Dry Eye Syndrome

- Historical perspectives
- Prevalence and economic implications
- Etiology of disease
- 2003 AAO guidelines for treatment
- Drug-therapy review
- Pharmacoeconomic data
- Proper medication use

Continuing education credit for physicians and pharmacists sponsored by The Chatham Institute

This program is supported by an educational grant from Allergan
The understanding of keratoconjunctivitis sicca (KCS), also known as dry eye syndrome, has changed in the past 5 years. Until recently, it was thought to be due to aqueous insufficiency. Today, it is understood that KCS is a multifactorial disease that also involves inflammation of the ocular surface and lacrimal gland, neurotrophic deficiency, and meibomian dysfunction. This change in understanding, reflected in the 2003 AAO Dry Eye Syndrome Preferred Practice Pattern that is summarized herein, has led to the development of new and effective medications.

This peer-reviewed publication gives physicians and pharmacists who serve on pharmacy and therapeutics committees up-to-date information about the most efficacious and cost-effective medical treatments available. Relatively little published data exist in a centralized format about medical therapies for dry eye syndrome, compared with information about other chronic conditions. This publication, a digest of existing knowledge and best practices, serves as a valuable tool for formulary decision makers and is an important contribution to the medical literature.

**A Tool for Formulary Decision Makers**

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P&T Digest
A PEER-REVIEWED COMPENDIUM OF FORMULARY CONSIDERATIONS

Dry Eye Syndrome

John D. Sheppard, MD, MMSc
Chief Medical Editor

mediamedia
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GENERAL INFORMATION

Continuing education credit is offered to physicians and pharmacists who read pages 6 through 41 of this publication, complete the post-test on pages 42 and 45, and fill out the appropriate evaluation form on either page 43 (physicians) or 44 (pharmacists).

PURPOSE AND OVERVIEW

This activity is designed to educate health care practitioners and managed care professionals about current and emerging treatments for dry eye syndrome. Recent developments in the etiology of dry eye have triggered the development of new pharmacotherapeutic treatment strategies, prompting physicians, patients, and payers to request information about the status and effectiveness of current and emerging therapies. The content of this program was developed on the basis of faculty perceptions of significant trends or issues.

Educational objectives

After reading this publication, the participant should be able to:

1. Describe the etiology of dry eye syndrome, or keratoconjunctivitis sicca (KCS), and risks of untreated disease.
2. Outline the prevalence of KCS and the economic implications thereof.
4. Explain the mechanisms of action of pharmacotherapies for KCS.
5. Summarize pharmacoeconomic data of emerging anti-inflammatory agents for KCS.
6. Identify considerations in proper handling and administration of preservative-free topical agents for KCS.

Target audiences

Managed care organization medical directors and pharmacy directors; practicing primary care physicians, ophthalmologists, and pharmacists; members of pharmacy and therapeutics committees.

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This activity has been planned and implemented in accordance with the ACCME Essential Areas, Elements, and Policies.

Pharmacy accreditation

The Chatham Institute is approved by the American Council on Pharmaceutical Education (ACPE) as a provider of continuing pharmaceutical education.

This activity provides 3.0 contact hours (0.3 CEU) of continuing education for pharmacists. Credit will be awarded upon successful completion of the post-test and the activity evaluation.

ACPE Universal Program Number (UPN): 812-000-03-016-H01.

Medium: Journal supplement.

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John D. Sheppard, MD, MMSc, acknowledges grant and research support from Alcon, Allergan, Bausch & Lomb, Ciba Vision, GlaxoSmithKline, Insite Pharmaceuticals, Isis Pharmaceuticals, Ista Pharmaceuticals, Lumenis, Novartis, Santen, and Science-Based Health. He has consulting relationships with Allergan, Bausch & Lomb, Ciba Vision, Insite Pharmaceuticals, Isis Pharmaceuticals, Ista Pharmaceuticals, Novartis, Santen, and Science-Based Health. He is on speaker’s bureau for Alcon, Allergan, Bausch & Lomb, Ciba Vision, Glaxo-SmithKline, Lumenis, Novartis, Santen, and Science-Based Health.

Steven E. Wilson, MD, acknowledges a consulting relationship with Allergan. He is on the speaker’s bureau for Allergan.

PUBLISHER’S STATEMENT

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Dry Eye Moves Beyond Palliative Therapy

JOHN D. SHEPARD, MD, MMSc

Eastern Virginia Medical School

SUMMARY

Keratoconjunctivitis sicca, or dry eye syndrome, is a complex condition characterized by inflammation of the ocular surface and tear-producing glands. Emerging awareness of the etiology of dry eye has led to the development of highly effective therapy. When dry eye is controlled, there is significant potential for cost savings.

Dry eye syndrome, also known as keratoconjunctivitis sicca, is a common condition reported by patients who seek ophthalmologic care. Knowledge of the pathophysiology of dry eye has made significant strides in recent years; today, what was once thought to be a simple matter of the eye not producing sufficient tear flow is understood within the ophthalmologic community to be a multifactorial disease. Many family physicians and payers, however, may still perceive dry eye to be little more than an irritation and thus may not be aware of emerging specific potent therapies.

Research has shown that dry eye is a complex condition, the hallmark of which is inflammation of the ocular surface and tear-producing glands (Stern 1998). This awareness has fostered the development of highly effective anti-inflammatory therapies. These treatments boast the potential for dramatic advances in quality of life for millions of people whose condition interferes with activities of everyday living.

Improved patient satisfaction and clinical outcomes alone should be the raison d’être for this volume of P&T Digest, which seeks to promote awareness of dry eye and innovative treatment strategies. The reality of medical practice in a managed care environment, however, is that therapy must not only be effective, but cost efficient. Anti-inflammatory therapy carries prospects for favorable pharmacoeconomics, in terms of reduced office visits and avoidance of complications, let alone enhanced patient satisfaction. When it comes to formulary considerations, health plans seek data that demonstrate each drug’s therapeutic effectiveness and potential for cost offset. The information herein is intended to help pharmacy and therapeutic committees with this task.

ETIOLOGY AND PREVALENCE

The theory and epidemiology of dry eye and therapeutic considerations are discussed at length elsewhere in this volume of P&T Digest. In general, dry eye comprises a heterogeneous assortment of conditions involving aqueous insufficiency, inflammation of the ocular surface, and tear-producing gland malfunction.

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surface and lacrimal glands, neurotrophic deficiency, and meibomian gland dysfunction. Iatrogenic disease, in which topical prescription medications create hypersensitivity or toxicity in the eye and oral medications create lacrimal hyposecretion, also can induce symptoms of dry eye.

Estimates of the prevalence of dry eye syndrome vary widely (see the following chapter, beginning on page 9), but as many as 40 million Americans may either have symptoms of dry eye or remain at risk for it. Postmenopausal women may be the largest risk group, due to decreases in hormonal levels that can lead to loss of anti-inflammatory protection and decreased lacrimal function. Individuals with concomitant inflammatory conditions, particularly allergies, asthma, and collagen vascular disease, are also at risk. Patients who have had eye surgery that could compromise the neurogenic support of the ocular-surface epithelium — LASIK, transplants, or older extracapsular cataract procedures, for instance — could have moderate to severe dry eye, but this condition is frequently unrecognized. This suggests at least some degree of undiagnosed disease that belies published estimates of prevalence; more importantly, these groups, taken together, make up a sizeable universe of dry eye candidates, with an equally impressive price tag.

This impressive demographic emphasizes the importance of early detection and effective treatment, not only from the perspective of function or comfort, but also in terms of recognition of what may be a systemic disease with potentially devastating effects on the individual. Patients with dry eye are at direct risk for potentially blinding infections, including bacterial keratitis (Lemp 1997), and they present with higher risks for routine procedures, such as LASIK. Indirectly, dry eye can be a marker for secondary conditions. The cornea has more nociceptors or pain receptors per square millimeter than any other place in the body, making it one of the most painful targets of diffuse autoimmune conditions. The ophthalmologist or primary care physician, then, must be attuned to the likelihood that a systemic disease is behind the patient’s complaints of dry eye.

Family physicians should always refer complaints of dry eye to an ophthalmologist. Ocular problems are unique — unfamiliar to many other physicians, in part because the instrumentation is foreign to every other specialty — making it difficult to diagnose and treat ocular conditions adequately in a family physician’s office, clinic, or emergency room.

NEW TREATMENT, COST-SAVING POTENTIAL

Before medical research transformed our understanding of dry eye, treatment had been limited to the use of artificial tears, ointments, and such nonpharmacologic therapies as punctal occlusion, environmental control, moisture-retaining eyewear, and surgery. Each had limited effectiveness, and few produced lasting improvement in patients’ quality of life.

Today, dry eye can be treated successfully with anti-inflammatory agents, the most beneficial of which is topical cyclosporine. In four multicenter, randomized, controlled clinical studies of approximately 1,200 patients with moderate to severe keratoconjunctivitis sicca, cyclosporine ophthalmic emulsion (0.05 percent) demonstrated statistically significant increases in Schirmer wetting at 6 months (Allergan 2003). This is the first prescription product for dry eye targeting well beyond palliative therapy, addressing the root inflammation of dry eye. Thus, demand for cyclosporine within this patient population may well prove to be high.

If so, this product will get the attention of managed care pharmacy directors and, one hopes, that of medical directors as well. Managed care organizations are routinely criticized for looking at expenditures in silo fashion, yet new systemic agents increasingly demonstrate a marked potential for offsetting nonpharmacy costs. When dry eye is controlled, there is significant potential for cost savings in a number of areas: complication costs, overutilization costs, opportunity costs, and intangibles. Some complication costs are derived from sequelae of untreated dry eye and can be significant. For instance, bacterial keratitis, mentioned earlier, is costly and can lead to corneal transplantation — a $20,000 procedure. Other complication costs can result from elective surgery. There are 1.5 million laser procedures and another 1.5 million cataract surgeries annually in the United States (Moretti 2000, Desai 2001), and dry eye is a potential complication of both procedures. When surgical patients take longer to heal and require more follow-up visits, there is added expenditure to the system.

Overutilization cost offsets represent another group
of potential savings. Some of these are easily identified, such as decreased use of artificial tears or reduced office-visit utilization that stems from poor patient satisfaction and compromised lifestyle due to dry eye symptoms. Until very recently, practitioners have been able to offer patients only palliative therapy; many of these individuals jump from physician to physician in search of relief from their progressively debilitating condition. In their modest way, these patients chronically and unnecessarily tax the health care system.

Other overutilization costs are more subtle. The more than 3 million elective eye procedures each year in the United States often involve patients who are predisposed to dry eye; cataract patients, for instance, tend to be older, while some LASIK patients dislike their contact lenses — often because their dry eyes make wearing contacts irritating or unbearable. Some of these elective procedures can, in fact, be avoided altogether by controlling the dry eye.

Yet another group of potential savings is in opportunity costs outside the health care system. These include indirect costs, such as loss of productivity attributed to morbidity, and reduced comfort and convenience to patients. Bacterial keratitis may result in permanent scarring. Without a corneal transplant, these patients can suffer loss of effectiveness relative to areas such as work performance, night driving, caring for family members, or engaging in a favorite activity. The projections can play out in various ways — a prospective fiscal analysis of this nature would hinge on the variables selected for study. Nevertheless, when opportunity costs are factored in, the overall costs to the health care system and to society are logarithmically accelerated.

Finally, intangibles include a satisfied patient population being offered a first-in-class drug therapy that represents a new paradigm in dry eye treatment. Contented patient clients reflect well on any health care organization, creating goodwill, an open dialog, new patient referrals, less confrontation, and more personable and appropriate access patterns.

NONECONOMIC CONSIDERATIONS

Opportunity costs could never be reflected in a health plan’s bottom line or in a P&T committee analysis. Yet, human factors — members’ quality of life, client satisfaction, and patient safety — merit consideration when decisions about access to new medications are made.

Dry eye is the most prevalent chronic ocular surface disease. Ophthalmologists share the frustration experienced by patients for whom artificial tears and punctal occlusion are ineffective. These treatments also are inconvenient; in such environments as airplanes, dry climates, or heated or air conditioned rooms, some patients must apply artificial tears several times each hour, with little lasting relief exacerbated by protracted blurred vision. Health plans can improve the satisfaction of millions of members who have moderate to severe dry eye disease by imparting appropriate access to newer treatments. Further gains might also be achieved through tasteful and intellectually sound marketing of newly available technology to selected existing patients, physicians, and potential clients. Rightly, such publicity should be limited through concerns regarding creation of excessive unnecessary demand.

Safety is a primary ingredient in the success of outcomes-driven medical practice. With the knowledge that has been obtained through study of the pathogenesis of dry eye, our approach to treatment has changed accordingly; over the past few years, ophthalmologists have begun to prescribe custom formulations of cyclosporine for dry eye patients. While these formulations have been reasonably efficacious in treating disease, they can be uncomfortable, difficult for patients to obtain, and — as off-formulary compounds — expensive for patients (Wilson 2001). Moreover, these compounds inherently possess a more threatening side-effect profile than do products that have or will eventually receive approval from the U.S. Food and Drug Administration.

We have learned that dry eye is a systemic disease and that it responds well to cyclosporine anti-inflammatory therapy. Agents coming to market and in development have altered the paradigm of treatment radically. This is an exciting time for medical professionals and for patients, who undoubtedly will clamor for access to these therapies. As new therapeutic options become available, an opportunity exists to create standards for their utilization that balances everyone’s interests while making them accessible to people who will benefit the most from them.

REFERENCES


Dry Eye: Prevalence, Utilization, and Economic Implications

MICHAEL D. DALZELL

Dry eye syndrome is believed to affect more than 4 million Americans (Schein 1997). The nature of the condition, however, suggests that the universe of individuals with untreated disease — whether the symptoms are ocular or otherwise in origin — may be larger. Dry eye is a common disorder, characterized by inflammation of the ocular surface and lacrimal glands. Often, dry eye symptoms serve as a marker for systemic illness.

This would suggest that health plans and practitioners that place an emphasis on detection and treatment of dry eye syndrome — sometimes dismissed as a trivial complaint — will benefit from improved clinical and financial outcomes. Beyond considerations of systemic illness, untreated dry eye itself can lead to corneal damage and visual impairment (Lemp 1987).

The next several pages provide a statistical snapshot of dry eye syndrome: its prevalence, populations at risk, potential complications, associated conditions, the demands dry eye places on health care utilization, and the ramifications for payers.

**Epidemiology**

The most commonly cited estimate of prevalence in the United States is derived from a population-based study of 2,482 elderly people in Maryland. About 1 in 7 subjects age 65 to 84 reported symptoms of dry eye often or all of the time. Extrapolated to the general population, Schein (1997) estimated that 4.3 million Americans in this age cohort suffer from ocular irritation and that 1 million have diagnosable disease. Moss (2000) reported similar overall prevalence (14.4 percent) in a larger cohort (3,722 subjects between ages 48 and 91).

