UPDATED EDITION

Diagnostic & Treatment Algorithms for Ocular Surface Disease States

Dry Eye

Part three of an ongoing series

New paradigms in the understanding and management of dry eye.

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Dear Colleagues:

It is our pleasure to present to you part 3 in a series of monographs on diagnostic and treatment algorithms for ocular surface disease states. First issued in 2008, the series has been updated for 2011 with the latest research. Part 1 focused on ocular allergy and part 2 on conjunctivitis.

This monograph will comprehensively review new and existing information as it relates to the understanding and management of dry eye. It also offers a consensus on the most effective ways to address and manage this condition. We hope you find the information contained here to be as valuable as we intended it to be and that it serves you well as a resource in practice.

This series has been made possible because of the generous support of Bausch + Lomb. Next up in the 2011 series is part 4, which will cover the topic of keratitis.

— The Authors

About the Authors

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PART 1: Epidemiology and Etiology of Dry Eye

Dry eye is a complex, multifactorial disease affecting the ocular surface and lacrimal glands.[1] Other than mild, episodic cases, untreated dry eye is typically progressive in nature. The prevalence of dry eye has been reported as between 14% and 33% of the population.[2] It is closely associated with increasing age and female gender. Based on data from the Women's Health Study and the Physicians Health Study, it is estimated that 3.23 million women and 1.68 million men, for a total of nearly 5 million Americans over age 50, suffer from dry eye.[3,4]

In the Blue Mountains Eye Study in Australia, 57.5% of participants aged 50 and older reported at least one dry eye symptom, and 16.6% reported moderate to severe symptoms.[5]

Reduced levels of sex hormones, particularly androgen, are thought to be a major factor in the pathophysiology of dry eye.[6,7] Declining hormone levels with age may be responsible for the "tipping point" at which women with normal ocular surfaces begin to suffer from dry eye symptoms.

In addition to age and gender, a number of other factors have been established as consistently associated with or suggestive of dry eye (*see table on opposite page*), while some conditions long considered to be associated with dry eye have not been established as such in the literature.[8]

Dry eye is the single most prevalent medically treatable eye disease seen in the typical clinical eye care practice in the United States. Dry eye is a leading reason for acute eye care office visits, and its symptoms account for nearly half of all primary or secondary eye care complaints.

Dry eye may be aqueous-deficient or evaporative in nature, and may be accompanied by anterior or posterior lid margin disease that also contributes to symptomatology. Among the most severe forms of aqueous-deficient dry eye is Sjögren's syndrome, commonly

associated with rheumatoid arthritis and other connective tissue diseases.[9] Non-Sjögren's aqueous deficiency may stem from lacrimal deficiencies or other factors.

Evaporative dry eye may be intrinsic—caused by meibomian oil deficiency or lid aperture problems, for example—or extrinsic and related to contact lens wear or other factors.

According to the DEWS report and other respected sources, a core mechanism in the initiation of dry eye is tear hyperosmolarity.[2,10] Tear hyperosmolarity activates a cascade of inflammatory events on the ocular surface and the release of inflammatory mediators into the tears. Meibomian gland dysfunction (MGD) likely plays a significant role in the etiology of dry eye, increasing aqueous evaporation, hyperosmolarity and tear film instability.[11] Tear film instability can also be caused by other factors without prior hyperosmolarity.

Allergy, the use of systemic drugs that decrease aqueous or oily secretions, chronic use of topical medications with toxic preservatives, and reduced blink rates during computer usage are common factors that can all contribute to an unhealthy ocular surface and reduced tear function.

Tear dysfunction results in lacrimal gland inflammation. Intercellular adhesion molecule-1 (ICAM-1), which has been shown to be upregulated in dry eyes, promotes lymphocyte activation and migration to the ocular surface, where the lymphocytes cause further lacrimal gland damage, as well as conjunctival epithelial cell apoptosis.[12] The inflamed lacrimal glands secrete cytokines, proteases, and other inflammatory mediators into the tears, continuing the cycle of decreased quantity and quality of tear production,[13] increasing lacrimal gland inflammation and ocular surface damage, and worsening symptoms.

