THE CURRENT UNDERSTANDING OF

DRY EYE DISEASE

The Role of Clinicians in Educating the Public

Insights from a Roundtable Discussion

PROGRAM CHAIR

PARTICIPANTS
Penny Asbell, MD, FACS, MBA: New York, New York, USA
Stefano Barabino, MD, PhD: Genoa, Italy
Christophe Baudouin, MD, PhD, FARVO: Paris, France
Eric D. Donnenfeld, MD: New York, New York, USA
Gerd Geerling, MD, PhD: Düsseldorf, Germany
Debra A. Schaumberg, ScD, OD, MPH: Boston, Massachusetts, USA

This medical education activity was supported by Pfizer Inc.
THE CURRENT UNDERSTANDING OF

DRY EYE DISEASE

The Role of Clinicians in Educating the Public

PROGRAM CHAIR
Anthony J. Bron, FRCOphth, FMedSci, FARVO
Professor Emeritus
Nuffield Laboratory of Ophthalmology
University of Oxford, UK

PARTICIPANTS
Penny Asbell, MD, FACS, MBA
Professor of Ophthalmology
Director of Cornea and Refractive Services
Department of Ophthalmology
Mount Sinai School of Medicine
New York, New York, USA

Stefano Barabino, MD, PhD
Associate Professor
Clinica Oculistica
Department of Neurosciences, Ophthalmology, and Genetics
University of Genoa
Genoa, Italy

Christophe Baudouin, MD, PhD, FARVO
Professor of Ophthalmology
Quinze-Vingts National Ophthalmology Hospital
Vision Institute, University of Paris 6
Paris, France

Eric D. Donnenfeld, MD
Clinical Professor of Ophthalmology
New York University
New York, New York, USA
Trustee of Dartmouth Medical School
Hanover, New Hampshire, USA
Chair of Cornea for the American Society of Cataract and Refractive Surgery (ASCRS)

Gerd Geerling, MD, PhD
Department of Ophthalmology
Heinrich-Heine-University
Düsseldorf, Germany

Debra A. Schaumberg, ScD, OD, MPH
Associate Professor of Medicine and Ophthalmology
Director of Ophthalmic Epidemiology
Brigham and Women’s Hospital
Harvard Medical School
Boston, Massachusetts, USA

Proprietary or commercial disclosures may be found after the references.
The International Dry Eye Workshop (DEWS) was held in 2007 and was published in Ocular Surface. The report is an evidence-based review of the present state of knowledge of dry eye disease (DED) and the methods used to evaluate, diagnose, and manage the disorder. In addition, the International Meibomian Gland Dysfunction Workshop was completed in 2010 and was published on March 2011. These 2 workshops summarize the findings of current research and identify future needs for a better understanding of the etiology, pathogenesis, and potential therapy of DED. It is therefore an excellent opportunity to assess the outcomes of these workshops, to obtain a global perspective and, at the same time, to consider the implications for ophthalmologists in Europe.

A group of renowned experts in anterior segment disease convened to share their insights into the current understanding of the disease and to think about the implications for their patients. The highlights of this discussion are presented here.

NEEDS OF CLINICIANS TO UNDERSTAND DRY EYE DISEASE

PROF GEERLING: There are 2 primary needs to better understand dry eye disease: First, a need to be aware of the differential diagnosis of DED, as has been reviewed in the Dry Eye Workshop (DEWS) and Meibomian Gland Dysfunction Workshop (MGD). Second, there is a need for diagnostic tools to differentiate between DED and MGD. Additionally, in Germany, ophthalmologists are looking for specific therapeutic approaches to DED, such as the use of anti-inflammatory agents to supplement the use of tear substitutes, which are used currently to restore tear volume.

PROF BRON: Yes, I agree. Tear substitutes can ameliorate symptoms and have some important therapeutic effects, but newer therapies can specifically target the disease process.

PROF BAUDOIN: In France, the situation is similar to that in Germany. There is typically limited knowledge about the pathophysiology of dry eye. This limited knowledge frustrates many ophthalmologists because they believe that their patients are not getting symptomatic relief from tear substitutes despite the availability of a large variety of these agents on the market. Since the availability of cyclosporine 5 years ago (not approved in France, but obtainable through hospital pharmacies), there has been an increasing recognition that inflammation is involved in DED.

PROF BRON: Cyclosporine, incidentally, is not approved in most countries in Europe, although it is available in Turkey.

