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The Nitty Gritty: Dry Eye Guidance for the Pharmacy Team

AN ONGOING CE PROGRAM
of the University of Connecticut
School of Pharmacy

EDUCATIONAL OBJECTIVES

After completing the continuing education activity, pharmacists and pharmacy technicians will be able to

- Describe the etiology and pathophysiology of dry eye disease (DED) and its impact on quality of life
- Identify available and emerging over-the-counter and prescription therapies to treat DED
- Optimize artificial tear selection based on patient-specific characteristics
- Infer when to refer patients to the pharmacist or an eye care provider for DED

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TARGET AUDIENCE: Pharmacists and pharmacy technicians who provide care for, have, or love someone who is affected by dry eye.

ABSTRACT: Dry eye disease (DED) is a multifactorial condition affecting the ocular surface and tear function. Symptoms include burning, itching, and watery eyes. DED affects millions of people in the United States. Many underlying factors contribute to DED making therapeutic management difficult. Left untreated, DED can result in visual changes affecting everyday activities such as reading and driving. Simple environmental changes often help alleviate symptoms. Before seeking healthcare professional assistance, many people self-treat with over-the-counter artificial tear products, leading to high costs and frustration. Treatment involves patient education, environmental and lifestyle modifications, topically applied products, and, in severe cases, surgical procedures. Several recently approved products offer alternative treatment approaches. A knowledgeable, informed pharmacy team is prepared to counsel patients on product choice and to make appropriate referrals contributing to better patient outcomes.

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FACULTY DISCLOSURE: Ms. Salvon has no financial relationships with an ineligible company.

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INTRODUCTION

The feeling of grit under the eyelids is uncomfortable, annoying, and frustrating and can pose a serious health issue. This feeling, often accompanied by burning, itching, redness, and visual disturbances, is a symptom of keratoconjunctivitis sicca, otherwise known as dry eye disease (DED). At its simplest, DED is inflammation of the cornea and conjunctiva from tear hyperosmolarity (higher concentration of solutes like salts, sugars, or other dissolved particles) and tissue dryness. Left untreated, DED may result in severe eye inflammation, corneal ulcers, and vision loss.[1]

DED affects approximately 16.4 million people, or 6.8% of the United States (U.S.) adult population.[2,3] DED is likely underreported and underdiagnosed, with estimates as high as 22.9 million adults experiencing symptoms.[2] Researchers estimate DED's global prevalence is as high as 50%.[4]

Despite this prevalence, experts began to recognize DED as a disease state only about 30 years ago.[5,6] Initially described as a component of Sjogren's syndrome (an autoimmune disease involving tear and saliva glands), DED emerged as a separate condition as ocular surface study progressed. The National Eye Institute first defined DED in 1995.[1]

The Tear Film and Ocular Surface Society (TFOS) is a non-profit organization focused on eye health research and education.[5] In 2015, the Dry Eye Workshop II (DEWS II), organized by TFOS, examined multiple aspects of DED. The workshop updated the definition, diagnosis, and classification of DED; the disease's impact; therapeutic management options; and clinical trial design.[5]

TFOS DEWS II defines DED as "… a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."[5] In simpler terms, DED occurs when the tear film, which keeps the eyes moist, becomes imbalanced, leading to problems like tear film instability, high concentration of substances in the tears, inflammation and damage on eye surface, and abnormal nerve sensations.

Many risk factors contribute to DED development (**Table 1**). Women are two to three times more likely to develop DED than men.[3,4] Risk of developing DED increases with age. Adults aged 50 or older are three times more likely to develop symptoms than those 18 to 49 years old.[2,3] However, DED's incidence is rising steadily in the younger population, possibly due to increased disease awareness.[3] Digital device use may also contribute. Studies show that using digital devices decreases blink rate and increases incomplete blinks, leading to ocular surface dryness and, ultimately, DED.[4,7]

DED impacts the American economy significantly. Several factors contribute to DED burden: direct costs of medical care, the impact of lost productivity, and the associated quality of life burden. In the U.S., estimates of direct medical costs exceed $3.84 billion, fueled by healthcare professional visits, pharmacologic therapies, and surgical procedures.[4,8] The cost of lost productivity (i.e., time spent seeking and receiving treatment, avoidance of aggravating work environments, and inability to perform work due to visual changes) is even more substantial. One study estimates that these indirect costs total $11,302 per patient annually.[8] If more than 16 million people have DED, that totals more than $150 billion annually.[4,8]

Table 1. Dry Eye Disease Risk Factors[1,4,5]

Modifiable	Non-modifiable
Androgen deficiency	Age ≥ 50 years
Computer use	Asian race
Contact lens wear	Connective tissue diseases (e.g., rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus)
Environment	Diabetes
Medications	Female sex
	Meibomian gland dysfunction