The nerves of the cornea are also important to corneal sensation and tear production. Abnormalities in these neuronal pathways, caused by inflammatory processes and/or ocular surgery, may also cause injury to the lacrimal glands and conjunctival epithelium.[7]

Further elucidating the inflammatory cycle, Stern, Pflugfelder and others have suggested that the ocular surface (cornea, conjunctiva, accessory lacrimal glands, and meibomian glands), along with the main lacrimal gland and the interconnecting neural reflex loops, comprise a delicately balanced functional unit.[13-15] When any part of this ocular surface/lacrimal gland reflex unit fails to work as it should, the volume and composition of

Risks Factors for Dry Eye

Consistent Association with Dry Eye is Well Documented

- Increasing age
- Female gender
- Hormone replacement therapy
- Omega-3 and Omega-6 fatty acids
- Systemic antihistamine use
- Connective tissue disease
- Refractive surgery
- Vitamin A deficiency
- Androgen deficiency
- Rosacea
- Long hours at computer

Association with Dry Eye is Suggested by Literature

- Asian race
- Certain medications:
  - Tricyclic antidepressants
  - Selective serotonin reuptake inhibitors
  - Diuretics
  - Beta-blockers
- Diabetes
- HIV
- Chemotherapy
- PK or large-incision corneal surgery
- Isotretinoin
- Low humidity environments

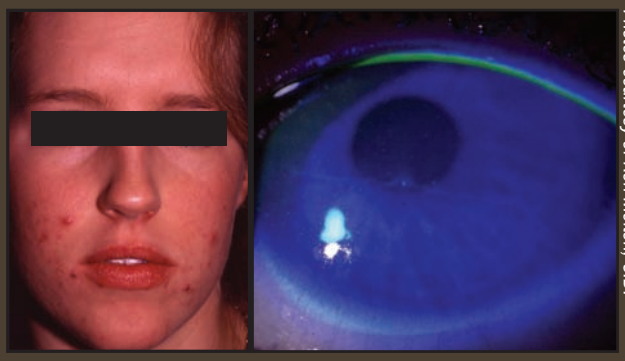
Evidence for an Association with Dry Eye is Unclear

- Cigarette smoking
- Hispanic ethnicity
- Anti-cholinergics:
  - Anxiolytics
  - Antipsychotics
- Alcohol
- Menopause
- Botox injection
- Acnes
- Gout
- Oral contraceptives
- Pregnancy

Adapted from The Epidemiology of Dry Eye Disease: Report of the Epidemiology Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf. 2007 Apr;5(2):93-107.

Clinical Pearl

Anecdotally, we have noticed that young patients with significant dry eye often have a history of isotretinoin (sold now as one of the generic brands Amnesteem, Claravis or Sotret)) use. The skin condition they were treating with it, cystic acne, is a chronic condition. Isotretinoin is an extremely drying agent that seems to have long-lasting impact on the ocular surface, inducing meibomian gland dysfunction and evaporative dry eye even after stopping the medication.



Photos courtesy of Ron Melton, O.D.

Patient receiving treatment with isotretinoin for cystic acne. Slit lamp exam shows scattered superficial punctate keratitis.

tears become insufficient for normal homeostasis and repair.

Impact of Dry Eye

The tear film is the first refractive surface of the eye and therefore critical to good vision, as well as comfort and protection from infection. Disruption of the tear film via the processes described above causes symptoms that can range from mild to quite severe, even debilitating. In utility assessments, patients have rated severe dry eye's impact on their quality of life on par with hospital dialysis and severe angina and higher than monocular blindness.[16,17]

As disease severity increases, patients are increasingly likely to report blurry, foggy or fluctuating vision that impairs visual function. The abnormal ocular surface is also less capable of responding to wind, low humidity, and allergens, so any environmental challenge further worsens patient symptoms.

PART 2: Diagnosis of Dry Eye

Despite what is now known about the role of inflammation in dry eye, it is not always easy to identify lacrimal inflammation clinically. Diagnosis and treatment is therefore more typically based on a combination of symptoms and objective clinical signs, which are not always well correlated.

Several protocols for classifying and treating dry eye have recently been proposed.[2,8] The clinician may also simply consider classifying patients qualitatively as having mild, moderate, or severe dry eye, with or without accompanying lid disease.

Although an understanding of etiology is certainly helpful, one need not identify evaporative dry eye versus aqueous deficient dry eye in the patient chart, nor does exact etiology necessarily change treatment recommendations.

