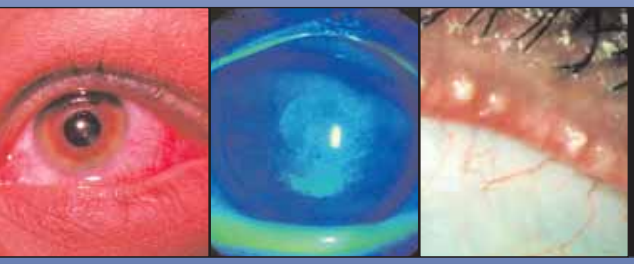
Supplement to

Glaucoma TODAY

July/August 2008

Glaucoma and the Ocular Surface



Once a patient with glaucoma is identified as having ocular surface disease, understanding the effect of topical therapy on the ocular surface is the next step to ensure long-term success.

Jointly sponsored by The Dulaney Foundation and *Glaucoma Today*.

This continuing medical educational activity is supported by an unrestricted educational grant from Alcon Laboratories, Inc.

Glaucoma and the Ocular Surface

Jointly sponsored by The Dulaney Foundation and *Glaucoma Today*.

Release date: July 2008

Expiration date: July 2009

This continuing medical educational activity is supported by an unrestricted educational grant from Alcon Laboratories, Inc.

STATEMENT OF NEED

Studies have shown that the incidence of ocular surface disease is significantly associated with age.[1,2] Given that aging is a risk factor for glaucoma, ophthalmologists are likely to see glaucoma patients with concomitant ocular surface disease. It is, therefore, incumbent upon clinicians to choose the most efficacious glaucoma treatments that will not compromise corneal integrity.

It has been estimated that more 3 million women and approximately 1.5 million men in the United States have some form of dry eye disease at 59 years of age or older.[3,4]

In fact, data from the Centers for Medicare & Medicaid Services show an increase in reported cases per 100 fee-for-service of dry eye during a 7-year period from 1991 to 1998 of 57.4% (from 1.22 to 1.92).[3] Posterior blepharitis is known to be quite prevalent in the United States.

1. Moss SE, Klein R, Klein BEK. Incidence of dry eye in an older population. *Arch Ophthalmol.* 2004;122:369-373.
2. Schein OD, Munoz B, Tielsch JM, et al. Prevalence of dry eye among the elderly. *Am J Ophthalmol.* 1997;124:723-728.
3. Schaumberg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. *Am J Ophthalmol.* 2003;136:318–326.
4. Miljanovic B, Dana MR, Sullivan DA, Schaumbert DA. Prevalence and risk factors for dry eye syndrome among older men in the United States. *Invest Ophthalmol Vis Sci.* 2007 (Abstract).

TARGET AUDIENCE

This activity is designed for ophthalmologists.

LEARNING OBJECTIVES

After successful completion of this program, participants should be able to:

- understand the importance of screening patients for ocular surface disease in the elderly and in those treated for glaucoma.
- identify common signs and symptoms of ocular surface disease.
- understand how to diagnose ocular surface disease.
- understand the effects of benzalkonium chloride (BAK) on the ocular surface and tear breakup time.
- utilize strategies for minimizing the risk of ocular surface disease in glaucoma patients.

METHOD OF INSTRUCTION

Participants should read the learning objectives and continuing medical education (CME) activity in their entirety. After reviewing the material, please complete the self-assessment test, which consists of a series of multiple-choice questions. To answer these questions online and receive real-time results, please visit http://www.dulaneyfoundation.org and click "Online Courses." Upon completing the activity and achieving a passing score of over 70% on the self-assessment test, you may print out a CME credit letter awarding 1 *AMA PRA Category 1 Credit™*. The estimated time to complete this activity is 1 hour.

ACCREDITATION/DESIGNATION

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of The Dulaney Foundation and Bryn Mawr Communications LLC, publisher of *Glaucoma Today*. The Dulaney Foundation is accredited by the ACCME to provide continuing education for physicians. The Dulaney Foundation designates this medical educational activity for a maximum of 1 *AMA PRA Category 1 Credit™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

DISCLOSURE

In accordance with the disclosure policies of The Dulaney Foundation and to conform with ACCME and FDA guidelines, anyone in a position to affect the content of a CME activity is required to disclose to the activity participants:

(1) the existence of any financial interest or other relationships with the manufacturers of any commercial products/devices, or providers of commercial services; and (2) identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

FACULTY DISCLOSURE DECLARATIONS

Donald L. Budenz, MD, MPH, has received grant/research support from Allergan, Inc., Carl Zeiss Meditec, Inc., and Pfizer Inc. He is a consultant to and serves on the speakers' bureaus of Alcon Laboratories, Inc., and Pfizer Inc.

Ronald L. Gross, MD, MPH, is a consultant and speaker, and receives clinical research grant support from Alcon Laboratories, Inc., and Allergan, Inc.

Stephen Pflugfelder, MD, receives research support from Allergan, Inc., and participates on its speaker's bureau for Restasis.

Michael B. Raizman, MD, MPH, is a consultant to, is on the speakers' bureau, and receives research support from Alcon Laboratories, Inc., Allergan, Inc., Bausch & Lomb, Inspire, ISTA, and Vistakon.

CONTENT VALIDATION

In compliance with ACCME standards for commercial support and The Dulaney Foundation's policy and procedure for resolving conflicts of interest, this CME activity was peer reviewed for clinical content validity to ensure the activity's materials are fair, balanced, and free of bias; the activity's materials represent a standard of practice within the medical profession; and any studies cited in the materials upon which recommendations are based are scientifically objective and conform to research principles generally accepted by the scientific community.

All those involved in the planning, editing, and peer review of this educational activity have indicated that they have no financial relationships to disclose relevant to the content of this activity.

FACULTY CREDENTIALS

Donald L. Budenz, MD, MPH, is Professor, Department of Ophthalmology, Epidemiology, and Public Health, Bascom Palmer Eye Institute, Miller School of Medicine, University of Miami. He may be reached at (305) 326-6000.

Ronald L. Gross, MD, MPH, is Professor of Ophthalmology and Clifton R. McMichael Chair of Ophthalmology at the Cullen Eye Institute, Baylor College of Medicine in Houston. He may be reached at (713) 798-4538.

Stephen C. Pflugfelder, MD, is Professor of Ophthalmology and Director of the Ocular Surface Center at the Cullen Eye Institute at Baylor College of Medicine in Houston. He may be reached at (713) 798-4732; stevenp@bcm.tmc.edu.

Michael B. Raizman, MD, MPH is a Clinical Ophthalmologist specializing in cataract and refractive surgery at Ophthalmic Consultants of Boston. He may be reached at (617) 314-2656.