Beyond monetary costs associated with DED, the disease also affects vision-related quality of life (VR-QoL). As DED progresses, visual quality decreases. Individuals with DED are three times more likely to report visual difficulties than those without.[4] This impacts many daily activities such as reading, driving, watching television, and smartphone use.[4] DED-associated pain and discomfort, along with difficulty in activities of daily living, impact mental health negatively.[8] A 2021 study examined self-reported health status and psychological burden in patients with DED. The study associated DED with having a negative self-perception of health status and experiencing increased psychological stress.[9]

A Deeper Look at DED

A better understanding of DED requires review of the surface anatomy of a healthy eye (see **Figure 1**). The eye's surface consists of the ocular surface and ocular adnexa (accessory anatomical parts).[10] The ocular surface includes the cornea, conjunctiva (including goblet cells), and tear film. The ocular adnexa includes the eyelids, lacrimal and meibomian glands, tear ducts, and the connecting muscles and nerves.[10]

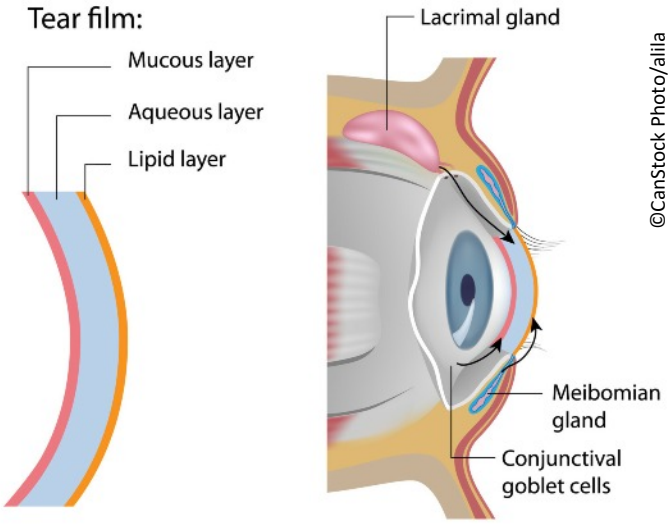

Figure 1. Anatomy of the Healthy Eye

Tears lubricate the eye, and the tear film—which provides nutrients and moisture, removes microbes, and smooths the ocular surface—has three layers[10,11]:

- Outermost lipid layer, produced by meibomian glands
- Aqueous layer, produced by the lacrimal gland
- Innermost mucin layer, produced by goblet cells

Tear film instability, primarily increased tear osmolarity, leads to ocular surface damage in DED.[7] DED's categorization is based on the mechanism leading to tear hyperosmolarity. In aqueous deficient dry eye disease (ADDE), decreased tear secretion increases tear film osmolarity. Increased evaporation of tears leads to hyperosmolarity in (you guessed it) evaporative dry eye disease (EDE).[5]

ADDE is further categorized based on the underlying cause: Sjogren's Syndrome or non-Sjogren's syndrome. As mentioned, Sjogren's syndrome is an autoimmune disease attacking the salivary and lacrimal glands resulting in dry mouth and eyes. Non-Sjogren's syndrome ADDE has various causes, including lacrimal deficiency, lacrimal gland duct obstruction, and systemic drugs. These mechanisms decrease tear secretion, resulting in tear hyperosmolarity.[5,10]

Meibomian gland dysfunction (MGD) is the primary cause of EDE.[12,13] Meibomian glands line the inside of the upper and lower eyelid. Lipid secretion by meibomian glands forms a coating on the aqueous layer, impeding tear evaporation and providing protection against environmental irritants. Risk factors for MGD include aging, hormonal changes, contact lens wear, diet, and systemic and topical medications.[13]

Separation of DED into ADDE and EDE implies mutual exclusivity, but many patients presenting with DED exhibit characteristics of both. Recent evidence indicates the two classifications co-exist, with more patients presenting with EDE due to MGD. [6,14,15] Regardless of the subtype or mechanism, the result is a vicious, self-perpetuating cycle of inflammation.[6,16] Tear film hyperosmolarity triggers an innate inflammatory immune response, activating CD4+ T-cells. This leads to conjunctival and corneal cell death and impaired lacrimal gland function, further decreasing tear production.[16,17] This further increases tear hyperosmolarity, which continues the cycle.

Diagnosing DED is problematic due to its multi-factorial nature and inconsistent symptom presentation. Exploring differential diagnoses using triaging questions is crucial to exclude diseases that mimic DED, including allergic, bacterial, or viral conjunctivitis; blepharitis; and rheumatic disorders.[5,18] A thorough patient history screens for risk factors such as smoking, contact lens wear, and certain systemic and topical medications. Several questionnaires also exist to help clinicians screen for DED. The Dry Eye Disease Questionnaire (DEQ-5) contains five items asking patients to rate the frequency of eye discomfort, eye dryness, and watery eyes during a typical day.[18] The Ocular Surface Disease Index (OSDI) is another popular questionnaire. The OSDI questionnaire asks a series of 12 questions assessing eye symptoms, vision issues (e.g., reading, driving), and environmental conditions.[18]

Patients with positive questionnaire results should progress to a more detailed tear film and ocular surface examination. A positive result in any of the following tests is diagnostic of DED[18]:

- **Tear breakup time (TBUT):** There are two methods for measuring TBUT, using fluorescein dye or illumination of the cornea. Both measure how long it takes for tears to break up after a blink. Lower TBUT scores indicate tear instability.
- **Osmolarity:** Clinicians use a device with a test strip to gain a sample of the tear film from both eyes to check tear osmolarity. An osmolarity of 308 mOsm/L or greater in either eye or a difference of more than 8 mOsm/L between the eyes is diagnostic of DED.
- **Ocular surface staining:** After applying dye to the lower eyelid's inner lining, clinicians examine the ocular surface for missing or damaged epithelial cells. Positive scores range from five to nine spots depending on the dye used.

