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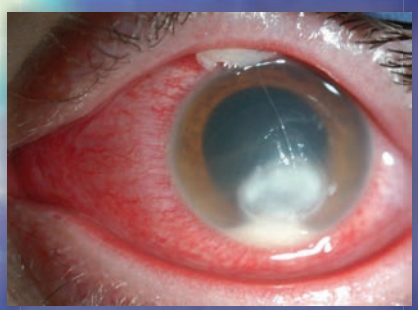
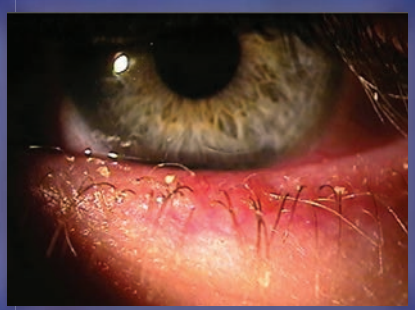
2015 Clinical Guide to OPHTHALMIC DRUGS


BY RON MELTON, OD, AND
RANDALL THOMAS, OD, MPH

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Why Drug Costs are Skyrocketing

By Agustin Gonzalez, OD

For the last few years, patients have complained of price increases and even shortages of some medications, which has frustrated many clinicians. Unfortunately, price increases and inflation are a common problem affecting everyday life, and medications are no exception.[1,2] But more recently, shortages of doxycycline and the increased cost of generic prednisolone formulations have perhaps hit eye care harder than any other medical group.[3]

drug shortage list in 2012.[4,5] A tablet that cost as little as 6 cents early in 2012 was being retailed at $4+ by November 2013—when it was even available.[5]

How did this increase happen?

Reasons for the Rise

Analysts and politicians have cited many factors—including greed, FDA regulations and the Affordable Care Act—but industry experts attribute price increases for these medications to consolidation, shortages in ingredients and decreased manufacturing.[6,7]

a price decrease while one-third noted price increases. Only 6% of the medications doubled in cost, and only about 12 medications and dosages had increases in cost by 20 times or more.[8]

The costly 12 were represented as various forms and/or dosages of just four molecules. The leader in cost was doxycycline, followed by the asthma medication albuterol. In the ophthalmic arena, doxycycline was not alone; a tube of erythromycin ointment that retailed for $4 in 2012 cost more than $25 by late 2013.

Drug Wholesale Price Increases Over Four Years

Medication	4Q 2010	1Q 2015	% increase
Cyclogyl 15ml (cyclopentolate 0.5%, Alcon)	$59.95	$94.50	58%
doxycycline 100mg 50 caps (generic)	$12.50	$44.50	256%
erythromycin ung 3.5gm (generic)	$10.95	$18.25	67%
pilocarpine 1% 15ml (generic)	$16.95	$91.00	437%
prednisolone acetate 1% 5ml (generic)	$8.75	$59.50	580%
proparacaine 15ml (generic)	$5.95	$29.50	396%
tobramycin + dexamethasone 2.5ml (generic)	$32.95	$49.50	50%
tropicamide 1% 15ml (generic)	$7.95	$8.50	7%

Often used in the treatment and management of meibomian gland disorders, doxycycline in particular has become the poster child for drug shortages and price increases. In a recent U.S. Senate hearing, it became the center of discussion on price increases and it led the FDA's

A 2014 report by Pembroke Consulting, which analyzed drug price data from the Centers for Medicare and Medicaid Services for the period of November 2012 to November 2013, can shed some light. Of the 16,000 generic drugs analyzed, roughly two-thirds saw

Prednisolone suspension also increased. Specifically, generic prednisolone could be purchased for $6 per bottle in 2012, but not for less than $90 per bottle in some markets by 2014.[8]

In the case of doxycycline, some

(continued on page 51)

Dear Optometric Colleagues:

Welcome to the *2015 Clinical Guide to Ophthalmic Drugs*.

For perspective, our math informs us that we have dilated well over 200,000 patients. (By the way, we have never experienced pharmacologic angle-closure.) We estimate that we have medically treated well over 50,000 patients, mostly involving steroid and glaucoma medicines. We enjoy highly diverse clinical practices, and continue to thoroughly enjoy caring for our patients. We contend that there is no such thing as a "medical model"—rather we should have an attitude and commitment to simply care for any condition with which our patients present. Consultation with surgeons should be predominantly for surgical care. It is that simple. For comparison, patients with heart conditions generally see nonsurgical cardiologists first, and are referred to cardiothoracic surgeons when surgical intervention is anticipated. From a public health and societal burden perspective, eye care should follow a parallel track. It is our hope that the knowledge and clinical insights we share in this *Drug Guide* will move our profession of optometry into this more comprehensive patient management approach.