CONTENTS

Epidemiology of Dry Eye and Ocular Surface Disease

The prevalence, definition, and impact of ocular surface disease in the United States.

BY STEPHEN PFLUGFELDER, MD

Ocular surface disease is a relatively common disorder among patients in the United States and may affect up to 10 million people. The two most common forms of ocular surface disease in patients 50 years of age or older are dry eye and posterior blepharitis (meibomian gland disease).

It has been estimated that more 3 million women and approximately 1.5 million men in the United States have some form of dry eye disease at 59 years of age or older.[1,2]

In fact, data from the Centers for Medicare & Medicaid Services show an increase in reported cases per 100 fee-for-service of dry eye during a 7-year period from 1991 to 1998 of 57.4% (from 1.22 to 1.92).[3] Posterior blepharitis is known to be quite prevalent in the United States.

In general, the incidence of ocular surface disease rises with age. For example, it has been noted in various large epidemiological studies that approximately 5% of the population 45 years of age or younger are diagnosed with ocular surface disease, and that percentage jumps to approximately 35% by 80 years of age.[4,5]

OCULAR SURFACE DISEASE DEFINED

The definition of ocular surface disease goes well beyond just dry eyes. It can be defined in several ways—dysfunctional tear syndrome, irritation of the ocular surface or lids, visual symptoms resulting from tear film abnormality. Overall, ocular surface disease results from some kind of compositional change that most often manifests as an unstable tear film.

The most common symptoms of dry eye include a burning sensation, itching, foreign-body sensation, blurred or fluctuating vision, and light sensitivity. At times, patients simply describe their symptoms as dryness. The signs of dry eye include redness of the eyes, as is evident in Figure 1.

Patients who present with blepharitis will usually complain of symptoms that include burning, watery eyes, foreign-body sensation, crusting of the lids, redness on the eyelids and ocular surface, light sensitivity, pain, and poor visual acuity.

Ocular surface disease can be linked to several factors including those that are environmental, genetic, and psychological. Topical medications can also exacerbate ocular surface disease via the preservatives that are used, which may be toxic to a compromised surface. The most commonly used preservative in topical eye drops, benzalkonium chloride (BAK), has been linked to a toxic response in some patients.[6-9] BAK alters corneal barrier function by breaking down the intercellular adhesion. More recent studies show that even low concentrations of BAK can cause apoptosis or programmed cell death in the corneal epithelium.[10]

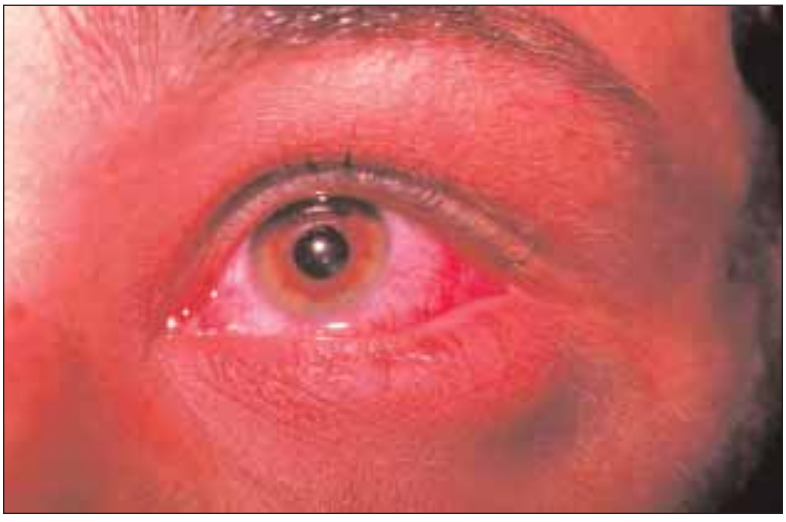


Figure 1. A patient presenting with dry eye disease will often have redness of the eyes, as is seen in this photo.

THE IMPACT OF OSD

The financial implications of dry eye disease are large. The added doctors visits and additional medications can affect patients significantly, especially considering that the population at risk, the elderly, are often on fixed incomes and have several other medications to pay for. Further, patients' productivity is affected by ocular surface disease.

> Topical medications can also exacerbate ocular surface disease via the preservatives that are used, which may be toxic to a compromised surface.

Quality of life is another significant area where there is an impact. A utility study performed by Schiffman et al[11] used a time-trade-off method to determine how patients viewed their dry eye disease in terms of quality of life compared with angina. The study found that patients with severe ocular surface disease were in the same range as those with severe angina. The impact of ocular surface disease on visual function is also significant. The more severe the corneal epithelial disease is from dry eye, the more impact there is on visual function. Sometimes, however, testing must be performed under special conditions to get a true reading of the impact on visual function. Patients often can read a well-illuminated eye chart just fine with their results indicating 20/20 vision, but visual function drops off when the patient is put in more challenging visual circumstances such as low or "washed out" lighting.

My colleagues and I performed a study that found that patients with dry eye had a significant decrease in low-contrast visual acuity.[12] In the study, the decrease in low-contrast visual acuity was shown to correlate directly with the severity of the patients' corneal epithelial disease and tear film stability.

Reversing contrast sensitivity loss from ocular surface disease requires a restoration of corneal epithelial health and the tear film's stability.

SUMMARY

I recommend that my patients with ocular surface disease avoid environmental circumstances that may exacerbate the condition, such as very dry air, direct positioning under an air conditioning vent such as in a car, and long periods of time viewing a computer monitor or video display terminal.

The recommendations that I have for ophthalmologists who are seeing patients with ocular surface disease is to be aware the ocular surface disease is a prevalent condition in the elderly population, and recent studies have shown it to be highly prevalent in patients with glaucoma. Ocular surface disease can have a significant impact on quality of life and also visual acuity outcomes, so it is important to address the condition immediately and consider alternatives to medications that exacerbate ocular surface disease when treating concomitant conditions such as glaucoma. ■