Clinicians also commonly deploy the Schirmer test to evaluate the eye's ability to produce tears. A notched paper strip placed over the lower eyelid stimulates tear production during the test. After five minutes, a length of wetting greater than 10 mm indicates normal tear function. Values less than 5 mm signify tear insufficiency.[18]

Pause and ponder: How would vision loss affect your everyday life?

Treatment Goals

Treatment goals for DED are to decrease ocular inflammation and restore ocular surface homeostasis (balance). DED's complexity and heterogeneous presentation necessitate an individualized approach. TFOS DEWS II recommendations emphasize identifying the disease's root cause to determine an appropriate management approach.[14] From there, the report outlines a stepwise, flexible approach to guide treatment based on patient-specific disease etiology and severity.[14] **Table 2** (next page) briefly summarizes recommended management steps.

NON-PHARMACOLOGIC TREATMENT

One of the first steps, patient education, is essential for successful disease management.[14] Patient education starts with thoroughly explaining DED's chronic nature, including the ongoing, often long-term nature of therapeutic management. Discussing the patient's home and work environment during the session may identify contributing factors.[14] The environment affects

Table 2. Treatment Steps in DED Management[14]	
Step 1: • Education • Environmental modifications • Lifestyle modifications • Dietary supplementation • Eyelid hygiene • Medication review • Artificial Tears	**Step 2:** • Preservative-free artificial tears • Prescription therapy • Tear Conservation • Overnight treatments • In-office treatments
Step 3: • Tear stimulation • Biological tear substitutes • Therapeutic contact lenses	**Step 4:** • Prescription therapy • Surgical intervention

overall health and well-being. Air pollution, low humidity, high altitude, and wind contribute to DED development.[14] Adding an air humidifier inside or using protective eyeglasses outside can help mitigate DED symptoms. Other strategies include minimizing exposure to digital screens, cigarette smoke, and air conditioning.[19]

Proper lid hygiene is important in managing many eye conditions, including DED.[14] Patients can use a cotton swab to scrub the eyelid with a dilute solution of baby shampoo to keep the area free of crusty build-up and environmental contaminants. Warm eye compresses also promote good lid hygiene and help alleviate DED symptoms. Unfortunately, lid hygiene adherence is poor, with estimates of just over 50% adherence at six weeks.[14] Reinforcing the importance of lid hygiene with patients is an important component of DED patient counseling.

Identifying medications that may contribute to DED is an important task for pharmacy staff. Many medication classes produce drying effects on the body, intentionally or as an adverse effect.[14,19] **Table 3** lists examples of medications that may worsen DED. Pharmacists and pharmacy technicians should review patient profiles to identify drying medications, including ophthalmic formulations, as medications for glaucoma (an eye condition causing progressive vision loss) may contribute to DED.[14] Mitigating options to consider include changing the route of administration from oral to topical, substituting with a therapeutic alternative, and adjusting doses.[14]

Diet and Nutrition

An emerging body of evidence suggests that certain diet changes and nutritional supplementation may play a role in DED treatment. Dehydration increases tear osmolarity, so maintaining adequate hydration is important to disease control.[14] Lactoferrin is an anti-inflammatory glycoprotein found in natural tears. Studies have found decreased lactoferrin levels in patients with DED leading researchers to the explore lactoferrin topical application and oral supplementation as treatment for the condition. One study found improved dry eye symptoms and tear film stability in patients taking an oral lactoferrin supplement.[20] Oral lactoferrin is available as a supplement in many retail locations.

Supplementation with omega-3 fatty acids also shows potential in DED. Omega-3 fatty acids block proinflammatory substances and are essential for ocular surface homeostasis.[14] Some studies have found that omega-3 fatty acid supplementation improves TBUT and Schirmer scores.[21,22] Conversely, The Dry Eye Assessment and Management (DREAM) trial reported no difference between groups receiving omega-3 fatty acids and placebo.[23] While oral omega-3 fatty acids show benefit for some patients, further study is necessary. These conflicting results prompted studies for alternative administration routes. Topical application of omega-3 fatty acids shows promise. A systematic review of 10 studies (five in animals and five in humans) showed overall improvement in ocular surface staining and TBUT.[24] Further study is necessary to