Symptoms

Symptoms of dry eye include dry, scratchy, gritty, sandy, stinging, burning, and/or fatigued eyes, and occasionally reflex watering. Often, these symptoms are the primary complaint driving the patient to seek an appointment with the eye care provider.

However, it behooves the clinician with an older or pre/post-surgical patient population to routinely ask about dry eye symptoms. In these important populations, glaucoma, cataracts, refractive surgery status, and other issues may take center stage, leading both patient and clinician to ignore treatable dry eye.

Age-related dry eye may trigger secondary conditions such as internal or external hordeola, or low-grade blepharitis. Clinicians should recognize and address the root cause of these conditions, the dry eye.

A formal questionnaire may be helpful in eliciting symptoms, but it is not necessary for the diagnosis and care of dry eye. A key question to ask is the timing of symptoms, as research has shown that patients with dry eye almost always have worse symptoms later in the day.[18]

However, those with meibomian gland dysfunction may have worse symptoms in the morning. With

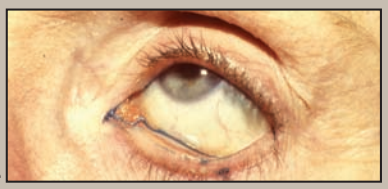


Photo courtesy of Ron Melton, O.D.

Ropy discharge seen in a patient with moderate dry eye that stains with lissamine green.

moderate dry eyes, it is common for patients to have a scant ropey or mucous discharge or to complain of their eyelids being stuck together in the morning. The key to distinguishing such symptoms from those of an early bacterial infection is the lack of conjunctival hyperemia in the dry eye.

Other dry eye symptoms can also mimic various other conditions. Itching, for example, is very commonly within the constellation of symptoms associated with dry eye disease, but the mention of this symptom can erroneously lead practitioners to a diagnosis of allergy.

Dry eye patients will often complain of "eye pain". On further questioning, the dry eye patient will likely say that the pain is quick but very sharp, like a pin-prick. Sharp, transient eye pain is often reported in patients with dry eye.

The patient may also experience epiphora. If tears are rolling down the cheek or if the symptom is unilateral, it is likely due to a stenotic or blocked nasolacrimal system. Laxity in the lower lid in older patients may also lead to epiphora. But a feeling of wetness or a watery characteristic to the tear film can be the result of compensatory activity of the accessory or main lacrimal glands. This makes the tears wetter, causing counterintuitive excess watering in a dry eye.

Finally, blurred or intermittent vision is a very important symptom that patients—and many clinicians—fail to associate with dry eye.

History

A thorough history is essential in differentiating dry eye from other conditions that affect the ocular surface and in assessing the impact of topical or oral medications and other ocular or systemic conditions. The table on page 3 lists medications and conditions associated with dry eye.

Particularly important, of course, is to understand whether the patient has any auto-immune or connective tissue disorders such as Sjögren's syndrome, rheumatoid arthritis, diabetes, thyroid disease or lupus. Patients may not connect these disorders to ocular symptoms unless specifically asked.

In the case of some systemic diseases, such as rosacea or diabetes, the disease itself must be well controlled in order for dry eye therapy to be effective in resolving ocular surface problems.[19] In a large study in Israel, patients with diabetes not only had a higher incidence of dry eye, but also needed to use artificial tears more often when glycemic control was poor.[20] In other systemic disorders, the medication used to control the disease may itself be responsible for the dry eye.

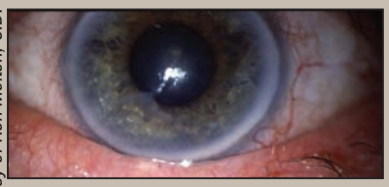


Photo courtesy of Ron Melton, O.D.

Telangiectasia of the lid margin in a patient with advanced dry eye. Also note absence of inferior lacrimal lake height classic in advanced dry eye states.

The clinician needs to know about current or prior contact lens wear and any eye drops the patient is using. Asking for specific details about eye drops can provide insight to the preservative load on the eye, as well as inappropriate use of vasoconstrictors or other topical agents.

Physical Exam

The physical exam should begin with careful observation of the facial and peri-orbital skin. One often sees ocular manifestations of rosacea before or along with very mild dermatologic signs; in other cases, the dermatologic evidence is clear, but the patient has never been diagnosed with rosacea.[19] In such cases, education and referral to another clinician for treatment of the skin issues is very important.