1. Schaumberg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. *Am J Ophthalmol.* 2003;136:318-326.
2. Miljanovic B, Dana MR, Sullivan DA, Schaumbert DA. Prevalence and risk factors for dry eye syndrome among older men in the United States. *Invest Ophthalmol Vis Sci.* 2007 (Abstract).
3. Ellwein LB, Urato CJ. Use of eye care and associated charges among the Medicare population: 1991-1998. *Arch Ophthalmol.* 2002;120:804-811.
4. McCarty CA, Bansal AK, Livingston PM, et al. The epidemiology of dry eye in Melbourne, Australia. *Ophthalmology.* 1998;105:1114-1119.
5. Lin PY, Tsai SY, Cheng CY, et al. Prevalence of dry eye among an elderly Chinese population in Taiwan: The Shipai Eye Study. *Ophthalmology.* 2003;110:1096-1101.
6. Debbasch C, Rat P, Warnet JM, De Saint JM, Baudouin C, Pisella PJ. Evaluation of the toxicity of benzalkonium chloride on the ocular surface. *Cutaneous and Ocular Toxicology.* 2000;19(2-3):105-115.
7. De Saint Jean M, Debbasch C, Brignole F, Rat P, Warnet JM, Baudouin C. Toxicity of preserved and unpreserved antiglaucoma topical drugs in an in vitro model of conjunctival cells. *Curr Eye Res.* 2000;20:85-94.
8. Cha SH, Lee JS, Oum BS, Kim CD. Corneal epithelial cellular dysfunction from benzalkonium chloride (BAC) in vitro. *Clin Exp Ophthalmol.* 2004;32:180-184.
9. Baudouin C, de Lunardo C. Short term comparative study of topical 2% cartelol with and without benzalkonium chloride in healthy volunteers. *Br J Ophthalmol.* 1998;82(1):39-42.
10. Pisella PJ, Debbasch C, Hamard P, Creuzot-Garcher C, Rat P, Brignole F, Baudouin C. Conjunctival proinflammatory and proapoproptic effects of latanoprost and preserved and unpreserved timolol: an ex vivo and in vitro study. *Invest Ophthalmol Vis Sci.* 2004;45(5):1360-1368.
11. Schiffman RM, Walt JG, Jacobsen G, Doyle JJ, Lebovics G, Sumner W. Utility assessment among patients with dry eye disease. *Ophthalmology.* 2003;110(7):1412-1419.
12. Chotikavanavich S, Li DQ, Paiva CS, Bian F, Farley WJ, Pflugfelder SC. Tear MMP-9 activity in dysfunctional tear syndrome. Presented at: the Association for Research in Vision and Ophthalmology Annual Meeting; April 27-May 1, 2008; Fort Lauderdale, FL.

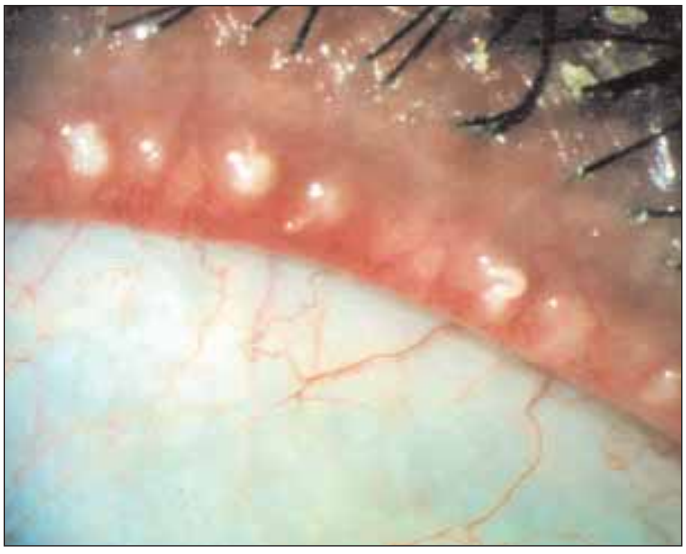
Testing for Ocular Surface Disease

A primer on which tests to perform and how to perform them.

BY MICHAEL B. RAIZMAN, MD, MPH

Ocular surface disease is prevalent among glaucoma patients in the United States—a study published in 2006 found that an average of approximately 65% of patients who have ocular surface disease have concomitant glaucoma.[1] The number of patients with glaucoma and blepharitis, the most common ocular surface disorder, may be even higher, although there are no studies showing this.

For general ophthalmologists and glaucoma specialist alike, it is important to recognize the signs and symptoms of ocular surface disease. For example, ocular surface reactions from glaucoma medications can commonly include a disruption of the epithelium and, less commonly, a follicular reaction to the formulation of glaucoma drops. It is important to note that allergic reactions are rare. The follicular reaction is a reaction to chronic exposure to the medication.



(Courtesy of Eric D. Donnenfeld, MD.)

Figure 1. Meibomian gland inspissations are visible along the upper lash line.

The standard evaluation of the ocular surface takes approximately 3 minutes—an evaluation that is easily incorporated into even the busiest of practices.

It is well documented that glaucoma drops, especially those containing benzalkonium chloride, can be irritating to the ocular surface.[2-4] Patients who already have a compromised ocular surface are more prone to develop significant ocular surface disease with many of the glaucoma drops.

INITIAL EVALUATION FOR OSD

I test every patient who is on glaucoma drops or who is about to start glaucoma drops by first evaluating the ocular surface. The standard evaluation of the ocular surface takes approximately 3 minutes—an evaluation that is easily incorporated into even the busiest practices.

The first, but often overlooked, test in evaluating patients for ocular surface disease is visual acuity. One of the first symptoms that is apparent with ocular surface disease is decreased vision—likewise, visual acuity is one of the first measures that improves upon treating the ocular surface.

After testing visual acuity, I like to look at the ocular surface in a stepwise fashion.

First, I examine the lid margin at the slit lamp to look for abnormal blood vessels on the margin, which would indicate blepharitis or irritation.

I will then look for crusting on the lashes or scaling or inflammation of the skin. Crusting is

(Courtesy of Eric D. Donnenfeld, MD.)

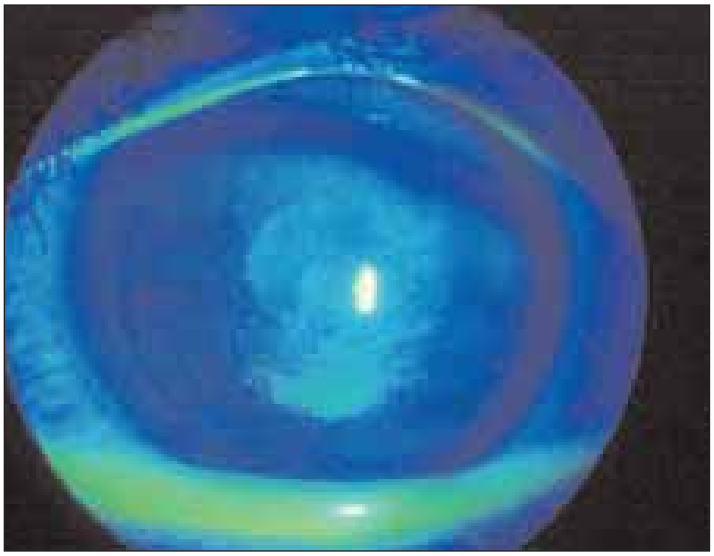


Figure 2. Fluorescein staining of the cornea reveals dry eye disease.

most commonly seen with the most common form of blepharitis, meibomian gland dysfunction. Flaking of the skin, which is less common, suggests seborrheic blepharitis.