Table 3. Examples of Medications that Worsen Dry Eye Disease[14,19]	
Drug Class	**Examples**
Antihistamines and decongestants	Chlorpheniramine Diphenhydramine Fexofenadine Loratadine Pseudoephedrine
Antidepressants • TCA • SSRI • SNRI	Amitriptyline Citalopram Duloxetine Fluoxetine Sertraline Venlafaxine
Anti-Parkinson's	Levodopa
Antipsychotics	Aripiprazole Perphenazine Quetiapine
Beta-blockers	Atenolol Carvedilol Metoprolol Propranolol
Diuretics	Furosemide Hydrochlorothiazide
Proton pump inhibitors	Omeprazole Pantoprazole
Hormone therapy	Estrogen
ABREVIATIONS: DED = dry eye disease; TCA = tricyclic antidepressants; SSRI = serotonin-selective reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor	

Table 4. Components of Artificial Tear Products[11,14,26]		
Component	**Purpose**	**Examples**
Viscosity-enhancing agents (lubricants)	• Aid lubrication • Increase tear film thickness • Protect ocular surface • Promote tear retention • Improve goblet cell density	• Carbomer 940 (polyacrylic acid) • Carboxymethyl cellulose (CMC) • Dextran • Glycerin • Hyaluronic acid (HA) • Hydroxypropyl-guar (HP-guar) • Hydroxypropyl methylcellulose (HP-MC) • Polyvinyl alcohol • Polyvinylpyrrolidone • Polyethylene glycol (PEG)
Lipids	• Restore the lipid layer • Increase lipid layer thickness • Prevent evaporation	• Mineral oil • Castor oil • Flaxseed oil
Osmoprotectants	• Balance osmotic pressure	• Trehalose • Levocarnitine • Erythritol • Betaine
Preservatives	• Prevent microbial growth in multi-dose formulations	• Benzalkonium chloride (BAK) • Sodium chlorite • Sodium perborate
Buffers	• Control pH	• Sodium borate • Sodium citrate • Sodium phosphate
Electrolytes	• Promote ocular surface homeostasis	• Potassium • Calcium • Magnesium • Phosphate

evaluate long-term efficacy and optimize dosage and delivery formulations.

Artificial Tears

Patients often attempt self-treatment before seeking healthcare professional assistance. Tear replacement with artificial tear (AT) formulations is essential for patient comfort and a mainstay of initial and ongoing therapy. Global sales of AT reached $2.64 billion in 2019, and experts predict this to reach $4.30 billion by 2027.[25] Many AT products line the pharmacy shelves, all touting their ability to lubricate the eye. Faced with the confusing array of products, patients often employ a trial-and-error approach for AT selection, leading to high costs and frustration. Knowing the differences between ATs enhances the pharmacy team's ability to counsel patients effectively.

AT supplementation is generally safe and well tolerated and associated adverse effects are mild, including blurred vision and ocular discomfort.[14] Most ATs are water-based with viscosity-enhancing agents added for lubrication. Osmolarity, viscosity, and pH vary between products. **Table 4** describes the components of AT products and their functions.

Viscosity-enhancing agents, or demulcents, are the most common ingredient in AT and typically listed as the active ingredient on product packaging. The higher the viscosity (i.e., the thicker the product), the longer the ocular surface retention time, but differences in viscosity can influence product choice. High viscosity can create visual disturbances and buildup on the eyelid leading to decreased adherence.[26] These products are best for nighttime use, and patients should use lower-viscosity products during the day.[26] Many products contain multiple viscosity-enhancing agents. Commonly paired agents include carboxymethyl cellulose (CMC) with hyaluronic acid (HA) and hydroxypropyl-guar (HP-guar) with HA.[14,26] Studies suggest that combining viscosity-enhancing components improves symptom control.[14]

There is significant interest in developing novel formulations to increase the spreading and retention time of applied drops.[14] Lipid-containing eye drops are gaining in popularity as understanding of DED's pathophysiology progresses.[14] Lipids restore and thicken the lipid layer of the tear film and prevent tear evaporation. Formulated as oil-in-water emulsions, lipid-containing products contain macro-, micro-, or nano-particles. Particle size is important. Macro particles are associated with cloudy, blurred vision. As particle size decreases, blurring decreases.[14]

Osmoprotectants balance osmotic pressure, as the name implies, to protect and prevent corneal and conjunctival cell death.[26] Levocarnitine and erythritol protect cells from hyperosmolar stress and improve DED's symptoms.[26] Clinical trials have shown that trehalose is more effective at improving ocular surface staining than saline.[14,26]

Multi-dose products contain preservatives to prevent microbial growth, but these can also worsen symptoms in DED. Benzalkonium chloride (BAK), the most common preservative, may cause corneal damage and interfere with tear film stability.[14] Newer "disappearing preservatives" (e.g., sodium chlorite, sodium perborate) have a lower impact on the ocular surface. Exposure to light or the ocular surface breaks down these compounds, minimizing toxicity.[14,27] Even newer preservatives carry risk, making preservative-free drops the best choice, especially in patients with severe DED. Preservative-free AT products are available in disposable single-use units but are generally more expensive.[14]

