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Dry Eye Syndrome Preferred Practice Pattern®

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CORNEA/EXTERNAL DISEASE PREFERRED PRACTICE PATTERN® DEVELOPMENT PROCESS AND PARTICIPANTS

The **Cornea/External Disease Preferred Practice Pattern Panel** members wrote the Dry Eye Syndrome Preferred Practice Pattern guidelines (PPP). The PPP Panel members discussed and reviewed successive drafts of the document, meeting in person twice and conducting other review by e-mail discussion, to develop a consensus over the final version of the document.

Cornea/External Disease Preferred Practice Pattern Panel 2022–2023
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The **Preferred Practice Patterns Committee** members reviewed and discussed the document during a meeting in June 2023. The document was edited in response to the discussion and comments.

Preferred Practice Patterns Committee 2023
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Christina J. Flaxel, MD
Steven J. Gedde, MD
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The Dry Eye Syndrome PPP was sent for review in July 2023 to improve the quality of the guideline, to gather feedback on the draft recommendations and to assess feasibility for and applicability to the target audience, including assessing the facilitators and barriers to implementing recommendations (e.g., U.S. ophthalmologists and other important groups, including patients, other physicians, international ophthalmologists, research organizations, ophthalmological organizations, and experts in the field). The PPP was sent for review to the following patient organizations to solicit the views and preferences of patients and the public: Consumers United for Evidence-Based Healthcare, American Foundation for the Blind, Foundation Fighting Blindness, Lighthouse Guild, National Federation of the Blind, and Prevent Blindness. All those who were returning comments were required to provide disclosure of relevant relationships with industry to have their comments considered (indicated with an asterisk below). Members of the Cornea/External Disease Preferred Practice Pattern Panel reviewed these comments and determined revisions to the document.

<u>Academy Reviewers</u>
Board of Trustees and Committee of Secretaries*
Council
General Counsel*
Ophthalmic Technology Assessment Committee
Cornea/External Disease Panel
Basic and Clinical Science Course Section 8
Subcommittee*
Practicing Ophthalmologists Advisory Committee for Education*

<u>Invited Reviewers</u>
American College of Surgeons, Advisory Council for Ophthalmic Surgery
American Foundation for the Blind
American Ophthalmological Society*

American Society of Cataract & Refractive Surgery
American Uveitis Society*
Asia Cornea Society*
Association for Research in Vision and Ophthalmology
Association of University Professors of Ophthalmology
Canadian Ophthalmological Society
Consumers United for Evidence-Based Health Care
Cornea Society*
Foundation Fighting Blindness
International Council of Ophthalmology
International Society of Refractive Surgery
Lighthouse Guild
National Eye Institute
National Federation of the Blind
National Medical Association, Ophthalmology Section
Ocular Microbiology and Immunology Group
Prevent Blindness
Women in Ophthalmology
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This guideline will be formally re-evaluated and updated on a 5-year cycle in 2028. A Summary Benchmark is a resource to facilitate application of the guideline and to provide criteria that could be used to measure the application of recommendations, which will be available to all at www.aao.org/ppp.

FINANCIAL DISCLOSURES

There is no external funding, including industry/commercial support, for the development of this PPP or for the distribution of the guidelines. The Academy has fully funded the development of this PPP, and the views or interests of the Academy have not influenced the final recommendations, which are based on evidence from systematic reviews. All those individuals significantly involved in the guideline development process, including guideline panel members, PPP Committee members, Secretary for Quality of Care, and Academy Staff, have declared competing/financial interests through a financial interest disclosure process as well as on the Open Payments website (available at https://openpaymentsdata.cms.gov/). The interests of the guideline panel members are provided at the beginning of each meeting and those with competing interests in a guideline topic do not participate in voting on areas of disagreement. In compliance with the Council of Medical Specialty Societies' Code for Interactions with Companies (available at https://cmss.org/code-for-interactions-with-companies/), relevant relationships with industry are listed. As per CMSS code, direct financial relationships with companies do not include food and beverage, research funds paid to the institution and relationships outside of the topic of the PPP. The Academy has Relationship with Industry Procedures to comply with the Code (available at www.aao.org/about-preferred-practice-patterns). A majority (64%) of the members of the Cornea/External Disease Preferred Practice Pattern Panel 2022–2023 had no direct financial relationships to disclose.

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The disclosures of relevant relationships to industry of other reviewers of the document from January to October 2023 are available online at www.aao.org/ppp.

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OBJECTIVES OF PREFERRED PRACTICE PATTERN® GUIDELINES

As a service to its members and the public, the American Academy of Ophthalmology has developed a series of Preferred Practice Pattern guidelines that **identify characteristics and components of quality eye care.** Appendix 1 describes the core criteria of quality eye care.

The Preferred Practice Pattern guidelines are based on the best available scientific data as interpreted by panels of knowledgeable health professionals. In some instances, such as when results of carefully conducted clinical trials are available, the data are particularly persuasive and provide clear guidance. In other instances, the panels have to rely on their collective judgment and evaluation of available evidence.

These documents provide guidance for the pattern of practice, not for the care of a particular individual. While they should generally meet the needs of most patients, they cannot possibly best meet the needs of all patients. Adherence to these PPPs will not ensure a successful outcome in every situation. These practice patterns should not be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the best results. It may be necessary to approach different patients' needs in different ways. The physician must make the ultimate judgment about the propriety of the care of a particular patient in light of all of the circumstances presented by that patient. The American Academy of Ophthalmology is available to assist members in resolving ethical dilemmas that arise in the course of ophthalmic practice.

Preferred Practice Pattern guidelines are not medical standards to be adhered to in all individual situations. The Academy specifically disclaims any and all liability for injury or other damages of any kind, from negligence or otherwise, for any and all claims that may arise out of the use of any recommendations or other information contained herein.

References to certain drugs, instruments, and other products are made for illustrative purposes only and are not intended to constitute an endorsement of such. Such material may include information on applications that are not considered community standard, that reflect indications not included in approved US Food and Drug Administration (FDA) labeling, or that are approved for use only in restricted research settings. The FDA has stated that it is the responsibility of the physician to determine the FDA status of each drug or device he or she wishes to use, and to use them with appropriate patient consent in compliance with applicable law.

Innovation in medicine is essential to ensure the future health of the American public, and the Academy encourages the development of new diagnostic and therapeutic methods that will improve eye care. It is essential to recognize that true medical excellence is achieved only when the patients' needs are the foremost consideration.

All Preferred Practice Pattern guidelines are reviewed by their parent panel annually or earlier if developments warrant and updated accordingly. To ensure that all PPPs are current, each is valid for 5 years from the "approved by" date unless superseded by a revision. Preferred Practice Pattern guidelines are funded by the Academy without commercial support. Authors and reviewers of PPPs are volunteers and do not receive any financial compensation for their contributions to the documents. The PPPs are externally reviewed by experts and stakeholders, including consumer representatives, before publication. The PPPs are developed in compliance with the Council of Medical Specialty Societies' Code for Interactions with Companies. The Academy has Relationship with Industry Procedures (available at www.aao.org/about-preferred-practice-patterns) to comply with the Code.

Appendix 2 contains the International Statistical Classification of Diseases and Related Health Problems (ICD) codes for the disease entities that this PPP covers. The intended users of the Dry Eye Syndrome PPP are ophthalmologists.

METHODS AND KEY TO RATINGS

Preferred Practice Pattern guidelines should be clinically relevant and specific enough to provide useful information to practitioners. Where evidence exists to support a recommendation for care, the recommendation should be given an explicit rating that shows the strength of evidence. To accomplish these aims, methods from the Scottish Intercollegiate Guideline Network[1] (SIGN) and the Grading of Recommendations Assessment, Development and Evaluation[2] (GRADE) group are used. GRADE is a systematic approach to grading the strength of the total body of evidence that is available to support recommendations on a specific clinical management issue. Organizations that have adopted GRADE include SIGN, the World Health Organization, the Agency for Healthcare Research and Quality, and the American College of Physicians.[3]

- All studies used to form a recommendation for care are graded for strength of evidence individually, and that grade is listed with the study citation.
- To rate individual studies, a scale based on SIGN[1] is used. The definitions and levels of evidence to rate individual studies are as follows:

I++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
I+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
I-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
II++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
II+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
II-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
III	Nonanalytic studies (e.g., case reports, case series)

- Recommendations for care are formed based on the body of the evidence. The body of evidence quality ratings are defined by GRADE[2] as follows:

Good quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Insufficient quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate Any estimate of effect is very uncertain

- Key recommendations for care are defined by GRADE[2] as follows:

Strong recommendation	Used when the desirable effects of an intervention clearly outweigh the undesirable effects or clearly do not
Discretionary recommendation	Used when the trade-offs are less certain—either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced

- The Highlighted Findings and Recommendations for Care section lists points determined by the PPP panel to be of particular importance to vision and quality of life outcomes.
- All recommendations for care in this PPP were rated using the system described above. Ratings are embedded throughout the PPP main text in italics.
- Literature searches to update the PPP were undertaken on March 3, 2022 and June 7, 2023 in the PubMed database. Complete details of the literature search are available at www.aao.org/ppp.

- Recommendations are based on systematic reviews, as per the Institute of Medicine (Clinical Practice Guidelines We Can Trust, 2011). In formulating the recommendations, the health benefits, side effects/harms/risks, and the balance of benefits and risks are reviewed and considered. Final decisions are arrived at through informal consensus techniques. If there are areas of disagreement, a vote will be conducted among the members of the guideline panel. If there are individuals with direct financial relationships in the area of disagreement, these individuals will refrain from the vote.

HIGHLIGHTED FINDINGS AND RECOMMENDATIONS FOR CARE

Dry eye syndrome is a common ocular condition that has a substantial impact on the quality of life of afflicted individuals owing to discomfort and visual disability. Dry eye may compromise results of cataract, corneal, and keratorefractive surgery.

Clinical examination is the gold standard for diagnosing dry eye syndrome (also known as dry eye disease or keratoconjunctivitis sicca). No single test is adequate for establishing the diagnosis of dry eye syndrome. The constellation of findings from multiple tests can add to the clinician's understanding of the patient's condition.

Pharmacological and procedural treatments are associated with improvements in patient symptoms and clinical signs; although these are rarely curative, long-term treatment is typically necessary.

U.S. Food and Drug Administration (FDA)-approved treatments for dry eye syndrome include topical loteprednol 0.25%, lifitegrast 0.5%, cyclosporine 0.05% and 0.09%, varenicline nasal spray, and perflurohexyloctane ophthalmic solution. They may lead to improvements of patient symptoms and/or signs but none has been proven more effective than the other in head-to-head trials.[4-6] No direct comparison in a prospective clinical trial is available in the literature.

Patients with dry eye syndrome considering keratorefractive and lens-based surgery should be cautioned that the dry eye symptoms could become worse after surgery. If pre-existing factors contributing to dry eye syndrome can be improved preoperatively, the chance of worsened dry eye syndrome can be reduced. Dry eye symptoms are common in the first few months after keratorefractive and lens-based surgery and often subside with time.

Dry eye syndrome is one of the main reasons for patient dissatisfaction following intraocular refractive and/or cataract surgery.[7] Dry eye symptoms that continue beyond the normal postoperative period of 3 months are seen in about one third of individuals.[8] Baseline ocular surface and tear film parameters predict the patients at risk.[9] Therefore, all patients undergoing lens-based surgery should be evaluated and managed for dry eye preoperatively and postoperatively.

Approximately 10% of patients with clinically aqueous tear deficiency dry eye have underlying Sjögren's syndrome.[10] A meta-analysis found that, among autoimmune diseases, primary Sjögren's syndrome is the most strongly associated with lymphoid proliferative malignancy.

INTRODUCTION

DISEASE DEFINITION

Dry eye syndrome (also known as dry eye disease or keratoconjunctivitis sicca) refers to a group of disorders of the tear film that are due to reduced tear production and/or tear film instability, associated with ocular discomfort and/or visual symptoms and inflammatory disease of the ocular surface.

PATIENT POPULATION

The patient population includes individuals of all ages who present with symptoms and signs suggestive of dry eye, such as ocular irritation (e.g., burning, gritty, or sandy sensation), redness, mucus discharge, fluctuating vision, and decreased tear meniscus or meibomian gland stasis and/or obstruction. However, some patients with these symptoms may prove to not have dry eye.

CLINICAL OBJECTIVES

- Establish the diagnosis of dry eye and differentiate it from other causes of ocular irritation and redness
- Identify the local, systemic, environmental, and life-style relative causes of dry eye disease
- Recommend appropriate therapy
- Relieve discomfort
- Prevent worsening of vision, symptoms, and clinical findings
- Educate and involve the patient in the management of the disease

BACKGROUND

Dry eye, either alone or in combination with other conditions, is a frequent cause of ocular irritation that leads patients to seek ophthalmologic care.[11] Even though these symptoms often improve with treatment, the disease usually is not curable, which may be a source of patient and physician frustration. Importantly, dry eye is also a cause of reduced visual function[12-15] and may compromise results of corneal, cataract, keratorefractive, and other anterior segment surgery.

