Management of Dry Eye Disease

Michael A. Lemp, MD

Abstract

The management of dry eye disease (DED) encompasses both pharmacologic and nonpharmacologic approaches, including avoidance of exacerbating factors, eyelid hygiene, tear supplementation, tear retention, tear stimulation, and anti-inflammatory agents. Artificial tears are the mainstay of DED therapy but, although they improve symptoms and objective findings, there is no evidence that they can resolve the underlying inflammation in DED. Topical corticosteroids are effective anti-inflammatory agents, but are not recommended for long-term use because of their adverse-effect profiles. Topical cyclosporine—currently the only pharmacologic treatment approved by the US Food and Drug Administration specifically for DED—is safe for long-term use and is disease-modifying rather than merely palliative. Treatment selection is guided primarily by DED severity. Recently published guidelines propose a severity classification based on clinical signs and symptoms, with treatment recommendations according to severity level.

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For author information and disclosures, see end of text.

Treatment options

There is a wide variety of pharmacologic and nonpharmacologic approaches to the management of dry eye disease (DED). These approaches are best described within categories that include avoidance of exacerbating factors, eyelid hygiene, tear supplementation, tear retention, tear stimulation, and anti-inflammatory agents.

Avoidance of exacerbating factors

Environmental modifications such as humidification, avoidance of wind or drafts, and avoidance of dusty or smoky environments may ameliorate DED symptoms. Lifestyle or workplace modifications may be helpful, for example, taking regular breaks from reading or computer use, and lowering the computer monitor below eye level so that the gaze is directed downward.[1-4] Increasing blink frequency[1] or fast blinking exercises[4] have also been recommended. If feasible, medications that exacerbate DED should be discontinued.[1] In an accompanying article in this supplement, Perry discusses modifiable risk factors for DED, including exacerbating medications.[5]

Eyelid hygiene

Washing the eyelid margin with a gentle soap decreases bacterial colonization. Bacterial colonization is believed to inhibit conjunctival goblet cell proliferation[6] and may also increase the breakdown of meibomian lipid.[2] Reducing colonization, therefore, may improve both the mucous and lipid layers of the tear film. Warm compresses may reduce evaporative loss by temporarily thickening the lipid layer.[6] Manual expression of the meibomian glands has been shown to increase lipid layer thickness and tear film stability in normal subjects.[7]

In a small nonrandomized study of patients with meibomian gland dysfunction (MGD), a daily regimen of eyelid scrubbing and warm compresses, plus meibomian gland expression performed as an office procedure every 6 weeks, resulted in less-solidified meibomian secretions and significantly increased lipid layer thickness. Patients also reported improvement of DED symptoms.[8]

Tear supplementation

Artificial tears are the mainstay of DED treatment. They are used in all stages of DED, either alone (in mild to moderate disease) or in combination with other treatments (in moderate to severe disease).[9]

Most tear supplements act as lubricants; other actions may include replacement of deficient tear constituents, dilution of proinflammatory substances, reduction of tear osmolarity,[2,9] and protection against osmotic stress.[10]

A wide variety of over-the-counter (OTC) artificial tear products is available. These products differ with respect to a number of variables that include electrolyte composition, osmolarity/osmolality, viscosity, the presence or absence of preservatives,[2] and the presence or absence of compatible solutes.[10]

- *Electrolyte composition*. Products that mimic the electrolyte composition of natural tears are available. Of the electrolytes, potassium and bicarbonate appear to be the most important.[2]
- *Osmolarity/osmolality*. DED patients have higher-than-normal tear film osmolarity (ie, crystalloid osmolarity, which relates to the concentration of small dissolved particles, such as ions). Although some studies suggest that artificial tears ideally should mimic the osmolarity of normal tears, others suggest that hypo-osmolar artificial tears are optimal.[9] Products with varying degrees of hypo-osmolarity have been developed.[2]

Colloid osmolality (which relates to macromolecule concentration) also varies among artificial tear products, and may be important because it influences water transport across the ocular surface epithelium. Theoretically, high colloid osmolality may be beneficial in reducing swelling of damaged epithelial cells.[2]

- *Viscosity*. Higher artificial tear viscosity increases tear retention time and may help protect the ocular surface. Viscosity agents used in artificial tears include carboxymethylcellulose (CMC), polyvinyl alcohol, polyethylene glycol, propylene glycol, hydroxypropyl-guar (HP-guar), and lipids such as those that make up castor oil or mineral oil.[2]

Lipid-containing artificial tear products such as Refresh Endura (with castor oil) and Soothe XP (with mineral oil) are intended to decrease tear evaporation by restoring the lipid layer of the tear film[2,11-13]; this may be particularly useful in patients with MGD.[11] HP-guar (in products such as Systane) is believed to form a bioadhesive gel when exposed to ocular pH, increasing aqueous retention and protecting the ocular surface by mimicking the mucous layer of the tear film.[14,15]

Hyaluronic acid is a naturally occurring viscoelastic substance[16] that may also have anti-inflammatory activity.[17] In small randomized trials, artificial tears containing sodium hyaluronate (SH) have demonstrated greater improvement of DED signs and/or symptoms compared with normal saline[18] and with other viscosity agents such as CMC[19] or hydroxypropyl-methylcellulose/dextran.[16] However, in another report, an SH-containing tear supplement was significantly less effective than topical cyclosporine in improving tear film stability and goblet cell density.[17] SH-containing artificial tear products are commercially available in some countries, but have not been approved by the US Food and Drug Administration (FDA) for use in the United States.[2]

