REVIEW OF OPTOMETRY

# The Golden Age Of Dry Eye Management

**Nearly 10% of the U.S. population has dry eye, but there are myriad options for treating this multifactorial disease.**

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**RELEASE DATE: NOVEMBER 2008**
**EXPIRATION DATE: NOVEMBER 30, 2009**

## GOAL STATEMENT:

Dry eye syndrome affects the quality of life of millions of people in the United States. It has varied causes and severities, and there is no single set of symptoms, so it can be difficult to classify once the initial diagnosis is made. This article reviews the various causes, diagnosis and treatment.

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## JOINT-SPONSORSHIP STATEMENT:

This continuing education course is joint-sponsored by the University of Alabama School of Optometry. This course is supported by an unrestricted educational grant from Alcon.

## DISCLOSURE STATEMENT:

Dr. Schachet is a member of the Alcon Speaker's Bureau, but has no other financial interest.

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Dry eye syndrome, one of the many conditions that affect the ocular surface, is estimated to involve nearly 10% of the U.S. population. As many as 20 million to 30 million people in the United States have early signs or symptoms of dry eye, and an estimated 6 million women and 3 million men have advanced effects of dry eye[1]—a condition that affects their quality of life.

Dry eye also appears to be more common in older individuals (45 years or older).[2] It has varied causes and severities and there appears to be no unified cause. There is no single set of symptoms in which the condition presents itself. So, it can be very difficult to classify after the initial diagnosis is made, rendering this condition very difficult to treat.

We'll review the various causes as well as diagnosis and treatment.

### Dry Eye Defined

The 1995 report of the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eye defines dry eye, or keratoconjunctivitis sicca, as a disorder of the pre-corneal tear film caused by tear deficiency or excessive tear evaporation that results in damage to the interpalpebral ocular surface and is associated with ocular discomfort.[3]

The Definition and Classification Subcommittee of the International Dry Eye Workshop (DEWS) of 2007 has somewhat modified this definition. DEWS determined that dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance and tear film instability, with potential damage to the ocular surface.[4] The DEWS definition also states that dry eye is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface. These features lead to the dry eye cascade of visual degradation, epithelial cell damage and discomfort.

Most individuals with this condition are female, ages 30 and older. According to the Women's Health Study, the prevalence of dry eye affects more women as they age.[5] Although the prevalence increases in men, too, it doesn't keep pace with the presence of dry eye in women. Also, women who used hormone replacement therapy (HRT) had a 69% greater risk of developing dry eye syndrome.[5] If estrogen therapy was combined with progesterone/progestin, the risk went up another 29%.[5] The risk of dry eye increased 15% for every three-year interval that the women remained on HRT.[5] Many patients develop a dry eye condition over years and decades before it is recognized.

## The Causes

Stephen Pflugfelder, M.D., a member of DEWS, says the sequence of events leading to dry eye or ocular surface disease is exacerbated by "an unstable tear film of altered composition that inadequately supports the health of the ocular surface."[6]

Many factors can cause dry eye or exacerbate an existing dry eye condition. These include:

- Extended visual tasks, such as prolonged computer use.
- Systemic medications that have drying side effects, including antihistamines, hormone replacement therapy, diuretics, antidepressants and antianxiety medications, cancer treatments and some sleep aids.[7]
- Excessive consumption of alcoholic beverages.[1]
- Long-term exposure to dry air, as found in the desert Southwest, for example, or windy climates.
- Extreme use of forced-air heat or air conditioning.
- Air pollutants, such as tobacco smoke, smog or excessive exhaust fumes.[8]
- Contact lens wear and refractive surgery. Dry eye symptoms may adversely affect contact lens wearing time (and often is the most common reason for discontinuing lens wear) or corneal healing, respectively.[9,10]
- Dietary considerations, such as the reduced intake of omega-3 fatty acids, increased omega-6 consumption, reduced water intake (individuals should drink at least eight glasses of water daily) and increased intake of soft drinks and/or caffeine (caffeine itself is a drying agent).