I look at the meibomian gland orifices (Figure 1) to assess whether they are patent or constricted. I press gently on the lids to express a bit of oil from the glands to assess the oil's thickness and to see if there is obstruction of the gland. Next, I look at the conjunctiva for hyperemia and follicles.

TEAR BREAKUP TIME ASSESSMENT

I evaluate the tear film by looking for debris and assessing the volume, which is best accomplished by looking at the meniscus on the lower lid. My next step in evaluating for ocular surface disease is assessment of the tear breakup time. This, I believe, is a critical assessment of the tear film function. I instill a drop of fluorescein (Figure 2) and have the patients blink and then keep their eyes open without blinking. At the slit lamp, I measure the time it takes for the fluorescein dye to first disperse on the corneal surface. A normal tear breakup time is approximately 10 seconds or greater.

OCULAR SURFACE EVALUATION

Although fluorescein dye can be used to assess the ocular surface, I prefer lissamine green or rose bengal because they are more sensitive. Fluorescein tends to stain only significant disruptions of the epithelial surface, indicating more advanced disease. More subtle cases of OSD on the conjunctiva can be detected by observing lissamine green or rose bengal staining on the conjunctiva. I prefer lissamine green because rose bengal can be uncomfortable for patients. Additionally, rose bengal leaves the ocular surface quite red, usually until after patients leave the office.

In some cases, I will perform a Schirmer's test with anesthesia—I do not test without anesthesia because it is uncomfortable for the patient. A Schirmer's test is not required for all patients with glaucoma. I tend to reserve this test for patients who are being evaluated specifically for ocular surface disease.

SUMMARY

The tests that I have outlined—visual acuity, lid margin and meibomian gland assessment, examination of the conjunctiva, tear film evaluation, tear breakup time, and ocular surface staining—are worth using for every patient in whom treatment with glaucoma drops is being considered or those patients who are being tested for ocular surface disease caused or exacerbated by their topical glaucoma therapy. ■

1. Tsai JH, Derby E, Holland EJ, Khatana AK. Incidence and prevalence of glaucoma in severe ocular surface disease. *Cornea.* 2006;25:530-532.
2. Baudouin C, de Lunardo C. Short term comparative study of topical 2% cartelol with and without benzalkonium chloride in healthy volunteers. *Br J Ophthalmol.* 1998;82(1):39-42.
3. De Saint Jean M, Debbasch C, Brignole F, Rat P, Warnet JM, Baudouin C. Toxicity of preserved and unpreserved antiglaucoma topical drugs in an in vitro model of conjunctival cells. *Curr Eye Res.* 2000;20:85-94.
4. Cha SH, Lee JS, Oum BS, Kim CD. Corneal epithelial cellular dysfunction from benzalkonium chloride (BAC) in vitro. *Clin Exp Ophthalmol.* 2004;32:180-184.

The Evolution of Topical Therapy for Glaucoma

By understanding toxicity, we can improve patients' response to IOP-lowering medications as well as their compliance with therapy.

BY RONALD L. GROSS, MD, MPH

Since the introduction of nonselective beta-blockers to the glaucoma treatment armamentarium in 1978, we have been in a period of great change in the medical therapy for glaucoma. The developments that have occurred have resulted in a marked improvement not only in our ability to lower IOP and treat glaucoma but also in being able to recognize the systemic side effects of our treatments. Additionally, better formulations of topical medications have allowed us to minimize the impact of medical therapy on the ocular surface. The underlying thread is we can now effectively treat glaucoma while minimizing the impact on our patients and their quality of life.

TOPICAL BETA-BLOCKERS

At the time of the introduction of timolol, the general perception was that topical drops would not result in the type of systemic side effects that had been described with the use of oral beta-blockers. It was swiftly noted, however, that side effects similar to what is seen with oral beta-blockers can occur in select patients.[1] Some of the side effects of topical beta-blockers include an exacerbation of reactive airway disease (similar to that which occurs with asthma), a decrease in heart rate, bradycardia, an exacerbation of congestive heart failure, and an increased incidence of depression. Other side effects of topical beta-blockers have been more recently identified. For example, this class of medication may mask the symptoms of hypoglycemia, so one must be careful in treating insulin-dependent diabetics.[2] Additionally, many allergists will not skin test or desensitize patients who are on topical beta-blocker therapy, because the beta-blockers may block the ability to resuscitate a patient in a case of anaphylaxis.[3-5]

There is also evidence that oral and topical beta-blockers can have an effect on plasma lipids.[6] Although oral beta-blockers have been shown to be protective against cardiovascular disease in many cases, topical beta-blockers have never been evaluated for this effect. It has been suggested, however, that in patients taking statins or similar treatments to address their plasma lipid levels, the use of topical agents may result in a change in the measured levels of plasma lipids.[6]

In regard to topical beta-blocker therapy and adherence, most systemic side effects will not significantly affect compliance, as they tend to be manifested as direct impact on a patient's health. Beta-blockers are generally well tolerated in regard to ocular side effects.

The introduction of selective beta-blockers, specifically the beta-1 selective betaxolol, allowed for an even lower incidence of side effects from this class of medica-

tion. Although the potential side effects still exist with selective beta-blockers, these are generally less severe and frequent.

> We can now effectively treat glaucoma while minimizing the impact on our patients and their quality of life.

ALPHA-2 AGONISTS

Alpha-2 agonists represent a newer class of glaucoma medication, introduced with apraclonidine (Iopidine; Alcon Laboratories, Fort Worth, TX) then followed by brimonidine (Alphagan; Allergan, Inc., Irvine, CA) in the late 1990s. With brimonidine, concerns still remain as to its systemic side-effect profile. For example, brimonidine is contraindicated for small children because it can cross the blood/brain barrier and result in somnolence and other central nervous system effects.[7,8] There are also some concerns regarding ocular side effects. A relatively high incidence of allergy has been reported, as compared with other available agents.[9] The allergic side effects have the potential to result in nonadherence to therapy.