At the slit lamp, one should look at the tear meniscus. A scant tear lake can be a confirming observa-

Clinical Pearl

If a patient's dry eye symptoms seem to be worse in the morning, ask whether he or she suffers from sleep apnea. Not only are sleep disorders themselves sometimes related to dry eye, but the continuous positive airflow pressure (CPAP) machines used to treat sleep apnea commonly induce dry eye.[21] Artificial tears and nighttime ointments may help alleviate the drying effects of the machines. Also rule out floppy eyelid syndrome (FES), as it can mimic dry eye symptoms and is also highly associated with sleep apnea.

Clinical Pearl

Patients with Sjögren's syndrome have a significantly higher incidence of several types of non-Hodgkin's lymphoma compared to the general population.[22] While still fairly rare, one in 12 Sjögren's patients will get this form of cancer, so a rheumatology referral can be life-saving.

tion in the diagnosis of dry eye.

Lid assessment with manual expression of the meibomian glands is a critical component of the dry eye exam. One should look for a consistent, uniformly smooth lid margin. In advanced lid disease, the meibomian glands start to displace and the lid margin is markedly irregular, a clear sign of moderate to advanced long-term disease that requires more aggressive therapy. The presence of telangiectasia on the lid margin is also an indicator of a more chronic condition. But it is important to note that in the early stages, the lid margin may appear perfectly normal until the glands are expressed.

Meibomian gland expression can be performed with a gloved finger pressed firmly across the lid margin from the nasal to the central eyelid four to six times. The secretions should be fairly clear; when the glands are not functioning properly, the secretions can range from mildly turbid to frothy or soapy to whitish-yellow and very thick, almost the consistency of toothpaste, or even no secretions at all.

Dry Eye Testing

To confirm a potential diagnosis of dry eye, objective clinical testing may be helpful. One of the more reliable tests is tear film break-up time (TFBUT).

To perform TFBUT testing correctly, wet a fluorescein strip lightly with one drop of non-preserved saline and touch it to the superior bulbar conjunctiva. Have the patient blink several times, close the eye fully, and then open. When the eye is open, observe the time required until the tear film breaks up. A break-up time of <10 seconds is a sign of dry eye. An exaggerated reaction of discomfort to the fluorescein in the eye can also be indicative of dry eye.

TFBUT testing performed immediately after contact lens removal or instillation of a topical anesthetic will not be accurate. Ideally, TFBUT testing should be performed at least several minutes after removing lenses, but before dilation or instillation of other drops or topical anesthetic. If the practice flow does not allow for TFBUT to be performed first, then it should be done last, at least 20 minutes after anesthetic drops have worn off.

It is also important to notice how the tear film breaks up. If it keeps breaking up in the exact same spot on the cornea, that can be an early indication of map-dot dystrophy in that location.

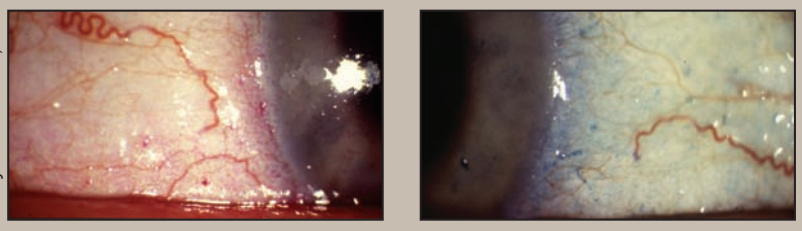
Schirmer's testing, while sometimes requested by a referral or for insurance coverage, has little value in the clinical diagnosis of dry eye because repeatability, sensitivity, and specificity of Schirmer's testing are all quite poor.

Corneal or conjunctival staining, preferably with lissamine green dye, is typically indicative of more advanced dry eye that should be managed aggressively. Rose bengal is certainly an appropriate and acceptable diagnostic agent, but is much more uncomfortable for patients, without any additional benefits over lissamine green. A new drop, Fluramene (EyeSupply), combines fluorescein and lissamine green in a single drop for easier diagnosis.

Staining is particularly helpful in quantifying the severity and/or progression of dry eye. Additionally, taking photographs of the lissamine green staining to demonstrate to the patient what is happening with the eye can facilitate patient education and treatment compliance.

Even with treatment, TFBUT does not always improve to what one would consider a normal baseline level, but ocular surface staining may diminish over time as therapy reduces the inflammation and surface damage.