The pH of ATs affects product activity, stability, patient comfort, and safety.[14] Adding electrolytes to reproduce the electrolyte profile of the tear film aids osmotic balance. Studies show that hypotonic solutions (i.e., having a lower osmotic pressure) decrease DED signs.[26]

No large-scale, randomized clinical trials have evaluated all currently available AT formulations. Some clinical trials evaluate individual AT products, and a few head-to-head studies exist.[16,28] Several published systematic reviews have concluded that ATs treat DED safely and effectively. One systematic review of more than 60 studies published in 2022 drew the following conclusions[27]:

- Combination formulations, including the following, may be more effective than single-ingredient products: CMC and HA, HA and trehalose, CMC and glycerin, and HA and coenzyme Q10.
- Formulations containing polyethylene glycol (PEG) may be more effective than those with CMC.
- Preservative-free formulations are preferable.
- Patients with EDE and/or MGD should use drops containing phospholipids.
- Patients should administer AT four times daily for one month to assess efficacy.
- Patience is key; sometimes, it may take up to four months of consistent use to see improvement.

Another literature review of 18 studies compared commercially available AT products and concluded that products containing CMC, hydroxypropyl methylcellulose (HPMC), or HA were the most beneficial in improving patient comfort level.[29] This study also determined that clinicians should recommend administration three to four times daily for two months to assess patient response before escalating therapy. The use of a preservative-free formulation is preferable.[29] If patients choose or clinicians recommend preservative-containing eye drops, administration should be limited to four to six times daily.[29] Researchers created a stepwise approach to selecting AT products[29]:

- **Step 1:** Start with CMC, HPMC, or HA-based formulations
- **Step 2:** Move to formulations with PEG or PEG and glycerin
- **Step 3:** Consider gel or lipid formulations
- **Step 4:** Progress to ointments, liposomal sprays, or prescription inserts

Both studies reached similar conclusions. Adherence and persistence are key to successfully evaluating an individual product, a fact that pharmacy staff should reiterate to patients. While some trial and error may be necessary, following the above recommendations allows patients and providers an organized approach to AT selection. While AT are a mainstay of early symptomatic treatment of dry eye disease, they do not address DED's underlying causes. Prescription therapies target the underlying inflammatory processes.

Hydroxypropyl cellulose ophthalmic insert (HCOI) is a prescription-only lubricant insert containing 5 mg of hydroxypropyl cellulose. The insert is preservative-free and designed to provide continuous lubrication throughout the day. Patients insert HCOI once daily using an applicator.[30] They rinse the applicator in hot water then use the grooved end to pick up the insert. Patients then place the insert in a pocket created by pulling out the outer corner of the eyelid. The HCOI softens and slowly dissolves, stabilizing and thickening the tear film, prolonging TBUT. One study comparing HCOI to using AT four or more times a day found increased TBUT and decreased foreign body sensation with HCOI compared to AT.[30,31] Reported adverse effects include blurred vision, eye irritation, eyelid matting, and light sensitivity.[30]

Pause and Ponder: A patient approaches the pharmacy counter with a plastic bag full of bottles of different brands of artificial tears. Dumping them on the counter, she states, "None of these work! I don't know what to do next." What advice would you give her?

PRESCRIPTION THERAPIES

Available prescription therapies (outlined in **Table 5**) target the inflammatory cycle of DED through different mechanisms with varying degrees of success.

Cyclosporine A

Cyclosporine A (CsA) is an anti-inflammatory immune modulator approved for use in DED more than two decades ago.[16] Calcineurin activates T-cells, increasing inflammatory cytokine production. CsA inhibits calcineurin to prevent T-cell activation, disrupting the inflammatory cycle in DED.[16]

Table 5. Prescription Therapies to Treat Dry Eye Disease[28,32-36]

Drug	Brand Name (Manufacturer)	Formulation(s)	Dosing	Supplied
Cyclosporine A	Restasis (Allergan)	0.05% emulsion	1 drop in each eye BID	Single-use vials
	Cequa (Sun Pharma)	0.09% solution	1 drop in each eye BID	Single-use vials
	Generic (Mylan)	0.05% solution	1 drop in each eye BID	Single-use vials
Lifitegrast	Xiidra (Novartis)	5% solution	1 drop in each eye BID	Single-use containers
Loteprednol	Eysuvis (Kala Pharma)	0.25% suspension	1-2 drops in each eye QID for up to 2 weeks	Multi-dose 10 mL bottle
Perfluorohexyloctane	Meibo (Bausch & Lomb)	100% solution	1 drop in each eye QID	Multi-dose 5 mL bottle
Varenicline	Tyrvaya (Oyster Point Pharma)	0.03 mg/0.05ml solution	1 spray in each nostril BID	Multi-dose nasal spray