PREVALENCE AND RISK FACTORS

Epidemiological information on dry eye disease has been limited by the lack of uniformity in its definition and the inability of any single diagnostic test or set of diagnostic tests to confirm or rule out the condition. Dry eye disease is a common condition that causes varying degrees of discomfort and visual disability. Although clinic-based studies have confirmed its frequency (17% of 2,127 consecutive new outpatients were diagnosed with dry eye following comprehensive examination), such studies may not reflect the overall population.[16] A population-based study of dry eye conducted in Australia, reported that of the 926 participants aged 40 to 97 years, 16.3% had a low Schirmer test (≤8 mm) and 10.8% had a high rose bengal score (≥4 van Bijsterveld score).[17] The prevalence of self-reported dry eye in 3,722 participants of the Beaver Dam Eye Study varied from 8.4% of subjects younger than 60 years to 19.0% of those over 80 years, with an overall prevalence of 14.4%.[18] The Men's Health Study revealed that the prevalence of dry eye in men increased from 3.9% to 7.7% when men aged 50 to 54 years were compared with men over 80 (n = 25,444). In this study, dry eye was defined as a reported clinical diagnosis or symptoms of both dryness and irritation either constantly or often.[19] In a similar Women's Health Study of over 39,000 women, the prevalence of dry eye was 5.7% among women younger than 50 and increased to 9.8% among women over 75. In this survey, the definition used for dry eye was the same as for the Men's Health Study.[20] In a clinic setting, 224 subjects identified with dry eye were far more likely to exhibit signs of evaporative dry eye resulting from meibomian gland dysfunction than from pure aqueous deficient dry eye.[21]

Estimates of dry eye prevalence based on treatment-derived data yield much lower percentages. A study evaluating medical claims data for nearly 10 million enrollees in managed care plans found that dry eye was diagnosed or treated with punctal occlusion in 0.4% to 0.5% of the enrollees.[19, 20, 22]

Many risk factors for dry eye have been proposed. Older age and female gender have been identified as major risk factors.[17, 18, 22-25] A Japanese study found an increased prevalence of dry eye disease among Japanese office workers using visual display terminals.[26] Concurrent use of glaucoma medication containing benzalkonium chloride was also shown to be a risk factor in patients.[27, 28] Rheumatoid arthritis was associated with dry eye in two studies.[17, 18] The Beaver Dam Eye Study found that after controlling for age and gender, smoking and multivitamin use were associated with an increased risk of dry eye, whereas caffeine use was associated with a decreased risk.[18] A Chinese study based on real-world data found an increased prevalence of dry eye disease among sleep disorder patients, and the use of a sedative-hypnotic might be associated with dry eye development.[29] An update to the Beaver Dam Eye Study[25] found that additional associated risk factors for dry eye included the use of antihistamines, antidepressant and antianxiety medications, and oral corticosteroids. Angiotensin-converting enzyme inhibitors were associated with a lower risk. Among the 25,665 postmenopausal women in the Women's Health Study, hormone replacement therapy, and, in particular, estrogen use alone was associated with an increased risk of clinically diagnosed dry eye disease or severe symptoms.[30, 31] *(I+, Moderate, Discretionary)* A large community-based study from China found a 17.5% prevalence of dry eye among patients with diabetes (mean age 68.9 ± 8.9 years), particularly those with poor metabolic control.[32]

Dry eye disease is often overlooked in the pediatric population due to its low prevalence, lack of awareness, and limited cooperation of pediatric patients with clinical examination. Clinicians should be aware that pediatric dry eye disease can be associated with several congenital (e.g., alacrima, ectodermal dysplasia, familial dysautonomia), autoimmune (e.g., juvenile rheumatoid arthritis, Sjögren's syndrome), dermatologic (e.g., acne rosacea, Stevens-Johnson syndrome), endocrine, nutritional (e.g., vitamin A deficiency, malabsorption syndromes, severely limited diets), systemic medication (oral isotretinoin therapy for acne vulgaris),[33] and post-infectious (e.g., measles, Epstein-Barr virus) causes. Dry eye can also result from or be exacerbated by environmental causes (e.g., allergy, extended screen time).[34, 35]

PATHOGENESIS

The ocular surface and tear-secreting glands function as an integrated lacrimal functional unit.[36] Disease or dysfunction of this functional unit results in an unstable and poorly maintained tear film that causes ocular irritation symptoms and possible damage to the ocular surface epithelium. Dysfunction may develop as a result of aging, a decrease in supportive factors (such as androgen hormones), blink and/or eyelid abnormalities, systemic inflammatory diseases (e.g., Sjögren's syndrome, autoimmune thyroid disease, or rheumatoid arthritis), ocular surface diseases (e.g., herpes simplex virus [HSV] keratitis), or surgeries that disrupt the trigeminal afferent sensory nerves (e.g., laser-assisted in situ keratomileusis [LASIK], small incision lenticule extraction [SMILE]), and systemic diseases or medications that disrupt the efferent cholinergic nerves that stimulate tear secretion.[37] Decreased tear secretion and clearance initiates an inflammatory response on the ocular surface that involves both soluble and cellular mediators.[38, 39] Clinical and basic research suggests that this inflammation plays a role in the pathogenesis of dry eye (see Figure 1).[40, 41]

In 2017, Zhang et al raised the concept of the ocular surface microenvironment, which is formed by different tissues, cells and matrices, and the ocular surface microbiome; these components work together to maintain the integrity and normal function of the ocular surface.[42] Compromise in one or more components can result in disrupted homeostasis of the ocular surface, leading to dry eye disease. With this hypothesis, successful treatment of dry eye should be aimed at restoring the homeostasis of the ocular surface microenvironment.

In 2017, the International Dry Eye Workshop (DEWS) II published its report by more than 150 dry eye experts and scientists who studied multiple aspects of dry eye disease and clarified the definition of the disease. The effort was initiated by the Tear Film and Ocular Surface Society (TFOS) and obtained unrestricted industry donations.[43]

Participants in DEWS II agreed that two major factors, deficient aqueous tear production and tear film instability, may cause dry eye independently. Those factors may also be present together and both contribute to dry eye symptoms and signs. Recent evidence suggests that tear film instability is more

presentation of dry eye,[21] however, it remains important because it can be associated with underlying systemic inflammatory/autoimmune diseases. Most patients have multiple factors contributing to dry eye. Many conditions, such as neurotrophic keratitis after herpes simplex virus (HSV)/varicella zoster virus (VZV) infection or LASIK, include aspects of decreased tear production and increased evaporative loss.

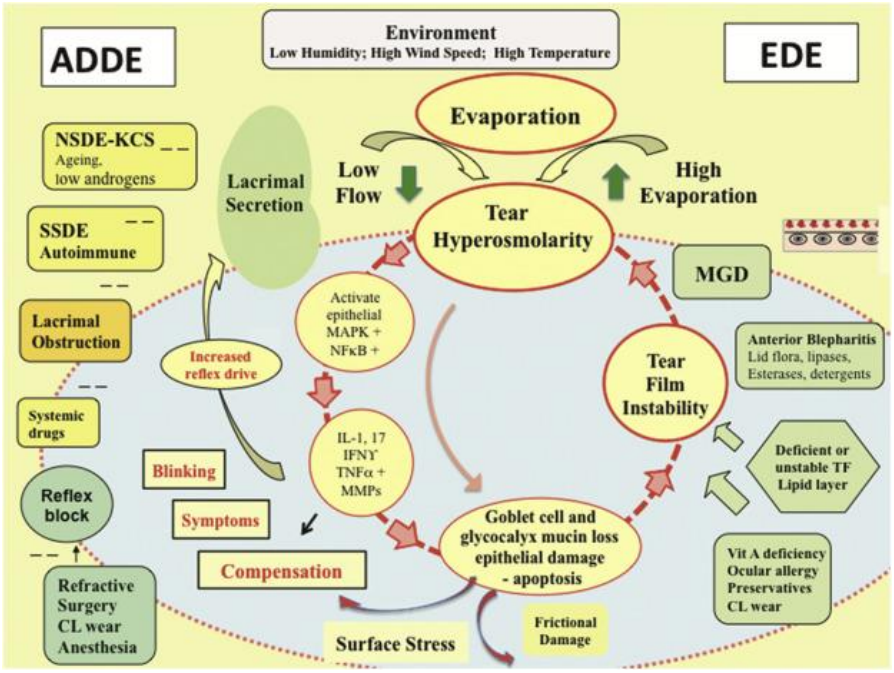

FIGURE 1. INFLAMMATORY MEDIATORS IN DRY EYE
Modified with permission from Craig JP et al. TFOS DEWS II report executive summary. *Ocul Surf*. 2017;15:802-812. ADDE: aqueous deficient dry eye; EDE: evaporative dry eye; NSDE: Non-Sjögren Syndrome Dry Eye; KCS: keratoconjunctivitis sicca; SSDE: Sjögren syndrome dry eye; MGD: meibomian gland disease dysfunction

ASSOCIATED CONDITIONS

Symptoms caused by dry eye may be exacerbated by the use of systemic medications such as diuretics, antihistamines, anticholinergics, antidepressants, and systemic retinoids (e.g., isotretinoin).[18, 19, 25, 27, 44-47] Instillation of any eye medications, especially when they are instilled frequently (e.g., more than four drops a day), may prevent the normal maintenance of the tear film and cause dry eye symptoms secondary to corneal epithelial breakdown from preservatives. In addition, environmental factors, such as reduced humidity and increased wind, drafts, air conditioning, or heating may exacerbate the ocular discomfort of patients with dry eye. Reduced blink rate associated with extensive screen time, reading or driving can worsen dry eye. Exogenous irritants and allergens, although not believed to be causative of dry eye, may also aggravate the symptoms.

Rosacea can exacerbate the symptoms of dry eye and ocular surface disease. Rosacea is a disease of the skin and eye that is observed more frequently in fair-skinned individuals,[48] but it can occur in people of all skin types. Characteristic facial skin findings include erythema, telangiectasia, papules, pustules, prominent sebaceous glands, and rhinophyma. Rosacea may be challenging to diagnose in patients with darker skin tones because it is difficult to visualize telangiectasia or facial flushing[48] and in children, since ocular symptoms can appear before the cutaneous symptoms of rosacea, leading to misdiagnosis.[49, 50] While rosacea is more prevalent in women, it can be more severe when it occurs in men.[51, 52] Because many patients exhibit only mild signs, such as telangiectasia and a history of easy facial flushing, the diagnosis of rosacea is often overlooked, especially in children who may present with ocular findings, such as chronic recurrent blepharokeratoconjunctivitis, punctate erosions, peripheral keratitis, meibomian gland disease, or recurrent chalazia, and who have subtle signs of rosacea prior to cutaneous manifestations.[53] Children with ocular rosacea often present with corneal involvement and asymmetry of ocular disease,[54, 55] and the potential for sight-threatening visual

impairment should be considered. Cutaneous rosacea is less frequent in children, and associated atopy is common.[54, 56] Children with a history of styes have an increased risk of developing adult rosacea.[57]

When there is an associated systemic disease such as Sjögren's syndrome, an inflammatory cellular infiltration of the exocrine glands (including lacrimal gland) leads to saliva- and tear-production deficiency (see Appendix 3). About 10% of patients with clinically significant aqueous deficient dry eye have an underlying primary Sjögren's syndrome.[58, 59] Primary Sjögren's syndrome is a multisystem disorder with increased risk of lymphoma.[60] About 5% of patients with Sjögren syndrome will develop some form of lymphoid malignancy.[61] A meta-analysis found that among rheumatic diseases, primary Sjögren's syndrome is the risk factor most strongly associated with lymphoid malignancy, with an incidence rate of 18.9% (95% CI, 9.4–37.9). This implies an increased incidence of 320 cases per 100,000 patient years.[62] Therefore, ophthalmologists caring for patients with clinically significant dry eye should have a high index of suspicion for Sjögren's syndrome and a low threshold for serological work-up for diagnostic purposes.