While Schein found no correlation of disease with age or sex, other researchers have made such associations. Moss noted that after age 59, prevalence more than doubled. A separate Australian study of 926 subjects age 40 and older found generally higher prevalence of dry eye in women (Figure 1).

**FIGURE 1 Prevalence by age and sex**

* As diagnosed by one or more tests.
† Self-reported symptoms, not including subjects with hay fever.

SOURCE: MCCARTY 1998
OVERVIEW

EPIDEMIOLOGY, continued

Claims-based studies
Claims-based prevalence estimates provide a different perspective from population-based studies. Claims studies measure the impact of symptoms that require medical attention — a perspective that is valuable to payers.

In one study of claims data in a managed care environment covering 12 million lives, researchers noted a strong connection between dry eye and both advancing age and sex (Figure 2). Females were more likely to have a dry eye-related diagnosis or procedure. Women experienced a sharp increase in prevalence earlier than men — around age 45, or roughly the onset of menopause.

Explaining variability in prevalence
Epidemiological studies of dry eye syndrome in the United States and other countries suggest wide differences in prevalence. The difficulty in pinpointing the extent of disease stems, in part, from a previous lack of understanding of the etiology of dry eye. As such, definitions of dry eye syndrome have differed from study to study, making results incomparable (Brewitt 2001). This is complicated by the lack of a standardized clinical testing protocol to diagnose the condition.

The effect of this diagnostic void is illustrated in Figure 3. In one study, four diagnostic tests yielded wide differences in results among patients who complained of one or more severe dry eye symptoms; the tests also varied greatly in their ability to discriminate between signs and symptoms. Relatively few patients received diagnoses compatible with their symptoms.

FIGURE 2 Rates of diagnoses and procedures, by age and sex

<table>
<thead>
<tr>
<th>Test</th>
<th>1997</th>
<th>1998</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorescein</td>
<td>689.6</td>
<td>567.7</td>
</tr>
<tr>
<td>Rose bengal</td>
<td>273.0</td>
<td>221.8</td>
</tr>
<tr>
<td>Schirmer</td>
<td>385.9</td>
<td>319.6</td>
</tr>
<tr>
<td>Tear-film breakup</td>
<td>1653.4</td>
<td>1427.8</td>
</tr>
</tbody>
</table>

SOURCE: YAZDANI 2001

Each of these diagnostic tests has limited usefulness when performed alone, yet performing multiple tests is rarely feasible or cost-effective. Pflugfelder (1998) has proposed an algorithm for determining the diagnostic utility of tests. Meanwhile, the emerging recognition of dry eye as a multifactorial inflammatory condition may lead to consensus on diagnostic testing, as well as a more thorough understanding of iatrogenic contributions to dry eye syndrome.

FIGURE 3 Test used to detect clinical signs
Percentages are of patients reporting ≥1 severe symptom

<table>
<thead>
<tr>
<th>Test</th>
<th>Test result (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorescein</td>
<td>33%</td>
</tr>
<tr>
<td>Rose bengal</td>
<td>20%</td>
</tr>
<tr>
<td>Schirmer</td>
<td>12%</td>
</tr>
<tr>
<td>Tear-film breakup</td>
<td>9%</td>
</tr>
</tbody>
</table>

Figures are rounded to nearest whole percentage point. SOURCE: MCCARTY 1998

HIGH-RISK POPULATIONS FOR DRY EYE SYNDROME

- Inflammatory disease (vascular, allergy, asthma)
- Autoimmune diseases (RA, lupus, colitis)
- Peri- and postmenopausal women and HRT patients
- Diabetes mellitus
- Thyroid disease
- Sjögren’s syndrome
- Corneal transplantation
- Previous keratitis or corneal scarring
- Extracapsular or intracapsular large-incision cataract surgery
- Laser in situ keratomileusis (LASIK)
- Systemic medications (diuretics, antihistamines, psychotropics, cholesterol-lowering agents)
- Contact lens wear
- Environmental conditions (allergens, cigarette smoke, wind, dry climate, air travel, chemicals, some perfumes)

Low patient satisfaction has been documented among individuals with moderate to severe dry eye syndrome (Lubniewski 1990). The chronic symptomatology of dry eye, as well as relatively ineffective traditionally available treatment modalities, spawns frustration and high health-resource utilization among patients seeking relief from the condition.

Office visits
In the Schein (1997) study, 73 percent of subjects who reported frequent dry eye symptoms visited an eye care professional in the past year. A smaller survey, conducted among patients participating in phase 2 trials of a cyclosporine A topical preparation for dry eye syndrome, found that 60 percent of dry eye patients visited a physician more than twice in the past year for their symptoms (Nelson 2000).

Forty-two percent of these patients had undergone punctal occlusion at least once in the past. Surveys of subpopulations have identified higher office utilization and frequent visits; Hirsch (1998), for instance, reported that 89 percent of Sjögren’s dry eye patients visited an ophthalmologist an average of 3.1 times per year for their symptoms, and more than one fourth of all subjects had visited other physicians at least once in the past year for their condition.

Pharmaceutical interventions
A recent study of resource utilization among non-Sjögren’s dry eye patients found high utilization of medical therapies — among products specifically designed to treat dry eye symptoms as well as other drugs (Figures 4 and 5).

Future trends
With the advent of medical therapy that addresses the underlying inflammatory nature of dry eye syndrome, there is potential for increased patient satisfaction — and, thus, fewer office visits and reduced utilization of tear substitutes and other pharmaceutical therapies. Studies that document this potential are reported in the chapter on pharmacoeconomics that begins on page 33.
OVERVIEW

ECONOMIC IMPLICATIONS

Relatively few data exist on direct and indirect costs of dry eye and its sequelae. Likely, this is due to the fact that until recently, when the etiology of this common disease became more fully understood, dry eye was viewed largely as an irritant and not necessarily a serious condition worthy of medical attention. Nelson (2000) challenged this view from an economic standpoint, arguing that older treatment modalities can lead to unacceptable costs and progressive use of health care resources. Emerging scientific knowledge about dry eye may prompt payers or the government to conduct comprehensive data analyses of the economic impact of dry eye.

Direct medical costs and complications

Small-scale models have been developed to estimate the cost of office visits, drugs, and procedures attributed specifically to dry eye. In one study, the cost of managing and treating dry eye patients with palliative medications, punctal plugs, and surgery, over the course of 1 year, was $357,050 for an organization covering 500,000 lives (Lee 2000). The authors speculated that a more effective dry eye intervention could improve cost effectiveness by decreasing patient demand for physician visits and procedures.

The multifactorial nature of dry eye makes a full accounting of direct medical costs complex. Because dry eye can be a marker for systemic illnesses, costs of treating dry eye symptoms are often figured under other diagnoses. Moss (2000) used a logistic model to calculate factors associated with dry eye, including arthritis and diabetes. This research also discovered a protective effect in total-to-HDL (high-density lipoprotein) cholesterol ratio (Figure 6).

FIGURE 6 Prevalence of comorbidities*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Odds ratio²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td>1.91</td>
</tr>
<tr>
<td>History of gout</td>
<td>1.42</td>
</tr>
<tr>
<td>History of thyroid disease</td>
<td>1.41</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.38</td>
</tr>
<tr>
<td>Total-to-HDL cholesterol ratio</td>
<td>0.93</td>
</tr>
</tbody>
</table>

* Adjusted for age and sex. 95-percent confidence interval.
† Per increment of 1 unit.

SOURCE: MOSS 2000

Moss also examined lifestyle factors, finding a surprise protective effect of caffeine and a contributing factor in multivitamin use (Figure 7). This research also identified an opportunity for physicians to counsel patients who smoke or drink heavily.

FIGURE 7 Lifestyle factors*

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Odds ratio²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smoker</td>
<td>1.82</td>
</tr>
<tr>
<td>Multivitamin use</td>
<td>1.41</td>
</tr>
<tr>
<td>History of heavy alcohol use</td>
<td>1.31</td>
</tr>
<tr>
<td>Caffeine</td>
<td>0.75</td>
</tr>
</tbody>
</table>

* Adjusted for age and sex. 95-percent confidence interval.

SOURCE: MOSS 2000

Dry eye is a direct complication of large-incision cataract procedures, corneal transplantation, and LASIK. Moss reported a 1.39 odds ratio in patients who had undergone any sort of lens surgery, while Breil (2002) found that dry eye is one of the most common postoperative complications of LASIK.

Indirect costs

Dry eye syndrome has the potential to reduce employee productivity significantly. In one study, dry eye patients experienced an average of 184 work days of reduced productivity, at an estimated annual cost of $5,362 per individual (Kozma 2000). Another study — this of a subset of dry eye patients, those with Sjögren's syndrome — indicated that symptoms interfered with the activities of daily living in all but 29 days of the year (Figure 8).

FIGURE 8 Interference with activities

Days per year among Sjögren's patients

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Days lost from work: 5</th>
<th>Leisure days with symptom interference: 123</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days worked with symptoms:</td>
<td>208</td>
<td></td>
</tr>
<tr>
<td>No reported effects:</td>
<td>29</td>
<td></td>
</tr>
</tbody>
</table>

SOURCE: HIRSCH 1998

² An odds ratio is calculated by dividing the odds in the treated group by the odds in the control group. Factors that cause harm have an odds ratio > 1.0. An odds ratio of 2.0 represents a 100-percent increased risk.
SUMMARY

Dry eye syndrome is far more prevalent than previously considered. There are significant comorbidities, associated diseases, and behavioral and environmental factors that may contribute to the severity of dry eye. Dry eye syndrome has significant economic implications, including costs associated with increased health care utilization, missed school and work, and leisure and quality-of-life issues. Dry eye presents important economic challenges to patients, physicians, and health care delivery organizations.

REFERENCES


Inflammation: A Unifying Theory
For the Origin of Dry Eye Syndrome

STEVEN E. WILSON, MD

Cole Eye Institute, Cleveland Clinic Foundation

SUMMARY

Dry eye syndrome has been difficult to diagnose and treat, due to its heterogeneity. These difficulties are being overcome, however, as evidence becomes available about a common etiology. An inflammatory mechanism apparently underlies the condition. This theory has been proven by use of immunomodulators that show efficacy in treating patients with dry eye syndrome.

Keratoconjunctivitis sicca (KCS), or dry eye syndrome, is a common ophthalmologic abnormality involving bilateral disruption of the precorneal tear film. It is caused either by inadequate tears or an inability to maintain an effective tear film. In KCS, the tear film is disrupted, causing a variety of symptoms (Table 1). Dry eye syndrome can occur in any age group, but is especially prevalent in people over age 65. It estimated that 10 to 15 percent of Americans in this age group have one or more symptoms of this disease (Schein 1997). In serious cases, dry eye syndrome can lead to photophobia and vision loss.

It is evident from its name that KCS is a drying inflammation: kerato (corneal) conjunctivitis (conjunctival inflammation) sicca (from the Latin sicco, meaning “to dry”). KCS can occur sporadically or as a chronic condition that becomes a self-perpetuating syndrome. This article will explore current trends in KCS etiology research.

Destruction of corneal and bulbar conjunctival epithelium from KCS can arise from many diverse causes (AAO 1998); it is often secondary to Sjögren’s syndrome, an autoimmune disease that results in dry eyes and mouth. Sjögren’s syndrome can occur with or without rheumatoid arthritis, lupus, or scleroderma. In Sjögren’s KCS, the exocrine glands secreting tears, saliva, and gastric excretions are inadequate. KCS — either Sjögren’s or non-Sjögren’s — is now believed to be an autoimmune state in which the epithelial cells of the lacrimal glands are detected as antigens by the immune system and attacked, damaged, or killed by activated T-cell lymphocytes.

A variety of factors can exacerbate KCS (Table 2). New evidence has shown that regardless of the predisposing factor(s), most KCS results from a localized immune-mediated inflammation affecting both the lacrimal glands and the ocular surface (Stern 2002).

Historically, KCS has been frustrating to study and treat, in part due to its diverse symptoms and disease variables. The heterogeneity of dry eye creates challenges in the diagnosis and treatment of individual cases. The high degree of variability in patient populations makes data analysis extremely difficult. Thus, the ability to postulate and prove a unifying etiology has been hindered by the multifactorial nature of KCS and the clinical conundrum of matching patients’ symptoms and diagnostic test results with patients’ actual disease severity.

1 Steven E. Wilson, MD, is director of corneal research at the Cole Eye Institute of the Cleveland Clinic Foundation. A board-certified ophthalmologist, Wilson recently came to Cleveland from the University of Washington in Seattle, where he directed an NEI-supported laboratory that investigates the function of growth factors and cytokines in controlling corneal wound healing. He has authored more than 300 papers, abstracts, and book chapters. After earning his medical degree from the University of California–San Diego, Wilson completed an ophthalmology residency at the Mayo Clinic and a fellowship in cornea, external disease, and refractive surgery at the Louisiana State University Eye Center in New Orleans. Wilson, who holds memberships in numerous professional societies, serves on the board of trustees of the Association of Research in Vision and Ophthalmology and on the executive board of the ISRS-RSIG for the American Academy of Ophthalmology.
A COMMON UNDERLYING ETIOLOGY

The pathophysiology of KCS has long been known to involve a disruption of the layer of tears that protects and nourishes the delicate eye tissues. The goal of therapy has been to normalize tear volume and composition, so that the eye tissues are properly lubricated, nourished, and protected. This has been accomplished to some extent by increasing tear secretion, reducing tear turnover, and/or promoting epithelial healing on the ocular surface using lubricants and emollients. If the KCS results from a systemic disorder, the systemic disease can be treated and the symptoms thereby decreased.

Local treatment strategies for the eye (aside from treating infections) have been essentially palliative, however, and do not address the inflammatory response. The treatment goal of this new approach to disease is to suppress the inflammation that underlies symptoms and signs.

The recent discovery of a neurological-inflammatory component has provided an explanation for the pathophysiology of KCS. If inflammation in KCS is considered not a symptom but a cause, then suppressing the cytokine-mediated inflammatory response that occurs at a histological level can be applied to KCS regardless of disease-state association. An emerging strategy for treatment of KCS is therapy with immunomodulators that address the local inflammation caused by cytokines that circulate in the lacrimal glands and conjunctiva, regardless of whether any associated disease state is local or systemic.

According to this new theory of KCS etiology, a cyclical syndrome causes the lacrimal glands to suffer from neurogenic inflammation, T-cell activation, and cytokine secretion into tears. The cytokine-laden tears inflame the ocular surface, disrupting sensory signals from the surface of the eye, so the normal stimulus for tear secretion is curtailed. In addition, the lacrimal glands, both primary and secondary, may be damaged or destroyed. This leads to a virtual shutdown of the lacrimal system and to a self-perpetuating inflammation that cannot be ameliorated by the eye’s normal defense system. The immune system itself is the problem (Figure 1, page 16). This localized inflammation cycle can be demonstrated in both Sjögren’s and non-Sjögren’s patients.