A new, 10-minute, in-office test for matrix-metalloproteinase 9 (MMP-9) has just become available (RPS InflammaDry Detector, RPS, Inc.). MMP-9, an inflammatory cytokine, is a



Photos courtesy of Ron Melton, O.D.

Rose bengal (left) and lissamine green (right) staining of the conjunctiva and cornea in a patient with Sjögren's Syndrome.

marker of ocular surface inflammation that is not present in a normal eye, so this test could be quite useful in identifying inflammation and predicting response to anti-inflammatories.

Tear hyperosmolarity is a well-established predictor of dry eye disease that may be useful as a diagnostic marker. Previously only performed in research laboratories, osmolarity testing may now be practical in the clinic with a new osmometer (TearLab Osmolarity System, TearLab Corporation) that requires only a tiny tear sample for testing. In one prospective multicenter study, it has been shown to have high levels of sensitivity and specificity for dry eye.[23] If this proves to be true, such tests would be a nice complement to other tools in the diagnostic evaluation of dry eye.

PART 3: Management of Dry Eye

As discussed above, clinicians can use a simple continuum to guide treatment decisions in dry eye. Patients can be qualitatively classified has having mild, moderate, or severe dry eye, with or without concomitant lid disease. The severity of the signs and symptoms should guide one's decisions on how aggressively to treat the condition.

Milder cases may benefit from artificial tears and environmental modifications alone. Significant corneal breakdown and/or lid irregularity, however, would indicate a more moderate to severe case that warrants more aggressive intervention.

MGD

Lid disease is often concomitant with dry eye, and the two conditions may affect one another, so in most cases they should be treated at the same time.

A three-part regimen of lid hygiene is essential, and may be all that is needed in milder cases.

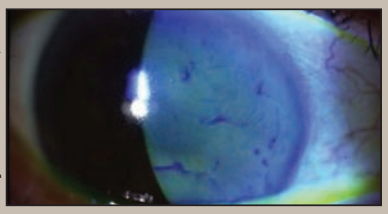


Photo ourtesy of Ron Melton, O.D.

Dry spots seen on the corneal surface associated with a reduced tear break-up time.

Patients should be instructed in proper technique and the order of the steps:

1. Warm compresses heat the meibomian oils and make them easier to express manually. A clean, wet washcloth, as hot as is comfortable, should be applied to the closed eyelids for 10 to 15 minutes, stopping halfway through to warm the cloth again. This should be done two to three times daily at first.

2. Massage the lids for several minutes.

3. Finally, cleanse away any expressed debris from the lids and lashes with lid scrubs. Commercial lid scrubs promote patient acceptance and compliance, but dilute baby shampoo is also effective if cost is a barrier.

"Milking" the glands with cotton-tip applicators rolled from the cul-de-sac to the lid margin or with a Mastrota meibomian paddle (OcuSoft) inserted behind the lower lid can be very helpful in highly symptomatic patients with clearly obstructed meibomian glands.

A new thermal pulsation device (LipiFlow, TearScience) designed by Donald Korb, O.D., automates and standardizes both the warming of the meibomian oils and the lid massage. It heats the palpebral surface of the upper and lower eyelids while simultaneously applying graded pulsatile pressure to the outer lid for 12 minutes. The treatment has been shown to significantly improve meibomian gland secretions and TFBUT compared to standardized warm compresses, and the effect on dry eye symptoms may last up to 12 months.[24,25] It is bundled with an ocular surface interferometer that may also help clinicians diagnose MGD by objectively quantifying lipid layer thickness.[26]

For moderate to severe cases of MGD, or if lid hygiene measures do not relieve symptoms, oral doxycycline for two to three months is recommended. Dosage may be between 20 and 50 mg once or twice daily. Doxycycline may be taken without regard to meals. Although esophageal erosion is a potential side effect, it can be avoided simply by not lying down after taking the medication. Another way to minimize GI and esophageal problems is by taking the pills with water, rather than acidic beverages.

For patients who cannot use the tetracycline drug class due to allergy, stomach issues, or pregnancy, another treatment option is oral erythromycin,[27] although it is not as effective as the tetracyclines.

