who have lower levels of corneal staining, owing to reduced corneal sensitivity with severe ocular-surface inflammation and disease.[31] Dry eye can also accompany systemic inflammatory diseases such as sarcoidosis.

SEX HORMONES

Androgen, estrogen, and progesterone receptors are expressed in the eye, including in the meibomian glands,[32] cornea,[33] conjunctiva,[34] and retinal pigment epithelium.[35] Sex hormones affect the surface of the eye by altering goblet-cell density and the production and quality of tears.[21] Moreover, dry eye is more common among postmenopausal women than among premenopausal women, and women with premature onset of menopause are more likely to have signs of ocular-surface damage than premenopausal women.[36] Women with premature ovarian failure are also at heightened risk for dry eye.[36]

The Women's Health Study showed an association between menopausal hormone therapy and an increased prevalence of dry eye.[37] Other studies have shown that menopausal hormone therapy, particularly estrogen-only therapy, is associated with decreased tear production and reduced intraocular pressure.[38]

Dry eye disease is more strongly associated with low androgen levels than with either high or low estrogen levels.[39] Androgens have a strong effect on the lipids in meibomian gland secretions through androgen receptor protein,[40] which is expressed throughout the eye (e.g., in the lacrimal gland, meibomian gland, cornea, and bulbar and fornical conjunctivae).[41,42] Androgen deficiency, which occurs as part of the congenital androgen insensitivity syndrome and with antiandrogen therapy, is associated with dry eye.[43] In addition, androgen deficiency is a feature of Sjögren's syndrome and may contribute to evaporative dry eye.[44]

ANATOMICAL AND NEUROLOGIC DISORDERS

Anatomical abnormalities of the eyelids can disturb tear function and dynamics. Disorders such as conjunctival chalasis and eyelid laxity (i.e., the floppy eyelid syndrome[45]), can lead to symptoms of dry eye. Conditions that affect muscular control of the face, such as stroke, injury, or Bell's palsy, can impair eyelid closure, resulting in lagophthalmos and leading to an extreme form of evaporative dry eye called exposure keratitis. Similarly, any condition (e.g., Parkinson's disease) or situation (e.g., prolonged screen viewing [on a computer, cell phone, or television, for example]) that reduces the blink rate can increase the risk of dry eye by promoting tear evaporation.[46-48]

COMPROMISED NEURAL FUNCTION

Abnormal ocular surface sensation is a feature of dry eye, stemming from impairment of the neural feedback loop that controls tear secretion. Compromise of this tear functional unit and its innervation exacerbates the symptoms of ocular surface disease.[49] Neuropathic pain can drive some symptoms, especially in the subtype of dry eye characterized by somatosensory dysfunction. Symptoms and signs of dry eye may arise in patients who have abnormal nerve function as a result of laser vision correction in which the corneal nerves are transected or in patients with coexisting sensory disorders such as fibromyalgia or migraine.[50] Ocular neural dysfunction probably plays a role in the discomfort associated with dry eye.

MEIBOMIAN-GLAND DYSFUNCTION

The number and distribution of meibomian glands differ between the upper and lower eyelids; although the lower lids are less prone to meibomian-gland dysfunction, they are more sensitive than the upper lids.[51,52] Meibomian-gland dysfunction is manifested as plugged gland orifices, thick secretions, a perturbed lipid layer in the tear film, and inflammation of the lid margin. Obstructive meibomian-gland dysfunction alters the lipid constitution of the tears and is the most common cause of evaporative dry eye. Without a sufficient lipid component, the aqueous tear component evaporates rapidly. Meibomian-gland dysfunction may be a primary disorder, or it may be a consequence of rosacea, certain forms of dermatitis, and fibrosing conjunctival disorders such as trachoma, erythema multiforme, and ocular cicatricial pemphigoid.[53]

GRAFT-VERSUS-HOST DISEASE

Dry eye affects about half of patients with chronic graft-versus-host disease (GVHD), which is a serious complication of allogeneic hematopoietic stem-cell transplantation. Combined with conjunctival inflammation and fibrosis, severe ocular dryness can worsen quality of life.[54] Immunologic sequelae of GVHD that contribute to dry eye include ocular surface infiltration — with donor-derived CD4+ and CD8+ T cells and the surface molecules necessary for antigen presentation — in the periductal area of the lacrimal gland.[55] The accumulation of inflammatory cytokines in the tear film also contributes to dry eye in patients with GVHD.