PROF BARABINO: The situation is very similar in Italy. One of the major problems in my country is that dry eye patients are not referred to an ocular surface specialist. Instead, they consult their pharmacist, who gives them artificial tears on nonspecific grounds. Next, they see a general practitioner, who also may not recognize dry eye as a disease. Even when patients do consult a general ophthalmologist, that physician often prescribes artificial tears without making a diagnosis of DED or distinguishing it from meibomian gland dysfunction. Therefore, it is imperative that both ophthalmologists and general practitioners become well informed about both diseases. Moreover, we need to educate patients about DED because they do not really understand the nature of the disease.

PROF ASBEll: There remains an underappreciation of dry eye disease by both European and US professionals. In the last decade, however, clinicians have had an increased understanding of the prevalence of DED and a growing acceptance of the concept that DED can negatively affect patient quality of vision as well as comfort. This may be less well understood in Europe. There is also an economic impact of DED that varies from country to country, which is hard to calculate since many patients are self-diagnosed and self-treated with over-the-counter remedies. A limited survey has been reported in Europe. Therefore, there is clearly an opportunity in Europe and in the United States, as well as in other parts of the world, to raise awareness of the prevalence of DED.

Evolving Concept of Dry Eye Disease

PROF BRON: The DEWS report defines dry eye disease as a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, tear film instability, and potential damage to the ocular surface. Dry eye disease is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface. Hyperosmolarity plays a causal role and is regarded as a gold standard in the diagnosis of DED. How has this concept evolved?

PROF SCHAUmBERG: Unlike the previous definition, the new definition of dry eye disease recognizes that the symptoms of the disease could cause both discomfort and visual problems and, thus, the new definition eliminates the disconnect that often exists between the symptoms and the appearance of the ocular surface.

PROF ASBEll: The 2007 DEWS report also expanded our understanding of the mechanism of dry eye disease.

“We have not yet convinced the entire ophthalmology community that inflammation is present in dry eye disease.” — PROF BAUDOIN

PROF BRON: We must remember that patients are focused primarily on the resolution of their symptoms and not on ocular surface signs. Ophthalmologists recognize the prime importance of symptoms, but they care about signs too, because these signs reflect eye pathology, which may predict later outcomes.

PROF DONNENFELD: In the past, dry eye disease was considered an irreversible, inevitable change due to age. Now we know that inflammation plays a major role in many cases of DED and that anti-inflammatory therapy can both improve the ocular surface and prevent disease progression.

PROF BRON: Initially, there was much resistance to the idea of inflammation of the ocular surface in dry eye disease because clinicians did not see a bright red eye. Instead, they saw subtle hyperemic changes. However, Paiva and Pflugfelder convinced the medical community that treating inflammation could reverse both patient symptoms and ocular surface signs.

PROF BAUDOIN: I believe that we have not yet convinced the entire ophthalmology community that inflammation is present in dry eye disease.
Understanding inflammation is undoubtedly a step forward in our comprehension of the pathogenesis of dry eye disease, but the problem of diagnosing inflammation on the ocular surface remains. There is a great need for simple approaches that can be used by the general ophthalmologist to quantify inflammation.

PROF BAUDOIN: Measuring inflammation remains a difficult task in clinical practice. Biopsies are invasive and difficult to propose to patients. Impression cytology appears to be a more appropriate way to assess the ocular surface because it allows for the quantification of squamous metaplasia, goblet cell counts, and identification of inflammatory cells. Flow cytometry is a biological technique that quantifies inflammatory markers expressed by conjunctival cells. It has been used in the clinical setting and in multicenter trials to quantify and monitor inflammation in dry eye disease. Human leucocyte antigen DR (HLA-DR) expression is a reliable marker for measuring inflammation in DED. Other techniques such as RT-PCR or tear cytokine measurements may also be used. ELISA (enzyme-linked immunosorbent assay) or multiplex bead analysis have been used successfully for assessing the presence of inflammatory cytokines or chemokines in the tears in DED. However, tear collection in DED patients remains difficult and the risk of protein dilution by reflex tearing cannot be ruled out.

**DRY EYE DISEASE TERMINOLOGY**

PROF BRON: The Delphi report provided a consensus approach to symptomatic ocular surface disease and generated a treatment algorithm based on the severity of symptoms and signs. The panelists were justifiably critical of the term “dry eye disease” because it contradicts the fact that patients may not always experience actual ‘dryness’ and, in fact, may have increased tearing as one of their symptoms as is the case in evaporative dry eye. Because of these conceptual difficulties, the panel created the term “dysfunctional tear syndrome”. This is a nice general term for symptomatic ocular surface disease, but it is not an appropriate term to replace “dry eye disease” itself, which is a subset characterized by tear hyperosmolarity.