High-viscosity agents tend to cause visual blurring; therefore, lower-viscosity agents are generally preferred for mild to moderate DED. However, in more severe cases, high-viscosity agents may be needed for symptom control.[9] Ophthalmic gels and ointments have higher viscosity than liquids; they are also associated with more visual blurring than liquids and, therefore, are usually reserved for overnight use.[9] Gels containing carbomers cause less blurring than petrolatum-based ointments,[2] perhaps because carbomer viscosity decreases rapidly on exposure to tear salts.[20]

- *Preservatives*. Preservatives are added to artificial tears to reduce the risk of bacterial contamination in multidose containers, and to prolong shelf life. There are 2 main types of preservatives: detergent and oxidative.[9]

Detergent preservatives act by altering bacterial cell membrane permeability.[9] Detergents have toxic effects on the ocular surface epithelium and, with frequent use, can cause epithelial irritation and damage. Patients with a compromised tear film are at higher risk. Benzalkonium chloride, the most widely used preservative in topical ophthalmic preparations, is an example of a detergent preservative.[2,9]

Oxidative preservatives penetrate the bacterial cell membrane and act by interfering with intracellular processes. They are sometimes referred to as "vanishing" preservatives because they dissipate on

contact with the eye and, therefore, are less likely than detergents to cause ocular damage.[9] However, they may not always dissipate completely in DED patients because of decreased tear volume.[2] Stabilized oxychloro complex is an example of an oxidative preservative.

Preserved tears are usually well tolerated in mild DED, when used no more than 4 to 6 times daily.[2] (Exposure to preservatives in other topical ophthalmic agents [eg, glaucoma medications] must also be taken into account.) If more frequent use is necessary, unpreserved tears are recommended.[2,9] Until recently, the FDA required unpreserved tears to be packaged in single-dose vials to avoid bacterial contamination; this makes them more expensive and less convenient to use.[2] However, an unpreserved product (Visine Pure-Tears) is now available in a multidose vial with a dispensing system designed to prevent contamination.[2,9]

- *Compatible solutes*. Osmotic stress occurs when the concentration of molecules and/or ions inside a cell differs from that outside the cell—as is the case in DED, in which the corneal epithelium is exposed to hyperosmolar tears. Under osmotic stress, the corneal epithelial cells tend to lose water, and may compensate by increasing their internal electrolyte concentration to stabilize their volume. However, elevated electrolyte concentrations can eventually lead to cellular damage.[10,21]

Compatible solutes are small nonionic molecules (eg, glycerin) that can be taken up by cells, increasing intracellular osmolarity without disrupting cellular metabolism. Artificial tears containing compatible solutes may thus provide protection against osmotic stress.[10,21] Products containing compatible solutes include Optive and Refresh Endura (with 0.9% and 1% glycerin, respectively).

Large, randomized, masked comparative trials of different artificial tear products have not been performed.[2] However, limited data suggest that there may be differences in product efficacy, for example:

- In small, randomized, comparative trials, a product containing polyethylene glycol, propylene glycol, and HP-guar, with the detergent preservative polyquaternium-1 (Systane), was significantly more effective than a CMC product preserved with stabilized oxychloro complex (Refresh Tears) in improving symptoms,[22,23] ocular surface staining,[22,23] and tear breakup time (TBUT).[24] Systane also improved TBUT significantly more than an unpreserved product containing glycerin, polysorbate 80, and castor oil (Refresh Endura).[24]
- A randomized, internally paired study compared a mineral oil–containing product (Soothe) versus Systane. Forty patients received a single drop of Soothe in one eye and a single drop of Systane in the other eye (the eye in which each treatment was used was randomly assigned). Both treatments significantly increased tear film lipid layer thickness, but the increase was significantly greater with Soothe than with Systane.[25] In a similarly designed trial (N = 41), Soothe increased lipid layer thickness significantly more than Refresh Dry Eye Therapy (a product similar to Refresh Endura, but preserved with stabilized oxychloro complex).[26]

Although artificial tears can improve symptoms and objective findings, there is no evidence that they can resolve the inflammation that accompanies DED.[2]

Autologous serum tears, produced from the patient's serum, have been used in severe DED. Autologous serum tears have biochemical and mechanical properties similar, but not identical, to those of normal aqueous tears.[27] They are unpreserved but can be stored frozen for 3 to 6 months,[27,28] so that blood donation is required 2 to 4 times a year.