The normal lacrimal system

Normally, the integrity of the lacrimal system is maintained by a precise interplay of secretions from primary and secondary glands located under the eyelids and from sebaceous glands on the flat rims of the eyelids that secrete an antievaporation lipid layer (Figure 2, page 16).

The tear drainage system is also important in normalizing hydration of the eye. Inflammation-induced dysfunction in this drainage system can precipitate KCS. The system includes the punctal opening (the tiny hole in the upper and lower eyelids). Blinking causes tears to enter the punctae, where they are drained through canaliculi into the lacrimal sac and the nasolacrimal duct into the nose.

Part of the function of tears is to protect the eye from microbial invasion. In a normally functioning adult eye, an anti-inflammatory component keeps the disruptive effect of irritation to a minimum. When this component is lacking, however, or when irritation is not controlled, the body’s immune system activates its inflammatory T-lymphocytes.

Cytokines are hormone-like proteins that regulate the immune response. They also damage tissue when overabundant (Table 3, page 17). Cytokines and other proinflammatory mediators lead to activation of more T-cells, production of more inflammatory substances, and tissue damage.

### TABLE 1
**Symptoms of keratoconjunctivitis sicca**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry sensation</td>
<td>Foreign body or “gritty” sensation</td>
</tr>
<tr>
<td>Dry sensation</td>
<td>Blurred vision</td>
</tr>
<tr>
<td>Irritation/redness</td>
<td>Contact lens intolerance</td>
</tr>
<tr>
<td>Redness</td>
<td>Increased frequency of blinking</td>
</tr>
<tr>
<td>Tearing</td>
<td>Mucous discharge</td>
</tr>
<tr>
<td>Burning/stinging</td>
<td></td>
</tr>
</tbody>
</table>

*SOURCE: PFLUGFELDER 2000a*

### TABLE 2
**Variables in keratoconjunctivitis sicca**

**Precipitating factors**
- Medication (e.g., anticholinergics)
- Environmental conditions (e.g., wind)
- Trauma (e.g., chemical burns) or corneal dystrophies
- Reading for lengthy periods (especially from a computer screen)

**Severity potential**
- Annoyance only
- Acute increase in severity (e.g., photophobia and blepharospasm)
- Loss of normal configuration of conjunctival fornices
- Ulceration, vascularization, and scarring of cornea
- Severe visual disability

**Duration**
- Sporadic, reversible
- Chronic irreversible deficiency of tear production
  - Waxing or waning
  - Constant condition

*SOURCE: STERN 2002*
Ordinarily, when any kind of an invasion or disruption is detected, more tears are produced to flush out the entire lacrimal system. In autoimmune diseases, however, the inflammatory response in the eye can attack healthy epithelial cells with enzymes that are meant to lyse invaders, damaging the matrix of tears and the conjunctiva.

Evidence from canine research shows that the origin of KCS is associated with lymphocytic infiltrations in both the conjunctiva and the lacrimal glands. Biopsies from dogs with dry eye syndrome demonstrate such lymphocytes (Figure 3). Total T-cells that are abnormally increased in dry eye syndrome can be seen by fluorescing T-cells in the conjunctiva of Sjögren’s and non-Sjögren’s patients.

The main and accessory lacrimal glands may be susceptible to inflammation due to an age- and hormone-related degenerative process. The change in tear secretions leads to the pathophysiology described above as a neurological inflammatory disease that becomes a constant cycle (Figure 4, page 18). As sensory input to the lacrimal glands decreases, the quantity and quality of tears is reduced, causing further irritation of the ocular surface.

**Cyclosporine as an anti-inflammatory agent in dry eye**

Marsh (1999) showed that corticosteroids could be used for treating severe dry eye in humans. Nevertheless, use of corticosteroids was limited by the known side effects of cataract formation, glaucoma, and infection. Cyclosporine A (CsA) was tested and found efficacious by ophthalmologists experimenting with it in severe, treatment-resistant KCS patients. Now, it is available as a topical anti-inflammatory for dry eye syndrome, formulated at doses thousands of times smaller than those used to avoid graft-versus-host disease in tissue transplantation.

Cyclosporine is an immunomodulator that primarily is used systemically in transplant, psoriasis, and rheumatoid arthritis patients. This agent’s anti-inflammatory effects arise primarily from its ability to prevent the activation of T-cells and resulting production of cytokines and other inflammatory agents. Until recently, there was no commercially available preparation of CsA for topical use in the eye. The preparation had to be custom formulated in irritating oils by pharmacists for ophthalmologists. Despite the fact that this use of CsA had not been systematically tested in humans, many ophthalmologists reported good results with few complications other than stinging.
CsA was approved in the United States in 1995 to treat chronic dry eye disease in dogs. Now that CsA has been tested in humans at a dose of 0.05 percent in a special vehicle, it can be used to increase tear production in patients whose production levels are presumed to be suppressed due to ocular inflammation associated with KCS.

The effect of CsA ophthalmic emulsion on inflammation arises from its ability to inhibit activation of T-cells by blocking their intracellular signal transduction cascade responsible for upregulation of NF-AT and NF-kB regulated genes, including genes for many cytokines (Table 4).

**Phase 2 and 3 clinical studies of cyclosporine for KCS**

A phase 2 study of CsA among 162 patients was undertaken using doses ranging from 0.05 percent to 0.40 percent twice a day. The results determined that doses of 0.05 percent to 0.10 percent were effective and well tolerated (Stevenson 2000).

At the small doses used in the phase 3 study, there was no evidence of the increased risk of infections and tumors observed with large doses of cyclosporine used for transplantation. With the fractional dose used for KCS (2,500 times smaller), there were no ocular infections related to CsA, nor was the drug detected in the blood of patients who were administered a 0.05 percent dose.

The 1-year results of phase 3 study of CsA (both Sjögren’s and non-Sjögren’s) are briefly described in Tables 5–7 on page 19, and then in more detail in the chapter “Medications for Dry Eye Syndrome: A Drug-Therapy Review,” which begins on page 26.

Use of cyclosporine resulted in both clinical improvements and a decrease in markers of immunity and inflammation in conjunctival biopsies. This improvement was evident especially during the first arm of the study (Sall 2000). The efficacy of the vehicle used for a comparison in the

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**TABLE 3 The role of cytokines and T-cells in adaptive immunity**

<table>
<thead>
<tr>
<th>Immunomodulator</th>
<th>Description and function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokines (Examples: interferon, interleukin, lymphokines)</td>
<td>These are proteins released by various types of cells including lymphocytes and corneal epithelial cells. Cytokines regulate the process of T-cell proliferation and differentiation, and serve an antiviral and anti-tumor function in the immune system. They promote allergic reactions, boost T-cell functions, and thus are used to evaluate immune activity.</td>
</tr>
<tr>
<td>T-cells</td>
<td>These are lymphocytes with antigen-receptor complexes on their surfaces. They are produced by the thymus and have the ability to lyse foreign or virus-infected cells. They reside primarily in the lymphatic system and secrete hormone-like peptides that mediate the immune response; they also regulate erythroid cell maturation in bone marrow.</td>
</tr>
<tr>
<td>CD3 cells</td>
<td>These are a subset of leukocytes involved in signal transduction in the cell membrane.</td>
</tr>
</tbody>
</table>

**TABLE 4 Anti-inflammatory activity of cyclosporine A**

- Binds to an intracellular protein
- Inhibits an activation enzyme (calcineurin)
- Inhibits expression of numerous genes essential for T-cell activation and proliferation
- Prevents replication of T-cells by blocking a transcription factor
- Keeps T-cells from expressing some cytokines or “homing” to inflammation site
- Promotes a gene (transforming growth factor) that inhibits the inflammatory response

---

**FIGURE 3 Evidence of inflammation in dry eye syndrome**

- Conunctiva
- Lacrimal gland
- T-cell infiltrations

SOURCE: STERN 1998
lymphocyte cell marker CD3 in Sjögren’s and non-Sjögren’s dry eye patients showed a reduction in T-lymphocyte infiltration after treatment with CsA. Comparing baseline stains with those after 6 months of CsA treatment, there was a 3- to 5-fold decrease in the number of CD3-positive cells in the conjunctiva of Sjögren’s and non-Sjögren’s patients. These similar results in Sjögren’s and non-Sjögren’s patients are consistent with a similar pathophysiology for both conditions (Figure 5).

Disruption of the tear film overlying the cornea generates variable irregular astigmatism. This results in blurred vision, an important efficacy measure of treatment. Blurred vision and reliance on artificial tears were included as endpoints in the phase 3 study (Table 7).

Patients in all groups were allowed to instill preservative-free artificial tears between doses of study medication throughout the trial. Reduced utilization of artificial tears was a gauge of symptom relief.

It should be noted that in clinical studies, CsA did not increase tear production in patients already taking topical anti-inflammatory drugs. This evidence served to confirm the unifying hypothesis of inflammation as the etiology of dry eye syndrome.

Although the anti-inflammatory theory has been corroborated by clinical efficacy of CsA in KCS, the dry eye induced by LASIK surgery is not expected to be eligible for anti-inflammatory treatment, as it has a different neurotrophic origin. LASIK patients who had preexisting dry eye may, however, benefit from CsA treatment.

**CONCLUSION**

Traditionally, KCS was difficult to diagnose and treat, due to its heterogeneity. An inflammatory mechanism apparently underlies the condition. This unifying theory has been proven by use of immunomodulators that showed...
ETIOLOGY

DRY EYE SYNDROME

The topical CsA phase 2 and phase 3 studies provided evidence of inflammation reduction after treatment. These findings were accompanied by subjective and objective symptom improvements. Difficulties in studying and treating this disease are being overcome as more evidence becomes available about a common etiology. For patients, this will mean less irritation and inflammation. It also should translate to a reduced reliance on artificial tears and ointments and fewer office visits.

REFERENCES


Guidelines for the Treatment Of Chronic Dry Eye Disease

JOHN D. SHEPPARD, MD, MMSc

SUMMARY
Keratoconjunctivitis sicca (KCS), also known as dry eye syndrome, dry eye disease, chronic dry eye disease, or keratitis sicca, refers to disorders of the tear film caused by reduced tear production, poor tear quality, or excessive tear evaporation. These disorders are associated with such symptoms of ocular discomfort as irritation, foreign body sensation, or redness, and may cause disease of the ocular surface.

Chronic dry eye disease (CDED) is highly heterogeneous, and patients present in many different ways. For example, patients with severe symptoms may reveal minimal signs upon examination, while patients with a multitude of seemingly significant findings at the slit lamp may have few complaints. The American Academy of Ophthalmology's newly released guidelines for diagnosis, treatment, and management reflect a universal acceptance by clinicians of dry eye — alone or in combination with other conditions — as an inflammatory ocular surface disorder that can be a cause of visual morbidity and may compromise the results of corneal surgery, cataract surgery, or other ocular surface procedures. Dry eye symptoms often improve with treatment, but the disease usually is not curable. Many of the ocular surface changes associated with KCS can be reversed with specific treatment.

To preserve or improve vision, prevent or minimize structural damage to the ocular surface, and alleviate patient discomfort, clinicians must be aggressive both in diagnosing possible underlying systemic inflammatory disease and in making ocular surface anti-inflammatory therapy a key component of their treatment approach. Environmental control, as well as a careful evaluation of systemic medications, also may yield clinical improvement.

Epidemiology of dry eye
The heterogeneity of dry eye, the lack of uniformity in its definition, and the inability of any single diagnostic test or set of tests to confirm or rule out dry eye definitively have limited the comparability of epidemiological data for this condition.

One clinic-based study found that 17 percent of 2,127 consecutive new outpatients were diagnosed with dry eye following a comprehensive examination (Hikichi 1995). In a population-based study in Australia, 16.3 percent and 10.8 percent of 926 participants, ages 40 to 97, tested positively for dry eye, based on a low Schirmer test or a high rose bengal score, respectively (McCarty 1998). An evaluation of claims data for nearly 10 million enrollees in managed care plans found that dry eye was diagnosed or treated in 0.5 percent of enrollees (Yazdani 2001).


Pathogenesis of dry eye
The ocular surface and tear-secreting glands function as an integrated unit to refresh the tear supply and to clear used tears (Stern 1998). Disease or dysfunction of this unit results in ocular irritation and dry eye syndrome. Decreased tear secretion and clearance initiate an inflammatory response on the ocular surface, and research suggests that this inflammation plays a role in the pathogenesis of dry eye (Pflugfelder 2000).

Dysfunction may develop from aging, a decrease in supportive factors (such as androgen hormones), systemic inflammatory diseases (such as rheumatoid arthritis), ocular surface diseases (e.g., herpes zoster ophthalmicus), surgery that disrupts the trigeminal afferent sensory nerves (including laser in situ keratomileusis [LASIK], extracapsular cataract extraction, or penetrating keratoplasty), and systemic diseases or medications that disrupt the efferent cholinergic nerves that stimulate tear secretion (Bacman 2001).

Associated conditions
Symptoms caused by dry eye may be exacerbated by systemic medications such as diuretics, antihistamines, anti-
cholinergics, antidepressants, HMG co-A reductase inhibitors, systemic retinoids, and isotretinoin (Moss 2000). Dry eye also may be made worse by environmental factors, including exogenous irritants and allergens, wind, drafts, air conditioning, heating, and reduced humidity.

In a study of Maryland residents age 65 or older, subjects with blepharitis associated with meibomitis were twice as likely to have dry eye symptoms as those without signs of meibomitis (Schein 1997).

Systemic diseases associated with dry eye include Sjögren’s syndrome, rosacea, viral infections such as acquired immune deficiency syndrome (Lucca 1990), hepatitis C (Abe 1999, Siagris 2002), primary and persistent Epstein-Barr virus infections (Pflugfelder 1987, Merayo-Lloves 2001, Pflugfelder 1993), and graft-versus-host disease in recipients of allogenic bone marrow or stem cell transplants (Ogawa 1999).

In Sjögren’s syndrome, an inflammatory cellular infiltration of the lacrimal gland leads to deficient tear production. Rosacea is associated with posterior blepharitis, poor tear quality, accelerated tear film breakup time (TBUT), and increased tear evaporation. Aqueous tear deficiency may develop in conditions such as lymphoma, sarcoidosis (Drosos 1989), hemochromatosis, and amyloidosis (Fox 1994).

Diseases such as ocular cicatricial pemphigoid and Stevens-Johnson syndrome produce tear deficiency due to inflammation, scarring, and destruction of the conjunctival goblet cells. Atopy may produce dry eye due to systemic antihistamine use or blepharitis and eczema.