PROF BARABINO: I agree. The term “dry eye disease” is incomplete, and yet “dysfunctional tear syndrome” is too complex and is difficult for patients to understand. A term in between the 2 would be of value, perhaps a term that includes the words “ocular surface”.

PROF SCHAUMBERG: My issue with the term “dysfunctional tear syndrome”, apart from its complexity, is that it points the finger at the tears, while the ocular surface is what is really affected.

PROF GEERLING: Events in the tears are important, but it is true, as you say, that it is problematic when a terminology is chosen for dry eye disease that relates to the tear film only, rather than to a specific anatomic structure such as the ocular surface.

PROF BRON: There is still some work to be done to arrive at a simple language that locks together the concept of dryness with increased saltiness of the tears—thus, incorporating both the aqueous-deficient and the evaporative forms of the disease.

**PATHOPHYSIOLOGY OF DRY EYE DISEASE**

PROF BAUDOIN: Two major mechanisms have been suggested for the pathophysiology of dry eye disease—Inflammation and hyperosmolality. Inflammation can be treated, but cannot be measured easily; hyperosmolality, however, can be measured quite easily. Sullivan and colleagues have shown that hyperosmolality is a better indicator of severity than the Schirmer test, tear breakup time, or staining with dyes.

PROF BRON: Prof Baudouin, please describe your “vicious circle” concept that is important for the understanding of the self-perpetuation of this disease.

PROF BAUDOIN: Tear hyperosmolality increases the disorders of corneal and conjunctival epithelial cells and goblet cell because it causes apoptosis. Most likely, the destruction of goblet cells, which is a hallmark of dry eye disease, is a major contributor to the disease. At the level of the cornea, activation of reflex arcs probably stimulates the ocular surface, further augmenting the neurogenic inflammation. This, in turn, leads to the release of inflammatory cytokines and the subsequent stimulation of inflammatory cells and lymphocytes. All those inflammatory or degenerative phenomena are additional events that cause further goblet cell destruction and tear film instability, resulting in a vicious circle (Figure 1).

![Figure 1: Pathophysiology of dry eye disease](EthisCommunications.com)
ENVIRONMENTAL FACTORS THAT AFFECT DRY EYE DISEASE

PROF SCHAU BERG: The effect of environmental stimuli on dry eye disease poses a complex issue. Recently, several important research articles have added significantly to our knowledge of the role of environmental stimuli. Patients often complain that reading and computer use exacerbate their DED symptoms. Himebaugh and colleagues have shown decreased blink rates and more central breakup of the tear film during computer use in people with DED compared with normal subjects.20

There is also the role of low humidity and its effects on patients with dry eye disease. For example, a study from Taiwan examined more than 3000 people,21 with approximately half the people investigated working in an indoor environment with moderate humidity. The study showed that working in this environment was significantly associated with a higher prevalence of DED.

Other studies have examined the issue of air travel. One study surveying 1246 Australian pilots showed a marked association between DED and the flight environment, with 72% of respondents reporting DED during flight, but only 5% reporting such symptoms at other times. 22

Lastly, studies from Asia—specifically Tibet,23 Mongolia,24 and India25—suggest that people living at high altitudes (ie, low humidity), have a very high prevalence (approximately 50%) of DED symptoms.

PROF BARABINO: A significant decrease in tear secretion from the lacrimal gland was observed 3 days after placing mice in a low-humidity chamber with a constant airflow, suggesting that low humidity stimulates a negative feedback loop. 26 One of the possible reasons for this is that chronic stress of the ocular surface could induce irreversible changes in the lacrimal gland, thereby decreasing its tear production.

PROF SCHAU BERG: Sometimes dry eye disease can be affected by low humidity alone, but the culprit may also be the actual movement of air over the ocular surface.

PROF BRON: Certainly, both low humidity and air movement increase evaporation. It seems that environmental factors such as humidity, high altitude, and extended viewing of computer monitors, among others, affect people in all professions and in all parts of the world. It is evident that both the clinicians and the public require more education about these aspects of dry eye disease.

EFFECT OF MEDICATIONS ON DRY EYE DISEASE

PROF BRON: What is the effect on dry eye disease of the internal environment created, for instance, by certain medications?

PROF SCHAU BERG: Medications play a very important role in dry eye disease. The Physicians’ Health Study27 and the Beaver Dam Eye Study28 showed that the use of antidepressants is associated with an increased risk of DED. Other commonly used medicines, such as antihistamines, beta-blockers, and anything with an anticholinergic effect, are also associated with increased DED symptoms.