To answer the allergic concerns, the manufacturer introduced a new formulation, brimonidine Purite (Alphagan P, Allergan) which is benzalkonium chloride (BAK) free. The incidence of allergy to brimonidine purite still exists, however, albeit less in frequency.[10] Other concerns regarding brimonidine include efficacy: Brimonidine is very efficacious at peak but somewhat less so at trough.[11]

TOPICAL CARBONIC ANHYDRASE INHIBITORS AND COMBINATION THERAPIES

The topical carbonic anhydrase inhibitors (CAIs) were developed to address the profound systemic side effects that were found with the oral CAIs. Although most systemic toxicity has been eliminated with the topical formulations, there are some local ocular side effects such as burning and stinging. These are particularly common with dorzolamide (Trusopt; Merck & Co. Inc., Whitehouse Station, NJ). This is improved with the suspension of brinzolomide (Azopt; Alcon Laboratories, Inc.), but all CAIs carry the side effect of taste alteration, most notable with carbonated beverages.[12] In regard to patient compliance, one can assume that the effects of burning, stinging, and taste alteration may play a role in a patient's adherence to therapy.

Although there is greater efficacy with the fixed combinations,[13,14] such as timolol and dorzolamide (Cosopt, Merck & Co., Inc.) and the more recently FDA-approved

TOPICAL GLAUCOMA MEDICATIONS: SYSTEMIC AND OCULAR SIDE EFFECTS*

Class	Systemic Side Effects	Ocular Side Effects
Nonselective beta-blockers	Decreased heart rate, bradycardia, arrhythmias, exacerbation of heart failure, masking of hypoglycemic symptoms, depression	Burning, redness, decreased ocular blood flow, decreased corneal sensation
Alpha-2 agonists	Hypotension, respiratory depression (in infants), central nervous system depression (in infants), sedation, fatigue	Redness, itching, pupillary dilation, lid retraction
Carbonic anhydrase inhibitors	Allergy, bitter taste, low blood counts	Stinging, irritation, red eyes
Prostaglandin analogs	No significant systemic side effects	Hyperemia, changes in periocular skin pigmentation, changes in iris color, eyelash growth

* Table information adapted from Kwon YH, Fingert JH, Greenlee EC. *A Patient's Guide to Glaucoma.* Coralville, IA: MedRounds Publications, Inc; 2006.

brimonidine and timolol combination (Combigan, Allergan, Inc.), it is important to note that along with the combined efficacy comes the potential for combined side-effect profiles.

PROSTAGLANDIN ANALOGS

Prostaglandin analogs have rapidly become the preferred treatment for the medical therapy of glaucoma. Prostaglandin analogs have unequaled efficacy in lowering IOP.[15] Additionally, once daily dosing has proved effective; in fact, prostaglandin analogs are less effective when dosed twice daily.[16] Finally, there are few if any systemic safety concerns.

There are, however, local ophthalmic topical concerns, primarily involving conjunctival injection; this is most likely related to the medication itself.[17] This side effect is seen most frequently with bimatoprost (Lumigan; Allergan, Inc.), least frequently with latanoprost (Xalatan; Pfizer, Inc., New York), with travoprost (Travatan; Alcon Laboratories, Inc.) being in between the two aforementioned medications.

Another ocular side effect is the darkened pigmentation that is seen on the skin around the eyes as well as eyelash growth and changes in iris color. These three side effects are most common with bimatoprost, but they have been noted with all three PGAs.[18-20] Both the skin pigmentation and the eyelash growth are reversible. Change in iris color is not and has been shown to be a permanent side effect.

It appears that change in iris color is related to an increased number of melanosomes within the melanosites in the iris stroma. These cells are competent, which means they do not release their pigment into the surrounding tissues; this is the reason the change is permanent. Clinically, it is difficult to detect brown eyes' becoming browner, but it can be easily noted in eyes with grey or green irides. At this point, there is no evidence to suggest that this is anything other than a cosmetic effect.

The initial formulations of latanoprost, bimatoprost, and travoprost all included BAK as a preservative. Prior to the introduction of PGAs, there was evidence that eliminating BAK as a preservative would result in a lower incidence of toxicity to the ocular surface.[21]

As stated earlier, the elimination of BAK as a preservative was accomplished with beta-blockers and the alpha agonist class with preservative-free timolol and with the brimonidine with Purite formulation, respectively. Most recently, BAK-free travoprost was introduced into the market. BAK-free travoprost (Travatan Z; Alcon Laboratories, Inc.) uses an alternative preservation system called Sofzia, which combines boric acid, propylene glycol, sorbitol, and zinc chloride. Thus, we now have an alternative to allow us to maintain the safety and efficacy of the PGAs and improve their tolerability to the ocular surface.

Recently, published data showed that as many as 48% of patients in the typical glaucoma-only practice have some evidence of ocular surface disease.[22] This figure is much higher than what has been typically quoted, which is approximately 15% of the elderly population.[23] The question that these figures might raise is whether the higher rate of ocular surface disease is due to the disease of glaucoma, which is unlikely, or whether the therapy that we are choosing for our patients is resulting in higher rates of ocular surface disease.

Patients with glaucoma are often on chronic topical therapy for the disease—for many years in most cases—and they may be receiving different drops in large amounts for the treatment of their glaucoma. The vast majority of our topical medications contain BAK, and there is solid information in the literature showing that higher concentrations, as well as a long exposure to BAK increases the toxicity that occurs.[24,25]

OCULAR SURFACE DISEASE SYMPTOMS AND SIGNS

The typical symptoms of ocular surface disease include tearing, burning, and difficulty reading or difficulty seeing the computer after a short time. It is well known that BAK can initiate or exacerbate ocular surface disease. Patients who are being treated for glaucoma are at particularly high risk because of the prevalence of ocular surface disease in elderly patients; in addition, they are at higher risk for ocular surface disease, because the majority of glaucoma medications contain some level of BAK.

The data that are available on the effects of BAK to the ocular surface include a study by Christophe Baudouin, MD, published in 1998.[26] In this study, he compared carteolol, a nonselective beta-blocker, with and without BAK, in regard to the effect on tear break-up time. He found that use of carteolol with BAK was associated with a significantly shorter tear breakup time—approximately 4.3 seconds less than baseline—indicating that the tear film in those eyes that received BAK-containing carteolol was not remaining intact or providing its protective function as well. The use of carteolol that did not contain BAK resulted in a minimal reduction of the tear breakup time compared to baseline of just over 1 second. These data suggest that the mere presence of BAK has a significant effect on the ocular surface.

In general, patients who suffer from substantial ocular surface disease are often unhappy. We must realize

that, at times, disconnects between signs and symptoms may exist. For example, patients may complain bitterly about typical signs of ocular surface disease, but we find very little in terms of physical findings. Conversely, some patients have enormous physical signs but have little in the way of symptoms and complaints. The majority of patients probably do have some sort of combination of both, but the signs and symptoms do not necessarily correlate. For patients who are symptomatic with ocular surface disease, glaucoma medications can have a significant effect on their quality of life. For those patients with milder ocular surface disease, the removal of BAK from their topical drops is a long-term investment to minimize the potential for worsening ocular surface disease.