ABBREVIATIONS: BID, twice daily; QID, four times daily

Many clinical trials have evaluated CsA's safety and efficacy in DED treatment.[5,1,37,14] Results consistently show that CsA improves Schirmer test scores, corneal staining results, and goblet cell density. Improvement often takes several months, making patient education key to adherence.[1,5,37,14] Topical CsA alleviates symptoms in approximately 50% of patients.[1] Patients using CsA experience decreases in blurred vision, ocular dryness, foreign body sensation, and watery eyes.[1,14] Treatment often causes stinging and irritation. Other adverse effects include blurred vision, ocular itching, eye redness, and foreign body sensation.[37] Pretreatment with an ophthalmic steroid such as loteprednol may decrease CsA's adverse effects.[1,38]

As a hydrophobic (water-fearing) substance, CsA is challenging to formulate into an ophthalmic topical formulation. Initially, products used castor oil and corn oil as vehicles, but poor bioavailability and adverse effects preclude their use.[16] The first commercially available CsA product, a 0.05% emulsion, uses a castor oil-in-water emulsion, which reduces but does not eliminate adverse reactions.[37]

Approval of CsA 0.09% nanomicellar solution introduced a novel formulation.[16,37] Clinical efficacy trials found a response as early as day 28.[16]At the end of 12 weeks, 17% of study participants receiving CsA 0.09% experienced increased tear production with a Schirmer score greater than 10 mm. Reported adverse effects included mild instillation site pain, eye irritation, blepharitis, and headache.[32] Preliminary studies suggest CsA 0.09% is more effective and better tolerated than CsA 0.05%.[16]

Lifitegrast

Approved in 2016, the novel drug lifitegrast is a lymphocyte function-associated antigen-1 (LFA-1) antagonist.[33] LFA-1 binds to intracellular adhesion molecule-1 during inflammation, activating T-cell migration and resulting in ocular inflammation. Lifitegrast binds to LFA-1, preventing this interaction and decreasing T-cell-mediated inflammation.[33] The U.S. Food and Drug Administration (FDA) approved this drug based on four randomized, double-masked, 12-week efficacy and safety trials. [33,39-41] All studies showed a reduction in patient-rated eye dryness scores at the end of 12 weeks. Patients in three of the four studies experienced reduced corneal staining scores.[33]

The one-year multicenter, randomized, placebo-controlled SONATA study evaluated lifitegrast safety.[42] Reported adverse effects included burning, reduced visual acuity, dry eye, and taste changes. Researchers observed no serious adverse events and discontinuation rates were 12.3% and 9% for lifitegrast and placebo, respectively.[42] A 2021 retrospective review of 600 patient charts examined real-world experience with lifitegrast in DED.[43] Most patients continued treatment for six months and showed improvement in DED symptoms. Patients also experienced improved quality of life at three and 12 months of treatment.[43]

Perfluorohexyloctane

Perfluorohexyloctane, formerly known as NOV3, reduces tear evaporation from the ocular surface.[44] The drug's exact mechanism in DED is unclear. In May 2023, the FDA approved an ophthalmic formulation containing perfluorohexyloctane for treating DED in adults 18 and older based on data from two phase 3 clinical trials: GOBI and MOJAVE.[44,45]

These trials evaluated efficacy and safety in more than 1,200 patients with DED meeting similar inclusion and exclusion criteria based on tear film break-up time, ocular surface disease scores, and MGD evaluations. Both trials were multi-center, randomized, double-masked, and saline-controlled.[44,45] GOBE and MOJAVE

results also consistently showed statistically significant reductions in reported symptoms of DED. Reported adverse events occurred in less than 4% of study participants and included blurred vision, blepharitis, instillation site pain, and conjunctival redness.[44,46] Patients must remove contact lenses before and for at least 30 minutes after administration of perfluorohexyloctane drops.[34]

Perfluorohexyloctane should be available in the second half of 2023.[44]

Short-Term Corticosteroids

Corticosteroids are potent inhibitors of inflammatory mediators.[14] Many clinical trials have demonstrated their efficacy in breaking the inflammatory cycle of DED. Unfortunately, long-term therapy is associated with increased intraocular pressure, cataracts, and risk of infection.[14]

Loteprednol is a synthetic corticosteroid derived from prednisolone. Its rapid breakdown into inactive metabolites reduces risk of adverse reactions.[47] A retrospective safety study concluded that loteprednol therapy carries a low risk of treatment-related elevated intraocular pressure compared to other steroids.[48] Several loteprednol ophthalmic formulations are available, but only the 0.25% suspension is FDA approved for the short-term treatment of DED. This formulation uses mucus-penetrating particle (MPP) technology to allow nanoparticle penetration through the mucin layer.[47,49]

The FDA approved loteprednol 0.25% suspension based on the STRIDE series of trials.[36] These trials randomized patients with DED to the drug or a vehicle control four times daily in both eyes for two weeks. All trials reported significant improvements in eye redness and discomfort at the end of two weeks.[36]