CLASSIFICATION OF DRY EYE DISEASE

PROF BRON: I think we are comfortable with the 2 established major categories of dry eye disease classification.1 First is aqueous-deficient DED. This can be subdivided into Sjögren Syndrome (primary or secondary) and non-Sjögren DED, which includes age-related DED. In this case, lacrimal function is impaired by invasion of the lacrimal gland with inflammatory cells. Lacrimal flow can also be reduced by cicatricial obstruction to the lacrimal ducts.

The second major category is evaporative DED. The DEWS report1 recognized an intrinsic form of DED that was lid-related, including not only meibomian gland dysfunction, but also poor lid congruity or lid dynamics, a low blink rate, and the toxicity of systemic retinoids used in the treatment of acne vulgaris. Another form of evaporative DED is that caused by damage to the ocular surface, due to vitamin A deficiency, topical preservatives, contact lens wear, and allergy (Figure 2).

PROF BRON: What is the effect on dry eye disease of the internal environment created, for instance, by certain medications?

PROF SCHAU BERG: Medications play a very important role in dry eye disease. The Physicians’ Health Study27 and the Beaver Dam Eye Study28 showed that the use of antidepressants is associated with an increased risk of DED. Other commonly used medicines, such as antihistamines, beta-blockers, and anything with an anticholinergic effect, are also associated with increased DED symptoms.

“IT IS IMPORTANT TO ACKNOWLEDGE THAT AQUEOUS-DEFICIENT AND EVAPORATIVE DRY EYE DISEASE ARE NOT MUTUALLY EXCLUSIVE. THEY CAN AND DO OCCUR IN COMBINATION; THEREFORE, THEY CAN PRODUCE COMPLEX HYBRID STATES.”

— PROF BRON

Another mechanism that may trigger dry eye disease is the feedback from the ocular surface through the lacrimal functional unit. When corneal sensation is impaired, a loss of sensory drive to the lacrimal gland occurs, that may reduce the secretory function of the lacrimal gland.29,30 It is important to acknowledge that aqueous-deficient and evaporative DED are not mutually exclusive. They can and do occur in combination; therefore, they can produce complex hybrid states.

Figure 2: Classification of dry eye disease.1 Reprinted with permission from Ethis Communications, Inc.
MGD, meibomian foam, and an increase in staphylococcal colonization of the lid margin. In addition to interpalpebral staining, cornea with lissamine green or fluorescein in the classical DED some inferior conjunctival staining may be present and is consistent with the presence of pathogenic staphylococci.

**Diagnosis of Dry Eye Disease**

**Prof Donnenfeld:** To diagnose dry eye disease, the clinician needs to start with symptoms of DED and the patient’s history.

Aqueous-deficient DED, in general, tends to worsen throughout the day as the aqueous component of the tears evaporates from the ocular surface, and causes a general irritation and foreign body sensations. Patients who have rheumatoid arthritis or who are taking certain medications, as discussed earlier, are most likely to have aqueous-deficient DED.

Evaporative DED tends to be worse in the morning, perhaps because of the abnormal lipids that have accumulated overnight, causing patients to experience burning. Patients with evaporative DED often have systemic skin disorders, such as acne vulgaris or rosacea.

On clinical examination, diagnosis can sometimes be made very easily by looking at the lids, because of telangiectasia, erythema, meibomian gland dysfunction with meibomian oil turbidity, and occluded meibomian glands. Aqueous-deficient DED tends to have a less plentiful tear film. Schirmer scores may be lower than normal and there tends to be interpalpebral staining of the conjunctiva and cornea with lissamine green or fluorescein in the classical DED distribution.

Patients who have evaporative DED often have clearly defined MGD, meibomian foam, and an increase in staphylococcal commensals on the lid margin. In addition to interpalpebral staining, some inferior conjunctival staining may be present and is consistent with the presence of pathogenic staphylococci.

**Prof Bron:** If a symptomatic patient has a normal Schirmer score, extensive MGD, and ocular surface staining, he or she can be reasonably diagnosed as having evaporative dry eye disease. It is when the Schirmer score is low and there is evidence of decreased aqueous production that clinicians must make a value judgment as to whether aqueous-deficient and evaporative dry eye are both present. As we have said, lacrimal deficiency and MGD can occur together in the same patient and result in a combined mechanism for dry eye. However, it is also possible that this hybrid state could come about in another way. For instance, if we suppose that there is an evaporative dry eye due to MGD, then, as the severity of the condition increases and the corneal surface is damaged, we can postulate that a loss of sensory drive to the lacrimal gland could reduce the compensatory lacrimal flow and result in an additional, functional aqueous deficiency.