DIABETES

Symptoms of dry eye are often reported by patients with type 1 or type 2 diabetes[56]; however, such patients may also have tear abnormalities without symptoms as a result of reduced corneal sensitivity. Diabetes-associated damage to the microvasculature of the lacrimal gland, autonomic neuropathy, and diabetic sensory neuropathy of the cornea affect the quality and quantity of tears.[57] Poor glycemic control is associated with increased use of artificial tear solutions.[58]

MEDICATIONS

Many systemic drugs have been reported to trigger dry eye, including diuretic agents (e.g., furosemide), beta-blockers (e.g., propranolol), other antihypertensive agents (e.g., candesartan), antihistamines (e.g., cetirizine), decongestants (e.g., pseudoephedrine), medications for Parkinson's disease (e.g., trihexyphenidyl), antidepressant agents (e.g., amitriptyline), anxiolytic agents (e.g., lorazepam), anticonvulsant agents (e.g., valproic acid), antipsychotic agents (e.g., thioridazine), antispasmodic agents, gastric-protection agents (e.g., ranitidine), oral contraceptives, and some herbal supplements (e.g., echinacea). Isotretinoin impairs meibomian-gland function, enhancing tear evaporation. Anticholinergic medications that cause dry mouth from parasympathetic blockade have similar ocular effects.[59] Medication-induced dry eye may be more prevalent among older people than among younger people because older people have additional risk factors and are more likely to be taking multiple medications. Just as oral polypharmacy is the most common cause of dry mouth, use of multiple ocular medications can cause dry eye.[60]

Toxic effects of preservatives in topical ocular medications (including benzalkonium chloride) can lead to conjunctival inflammation and tear-film instability, thereby causing or exacerbating symptoms and signs of dry eye.[61] In patients requiring frequent treatment with artificial tears, preservative-free formulations or those with dissipating preservative ingredients may be helpful. Preservatives in topical antiglaucoma drugs can induce ocular surface irritation and dry eye symptoms.[62]

Treat Lid Disease

- Lid hygiene
- Warm compress
- Expression of meibomian glands
- Topical antibiotics
- Topical glucocorticoids
- Tea tree oil (treatment of demodex)
- Oral macrolides or tetracyclines
- Topical androgens

Reduce Inflammation

- Cyclosporine ophthalmic emulsion
- Lifitegrast ophthalmic solution
- Short-term topical glucocorticoids
- Avoidance of topical preservatives

Enhance Tear Volume or Quality

- Topical lubricants, including gel and ointment
- Punctal plugs or occlusion
- Diquafosol tetrasodium ophthalmic solution
- Autologous serum
- Therapeutic contact lenses

Make Lifestyle and Dietary Changes

- Protective eyewear
- Increased ambient humidity
- Reduced screen time
- Increased fluid intake
- Adequate sleep
- Essential fatty acids or other effective supplements
- Avoidance of environmental triggers
- Avoidance of medication triggers

Figure 3. **Therapeutic Strategies in Use or Under Development for Dry Eye.**

THERAPEUTIC STRATEGIES

Decisions about treatment for dry eye that is not a consequence of other, underlying conditions should be guided by consideration of the cause and severity of the disease. Since dry eye is a multifactorial disease, therapeutic strategies should address the various disease components. Recent reviews summarize current treatment strategies.[63,64] These include the administration of artificial tear formulations of varying viscosities and compositions that are intended to enhance tear volume or quality, reduction of inflammation, modification of diet or lifestyle, and treatment of any associated eyelid disease (Fig. 3).[65]

TEAR VOLUME AND QUALITY

Three basic strategies can be used in the treatment of aqueous-deficient or evaporative dry eye: increase the amount of liquid on the ocular surface, decrease tear evaporation, and augment the lipid content or lubricity of the tears. All three are aimed at increasing tear volume or improving the quality of the tear film, and treatment should be tailored to the pattern of disease presentation.

Numerous topical lubricants, including drops, gels, and ointments, are available for dry eye. Many formulations of artificial tears are available over the counter. The features of topical lubricants and their clinical usefulness in the treatment of dry eye symptoms have been reviewed elsewhere.[66] Polymer hydroxypropyl guar gellable lubricant eyedrops (Systane Lubricant Eye Drops, Alcon) effectively relieved signs and symptoms of moderate dry eye, with measurable improvements in both objective staining and subjective questionnaire measures, in 168 patients after 28 days.[67] Topical lubricants are designed to support the quality and quantity of the tear film. The frequency of application of ocular lubricants is based on the needs of the individual patient and can range from once a day to once an hour.