Aqueous tear deficiency may develop in other systemic conditions such as lymphoma, sarcoidosis,[63, 64] hemochromatosis, and amyloidosis[65] that result in infiltration of the lacrimal gland and replacement of the secretory acini. Dry eye may develop in patients with systemic viral infections; it has been reported in patients infected by the retroviruses Epstein-Barr virus,[66] human T-cell lymphotropic virus type 1, and human immunodeficiency virus (HIV).[67] Dry eye was diagnosed in 21% of a group of patients with AIDS,[68] and a condition known as diffuse infiltrative lymphadenopathy syndrome has been reported in patients with HIV infection, most of whom were children.[67] Decreased tear secretion and reduced tear concentrations of lactoferrin have been reported in patients with hepatitis C.[69, 70] Lacrimal gland swelling, dry eye, and Sjögren's syndrome have been associated with primary and persistent Epstein-Barr virus infections.[66, 71-73] Severe dry eye has been reported in recipients of hematopoietic stem cell transplants with or without the development of graft-versus-host disease (GVHD).[74, 75] In chronic GVHD, there is infiltration and fibrosis of the lacrimal glands and conjunctiva as a result of T-cell interaction with fibroblasts.[74, 76, 77] Diseases such as ocular mucous membrane pemphigoid and Stevens-Johnson syndrome produce tear deficiency as a result of inflammation, scarring, and destruction of the conjunctival goblet cells. Atopy may produce dry eye that results from blepharitis, conjunctival scarring, or antihistamine use. More generally, since dry eye is known to be most common in postmenopausal women, its occurrence in younger patients and males should be viewed with suspicion of systemic or local associated conditions.

Eyelid conditions associated with dry eye include eyelid malposition, lagophthalmos, exophthalmos, thyroid-associated ocular disease, and blepharitis as well as neuromuscular disorders that affect blinking (e.g., Parkinson disease, Bell's palsy).[78] Orbital/eyelid surgery, radiation, and injury may also lead to dry eye. Incomplete blinking was shown to be associated with a two-fold increase in evaporative dry eye with greater levels of meibomian gland dropout as well as poor meibum quality and decreased tear film lipid-layer thickness.[79]

Increased screen time (e.g., video monitor, television, cellular phones) may reduce blink rate and exacerbate dry eye and ocular surface disease in adults and in children.[80]

NATURAL HISTORY

Dry eye varies in severity, duration, and etiology.[81] In the majority of patients, the condition is not sight-threatening and is characterized by fluctuating vision and troublesome symptoms of irritation that are usually worse at the end of the day. In some individuals, exacerbating factors such as systemic medications that decrease tear production or environmental conditions that increase tear film instability may lead to an acute increase in the severity of symptoms. Elimination of such factors often leads to marked improvement. The disease may exhibit chronicity, characterized by fluctuating severity of symptoms and/or a gradual increase in symptom severity with time.

Reversible conjunctival squamous metaplasia and punctate epithelial erosions of the conjunctiva and cornea, diagnosed by performing ocular surface dye staining, develop in many patients who have clinically significant dry eye. Patients with severe dry eye and underlying inflammatory systemic conditions may develop complications such as ocular surface keratinization, conjunctival fibrosis/cicatricial changes, limbal stem cell deficiency, corneal scarring, thinning, neovascularization and microbial or sterile corneal ulceration with possible perforation, and severe visual loss.[82]

CARE PROCESS

PATIENT OUTCOME CRITERIA

Outcome criteria for treating dry eye include the following:

- Reduce or alleviate signs and symptoms of dry eye, such as ocular irritation, redness, or mucous discharge
- Maintain or improve visual function
- Reduce or prevent ocular surface damage

DIAGNOSIS

Many ocular surface diseases produce symptoms that are similar to those associated with dry eye, including foreign body sensation, mild itching, irritation, and soreness. Identifying characteristics of the causative factors, such as adverse environments (e.g., air travel, low humidity, air drafts from fans or an air conditioner vent, ill-fitted sleep apnea devices), prolonged visual efforts (e.g., reading, digital devices), or symptomatic relief with the use of artificial tears is helpful in diagnosing dry eye. Supporting clinical observations and tests are used to confirm the diagnosis. A diagnostic classification scheme is shown in Figure 2.

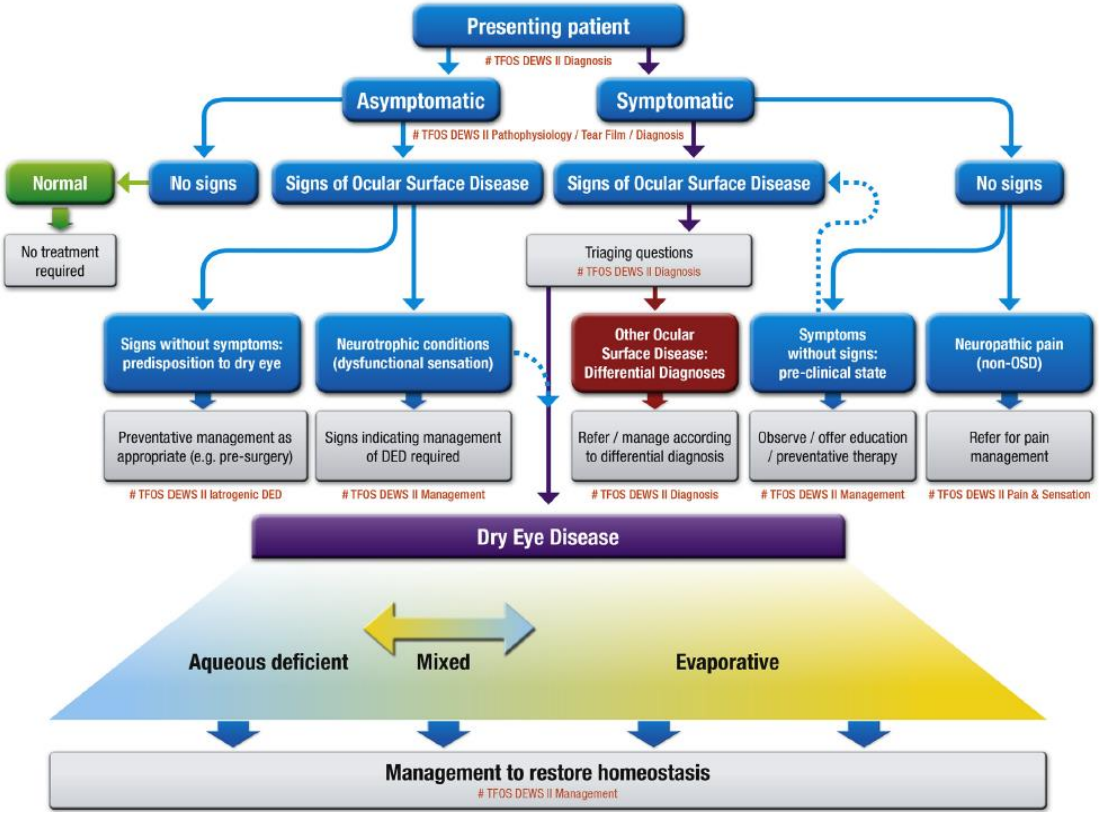

FIGURE 2. CLASSIFICATION OF DRY EYE DISEASE

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DED = dry eye disease (also known as dry eye syndrome); OSD = ocular surface disease.

History

The following elements of the patient history may be helpful:

- Symptoms and signs (e.g., irritation, tearing, burning, stinging, dry or foreign body sensation, mild itching, photophobia, blurry vision, contact lens intolerance, redness, mucous discharge, increased frequency of blinking, eye fatigue, diurnal fluctuation, symptoms that worsen later in the day)
- Exacerbating conditions (e.g., air travel, decreased humidity, fans, prolonged visual efforts associated with decreased blink rate such as reading and digital devices, poorly fitted sleep apnea devices)
- Duration of symptoms

There are several validated representative questionnaires that may be useful in completing the patient history, including the following[50, 83]:

The NEI-VFQ25: This questionnaire was created by the National Eye Institute (NEI) to assess the effect of visual impairment on the patient's current health-related quality of life and includes questions dealing with irritation in and around the eye.[84, 85]

Ocular Surface Disease Index (OSDI): The questionnaire has three subscales: ocular symptoms, vision-related function, and environmental triggers. The OSDI has demonstrated good specificity (0.83) and a moderate sensitivity (0.60) when distinguishing between patients with dry eye syndrome and normal subjects.[86]

Standard Patient Evaluation of Eye Dryness Questionnaire (SPEED): The questionnaire was designed to track progression of dry eye syndrome over time. Validity of this questionnaire was determined by seeing how well it was able to segregate patients based on their symptoms relative to the OSDI questionnaire. The resulting sensitivity and specificity were 0.90 and 0.80, respectively.[87]

The ocular history may include recording information about the following:

- Topical medications and their associated preservatives (e.g., artificial tears, eyewash, antihistamines, glaucoma medications, vasoconstrictors, corticosteroids, antiviral medications, homeopathic or herbal preparations), which should be discussed and considered
- Contact lens history
- Allergic conjunctivitis
- Ocular surgical history (e.g., prior keratopl: asty, cataract surgery, keratorefractive surgery)
- Ocular surface disease (e.g., HSV, VZV, ocular mucous membrane pemphigoid, aniridia)
- Eyelid surgery (e.g., punctal cautery, prior ptosis repair, blepharoplasty, entropion/ectropion repair)
- Bell's palsy, cranial nerve injury
- Eye cosmetic use (e.g., eyeliner, eyelash growth products)

The medical history/review of symptoms may consider the following elements:

- Digital screen use
- Smoking or exposure to second-hand smoke
- Dermatological diseases (e.g., rosacea, psoriasis, varicella zoster virus)
- Technique and frequency of facial washing, including eyelid and eyelash hygiene
- Seasonal allergies/atopy
- Systemic inflammatory diseases (e.g., Sjögren's syndrome, GVHD, rheumatoid arthritis, systemic lupus erythematosus, Stevens-Johnson syndrome, sarcoidosis, scleroderma)
- Other systemic conditions (e.g., lymphoma, sarcoidosis)
- Systemic medications (e.g., antihistamines, diuretics, hormones and hormonal antagonists, antidepressants, cardiac antiarrhythmic drugs, isotretinoin, diphenoxylate/atropine, beta-adrenergic antagonists, chemotherapy agents, dupilumab, any other drug with anticholinergic effects)

- Trauma (e.g., mechanical, chemical, thermal)
- Chronic viral infections (e.g., hepatitis C, HIV)
- Nonocular surgery (e.g., bone-marrow transplant, head and neck surgery, trigeminal neuralgia surgery)
- Orbital radiation
- Neurological conditions (e.g., Parkinson disease, Bell's palsy, Riley-Day syndrome, trigeminal neuralgia)
- Diet/nutrition (e.g., vitamin A deficiency, severely limited diet in patients with autism spectrum disorder)[88]
- Gastrointestinal surgical history (e.g., gastric bypass, pancreatic surgery)[89]
- Nonocular symptoms:
  - Dry mouth, dental cavities, oral ulcers
  - Fatigue
  - Joint pain/muscle ache
  - Menopause

Examination

All patients should have a comprehensive medical eye evaluation and follow-up at the recommended intervals.[90] This should include the evaluation of tear film and the ocular surface, particularly in preoperative cataract and refractive surgery patients. Additional evaluation of a patient who presents with symptoms suggestive of dry eye should include further testing relevant to dry eye.[90]

The external examination and slit-lamp biomicroscopy are used to document the signs of dry eye; assess the quality, quantity, and stability of the tear film; and determine other causes of ocular irritation.

The external examination may include the following:

- Skin (e.g., scleroderma, facial changes consistent with rosacea, seborrhea)
- Eyelids: incomplete closure/malposition, incomplete or infrequent blink, eyelid lag or retraction, erythema of eyelid margins, abnormal deposits or secretions, entropion, ectropion, blepharospasm. Eyelid eversion is needed to evaluate the status of tarsal conjunctiva (e.g., inflammation, signs of allergy, fibrosis)
- Adnexa: enlargement of the lacrimal glands
- Proptosis
- Cranial nerve function
- Hands: joint deformities (e.g., ulnar deviation of the fingers) characteristic of rheumatoid arthritis, Raynaud phenomenon, splinter hemorrhages underneath the nails

The slit-lamp biomicroscopy evaluation should focus on the following:

- Tear film: height of the meniscus along the inferior eyelid, debris, increased viscosity, mucous strands, foamy discharge on the lid margin, tear break-up time and pattern
- Eyelashes: trichiasis, distichiasis, madarosis, collarettes, deposits
- Anterior and posterior eyelid margins: abnormalities of meibomian glands (e.g., orifice metaplasia, reduced expressible meibum, atrophy), character of meibomian gland secretions (e.g., turbid, thickened, foamy, deficient), vascularization crossing the mucocutaneous junction, keratinization, scarring, eyelid margin hyperemia
- Puncta: patency and position, presence and position of plugs
- Conjunctiva:
  - Inferior fornix and tarsal conjunctiva (e.g., mucous threads, scarring, erythema, papillary reaction, follicle enlargement, keratinization, subepithelial fibrosis, foreshortening, symblepharon)
  - Bulbar conjunctiva (all four quadrants) (e.g., punctate staining with fluorescein, lissamine green, and/or rose bengal dyes; hyperemia; conjunctivochalasis; localized drying; keratinization, chemosis, chalasis, follicles). Lissamine green staining of conjunctiva may aid in early diagnosis in Sjögren's syndrome.