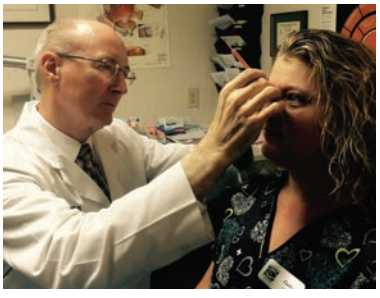
We are consultants to the sponsor of this publication and we do discuss their products; however, we have a much greater duty to you, our colleagues. Therefore we pledge to you that the information you find herein is accurate and scientifically sound. Perhaps more importantly, we season our nearly 70 combined years of intensive patient care with what we learn through consistent perusal of the peer-reviewed professional literature.

Our hope is that by reading this content, you can better serve your patients and our profession.

Sincerely,

Randall Thomas, OD, MPH

Ron Melton, OD



Disclosure: Drs. Melton and Thomas are consultants to, but have no financial interests in, the following companies: Bausch + Lomb/Valeant and Icare.

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A Peer-Reviewed Supplement

Note: The authors present unapproved and "off label" uses of specific drugs in this guide.

Allergy Management

Pollen may come and ragweed may go, but ocular allergies seem to be a problem year round.

Take note that one in four of your patients will have seasonal or perennial allergic conjunctivitis.[1]

Regardless of the type of allergy, we ask the patient the same basic question: "Is burning or is itching your main symptom?" Most patients can give a clear answer to this fundamental question.

For the few patients who feel the symptoms of burning and itching are about equal, or can't decide which symptom is most bothersome, treatment with a topical corticosteroid usually quells both complaints.

If itching is the predominant symptom, then medication selection takes one of two paths:

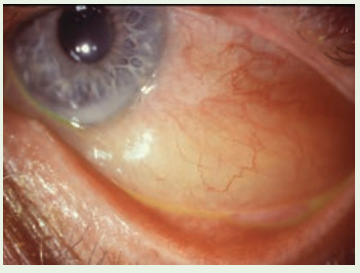
Symptoms Only

If there are minimal associated signs of allergy such as chemosis, conjunctival injection and/or eyelid edema, then an antihistamine/mast cell stabilizer is an excellent clinical approach. Within this class, there are six drugs from which to choose:

- Alcaftadine (Lastacaft, Allergan)
- Azelastine (Optivar, Meda Pharmaceuticals; and generic)
- Bepotastine (Bepreve, Bausch + Lomb)
- Epinastine (Elestat, Allergan)
- Ketotifen (Zaditor, Alcon; and generic. This drop is OTC.)
- Olopatadine (Pazeo, Pataday, Patanol, Alcon)

Of these, all are rated pregnancy category C except for

'Is it Burning or is it Itching?'



- **Itching.** If itching is primarily expressed, determine if it is an isolated symptom or if it is associated with concurrent inflammatory signs, and then treat accordingly. Remember:

Symptoms only—use an antihistamine/mast cell stabilizer.

Symptoms with signs—use a steroid such as Lotemax, Alrex or FML.

- **Burning**. If itching is not the primary symptom, then be sure to consider dry eye as the foundational condition and treat accordingly. If the main symptom is burning, then a thorough dry eye evaluation is in order.

There is no rule in the rulebook that says you can't have two problems at the same time. So, because dry eye is very prevalent, always identify and manage this disease whether or not it is concomitant with allergic eye disease.

A New Rendition of Olopatadine

Olopatadine has been the top prescribed topical antihistamine/mast-cell stabilizer drug for a long time. Recall that olopatadine was first approved for allergic conjunctivitis as 0.1% Patanol (Alcon) to be dosed twice a day, and then as 0.2% Pataday (Alcon) dosed once a day.

Now the third wave comes to market as a 0.7% concentration called Pazeo, also used once daily. We expect Pazeo will compete in the "once daily" market with Lastacaft (alcaftadine 0.25%, Allergan).