One role for topical steroids in DED is pre-treatment prior to topical CsA therapy. A 2014 study compared loteprednol versus AT during a two-week lead-in period to CsA.[38] Patients self-administered either loteprednol or AT four times daily for two weeks, followed by CsA twice daily plus either loteprednol or AT twice daily for an additional six weeks. Both groups showed improved ocular staining and OSDI and Schirmer scores. Loteprednol provided more rapid relief of DED symptoms and resulted in a lower CsA discontinuation rate than AT.[38]

Patients with moderate-to-severe DED with adequate long-term control may still experience periodic symptom exacerbation. Short-term pulse steroid therapy (using steroids of a week or two, then tapering and resuming if necessary) can be useful for patients with symptom exacerbations.[14]

Varenicline Nasal Spray

Pharmacy staff may recognize varenicline as a treatment for smoking cessation, but a newer nasal spray formulation shows utility for treating DED. Tear film production results from stimulating afferent nerves in the cornea and conjunctiva and parasympathetic nerves in the lacrimal gland, meibomian glands, and goblet cells.[50,51] This neural pathway is accessible through central nervous system or peripherally through the nasal cavity. While the drug's mechanism in DED is not fully understood, experts theorize that varenicline, a cholinergic agonist, activates this pathway to stimulate tear production.[50,51]

The randomized, double-masked, vehicle-controlled, 28-day ONSET-1 and ONSET-2 trials evaluated varenicline nasal spray's safety and efficacy.[50,51] Participants self-administered one spray of varenicline solution or vehicle in each nostril twice daily. Both studies found a significant improvement in tear production measured by Schirmer scores. The most common patient-reported adverse effects included sneezing, cough, throat irritation, and nasal irritation.[50,51] The 2021 MYSTIC study examined varenicline nasal spray's long-term safety and efficacy compared to placebo over a 12-week period.[52] Patients reported no severe or serious adverse events during the study; sneezing was the most common adverse reaction, occurring in 82% of patients.[52]

Varenicline packaging includes two glass bottles, each containing a 15-day drug supply. Patients must initially prime the bottle by pumping seven sprays into the air away from the face. Re-priming by pumping one spray into the air is necessary after five days of nonuse.[35]

Steps for administration of varenicline nasal spray[35]:

- Blow nose if needed to clear nostrils
- Remove the cap and clip from the bottle
- Hold the bottle upright, placing one finger on each side of the applicator and thumb on the bottom of the bottle
- Tilt head back slightly
- Insert the applicator tip into one nostril, pointing it toward the ear on the same side of the nostril, leaving space between the tip and the wall of the nostril
- Place tongue on roof of mouth and breath gently while pumping one spray into the nostril
- Repeat in other nostril
- Wipe the applicator with a clean tissue and replace the cap and clip

Antibiotics

Clinicians sometimes use oral or topical antibiotics with anti-inflammatory effects off-label to treat DED due to MGD.[14] Many patients experience MGD due to overgrowth of eyelid flora, so reduction of eyelid flora and inflammation improves patient-reported symptoms.[53] Oral administration of doxycycline and minocycline in small doses (40 to 400 mg of doxycycline and 50 to 100 mg of minocycline) to treat MGD improves patient-reported symptoms.[1,53] Unfortunately, gastrointestinal adverse effects limit the use of these medications. One study found that azithromycin 1% eyedrops improved eyelid inflammation and tear film lipid layer stability.[54]

EMERGING THERAPIES

New and novel therapies are also in the pipeline for DED treatment. Pharmacy staff should be aware of their potential place in therapy and prepared to incorporate them upon approval.

Reproxalap

Exploring another causative mechanism in DED, reproxalap is a reactive aldehyde species (RASP) inhibitor. RASP molecules are found at the top of the inflammatory cascade and are elevated in many inflammatory diseases. They bind to and disrupt the function of enzymes and ion channels, which activates pro-inflammatory mediators. RASP inhibition, therefore, decreases pro-inflammatory substances associated with DED.[55,56]

A randomized, double-masked, phase 2a trial evaluated the efficacy of three formulations of reproxalap: 0.1% and 0.5% solutions and a 0.5% lipid solution.[55] Participants used the products four times daily for 28 days. The study found a significant improvement in four questionnaire scores, Schirmer test values, tear osmolarity, and tear staining scores. Within one week, patients reported symptom improvement. Researchers concluded that reproxalap could potentially alleviate DED symptoms.[55]

A separate randomized, double-masked, phase 2b trial compared reproxalap 0.01% and 0.25% to a control vehicle solution.[56] Patients self-administered drops four times daily for a total of 12 weeks. The study found statistically significant improvements in ocular dryness and staining over 12 weeks.[56]

A 2021 tolerability study compared ocular adverse effects between two formulations of reproxalap 0.25% (one solution, one lipid-based) and lifitegrast 5% solution.[57] Over seven days, study participants received one dose of each solution with a 3-day washout period between administrations. Researchers assessed adverse effects after 1 hour. Reproxalap formulations were similar to one another and superior to lifitegrast in ocular discomfort, blurry vision, and dysgeusia.[57]

Reproxalap offers a novel approach to treating the underlying inflammatory process involved in DED. Preliminary study results show improvements in DED symptoms and better patient tolerability, potentially leading to lower discontinuation rates and improved patient outcomes.