- Cornea: localized interpalpebral drying, punctate epithelial erosions assessed with fluorescein dye, punctate staining with rose bengal or fluorescein dyes, filaments, epithelial defects, basement membrane irregularities, mucous plaques, keratinization, pannus formation, thinning, infiltrates, ulceration, scarring, neovascularization, evidence of corneal or refractive surgery

Diagnostic Tests

A detailed review of systems should be performed for any patient who has clinically significant dry eye. Diagnostic testing is based on the review of systems and other clinical findings suggestive of dry eye.

Table 1 lists characteristic findings for each diagnostic test for each condition. For more details see Appendix 5.

TABLE 1 CHARACTERISTIC FINDINGS FOR DRY EYE SYNDROME DIAGNOSTIC TESTS

Test	Characteristic Findings
Aqueous tear production (Schirmer test)	Schirmer I test (without anesthesia), measures both basic and reflex tearing. Less than 5.5 mm of wetting after 5 minutes is diagnostic of aqueous tear deficiency. Schirmer II test (with anesthesia) measures reflex secretion by stimulating nasal mucosa with cotton-tip applicator. Wetting of less than 15 mm after 2 minutes is considered abnormal. (See Appendix 5 for additional information.)
Fluorescein dye disappearance test/tear function index	Test result is compared with a standard color scale.[91]
Fluorescein tear break-up time	Less than 10 seconds is considered abnormal.
Ocular surface dye staining (example: fluorescein, lissamine, rose bengal)	Staining of inferior cornea and bulbar conjunctiva within the palpebral fissure is typical.
Lacrimal gland function	Indicates decreased tear lactoferrin concentration.
Tear osmolarity	Elevated; test-to-test variability; differences between the eyes are considered abnormal.[92-95]
Matrix metalloproteinase-9	Indicates presence of inflammation.

A rapid tear break-up time may indicate an unstable tear film with normal aqueous tear production, and there may be minimal or no dye staining of the ocular surface.[96] Corneal sensation should be assessed when trigeminal nerve dysfunction is suspected.[97]

The workup for ocular surface disease may include one or more of the following tests: tear osmolarity, point of care matrix metalloproteinase-9, Schirmer with or without anesthesia, fluorescein dye disappearance, tear break-up time, ocular surface dye staining (with rose bengal, fluorescein, and/or lissamine green), meibomian gland expressibility, and lacrimal gland function.

The instability of the tear film may be confirmed with an FDA-approved commercial device that measures tear osmolarity.[98] Several studies using this device have demonstrated tear hyperosmolarity and/or significant osmolarity differences between the eyes in patients with aqueous tear deficiency or evaporative dry eye.[92, 93] Tear film osmolarity levels may show variable association with clinical signs or symptoms, making the results of this test occasionally difficult to interpret.[94, 95] Rather than relying solely on a single measure of tear osmolarity, correlation with clinical findings or differences in osmolarity over time or under different conditions is more informative for confirming the diagnosis of dry eye. More recent studies confirm that normal subjects have exceptionally stable tear film osmolarity, whereas tear osmolarity values in dry eye subjects become unstable quickly and lose homeostasis with environmental changes.[98] These data reinforce the long-held belief that the increased evaporation of tears resulting in hyperosmolarity (i.e., evaporative dry eye) is a core mechanism of tear film instability.

A commercially available point-of-care matrix metalloproteinase-9 test can be used as an aid in the diagnosis of dry eye. The binary nature of this test can be used to assess change in the disease state. Although the test does not differentiate dry eye from other inflammatory ocular surface diseases, it may aid in the management.[99]

A laboratory and clinical evaluation for autoimmune disorders should be considered for patients with significant dry eye accompanied by other signs and symptoms of an autoimmune disorder (e.g., dry mouth) or a family history of an autoimmune disorder. Table 2 summarizes the diagnostic tests ordered for possible underlying systemic conditions in patients with dry eye.

TABLE 2 DIAGNOSTIC TESTS ORDERED FOR POSSIBLE UNDERLYING SYSTEMIC CONDITIONS IN PATIENTS WITH DRY EYE

Suspected Underlying Condition	Diagnostic Testing
Sjögren's syndrome	SSA, SSB, ANA, RF, SP1, CA6, PSP
Thyroid eye disease	Antithyroid peroxidase antibody, antithyroglobulin antibody, orbital imaging (CT or MRI scan)
Sarcoidosis	Serum lysozyme, ACE, chest CT to determine extent of disease (consult with a pulmonologist as necessary), conjunctival biopsy[100]
Ocular mucous membrane pemphigoid	Conjunctival biopsy with light microscopic as well as immunofluorescent or immunohistochemical studies

ACE = angiotensin-converting enzyme; ANA = antinuclear antibody; CA6 = carbonic anhydrase 6; CT = computed tomography; PSP = parotid secretory protein; RF = rheumatoid factor; SP1 = salivary protein 1; SSA = anti-Sjögren syndrome A antibody (anti-Ro); SSB = anti-Sjögren syndrome B antibody (anti-La)

A high degree of suspicion for Sjögren's syndrome is appropriate in patients who have clinically significant dry eye and dry mouth symptoms. For patients who are suspected of having a Sjögren's syndrome, a serological examination for anti-Sjögren syndrome A antibody (SSA or anti-Ro), anti-Sjögren syndrome B antibody (SSB or anti-La), rheumatoid factor, and antinuclear antibody should be ordered. A point-of-care test is available that includes the traditional serology as well as additional biomarkers (salivary protein 1 [SP1], carbonic anhydrase 6 [CA6] and parotid secretory protein [PSP]) for Sjögren's syndrome. Additional studies are needed to determine if these biomarkers, especially CA6, are indicators of early Sjögren's syndrome or another form of autoimmune dry eye disease.[101] Patients who might have thyroid eye disease should be tested for antithyroid peroxidase antibody and antithyroglobulin antibody. Orbital imaging, such as a CT or MRI scans, can be used to assess extraocular muscle thickening in patients who have thyroid disease. Conjunctival biopsy is appropriate for any patients who have significant chronic conjunctivitis with a nodular appearance or cicatrization (subepithelial fibrosis or fornix foreshortening).

In recent years, new imaging devices have been introduced as automated and noncontact methods for evaluating the health of the ocular surface. One of these devices is a placido-ring corneal topographer and a color camera that can image the meibomian glands (meibography) as well as evaluate tear film break-up time, the tear meniscus height, and the lipid layer. Another commercially available device operates on the principle of white light interferometry and provides an interferometry color assessment of the tear film by specular reflection. It also captures blink dynamics (complete vs. incomplete blinks).

CLASSIFICATION OF DRY EYE SYNDROME

Dry eye is generally classified according to a combination of symptoms and signs. In this PPP, dry eye is classified as mild, moderate, and severe based on both symptoms and signs, but with an emphasis on symptoms over signs.[102] Owing to the nature of dry eye syndrome, this classification is imprecise because characteristics at each level overlap.

Patients with mild dry eye syndrome may have symptoms of irritation, itching, soreness, ocular discomfort, burning, or intermittent blurred vision. The diagnosis of dry eye in its mild form is difficult to make because of the inconsistent correlation between reported symptoms and clinical

signs.[103] Patients can identify ocular dysesthesia related to contact lens wear or other causes as dryness, even when tear function is normal.[104, 105] More-effective relief of patient symptoms can be achieved if the ophthalmologist can differentiate conditions related to dry eye from other causes. Because most dry eye conditions have a chronic course, repeated observation and reporting of symptoms over time will allow clinical diagnosis of dry eye in most cases.

Patients with moderate dry eye syndrome have increased discomfort and frequency of symptoms, and the negative effect on visual function may become more consistent. Patients with severe dry eye syndrome have an increasing frequency of visual symptoms that may become constant as well as potentially disabling.

Dry eye syndrome is also categorized into one of two forms, aqueous tear deficiency and evaporative, or the mixture of these two types. These conditions coexist in the majority of patients with the disease.

MANAGEMENT

Patients with dry eye symptoms often have many contributory factors. It is imperative to treat any causative factors that are amenable to treatment. Tear replacement is frequently unsuccessful when used as the sole treatment if additional causative factors are not concomitantly addressed.

Patient education is a critically important aspect of successful management of this condition. The ophthalmologist should educate the patient about the natural history and chronic nature of dry eye. Realistic expectations for therapeutic goals should be set and discussed with the patient.

Table 3 lists a staged approach to treating dry eye syndrome. Specific therapies may be chosen from any category regardless of the level of disease severity, depending on physician experience and patient preference.

TABLE 3 STAGED MANAGEMENT AND TREATMENT RECOMMENDATIONS FOR DRY EYE SYNDROME[*†‡]

Step 1

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

Step 2

If the above options are inadequate consider:

- Nonpreserved ocular lubricants to minimize preservative-induced toxicity
- Tea tree oil or lotilaner drop treatment for *Demodex* (if present), also off-label use of ivermectin 1% cream for *Demodex*
- Tear conservation
  - Punctal occlusion
  - Moisture chamber spectacles/goggles
- Overnight treatments (such as ointment or moisture chamber devices)
- In-office, physical heating and expression of the meibomian glands (including thermal pulsation devices)
- Prescription drugs to manage DED[§]
  - Topical antibiotic or corticosteroid applied to the lid margins short-term for anterior blepharitis (if present)
  - Topical corticosteroid (limited duration)
  - Topical secretagogues
  - Topical nonglucocorticoid immunomodulatory drugs (such as cyclosporine)
  - Topical LFA-1 antagonist drugs (such as lifitegrast)
  - Topical water-free lipophilic liquid (perfluorohexyloctane)
  - Nasal spray (such as varenicline), cholinergic neuroactivation via the trigeminal parasympathetic pathway
  - Oral macrolide or tetracycline antibiotics

TABLE 3 STAGED MANAGEMENT AND TREATMENT RECOMMENDATIONS FOR DRY EYE SYNDROME*†‡

Step 3

If the above options are inadequate consider:

- Oral secretagogues
- Autologous/allogeneic serum eye drops
- Platelet-rich plasma eye drops
- Blood based products
- Therapeutic contact lens options
  - Soft bandage lenses with caution
  - Rigid scleral lenses

Step 4

If the above options are inadequate consider:

- Topical corticosteroid for longer duration
- Amniotic membrane grafts
- Surgical punctal occlusion (punctal cautery)
- Other surgical approaches (e.g., tarsorrhaphy, minor salivary gland transplantation)

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DED = dry eye disease; LFA-a = lymphocyte function–associated antigen 1; MGD = meibomian gland dysfunction.

* Potential variations within the disease spectrum are acknowledged to exist between patients and the management options listed above are not intended to be exclusive. The severity and etiology of the DED state will dictate the range and number of management options selected from one or more steps.

† One or more options concurrently within each category can be considered within that step of the dry eye disease state. Options within a category are not ranked according to importance and may be equally valid.

‡ It should be noted that the evidence available to support the various management options differs and will inevitably be lower for newer management options. Thus, each treatment option should be considered in accordance with the level of evidence available at the time management is instigated.

§ The use of prescription drugs needs to be considered in the context of the individual patient presentation, and the relative level of evidence supporting their use for those specific indications, as this group of agents differs widely in mechanism of action.

Mild Dry Eye

Because of the inconsistent correlation between reported symptoms and clinical signs[103] as well as the relatively poor specificity and/or sensitivity of clinical tests,[106, 107] patients with suggestive symptoms without signs should be placed on trial treatments with artificial tears when other potential causes of ocular irritation have been eliminated. For patients with a clinical diagnosis of mild dry eye, potentially exacerbating exogenous factors such as antihistamine or diuretic use, cigarette smoking and exposure to second-hand smoke, and environmental factors such as air drafts and low-humidity environments should be addressed. Cigarette smoking has been found to be associated with dry eye because of the adverse effects on the lipid layer of the precorneal tear film and tear proteins.[108, 109] Humidifying ambient air and avoiding air drafts by using side shields on spectacles and by changing the characteristics of airflow at work, at home, and in the car may be helpful. Measures such as lowering the computer screen to below eye level to decrease eyelid aperture,[110] scheduling regular breaks, and increasing efforts to consciously blink fully and wearing moisture chamber goggles[111] may decrease the discomfort associated with computer and reading activities.[112]

As the severity of the dry eye increases, aqueous enhancement of the eye using topical agents is appropriate. Emulsions, gels, and ointments can be used. In general, the thicker the agent, the longer lasting the effect, which may reduce the number of applications. However, due to increased viscosity, these agents may have more tendency to blur vision. The use of artificial tears may be increased, but the practicality of frequent tear instillation depends on the lifestyle and manual dexterity of the patient. Tear substitutes with preservatives may be sufficient for patients with mild dry eye and an otherwise healthy ocular surface. When tear substitutes are

used frequently and chronically (e.g., more than four times a day), nonpreserved tear substitutes are generally recommended. A systematic literature review found that artificial tears are safe and an effective modality for treating dry eye.[113] The literature indicated that most artificial tears may have comparable efficacies, but the authors cautioned that there were significant inconsistencies in study designs and reporting trial results.