**Natural history**

CDED varies in severity, duration, and etiology (Lemp 1995). In most patients, it does not threaten sight but is characterized by troublesome symptoms of irritation. When dry eye is caused by an irreversible deficiency of tear production or a chronic condition such as blepharitis that leads to increased tear evaporation, symptom severity may wax and wane, or gradually increase over time.

Reversible conjunctival squamous metaplasia and punctate epithelial erosions of the conjunctiva and cornea develop in many patients who have moderate to severe dry eye. Rarely, patients with severe dry eye will develop complications such as ocular surface keratinization; corneal ulceration, scarring, thinning (ectasia), or neovascularization; microbial keratitis; and sterile corneal keratolysis, with possible perforation and severe visual loss.

**DIAGNOSIS, TREATMENT, AND MANAGEMENT**

According to guidelines established in the AAO’s 2003 *Preferred Practice Pattern*, the goals of diagnosing, treating, and managing patients with dry eye are: to establish the diagnosis of dry eye, differentiating it from other causes of irritation and redness; to identify the causes of

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**FIGURE 1 Modified diagnostic classification scheme for dry eye**

1. Ocular irritation syndrome
2. Tear film instability
3. Ocular surface disease

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**SOURCE:** LEMP 1995
DETECTION AND TREATMENT

dry eye; to establish appropriate therapy; to relieve discom-
"comfort; to prevent complications, including visual loss, in-
festation, and structural damage; and to educate pa-
tients and involve them in managing their disease.

In moderate to severe cases that are unresponsive to
"treatment or when systemic disease is suspected, timely
"referral to an ophthalmologist with experience in man-
"aging this condition is recommended. Referral to an
"internist or rheumatologist can be considered for pa-
tients with systemic immune dysfunction or for individu-
"als requiring immunosuppressive therapy (AAO 2003).

The most important aspects of caring for patients with
dry eye are to educate them about the chronic nature of
the disease process and to provide specific instructions for
therapeutic regimens. It is helpful to discuss realistic ex-
"pectations, in terms of therapeutic goals. It also is essen-
tial to assess, periodically, the extent of their under-
standing of the disease and adherence to treatment.

Diagnosis

Many ocular surface diseases produce symptoms simi-
lar to those associated with dry eye, such as foreign-
body sensation, mild itching, burning, blurred vision, ir-
ritation, and soreness. The initial evaluation of a patient
"presenting with symptoms that are suggestive of dry eye
should include those features of the comprehensive adult
eye evaluation relevant to dry eye (AAO 2003).

It is often difficult to diagnose patients with mild dry
eye syndrome because of the inconsistent correlation be-
"tween reported symptoms and clinical signs (Schein
1997) and the relatively poor sensitivity and/or specificity
of existing diagnostic tests (AAO 2003). When environ-
"mental factors and other potential causes of ocular irrita-
"tion (see page 10) have been eliminated from consid-
"eration, patients with suggestive symptoms who do not
have overt signs of disease should be placed on trial treat-
"ments, such as artificial tears or, where appropriate, trial
"discontinuation of systemic antihistamines (AAO 2003).

Because most dry eye conditions are chronic, repeat
"observation and the reporting of symptoms over time
will allow a more accurate clinical diagnosis of dry eye.
A diagnostic classification scheme, adapted from a Na-
"tional Eye Institute Workshop, is shown in Figure 1 on
page 21 (Lemp 1995). Participants in this workshop
agreed that two major factors — deficient aqueous tear
production and increased evaporative loss — may cause
dry eyes independently but also may contribute con-
"currently to dry eye symptoms and signs.

Patient history

According to the AAO 2003 guidelines, the history of
the patient’s illness should include symptoms and signs re-
"lating to the eyes such as dry sensation, irritation, tearing,
burning, stinging, foreign-body sensation, photophobia,
blurred vision, contact lens intolerance, redness, mucus-
ous discharge, increased frequency of blinking, itching, and di-
urnal fluctuation; exacerbating conditions, such as wind,
air travel, or low humidity; prolonged visual effort that is
associated with a decreased rate of blinking; duration of
symptoms; and any topical medications that have been
used, as well as their effects on symptoms.

The patient’s ocular and medical histories should in-
clude the factors listed in Table 1. In addition, the medi-
cal history should describe use of systemic medications,
including antihistamines, diuretics, hormones and hor-
monal antagonists, antidepressants, cardiac antiarrhyth-
mic drugs, diphenoxylate/atropine, isotretinoin, beta
blockers, chemotherapy agents, HMG co-A reductase
inhibitors, and any drug with anticholinergic effects.

Physical examination

The physical examination should include a visual acu-
ity measurement, an external examination, and a slit-
lamp biomicroscopy. The external examination and the
biomicroscopy serve to document signs of dry eye, assess
the presence and severity of deficient aqueous tear pro-
duction and/or increased evaporative loss, and exclude
other causes of ocular irritation.

The examination and biomicroscopy should focus on
"factors listed in Table 2. Additionally, at the slit lamp, the
clinician should direct attention toward the four punc-
tums, noting patency or closure, juxtaposition to the bul-
bar conjunctiva, and the size of the opening when patent.

Diagnostic tests

The poor correlation between reported symptoms and
clinical signs, coupled with the aforementioned
limitations of clinical tests, make it difficult to diagnose
dry eye in its mild form. For patients with mild irritation
symptoms, a rapid TBUT may detect an unstable tear
film with normal aqueous tear production, and ocular
surface dye staining may detect a minimal pattern or no
pattern. For patients with moderate to severe aqueous
tear deficiency, the diagnosis can be made with one or
more of the following tests: TBUT, ocular surface dye-
staining pattern (rose bengal, fluorescein, or lissamine
green), or Schirmer wetting test.

These tests should be performed in the above se-
quence, because the Schirmer test can disrupt tear film
stability and cause false-positive ocular surface dye stain-
ing. Other tests may be helpful in evaluating selected
patients, but some have limited availability. These tests
include tear osmolarity, fluorescein clearance, impression
cytology, tear function index, and tear protein analysis
(including lactoferrin, lysozyme, immunoglobulin, and
albumin) (AAO 2003).
Corneal sensation should be assessed when trigeminal nerve dysfunction is suspected (Heigle 1996). A laboratory and clinical evaluation for autoimmune disorders should be considered for patients with significant dry eyes, other signs and symptoms of an autoimmune disorder (e.g., dry mouth, rash, arthritis, colitis, or renal dysfunction), or a family history of autoimmune disorders.

**Treatment**

Patients with a clinical diagnosis of mild dry eye may benefit from behavioral and environmental modification, such as learning to take breaks while reading, lowering the computer monitor to decrease lid aperture, and humidification of the environment (Nordstrom 1995). Because dry eye can be iatrogenic, elimination of exogenous medical factors, such as prescription regimens that include ocular topical preservatives or systemic antihistamines or diuretics, may help.

For patients with mild disease, use of tear substitutes is indicated. As the severity of dry eye increases, nonpreserved tear substitutes or emulsions, gels, and ointments may be used instead of conventional preserved tear substitutes. Noninvasive therapies such as spectacle side shields, moisture inserts, and moisture chambers are appropriate for more severe disease, but these tend to be unpopular among patients for cosmetic reasons (AAO 2003).

**Medications**

Pilocarpine and cevimeline, two cholinergic agonists, have been approved by the U.S. Food and Drug Administration to treat the symptoms of dry mouth in patients with Sjögren’s syndrome (Vivino 1999, Fox 2001). These oral medications stimulate secretion of the salivary and sweat glands and appear to improve tear production, but most clinical studies demonstrate greater improvement in dry mouth than dry eye (Vivino 1999, Nelson 1998).

Patients treated with pilocarpine at a dosage of 5 mg orally, 4 times daily, experienced a significantly greater overall improvement in the ability to focus their eyes during reading, as well as improvements in symptoms of blurred vision, compared to placebo-treated patients. (AAO 2003, Vivino 1999). The most common side effect from this medication class is excessive sweating.

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**TABLE 1** AAO guidelines: patient history

<table>
<thead>
<tr>
<th>Ocular history should describe:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Contact lens use, lens material, solutions, wearing schedule, lens care</td>
</tr>
<tr>
<td>• Allergic conjunctivitis</td>
</tr>
<tr>
<td>• Corneal history (prior keratoplasty, LASIK, photorefractive keratectomy, radial keratotomy, or extracapsular cataract extraction)</td>
</tr>
<tr>
<td>• Punctal plugs or surgery</td>
</tr>
<tr>
<td>• Eyelid surgery (prior ptosis repair, blepharoplasty, entropion/ectropion repair)</td>
</tr>
<tr>
<td>• Chronic ocular surface inflammation (acid or alkaline burns, ocular cicatricial pemphigoid, or Stevens-Johnson syndrome)</td>
</tr>
</tbody>
</table>

**Medical history should include:**

- Smoking, menopause, and atopy
- Dermatological diseases (including seborrhea, eczema, rosacea)
- Trauma (including exposure to chemicals, ultraviolet light, dust, sawdust, fumes)
- Systemic inflammatory diseases (Sjögren’s syndrome, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, graft-versus-host disease)
- Chronic viral infections, such as chronic hepatitis C or human immunodeficiency virus
- Surgery (bone marrow transplant, head and neck surgery)
- Radiation of orbit
- Neurological conditions (including Parkinson’s disease, Bell’s palsy, and Riley-Day syndrome)
- Xerostomia (dry mouth), dental cavities, and oral ulcers

**TABLE 2** AAO guidelines: physical exam

**External examination should focus on:**

- Skin (scleroderma, facial changes indicating rosacea)
- Eyelids (incomplete closure/malposition, erythema of eyelid margins, incomplete/infrequent blinking, abnormal deposits/secretions, entropion, ectropion)
- Adnexa (enlargement of the lacrimal glands)
- Proptosis
- Cranial nerve function (including cranial nerve V, VII)
- Disorders affecting the hand (joint deformities characteristic of rheumatoid arthritis, gout, or psoriasis)

**Slit-lamp biomicroscopy should include attention to:**

- Tear film (height of meniscus, debris, foam)
- Eyelashes (trichiasis, distichiasis, madarosis, deposits)
- Anterior/posterior eyelid margins and character of meibomian gland secretions
- Vascularization crossing the mucocutaneous junction, keratinization, and scarring
- Puncta (patency and position)
- Conjunctiva (inferior fornix and tarsal conjunctiva, and bulbar conjunctiva)
- Cornea (localized interpalpebral drying, punctate epithelial erosions, filaments, macroepithelial defects, punctate staining with rose bengal or fluorescein dyes, mucous plaques, keratinization, pannus formation, thinning, infiltrates, ulceration, neovascularization, and scarring)

**SOURCE:** AAO 2003
DETECTION AND TREATMENT

occurred in more than 40 percent of patients.

Cevimeline also has been found to improve ocular irritation symptoms and aqueous tear production (Petrone 2002) and may have fewer adverse systemic side effects than oral pilocarpine (AAO 2003).

Anti-inflammatory therapies may be considered in addition to aqueous enhancement therapies. In clinical trials, topical cyclosporine has been reported to increase aqueous tear production and decrease ocular irritation symptoms in dry eye treatment (Gunduz 1994, Sall 2000). Clinically significant improvements in Schirmer wetting, punctate keratopathy, quality-of-life measures, and artificial tear use proved sufficient for FDA approval of the first prescription medication for dry eye disease on Dec. 24, 2002 — a topical, preservative-free 0.05 percent cyclosporine emulsion. The proprietary emulsion preparation is ideally formulated to distribute the relatively insoluble cyclosporine molecule to the ocular surface with maximal bioavailability. Previous formulations by compounding pharmacies utilizing much higher concentrations — as high as 4 percent — do not achieve tissue levels equivalent to the approved emulsion.

Cyclosporine is an 11-amino-acid cyclopeptide, produced as a metabolite by the fungus species Beauveria nivea. Cyclosporine prevents activation and nuclear translocation of cytoplasmic transcription factors that are required for T-cell activation and inflammatory cytokine production. It also inhibits mitochondrial pathways of apoptosis and has been reported to heal paracentral sterile corneal ulcers associated with Sjögren’s syndrome and rheumatoid corneal ulceration (Kervick 1992). Cyclosporine therapy appears to address all three tear film components (aqueous, oil, and mucin), and therefore the three types of tear deficiency that may occur in various combinations in dry eye disease.

Nonpreserved topical corticosteroids have been reported to decrease ocular irritation symptoms, reduce corneal fluorescein staining, and improve filamentary keratitis (Marsh 1999, Prabhasawat 1998). Low-dose corticosteroid therapy can be used at infrequent intervals for short-term (2-week) suppression of irritation secondary to inflammation.

Patients with systemic disease such as primary Sjögren’s syndrome, or with connective tissue disease such as rheumatoid arthritis, should be managed in conjunction with the appropriate medical specialist. Anti-inflammatory/immunosuppressive therapy may be appropriate for patients with a systemic disease such as rheumatoid arthritis (AAO 2003).

Surgical treatment

Surgical treatment is generally reserved for patients with symptomatic, moderate, or severe disease, and for whom medical treatment has been inadequate or impractical (AAO 2003).

Aqueous enhancement by means of punctal occlusion can be accomplished surgically with semipermanent plugs (silicone or thermal labile polymer) that are lodged at the punctal orifice (AAO 1997, AAO 1998, AAO 2003), or by permanent occlusion with thermal or laser cautery. Prior to permanent or semipermanent punctal occlusion, temporary slow-dissolving collagen punctal plugs can be placed in most patients’ lower punctum. Because an occluded punctum can trap inflammatory mediators, inflammation, logically, should be controlled prior to punctal occlusion. Nevertheless, many patients with successful or partially helpful punctal occlusion procedures obtain additional benefit from subsequent initiation of topical anti-inflammatory therapy.

Eyelid abnormality as a result of blepharitis, trichiasis, or lid malposition (e.g., entropion/ectropion, lagophthalmos) should be corrected prior to permanent punctal occlusion (AAO 2003).

Semipermanent plugs are reversible if the patient develops symptoms of epiphora, while cautery is not readily reversible. Therefore, a trial occlusion with collagen plugs should be performed first. To minimize the possibility of epiphora, no more than one punctum should be cauterized in each eye. The lower punctum is preferable for occlusion, as it is usually larger and more accessible. It is important to inspect the upper punctum first for both patency and integrity, before occluding the lower punctum. In general, laser cautery is not as effective as thermal cautery in achieving permanent, complete occlusion and is more expensive.

Tarsorrhaphy can be performed to decrease tear evaporation in patients with severely dry eyes, and for whom all other medical and surgical therapies have been exhausted.