Several small, randomized studies investigating autologous serum tears versus unpreserved saline drops,[29] unpreserved artificial tears,[30] and/or other conventional treatment[28] suggest that autologous serum tears are effective in improving symptoms and signs of severe or refractory DED—although, in one of these studies, only nonsignificant trends were observed.[29] A randomized study in post–laser-assisted in situ keratomileusis (LASIK) DED demonstrated significant improvement in rose bengal staining and TBUT, but not in the Schirmer test or symptom scores, with autologous serum tears compared with artificial tears.[31] Differences in efficacy may result from differences in production, storage, and treatment protocols. An optimized production protocol has recently been published.[2]

Few complications have been reported with autologous serum tears; however, circulating antibodies in serum could theoretically cause an inflam-

matory response.[27] Other potential adverse effects (AEs) from prolonged exposure of the ocular surface to serum components have not been ruled out.[28]

Tear retention

Lacrimal outflow occlusion slows tear clearance, and is indicated in patients with aqueous-deficient DED.[2] However, it is relatively contraindicated in the presence of clinically apparent inflammation. When inflammation is present, occlusion prolongs ocular surface exposure to abnormal tears containing proinflammatory cytokines; therefore, treatment of inflammation before plug insertion is usually recommended.[2,32,33]

Punctal plugs are the most commonly used means of occlusion, and have been shown to improve DED symptoms and signs in a number of clinical studies. There are 2 main types of punctal plugs: absorbable and nonabsorbable. Absorbable plugs are made of collagen or various polymers, and may last for days to months.[2] Some newer absorbable materials may last as long as 6 months.[33] Nonabsorbable plugs, often made of silicone or hydrophilic acrylic, are intended to be permanent.

A common complication of punctal plugs is epiphora (tear overflow). Mild epiphora has been reported in up to 36% of patients. Epiphora is usually well tolerated, but as many as 5% of patients request plug removal.[33] Other AEs include infection[2] and conjunctival irritation.[33] Short-term absorbable plugs may be used initially to predict which patients are likely to tolerate nonabsorbable plugs; however, this test is not completely reliable.[33]

Spontaneous extrusion of plugs occurs in up to 50% of patients within 3 months, requiring replacement. In contrast, internal migration is uncommon but troublesome, because removal of a migrated plug may require surgery. If not removed, a migrated plug can cause complete occlusion, which may lead to epiphora, infection, or fistulas. Newer plug designs minimize the risk of spontaneous extrusion or migration.[33]

Intracanalicular plugs are an alternative to punctal plugs with less risk of extrusion or conjunctival irritation. However, canalicular inflammation or infection may occur. Furthermore, removal is more difficult than with punctal plugs, requiring more invasive procedures.[33]

Surgical occlusion (eg, using electrocautery, laser, or glue) is an option for patients who tolerate plugs but repeatedly extrude them. However, the wide choice of reversible devices currently available has decreased the need for occlusive surgery.[33]

Moisture spectacles/goggles reduce tear evaporation by increasing humidity around the eye. The patient's glasses can be modified using commercially available top and side shields or swimming goggles can be used.[34] However, evidence of efficacy is limited[2] and adherence may be poor for cosmetic reasons.[1]

Therapeutic contact lenses (also called bandage contact lenses) may be used in severe DED, or when other therapy has failed, to help retain the tear film and/or promote ocular surface healing.[35] For example, therapeutic contact lenses may be useful in the management of filamentary keratitis.[35-37] However, because contact lenses can also exacerbate DED, patients using them for DED must be monitored closely.[35]

Silicone hydrogel lenses have been recommended for use in DED because of their high oxygen permeability and relatively low water content. The low water content makes them less likely to dehydrate[35] in the presence of a hyperosmolar tear film.

The Boston scleral lens is a therapeutic contact lens that is custom-manufactured using a computer-assisted design program.[38,39] It is a rigid gas-permeable lens that vaults the cornea and rests entirely on the sclera, creating a fluid-filled precorneal space.[38,40] In this way, it provides a "liquid bandage" for the corneal surface, reducing or eliminating desiccation, hyperosmolarity, and friction with the eyelids.[39] It is also fluid-ventilated—designed with channels that allow tears to flow into the precorneal space, avoiding the development of negative pressure.[38,40]

The Boston scleral lens is indicated for management of severe, refractory ocular surface disease, for example, to relieve disabling pain and photophobia or treat persistent epithelial defects.[38-40] It is also used to improve visual acuity when conventional lenses are inadequate or are not tolerated.[38] Successful use has been reported in DED, including DED with filamentary keratitis[38,40] and severe DED secondary to graft-versus-host disease,[38,39] Sjögren syndrome,[38] or radiation.[38] Additional information about the Boston scleral lens can be obtained from the Boston Foundation for Sight at http://www.bostonsight.org or (781) 726-7337.

Tarsorrhaphy (closure of the eyelids) is reserved for severe or refractory DED.[1,34] Methods include:

- Short-term tarsorrhaphy using, for example, tape, adhesive glue (lasts a few days), or botulinum toxin (lasts an average of 16 days).[41]
- Temporary suture tarsorrhaphy (lasts as long as 4-6 weeks).[41]
- "Permanent" tarsorrhaphy. The lid margins are excised and sutured so that they heal together. The procedure can be reversed later.[41]

In most cases, only the lateral portions of the lids are closed to narrow the palpebral aperture, decreasing evaporation.[34,41] A partially open eye allows partial vision, administration of drops, and corneal examination; it also allows more oxygen to reach the cornea.[41] However, if partial closure fails, complete closure may be indicated.[34]

In a retrospective review of 77 tarsorrhaphy patients, complications included trichiasis (ingrown eyelashes) in 18.2%; adhesion of the upper and lower lids after tarsorrhaphy removal in 2.6%; pyogenic granuloma in 1.3%; and keloid formation in 1.3%. All of these complications occurred in patients with permanent tarsorrhaphies. Other reported complications have included lid margin deformities, suture granulomas, focal cellulitis, skin breakdown, and distichiasis.[41]