In patients with blepharitis, MGD and an inflammatory dry eye, loteprednol etabonate 0.5%/tobramycin 0.3% (Zylet, Bausch +

Managing Dry Eye Symptoms

The following simple environmental modifications can greatly reduce dry eye symptoms:

- Turn ceiling fans off or to slower speed.
- Position computer monitor at eye level or below.
- Take 5- to 10-minute break per hour from computers and electronic devices.
- Re-direct fans and A/C vents away from the face.
- Consider intra-nasal steroid sprays as an alternative to systemic antihistamines for the treatment of allergic sinusitis.
- Increase ambient humidity at home or work with a humidifier
- Use Panoptx (or other wrap-style sunglasses) outdoors.
- Reduce contact lens wearing time or switch to more frequent replacement.
- Get enough sleep.

Lomb), is the ideal way to get the inflammatory components of both the ocular surface and lid disease under control. Zylet has a lower risk of IOP elevation compared with ketone corticosteroids due to its rapid de-esterification to inactive metabolites. It also lacks the ability to form Schiff base intermediates with lens proteins, a common first step in cataractogenesis.[28]

Topical azithromycin (AzaSite, InSite Vision Incorporated/ Merck) has also been shown to be useful in the treatment of lid disease.[29–31] In young children, or if cost is a barrier, bacitracin or Polysporin ointment at bedtime may be considered.

Ongoing use of warm compresses and appropriate artificial tears over the long term will be necessary. Any time there is meibomian gland involvement or dysfunction, one can expect to see a decreased lipid layer that benefits from replacement with a lipid-enhancing artificial tear such as Soothe XP (Bausch + Lomb) or Systane Balance (Alcon).[32]

Dry Eye

• ***Artificial tears.*** Artificial tears remain the first line of defense against dry eye. The quality of artificial tear products has improved markedly in recent years, to the point that most clinicians now specifically recommend lipid-based or other advanced tear technologies for their patients, rather than just handing the patient a selection of tear samples.

According to Foulks, there is a strong correlation among dry eye symptoms, tear film osmolarity, and the state of the lipid layer of the tear film.[33] The active ingredient in Soothe XP has been shown to more than double lipid layer thickness, helping to stabilize both the lipid and aqueous layers of the tear film, as well as the interface between those two layers.[32,34]

A typical regimen for mild dry eye should begin with artificial tears q.i.d. Soothe XP, and indeed, most artificial tears, can be used as needed during contact lens wear, despite the labels cautioning against use with contact lenses. Use of these drops with contact lenses has not been evaluated in clinical trials, but in our experience, they are not detrimental to the lenses and are excellent rewetting drops. In fact, an artificial tear will be much more effective than contact lens re-wetting drops in relieving symptoms.

Having a "tear of choice" simplifies one's approach to dry eye, but it is always necessary to have alternatives, as every patient is different. Tears with mild, transient preservatives are ideal for most dry eye patients because they are convenient, yet still nontoxic to the ocular surface. In more severe cases with ocular surface breakdown, one should certainly avoid toxic preservatives, and consider switching to non-preserved tears.

Nighttime ointments are helpful for those with lagophthalmos or incomplete lid closure, as well as those with very advanced dry eye.

Lacrisert (Aton Pharma, Inc.) is another effective therapy for advanced cases. This slow-release artificial tear is a dry pellet of hydroxypropyl cellulose. It is designed to be placed deep in the cul-de-sac, where it imbibes residual fluid and then releases the polymer over 24 hours. Most pharmacists are unfamiliar with this product, so it is best to obtain samples from the manufacturer and teach the patient in the office how to insert it.

Even high-quality and long-lasting tears have a primarily palliative effect and do not address the underlying inflammation. If patients start out with more advanced disease or continue to be symptomatic after a month of artificial tear use, one should move to more targeted anti-inflammatory therapy.

• ***Anti-inflammatory therapy.*** In recent years, the paradigm shift in dry eye treatment has been toward earlier and more aggressive management of dry eye inflammation. The inflammatory component of dry eye may be treated with topical anti-inflammatory drops.[35] Corticosteroids are the only therapeutic class that quickly and thoroughly suppresses ocular surface inflammation.

Studies have shown that the use of the topical ester steroid, loteprednol etabonate 0.5% (Lotemax, Bausch + Lomb), may be beneficial in patients who have dry eye with at least a moderate inflammatory component.[36] Dosed q.i.d. for two to four weeks, then b.i.d. for another four to six weeks, along with tears, loteprednol addresses inflammation immediately to provide rapid relief of symptoms.