Another study showed that diquafosol tetrasodium ophthalmic solution provided a clinical benefit in the treatment of dry eye through a purinergic receptor–mediated mechanism that stimulated tear fluid secretion; a formulation is available in Japan.[68] Topical therapies also include eyedrops prepared with sterile, saline-diluted serum derived from the patient's blood for severe cases of dry eye.[69]

Occasionally, surgery is used to plug puncta, thereby diminishing tear outflow and increasing moisture on the ocular surface. However, lacrimal or punctal plugs are usually temporary solutions, lasting on the order of months to a few years. Surgical approaches for correcting anatomical abnormalities, such as chalasis, can ameliorate dry eye in some cases.

Various lines of research are exploring ways to enhance the lipid content of tears, reducing evaporation, or to increase the lubricity of tears. Some approaches, including administration of essential fatty acids, cyclooxygenase inhibitors, and resolvin analogues, not only boost the lipid content of tears but also reduce inflammation.[70] A small trial showed that an over-the-counter product (Soothe XP, Bausch & Lomb) increased the lipid-layer thickness of the tear film in patients with dry eye due to meibomian-gland dysfunction.[71]

To reduce the risk of dry eye related to the toxic effects associated with antiglaucoma drops, selected patients with primary angle-closure glaucoma may be treated with laser trabeculoplasty. This treatment, which targets the trabecular meshwork to reduce ocular pressure, can reduce dependence on topical drops, minimizing damage to the ocular surface from preservatives.[72]

REDUCTION OF INFLAMMATION

A mainstay of dry eye treatment, based on the critical role of inflammation, is 0.05% cyclosporine ophthalmic emulsion (Restasis, Allergan). This prescription-based, nonglucocorticoid immunomodulatory agent, applied topically (one drop twice daily), increases tear production by decreasing ocular surface inflammation and directly affecting lacrimal-gland function. Cyclosporine ophthalmic emulsion has been shown to be effective for dry eye in randomized clinical trials.[73]

In July 2016, the Food and Drug Administration (FDA) approved 0.5% lifitegrast ophthalmic solution (Xiidra, Shire) for treating signs and symptoms of dry eye disease. Applied topically as one drop twice daily, this medication is the first in a new class of drugs, called lymphocyte function–associated antigen 1 (LFA-1) antagonists. The second of two drugs approved by the FDA for dry eye disease,[74] this medication is a welcome addition to the clinical armamentarium and a source of new hope for affected patients. Unlike topical lubricants, the two FDA-approved therapies for dry eye (Restasis and Xiidra) must be administered for a period of up to several months to achieve therapeutic effects.

Research points to other ways of reducing inflammation as potential treatments for dry eye. A study in a mouse model of dry eye showed that topical TNF-α–stimulated gene 6 (TSG-6) protein was as effective in the treatment of inflammation-mediated dry eye as cyclosporine ophthalmic emulsion administered as eyedrops.[75] The study also showed that topical prednisolone suppressed inflammation but induced corneal epithelial apoptosis. A preclinical study of a dexamethasone-loaded nanowafer applied to the eye yielded promising results. Once-a-day treatment on alternate days over a period of 5 days (i.e., days 1, 3, and 5) restored a healthy ocular surface and corneal barrier function, with efficacy similar to that of twice-daily topical dexamethasone eyedrops.[76] Translational research is needed to further develop these and other innovative approaches while minimizing adverse effects.

LIFESTYLE AND DIETARY APPROACHES

Lifestyle approaches to the management of dry eye include ensuring adequate fluid intake, moderating alcohol use, using humidifiers or protective eyewear, and when possible, avoiding air conditioning and forced-air heating. Sleep deprivation can trigger dry eye symptoms,[77] so adequate sleep is also important.