According to clinical studies using the conjunctival allergen challenge, the effectiveness of Pazeo was relatively similar to Pataday and Patanol at the onset of action, but slightly more evident at 24 hours. The safety profile of Pazeo was also comparable to Pataday and Patanol.

Lastacaft, which is pregnancy category B. Notwithstanding other fine differences, all of the antihistamine subtype 1 receptor blockers nicely suppress ocular itching. All are dosed initially BID (except Pazeo, Pataday and Lastacaft, which are dosed QD). After two weeks at BID, have the patient try to reduce the drop to once-daily "maintenance" therapy. In our experience, once symptomatic itching has been brought under control, it takes less pharmacological intervention to maintain control. Then again, many patients seem best served with enduring BID therapy.

Perhaps the best news for the consumer was the loss of patent protection for Zaditor. Since 2007, ketotifen has been available generically and OTC. In addition to Zaditor, there are several "brand name" OTC ketotifen preparations, such as Alaway (Bausch + Lomb) and Refresh Eye Itch Relief (Allergan). All come in 5ml bottles (except for Alaway and TheraTears Eye Itch Relief, each of which comes as a 10ml bottle.) Interestingly, our casual observations in a variety of pharmacies reveal that the cost of these 10ml bottles is very near (and occasionally cheaper) than the price of their 5ml competitors.

When a prescription medication is preferred, perhaps a 10ml bottle of Bepreve (using a standard co-pay) would be of greatest cost value to the patient.

Symptoms Plus Signs

The other side of the coin in allergy presentation is the patient who

Ocular Allergy Medicines

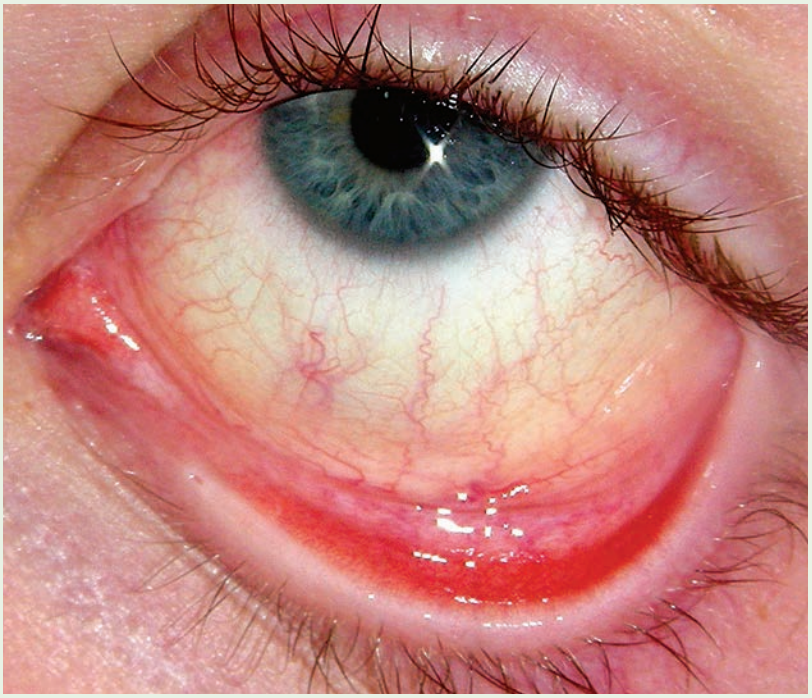
BRAND NAME	GENERIC NAME	MANUFACTURER	PEDIATRIC USE	BOTTLE SIZE(S)	DOSING
Acute Care Products					
Acular LS	ketorolac tromethamine 0.4%	Allergan	3 years	5ml, 10ml	QID
Alaway (OTC)	ketotifen fumarate 0.025%	Bausch + Lomb	3 years	10ml	BID
Alrex	loteprednol etabonate 0.2%	Bausch + Lomb	12 years	5ml, 10ml	QID
Bepreve	bepotastine besilate 1.5%	Bausch + Lomb	2 years	5ml, 10ml	BID
Claritin Eye (OTC)	ketotifen fumarate 0.025%	Schering-Plough	3 years	5ml	BID
Elestat	epinastine HCl 0.05%	Allergan	3 years	5ml	BID
Emadine	emedastine difumarate 0.05%	Alcon	3 years	5ml	QID
Lastacaft	alcaftadine 0.25%	Allergan	2 years	3ml	QD
Optivar	azelastine hydrochloride 0.05%	Meda	3 years	6ml	BID
Pataday	olopatadine hydrochloride 0.2%	Alcon	3 years	2.5ml	QD
Patanol	olopatadine hydrochloride 0.1%	Alcon	3 years	5ml	BID
Pazeo	olopatadine hydrochloride 0.7%	Alcon	2 years	2.5ml	QD
Refresh (OTC)	ketotifen fumarate 0.025%	Allergan	3 years	5ml	BID
Zaditor (OTC)	ketotifen fumarate 0.025%	Alcon	3 years	5ml	BID
Chronic Care Products					
Alamast	pemirolast potassium 0.1%	Santen	3 years	10ml	QID/BID
Alocril	nedocromil sodium 2%	Allergan	3 years	5ml	BID
Alomide	lodoxamide tromethamine 0.1%	Alcon	2 years	10ml	QID
Crolom	cromolyn sodium 4%	Bausch + Lomb	4 years	10ml	QID
Opticrom	cromolyn sodium 4%	Allergan	4 years	10ml	QID