Tear stimulation: secretagogues

Cholinergic agents (ie, muscarinic acetylcholine receptor agonists) are sometimes given orally to treat aqueous-deficient DED. Two agents, pilocarpine and cevimeline, have FDA-approved indications for treatment of dry mouth associated with Sjögren syndrome; however, they are off-label for treatment of dry eye.[42,43]

Pilocarpine. Two multicenter, 12-week, randomized, placebo-controlled trials of oral pilocarpine have been conducted, involving a total of 629 patients with Sjögren syndrome. In these trials, pilocarpine significantly improved global assessment of DED symptoms[44-46] at doses of 5.0 to 7.5 mg QID.[46] Pilocarpine also significantly decreased the use of artificial tears and improved salivary flow (measured by 5-minute saliva sample collection).[44]

A single-center, randomized trial of pilocarpine (5 mg BID) versus punctal occlusion versus artificial tears alone involved 85 Sjögren syndrome patients. (All patients received artificial tears.) Pilocarpine significantly improved global symptom assessment compared with the other 2 groups; it also significantly improved rose bengal staining, but not Schirmer scores or goblet cell numbers.[47]

In the placebo-controlled trials, the most common drug-related AE was sweating.[44-46] Other AEs probably related to pilocarpine included urinary frequency, flushing, and hypersalivation.[46] Headache, nausea, rhinitis, and dizziness were also common, but occurred with similar frequency in the pilocarpine and placebo groups.[46] AEs were typically mild to moderate, and were roughly dose-dependent.[46] No serious AEs were reported.[44-46] Among patients receiving pilocarpine 5.0 to 7.5 mg QID, 3.9% to 8.6% withdrew because of AEs, compared with 4.0% to 4.7% of those receiving placebo.[44]

Cevimeline. Two multicenter, randomized trials of oral cevimeline have been conducted, involving a total of 257 patients with Sjögren syndrome. In the first trial, 197 patients were randomized to cevimeline (15 or 30 mg TID) or placebo for 12 weeks. The 30-mg dose significantly improved both Schirmer scores and global symptom self-assessment, compared with placebo. The 15-mg dose also relieved some symptoms and improved Schirmer scores, but less so than the higher dose. Common drug-related AEs included increased sweating and nausea. Headache and diarrhea were also common, but occurred with similar frequency in the cevimeline and placebo groups. AEs led to withdrawal in 16.1% of the cevimeline 30-mg group, 13.8% of the 15-mg group, and 4.3% of the placebo group.[48]

In the second trial, 60 patients were randomly assigned to cevimeline (20 or 30 mg TID) or placebo for 4 weeks. Compared with placebo, both cevimeline doses improved subjective symptoms, tear dynamics, ocular surface condition, and global assessment; however, statistical significance was not reached for all parameters at all time points, and not all parameters showed a dose response. The 20-mg dose demonstrated the most consistent improvements at 4 weeks. Inconsistencies in the results may be attributed, in part, to the fact that the study was underpowered (the intended enrollment of 80 patients was not reached), and to between-group differences at baseline. The most common AEs were gastrointestinal symptoms (including nausea and diarrhea) and increased sweating, all mild to moderate.[49]

Anti-inflammatory agents

Topical corticosteroids are approved by the FDA for corticosteroid-responsive inflammatory conditions of the conjunctiva, cornea, and anterior globe. This indication can be interpreted as including DED.[2]

Several randomized trials have demonstrated that short-term topical corticosteroid use (as long as 4 weeks) improves signs and symptoms of DED[2]:

- In a single-blind trial, 32 DED patients were randomly assigned to 30 days of treatment with either a topical corticosteroid, fluorometholone; a topical nonsteroidal anti-inflammatory drug (NSAID), flurbiprofen; or artificial tears alone. (All patients received artificial tears, but these were used QID in the artificial tears–only group, and as many as 8 times daily in the corticosteroid and NSAID groups.) The corticosteroid group had significantly improved symptom scores on days 15 and 30, compared with the other groups. Corneal staining and goblet cell numbers were also improved with topical corticosteroid treatment compared with the other 2 treatments.[50]
- In a double-blind, placebo-controlled trial, 64 DED patients were randomized to either a topical corticosteroid (loteprednol etabonate 0.5%) or vehicle, QID for 4 weeks. Both groups experienced a significant treatment effect compared with baseline, but the primary subjective and objective outcomes (worst symptom score and fluorescein staining score, respectively) did not differ between the groups. A post-hoc subset analysis suggested that patients with at least moderate clinical inflammation are more likely to show significant benefits with loteprednol.[51]
- In a double-blind trial, 41 DED patients each received prednisolone 0.1% in one randomly selected eye, versus hyaluronic acid 0.1% in the other eye, TID for 28 days. Compared with baseline, both treatments improved symptom scores and TBUT, but not Schirmer scores. Prednisolone was significantly better than hyaluronic acid in improving symptom scores at day 28; however, there was no between-group difference in TBUT. Prednisolone, but not hyaluronic acid, improved impression cytology scores and decreased the tear concentration of neurotrophic growth factor (NGF). (Elevated NGF levels are associated with inflammation.[52])