Management

The purpose of the follow-up evaluation, as outlined in the AAO 2003 guidelines, is to assess the patient’s response to therapy and the need to adjust treatment, to monitor for structural ocular damage, and to provide reassurance to the patient. The follow-up evaluation’s frequency and composition is determined by disease severity, the therapeutic approach, a patient’s personality and adherence to therapy, and the response to therapy.

Patients with mild dry eyes can be seen once or twice per year for follow-up if symptoms are controlled by therapy. Patients with sterile corneal ulceration associated with dry eye require careful, sometimes daily, monitoring. Patients with existing dry eye, on the other hand, should be cautioned that LASIK or photorefractive keratometry may worsen their condition.
CONCLUSIONS

The AAO Preferred Practice Pattern for dry eye syndrome was developed as practitioners of ophthalmology and optometry have come to understand the inflammatory nature of the condition. Since then, discoveries about the etiology of dry eye disease and the subsequent development of new therapies to treat — rather than palliate — have effectively launched a new era for millions of people who suffer from the sometimes devastating consequences of dry eye.

Eye care professionals are engaged in discussions regarding the appropriate use of these emerging therapies as first-line treatments. Certainly, high-risk individuals, postmenopausal females, patients requiring 4 or more drops of artificial tears per day, and patients with rheumatologic conditions should strongly be considered candidates for anti-inflammatory therapy. Clinicians are well aware that the severely dry patient of today, with compromised vision due to central corneal ulceration, was the mildly dry eye patient of yesterday. CDED is progressive and intimately associated with the aging process, akin to glaucoma, hypertension, and hypercholesterolemia. Perhaps early intervention and preventive strategies will not only avoid significant morbidity and discomfort, but enable overall cost savings through proactive selective intervention. Ultimately, decisions will be made on the basis of everyday clinical evidence, just as the FDA has ruled on the appropriate use of these emerging therapies for keratoconjunctivitis sicca.

The potential for improved quality of life, decreased routine and emergent visits to the ophthalmologist, and the implications for reducing costs and complications of treatment are enormous. These considerations, discussed throughout this publication, represent state-of-the-art, patient-oriented, quality-conscious eye care.

REFERENCES


Medications for Dry Eye Syndrome: A Drug-Therapy Review

HENRY D. PERRY, MD
ERIC D. DONNENFELD, MD
Ophthalmic Consultants of Long Island

SUMMARY

Early interventions were palliative, attempting to replace water lost from the tear film. Today, therapy is directed at the underlying inflammation, a recognized component of dry eye syndrome, and at the resulting progressive changes to the ocular surface. This approach offers promise of lasting relief to patients with moderate to severe symptoms.

Research into dry eye syndrome (keratoconjunctivitis sicca) has advanced dramatically in the last decade, providing a better understanding of the pathophysiology, underlying mechanisms, and natural history of the disease. This advance in knowledge has been accompanied by a more focused therapeutic approach, with new treatments targeted at underlying pathophysiologic processes. Whereas early interventions for dry eye syndrome attempted to simply replace water lost from the tear film, today there exists a new therapy directed at the underlying inflammation, now a recognized component of dry eye syndrome, and at the progressive changes in the ocular surface that occur over time with the disease (Table 1, page 28).

More than 4 million people in the United States are thought to suffer from dry eye syndrome (Schein 1997), and as much as 25 percent of patients visiting eye care clinics describe dry eye symptoms (Hikichi 1995; Doughty 1997). The United States Food and Drug Administration’s recent approval of cyclosporine ophthalmic emulsion 0.05 percent as the first prescription medication to treat keratoconjunctivitis sicca may herald the start of a new therapeutic era. This new therapeutic focus corrects underlying pathologies that lead to dry eye and uses pharmacologic agents with anti-inflammatory/immunomodulatory mechanisms to manage the signs and symptoms of disease and to control or reverse corneal damage. Other novel and exciting treatments are in the pipeline as well, and these could contribute to this evolving paradigm.

TREATMENT APPROACHES: AN OVERVIEW

Traditionally, the approach to the treatment of dry eye syndrome has been palliative, relying predominantly on replacement of tears to curb symptoms without addressing the underlying disease process. Over the years, improvements were made in the formulation of artificial tears and lubricants—including the addition of demulcents to improve viscosity and lubricant properties, and the development of preservative-free solutions to avoid causing corneal toxicity. Yet, despite their widespread

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use and proven activity relative to improving ocular lubrication, increasing humidity at the ocular surface, and even contributing to improved vision, these products generally failed to accurately reproduce natural tears, could not acceptably substitute for the continuous flow of natural tears, and did not correct underlying pathology or tissue damage that can occur over time with dry eye syndrome (Calonge 2001, Lemp 1994, Murube 1998a, Murube 1998b, Pflugfelder 1998, Liu 1999).

Alternative therapeutic interventions were aimed at tear preservation or stimulation of natural tears. Canalicul or punctal tamponade occlusion is a popular non-pharmacologic approach to improving aqueous tear film content (both quantity and quality), with the result of improving signs and symptoms of dry eye (Lemp 1994, Murube 1996, Willis 1987). While this technique can be helpful for relieving dry eye symptoms, it carries a risk of decreased tear production, clearance, and ocular surface sensation (Yen 1999) and exacerbates the already delayed tear clearance and turnover rate (Macri 2000), ultimately resulting in desensitization of the corneal surface and possible inflammation.

Overall, these palliative therapies have been recognized as having limited value for long-term control or cure of progressive dry eye syndrome. In the last quarter century, however, research began to focus more aggressively on the pathophysiology of dry eye syndrome, yielding several important findings that suggest an inflammatory etiology.

It is now recognized that dry eye syndrome results from an underlying cytokine and receptor-mediated inflammatory process affecting the lacrimal glands (Mirch-eff 1994, Pflugfelder 1986, Pflugfelder 1999, Stern 1998, Williamson 1973). The observed inflammation, in turn, can either decrease tear production or alter the contents of the tear film and disrupt homeostasis at the ocular surface, ultimately leading to keratoconjunctivitis sicca. These findings have redirected treatment efforts toward more targeted therapies aimed at resolving the underlying inflammation. Anti-inflammatory/immunomodulatory treatments — most notably cyclosporine A — are now becoming standard therapy for moderate to severe dry eye syndrome.

**Review of drug therapy options**

**Newer agents**

*Cyclosporine A.* Cyclosporine A is a well-known immunomodulator, most commonly used to prevent rejection after organ/tissue transplantation. It also confers anti-inflammatory activity and, in dry eye syndrome, thereby prevents T-cells from releasing cytokines (primarily interleukin-6) that incite the inflammatory component of dry eye. Early studies suggesting its utility in dry eye syndrome came from dog studies in which topical application of cyclosporine ophthalmic emulsion twice daily reduced lymphocyte infiltration in the lacrimal glands and conjunctiva (Kaswan 1989, Gao 1998, Tsubota 1998). Cyclosporine A also was associated with reduced apoptosis of lacrimal glands and conjunctival epithelial cells in dogs, effects that contribute to reduced inflammation and clinical improvement of dry eye (Gao 1998). The earliest human studies in keratoconjunctivitis sicca revealed that topical eye treatment with cyclosporine A relieved the signs and symptoms of the disease (Power 1993, Gunduz 1994, Laibovitz 1993). More recent data from two United States phase 3 randomized, multicenter, double-blind, 6-month protocols establish the efficacy, safety, and anti-inflammatory activity of cyclosporine A ophthalmic emulsion compared with castor oil-based topical emulsion vehicle alone in patients with moderate to severe dry eye syndrome (Sall 2000). In the combined results from these studies (N=877), both objective (corneal staining, Schirmer test) and subjective (blurred vision, need for concomitant artificial tears, physician evaluation of global response to treatment) measures of treatment efficacy were significantly better with cyclosporine 0.05 percent emulsion than with vehicle (p<0.05). Especially notable is the improvement in corneal staining (Figure 1, page 29), which indicates that cyclosporine ophthalmic emulsion suppresses the inflammatory processes underlying dry eye syndrome in these patients, and by doing so, improves the integrity of the ocular surface. This pathophysiologic benefit contributes to enhanced vision and normalized lacrimal gland response to blinking and other stimuli — and hence to the Schirmer value improvements in this study (Figure 2, page 30).

The first (and currently only) cyclosporine ophthalmic emulsion 0.05 percent was recently approved by the FDA for the safe and effective treatment of underlying inflammation in dry eye syndrome. This is the only treatment available that addresses the immunogenic and inflammatory causes of dry eye syndrome and is not solely palliative. It is a sterile, preservative-free emulsion that appears white opaque to slightly translucent. It has a favorable safety profile, the most common adverse event being mild ocular burning and stinging — effects that

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3 Table 2, page 29, lists the trade names of generic agents.
Methylprednisolone or lotaprednol etabonate — has been shown to reduce early inflammation in dry eye syndrome (Marsh 1999, Prabhasawat 1998). This effect has been linked to reduced levels of the chemotactic cytokine IL-8 in the conjunctival epithelium (Pflugfelder).

**Topical corticosteroids.** Immunomodulation with topical nonpreserved corticosteroid therapy — such as methylprednisolone or lotaprednol etabonate — has been shown to reduce early inflammation in dry eye syndrome (Marsh 1999, Prabhasawat 1998). This effect has been linked to reduced levels of the chemotactic cytokine IL-8 in the conjunctival epithelium (Pflugfelder).

### TABLE 1  
Options for dry eye syndrome

**List is not inclusive**

<table>
<thead>
<tr>
<th>Product</th>
<th>How supplied</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Targeted therapies</strong></td>
<td></td>
<td></td>
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<tr>
<td><em>Immunomodulators:</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine A</td>
<td>unit dose vials (0.4 mL)</td>
<td>1 drop 2x daily</td>
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<tr>
<td><em>Mucolytic agents:</em></td>
<td></td>
<td></td>
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<tr>
<td>N-acetylcysteine</td>
<td>10–20% drops</td>
<td>1–2 drops up to 4x daily</td>
</tr>
<tr>
<td><em>Antibiotics:</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Topical:</strong> various, e.g.:</td>
<td></td>
<td></td>
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<tr>
<td>bacintrac, chlortetracycline</td>
<td></td>
<td></td>
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<tr>
<td><strong>Systemic:</strong> doxycycline</td>
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<tr>
<td><strong>Palliative therapies</strong></td>
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<tr>
<td><strong>Artificial tears:</strong></td>
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<td></td>
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<tr>
<td>Low viscosity (carboxymethylcellulose based): various, e.g.:</td>
<td></td>
<td></td>
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<tr>
<td>GenTeal</td>
<td>multi dose</td>
<td></td>
</tr>
<tr>
<td>Refresh Plus</td>
<td>unit dose</td>
<td></td>
</tr>
<tr>
<td>Refresh Tears</td>
<td>multi dose</td>
<td></td>
</tr>
<tr>
<td>TheraTears</td>
<td>unit and multi dose</td>
<td></td>
</tr>
<tr>
<td>Moderate viscosity (hydroxymethylcellulose based): various, e.g.:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bion Tears</td>
<td>unit dose, preservative free</td>
<td></td>
</tr>
<tr>
<td>Ocucoat</td>
<td>unit dose, preservative free</td>
<td></td>
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<tr>
<td>High viscosity: various, e.g.:</td>
<td></td>
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<tr>
<td>Refresh Celluvisc</td>
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<tr>
<td>Refresh Liquigel</td>
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<tr>
<td>AquaSite</td>
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<tr>
<td>Murocel</td>
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<tr>
<td><strong>Gel formulations:</strong> various, e.g.:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GenTeal Gel</td>
<td>tube delivery system</td>
<td></td>
</tr>
<tr>
<td>Tears Again</td>
<td>tube delivery</td>
<td></td>
</tr>
<tr>
<td><strong>Lubricating ointments:</strong></td>
<td></td>
<td></td>
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<tr>
<td>HypoTears</td>
<td></td>
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<tr>
<td>Refresh PM</td>
<td></td>
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<tr>
<td>Tears Naturale PM</td>
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<tr>
<td><strong>Therapeutic plug</strong></td>
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<tr>
<td>Hydroxypropyl cellulose insert</td>
<td>5 mg water-soluble rod</td>
<td>1–2 rods per eye daily</td>
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<tr>
<td><strong>Secretagogues:</strong></td>
<td></td>
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<tr>
<td>Eledoisin</td>
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<tr>
<td>Pilocarpine</td>
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<tr>
<td><strong>Corticosteroids:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loteprednol etabonate</td>
<td>1–2 drops</td>
<td>4x daily</td>
</tr>
<tr>
<td>Prednisolone acetate</td>
<td>2 drops</td>
<td>4x daily</td>
</tr>
</tbody>
</table>

*ADAPTED FROM PACKAGE INSERTS*
Symptomatic relief has been reported to extend for months after the steroid application has been stopped (Marsh 1999). Long-term use of this class, however, is associated with severe side effects, including ocular hypertension, cataract formation, glaucoma, and infection. For this reason, these drugs should be reserved for symptoms that are severe and recalcitrant to aggressive application of artificial tears, and used only for acute treatment (<2 weeks) of dry eye exacerbations.

**Older agents**

**Tear substitutes.** Until the recent identification of inflammation as an important etiology in dry eye syndrome, the most commonly used treatment for dry eyes was topically applied artificial tears and lubricants. Although solely a palliative therapy, artificial tears are useful in mild dry eye syndrome for the simple relief of dry eye symptoms, including scratchiness and dryness. These over-the-counter products are formulated from one of a variety of linear polymers that simulate the cell-surface glyco-proteins that maintain ocular hydration. Over the years, manufacturers have attempted to closely mimic natural tears, which contain lipid (surface layer that retards evaporation), substantial amounts of water with dissolved salt and proteins (aqueous layer), and mucin (the film that coats the corneal surface). Despite these attempts to improve composition, however, these products have inherent limitations; natural tears have a complex composition that artificial tears cannot fully substitute, while the mucus layer of the tear film has not been satisfactorily reproduced (Calonge 2001).

Artificial tear products currently are available in various formulations, including solutions, gels, and ointments. The key differences in these products are viscosity, composition, and preservative vs. preservative-free formulation. Viscosity describes the relative density of the formulation — which reflects its mucoadhesive properties and therefore the degree of contact time with the ocular surface — and generally ranges from 1.5 mL pas (Pascal seconds, a standard of measurement for viscosity) to 15 mL pas, with an average of 5.0 mL pas. Agents added to artificial tears to increase viscosity include carboxymethylcellulose, dextran 70, gelatin, hydroxypropyl methylcellulose, methylcellulose, PEG, poloxamer 407, polysorbate 80, propylene glycol, polyvinyl alcohol, and polyvinylpyrrolidone. Products with low viscosity are commonly used early in the progression of dry eye syndrome, as they are less likely to disrupt vision. As dry eye syndrome progresses, more viscous tear products are needed to achieve symptomatic control, but these are associated with progressive blurring of vision. Lubricant ointments are reserved primarily for overnight treatment.