## A Historical Perspective

An understanding of dry eye disease starts with the historical perspective of the tear layer and ocular surface. E. Wolff first described the multi-layer tear film in 1946.[11] This concept involves three distinct and separate layers of the tears: the aqueous, mucin and lipid layers. Each layer, he said, has its own function.

In 1973, Frank J. Holly, Ph.D., explained that mucin had a much greater role than previously thought.[12] The soluble mucins are produced primarily from the goblet cells and the insoluble mucins from the corneal epithelial cells. So, if there is a deficiency in mucin production, breaks in the surface tension of the ocular surface would result, and the tear film would not spread evenly over the corneal epithelium.

In 1997, Scheffer Tseng, M.D., Ph.D., showed that the ocular surface and tear film interacted in such a way that the layers do not have separate functions after all. Rather, they are inextricably intertwined to produce a healthy ocular surface.[13] This led to the realization that dry eye is not simply a disease process but a complex, multifactorial disorder. When we think of the tear layer, we must think globally to understand what might have resulted in the dry eye condition.

Some facts: The pH of a normal tear film is about 7.4, but for a dry eye it is about 7.9. Also, the osmolarity of the tear film is higher for the dry eye than the normal eye.[14,15] Cholinergic drugs increase tear production, while anti-cholinergic drugs decrease tear production.[16] Finally, tear production is increased with androgen hormones and decreased with estrogen hormones.[17]

## The Role of Inflammation

The most recent concept in dry eye pertains to the role of inflammation. Opinions vary as to whether inflammation initiates or occurs in the middle of the dry eye cycle. Still, once inflammation begins, damage can occur to the ocular structures. This, in turn, perpetuates and intensifies the signs and symptoms of dry eye. No matter what the cause, we must break the cycle in this cascade.

Inflammation can be present with Sjögren's and non-Sjögren's types of dry eye, and may be present in the lacrimal glands, conjunctiva and meibomian glands. Inflammation is mediated by pro-inflammatory cytokines in the tear layer; delayed tear clearance accentuates this effect. Also, inflammation adversely affects neural transmission, a key component in the health of the tear film.

The condition of the meibomian glands is one of the most common concerns with dry eye.[18] Dry eye often begins in the meibomian glands or may be exacerbated due to the inflammatory nature of meibomian gland dysfunction. These glands provide the sebaceous layer of the tear film; when this layer is abnormal, tear break-up time is reduced, and the tear film evaporates too quickly.

This may initiate the dry eye cycle. Debris and toxins, resulting from chronic infections of the meibomian glands and the eyelids (marginal blepharitis), are released into the tear film, creating ocular irritation and redness. Left untreated, internal hordeola, pannus, corneal ulcers and corneal scarring may result.

Look at the meibomian glands with transillumination to determine if they appear normal or appear to have lost their structure entirely; this will help you determine the extent of the problem. When the meibomian glands seem to have dropped-out from view with transillumination, the treatment protocol will need to be more aggressive than if in earlier stages of degradation.

## Making the Diagnosis

Several tests can aid in diagnosis of dry eye. The first is always a good history. Some things to look for:

- *Systemic conditions that increase the likelihood of dry eye symptoms.* Ask about a history of collagen vascular or autoimmune diseases that may increase the risk. Rheumatoid or osteoarthritis, systemic lupus erythematosus and fibromyalgia may increase the risk of dry eye or at least warrant further testing.
- *Other ocular conditions.* Patients with keratoconus or those with epithelial basement membrane dystrophy (EBMD) or map-dot dystrophy are certainly at risk. Patients with EBMD (map-dot dystrophy) have recurring erosions, so we manage them as though they are dry eye patients. Reduced contact lens wearing time in keratoconus patients may be due to dry eye as well.
- *Medications.* Several types of medications increase a patient's risk of dry eye. Among them: selective serotonin reuptake inhibitors, which are used to treat depression and anxiety disorders.[7] These medications include Prozac (fluoxetine, Eli Lilly), Paxil (paroxetine, GlaxoSmithKline), Zoloft (sertraline, Pfizer) and Lexapro (excitalopram oxalate, Forest Pharmaceuticals). A newer drug, Cymbalta (duloxetine, Eli Lilly), a reuptake inhibitor of both serotonin and norepinephrine, also falls into this category of potential drying agents.