In another trial, 15 patients with Sjögren syndrome received unpreserved methylprednisolone 1%, TID for 2 weeks, followed by punctal occlusion. This group was compared with 15 Sjögren syndrome patients who were treated directly with punctal occlusion alone. The group initially treated with the corticosteroid had significantly improved symptoms and corneal staining at 1 week and at 2 months, compared with the group receiving only punctal occlusion.[53]

Although topical corticosteroids are effective, they are generally recommended only for short-term use because prolonged use may result in AEs including ocular infection, glaucoma, and cataracts. However, corticosteroids may differ in their propensity to cause these complications. For example, some evidence suggests that loteprednol, which is rapidly metabolized to inactive metabolites, may have a better safety profile than other corticosteroids.[51] In a summation of randomized studies, treatment with loteprednol etabonate (0.5% concentration) for >28 days resulted in a 2% incidence of elevated intraocular pressure, compared with a 7% incidence with prednisolone acetate (1% concentration) and 0.5% incidence with placebo.[54]

Oral tetracyclines have been used off-label to treat DED, primarily DED associated with ocular rosacea. Although oral doxycycline has an FDA-approved indication for inflammatory lesions (papules and pustules) of rosacea, it is not FDA approved for ocular rosacea.[55]

It has been suggested that reduction of bacterial flora may decrease the breakdown of meibomian lipid. However, tetracyclines are used in DED primarily for their anti-inflammatory rather than antibacterial actions. Mechanisms may include decreased matrix metalloproteinase activity, and decreased production of proinflammatory cytokines such as interleukin (IL)-1 and tumor necrosis factor-alpha.[2] Several small, randomized clinical trials, mostly in ocular rosacea, provide limited evidence of efficacy.

- Oral oxytetracycline, topical fusidic acid, and the 2 agents combined (neither agent available in the United States) were compared in a double-blind, partial crossover study involving 43 patients with long-term blepharitis (of whom 18 had rosacea). All patients received double placebo during run-in and washout periods. Among the patients with blepharitis and rosacea, 75% had symptomatic improvement with fusidic acid, 50% with oxytetracycline, but only 35% with the combination. Among the patients with nonrosacea blepha-

ritis, none responded to fusidic acid alone, but 25% improved with oxytetracycline and 30% with the combination. No statistical analysis was reported for comparison among the active treatments.[56]

- In a double-blind trial involving 35 patients with ocular rosacea, oral oxytetracycline significantly improved nonspecific clinical signs compared with placebo.[57]
- Twenty-eight patients with ocular rosacea were randomized to either oral tetracycline (250 mg QID for 4 weeks, then 250 mg BID for 5 months) or meibomian gland expression. Compared with baseline, tetracycline significantly improved TBUT but not Schirmer scores. Meibomian gland expression produced no significant improvement in either measurement compared with baseline. No between-group statistical analysis was reported.[58]

No randomized trials of doxycycline or minocycline for ocular rosacea or DED have been published.

Topical cyclosporine was approved by the FDA in December 2002. According to product information, cyclosporine ophthalmic emulsion 0.05% (Restasis) is indicated "to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs."[59]

Topical cyclosporine is currently the only pharmacologic treatment that is FDA approved specifically for DED. As previously noted, topical corticosteroids are approved for corticosteroid-responsive inflammatory conditions of the ocular surface (which presumably include DED); oral doxycycline is approved for inflammatory skin lesions of rosacea (but not for ocular rosacea); and pilocarpine and cevimeline are approved for dry mouth (but not dry eye) symptoms associated with Sjögren syndrome.

Evidence suggests that cyclosporine is disease-modifying rather than merely palliative. In studies of DED patients, cyclosporine reduced conjunctival IL-6 levels,[60] decreased activated lymphocytes in the conjunctiva,[61] reduced conjunctival inflammatory and apoptotic markers,[62,63] and increased conjunctival goblet cell numbers.[64]

Pivotal clinical trials. The efficacy and safety of cyclosporine ophthalmic emulsion (0.1% and 0.05%) in moderate to severe DED were demonstrated in two 6-month, multicenter, randomized, double-blind, vehicle-controlled phase 3 trials. Although both cyclosporine and vehicle significantly decreased symptoms and objective signs compared with baseline, cyclosporine was significantly more effective than vehicle in improving several efficacy outcomes. Two objective outcomes—corneal fluorescein staining and the Schirmer test with anesthesia—were significantly more improved with cyclosporine (both 0.05% and 0.1%) than with vehicle. Three subjective outcomes—blurred vision, need for artificial tears, and physician's evaluation of global response—were significantly improved with cyclosporine 0.05% (but not 0.1%) compared with vehicle. There were no between-group differences in conjunctival staining, Schirmer test without anesthesia, or symptoms other than blurred vision.[65]

Most AEs reported during the phase 3 trials were mild to moderate and transient. The most common treatment-related AEs were ocular burning and stinging, occurring in 16.1% and 4.5%, respectively, of the cyclosporine 0.1% group; 14.7% and 3.4% of the cyclosporine 0.05% group; and 6.5% and 1.4% of the vehicle group. Burning and/or stinging led to discontinuation in 3.1% of the cyclosporine 0.1% group, 1.7% of the cyclosporine 0.05% group, and 1.7% of the vehicle group. The investigators noted that only 2 patients (both in the vehicle group) developed ocular infection during treatment.[65]