**Etiologies of Dry Eye Disease**

**Prof Donnenfeld:** Aqueous-deficient dry eye disease begins with abnormalities of the lacrimal gland, which not only reduce the amount of aqueous, but also reduce the associated defense proteins found in the tear film. Inflammatory events in the gland can have this result. Furthermore, low androgen levels can negatively influence aqueous production. Meibomian gland dysfunction, which is also associated with androgen dysfunction, is responsible for evaporative DED. As discussed earlier, medications such as diuretics and topical ocular medications with preservatives, particularly artificial tears, can play a very significant role.

**Prof Baudouin:** Preservatives can be detrimental to the ocular surface. Benzalkonium chloride (BAK) may cause or aggravate dry eye disease. Short exposure to BAK has been shown to decrease goblet cell density in humans. Long-term exposure to antiglaucoma drugs with preservatives also cause decreased goblet cell density. Many experimental reports have been published showing the overall toxicity of BAK to the ocular surface, even at low concentrations, and possible direct proinflammatory properties have been suggested. In addition, as a surface-active detergent, BAK also destabilizes the lipid layer of the tear film, increasing evaporative loss. The result of both mechanisms, namely the mucus and lipid layer alterations, is a globally impaired tear film with tear instability and excessive evaporation.

**Prof Donnenfeld:** An important etiology for dry eye disease that is often overlooked is ocular surgery. A meta-analysis study examining the incidence of DED after LASIK (laser-assisted in situ keratomileusis) surgery, found that 20% of LASIK patients experienced dryness symptoms that were significantly worse than those experienced preoperatively. This indicates that DED symptoms are more common complications of ocular surgery.

**Prof Bron:** Prof Donnenfeld, does that worsen the risk of regression after surgery?

**Prof Donnenfeld:** Yes, there are articles by several authors, including Marguerite McDonald and John Hovanesian, that have shown that dry eye disease can affect postoperative results. De Paiva and Ursea showed that DED was associated with regression, suboptimal outcomes, and low patient satisfaction. The etiology of this relationship stems from the negative effect of surgical trauma, specifically because of the damage to the corneal nerves caused by the incision and photoablation. Damage to these nerves, which are responsible for innervating the cornea, can disrupt the normal feedback loop from the cornea, which normally drives lacrimal tear production. Recent evidence suggests that topical cyclosporine may reduce the risk of DED after intraocular lens implantation and LASIK by having a direct effect on corneal nerve repair.

**Prof Bron:** Prof Donnenfeld, do you think neuropathic input can also cause pain independent of a dry eye disease mechanism?

**Prof Donnenfeld:** Yes, I do. In my opinion, it is an etiology that is sometimes overlooked. Some patients have significant neurogenic pain following surgery without associated corneal staining. Wilson and colleagues have made a very strong case that what is classified as dry eye disease following LASIK may actually be a neurological disease, which they have termed LASIK-induced neuroepitheliopathy, or LINE.
PREVALENCE OF DRY EYE DISEASE

PROF SCHAUMBERG: There are a large number of studies of the prevalence of dry eye disease across the globe, including the United States, Australia, Canada, Europe, and Asia. We have learned from the prevalence studies that DED symptoms are very common, with DED ranging from 3% to 15% in patients aged 50 years and older, which is the age of populations examined in most of these studies. The study in Spain reported a prevalence of 11% or 12%. Asian studies generally show a higher prevalence, approximately double that reported in either the United States, Australia, or Europe.

PROF BROWN: How does the prevalence of meibomian gland dysfunction relate to the prevalence of dry eye disease?

PROF SCHAUMBERG: There have been fewer studies looking at meibomian gland dysfunction, but in my opinion, the trends are similar, with higher levels of MGD in the Asian populations compared with the Caucasian populations.

EMERGING DIAGNOSTIC TECHNIQUES

PROF ASBELL: Minimally invasive diagnostic methods are the future of dry eye disease diagnosis. First, we need to be able to diagnose DED, differentiate it from other types of external diseases, and then to classify the DED subtypes. Second, we would like to better classify disease severity because the current severity grading is difficult to put into practice. Third, we need tests that can quantify changes on the ocular surface and tear film that result from treatment.

Some of the interesting new diagnostic areas include the evaluation of tear osmolarity, examining tears with optical coherence tomography (OCT), measuring tear height and tear volume, and looking at the contents of the tears both by proteomics and by measuring inflammatory cytokines.

“Minimally invasive diagnostic methods are the future of dry eye disease diagnosis.”

PROF ASBELL

Another exciting possibility is the use of impression cytology combined with flow cytometry, to examine specific inflammatory biomarkers. This approach was pioneered by Prof Baudouin.