Compounds included to replicate the lipid occlusive layer are white petrolatum, mineral oil, lanolin, or lanolin alcohols. The mucin layer, which allows the solution to spread over the ocular surfaces, is simulated by use of polysorbate 20 and 80, poloxamer 282, or tyloxapol. In addition, many tear supplements contain preservatives to stabilize the pro-
PHARMACOTHERAPEUTIC OPTIONS

duct for longer periods. Benzalkonium chloride (BAK), benzethonium chloride, cetylpyridinium chloride, chlorobutanol, EDTA, phenylmercuric nitrate, phenylmercuric acetate, methyl/propylparaben, thimerosal, phenylethyl alcohol, sodium benzoate, sodium propionate, and sorbic acid are the most commonly used additives. Preservatives — extensive data have been reported on BAK — can induce corneal desquamation or cause irritation or allergic reactions, particularly as daily use increases due to worsening dry eye (Becquet 1998, Burstein 1980, Lopez Bernal 1991, Tripathi 1989); the development of preservative-free products has relieved some of the burden of this potential complication (Debbasch 2001). While preservative-free solutions do not worsen corneal barrier function, however, they have not been found to normalize it either.

Secretagogues. There are a number of drugs that have been used with some success to stimulate the lacrimal glands to produce tears. Pilocarpine in particular has been shown to increase tear volume and flow and improve dry eye symptoms in patients with Sjögren's syndrome (Mathers 2000, Vivino 1999). Eledoisin, an endekapeptide, has yielded improved tear production and flow (Gobbels 1991), although clinical improvement of dry eye signs and symptoms has never been formally documented. Bromhexine and ambroxol have met with equivocal results in clinical trials (Ichikawa 1988, Avisar 1988). As a rule, these agents are infrequently prescribed due to the limited data, absence of compelling evidence of improvement, and the associated adverse effects, including generalized nausea, sweating, and rashes. Furthermore, some authors have suggested that generating tears from inflamed lacrimal glands may worsen dry eye by distributing proinflammatory cytokines to the ocular surface; when the glands are substantially damaged, this approach may fail to produce tears at all (Calonge 2001).

Therapeutic ocular inserts. An artificial tear insert that provides long-term slow release of artificial tear polymers is an alternative, if rarely used, therapy for moderate-to-severe dry eye. This approach is most beneficial for those patients with moderate dry eye for whom artificial tear lubrication does not resolve symptoms or is required at increasingly frequent intervals. There is currently only one therapeutic insert manufactured, which contains hydroxypropyl cellulose in a sterile, translucent, water-soluble rod. Each insert, applied once or twice daily inside the inferior cul de sac of the eyelid, dissolves over 14 to 18 hours. The slow release of the tear substance stabilizes and thickens the precorneal tear film and prolongs tear film breakup time. It also lubricates the eye and, in some patients, may halt or reverse progressive visual damage. The system, however, is difficult to handle, and many patients find it uncomfortable.

Mucolytics. Patients with keratoconjunctivitis sicca are prone to development of corneal mucous plaques, which are composed of mucus, epithelial cells, and proteinaceous and lipoidal material that cling to the corneal surface (Lemp 1994, Thermes 1991). These plaques may collect external dust and bacteria and cause vision difficulties, foreign body sensation, and substantial pain. Topical mucolytic agents, such as N-acetylcysteine 20 percent (Mucomyst) diluted to a 10-percent solution with artificial tears, can be used to break down mucin molecules, dissolve corneal filaments, and release the mucoid plaque in patients with this condition. This solution may smell like rotten eggs, requires refrigeration, and, if formulated without preservatives, must be discarded after 30 days. It is not commercially available as a topical agent, though it can be readily compounded but at high expense for a relatively small amount.

Antibiotics. Some patients who experience poor con-
control of moderate dry eye symptoms with artificial tears will benefit from antibiotic therapy. Antibiotics contribute to reduced inflammation and improved lipid production in dry eye syndrome. Topical bacitracin polymyxin B or tetracycline-based ointments can be used to supplement hot compresses and lid scrubs to some benefit. Systemic administration of low doses of doxycycline, which decreases the viscosity of naturally secreted oils, may also yield positive results in patients with meibomian gland dysfunction over a 6- to 8-week course of therapy (Gilbard 1999).

**Treatments under investigation**

*Hormones.* Sexual hormones have been reputed to contribute to an anti-inflammatory state at the ocular surface (Stern 1998, Sullivan 1999a), leading investigators to consider their potential role in the therapy of dry eye syndrome. Topical application of an estradiol ointment to 22 postmenopausal women was shown in one study to confer modest improvement in Schirmer tests and rose Bengal staining (Akramian 1998). Additionally, the presence of androgen receptors on the ocular surface may indicate a potential therapeutic role in dry eye syndrome that warrants further study (Smith 1999). In animal models, systemic administration of androgens has reduced lymphocytic infiltration at the lacrimal gland and improved lacrimal gland function (Sullivan 1997, Sullivan 1999b). Currently, an androgen ointment product is in phase 3 trials.

**P2Y2 receptor agonists.** The P2Y2 receptor in the eye stimulates ocular hydration and lubrication by mediating mucosal secretion of mucin as well as salt, water, mucus, and other tear components from conjunctival goblet cells. Mucin is the component of the tear film that maintains tear stability and protects against damage to the ocular surface. Stimulation of the P2Y2 receptor can be accomplished by administration of adenine analogues in both rabbits and humans (Jumblatt 1998), suggesting a novel pathway for therapeutic modulation of tear film. A phase 2 study of a novel P2Y2 receptor agonist has been completed at 12 ophthalmology centers in the United States. Dequafosol, a P2Y2 agonist in topical eye drop form, provided both objective and subjective improvements in ocular parameters when compared with placebo in the treatment of moderate to severe dry eye syndrome (Li 2001). Phase 3 studies will determine the precise role of these agents in the treatment of dry eye syndrome.

**Tetracyclines.** A collagenase enzyme — MMP9 — has been found to be elevated in the ocular fluid of patients with aqueous tear deficiency (related to Sjögren’s syndrome) compared with normal controls. This elevated enzyme level might reflect a mechanism by which pro-inflammatory molecules are cleaved to achieve activation of IL-1 as part of the inflammatory process. Tetracyclines are potent inhibitors of this enzyme and are being investigated for a role in the management of inflammation in the genesis of dry eye syndrome (Solomon 2001).

*Retinoic acid.* Retinol is present in tears and deficient in dry eye syndrome, leading some investigators to suggest a role for retinol replacement therapy. Results with topical administration of retinoic acid have been variable, however, with evidence that its particular value is to reverse keratinization, which occurs only in extremely severe cases of dry-eye related disease (Calonge 2001).

**CONCLUSION**

The treatment of dry eye syndrome has relied predominantly on artificial tears and lubricants. This palliative approach generally has been successful at relieving the signs and symptoms of mild to moderate disease and, in rare cases, has slowed the progressive damage to the cornea and conjunctiva that occur over time with dry eye. Nevertheless, these products do not address the underlying disease process and, in some cases (particularly with artificial tears containing BAK or certain other preservatives), can be toxic and allergic, worsening the clinical markers of the disease.

Increasing research and advancing knowledge has identified an inflammatory component to dry eye syndrome and has focused treatment efforts at addressing this newly identified etiology. Topical cyclosporine emulsion 0.05 percent is the first and currently only FDA-approved targeted immunomodulatory/anti-inflammatory product to combat the underlying source of disease. Other similarly targeted agents are under investigation and, if approved, will likely contribute to the start of an entirely new management standard — one based on control of inflammatory sources and immunologic mechanisms — for the treatment of dry eye syndrome.

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Considerations in the Pharmacoeconomics of Dry Eye

Jan D. Hirsch, PhD

Prescription Solutions

SUMMARY

Dry eye disease diminishes the quality of patients’ lives and drives utilization of health care resources. Until recently, all treatments for dry eye have been palliative. A new treatment, cyclosporine A ophthalmic emulsion, addresses the disease’s underlying causes. It warrants pharmacoeconomic analysis to determine its place in managed care.

Pharmacoeconomic (PE) research identifies, measures, and compares the costs and consequences of pharmaceutical product and service utilization. In this definition, costs refer to resources consumed; the consequences of using pharmaceutical products and services are considered to be the outcomes derived. A system for classifying the full range of outcomes is the ECHO (Economic, Clinical, and Humanistic Outcomes) model, proposed by Kozma (1993). Economic outcomes in the ECHO model include direct medical costs, such as the costs of the drug, administration, and treatment of adverse effects; direct nonmedical costs, such as patient transportation; indirect costs, such as lost work days, lost earnings, and decreased productivity; and intangible costs related to pain and suffering. Clinical outcomes include efficacy, onset of action, percentage of patients who become free of symptoms, symptom recurrence, and adverse effects. Humanistic outcomes include health-related quality of life, return to normal functioning, and patient satisfaction with therapy. Some variables may relate not only to patients but also to caregivers and significant others.

This chapter considers the economic and quality-of-life burden of moderate to severe chronic dry eye syndrome, then introduces PE analysis techniques that can be used to evaluate treatments for chronic disease.

BURDEN OF DRY EYE

Dry eye syndrome is common, but its prevalence is somewhat difficult to pinpoint, primarily because the disease is multifactorial, definitions differ, and research is sparse. Furthermore, diagnostic techniques lack standardization and are inconclusive in milder cases. Clinical signs do not always correlate with symptoms, except in moderate to severe cases and in association with autoimmune diseases, such as Sjögren’s syndrome (Nichols 1999).

In a German study, 22.8 percent of women and 9.9 percent of men age 55 to 59 reported often experiencing a sandy sensation in the eyes. In the Canadian Dry Eye Epidemiology Study, optometrists surveyed all patients using a standard questionnaire; researchers reported that, across all age groups, 28.7 percent reported dry eye symptoms, 7.6 percent indicated constant but moderate symptoms, and 1.6 percent complained of severe symptoms (Brewitt 2001). In the United States, researchers at...
the Schepens Eye Research Institute — using a broad definition of dry eye syndrome — estimate that 10 million Americans suffer from its symptoms (Schepens 2001). Other estimates of prevalence are reported elsewhere in this publication.

Because this chapter focuses on treatment of moderate to severe dry eye syndrome, it is useful to consider the prevalence of the disease in terms of the percentage of patients with symptoms severe enough to seek health care services. In a survey of third-party payers, Nelson and colleagues (2000) reported the prevalence of dry eye syndrome to be 0.19 percent among managed care plan participants, 0.21 percent among persons covered by commercial payers, 0.35 percent among Medicaid recipients, and 1.30 percent among Medicare recipients.

Many factors — ranging from autoimmune diseases such as Sjögren’s syndrome to age-related changes (e.g., menopause) to environmental conditions (e.g., contact lens wear) — can cause dry eye syndrome (Albietz 2001). Persistent uncontrolled dry eye can lead to superficial punctate staining, epithelial erosions, corneal filaments, and persistent epithelial defects. In the most severe cases, corneal ulcers occur. Clearly, moderate to severe dry eye is painful and debilitating, and the burden of dry eye can be substantial in terms of both economic and humanistic outcomes.

### Economic impact

Until the recent market availability of cyclosporine A (CsA) ophthalmic emulsion, then-available treatments not only failed to provide adequate relief of symptoms but also failed to stop progression of the disease. Dry eye is a chronic progressive inflammatory condition and is by no means self-limited. In turn, as dry eye severity increased, both individual and societal treatment costs increased.

A survey of Sjögren’s syndrome patients indicated that sufferers used drops and ointments, on average, more than 7 times daily, and nearly 1 in 3 had received punctal occlusion. Despite these measures, 89 percent visited their ophthalmologist an average of 3.1 times a year for relief from their symptoms, and 28 percent consulted other physicians for help with their dry eye problems. On average, these patients went to work despite their symptoms on 208 days annually and missed 5 work days due to their dry eye symptoms or treatment. Patients also reported that dry eye symptoms interfered with leisure activities on 123 days of the past year (Hirsch 1998).

In a survey of patients without Sjögren’s syndrome, Nelson (2000) confirmed that dry eye can be chronic and devastating; on average, patients responding to the study had been diagnosed 9.23 +/- 7.19 years previously, 52 percent described their symptoms as severe or very severe, and 22 percent indicated their symptoms were moderate. Half of the patients who revealed their ages were at least 65. Of the 70 respondents, only two reported using no topical treatments, such as artificial tears and lubricants; at least 61 percent reported using them always or regularly. More than 40 percent had received punctal occlusion; 27 percent reported using other medications — analgesics, antibiotics, anti-inflammatory agents — to treat their dry eye; 60 percent said they visited a physician at least twice in the past year because of dry eye, and 84 percent sought the aid of an ophthalmologist.

These researchers also noted that about 73 percent of respondents indicated that, despite all the treatments they were using, dry eye interfered with the activities of daily life; 76 percent (53 of 70) indicated that their symptoms had not improved or had worsened over the course of the previous year. This team’s findings of the impact of the symptoms of dry eye on quality of life are summarized in Table 1. Annually, these patients lost 2 work days because of their dry eye symptoms, and went to work despite the interference on 191 days, presumably reducing their efficiency and effectiveness.

Reviewing cases from a managed care database, researchers showed that patients with dry eye syndrome experienced a significantly greater increase in total costs after diagnosis than a matched control group (Smeeding 2001). These researchers suggested a link between dry eye and several other costly ophthalmic conditions, such as glaucoma. After dry eye syndrome diagnosis, total charges increased significantly more in the dry eye group (22 percent) as compared to the control group (15 percent, p<0.001). The higher management costs associated with dry eye syndrome were primarily from more frequent visits to physicians. In addition, dry eye patients were also more likely than controls to receive artificial tears, ophthalmic antibiotics, and corticosteroids. Although artificial tear preparations are sold over the counter, topical antibiotics and corticosteroids are both costly and fraught with potential side effects that increase the need for clinical evaluation — thereby increasing utilization costs.

### Humanistic impact

Recognizing that the impact of moderate to severe dry eye is symptom-driven, several research groups have developed patient questionnaires to quantify the impact of dry eye in terms of clinical outcomes (e.g., pain) and functional activities (e.g., daily activity impairment). Studies evaluating the validity and reliability of these instruments also provide insight into the effect of dry eye symptoms on patients’ daily lives.

In a study testing the performance and repeatability of the National Eye Institute Visual Function Question-
naire, researchers confirmed that the 25-question VFQ-25 is a reliable tool for quantifying dry eye pain and concluded that low-vision patients with diagnostically confirmed dry eye experience more ocular pain than do other low-vision persons. Further, the VFQ-25 can be used to stage dry eye (Nichols 2002). Table 2, on page 36, lists sample questions from the VFQ-25; the entire questionnaire can be viewed online at «www.nei.nih.gov/resources/visionfunction/vfq_ia.pdf».