A multicenter, nonrandomized, open-label, phase 3 extension trial was conducted to further evaluate safety. Four hundred twelve patients who had previously been treated with cyclosporine (0.1% or 0.05%) for 6 to 12 months subsequently received cyclosporine 0.1% for an additional 1 to 3 years. The most common AEs were burning (10.9%), stinging (3.9%), and conjunctival hyperemia (3.4%). Most AEs were mild to moderate; no serious AEs occurred. Efficacy evaluation (for the first year only of the extension studies) showed that previous improvements in objective and subjective outcomes were maintained. More than 95% of responding patients said they would continue cyclosporine, and nearly 98% said they would recommend it to others.[66]

Systemic exposure. In the phase 3 trials, cyclosporine blood levels were measured in 128 patients. Even after 9 to 12 months of treatment, trough levels were below the quantification limit of 0.1 ng/mL in 100% of samples collected from patients receiving 0.05% cyclosporine, and in all but 5.5% of samples collected from patients receiving 0.1% cyclosporine. Among the 5.5%, none had levels >0.3 ng/mL.[67]

Serial postdose samples were also collected from 26 patients after 9 to 12 months of treatment. Only 1.4% of samples—all from patients receiving 0.1% cyclosporine—were above the quantification limit, and those were barely detectable.[67]

These blood levels are orders of magnitude lower than those occurring during oral immunosuppressive therapy with cyclosporine.[67] Furthermore, in the extension studies, nonocular AEs occurred in only 1% of patients (2 cases of moderate headache, 1 moderate allergic reaction, and 1 mild case of alopecia).[66] Thus, it can be concluded that the risk of systemic toxicity is minimal.

Topical NSAIDs have been used off-label in DED. Two small randomized trials provide limited evidence of efficacy.

- In a 28-day open-label trial, topical diclofenac 0.1% QID was compared with saline 5% QID in 32 patients with secondary Sjögren syndrome and filamentary keratitis. Both treatments resulted in disappearance of filaments by day 28; however, the diclofenac group improved significantly more rapidly. Symptomatic improvement was also significantly faster with diclofenac.[68]
- In a 6-week open-label trial in 52 DED patients, topical ketorolac 0.4% significantly reduced symptoms and corneal staining when used adjunctively during induction of topical cyclosporine therapy, compared with cyclosporine alone.[69]

Despite some evidence of efficacy, serious safety concerns have been raised regarding the use of topical NSAIDs in DED. NSAIDs (especially diclofenac) reduce corneal sensitivity, potentially contributing to corneal damage in DED by interfering with reflex tearing and blinking. Cases of corneal melting have been reported, especially in postoperative settings.[70,71] Because topical NSAIDs can promote corneal melting in patients with a compromised ocular surface, their use in DED is controversial. Some experts feel that they have no role in the treatment of DED.

Nutritional supplements

Essential fatty acids (EFAs) may, theoretically, benefit DED in 2 ways: by reducing inflammation and by altering the composition of meibomian lipids.[72] There are at least 2 EFA nutritional supplements marketed specifically for DED: one containing omega-3 fatty acids from flaxseed and fish oil,[73] and another containing a blend of omega-3 and omega-6 fatty acids (docosahexaenoic acid/eicosapentaenoic acid [DHA/EPA] from cod liver oil and gamma-linolenic acid [GLA] from black currant seed oil, respectively).[74] However, evidence for EFA efficacy is limited and conflicting.

Epidemiologic data from the Women's Health Study (WHS) showed an association between higher dietary omega-3 fatty acid intake and a lower risk of DED. Omega-6 fatty acid intake was not independently associated with DED; however, a higher omega-6:omega-3 ratio was associated with significantly greater DED risk.[75] Several small clinical trials of EFA nutritional supplements have also been conducted (described below).

Omega-3 fatty acids. In a randomized, double-blind, placebo-controlled trial involving 41 patients with Sjögren syndrome, an omega-3 supplement improved DED symptoms more than placebo; however, the difference did not reach statistical significance ($P = .082$).[76]

Omega-6 fatty acids. The WHS data suggest that omega-6 fatty acid supplementation should not improve DED; however, small clinical trials have given conflicting results:

- Two randomized trials of omega-6 fatty acids in Sjögren syndrome patients (N = 28 and N = 90) showed no significant improvement in DED signs or symptoms compared with placebo.[77,78] In one of the trials, however, the active treatment group had significant improvement versus baseline, whereas improvement in the placebo group versus baseline did not reach statistical significance.[77]
- In contrast, 2 other randomized trials (N = 26 and N = 40) demonstrated significant improvement of DED symptoms and some objective signs with the omega-6 fatty acids linoleic acid (LA) plus GLA, compared with placebo.[79,80]
- A randomized trial of prophylactic LA plus GLA versus no omega-6 treatment was conducted in 60 patients undergoing photorefractive keratectomy. Significant postoperative differences were found in DED symptoms and

some objective signs, in favor of LA plus GLA.[81]

- A randomized trial of LA plus GLA versus lid hygiene versus both treatments in 57 patients with MGD demonstrated that combined treatment was more effective than either treatment alone.[72]

The positive clinical trials of omega-6 fatty acids were all conducted in Italy, whereas the negative trials were conducted in North America, the United Kingdom, and Scandinavia. In light of the WHS findings described above, one may speculate that the conflicting results could be explained by differences in dietary omega-6:omega-3 fatty acid ratios among these countries. Differences in study design, as well as limitations caused by small study size, may also account for the discrepant results.