I think the next diagnostic area that has gained momentum lately is the improved evaluation of the eyelids and meibomian gland dysfunction and, specifically, the recognition of how lid disease and meibum alterations contribute to changes in the tear film and the ocular surface. There is certainly a high level of interest among ophthalmologists in obtaining better biomarkers and more objective examination techniques.
metrics to help in the diagnosis of DED. Currently, scientists from Europe and Singapore are collaborating to explore such techniques in other human disease models. Their work may lead to breakthroughs and a better understanding of DED.

**PROF BARABINO:** With respect to the use of lissamine green or rose bengal as a diagnostic tool for dry eye disease, it has to be pointed out that both vital stains are available in Europe, but their use is limited to some ocular surface specialists. In fact, there is evidence that ophthalmologists in Italy use lissamine green less than 10% of the time. Lissamine green is very important because, as does rose bengal, it can quantify both corneal and conjunctival damage, but without the discomfort induced by rose bengal’s intrinsic toxicity or the phototoxicity induced by ultra-violet exposure.

**PROF BRON:** This is an important point because lissamine green is hardly used in the United Kingdom, and rose bengal is unavailable. In the past, clinicians used rose bengal routinely, but when it was withdrawn from the market and lissamine green became available, clinicians did not switch to lissamine green; and so, a real diagnostic opportunity has been lost. It seems that residents in training hesitate before using lissamine green because it is unfamiliar to them or because it might stain the lids if not used properly. As a result, these clinicians are failing to examine the ocular surface directly.

**PROF DONNENFELD:** A study by Sullivan and colleagues on tear osmolarity and dry eye disease severity showed that the second highest correlation with DED severity was conjunctival staining, followed by corneal staining. Therefore, if a tear osmolarity sensor is not available, in my opinion, conjunctival staining is the second most useful way to diagnose DED.

**PROF ASBELL:** The other point to emphasize is that when examining the eye, clinicians often ignore the lid, the meibomian gland orifices, and the quality of expressed meibum, thereby missing an important part of the examination in patients with ocular surface disease.

**MANAGEMENT OF DRY EYE DISEASE**

**PROF GEERLING:** There is extensive variation across nations in the management of dry eye disease, in no small part due to differences in the availability of certain drugs. The majority of patients, regardless of disease subtype, are treated first with lubricants because these are widely available.

“There is extensive variation across nations in the management of dry eye disease, in no small part due to differences in the availability of certain drugs.” — PROF GEERLING

There is a huge need in the early stages, however, for additional nonpharmacologic management. This includes instructing patients about etiologies; use of lid hygiene and lid warming (eg, in meibomian gland dysfunction-associated dry eye); and avoidance of risk factors or exacerbating conditions such as certain medications, low-humidity environments, and specific head positions during computer use. However, these nonpharmacologic treatments have poor compliance among patients. Other measures, such as anti-inflammatory medication, are generally more accepted by patients.

Surgical measures, such as punctal plugging in aqueous-deficient dry eye and systemic tetracycline derivatives, which are thought to be effective in patients with MGD, are limited to the severe form of the disease. These treatments, even if available, are frequently underused.

**PROF BRON:** Some experts have suggested using a short course of topical steroids prior to inserting punctal plugs in patients with moderate or severe aqueous-deficient dry eye disease. The rationale is that punctal plugs may not only conserve the tears, but may also conserve inflammatory mediators. Thus, the steroids can be useful initially to damp down the inflammation, and possibly increase the effectiveness of the plugs.

Prof Asbell, do you use a severity-specific protocol for management of DED?

**PROF ASBELL:** I often direct my treatment according to the patient’s symptoms because that is the key reason for the patient seeking treatment. If the patient is satisfied with what is being done, I continue using that treatment. If the patient is not satisfied, I explore other treatments.

With respect to the various artificial tear preparations, I look at the differences among them. I do not think all of them work well for everybody. For mild disease, I generally start out with a multiuse bottle, since it is cost-effective and convenient. I tend to choose preparations that are available without BAK because that preservative is particularly toxic to the ocular surface. If the response is not satisfactory, I move to unit-dose artificial tears. I reserve topical cyclosporine for those patients who have severe findings.

Recently, I have also been prescribing a low-dose nonpreserved steroid (dexamethasone, 0.01%), which is available in the United States only through a compounding pharmacy—a pharmacy that will prepare, on request, specific eye drop formulations that are not commercially available. This very-low-dose steroid medication does not appear to induce elevated intraocular pressure, a side effect we often find with higher-dose steroids. Yet, it can be effective for many patients with inflammatory ocular surface disease.

Another treatment option approved by the US Food and Drug Administration is a hydroxypropyl cellulose ophthalmic insert, which is a tear pellet that is placed in the lower lid cul-de-sac. The pellet melts with the patient’s own tears, providing lubrication over a period of time. These lubricants can be a little thick and sometimes interfere with vision. Therefore, I suggest placing the pellet at night to provide lubrication overnight and possibly even provide some early morning comfort.