Citing poor correlation between dry eye symptom assessment and objective test results, another team of researchers evaluated the Dry Eye Questionnaire (DEQ) in an assessment of confirmed dry eye patients (with and without Sjögren’s syndrome) and controls. Concentrating on frequency and intensity of symptoms, they found that 10 percent of controls, 30 percent of dry eye patients without Sjögren’s syndrome, and 60 percent of dry eye patients with Sjögren’s syndrome had so much eye pain and trouble that they frequently halted their daily activities and closed their eyes to gain relief. The researchers also determined that symptom intensity increases as the day progresses, and they suggested that further testing of the DEQ is needed (Begley 2002).

Using another set of patient questionnaires, the Dry Eye Disease Impact Questionnaire (DEDIQ), the Ocular Surface Disease Index (OSDI, a valid and reliable tool for measuring disease severity, which has the psychometric properties necessary to be used as a clinical-trial end point [Schiffman 2000]), the Facial Expression Subjective Scale, and the SF-12 Health Survey, researchers determined that 53 percent of dry eye patients rated their symptoms as severe to very severe; their average OSDI score was 0.41 (Kozma 2000). In the OSDI system, a score of 0 indicates no disability and a score of 1 means complete disability due to dry eye symptoms. Their SF-12 physical and mental summary scores were 42.3 and 50.2, respectively, compared to a United States norm of 50.0. Only 25 percent of these patients reported symptom improvement after 1 year of treatment, while the other 75 percent complained that their symptoms failed to improve or worsened.

Although researchers have used several validated instruments to assess dry eye, each of the available methodologies constructs a multidimensional profile of the patient’s health status. In a landmark study, researchers applied, for the first time, several standard methodologies for assessing an indexed type of humanistic outcome called utilities (Walt 2001). Health utilities are fundamental values that represent a subject’s preferences for specific outcomes, relative to states of health or treatments, and can be used to compare the relative impact of different diseases. In the OSDI study, patients with the severe dry eye rated its impact as comparable to Class III/IV angina (see Figure, page 36). They suggested that an effective dry eye treatment could be expected to restore patient benefits of a magnitude comparable to those associated with treating severe angina. This study also indicated that dry eye utilities vary in a manner consistent with disease severity.

### Treatment Options and Relative Costs

As the above research suggests, dry eye symptoms persist or worsen despite standard therapies. Typically, as with mild dry eye, patients with moderate to severe dry eye rely on artificial tears. The mainstay of therapy for dry eye syndrome, artificial tears are palliative, applied several times daily, to substitute for natural tears that are deficient in quality or quantity. Other treatment options for more severe dry eye syndrome include punctal occlusion with temporary or permanent plugs, electrocautery surgery, and, for patients with Sjögren’s syndrome, hormone replacement therapy.

Recently approved by the United States Food and Drug Administration, topical CsA is intended to address the underlying inflammatory causes of dry eye syndrome and provide far more than palliative therapy for many dry eye patients (Allergan 2002). Although the exact mechanism of action of this product is not fully understood, it is thought to act as a partial immunomodulator and anti-inflammatory, arresting T-cell activation, thereby preventing T-cells from releasing cytokines that begin the inflammatory cycle of dry eye. As CsA is utilized and its

### Table 1

<table>
<thead>
<tr>
<th>Patients who said dry eye symptoms interfered with activities most or all of the time (%)</th>
</tr>
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<tbody>
<tr>
<td>Quality-of-life factors</td>
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<tr>
<td>Loss of confidence</td>
</tr>
<tr>
<td>Decrease of leisure time</td>
</tr>
<tr>
<td>Frustration with daily activities</td>
</tr>
<tr>
<td>Change of activities</td>
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<tr>
<td>Depression, unhappiness</td>
</tr>
<tr>
<td>Need for assistance</td>
</tr>
<tr>
<td>Missed outings</td>
</tr>
<tr>
<td>Decrease of work time</td>
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<tr>
<td>Change of work</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>None of the above</td>
</tr>
<tr>
<td>Vision-related activities</td>
</tr>
<tr>
<td>Nighttime driving</td>
</tr>
<tr>
<td>Reading</td>
</tr>
<tr>
<td>Working at electronic monitor</td>
</tr>
<tr>
<td>Watching television</td>
</tr>
</tbody>
</table>

Source: Nelson 2000
place in practice becomes clearer, the role of traditional palliative agents may change significantly.

**Pharmacoeconomic analysis of dry eye**

The burden of dry eye syndrome has been assessed across the full range of outcomes. However, in the routine assessment of its therapies, researchers customarily have focused mainly on safety and efficacy factors. A comprehensive evaluation of these treatments should also include investigation of their broader impact, focusing on their ability to relieve the economic and humanistic burdens of dry eye syndrome on both individual patients and society. Only a few studies have included economic or humanistic assessments of any kind, notably studies for punctal occlusion and the newly approved ophthalmic cyclosporine formulation.

**Punctal occlusion**

Although punctal occlusion has been used to treat dry eye patients for 40 years, few clinical studies have adequately characterized the benefits of this procedure.

In a controlled, double-masked, prospective study, researchers in Mexico recently determined that patients who received bilateral collagen and silicone lacrimal occlusion implants in both the superior and inferior canaliculi experienced progressive clinical improvement over time (Nava-Castaneda 2003). At 8 weeks, suffering had been relieved by more than 90 percent, compared with baseline readings. At 6 months, 86 percent of treated pa-
tients remained free of symptoms. In contrast, symptoms remained unchanged among patients in the sham procedure group. In addition, the researchers also reported a change in resource utilization; 76 percent of patients had stopped the daily use of eye lubricants, thus relieving a portion of the patient’s economic burden.

Retrospectively, researchers at Wills Eye Hospital, Philadelphia, established that punctal plug insertion is a simple method that is safe and effective in the treatment of a wide range of diseases of the ocular surface and aqueous tear deficiency, including toxic epidermolytic that cannot be controlled by artificial tears (Ming-Chen 2002). In addition, they focused on a common event that has an economic impact — spontaneous plug extrusion, which requires repeated medical visits and procedures. Of 312 plugs inserted, 14 were removed — 11 because of epiphora and three due to conjunctival erosions. Overall success was about 77 percent, but would have been about 10 percentage points higher if only patients with dry eye had been included in the study. One reason for suboptimal clinical results was undiagnosed blepharitis, which often coexists with dry eye. The authors also noted that clinicians should carefully choose plug size and monitor patients; these could have added economic benefits.

Using data from the literature and expert opinion, Lee and colleagues developed a Markov economic model to assess the medical costs and outcomes of dry eye syndrome (Lee 2000). They reported that, over the course of 1 year, the cost of managing and treating a population of dry eye patients with palliative medications, punctal plugs, and surgery is estimated to be $357,050 for an organization covering 500,000 lives. These researchers suggest their model could be used to quantitatively assess the impact of new treatments on health-system budgets and speculated that a more effective dry eye intervention could improve cost effectiveness by decreasing patient demand for physician visits and procedures.

Cyclosporine A ophthalmic emulsion

With the recent approval of CsA ophthalmic emulsion, investigators have renewed reason to apply PE assessment to dry eye syndromes. Pertinently, Lee and colleagues developed a Markov economic model to assess the medical costs and outcomes of dry eye syndrome (Lee 2000). They reported a change in resource utilization; 76 percent of patients had stopped the daily use of eye lubricants, thus relieving a portion of the patient’s economic burden.

Basic principles of pharmacoeconomic research

PE evaluations estimate the value of the economic, clinical, and humanistic outcomes resulting from different treatments, which are compared to help decision makers determine optimal therapeutic approaches for their patient populations. Several types of analyses are available, including cost-minimization, cost-effectiveness, cost-benefit, and cost-utility analyses. Each type of analysis expresses resources consumed in terms of monetary units, but uses a different unit to express the outcome.

Cost minimization is the simplest of these analyses, because it assumes that the outcomes of the therapies being compared have been proven equivalent among treatment groups. This reduces the analysis to a monetary comparison of resources consumed.

A cost-effectiveness comparison of two or more treatments analyzes the dollars spent in consumed resources and the clinical outcomes derived from this expenditure. Because it uses natural units of medical outcomes (e.g., life-years gained, percentage of successfully treated patients) to compare medical treatments, this type of PE analysis — more than any — parallels the medical thought process and is intuitively accepted within the medical community. That is why, in medical-decision making, cost effectiveness is the most commonly performed of the four analyses. A cost-effectiveness evaluation, however, cannot be used to compare treatments with dissimilar outcomes.

In a cost-benefit analysis, the outcomes of two dissimilar treatment groups, inherently expressed in dissimilar natural units, can be estimated in terms of monetary units. This conversion allows the investigator to compare dollars with dollars: dollars spent in consumed resources with the dollar value gained in clinical outcomes. Thus, a cost-benefit analysis allows the investigator to compare costs and outcomes of unrelated health care interventions, such as the treatment of glaucoma and dry eye syndrome.

A cost-utility analysis evaluates the effect of treatment on societal outcomes, typically expressing results in terms of health utilities or quality-adjusted life years. A cost-utility evaluation allows the investigator to include the humanistic outcomes of patient preferences or quality of life when comparing products or programs with dissimilar outcomes measures. This analysis technique, in effect, expands cost-benefit analyses beyond expressing outcomes as monetary units.

The clinical characteristics of a disease and the resulting burden determine the relevance of each type of outcome for a PE analysis. For example, lost work days are relevant in the evaluation of asthma or migraine, in which symptoms can temporarily debilitate sufferers. More relevant to a symptom-silent disease (such as early-stage glaucoma) would be, for example, the cost of noncompliance, which generates greater downstream expenditures associated with more invasive therapies. In the case of moderate to severe dry eye syndrome, the burden of disease data indicates that both economic and humanistic outcomes are important to consider.
eye treatments. So far, studies have included analyses from the economic perspective regarding reduction in artificial tear and medication use after CsA treatment.

In a double-masked phase 2 study of CsA, the use of artificial tears generally decreased at weeks 4, 8, and 12 during therapy, and at weeks 2 and 4 after it (Stevenson 2000).

In a phase 3 trial of 0.05 percent and 0.1 percent CsA emulsions, patients instilled 1 drop of the study medication in each eye twice daily and were allowed to use artificial tears as adjunctive medication at will. Over the course of the study, patients applying the CsA formulation decreased their reliance on artificial tears (Sall 2000).

A 1-year observational study using the DEDIQ determined that CsA 0.05 percent is highly efficacious in treating dry eye syndrome. Of 181 enrolled subjects in a private ophthalmology practice, more than 60 percent reported symptom improvement. From an economic perspective, total medication orders, including those used for dry eye (nonsteroidal anti-inflammatory drugs, antihistamines, artificial tears, ophthalmic antibiotics, and ophthalmic/antibiotic steroid combinations) fell 55 percent in the post-CsA treatment period (Cross 2002).

CONCLUSION

Providing optimal medical care of dry eye syndrome requires planning that is based not only on drug safety and efficacy, but also on data relating the full value of medical treatments, that is, changes in economic and humanistic outcomes that are achieved due to the treatment effect. Applying PE methods to assess the value of treatments systematically can improve both the overall quality and efficacy of dry eye medical care.

Although full-range PE studies of dry eye syndrome remain to be conducted, the course of such analyses is clear. Researchers must determine which therapies or regimens provide the greatest effect in terms of relieving the clinical, economic, and humanistic burden of dry eye syndrome, for specific patient groups at the most effective cost.

REFERENCES


Issues in the Use Of Preservative-Free Topicals

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ERIC D. DONNENFELD, MD
Ophthalmic Consultants of Long Island

SUMMARY

In a perfect world, patients would use medications as prescribed. In reality, patients may cut corners, especially if they may save money by doing so. Clinicians and pharmacists must acknowledge this tendency, yet at the same time protect patients from using contaminated ophthalmologic agents and strive to achieve optimal clinical outcomes.

In treating dry eye syndrome, appropriate product administration is an important but often neglected issue. At present, concerns about product administration apply only to topical artificial tear preparations, but in the future physicians will have the option of treating the underlying cause of the disease, rather than its effects, in many patients. This is because the Food and Drug Administration recently approved a new dry eye medication, a 0.05 percent cyclosporine A (CsA) ophthalmic formulation, marketed by Allergan as Restasis (Allergan 2002). CsA is contraindicated in patients with active ocular infection or suspected or known hypersensitivity to any of its components, and therefore is not appropriate for a subset of patients.

In brief, CsA restores tear function. Unlike artificial tear medications, which dry eye sufferers may apply four or more times daily, CsA is applied twice daily. Because its clinical benefits become apparent after about 3 months of therapy, it is reasonable to suspect that patients put on a CsA regimen will continue to use artificial tear formulations during the initial months of therapy. They also may continue to use artificial tears adjunctively thereafter, but probably at a lower daily dosage and with an end in sight.

Until CsA gains broad utilization, the artificial tear preparations — liquids, gels, and ointments — will continue to represent the mainstay of dry eye treatment. By increasing humidity at the ocular surface, improving lubrication, and smoothing the corneal surface, artificial tears provide temporary, albeit strictly palliative, relief from the effects of dry eye.

Common artificial tear ingredients include tonicity, buffering, viscosity, wetting, and lubricating agents; antioxidants; and preservatives (Power Graphics 1999). Tonicity agents adjust the preparation’s osmolality. Buffering agents adjust its pH level to between 6 and 8. Viscosity agents slow the flow of the solution through the eye’s drainage ducts, to extend its usefulness. Wetting agents facilitate the spread of the material over the ocular surfaces, and lubricating agents supplement the lipid occlusive layer. Antioxidants prevent deterioration of the product when it is exposed to oxygen. Preservatives retard the growth of bacteria, increasing the shelf life of artificial tear formulations in multiple-use vials.

Why use preservatives?

Today, both preserved and preservative-free artificial tear formulations are available. Preserved products, which on a per-use basis generally tend to cost less than nonpreserved formulations, are packaged in multidose bottles. Preservative-free formulations are sold in single-dose vials. The FDA and the U.S. Pharmacopoeia mandate the inclusion of preservatives for all multidose topical ophthalmic medications (Abelson 2002). Over the years, pharmaceutical companies have replaced harsher preservatives in artificial tear preparations with gentler ingredients.