In fact, any topical corticosteroid can be effective in treating dry eye, but there are significant differences in the safety profiles of different steroid classes. With long-term use of four weeks or longer, loteprednol has far less propensity to cause clinically significant elevation of IOP than most ketone steroids, such as prednisolone and dexamethasone. In terms of safety, loteprednol is essentially comparable to vehicle/placebo.[37]

Many glaucoma patients have concomitant dry eye, attributable to age and the use of topical preserved medications, and these patients are more likely to be steroid responders. As a precaution, one should watch IOP carefully in glaucoma/dry eye patients, especially during the first few weeks.

But even in known steroid responders, the IOP response to loteprednol etabonate 0.5% is neither clinically nor statistically significant.[38] Additionally, there have been no cases of cataract in patients using this medication reported in the literature. The safety of loteprednol makes it much easier to consider long-term corticosteroid therapy for patients suffering from chronic dry eye. Even in the mild to moderate dry eye, if the patient is symptomatic enough to have made an appointment, a short course of topical steroid therapy for four to eight weeks can greatly reduce the symptoms.

Although it is preferred to avoid using corticosteroids while wearing contact lenses, studies have shown that contact lens wearers can safely use topical steroids even while wearing their contact lenses. In studies of treatment for giant papillary conjunctivitis (GPC), one study protocol called for q.i.d. loteprednol instillation on top of the contact lenses, for four weeks. In this study of 110 patients, there were no infections or corneal complications using this protocol.[39] However, one might want to watch IOP a bit more closely because the contact lens could act as a steroid depot.

Alternatively, steroid drops can be instilled about 10 minutes before putting contact lenses on in the morning and again in the evening after lens removal. Daily disposable or at least more frequent replacement lenses and/or reduced wear time can also alleviate dry eye symptoms.

Cyclosporine ophthalmic emulsion 0.05% (Restasis, Allergan) may be considered in the treatment of dry eye as well, depending on severity and clinician preferences. Restasis inhibits activation of inflammatory T-lymphocytes and induces immune cell apoptosis, stimulating lacrimal gland tear production.[40,41] It has also been shown to reduce the levels of interleukin-6, an inflammatory cytokine, in moderate to severe dry eye patients treated for six months.[42] In pivotal clinical trials, 59% of patients achieved improvement from baseline Schirmer scores at six months.[43] Compared to vehicle, the cyclosporine eye drops also significantly reduced dependence on artificial tears at six months.

Patients typically have a burning sensation during the first few weeks when putting cyclosporine drops on an inflamed eye. For this reason, many clinicians prefer to use it in conjunction with loteprednol etabonate, which can achieve more immediate inflammatory relief and reduce the burning sensation.[44]

On an ongoing basis, an artificial tear that preserves and protects the tear film can protect against re-initiation of the inflammatory process. Short pulsing (twice daily for a few days to a week) with corticosteroids can address any inflammatory breakthrough to keep symptoms fully under control. Other effective long-term medications include cyclosporine A, which has been studied out to three years of use, and nutritional supplements.[45]

• ***Nutritional supplements.*** The Women's Health Study suggests that increased dietary intake of fish oils may reduce dry eye,[46] while other studies have suggested that nutritional supplementation with essential omega-3 fatty acids is helpful.[47] Omega-3 and omega-6 fatty acids, from fish, flaxseed, or other sources are good for the hair, skin, heart, and general human health, so taking a supplement or increasing fish consumption is a positive step that patients can take that will complement any systemic or topical therapies for dry eye. This can

be recommended very early in the disease course, for mild dry eye and throughout the entire continuum of the disease.

There is no consensus on the best form of fatty acids. The typical recommended supplement dose is 2000 mg/day. Higher-quality supplements may be purer, with less chance of side effects, but there is no strong evidence favoring one particular formulation over any other. In fact, the lowest cost form may be better than not taking the supplements at all.

• ***Punctal occlusion.*** In the past, punctal plugs were typically used immediately if artificial tears failed to resolve symptoms. In recent years, they have moved down on the therapy ladder and may actually be underutilized currently.