After you record the history, examine the patient. Be sure to:

- *Examine the lid margins for blepharitis/meibomitis.*
- *Pay special attention to the tear layer during the biomicroscopic examination.* Look at the tear meniscus height and tear film break-up time (TFBUT), any evidence of fluorescein staining on the cornea and tear consistency, looking at thickness, debris, oil and sebaceous secretions.
- *Perform further tests, such as a Schirmer test or phenol red thread test, to rule out dry eye.* The Schirmer test measures tear production, while the phenol red thread test measures the fluid present in the conjunctival sac. Lissamine green staining would follow; any staining of the bulbar conjunctiva indicates dryness of the conjunctiva. Finally, use collagen plugs to test for subjective responses to increased tear volume over several days, indicating a possible need for non-dissolvable plugs.
- *Look beyond the eyes.* Look for signs of acne rosacea by examining the nose and forehead of men and the cheeks of women for signs of telangiectasia. Also, look at the patient's hands for typical changes

suggestive of rheumatoid arthritis or osteo-arthritis. Distal joints of the hands could reveal the presence of Heberden's nodes, which involve nodular swelling of the distal joints. This suggests osteoarthritis, even if the patient isn't aware of other symptoms.

## A 'Cookbook' Approach?

Once you establish that a dry eye condition exists, the treatment goal is to create a more normal tear film environment for epithelial healing to take place. We must stabilize the tear film by increasing lubricity, increasing aqueous production, decreasing inflammation, or using some combination of these approaches.

In 2006, the Dysfunctional Tear Film Study Group, with its Delphi Panel, tried to determine how to manage dry eye syndrome. The group attempted to categorize dry eye into four general categories and proposed a "cookbook"-type approach to managing the disease based upon the level of the severity.[19] *(See Delphi Panel Consensus for Dry Eye Management," below.)*

**Delphi Panel Consensus for Dry Eye Management[19]**

| Severity | Signs and Symptoms | Recommended Treatment |
|---|---|---|
| **1** | Mild to moderate symptoms; no signs.<br>Mild to moderate conjunctival signs. | Patient counseling, preserved tears, environmental management, use of hypoallergenic products, water intake. |
| **2** | Moderate to severe symptoms. Tear film signs, mild corneal punctate staining, corneal staining, visual signs. | Unpreserved tears, gels, ointments, cyclosporine A, secretagogues, topical steroids, nutritional support (flaxseed oil). |
| **3** | Severe symptoms. Marked corneal punctate staining, central corneal staining, filamentary keratitis. | Tetracyclines, punctal plugs. |
| **4** | Severe symptoms. Severe corneal staining, erosions, conjunctival scarring. | Systemic anti-inflammatory therapy, oral cyclosporine, moisture goggles, acetylcysteine, punctal cautery, surgery. |

Some doctors believe they failed to address a first-line approach to dry eye treatment before the disease progresses to the more severe stages. Others criticize the early use of cyclosporine and recommended later use of punctal/lacrimal occlusion instead of the opposite approach. Still, this was an attempt to develop a protocol for treating dry eye.

## Lubricant Drops

Lubricant eye drops all have differing active and inactive ingredients. The four categories are based on the science behind the product.

- *Cellulose derivative products.* These further break down in carboxymethylcellulose (CMC) products, such as Refresh Tears (Allergan) or Refresh Liquigel (Allergan), and hydroxymethylcellulose (HPMC) products such as Tears Naturale (Alcon), Genteal (Novartis) or TheraTears (Advanced Vision Research).
- *Glycerin-containing products.* These break down into two additional categories: glycerin plus CMC as in Visine Tears Dry Eye Relief (Pfizer) or Optive Lubricant Eye Drops (Allergan), and glycerin plus HPMC as in Tears Naturale Forte (Alcon) or Advanced Eye Relief Dry Eye (Bausch & Lomb).
- *Oil-based emulsion products,* such as Refresh Endura (Allergan), which contains castor oil, and Soothe (Bausch & Lomb), which uses mineral oil as a primary ingredient.
- *Polyethylene glycol (PEG) and propylene glycol (PG) products,* such as Systane (Alcon) and Systane ULTRA lubricant eye drops (Alcon).