Preservatives have benefits when used in ophthalmic topical medications, but experts caution against prolonged use of artificial tears containing preservatives, especially benzalkonium chloride (BAK) and chlorobutanol, which have been shown to irritate users (Abelson 2002). They further advise that, in contrast to BAK, sorbic acid infrequently causes adverse reactions, polyquaternium-1 causes only superficial epithelial damage, and sodium perborate converts to hydrogen peroxide on exposure to air and then breaks down into oxygen and water. Stabilized oxychloro complex has been found to be safe and well tolerated, even with frequent use.
Although preservative-free artificial tear solutions were developed for patients who demonstrate sensitivity to preservatives, the general avoidance of preservatives may be wise. In a rat model, researchers demonstrated that, especially over the long term, most preservatives used in ophthalmic eyedrops have the potential to damage human conjunctival and corneal epithelial cells (Becquet 1998). Although preservatives interfere with the growth, multiplication, and metabolism of microbes, they have a similar effect on eukaryotic cells, which explains their cytotoxicity and inflammatory cell response. Even at lower concentrations, and after a single instillation, BAK was toxic to the corneoconjunctival surface. These researchers warn that prolonged exposure to preservatives is likely to produce subclinical inflammation, which might lead to chronic irritation and fibrosis that can worsen dry eye syndrome.

Several researchers indicate that the negative effects of preservative-free artificial tears on the eye are minor, if not negligible (Albietz 2001a, Albietz 2001b, Berdy 1992, Pisella 2002, Schein 1992). The primary concern relating to the use of preservative-free artificial tear formulations is contamination of the contents once the patient opens the container and applies the medication. The contamination typically is due to contact with the patient’s cornea, conjunctiva, eyelashes, or hands. Even bacteria that are not pathologic may alter the pH value of the medication and interfere with efficacy.

A decade ago, researchers determined that patients using ocular-surface medications can trigger a cycle of microbial contamination between their conjunctivae and the container (Schein 1992). This team studied 220 in-use medications obtained from 101 patients with nonmicrobial ocular-surface disease. They cultured the bottle caps, a drop from each bottle obtained by inversion, and the contents of the bottle. They also obtained conjunctival cultures from the patients using the medications and 50 age-matched controls. They harvested pathological organisms from the conjunctivae of 34 percent (34/101) of patients but only 10 percent (5/50) of the controls.

To test the susceptibility of unpreserved eye drops to contamination, British researchers inoculated 21 different unpreserved eye drop formulations with a known quantity of four different microorganisms and stored the containers at different temperatures for as long as 28 days (Oldham 1996). They recommend that unpreserved eye drops be stored at between 2 degrees and 8 degrees Celsius (35.6 to 46.4 degrees Fahrenheit) after opening, and confirmed that, in general, drops containing alcohols or antibiotics should be discarded after 7 days. The Lothian Joint Formulary (NHS 2002) recommends that eye drops in multiple-use containers be discarded 4 weeks after opening and that unpreserved drops be discarded 1 week after opening. Neither of these products need refrigeration.

**PRODUCT USE ISSUES**

For patients who need to instill artificial tears several times daily, larger containers of medication are desirable. British researchers observed that patients who frequently apply eye drops may need to carry multiple single-dose containers, which are cumbersome (Oldham 1996). They also recognized that purchasing single-dose containers can be more than 1,000 percent as expensive.

It can be expected, then, that patients who purchase unpreserved medications in single-dose vials will try to derive the most benefit from their dollars. A single-dose vial can provide 10 or more drops, all of which may be used to relieve symptoms in one eye; a patient who uses the entire vial in a day does not risk contamination. Yet a patient requiring 4 drops daily may be tempted to save the remaining medication for use beyond the first day.

In our practice, we therefore advise patients that preservative-free artificial tears are free of contamination the day they are opened, are probably not contaminated on the second day, but are likely contaminated on the third day and must be discarded. Our goal is to make sure that the patient at least reduces the risk of infection to a level with which we are relatively comfortable. Considering that the dry eye medications we prescribe have been tested and remained uncontaminated when exposed to room air for as long as 28 days, we are confident that our warning suffices to prevent patients from instilling contaminated medications.

**Compliance**

Patients with dry eye may become noncompliant with an established regimen for different reasons. Some will use too much medication because their artificial tears provide insufficient relief. Some may be unable to apply the medication correctly.

In a study of noncompliance in 200 patients using eyedrops (mean age, 26 years; range, 9 to 92 years), the main reasons that emerged for noncompliance were poor motivation (stemming from inadequate understanding of the function of the medication) and inability to use eye drops properly (Winfield 1990). Sixty-two percent consistently self-administered their drops, 17 percent self-medicated when no help was available, 21 percent always obtained help, and 8 percent never tried to administer their medication. Approximately half the patients had difficulty aiming the drop. Other problems included inability to squeeze the container well enough, blinking, and inability to see the tip of the container. In particular, arthritic patients experienced physical difficulties.
with administration. These researchers also reported that most patients were reluctant to admit they were experiencing problems with the process.

In a separate survey of patients by telephone, 50 percent (114/229) of patients with dry eye said they continued to use the artificial tear solutions they had been prescribed, while 53 percent (47 of 89) reported discontinued use of prescribed ointments (Swanson 1998). This research detected “extreme” variability in the amount of artificial tear medication used, from patient to patient, and day to day. Patients appeared to titrate their artificial tear dosage to their symptoms on a daily basis; this researcher recommends patient education to foster compliance.

<table>
<thead>
<tr>
<th>TABLE</th>
<th>Discussion points for optimizing benefit from ophthalmic medications</th>
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| **General instructions** | - If using two different types of eye drops, instill the first, wait 5 minutes, then instill the second.  
- If using drops and ointment, instill the drop first, wait 5 minutes, then apply ointment.  
- When using products in single-use vials, agitate the container so that the color and/or opaqueness of its contents are uniform. |
| **Preventing contamination** | - Wash hands before opening container.  
- Prevent container tip from touching the eye.  
- When finished, tighten container cap.  
- Single-use vials should be used immediately after opening and discarded after use. |
| **Eye drops** | - Lean head back.  
- Instill eye drops by gently sliding skin below eyelid over prominent point of cheekbone to form pocket.  
- Put one drop into pocket.  
- Close eye and refrain from blinking for about 1 minute.  
- Press tightly (but not tightly enough to cause injury) with one finger on inside corner of eye for about 30 seconds after instilling drop.  
- Use only 1 drop at a time.  
- The eye's conjunctival fornix can accommodate only 1 drop at a time. Any fluid beyond 1 drop will overflow. |
| **Ointment** | - Start at inside corner of eye.  
- Squeeze thin line (about 0.5 cm) of medication along inside of lower lid.  
- Blink. |
| **Product administration** | To help patients achieve optimal benefit from ophthalmic medications, clinicians and pharmacists need to discuss the benefits of the chosen therapy with patients and their at-home care providers, and the correct way to apply the medication (see Table). |
| **CONCLUSION** | Although new ophthalmic drug-delivery systems alleviate dry eye somewhat, and a new CsA ophthalmic emulsion may alleviate the syndrome in many patients, proper administration of dry eye medications remains vital to successful treatment. The trend toward preservative-free medications means patients and their caregivers must exercise care during administration to prevent contamination of the remaining contents in the vial. Patients should be cautioned not to instill more than one drop of medication at a time, to prevent wasting the medication. Eye care clinicians can help patients achieve optimal relief by providing a combination of the most appropriate medication with the education on proper self-medication. |

**REFERENCES**


CONTINUING EDUCATION POST-TEST

P&T Digest
Dry Eye Syndrome

Please tear out the combined answer sheet/evaluation form on page 43 (physicians) or page 44 (pharmacists). On the answer sheet, place an X through the box of the letter corresponding with the correct response for each question. There is only one correct answer to each question.

1. Symptoms of dry eye syndrome, or keratoconjunctivitis sicca, include all but which of the following?  
   a. Gritty sensation under eyelids.  
   b. Numbness.  
   c. Mucous discharge.  
   d. Increased frequency of blinking.  
   e. Redness.

2. Despite improving ocular lubrication and increasing humidity at the ocular surface, artificial tears and lubricants fail to:  
   a. Accurately reproduce natural tears.  
   b. Improve vision.  
   c. Correct the underlying pathology that can occur with dry eye.  
   d. Answers “a” and “c.”

3. The AAO 2003 guidelines include all but which of the following goals for managing patients with dry eye?  
   a. To establish appropriate therapy.  
   b. To educate the patient.  
   c. To prevent complications.  
   d. To reduce the use of concurrent therapies.  
   e. To identify the causes of the condition.

4. In a population-based study, Schein (1997) estimated that dry eye symptoms are present in:  
   a. 1 million elderly Americans.  
   b. 1 in 7 elderly Americans.  
   c. 1.30 percent of Medicare managed care covered lives.  
   d. 0.21 percent of commercial managed care covered lives.

5. Contamination of preservative-free artificial tear products typically is due to:  
   a. Improper manufacturing practices.  
   b. Contact with the patient’s cornea, conjunctiva, eyelashes, or hands.  
   c. Airborne microbes.  
   d. The patient’s sneezing or coughing.

6. Artificial tears are best described as:  
   a. Preventive therapy.  
   b. Curative therapy.  
   c. Palliative therapy.  
   d. Counterintuitive therapy.

7. Dry eye can occur sporadically or as a chronic condition that becomes a self-perpetuating syndrome.  
   a. True.  
   b. False.

8. Topical corticosteroids should:  
   a. Be reserved for patients who experience severe and recalcitrant symptoms.  
   b. Be considered as front-line therapy for patients on antihistamine therapy.  
   c. Be used for 2 weeks or less for severe exacerbations of dry eye syndrome.  
   d. Answers a and c.  
   e. All the above.

9. For patients with severe dry eye, a diagnosis usually is supported by the following:  
   a. Schirmer wetting test.  
   b. Ocular surface dye-staining pattern.  
   c. Tear break-up time test.  
   d. All the above.

10. Dry eye syndrome has numerous risk factors. Which of the following are risk factors for dry eye syndrome?  
    a. Vitamin A deficiency.  
    b. Hormone replacement therapy.  
    c. Arthritis.  
    d. Answers b and c.  
    e. All the above.

11. Preservative-free artificial tears were developed:  
    a. For patients who demonstrate sensitivity to preservatives.  
    b. Because preservatives are known carcinogens.  
    c. To reduce the cost of the medication.  
    d. To encourage the use of more medication.

12. In a survey of third-party payers, prevalence of dry eye syndrome among persons covered by commercial plans was determined to be:  
    a. 0.21 percent.  
    b. 0.35 percent.  
    c. 1.30 percent.  
    d. 10.00 percent.

continued on page 45
CONTINUING EDUCATION ANSWER SHEET/CERTIFICATE REQUEST

P&T Digest
Dry Eye Syndrome

CME CREDIT FOR PHYSICIANS
Sponsored by The Chatham Institute

See page 44 for answer sheet for pharmacists

I certify that I have completed this educational activity and post-test and claim ______ credits.

Signature: _______________________________________
First name, MI ____________________________________
Last name, degree ________________________________
Title ___________________________________________
Affiliation _______________________________________
Specialty ________________________________________
Address ________________________________________
City _____________________ State  _____  ZIP ________
Daytime telephone (_______) _______________________
Fax (________) ___________________________________
E-mail __________________________________________

Physician — Maximum of 3.0 category 1 credits toward AMA Physician’s Recognition Award.

To receive CME credit, complete answer sheet/evaluation form and mail or fax to:

Office of Continuing Education
The Chatham Institute
26 Main Street, 3rd Floor
Chatham, NJ 07928
Fax: (973) 701-2515

Credit will be awarded upon successful completion of assessment questions (70 percent or better) and completion of program evaluation. If a score of 70 percent or better is not achieved, no credit will be awarded and the registrant will be notified.

Please allow up to 6 weeks for processing.

The cost of this activity is provided at no charge to the participant through an educational grant from Allergan.

CMC3000

EXAMINATION: Place an X through the box of the letter that represents the best answer to each question on pages 42 and 45. There is only ONE answer per question. Place all answers on this answer form:

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PROGRAM EVALUATION
So that we may assess the value of this self-study program, we ask that you please fill out this evaluation form.

Have the activity’s objectives been met? Yes _____ No _____
If no, please explain: ______________________________

Was this publication fair, balanced, and free of commercial bias? Yes _____ No _____

If no, please explain: ______________________________

Did this educational activity meet my needs, contribute to my personal effectiveness, and improve my ability to:

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Treat/manage patients?  5  4  3  2  1  n/a
Communicate with patients?  5  4  3  2  1  n/a
Manage my medical practice?  5  4  3  2  1  n/a
Other ____________________  5  4  3  2  1  n/a

Effectiveness of this method of presentation:

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Time spent reading this publication: H ____ M ________

What other topics would you like to see addressed?

Comments: ____________________________________________________________
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To receive continuing education credit, please answer all information requested below. This assures prompt and accurate issuance of your continuing education certificate.

The program is approved for 3.0 contact hours (0.3 CEU).

ACPE program number: 812-000-03-016-H01.

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CONTINUING EDUCATION SELF-TEST, continued

P&T Digest
Dry Eye Syndrome

13. If inflammation is considered to be a cause of dry eye syndrome, then suppressing the cytokine-mediated inflammation response that occurs at a histological level can apply to dry eye regardless of the disease-state association.
   a. True.
   b. False.

14. In tears, lipid is:
   a. A mixture of water, salt, and proteins.
   b. A surface layer that retards evaporation.
   c. The film that coats the corneal surface.
   d. A secretion that degrades the quality of the tears.

15. The use of tear substitutes is indicated for patients with mild dry eye syndrome. For patients with more severe disease, which of the following is not necessarily indicated?
   a. Spectacle side shields.
   b. Nonpreserved tear substitutes or ointments, gels, and emulsions.
   c. Laser surgery.
   d. Moisture inserts.
   e. None of the above.

16. A 1998 study of individuals with Sjögren's syndrome found that, on average, this subset of dry eye patients experiences ocular irritation that interferes with activities of daily living on all but 29 days each year.
   a. True.
   b. False.

17. Overutilization costs in dry eye syndrome frequently arise from:
   a. Corneal transplantation.
   b. Low patient satisfaction with palliative therapy.
   c. A loss of productivity.
   d. None of the above.

18. In a survey of patients with dry eye disease, which quality-of-life factor was most often mentioned as being affected by the disease?
   a. Decrease of leisure time.
   b. Decrease of work time.
   c. Depression, unhappiness.
   d. Loss of confidence.

19. Which of the following statements is true?
   a. Cytokines are hormone-like proteins that regulate the immune response.
   b. Cytokines are a subset of leukocytes involved in signal transduction in the cell membrane.
   c. Cytokines have antigen-receptor complexes on their surfaces.
   d. The underproduction of cytokines can damage tissue.

20. In dry eye syndrome, cyclosporine A:
   a. Mediates mucosal secretions.
   b. Promotes cytokine release to reduce inflammation.
   c. Prevents release of cytokines that incite inflammation.
   d. Inhibits release of a collagenous enzyme that incites inflammation.