It is important to consider, however, that not all patients have ocular surface disease or will be affected by the BAK content in glaucoma medications. The goal of glaucoma therapy, of course, is to lower IOP and prevent further vision loss. Therefore, it is important to carefully select the best medication for the individual patient. For example, hyperemia may be a significant side effect of the prostaglandin analogs,[18-20] so some patients may elect to be treated with another class of glaucoma medication or with a prostanglandin analog that has a lower incidence of hyperemia such as latanoprost.[27]

SUMMARY

In summary, my recommendations for choosing a glaucoma medication while considering toxicity and the effect of the agent on the ocular surface follows. First, it is important to adequately lower the IOP and prostaglandin analogs give us the best chance with monotherapy. Second, consider patients' safety, both in terms of potential systemic side effects as well as ocular side effects affecting the ocular surface. Identify the patient with OSD and pay attention to the condition of the ocular surface and how the selected medication affects it. Third, consider the tolerability of the medication, primarily hyperemia—it is not dangerous, but is often troublesome to the patient. Finally, we now have the ability to effectively treat glaucoma by lowering IOP while having a minimal effect on the ocular surface with BAK-free glaucoma medications in several different classes of IOP-lowering therapy. Therefore, we can minimize a patient's risk of exacerbating OSD or developing it in the future. ■

1. Taniguchi T, Kitazawa Y. The potential systemic effect of topically applied beta-blockers in glaucoma therapy. *Curr Opin Ophthalmol.* 1997;8(2):55-58.
2. Kerr D, MacDonald IA, Heller SR, Tattersall RB. Beta-adrenergic blockade and hypoglycaemia. A randomised, double-blind, placebo controlled comparison of metoprolol CR, atenolol, and propranolol LA in normal subjects. *Br J Clin Pharmacol.* 1990;29:685-693.
3. Newman BR, Schultz LK. Epinephrine-resistant anaphylaxis in a patient taking propranolol hydrochloride. *Ann Allergy.* 1981;47:35-37.
4. Kaplan AP, Anderson JA, Valentine MD, et al. Beta-adrenergic blockers, immunotherapy, and skin testing. *J Allergy Clin Immunol.* 1989;84(1):129-130.
5. Jacobs RL, Rake GW, Fournier DC, et al. Potentiated anaphylaxis in patients with drug-induced beta-adrenergic blockade. *J Allergy Clin Immunol.* 1981;68(2):125-127.
6. Mitchell P, Wang JJ, Cumming RG, House P, England JD. Long-term topical timolol and blood lipids: the Blue Mountains Eye Study. *J Glaucoma.* 2000;9(2):174-178.
7. Mungan N. Hypotension and bradycardia in infants after the use of topical brimonidine and beta-blockers. *J AAPOS.* 2003;7(1):69-70.
8. Enyedi LB, Freedman SF. Safety and efficacy of brimonidine in children with glaucoma. *J AAPOS.* 2001;5(5):281-284.
9. Manni G, Centofanti M, Sacchetti M, et al. Demographic and clinical factors associated with development of brimonidine tartrate 0.2%-induced ocular allergy. *J Glaucoma.* 2004;13(2):163-167.
10. Katz LJ. Twelve-month evaluation of brimonidine-purite versus brimonidine in patients with glaucoma or ocular hypertension. *J Glaucoma.* 2002;11(2):119-126.
11. van der Valk R, Webers C, Schouten J, Zeegers M, Hendrikse F, Prins M. Intraocular pressure–lowering effects of all commonly used glaucoma drugs. A meta-analysis of randomized cinical trials. *Ophthalmology.* 2005;112:1177-1185.
12. Mincione F, Scozzafava A, Supuran CT. The development of topically acting carbonic anhydrase inhibitors as antiglaucoma agents. *Curr Pharm Des.* 2008;14(7):649-654.
13. Rolle T, Tofani F, Brogliatti B, Grignolo FM. The effects of dorzolamide 2% and dorzolamide/timolol fixed combination on retinal and optic nerve head blood flow in primary open-angle glaucoma patients. Eye. 2008 Jan 18. [Epub ahead of print]
14. Brandt JD, Cantor LB, Katz LJ, Batoosingh AL, Chou C, Bossowska I; Ganfort Investigators Group II. Bimatoprost/timolol fixed combination: a 3-month double-masked, randomized parallel comparison to its individual components in patients with glaucoma or ocular hypertension. *J Glaucoma.* 2008;17(3):211-216.
15. Camras CB, Alm A, Watson P, Stjernschantz J. Latanoprost, a prostaglandin analog, for glaucoma therapy. Efficacy and safety after 1 year of treatment in 198 patients. Latanoprost Study Groups. *Ophthalmology.* 1996;103(11):1916-1924.
16. Stewart WC, Day DG, Stewart JA, Schuhr J, Latham KE. The efficacy and safety of latanoprost 0.005% once daily versus brimonidine 0.2% twice daily in open-angle glaucoma or ocular hypertension. *Am J Ophthalmol.* 2001;131(5):631-635.
17. Alm A, Stjernschantz J; Scandinavian Latanoprost Study Group. Effects on intraocular pressure and side effects of 0.005% latanoprost applied once daily, evening or morning. A comparison with timolol. *Ophthalmology.* 1995;102:1743-1752.
18. Xalatan [package insert]. New York, NY: Pfizer, Inc.
19. Lumigan [package insert]. Irvine, CA: Allergan, Inc.
20. Travatan [package insert]. Fort Worth, TX: Alcon Laboratories, Inc.
21. Debbasch C, Rat P, Warnet JM, De Saint JM, Baudouin C, Pisella PJ. Evaluation of the toxicity of benzalkonium chloride on the ocular surface. *Cutaneous and Ocular Toxicology.* 2000;19(2-3):105–115.
22. Fechtner RD, Budenz DL, Godfrey DG, Steward WC, Jasek MC. Prevalence of ocular surface disease symptoms in glaucoma patients on IOP-lowering medications. Poster presented at: The American Glaucoma Society 18th Annual Meeting; March 8, 2008; Washington, DC.
23. Schein OD, Munoz B, Tielsch JM, Bandeen-Roche K, West S. Prevalence of dry eye among the elderly. *Am J Ophthalmol.* 1997;124:723–728.
24. De Saint Jean M, Debbasch C, Brignole F, Rat P, Warnet JM, Baudouin C. Toxicity of preserved and unpreserved antiglaucoma topical drugs in an in vitro model of conjunctival cells. *Curr Eye Res.* 2000;20:85–94.
25. Cha SH, Lee JS, Oum BS, Kim CD. Corneal epithelial cellular dysfunction from benzalkonium chloride (BAC) in vitro. *Clin Exp Ophthalmol.* 2004;32:180-184.
26. Baudouin C, de Lunardo C. Short term comparative study of topical 2% carteolol with and without benzalkonium chloride in healthy volunteers. *Br J Ophthalmol.* 1998;82(1):39–42.
27. Noecker RS, Dirks MS, Choplin NT, et al. A six-month randomized clinical trial comparing the intraocular pressure-lowering efficacy of bimatoprost and latanoprost in patients with ocular hypertension or glaucoma. *Am J Ophthalmol.* 2003;135:55–63.