Mucolytics

Topical acetylcysteine was mentioned in the literature as a DED treatment as early as the 1960s,[82] and is still sometimes used in DED patients with dense mucus accumulation,[83] for example, in filamentary keratitis.[37,84] Acetylcysteine is not commercially available as a topical ophthalmic agent.[83] Inhalational acetylcysteine (FDA approved for use as a bronchial mucolytic) has been diluted for off-label use as a topical ophthalmic agent.

Topical vitamin A (retinol)

Vitamin A deficiency is a known cause of xerophthalmia; however, most DED patients are not vitamin A–deficient. Because retinol is present in tears, it has been hypothesized that DED may be associated with local retinol deficiency at the ocular surface.[83] Based on this hypothesis, topical retinol has been used to treat various forms of DED, with variable results.[83] Limited data suggest a possible role in reversing squamous metaplasia and keratinization of the ocular surface in severe DED, for example, in cicatrizing conjunctivitis or graft-versus-host disease.[83,85-87] However, the use of topical retinol in DED remains controversial.[83]

Guidelines and treatment selection

Previous practice guidelines have used an eti-

Table 1. DEWS Dry Eye Severity Grading Scheme[2]

Dry Eye Severity Level	1	2	3	4*
Discomfort, severity & frequency	Mild and/or episodic; occurs under environmental stress	Moderate episodic or chronic, stress or no stress	Severe frequent or constant without stress	Severe and/or disabling and constant
Visual symptoms	None or episodic mild fatigue	Annoying and/or activity-limiting episodic	Annoying, chronic and/or constant, limiting activity	Constant and/or possibly disabling
Conjunctival injection	None to mild	None to mild	+/-	+/++
Conjunctival staining	None to mild	Variable	Moderate to marked	Marked
Corneal staining (severity/location)	None to mild	Variable	Marked central	Severe punctuate erosions
Corneal/tear signs	None to mild	Mild debris, ↓ meniscus	Filamentary keratitis, mucus clumping, ↑ tear debris	Filamentary keratitis, mucus clumping, ↑ tear debris, ulceration
Lid/meibomian glands	MGD variably present	MGD variably present	Frequent	Trichiasis, keratinization, symblepharon
TBUT (sec)	Variable	≤10	≤5	Immediate
Schirmer score (mm/5 min)	Variable	≤10	≤5	≤2

*Must have signs AND symptoms.
DEWS indicates Dry Eye WorkShop; TBUT, tear breakup time; MGD, meibomian gland dysfunction.
Modified from International Task Force guidelines for the classification of dry eye disease.[32]

ology-oriented approach to DED.[1,34] However, commonly used etiologic classifications (eg, aqueous-deficient vs evaporative, Sjögren vs non-Sjögren) often are not helpful in establishing a treatment plan.[32]

International Task Force (ITF) guidelines, published in 2006, propose a classification of DED severity based on clinical signs and symptoms. The ITF also developed treatment algorithms according to severity classification and the presence or absence of lid margin disease.[32] In 2007 the Management and Therapy Subcommittee of the International Dry Eye WorkShop (DEWS) adopted a modified form of the ITF severity grading, as shown in **Table 1**.[2] The DEWS treatment recommendations were based on the modified severity grading.

Cyclosporine versus other anti-inflammatory agents

As discussed above under **Treatment options,** topical cyclosporine has demonstrated long-term efficacy and safety in the treatment of DED. In contrast, topical corticosteroids are effective but are not recommended for long-term use because of their AEs. Oral tetracyclines have been used for their anti-inflammatory activity, primarily in DED associated with ocular rosacea; however, this use is off-label and is based on limited evidence. Topical NSAIDs have also been used off-label, but whether they have any role in DED has been questioned because of reports of serious AEs in patients with a compromised ocular surface.

Cyclosporine versus punctal plugs

In the ITF algorithm for treatment of DED without lid margin disease (**Table 2**), topical cyclosporine is recommended as a treatment option for DED at level 2 severity (but only in the presence of clinically evident inflammation), whereas punctal plugs are recommended at level 3 severity (after control of inflammation).[32] In contrast, the DEWS recommendations list both cyclosporine and punctal plugs as level 2 options, without specifying the presence or absence of clinical inflammation.[2] Thus, there appears to be no clear consensus regarding the relative roles of cyclosporine versus punctal plugs.