**PROF BAUDOIN:** We also have the tear pellets in France. Mainly Sjögren syndrome patients, who instill many, many eye drops each day, use these pellets.

**PROF BRON:** When do you offer conserving spectacles?

**PROF ASBELL:** The idea of using conserving spectacles to decrease evaporation is appealing. However, these spectacles are not easy to get for my patients in New York.
PROF BRON: In the United Kingdom, one can get commercial conserving spectacles, or the optometry departments will make them. They are very helpful if the patient can accept them cosmetically.

PROF BAUDOIN: Conserving spectacles are not available in France. With respect to management, ophthalmologists are convinced that preservatives are toxic for the ocular surface, especially in dry eye disease, so they worry about preservatives in artificial tears. Ocular surface specialists will frequently use anti-inflammatory eye drops. Additionally, in France, there is preservative-free steroid and topical cyclosporine. Hospital pharmacists can prepare cyclosporine, or commercial cyclosporine can be imported with a specific authorization. We also use systemic doxycycline, which is particularly prescribed in meibomian gland dysfunction and rosacea patients. In such patients, topical azithromycin, recently introduced in France, is under investigation.

PROF DONNENFELD: As mentioned earlier, commercial topical cyclosporine is not available in the European Union, but people do formulate it for treatment of dry eye disease. Erythromycin and azithromycin have been of interest as systemic or topical treatments of meibomian gland dysfunction in younger patients.

PROF GEERLING: Metronidazole topical gel, 0.75%, is available for topical treatment of inflammatory changes associated with rosacea in Germany, the United Kingdom, and the United States. It has been used successfully for evaporative dry eye disease, meibomian gland dysfunction, and blepharitis.54 We often initiate treatments simultaneously simply because patients have been suffering for so long and want rapid relief. Punctal plugging is effective in patients with a zero Schirmer score. I choose not to use a topical steroid unless there is obvious inflammation. I expect that the frequent instillation of artificial tears may dilute any inflammatory markers on the surface. In addition, patients prefer not to apply too many eye drops.

PROF DONNENFELD: In our practice, we are strong believers of the use of combination immunomodulation. By adding a corticosteroid to cyclosporine, you obtain a more rapid effect and alleviate the burning and irritation that is sometimes associated with cyclosporine therapy.

PROF BARABINO: inflammation certainly plays a pivotal role in dry eye disease pathogenesis and, therefore, we need to focus simultaneously on tear replacement and anti-inflammatory therapy. I do not think we need to eliminate inflammation, but we need to modulate it by using soft steroids or using other commercial corticosteroids in diluted formulations or at reduced dosage. We need to be dynamic in our approach and adjust anti-inflammatory therapy according to changes in ocular surface conditions with time. For example, in some of my patients I control inflammation by using steroids twice a week, which has a positive effect on ocular surface inflammation and may help tear substitutes to adhere to ocular surface epithelia. At the same time, at this dosage, the well-known negative effects of steroids can be limited. Most Italian ophthalmologists do not feel comfortable prescribing chronic corticosteroid therapy, but if it is used cautiously, it may be beneficial.60,61 Regarding the use of systemic omega-3 fatty acids, I totally agree with Prof Donnenfeld, that in most cases they are very helpful in improving patients’ symptoms, as my group had demonstrated some years ago.62

PROF BRON: Steroids are potentially risky in dry eye disease because the ocular surface is already damaged, possibly enhancing their entry into the eye. Newer steroidal agents, such as soft steroids and glucocorticoid receptor agonists, are becoming commercially available. They are interesting agents because of their favorable safety profiles. However, if patients are prescribed steroid therapy, how can a clinician make sure that patients do not use them indiscriminately?

PROF GEERLING: I prescribe only 1 bottle, which ensures that the patient runs out of supply within a month. Furthermore, I reexamine and reevaluate my patients at 6 weeks, including assessment of intraocular pressure.

There are many other modalities for the off-label medical treatment of dry eye disease, including systemic tetracyclines, acetylcysteine, and even retinoic acid for secondary surface changes such as keratinisation, but some of these agents are difficult to obtain. Another medication that is even more challenging to obtain is a form of nutrient tear substitute. We produce these autologous serum drops to add nutrients to the tear film. Patients often benefit immensely, but supplying this blood-derived medication on a permanent basis requires the distributor to have a specific license for the product. Currently, only 4 universities in Germany have this license, so it is nearly always unavailable unless a patient happens to live near one of these institutions. I believe that this is the same situation throughout the continent.
PHYSICIANS’ UNDERSTANDING OF DRY EYE DISEASE

PROF BAUDOIN: I treat severe dry eye disease the same way, including the occasional use of autologous serum.