Contributing ocular factors such as blepharitis or meibomitis should also be treated (see Blepharitis PPP[50]). Eyelid abnormalities resulting from blepharitis,[50] trichiasis, or eyelid malposition (e.g., lagophthalmos, entropion/ectropion) should be corrected.

Moderate Dry Eye

In addition to the treatments for mild dry eye, the following medications, surgical procedures, and other treatments may be helpful for moderate dry eye. Anti-inflammatory therapies may be considered in addition to aqueous enhancement therapies. Cyclosporine is a fungus-derived peptide that prevents activation and nuclear translocation of cytoplasmic transcription factors that are required for T-cell activation and inflammatory cytokine production. It also inhibits mitochondrial pathways of apoptosis. In one study, topical cyclosporine 0.05% demonstrated a statistically significant 10-mm increase in Schirmer test results compared with vehicle at 6 months for those patients whose tear production was presumed to be decreased because of ocular inflammation.[114] This effect was noted in 15% of cyclosporine-treated patients compared with 5% of vehicle-treated patients. Although the drop is typically well tolerated, ocular burning was reported in 17% of the patients.[115] A subsequent small study demonstrated the efficacy of cyclosporine 0.05% in the treatment of dry eye in patients who had undergone punctal occlusion.[116] Another study evaluated the efficacy of topical cyclosporine 0.05% in patients with mild, moderate, and severe dry eyes. The authors demonstrated success in 74%, 72%, and 67% of patients, respectively.[117] The dose can be decreased to once a day in a portion of the patients after 1 full year of twice-daily therapy without a decrease in beneficial effects.[118] A retrospective, small-scale, clinical study reported prolonged improvement of dry eye signs but not symptoms after a median 23 (7–51) months of topical cyclosporine lasting for a median of 20 (8–41) months.[4, 5] Topical cyclosporine may be a disease-modifying agent for dry eye syndrome.[119-124] In 2019, a Cochrane review analyzed results of 30 randomized controlled trials (4,009 participants) with an average follow-up of 6 weeks to 12 months. The review concluded that the evidence is inconsistent about the effects of topical cyclosporine on ocular discomfort, ocular surface and tear film parameters such as fluorescein staining, Schirmer test, and TBUT. The study also concluded that cyclosporine may increase the number of goblet cells of the conjunctiva; however, evidence is lacking that this translates into improvement of conjunctival mucus production. A well-planned, long-term, large clinical trial is needed to better assess the effects of topical cyclosporine as a possible disease-modifying agent.[125]

In 2016, the FDA approved lifitegrast ophthalmic solution 5% for treatment of signs and symptoms of dry eye syndrome. The exact mechanism of action of lifitegrast in the treatment of dry eye is unknown. It is theorized that the mechanism involves blocking the interaction between lymphocyte function-associated antigen 1 (LFA-1) and its ligand intracellular adhesion molecule 1 (ICAM-1); ICAM-1, which is upregulated in dry eye,[126] binds to LFA-1, a surface protein found on lymphocytes. This interaction contributes to the formation of an immunologic synapse that results in T-cell activation and migration to target tissues. Topical lifitegrast 5% was approved by the FDA for treatment of dry eye. Published studies show benefit in signs (corneal and conjunctival staining) and/or symptoms (eye dryness score and ocular discomfort) over a period of 3 months of using lifitegrast.[127-129] Although, the drug seems to be safe over 12 months, long-term effects are unknown.[130]

Corticosteroids have been reported to decrease ocular irritation symptoms, decrease corneal fluorescein staining, and improve filamentary keratitis.[131-133] In one study, a 2-week pretreatment of patients with a topical nonpreserved corticosteroid before punctal occlusion was reported to reduce ocular irritation symptoms and corneal fluorescein staining.[134] Commercially available loteprednol etabonate 0.25% was used in a prospective randomized study, and over a 2-week period of use there was a beneficial effect in patients' symptoms and conjunctival hyperemia findings but not in ocular surface staining, Schirmer test results, or use of artificial tears. Extending the treatment to 4 weeks did not show any further beneficial effects or increase in side-effect profile.[131] Low-dose topical corticosteroid therapy can be used at infrequent intervals

for short periods of time (i.e., several weeks) to suppress ocular surface inflammation. Patients who have been prescribed topical corticosteroids for dry eye should be monitored for adverse effects such as increased intraocular pressure and cataract formation.[135]

Use of oral fatty acid supplements for dry eye treatment has been previously reported[136, 137] to be potentially beneficial.[138, 139] However, a large-scale, masked, prospective study found no benefit of oral fatty acids supplements over 12 months compared with placebo in moderate to severe dry eye patients.[140-142] *(I-, Moderate, Discretionary)* There have been other reports of some improvement in patients with blepharitis when omega-3 supplements were used as adjunctive therapy.[143, 144] *(I+, Moderate, Discretionary)* An important obstacle in conducting high-quality trials of these supplements is the lack of standardization in the various formulations in a largely unregulated industry. The association between the use of long-chain omega-3 supplements and risk of prostate cancer remains unclear. Two meta-analyses concluded that there is no evidence that consuming these supplements affects the risk of prostate cancer.[145, 146]

A new aqueous nasal spray containing a highly selective nicotinic acetylcholine receptor agonist, varenicline, has been FDA approved for treatment of signs and symptoms of dry eye syndrome. Varenicline works as a neuroactivator of tear film production. Nicotinic acetylcholine receptors (nAChRs) are present on the trigeminal nerve within the nasal mucosa and can mediate afferent signals in response to nasal stimuli, activating nAChRs that stimulate the lacrimal functional unit. A randomized, phase-3 trial showed that the varenicline nasal spray was well tolerated and showed a clinically meaningful effect on signs and symptoms of dry eye syndrome.[147]

A novel, nonaqueous, single-entity, preservative-free ophthalmic drop consisting of perfluorohexyloctane (an anhydrous, semifluoreinated alkane) has recently obtained FDA approval for the management of signs and symptoms of dry eye. In a randomized, multicenter, double-masked phase-3 trial, perfluorohexyloctane ophthalmic drops demonstrated statistically significant clinical improvements versus hypotonic saline in patients with dry eye secondary to meibomian gland dysfunction.[148] In another multicenter randomized clinical trial, 312 Chinese patients were randomized to receive either perfluorohexyloctane or 0.6% NaCl drops four times daily for 2 months. This study demonstrated that perfluorohexyloctane eye drops significantly improved signs and symptoms of dry eye syndrome secondary to meibomian gland dysfunction.[149]

For patients with aqueous tear deficiency, punctal occlusion is considered when the medical means of aqueous enhancement are ineffective or impractical. Punctal plugs are best used once tear homeostasis is achieved. A Cochrane Collaboration review found limited evidence in seven randomized controlled trials that silicone plugs may provide symptomatic relief in patients with severe dry eye.[150] *(I-, Insufficient, Discretionary)* Punctal occlusion can be accomplished with materials such as silicone, collagen, or thermal labile polymer plugs that are lodged in the punctal orifice. The effectiveness of increasing the lower tear meniscus was similar with upper or lower tear duct occlusion.[151] Silicone plugs placed in the punctum have been shown to improve dry eye signs and symptoms and they may be retained for many years without complications, provided they are appropriately sized. The largest plug that can be inserted should be used to reduce the likelihood of extrusion.[150] *(I-, Insufficient, Discretionary)* In some patients they may irritate the conjunctival surface because of their shape and positioning.[152-154] Silicone plugs have the advantage of being removable if the patient develops irritation or symptoms of epiphora. One study found that 56% of silicone plugs were retained after 2 years, but in those patients whose plugs were spontaneously lost, 34% were reported to have canalicular stenosis at 2 years.[155] Patients who benefit from having punctal plugs in place but spontaneously lose them may have the lost plug(s) replaced or undergo permanent closure of their punctum by thermal cautery or alternative means. Punctal plugs that are displaced into the lacrimal system may pass through the entire system, but blockage with secondary infection has been reported.[156, 157] Surgical removal is rarely necessary. Thermal labile polymer plugs are placed intracanalicularly, and they have the advantage of not irritating the ocular surface. However, they have been associated with the occurrence of epiphora, canaliculitis, dacryocystitis, and keratitis.[156, 158] There is a debate on the utility of punctal plugs, whether they should be used in patients with concomitant inflammatory ocular diseases, such as rosacea conjunctivitis and/or allergic conjunctivitis.

Eyeglass side shields and moisture chambers are noninvasive therapies that can be used. These types of eyeglasses are frequently worn by motorcyclists and mountain climbers and can be

purchased at stores or online. Slow-release hydroxypropyl cellulose inserts are occasionally helpful for patients who are unable to apply artificial tears.[159, 160] Other available therapies,[161] including labial/buccal mucous membrane and minor salivary gland transplantations, have shown good results in patients with SJS and ocular cicatricial pemphigoid.[162, 163]

Severe Dry Eye

In addition to the treatments for mild and moderate dry eye, the following treatments may be considered for severe dry eye.

Permanent punctal occlusion can be accomplished by means of thermal or laser cautery. In general, laser cautery is not as effective as thermal cautery in achieving permanent, complete occlusion, and it is more expensive. The main disadvantage of punctal cautery is that it is not readily reversible. If occlusion with cautery is planned, a trial occlusion with nonpermanent implants generally should be performed first to screen for the potential development of epiphora. Silicone punctal plugs are more useful for this purpose. A stepwise approach to cautery occlusion is generally recommended so that no more than one punctum is cauterized in each eye at a treatment session. A limited tarsorrhaphy can be performed to decrease tear film instability in patients with severe dry eye who have not responded to other therapies.[164]

Autologous serum and autologous plasma rich in growth factors drops[165, 166] have been reported to improve ocular irritation symptoms as well as conjunctival and corneal dye staining in patients with Sjögren's syndrome[167, 168] *(I+, Insufficient, Strong)* and GVHD.[169, 170] A systematic review reported a benefit in symptoms with 20% autologous serum compared with artificial tears over 2 weeks.[170] *(I-, Insufficient, Discretionary)* For patients for whom repeated blood sampling is not possible, allogeneic serum eye drops have been shown to be an effective and safe alternative.[171-174]

Filamentary keratitis may be present in patients with severe dry eye syndrome and can be treated by debriding the filaments with a moistened cotton-tip applicator, dry cellulose sponge, or forceps. Applying topical mucolytic agents, such as N-acetylcysteine 10% can decrease the viscosity of the mucinous tear film. Soft contact lenses are effective in preventing recurrence of filamentary keratitis but may be poorly tolerated if the patient has severe dry eye. If the patient has associated neurotrophic keratopathy, contact lenses should be used with caution owing to risk of infection. The insertion of a self-retaining or sutureless amniotic membrane in refractory cases should be considered but with recognition of the short-term effect.

Rigid gas-permeable scleral lenses have been used successfully in the treatment of severe dry eye for years.[175-177] Use of scleral lenses[178] may be limited by fitting difficulties (particularly in the presence of conjunctival cicatrization), cost, and patient willingness and ability to manage lens insertion and removal. Soft contact lenses may provide symptomatic relief in selected cases. The additional risk of infection, particularly with extended wear of soft lenses, must be considered.

Oral medications are available to treat severe dry eyes, especially for patients with combined dry eye and dry mouth (Sjögren's syndrome).[179-182] *(I-, Moderate, Discretionary)* Cholinergic agonists such as cevimeline have been approved by the FDA to treat the symptoms of dry mouth in patients with Sjögren's syndrome. Cevimeline has been found to improve ocular irritation symptoms and aqueous tear production.[181] Cevimeline may have fewer adverse systemic side effects than oral pilocarpine. These medications bind to muscarinic receptors, which stimulate secretion of the salivary and sweat glands, and they also appear to improve tear production. Most clinical studies demonstrate greater improvement in dry mouth than dry eye.[179, 183] Patients treated with pilocarpine at a dose of 5 mg orally four times a day experienced a significantly greater overall improvement in the ability to focus their eyes during reading and in symptoms of blurred vision compared with placebo-treated patients with Sjogren syndrome, although disappointingly, there was no improvement in light sensitivity, ocular discomfort, and other symptoms of dry eye disease.[179] The improvement in visual symptoms may be related to the miosis effect of pilocarpine. The most common side effect from this medication was excessive sweating, which occurred in over 40% of patients. Two percent of the patients taking oral pilocarpine withdrew from the study because of this and other drug-related side effects.

Follow-up Evaluation

The purpose of the follow-up evaluation is to assess the response to therapy as a basis for altering or adjusting treatment as necessary, to monitor for ocular surface damage, and to provide reassurance. The frequency and extent of the follow-up evaluation will depend on the severity of disease, the therapeutic approach, and the response to the therapy. For example, patients with sterile corneal ulceration associated with dry eye may require daily follow-up.