A meta-analysis on diet supports a therapeutic role for polyunsaturated fatty acids.[78] Certain foods, such as fish and flaxseed, contain n–3 and n–6 fatty acids. Women who consume two or more servings of tuna weekly are less likely to report dry eye symptoms than women with lower levels of tuna consumption.[79] Use of n–3 fatty acid supplements may enhance tear production and quality.[80,81] A recently completed randomized, controlled clinical trial showed that daily supplements of 3000 mg of n–3 fatty acids for 12 months yielded no significantly better outcomes than placebo.[82] Phytoestrogen supplements have been associated with decreased signs and symptoms of dry eye disease,[83] and oral flaxseed oil has been reported to reduce inflammation, leading to amelioration of symptoms in patients with Sjögren's syndrome.[84]

TREATMENT OF LID DISEASE

The mainstay of treatment for meibomian-gland disease (posterior blepharitis) is lid hygiene. The use of warm compresses combined with mechanical cleansing of the eyelid margins decreases the bacterial load and enhances gland function by softening secretions and relieving gland duct obstruction. Topical antibiotics, including azithromycin, topical low-dose glucocorticoids, and combinations of the two agents can also be used for short-term treatment. Oral tetracyclines can be used for longer periods. Antibiotics may have therapeutic effects through antiinflammatory mechanisms rather than through, or in addition to, their antibacterial properties.

HORMONE THERAPY

Despite the greater prevalence of dry eye among women than among men and the intriguing connections between sex hormone levels and the risk of dry eye, reports on the effects of systemic hormone therapy on dry eye symptoms are contradictory.[85] Research findings suggest a potential role for androgens as topical therapy for dry eye.[86] More work is needed to assess levels of hormones within ocular tissues and to enhance our understanding of the complex relationships among various hormonal components that are critical for maintaining ocular surface homeostasis. On the basis of current knowledge, hormone therapy cannot be recommended for dry eye.

FUTURE DIRECTIONS

The poor correlation between objectively measured signs and patient-reported symptoms of dry eye complicates the job of clinicians, who need precise diagnostic and monitoring tools to evaluate patients. Efforts to provide new tools for the clinic will probably require interdisciplinary research bridging medicine, engineering, fluid dynamics, and lipid measurement technology. Research to develop better delivery formulations and dry eye treatments is ongoing.[87-89]

Clinical studies also show promise for the use of mucin secretagogues in combination therapy for dry eye.[90] Despite these ongoing advances, development of effective therapies is hampered by extensive evidence gaps related to ocular pain and neural regulation of the ocular surface.

Little is known about ocular pain, and no analgesics are available for ocular use. The field could benefit from the development of tools to evaluate the ocular sensory apparatus; these tools could be used in therapeutics development and to assess patients' reports of pain in the clinic.

A recent study suggested that chronic ocular pain coincides with dysfunction of the ocular sensory apparatus and may be manifested as spontaneous dysesthesias, allodynia, hyperalgesia, and corneal-nerve morphologic and functional abnormalities.[91] There are extensive evidence gaps related to neural regulation of the ocular surface, including meibomian-gland secretion and mucin release. There is also a lack of biomarkers for dry eye disease, which are needed to improve diagnosis and treatment. In people with Sjögren's syndrome, down-regulation of *PAX6* — the master regulator of corneal lineage commitment — is inflammation-dependent and linked to ocular surface damage.[92] Further clinical studies will determine whether *PAX6* can serve as a biomarker or a potential therapeutic target for Sjögren's syndrome. Moreover, other promising research led to the finding that the multifunctional protein clusterin (CLU) is the most highly expressed transcript in the human cornea, with the protein product localized to the apical layers of the mucosal epithelia of the cornea and conjunctiva. CLU protein is also present in human tears. Preclinical studies have shown that above a threshold concentration, CLU helps seal the ocular surface barrier, thus protecting the eye from desiccating stress. CLU not only may be a promising biomarker but also may be the basis for developing new therapeutics for dry eye disease.[93]

CONCLUSIONS

Dry eye disease can have serious deleterious effects on physical and psychological health, and the societal costs attributable to this condition are consequential in terms of direct costs of care and lost productivity. Management of dry eye could benefit from a more precise means of assessing the components of ocular surface health, including biomarkers of active disease and identification of the major drivers of symptom-related disease development. Approaches to evaluating more aspects of tear-film function and biochemical properties are needed. The lack of correlation between ocular signs as currently assessed and patient-reported symptoms of discomfort reflects our incomplete understanding of this vexing disease. Novel approaches and technological advances to enhance our knowledge of normal function and how disease perturbs the ocular surface are sorely needed.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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