In a small comparative trial, 30 patients with moderate DED were randomized to 6 months of treatment with either cyclosporine 0.05% or lower-lid punctal plugs, or both. Outcome measures included rose bengal staining, Schirmer scores without anesthesia, and artificial tear use.[88]

- At 1 and 3 months, both of the plug-containing regimens significantly improved Schirmer scores compared with baseline and with cyclosporine alone. Cyclosporine alone produced no initial Schirmer score response; however, by 6 months, all 3 groups had significant improvement compared with baseline, with no significant between-group differences.[88]
- In contrast, both of the cyclosporine-containing regimens significantly improved rose bengal staining at 3 and 6 months compared with baseline; there was no statistical difference between cyclosporine with versus without plugs. Plugs alone did not improve staining scores at any time point compared with baseline.[88]
- Artificial tear use declined significantly in all 3 groups compared with baseline, at all time points except in the cyclosporine-only group at 1 month. At 6 months there was no statistical difference between combination treatment and cyclosporine alone; however, combination treatment was significantly superior to plugs alone.[88]

The investigators concluded that all 3 treatments were effective, but that plugs were more

Level 1:
Education and counseling Environmental management Elimination of offending systemic medications Preserved tear substitutes, allergy eye drops
Level 2:
If Level 1 treatments are inadequate, add: Unpreserved tears, gels, ointments Steroids Cyclosporine A Secretagogues Nutritional supplements
Level 3:
If Level 2 treatments are inadequate, add: Tetracyclines Autologous serum tears Punctal plugs (after control of inflammation)
Level 4:
If Level 3 treatments are inadequate, add: Topical vitamin A Contact lenses Acetylcysteine Moisture goggles Surgery

Modified from International Task Force dysfunctional tear syndrome treatment algorithm.[32]

beneficial for immediate relief of dryness, whereas cyclosporine improved ocular surface health over time. The combination of the 2 treatments produced the greatest overall improvement.[88]

Summary

Pharmacologic and nonpharmacologic approaches to management of DED include:

- Avoidance of exacerbating factors such as low humidity, wind or drafts, dust or smoke, prolonged visual tasks, exacerbating medications.
- Eyelid hygiene (particularly in patients with MGD).
- Tear supplementation—for example, artificial tears, autologous serum tears.
- Tear retention—for example, punctal plugs, moisture spectacles/goggles, therapeutic contact lenses, tarsorrhaphy.
- Tear stimulation—for example, oral cholinergic agents such as pilocarpine or cevimeline (used off-label for aqueous-deficient DED).
- Anti-inflammatory agents—for example, topical corticosteroids, oral tetracyclines, topical cyclosporine.
- Other therapies—for example, nutritional supplements (essential fatty acids); mucolytics (topical acetylcysteine, used off-label in DED with filamentary keratitis); and topical vitamin A (off-label and controversial, but possibly useful in severe DED with squamous metaplasia or ocular surface keratinization).

Artificial tears are the mainstay of DED therapy. Most tear supplements act as lubricants; other actions may include replacement of deficient tear constituents, dilution of proinflammatory substances, reduction of tear osmolarity, and protection against osmotic stress. A wide variety of OTC artificial tear products are available, which differ with respect to a number of variables that include:

- *Electrolyte composition*. Potassium and bicarbonate appear to be the most important.
- *Osmolarity/osmolality*. Some studies suggest that artificial tears should ideally mimic the osmolarity of normal tears; however, others suggest that hypo-osmolar artificial tears are optimal.
- *Viscosity*. Higher viscosity increases tear retention time and may help protect the ocular surface, but is more likely to cause visual blurring. Viscosity agents used in artificial tears include CMC, HP-guar, and lipids such as those that make up castor oil or mineral oil. Lipid-containing products are intended to decrease tear evaporation by restoring the lipid layer of the tear film. HP-guar is believed to form a bioadhesive gel, mimicking the mucous layer of the tear film.
- *Preservatives*. There are 2 main types of preservatives: detergent (eg, benzalkonium chloride) and oxidative (eg, stabilized oxychloro complex). Detergents can irritate or damage the ocular surface with frequent use; oxidative preservatives are less likely to do so. Preserved tears are usually well tolerated in mild DED when used no more than 4 to 6 times daily. If more frequent application is required, unpreserved tears should be used.
- *Compatible solutes*. These are small nonionic molecules (eg, glycerin) that are taken up by ocular surface epithelial cells. Because they increase intracellular osmolarity without disrupting cellular metabolism, they may protect against osmotic stress.

Although artificial tears can improve DED symptoms and objective findings, there is no evidence that they can resolve the inflammation that accompanies DED. Therefore, anti-inflammatory therapy may be indicated, including:

- *Topical corticosteroids*. Although effective, these agents are generally recommended only for short-term use because prolonged use may result in AEs including ocular infection, glaucoma, and cataracts.
- *Oral tetracyclines*. Based on limited evidence, oral tetracyclines have been used off-label to treat DED, primarily DED associated with ocular rosacea.
- *Topical cyclosporine*. Topical cyclosporine is currently the only pharmacologic treatment that is FDA approved specifically for DED. Although its onset of action is relatively slow, it is safe for long-term use and appears to be disease-modifying rather than merely palliative. The most common AE is transient burning or stinging. Because blood levels are negligible even after long-term use, the risk of systemic toxicity is minimal.

Topical NSAIDs have been used off-label in DED; however, their use is controversial because they can promote corneal melting in patients with a compromised ocular surface. Some experts feel that they have no role in DED therapy.

Treatment selection is guided primarily by DED severity. ITF guidelines, published in 2006, proposed

a DED severity classification based on clinical signs and symptoms. The ITF also developed a treatment algorithm according to severity grading and the presence or absence of lid margin disease. In 2007 the DEWS Management and Therapy Subcommittee published treatment recommendations based on a modified form of the ITF severity classification.

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Address Correspondence to: Michael A. Lemp, MD, 4000 Cathedral Avenue, NW #828B, Washington, DC 20016. E-mail: malemp@lempdc.com.

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