PROVIDER AND SETTING

Because dry eye can be associated with systemic immunological disorders and the use of systemic medications, broad medical skills and training, such as those provided by ophthalmologists, are important for appropriate diagnosis and management. Patients with dry eye syndrome should be evaluated by an ophthalmologist in any of the following circumstances:

- Moderate or severe pain
- Lack of response to the therapy
- Corneal infiltration or ulceration
- Progressive conjunctival scarring
- Vision loss

COUNSELING AND REFERRAL

The most important aspects of caring for patients with dry eye are to educate them about the chronic nature of the disease process and to provide specific instructions for therapeutic regimens. It is helpful to periodically reassess the patient's compliance and understanding of the disease, the benefits of treatment and potential complications, and to re-inform the patient as necessary. The patient and physician together can establish realistic expectations for effective management.

Referral of a patient with dry eye may be necessary, depending on the severity of the condition and its responsiveness to treatment. In moderate to severe cases that are unresponsive to treatment or when systemic disease is suspected, timely referral to an ophthalmologist who is knowledgeable and experienced in the management of these entities is recommended. Referral to an internist or rheumatologist can be considered for patients with systemic immune dysfunction or for those who require immunosuppressive therapy. Patients with systemic disease such as primary Sjögren's syndrome, secondary Sjögren's (associated with a connective-tissue disease), or connective tissue disease such as rheumatoid arthritis should be managed by an appropriate medical specialist. Patient support groups such as the Sjögren's Syndrome Foundation (www.sjogrens.org) may help patients adjust to their condition. Some patients may benefit from professional counseling as an aid in coping with chronic dry eye.

Patients with severe dry eye are at greater risk for contact lens intolerance and associated complications. Patients who have dry eye and are considering keratorefractive surgery, particularly LASIK, should be cautioned that keratorefractive surgery may worsen their dry eye symptoms.[184] Effective treatment for dry eye should be achieved before undergoing keratorefractive surgery.[185] Uncontrolled dry eye syndrome is a contraindication for keratorefractive surgery.[186]

SOCIOECONOMIC CONSIDERATIONS

Dry eye is a common ocular condition that has a prevalence as high as 33% in Japan.[187] In the United States, two large cross-sectional surveys, the Women's Health Study and the Physician's Health Studies, demonstrated that the prevalence of physician-diagnosed dry eye or severe dry eye symptoms was 7.8% in women and 4.3% in men 50 and older.[19, 20] Claims data from a large U.S. managed care database (reflecting only individuals who seek medical care and are diagnosed with dry eye) suggest that the prevalence of clinically diagnosed dry eye is 0.4% to 0.5% over all ages and that it is highest among women and the elderly (65 years and older).[22] A systematic review and meta-analysis concluded that the incidence and prevalence of dry eye and meibomian gland disease in the United States are uncertain and emphasize the importance of future studies with consistent and validated definitions. The study found an incidence of dry eye in young adults of 3.5% and of almost 8% in patients older than 68. No studies reported incidence of meibomian gland disease.[188]

A similar estimate was obtained from the Dry Eye Management Outcomes Simulation.[189] In this study, data from multiple sources were used to estimate medical costs and outcomes of dry eye. The

prevalence in a typical managed care population was estimated at approximately 1%. Of these cases, about 60% are mild in severity, 30% moderate, and 10% severe. Of individuals with mild dry eye, only about 20% seek medical care compared with 50% of those with moderate disease and 100% of those with severe disease. This suggests that approximately 0.4% of individuals in a typical managed care population seek medical care for and are diagnosed with dry eye.

Dry eye causes considerable burden to the patient as well as the society. Studies suggest that dry eye is associated with significant impact on visual function such as reading and driving,[190] daily activities, social and physical functioning, workplace productivity, and quality of life.[191-193] A study of dry eye and quality of life found decreased quality of life for all severity levels of dry eye syndrome, with an effect on quality of life for severe dry eye comparable to that reported for moderate angina.[194] One study of a cohort of dry eye patients found a strong association with anxiety and depression.[195] Several other studies demonstrated a relationship between depression and dry eye symptoms (with or without dry eye signs) independent of the medications used to treat depression.[196, 197] Other research suggests that patients with dry eye are more likely to report pain, limitations of activities of daily living, and lower quality of life.[28, 191, 198] In particular, the vision-related quality of life is significantly influenced by dry eye owing to impairment of reading ability.[13-15]

Although scarce, the existing data on the economics of dry eye suggest that the economic impact is substantial. Direct medical costs (e.g., office visits, prescription and over-the-counter medications, specialized eyewear, humidifiers, in-office procedures), direct nonmedical costs (e.g., patient transportation), indirect costs (e.g., lost work time and productivity, changes in type of work), and intangible costs (e.g., reduced quality of life; lost leisure time; impaired social, emotional, and physical functioning) determine the total cost of dry eye to the patient as well as to society.[199, 200] In a study involving 2171 dry eye patients recruited from online databases, both the direct costs (i.e., ocular lubricants, cyclosporine, punctal plugs, physician visits, and nutritional supplements) and the indirect costs (i.e., productivity lost due to absenteeism) of their care were considered. The analysis estimated the average annual cost of treating a patient with dry eye at $783 (with a range of $757 to $809 across sensitivity analyses) and the overall burden of such treatment to the U.S. health care system at $3.84 billion. From the societal perspective, the average annual cost of managing dry eye was estimated at $11,302 per patient and $55.4 billion for U.S. society overall.[201] A study from England reported that, in 2014, over 6.4 million items were prescribed at a cost of over £27 million to society.[202]

Three survey studies found that the impact of dry eye on health care utilization is substantial, particularly in patients with Sjögren's syndrome.[203-205] Various studies reported that dry eye in patients with Sjögren's syndrome in particular interfered with work an average of 184 to 200 days per year. It also caused 2 to 5 days of absenteeism per year,[203, 205, 206] with an estimated productivity loss of more than $5,000 per patient per year.

Dry eye is a chronic condition. Several therapies, mostly palliative, have been shown to improve symptoms of dry eye. Although it seems likely that these therapies would also improve quality of life and productivity and reduce overall health care utilization, few clinical studies have assessed patient-reported outcomes (e.g., quality of life), or economic measures, particularly the cost of therapy. Long-term topical treatment for dry eye syndrome is costly, and in the case of tear supplements, this cost is usually not covered by an insurance plan.

APPENDIX 1. QUALITY OF OPHTHALMIC CARE CORE CRITERIA

Providing quality care
is the physician's foremost ethical obligation, and is
the basis of public trust in physicians.
AMA Board of Trustees, 1986

Quality ophthalmic care is provided in a manner and with the skill that is consistent with the best interests of the patient. The discussion that follows characterizes the core elements of such care.

The ophthalmologist is first and foremost a physician. As such, the ophthalmologist demonstrates compassion and concern for the individual, and utilizes the science and art of medicine to help alleviate patient fear and suffering. The ophthalmologist strives to develop and maintain clinical skills at the highest feasible level, consistent with the needs of patients, through training and continuing education. The ophthalmologist evaluates those skills and medical knowledge in relation to the needs of the patient and responds accordingly. The ophthalmologist also ensures that needy patients receive necessary care directly or through referral to appropriate persons and facilities that will provide such care, and he or she supports activities that promote health and prevent disease and disability.

The ophthalmologist recognizes that disease places patients in a disadvantaged, dependent state. The ophthalmologist respects the dignity and integrity of his or her patients and does not exploit their vulnerability.

Quality ophthalmic care has the following optimal attributes, among others.

- The essence of quality care is a meaningful partnership relationship between patient and physician. The ophthalmologist strives to communicate effectively with his or her patients, listening carefully to their needs and concerns. In turn, the ophthalmologist educates his or her patients about the nature and prognosis of their condition and about proper and appropriate therapeutic modalities. This is to ensure their meaningful participation (appropriate to their unique physical, intellectual and emotional state) in decisions affecting their management and care, to improve their motivation and compliance with the agreed plan of treatment, and to help alleviate their fears and concerns.
- The ophthalmologist uses his or her best judgment in choosing and timing appropriate diagnostic and therapeutic modalities as well as the frequency of evaluation and follow-up, with due regard to the urgency and nature of the patient's condition and unique needs and desires.
- The ophthalmologist carries out only those procedures for which he or she is adequately trained, experienced and competent, or, when necessary, is assisted by someone who is, depending on the urgency of the problem and availability and accessibility of alternative providers.
- Patients are assured access to, and continuity of, needed and appropriate ophthalmic care, which can be described as follows.
  - The ophthalmologist treats patients with due regard to timeliness, appropriateness, and his or her own ability to provide such care.
  - The operating ophthalmologist makes adequate provision for appropriate pre- and postoperative patient care.
  - When the ophthalmologist is unavailable for his or her patient, he or she provides appropriate alternate ophthalmic care, with adequate mechanisms for informing patients of the existence of such care and procedures for obtaining it.
  - The ophthalmologist refers patients to other ophthalmologists and eye care providers based on the timeliness and appropriateness of such referral, the patient's needs, the competence and qualifications of the person to whom the referral is made, and access and availability.
  - The ophthalmologist seeks appropriate consultation with due regard to the nature of the ocular or other medical or surgical problem. Consultants are suggested for their skill, competence, and accessibility. They receive as complete and accurate an accounting of the problem as necessary to provide efficient and effective advice or intervention, and in turn respond in an adequate and timely manner.
  - The ophthalmologist maintains complete and accurate medical records.

- On appropriate request, the ophthalmologist provides a full and accurate rendering of the patient's records in his or her possession.
- The ophthalmologist reviews the results of consultations and laboratory tests in a timely and effective manner and takes appropriate actions.
- The ophthalmologist and those who assist in providing care identify themselves and their profession.
- For patients whose conditions fail to respond to treatment and for whom further treatment is unavailable, the ophthalmologist provides proper professional support, counseling, rehabilitative and social services, and referral as appropriate and accessible.

- Prior to therapeutic or invasive diagnostic procedures, the ophthalmologist becomes appropriately conversant with the patient's condition by collecting pertinent historical information and performing relevant preoperative examinations. Additionally, he or she enables the patient to reach a fully informed decision by providing an accurate and truthful explanation of the diagnosis; the nature, purpose, risks, benefits, and probability of success of the proposed treatment and of alternative treatment; and the risks and benefits of no treatment.
- The ophthalmologist adopts new technology (e.g., drugs, devices, surgical techniques) in judicious fashion, appropriate to the cost and potential benefit relative to existing alternatives and to its demonstrated safety and efficacy.
- The ophthalmologist enhances the quality of care he or she provides by periodically reviewing and assessing his or her personal performance in relation to established standards, and by revising or altering his or her practices and techniques appropriately.
- The ophthalmologist improves ophthalmic care by communicating to colleagues, through appropriate professional channels, knowledge gained through clinical research and practice. This includes alerting colleagues of instances of unusual or unexpected rates of complications and problems related to new drugs, devices or procedures.
- The ophthalmologist provides care in suitably staffed and equipped facilities adequate to deal with potential ocular and systemic complications requiring immediate attention.
- The ophthalmologist also provides ophthalmic care in a manner that is cost effective without unacceptably compromising accepted standards of quality.

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APPENDIX 2. INTERNATIONAL STATISTICAL CLASSIFICATION OF DISEASES AND RELATED HEALTH PROBLEMS (ICD) CODES

Dry eye includes entities with the following ICD-10 classifications:

	ICD-10 CM
Dry eye, unspecified, right lacrimal gland	H04.121
Dry eye, unspecified, left lacrimal gland	H04.122
Dry eye, unspecified, bilateral lacrimal gland	H04.123
Dry eye, keratoconjunctivitis sicca (not specified as Sjögren)	H16.22-
Dry eye, Sjögren syndrome, sicca syndrome	M35.00
Dry eye, Sjögren syndrome, with keratoconjunctivitis	M35.01
Filamentary keratitis	H16.12-
Exposure keratoconjunctivitis	H16.21-
Punctate keratitis	H1.14-

CM = Clinical Modification used in the United States; ICD = International Classification of Diseases; (–) = 1, right eye; 2, left eye; 3, bilateral

Additional information:

- Certain ICD-10 CM categories have applicable 7th characters. The applicable 7th character is required for all codes within the category, or as the notes in the Tabular List instruct. The 7th character must always be the 7th character in the data field. If a code that requires a 7th character is not 6 characters, a placeholder X must be used to fill in the empty characters.
- For bilateral sites, the final character of the codes in the ICD-10 CM indicates laterality. If no bilateral code is provided and the condition is bilateral, separate codes for both the left and right side should be assigned. Unspecified codes should only be used when there is no other code option available.
- When the diagnosis code specifies laterality, regardless of which digit it is found in (i.e., 4th digit, 5th digit, or 6th digit):
  - Right is always 1
  - Left is always 2
  - Bilateral is always 3

APPENDIX 3. SJÖGREN'S SYNDROME

Sjögren's syndrome is defined as dry eye and dry mouth associated with systemic immune dysfunction. About 10% of patients with clinically significant dry eye have an underlying Sjögren's syndrome.[58, 59] A significant proportion of the patients may not have been diagnosed at the time they present to the ophthalmology clinic with dry eye complaints.