PROF BARABINO: Ophthalmologists are increasingly interested in the treatment of dry eye disease. This year we have launched an online course on ocular surface disease with the intention of reaching more than 1000 ophthalmologists in Italy each year. We strongly believe that education is the most important way to improve our knowledge of DED treatment. We are hoping that in the future, our course can be translated to make it available to other European countries and to encourage the participation of other European oculary surface experts. We are also producing a document for the Italian government to increase the understanding of DED as an important chronic disease. We could possibly collaborate with other countries to do this throughout Europe.

“We strongly believe that education is the most important way to improve our knowledge of dry eye disease treatment.”

PROF BRON: In summary, dry eye disease is prevalent all over the world and has many causes. It adversely affects ocular comfort, vision, and quality of life. The DEWS report broadened the definition of DED and confirmed its major forms as aqueous-deficient and evaporative dry eye. The recently published meibomian gland dysfunction workshop report emphasized the importance of evaporative dry eye, of which the most common cause is MGD.

The presence of MGD is sometimes overlooked, but it can be readily diagnosed by routine lid inspection and meibum expression. Our discussion highlighted the causal role of tear hyperosmolarity in DED and the importance of ocular surface inflammation. Inflammation is an important therapeutic target. There is a need to identify inflammatory biomarkers to aid diagnosis, and to monitor severity and the response to treatment. One of the consequences of surface inflammation is epithelial damage and increased tear film instability, causing a vicious circle that amplifies and perpetuates the disease. An avoidable contributor to this vicious circle is the frequent use of preserved eye drops.

Many other aspects of dry eye disease were discussed, more than can be summarized here, but an important conclusion of the roundtable was that ophthalmologists can do a better job to promote a clearer understanding of dry eye disease, among themselves, other physicians, and members of the public. It is our hope that this report will provide some impetus to this intent.

FINANCIAL DISCLOSURES

The authors have made the following disclosures: Prof Asbell received an honorarium from Pfizer for participation in this project; she has other relevant financial relationships as follows: consultancy/Addition, Alcon, Aton Pharma, Bausch + Lomb, Candeo Clinical/Science Communications, Inspire, Johnson & Johnson, Merck, Otsuka, Pfizer, Santen, Vindico Medical Education, Vistakon; grant/research funding to institution– Alcon, Aton Pharma, Bausch + Lomb, Inspire, Martin and Toni Sosnoff New Works Fund, National Institutes of Health, Pfizer–Research to Prevent Blindness. Prof Barabin received an honorarium from Pfizer for participation in this project; he has no other disclosures to make. Prof Baudouin received an honorarium from Pfizer for participation in this project; he has other relevant financial relationships as follows: consultancy–Aucela, Actelion Pharmaceuticals, Alcon, Ato Pharma, AOPharma, Bausch + Lomb, Clinac, FZG Discovery, Novagali Pharma, Novalag, Otsuka, Pfizer, Takeda, OcUSense/TearLab; stock– OcuSense/TearLab. Prof Connenfeld received an honorarium from Pfizer for participation in this project; he has other relevant financial relationships as follows: consultancy–Alcon, Allergan, Bausch + Lomb, Inspire/Merck, Pfizer. Prof Geerling received an honorarium from Pfizer for participation in this project; he has other relevant financial relationships as follows: board membership–Alcon, Allergan, Bausch + Lomb, Pfizer; expert testimony–Santen, Voisin Consult; speakers bureau– Bausch + Lomb; manuscript preparation– Alcon. Prof Schaumberg received an honorarium from Pfizer for participation in this project; she has other relevant financial relationships as follows: board membership–SARcode, Mimetogen; consultancy–Alcon, Allergan, Bausch + Lomb, Celtic Pharma, Eleven Biotherapeutics, Inspire/Merck; grants to institution–Pfizer; development of educational presentations–Allergan; stock– Tearlab, Mimetogen.

CORRESPONDENCE

Anthony J Bron, FRCOphth, c/o MedEdicus, 73 Redding Road, PO Box 839, Georgetown, CT 06839, USA; email: ctornallyay@medicus.com.

GRANT SUPPORT

This medical education activity is supported through an educational grant from Pfizer Inc. The views and opinions expressed in this educational activity are those of the authors and do not necessarily represent the views of MedEdicus LLC, Pfizer Inc, or EveryTime. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

©2011 MedEdicus LLC. All rights reserved.
REFERENCES