Management of Ocular Surface Disease in Patients With Glaucoma

Targeting treatment to the underlying condition can help clear OSD and get patients back on IOP-lowering therapy.

BY DONALD L. BUDENZ, MD, MPH

Patients with glaucoma are often asymptomatic in direct relation to their glaucoma. However, many have complaints from ocular surface disease (OSD), which include foreign body sensation, pain, and generalized discomfort. Some patients experience dry eyes, tearing, and itching; any of these complaints can be due to OSD or blepharitis or, in some cases, allergic conjunctivitis. Once a patient presents with symptoms such as these, a differential diagnosis is necessary, along with an investigation into the causative factors.

A new study of 630 patients from 10 sites that was presented at the annual meeting of the American Glaucoma Society earlier this year found that the prevalence of patients who are on topical medications for glaucoma and who have OSD was 48.4%.[1] The data collected in this clinic-based survey that spanned a variety of geographic regions in the United States are interesting, in light of the fact that a population-based survey of older patients in the United States found a 15% prevalence of OSD.

In my own practice at Bascom Palmer in South Florida, I would estimate the prevalence of OSD in patients with glaucoma to be higher than what was found in the studyby Fechtner et al. Although it is quite humid in South Florida throughout the year, people tend to stay inside where air conditioners are running, causing artificially dry environments.

This article will discuss my clinical experience in diagnosing OSD and managing my patients to the point where I can resume effective glaucoma therapy.

ALLERGY AND TOXICITY TO BENZALKONIUM CHLORIDE: BACKGROUND

Allergy. Allergic reactions and toxicity to benzalkonium chloride (BAK) have been well documented with various topical preparations for the eye.[2-5] In my experience with patients with glaucoma, when there is an allergy to BAK, it is immediately apparent. No matter what class of medication the patient is on, he experiences immediate hypersensitivity—itching and periorbital redness. The prevalence of BAK allergy is not known, but I would estimate that it is probably less than 5% and possibly as low as 1%.

A BAK allergy can usually only be discerned by taking the patient off all of his glaucoma medications and then running a trial by reintroducing them one drop at a time. Frequently, these patients will be taking multiple medications, and it becomes hard to tell whether they are allergic to the drug itself or its preservative. In these cases, it becomes necessary to dig a little deeper to determine what is causing the intolerance.

A higher concentration of BAK instilled more frequently has been shown to result in higher levels of toxicity.

Toxicity. Some patients, although not necessarily allergic to BAK, are sensitive to the preservative. This is a n effect of toxicity, which is related to both dose and duration. A higher concentration of BAK instilled more frequently has been shown to result in higher levels of toxicity.[6] Further, the longer a patient is taking a medication with BAK, the more toxicity will occur.

Symptoms of toxicity include foreign body sensation, tearing, and discomfort. Signs include redness of the eyes and punctate epithelial erosions, which tend to be diffuse rather than localized inferiorly, as in traditional dry eye syndrome. Patients are less likely to experience itching, which is more common, as stated before, with BAK allergy, seasonal allergies, and blepharitis. Toxicity is usually slower to manifest, and does so more subtly, than an allergic reaction.

CHOICES FOR BAK-FREE THERAPY

The topic of preservatives in glaucoma medications can be somewhat confusing because, although there are some medications that have been developed with alternative preservative systems, there is only one truly preservative-free glaucoma medication: preservative-free timolol (Timoptic in Ocudose 0.25%; Merck & Co., Inc., Whitehouse Station, NJ). Preservative-free timolol comes in a sterile, unit-dose container, which makes this alternative very expensive.

There are, however, a number of medications that contain alternative preservatives to BAK:

Beta-blockers. From the beta-blocker class, there is, as mentioned, preservative-free timolol, and also timolol preserved with benzododecinium bromide 0.012% (Timoptic XE; Merck & Co., Inc.). It is important to note that the brand Timoptic XE is prescribed. The generic timolol contains BAK.

Carbonic anhydrase inhibitors. Although there is no topical drug from the carbonic anhydrase inhibitor (CAI) class without BAK, one must not forget oral CAIs as an alternative. Oral CAIs, such as acetazolamide and methazolamide, are well tolerated by many of our patients and represent a viable alternative to BAK-containing drops.

Alpha-2 agonists. In the alpha agonist group, brimonidine with Purite (Alphagan P; Allergan, Inc., Irvine, CA) has been available and in use for several years. One should note, however, that generic brimonidine contains BAK.

Prostaglandin analogs. Most recently, travoprost with Sofzia (Travatan Z; Alcon Laboratories, Inc., Fort Worth, TX), is available for our patients who respond most favorably to a prostaglandin analogue yet have problems with BAK.

With these five alternatives to BAK-containing glaucoma drops, one can construct a regimen that is well suited to glaucoma patients with OSD.

SCENARIOS AND TREATMENT

There are a number of different scenarios for a patient presenting with OSD.

New patient needing initiation of glaucoma therapy, has symptoms of dry eye. A new patient comes in needing glaucoma therapy to lower his IOP but has complaints that may be related to OSD. I would most likely treat the conditions simultaneously with a BAK-free glaucoma drop as well as BAK-free artificial tears.

Patient on chronic glaucoma therapy, presents with OSD symptoms. Another type of patient I may see is someone who has been on chronic glaucoma therapy and, during monitoring, has developed symptoms of OSD. For this patient, I would need to do a small amount of investigative work. Does the patient have dry eye or blepharitis? Even within the classification of dry eye, there are multiple causes that warrant investigation. Is the issue tear deficiency, or are the tears not viscous enough? Fortunately, both of these situations would most likely be resolved by using BAK-free tears.

Blepharitis is managed in the traditional way, with a twice daily lid hygiene regimen of hot compresses and baby shampoo lid scrubs. Artificial tears four times daily can also help with symptoms of blepharitis.