Sjögren's syndrome is characterized by infiltration of the lacrimal and salivary glands with lymphocytes with secondary compromise of gland function. Systemic disease and symptoms may include arthralgia, myalgia, or fatigue. Patients with primary Sjögren's syndrome may also have associated thyroid dysfunction or autoimmune thyroiditis.[207] Patients with secondary Sjögren's syndrome have a distinct autoimmune disease such as rheumatoid arthritis, scleroderma, or systemic lupus erythematosus. Patients with Sjögren's syndrome, whether they have secondary autoimmune disease or not, should be comanaged with a rheumatologist owing to the many possible comorbid systemic conditions. An epidemiologic study performed in Sweden reported that the prevalence of Sjögren's syndrome is approximately 0.4%.[208] A Greek epidemiologic study reported the annual incidence of Sjögren's syndrome as 5.3 per 100,000 and a prevalence of 92.8 cases per 100,000, with a female-to-male ratio of 20:1.[209] Women are much more commonly diagnosed with Sjögren's syndrome than men.[210, 211] A study in Slovenia estimated the annual incidence of primary Sjögren's syndrome as 3.9 per 100,000.[212] Sjögren's syndrome should be suspected if intrinsic tear-production deficiency is detected in nonelderly women, especially if it is rapid in onset and/or marked in severity. Diagnosis and treatment of underlying systemic immune disorders may decrease morbidity and may even be lifesaving. Patients with dry eye syndrome associated with Sjögren's syndrome may develop other ocular manifestations of immune dysfunction, including scleritis, sterile keratitis, and uveitis. Patients are also at increased risk for potentially life-threatening vasculitic or lymphoproliferative disorders. Studies have shown that patients with decreased C4 levels at the time of diagnosis of Sjögren's syndrome had a higher risk of developing lymphoma.[213, 214]

Defined, objective criteria for diagnosing and classifying Sjögren's syndrome have been proposed. The latest classification criteria are based on the weighted sum of five items: anti-SSA/Ro antibody positivity and focal lymphocytic sialadenitis with a focus score of ≥1 foci/4 mm^2, each scoring 3; an abnormal ocular staining score of ≥5 (or van Bijsterveld score of ≥4), a Schirmer test result of ≤5 mm/5 minutes without anesthesia, and an unstimulated salivary flow rate of ≤0.1 ml/minute, each scoring 1. Individuals with signs and/or symptoms suggestive of Sjögren's syndrome who have a total score of ≥4 for those items meet the criteria for primary Sjögren's syndrome.[215, 216]

A panel of experts, with support from the Sjögren's Syndrome Foundation, also published a set of clinical guidelines on the management of patients with Sjögren-related dry eye as follows. "Evaluation of the patients should include symptoms of both discomfort and visual disturbance as well as determination of the relative contribution of aqueous production deficiency and evaporative loss of tear volume. Objective parameters of tear film stability, tear osmolarity, degree of lid margin disease, and ocular surface damage should be used to stage severity of dry eye syndrome to assist in selecting appropriate treatment options. Patient education about the nature of the problem, aggravating factors, and goals of treatment is critical to successful management. Tear supplementation and stabilization, control of inflammation of the lacrimal glands and ocular surface, and possible stimulation of tear production are treatment options that are used according to the character and severity of dry eye syndrome."[217]

An outcomes-based review of treatment options for patients with dry eye secondary to Sjögren's syndrome has recently been published.[218] Although there was paucity of rigorous clinical trials to support therapy recommendations, topical lubricants, topical anti-inflammatory therapy, and tear-conserving strategies seemed effective. The efficacy of oral secretagogues was greater in the treatment of oral dryness than ocular dryness. Although oral hydroxychloroquine is commonly prescribed to patients with Sjögren's syndrome to alleviate fatigue and arthralgias, the literature did not demonstrate strong evidence for the efficacy of this treatment for dry eye. Another systematic review of controlled trials confirmed benefits for oral secretagogues (pilocarpine and cevimeline) for sicca features (mostly oral) and topical anti-inflammatories (cyclosporine) for moderate or severe dry eye.[219] Anti-tumor necrosis factor agents were not found to be effective, and the evidence for efficacy of rituximab was not strong.

TABLE A3-1 SJÖGREN'S SYNDROME DIAGNOSTIC CRITERIA

European-American Consensus

- Unstimulated salivary flow rate abnormal ≤0.1mL/minute (1 point)
- Abnormal Schirmer test (<5 mm in 5 minutes) (1 point)
- Abnormal findings with lissamine green or fluorescein staining (≥5 in Ocular Staining Score or ≥4 in van Bijsterveld Score) (1 point)
- Autoantibody detection: anti-Ro/SSA (3 points)
- Histology-focal lymphomatic sialadenitis, focus score ≥1 focus/4 mm2, 1 focus = 50 lymphocytes/4 mm2 (3 points)

Diagnosis is considered established if score is ≥4 points, after application of inclusion and exclusion criteria

- Inclusion criteria:
  - Dryness of eyes and/or mouth for at least 3 months, not explained otherwise (e.g., drug related)
- Exclusion criteria:
  - Status following head/neck radiation
  - HIV/AIDS
  - Sarcoidosis
  - Active hepatitis C infection
  - Amyloidosis
  - GVHD
  - IgG4-related disease

APPENDIX 4. NEUROPATHIC OCULAR PAIN

Neuropathic ocular pain (NOP) is caused by a dysfunction of the nerves that travel via the nasociliary branch of the ophthalmic division of the trigeminal nerve (cranial nerve V1) to innervate the ocular surface (peripheral nerves) or by dysfunction in central nerves that connect the ocular surface to the brain (e.g., thalamus, higher cortical areas).[220] Neuropathic ocular pain can develop after ocular surgeries (e.g., refractive surgery, cataract extraction), postinfection (e.g., post-herpetic neuralgia), and as a result of chronic ocular surface abnormalities (e.g., inflammation, aqueous tear deficiency), or it can occur idiopathically.[221] Neuropathic ocular pain can also occur with other pain conditions, such as migraine[222] and fibromyalgia,[223] or after trauma, such as after traumatic brain injury.[224] As with any neuropathic pain state, with NOP, nerves in the trigeminal pathway become hyperexcitable and fire spontaneously, leading to chronic pain that is often described as burning, stinging, or aching. Many individuals also complain of photophobia and wind hyperalgesia.[221, 225]

Identifying a neuropathic contribution to pain can be challenging, because individuals with NOP can also have ocular surface disorders, such as aqueous tear deficiency and meibomian gland dysfunction.[226] Environmental stimuli and tear film abnormalities can trigger the corneal nociceptors, resulting in pain.[227] The first step in the evaluation is a thorough ocular surface and tear parameter examination to evaluate for nociceptive sources of pain, which can include aqueous tear deficiency, tear film instability, inflammation, and epithelial erosions among others.[220, 228, 229] The examination also should include an assessment of patients' symptoms. In general, individuals with NOP have symptoms that outweigh the observed signs of disease. Some questionnaires, like the Neuropathic Pain Symptom Inventory (NPSI)-Eye[230] or the Ocular Pain Assessment Survey (OPAS)[229] have questions about neuropathic pain qualities, such as burning pain or sensitivity to wind and light. Other clues to NOP are ocular symptoms that persist despite appropriate treatment and/or resolution of tear film and ocular surface abnormalities.[220] If a diagnosis of NOP is suspected, the "anesthetic challenge test" can aid in localizing the pain. For the test to be informative, pain must be present before anesthetic placement. If after instilling the anesthetic drop, the patient experiences an improvement in pain, this suggests a nociceptive or peripheral neuropathic component to the pain. If the pain does not improve, it suggests a central or nonocular cause of pain.[221, 231]

Treatment options depend on the location of nerve dysfunction. For peripheral NOP (or corneal neuropathic pain), topical nerve regenerative therapies, like autologous serum tears, can be used.[232, 233] For individuals with a central component to pain, or with systemic comorbidities (e.g., fibromyalgia), oral neuromodulators (e.g., pregabalin, gabapentin, duloxetine, amitriptyline, nortriptyline, low-dose naltrexone)[234] alone or in combination have been used with varying success. In individuals with light sensitivity and headache, adjuvant strategies used for migraine, such as using a transcutaneous electrical nerve stimulation device[235] and periorbital botulinum toxin A injections,[236] can be considered. In individuals with cutaneous allodynia (pain to light touch around eye) or postsurgical pain, periocular nerve blocks consisting of a corticosteroid with a long-acting sodium channel blocker can be used.[234, 237-239] Oftentimes, a combination of approaches is used. All neuromodulators require time to take effect, with about 3 to 4 months at a therapeutic dose, to see a reduction in pain.[234] It is thus crucial to set up expectations early and encourage patients to continue the treatment even if they don't feel immediate relief.

Additionally, patients with NOP often experience concomitant anxiety, depression, and other mood disorders, adding an emotional component to the pain.[240] This is likely caused by the wiring of the corneal nerves to areas of the brain involved in emotional processing, such as the prefrontal cortex, amygdala, and insula, along with the chronic, debilitating nature of the pain.[241] As such, complimentary therapies such as acupuncture, cognitive behavioral therapy, or hypnosis should be considered. Overall, NOP warrants a multidisciplinary approach requiring involvement of multiple specialties (e.g., ophthalmologists, pain specialists, neurologists, and mental health professionals) to manage the condition holistically.[234]

APPENDIX 5. DIAGNOSTIC TESTS

This appendix summarizes the applicability of currently utilized tests to diagnose tear film and ocular surface disorders. These tests include the tear break-up time test to evaluate tear film stability, ocular surface dye staining to evaluate ocular surface disease, the Schirmer test and fluorescein disappearance test to evaluate aqueous tear production and clearance, and the tear osmolarity test.

TEAR BREAK-UP TIME TEST

Tear break-up time is determined by instilling fluorescein dye in the inferior cul-de-sac and then evaluating the stability of the precorneal tear film.[96] The test is performed by moistening a fluorescein strip with sterile nonpreserved saline and applying it to the inferior tarsal conjunctiva. Fluorescein-anesthetic combination drops are not ideal for this purpose, as the anesthetic may affect the result of the test. After several blinks, the tear film is examined using a broad beam of the slit-lamp biomicroscope with a cobalt blue filter. The time lapse between the last blink and the appearance of the first randomly distributed dark discontinuity in the fluorescein-stained tear film is the tear break-up time. The tear break-up time should be evaluated before the instillation of any eyedrops and before the eyelids are manipulated in any way.

Recurrent tear break-up in the same area may indicate localized anterior basement-membrane abnormalities. Break-up times less than 10 seconds are considered abnormal.[96] A rapid tear break-up time is observed in both aqueous tear deficiency and meibomian gland disease.[96]

OCULAR SURFACE DYE STAINING

Fluorescein, rose bengal, or lissamine green dyes may be used to assess the ocular surface.

Fluorescein dye stains areas of the corneal and conjunctival epithelium where there is sufficient disruption of intercellular junctions to allow the dye to permeate into the tissue.[242] A saline-moistened fluorescein strip or topical instillation of a 1% to 2% sodium fluorescein solution is used to stain the tear film. After instilling the dye, the ocular surface is examined through a biomicroscope using a cobalt blue filter. Staining may become more apparent after about 2 minutes, and it is more intense when it is observed with a yellow filter. Mild fluorescein staining can be observed in normal eyes and may be more prominent in the morning. Exposure-zone punctate or blotchy fluorescein staining is observed in dry eye, and staining is more easily visualized on the cornea than on the conjunctiva.

Rose bengal staining of the tear film may be performed using a saline-moistened strip or 1% solution. (Patients should be informed that the drop might irritate the eye, and, therefore, it is typical to use a topical anesthetic prior to instillation.) The saline drop used to moisten the strip should remain in contact with the strip for at least a minute to achieve an adequate concentration of rose bengal to stain the ocular surface. Rose bengal staining is more intense on the conjunctiva than on the cornea. The dye stains ocular surface cells that lack a mucous coating as well as debris in the tear film;[242] the staining may be easier to observe with a red-free filter.