Punctal occlusion can be very effective, provided that any ocular surface inflammation is suppressed first.[48,49] There are also still some circumstances where plugs are the best first-line option for the treatment of dry eye (see "When to Plug First," above). Punctal occlusion is one of the few dry eye interventions we have that is not dependent on patient compliance, and plugs may reduce dependency on topical therapy. Recent studies have shown that even when the plug is spontaneously lost, it causes some canalicular stenosis that continues to be mechanically therapeutic for several years.[50]

If the patient remains symptomatic after an initial course of topical anti-inflammatory medications, one should consider punctal occlusion. Practitioners typically plug both lower puncta with silicone plugs. Other approaches include plugging the lower punctum on the more symptomatic eye and determining the effectiveness at a one-month follow-up visit; or inserting regular silicone plugs in both lower puncta, along with flow-controller plugs in the upper puncta, in a step-wise manner.

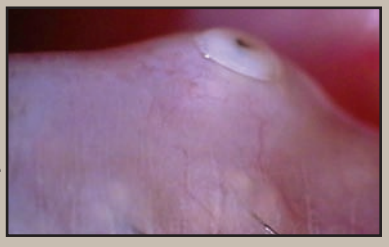


Photo courtesy of Ron Melton, O.D.

Silicone punctal plug.

Temporary occlusion with dissolvable collagen plugs may be an option for the clinician unsure of their effectiveness or when considering aggressive occlusion of all four puncta. Some have found six-month collagen plugs to be particularly helpful post-LASIK.

Intracanalicular plugs are not recommended. These have been associated with rare, but serious complications, including canaliculitis and the potential need for surgical removal.[51–53]

• ***Antibiotic therapy.*** Oral doxycycline is appropriate for MGD, as discussed previously, and for dry eye in a patient with rosacea. Otherwise, ocular surface symptoms are better controlled with topical therapies.

Patients with blepharitis have in the past been treated with antibiotic ointments without great efficacy. Typically these eyes have decreased TFBUT and decreased inferior lacrimal lake volume, and they usually lack sufficient tears to wash away the ointment, so the patient ends up with chronically blurred vision. A combination antibiotic-steroid eye drop, such as Zylet, or an antibiotic, such as AzaSite, may be more appropriate.

• ***Other considerations.*** Oral pilocarpine (Salagen, MGI Pharma, Inc.), usually dosed 5 mg t.i.d. or q.i.d. may be effective for some patients. Side effects such as scalp sweats have been reported at higher doses. A better alternative with fewer side effects for patients with dry eye (or dry mouth) is oral cevimeline (Evoxac, Daiichi Sankyo, Inc.) 30 mg t.i.d.[54]

Autologous serum eye drops have been shown to have some benefits.[55] The patient's response may be related to the degree of inflammation present in the blood when it is drawn. There is a risk of infection, so autologous serum is rarely used except as a last resort for extremely symptomatic patients.[56] A lower-risk alternative may be drops containing 5% albumin, the key protein in serum.

For the most severe cases, one

When to Plug First

If there is a significant inflammatory component, that should be addressed first before punctal occlusion. However, in some cases of non-inflammatory dry eye such as those listed below, patients respond very well to punctal occlusion as the initial intervention.

- Post-LASIK dry eye
- Any form of neurotrophic keratopathy
- Lagophthalmos
- Dry eye secondary to anticholinergic or antimuscarinic medications, e.g., Detrol LA (tolterodine tartrate, Pfizer) for overactive bladder.

might also consider 3% testosterone cream that can be made up in the pharmacy and applied to the upper lids twice daily. There is some rationale for estrogen or androgen-based eye drops and even for topical omega-3 and omega-6 fatty acid drops.[57,58]

Conclusions

Management must begin with environmental modifications and high-quality artificial tears. Additional therapies must address the inflammation responsible for symptoms.

We propose a treatment paradigm that incorporates artificial tears, topical anti-inflammatory medications such as corticosteroids and/or cyclosporine, punctal occlusion and nutritional supplementation, based on the severity of signs and symptoms.

In summary, dry eye is a complex condition that is typically inflammatory in nature and may also involve concomitant lid or skin disease, allergy, or other systemic or ocular surface conditions.

Given that symptoms do not always correlate with clinical signs, clinicians must use the severity of patient symptoms, along with a thorough history and exam, to diagnose dry eye and guide treatment decisions. Proactive treatment of dry eye can significantly improve vision, quality of life, and surgical outcomes, and represents a significant opportunity for increasing patient loyalty and practice revenues.

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