Cationic Cyclosporine

A cationic (positively charged) 0.1% CsA nanoemulsion is available in Europe to treat DED.[58] Experts theorize that a cationic emulsion increases the surface time of CsA on ocular tissues. All FDA-approved products are anionic (negatively charged). Clinical trials are evaluating CsA 0.1% nanoemulsion for FDA approval.[58]

PHARMACY TEAMS: FRONT-LINE SUPPORT

Pharmacists and pharmacy technicians are among the most accessible healthcare providers. People routinely turn to neighborhood pharmacies for advice on many health topics. Most people self-treat dry eye symptoms long before seeking professional help. These facts make the pharmacy team essential in supporting people suffering from DED. The **SIDEBAR** provides basic counseling information about eye products.

Knowledge of risk factors, including precipitating medications (revisit **Table 3** for a refresher), aids in identifying patients at risk for developing DED. Technicians are often the first point of contact at the pharmacy counter, routinely fielding questions. Actively listening and asking open-ended questions help gather necessary information. Patients reporting dry eye symptoms or buying AT products may need counseling or a referral to a pharmacist or an eye care professional.

Educating patients about avoiding certain environmental factors is important. Remind patients that minimizing exposure to wind or smoke, taking a break from digital screens, and using a humidifier may help alleviate symptoms. Adherence to therapeutic interventions is key in DED treatment. Some interventions, such as lid hygiene, are time-consuming, and many patients stop after only a few days. Reinforcing the importance of lid hygiene with patients is an important component of DED patient counseling. Advising patients on selecting an appropriate AT product decreases frustration and increases overall patient satisfaction. Proper administration of ophthalmic preparations can be difficult for some patients, particularly older individuals. Taking the time to counsel on proper technique sets patients up for successful administration and improved outcomes.

SIDEBAR: Counseling Tips for Eyedrop and Eye Ointment Administration[59,60]

Proper administration of ophthalmic formulations is key to their success. Administration is awkward, and many patients struggle with it. Advising patients on proper technique is a key role for the pharmacy team. General tips for all ophthalmic products include

1. Confirm you have the correct product
2. Check expiration date
3. Read the directions
4. Wash your hands
5. If using both eyedrops and eye ointment, wait five to ten minutes between drops, and administer the eyedrops at least 10 minutes before the ointment
6. Using a mirror may make it easier to see what you are doing

Eyedrops:

1. Gently shake the bottle
2. Be sure the eye dropper is clean, and do not let it touch any surface
3. Tilt your head back and look up
4. Pressing your finger gently on the skin just beneath the lower eyelid, pull your lower eyelid down and away from your eyeball to make a "pocket" for the drops
5. With the other hand, hold the eye drop bottle upside down with the tip just above the pocket
6. Squeeze the prescribed number of eye drops into the pocket
7. If you think you did not get the drop of medicine into your eye properly, use another drop
8. Blink a few times so that the medicine spreads across your eye
9. For at least 1 minute, close your eye and press your finger lightly on your tear duct (small hole in the inner corner of your eye) to keep the eye drop from draining into your nose
10. Wash your hands
11. Wait at least 10 minutes before you use other eye products, especially ointments, gels, or other thick eye drops

Eye ointment:

1. Be sure the top of the ointment tube is clean, and don't let it touch any surface, including the eye, eyelid, or lashes. (If it does, call your pharmacy and arrange to get another tube of eye ointment.)
2. Tilt your head back and look up
3. With one hand, pull the lower eyelid down with one or two fingers to create a small pouch
4. With the other hand, position the medicine above your eye
5. Put a thin line of ointment in the pouch. Close the eye for 30 to 60 seconds to let the ointment absorb
6. Wash your hands
7. Eye ointments can cause some temporary blurring of vision

Patients with severe refractory DED may not benefit enough from lifestyle modifications and pharmacologic therapy. Many other interventions exist including[14]

- Punctal plugs blocking the tear ducts to promote tear conservation
- Pulsed light therapy delivered in office with a handheld flash gun
- Tear stimulation utilizing topical and systemic secretagogues
- Biological tear substitutes utilizing patient-derived serum
- Use of therapeutic contact lenses made of silicone hydrogel
- Surgery to correct any causative physiological abnormalities

Pharmacy staff should recognize when patients with worsening DED symptoms may require escalation of therapy and refer them to an eye care provider when appropriate.

Pause and Ponder: Consider your home and work environment. Could you take steps to minimize conditions contributing to developing dry eye?

CONCLUSION

You may have noticed a recurring theme throughout this activity: education. Helping patients understand the chronic nature of DED and navigate treatment options improves patient care and outcomes. Education must include the entire pharmacy team. Understanding the roles of each treatment allows for effective management and counseling. Educated pharmacy teams can assist patients with product selection, counsel on the timing and administration of treatments, improve safety, and provide referrals when appropriate.

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