When using lissamine green dye, waiting 1 to 2 minutes lessens the ability to see the staining pattern. It is different from fluorescein, which requires about 2 minutes to highlight the punctate erosions. The lissamine green dye has a staining profile similar to that of rose bengal dye,[243-245] but it causes less ocular irritation.[244, 245] It is not recommended for evaluating corneal epithelial disease. Diffuse corneal and conjunctival staining is commonly seen in viral keratoconjunctivitis and medicamentosa. Staining of the inferior cornea and bulbar conjunctiva is typically observed in patients with staphylococcal blepharitis, meibomian gland disease, lagophthalmos, and exposure, whereas staining of the superior bulbar conjunctiva is typically seen in superior limbic keratoconjunctivitis. A pattern of exposure-zone (interpalpebral) corneal and bulbar conjunctival staining is typically seen with aqueous tear deficiency.[246, 247]

CORNEAL SENSATION TESTING

Corneal sensation is tested prior to any drops being placed in the eye, especially topical anesthetics. Using a cotton tip applicator with the tip twisted to bring the cotton fibers to a fine point, it can be used to test sensation. Unflavored dental floss can also be used. Normal sensation is any touching of the cotton fibers or dental floss that causes sensation. Neurotrophic keratopathy can be grossly graded

by the amount of material needed to cause a sensation. The Cochet-Bonnet aesthesiometer is a device that tests corneal sensation quantitatively by using a nylon filament that can be retracted, creating a stiffer and stiffer filament. The lower the number, the less of the fiber is exposed, indicating decreased corneal sensation.

SCHIRMER TEST

The Schirmer test can be performed to evaluate aqueous tear production, but it is well recognized that it gives variable results and should not be used as the sole criterion for diagnosing dry eye. It is performed by placing a narrow filter-paper strip in the inferior cul-de-sac, usually the temporal one third of the lid. Aqueous tear production is measured by the length in millimeters that the strip wets during the test period, generally 5 minutes.[247] Schirmer testing may be performed with or without the use of topical anesthesia. Schirmer I is classically done without anesthesia. The Schirmer test with anesthesia (Schirmer II), also referred to as a basic secretion test, has been reported to give more variable results than the Schirmer test done without anesthesia. Measurements of less than 3 mm after 5 minutes, with anesthetic, are highly diagnostic of aqueous tear deficient dry eye. Measurements between 3 and 10 mm can be considered equivocal[107, 248, 249] Although no absolute cutoff has been established for this test, less than 10 mm of strip wetting in 5 minutes is suggestive of abnormality in patients tested without anesthesia.[96] A Schirmer basal secretion score of 5 to 10 mm is relatively insignificant.[250] Schirmer I (without topical anesthesia) of less than 5.5 mm of wetting after 5 minutes is diagnostic of aqueous tear deficiency. The Schirmer II test measures reflex secretion. Once the filter paper has been inserted in the inferior fornix, a cotton-tipped applicator is used to stimulate the nasal mucosa. Wetting of less than 15 mm after 2 minutes is considered abnormal. If topical anesthesia is applied, excess fluid should be gently removed from the cul-de-sac prior to insertion of the filter paper. Although an isolated abnormal result can be nonspecific, serially consistent low results are strongly suggestive of aqueous tear deficiency.

FLUORESCEIN DYE DISAPPEARANCE TEST/TEAR FUNCTION INDEX

The clearance or turnover of tears on the ocular surface can be assessed using a number of tests, including the fluorescein disappearance test and tear function index.[91,251] These tests are performed by instilling a measured amount of fluorescein dye on to the ocular surface, then assessing clearance of the dye by visually comparing the residual dye in the inferior tear meniscus with the Schirmer strip that has been placed onto the ocular surface with a standard color scale.[91,251] This test assesses aqueous tear production, tear volume, and tear drainage. It has been found to show better correlation with the severity of ocular irritation symptoms and corneal fluorescein staining than the Schirmer test.[252,253]

TEAR OSMOLARITY TEST

Tear osmolarity has long been thought to be a key feature of dry eye.[254-256] However, the test did not gain popularity until after the U.S. Food and Drug Administration (FDA) cleared a commercially available device (TearLab, San Diego, CA) in 2009 to be used as a point-of-care laboratory test to diagnose dry eye. Since then, a number of studies have been published reporting on the utility of this device. A current review of the literature demonstrates conflicting results. There are a number of studies published by independent researchers suggesting that osmolarity exhibits the strongest correlation with disease severity of any single objective metric in clinical use[92, 257-260] and predicts response to therapeutic interventions.[261-263] At the same time, tear osmolarity has also been criticized by others for its lack of correlation to symptoms and to the other objective dry eye signs.[95, 264]

At a cutoff of 312 mOsms/L, tear hyperosmolarity is noted to have 73% sensitivity and 92% specificity for diagnosing dry eye.[92] By contrast, the other clinical tests commonly used in diagnosing dry eye have either poorer sensitivity (corneal staining, 54%; conjunctival staining, 60%; meibomian gland grading, 61%) or specificity (tear film break-up time, 45%; Schirmer test, 51%). However, these numbers, in isolation, are not particularly helpful and should be considered within the context of symptoms and other clinical findings. Rather than relying solely on an absolute number obtained via one-time measurement, correlation with clinical findings or differences in osmolarity over time or under different conditions would seem to be more important to confirm the diagnosis of dry eye and to monitor progression and response to treatment. Indeed, most recent studies confirm that normal subjects have exceptionally stable tear film osmolarity, whereas tear osmolarity values in dry eye subjects become unstable quickly and lose homeostasis with environmental changes.[98]

A large-scale, prospective clinical study indicated that individuals with dry eye symptoms but no significant ocular surface or tear film abnormalities seem to have higher and more variable osmolarity measurements than controls, potentially indicating that changes in osmolarity precede clinical findings.[265] Taking multiple measurements over time is required to diagnose dry eye in patients with milder disease.[98]

In the hands of a rheumatologist or general practitioner who is unable to do a comprehensive external or slit-lamp examination, osmolarity testing may be of benefit in diagnosing dry eye. More research and experience with this measurement device will help determine its value and clinical relevance.

MATRIX METALLOPROTEINASE-9 TEST

A commercially available point-of-care matrix metalloproteinase-9 test can also be used to aid in the diagnosis of dry eye. The qualitative nature of this test can be used to assess change in the disease state. Although the test does not differentiate dry eye from other inflammatory ocular surface diseases, it may aid in the management.

LITERATURE SEARCHES FOR THIS PPP

Literature searches of the PubMed database were conducted on March 3, 2022; the search strategies are listed below. Specific limited update searches were conducted on June 7, 2023. The searches had added filters for human, English-language randomized controlled trials and systematic reviews and date limiters to capture literature published since June 27, 2018. The panel analyzed 4,327 studies of which 50 were included in the PPP. The literature searches with the disease condition and the search term, patient values and patient preferences didn't yield results. The literature searches for economic evaluation and treatment cost yielded 66 studies, 66 of which were provided to the panel, 1 of which merited inclusion in the PPP.

Dry Eye All: ("dry eye syndromes"[MeSH Terms] OR dry eye[tiab])

Epidemiology: ("dry eye syndromes/epidemiology"[majr:noexp]) OR ("dry eye syndromes/ethnology"[majr:noexp]) OR ((dry eye[tiab] AND (prevalence[tiab] OR epidemiolog*[tiab] OR ethn*[tiab]))

Etiology: (("dry eye syndromes/etiology"[majr:noexp]) OR (dry eye[tiab] AND etiolog*[tiab]))

Risk Factors: ("dry eye syndromes"[majr:noexp] OR dry eye[tiab]) AND ("risk factors"[MeSH Terms] OR risk factor*[tiab])

Quality of Life: (dry eye syndromes[majr:noexp] OR dry eye[tiab]) AND ("quality of life"[MeSH Terms] OR quality of life[tiab])

Cost of Illness: ("dry eye syndromes"[majr:noexp] OR dry eye[tiab]) AND ("cost of illness"[MeSH Terms] OR "cost benefit analysis"[MeSH Terms] OR cost*[tiab])

Economics: ("dry eye syndromes/economics"[mh:noexp]) OR (dry eye[tiab] AND economic*[tiab])

Therapy: ("dry eye syndromes/drug therapy"[majr:noexp] OR "dry eye syndromes/diet therapy"[majr:noexp] OR "dry eye syndromes/surgery"[majr:noexp] OR "dry eye syndromes/therapy"[majr:noexp])

Pathology, Physiology: (("dry eye syndromes/pathology"[MAJR:noexp]) OR ("dry eye syndromes/physiology"[MAJR:noexp]) OR ("dry eye syndromes/physiopathology"[MAJR:noexp]))

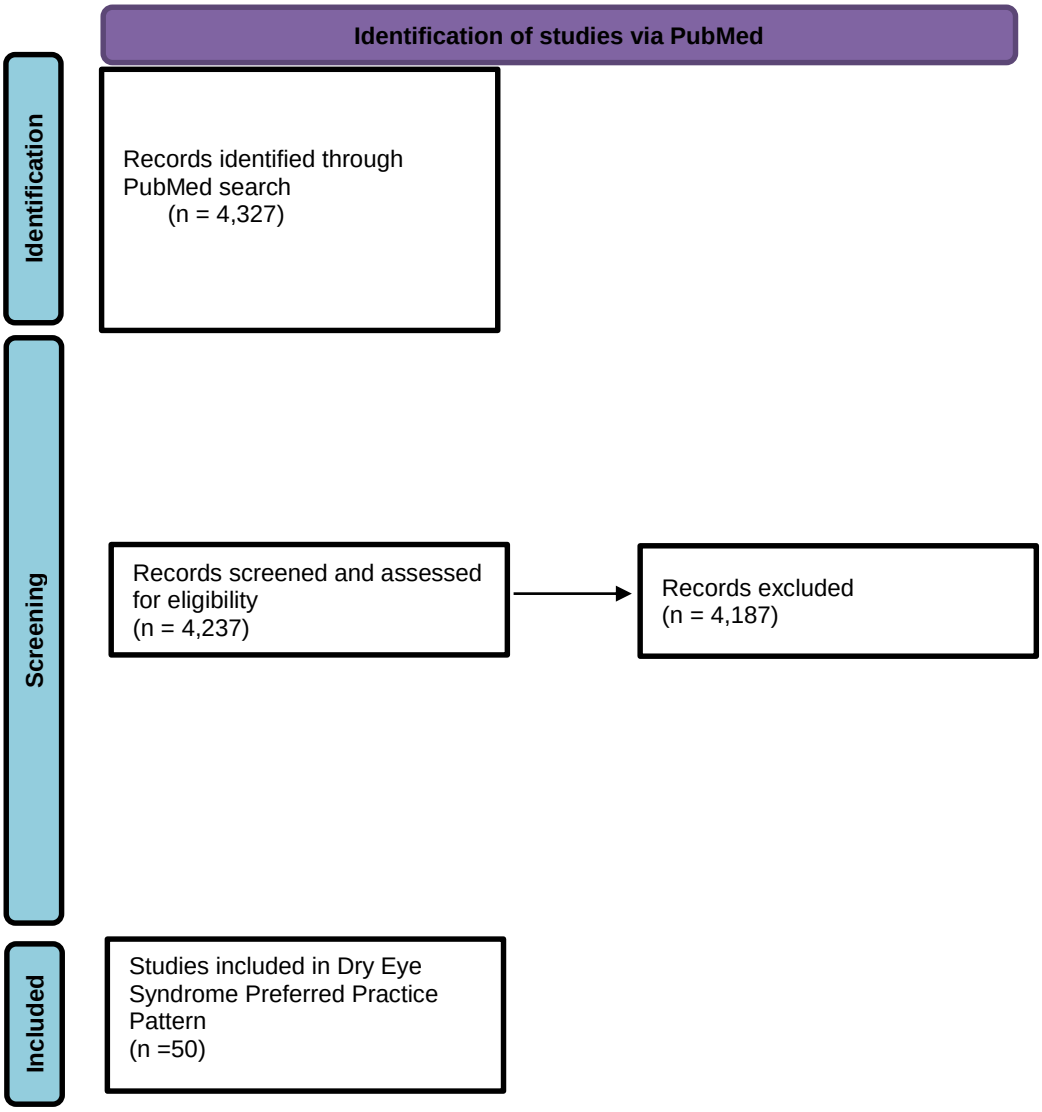
Disease Progression: ("dry eye syndromes"[Mh:noexp] OR dry eye[tiab]) AND ("disease progression"[MeSH Terms] OR disease progress*[tiab])

Diagnosis: ("dry eye syndromes/diagnosis"[MAJR:noexp])

Prevention and Control: "dry eye syndromes/prevention and control"[MAJR]

Quality of Life: ("dry eye syndromes"[MESH Terms] OR "dry eye"[tiab]) AND ("quality of life"[MeSH Terms])

Patient Values: dry eye syndromes[tiab] AND (patient values[tiab] OR patient preferences[tiab])



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

RELATED ACADEMY MATERIALS

Basic and Clinical Science Course
External Disease and Cornea (Section 8, 2023–2024)

Patient Education Brochure
Dry Eye (2022)
Spanish Language Brochure: Ojo Seco (2021)

Ophthalmic Technology Assessments – Free download available at www.aao.org/ota
Autologous Serum-Based Eye Drops for Treatment of Ocular Surface Disease OTA

Preferred Practice Pattern® Guidelines – Free download available at www.aao.org/ppp.
Comprehensive Adult Medical Eye Evaluation (2020)
Pediatric Eye Evaluations (2022)

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