Patient on multiple glaucoma medications, presents with severe OSD. Rarely, I will see a patient who has severe OSD and is either currently taking multiple glaucoma medications or has been on such a regimen in the past. These patients not only have symptoms but also signs of OSD (ie, periocular erythema, excoriation of the skin, red eyes). Upon my earlier encounters with one of

these patients, I did not know how to manage the case and would refer the patient to a cornea subspecialist.

The first therapeutic maneuver from a cornea specialist's standpoint is to immediately stop all of the patient's glaucoma drops. In the 1990s, all of the medications for glaucoma contained BAK, and cornea specialists were well aware of the deleterious effects of BAK to the ocular surface. Thus, the first step would be to stop the insult to the eye as soon as possible to clear up the OSD. I will then use BAK-free artificial tears to help clear the OSD. My cornea colleagues at Bascom Palmer Eye Institute have developed a list of the artificial tear preparations that contain BAK, so I can give this to my patients to ensure that when they pick up their drops, they know which formulations to avoid. During the OSD-clearing time, I am left with no IOP-lowering option other than to use oral CAIs or laser in the interim; OSD usually takes between 4 to 6 weeks to clear, after which I reintroduce topical glaucoma therapy with BAK-free or preservative-free drops one at a time.

RECOMMENDATIONS

My recommendations to physicians who see patients with glaucoma who present with OSD include the following.

Do not continually pour artificial tears on the eye when patients complain of OSD. As ophthalmologists, regardless of our subspecialty, we are all treating the whole eye.

Be a detective. If the problem is OSD, we should then minimize BAK in both the glaucoma drops and any artificial tear preparations that we prescribe.

Consider options outside of artificial tears. Alternatives include cyclosporine A (Restasis; Allergan, Inc.) or punctual plugs.

Consider a corneal consultation. It is acceptable to refer a patient to a cornea colleague when tears/and or other measures that you have undertaken do not work to resolve the issue of OSD.

Let the OSD exam stand alone. If you do decide to undertake the detective work yourself in differential diagnosis, consider scheduling a separate appointment for OSD evaluation. At that visit, I would encourage you not to measure IOP, because even topical anesthetics can interfere with your workup. Rather, focus on the OSD evaluation.

SUMMARY

Upon proper diagnosis, we can then target our therapy directly to the individual situation. Rather than adding artificial tears to an already complicated regimen for patient, we can have a clear plan to resolve the patient's OSD. Most importantly, the availability of BAK-free glaucoma drops in almost every class of medication, as well as BAK-free artificial tears, enables us to build an IOP-lowering regimen for our patients with OSD. ■

1. Fechtner RD, Budenz DL, Godfrey DG, Steward WC, Jasek MC. Prevalence of ocular surface disease symptoms in glaucoma patient on IOP-lowering medications. Poster presented at: the American Glaucoma Society 18th Annual Meeting; March 2008; Washington, DC.
2. Debbasch C, Rat P, Warnet JM, De Saint JM, Baudouin C, Pisella PJ. Evaluation of the toxicity of benzalkonium chloride on the ocular surface. *Cutaneous and Ocular Toxicology.* 2000;19(2-3):105-115.
3. De Saint Jean M, Debbasch C, Brignole F, Rat P, Warnet JM, Baudouin C. Toxicity of preserved and unpreserved antiglaucoma topical drugs in an in vitro model of conjunctival cells. *Curr Eye Res.* 2000;20:85-94.
4. Cha SH, Lee JS, Oum BS, Kim CD. Corneal epithelial cellular dysfunction from benzalkonium chloride (BAC) in vitro. *Clin Exp Ophthalmol.* 2004;32:180-184.
5. Baudouin C, de Lunardo C. Short term comparative study of topical 2% carteolol with and without benzalkonium chloride in healthy volunteers. *Br J Ophthalmol.* 1998;82(1):39-42.
6. Yee RW. The effect of drop vehicle on the efficacy and side effects of topical glaucoma therapy: a review. *Curr Opini Ophthalmol.* 2007;18(2):134-139.

INSTRUCTIONS FOR CME CREDIT

1 *AMA PRA Category 1 Credit™* Expires July 2009

CME credit is available electronically via www.dulaneyfoundation.org.

To answer these questions online and receive real-time results, please visit **www.dulaneyfoundation.org** and click "Online Courses." If you are experiencing problems with the online test, please e-mail us at **support@dulaneyfoundation.org** and explain the details of any problems you encounter with the Web site. Alternatively, you can fax your exam to us at +1-610-771-4443. Indicate how you would like to receive your certificate below. Please type or print clearly or we will be unable to issue your certificate.

Name _____ ❑ MD participant ❑ non-MD participant

Phone (required) _____

I would like my certificate sent via ❑ fax _____

I would like my certificate sent via ❑ e-mail _____

CME QUESTIONS

1. What is the prevalence of dry eye in the United States?
a. 1 in 10 patients
b. 1.5 million men
c. 3 million women
d. 5 million men
e. both b and c

2. The most common symptom of ocular surface disease (OSD) is:
a. burning sensation
b. itching
c. foreign-body sensation
d. light sensitivity
e. all of the above

3. A quality-of-life study by Schiffman et al found that patients equated severe dry eye with:
a. chronic lung disease
b. severe angina
c. death
d. rheumatoid arthritis
e. none of the above

4. Standard testing for OSD includes the following:
a. visual acuity
b. lid margin
c. corneal staining with lissamine green
d. meibomian gland expression
e. all of the above

5. Fluorescein dye is used to detect the most subtle OSD:
a. true
b. false

6. Abnormal blood vessels on the lid margin are an indication of:
a. ocular allergy
b. dry eye
c. blepharitis
d. none of the above

7. The systemic side effects of beta-blockers include:
a. decreased heart rate
b. masking of hypoglycemic symptoms
c. exacerbation of reactive airway disease
d. all of the above

8. Prostaglandin analogs are more effective when dosed twice daily versus once daily.
a. true
b. false

9. Recent data showed the prevalence of OSD among patients with glaucoma to be approximately:
a. 89%
b. 15%
c. 36%
d. 48%

10. Dr. Budenz's recommendations for treating a patient who is on glaucoma drops and presents with symptoms of OSD are:
a. keep the patient on topical glaucoma therapy and treat the OSD with artificial tears
b. stop all glaucoma medications and treat the OSD with any type of artificial tear
c. stop all glaucoma medications and treat the OSD with BAK-free artificial tears
d. switch the patient to a BAK-free glaucoma medication

Sponsored by The Dulaney Foundation

Supported by an unrestricted educational grant from Alcon Laboratories, Inc.

Glaucoma TODAY