A recent addition, Systane ULTRA, spreads evenly over the cornea, has prolonged retention time and shows objective and subjective improvement in patient signs and symptoms.[4] The drop was formulated to balance viscosity and elasticity. The reason: Normally, increased viscosity means increased blur, while decreased elasticity means decreased corneal retention time. This drop contains what its manufacturer describes as an "intelligent delivery system." The interactions of active and inactive ingredients follow an "intelligent" biochemical design in which each action leads to another, eventually rebuilding the tear film and the underlying epithelial cells.

Systane ULTRA contains PG and PEG as active demulcents, polyquad as its preservative and a pH stabilizer to get the pH to 7.9. Sorbitol was added to create a loosely held cross-linking to the HP Guar and effectively inactivate some of the borate cross-links, which normally bind to the HP Guar, thus increasing viscosity. On the eye, sorbitol dissipates very quickly, optimizing viscosity. None of my patients have reported blur, however. The borate cross-links with the HP Guar to begin rebuilding the tear film. These interactions in the presence of the PEG and PG effect the elasticity change that occurs and rebuilds the tear layer.

**New Beginnings for Old Treatment**

There are several emerging strategies for dry eye treatment to look forward to in the future, such as natural hormonal controls, secretagogues, mucomimetics, anti-evaporatives, new anti-inflammatories and other improved polymers for use with dry eye patients.

An older dry eye treatment, autologous serum therapy, is finding a new beginning. This procedure utilizes autologous platelet concentrate mixed with calcium chloride and thrombin for gelling to be applied to the corneal surface.[23] A venous blood draw is performed and centrifuging techniques are used to obtain adequate serum volume. The residual concentrate can be mixed with lubricating eye drops to gel at a 25% concentrate to be used for adjunct therapy. The gelling seems to prolong the effect of numerous growth factors and other essential components and enhances epithelial surface proliferation and differentiation during the healing phase.

This technique was first used successfully in 1984 for keratoconjunctivitis sicca (KCS) in a 50/50 mixture of autologous serum with preservative-free sterile saline.[24] Other researchers have experimented using 20% autologous serum drops to treat neurotrophic keratitis, recurrent erosion, KCS, Sjögren's syndrome, superior limbic keratoconjunctivitis and ocular surface reconstruction surgery.

Future studies will examine the possibility of using platelet gelling on multiple occasions in home settings instead of hospital settings as it is currently done. Lastly, researchers believe that the optimal serum drop concentration has not yet been found and future work needs to be done on this dilemma as well.[23] One caveat: This procedure should be avoided in host-graft disease patients.

## Other Regimens

While inflammation has become a primary concern, not all dry eye is inflammatory.[13] At times, we may need a treatment regimen that combines more than one product in to stabilize the tear film. Products such as Restasis (cyclosporine, Allergan) and anti-inflammatories such as Lotemax or Alrex (loteprednol etabonate 0.5% and 0.2%, respectively, Bausch & Lomb) may be used alone or in combination along with lubricating drops, gels or ointments for more aggressive therapy.

Punctal occlusion is another option. The rationale is that, if done properly, "normal tears" can adequately lubricate the ocular surface. This is accomplished by plugging the tear ducts (sometimes two puncta or all four in more severe cases). The types of plugs used depends on the preference and comfort level of the doctor; there is no right or wrong approach; it just depends on your comfort level. One advantage to using short-term plugs: their ability to dissolve quickly, especially if epiphora results.

These various measures may be used in concert with one another or alone, depending on what you want to accomplish with a given patient.[20]

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