Itchy Eyes Are Often Dry Eyes

Most patients with "itchy eyes" (consistent with allergic conjunctivitis) also have dry eyes and redness. Specifically, the odds of patients with "itchy eyes" who also have dry eyes are 2.11 times that of patients with non-itchy eyes. The odds of these patients also experiencing redness were 7.34 times that of patients with non-itchy eyes.

These results suggest that some symptomatic patients concomitantly have features of allergic conjunctivitis and dry eye syndrome.

Hom MM, Nguyen AL, Bielory L. Allergic conjunctivitis and dry eye syndrome. Ann Allergy Asthma Immunol. 2012 Mar;108(3):163-6.



Dosing of Topical Antihistamine

Which is better: a once-daily drop or a twice-daily drop? We've found that many of our allergy patients simply tend to dose their allergy drops as needed. So, for many patients (especially those with suboptimal tear function), a second drop in the afternoon provides therapeutic enhancement. This is particularly true if the patient has been working outdoors (mowing the grass, for instance). In these situations, a second drop tends to flush out allergens and further suppresses the downstream sequelae of histamine release.

On the other hand, one drop a day is the preferred approach for patients whose allergic symptoms are well controlled with once-daily instillation. In the end, as always, patient care must be individualized.

For patients with severe allergy expression, consider both an antihistamine/mast cell stabilizer twice daily and Alrex (loteprednol 0.2%, Bausch + Lomb) or Lotemax gel (loteprednol 0.5%, Bausch + Lomb) QID along with cold compresses.

After the condition has settled down, maintain the patient on the antihistamine/mast cell stabilizer once or twice daily as needed.

McCabe CF, McCabe SE. Comparative efficacy of bepotastine besilate 1.5% ophthalmic solution versus olopatadine hydrochloride 0.2% ophthalmic solution evaluated by patient preference. Clin Ophthalmol. 2012;6:1731-8.

presents with predominant itching plus one or more concurrent signs such as conjunctival redness, chemosis and/or eyelid edema. For this subset of patients, a topical corticosteroid such as Alrex (loteprednol 0.2%, Bausch + Lomb), or off-label use of Lotemax Gel (loteprednol 0.5%, Bausch + Lomb) or FML ophthalmic suspension (fluorometholone 0.1%, Allergan) is more appropriate treatment.

The only other decision involves the frequency of instillation; we typically prescribe a steroid Q2H for two days, then QID for one week, followed by BID for one more week. Once the inflammatory signs are controlled, then consider switching the patient to an antihistamine/mast cell stabilizer for ongoing symptom control. Long-term treatment with Alrex BID as maintenance therapy can be done if a steroid is what best controls their disease.

According to a conversation we had with Mark Abelson, MD, a world-renowned ocular allergist at Harvard Medical School, there is little clinical use for pure mast cell stabilizing drugs. He says that the antihistamine/mast cell stabilizer drugs more effectively stabilize the mast cell membranes than stand-alone mast cell stabilizers such as pemirolast (Alamast), nedocromil (Alocril) or cromolyn sodium (generic).

Based on this expert opinion, we no longer prescribe these pure mast cell stabilizers.

Remember, allergy is an expression of inflammation. Cold compresses can be helpful in all ocular surface inflammatory diseases. ■

1. Abelson M, Smith L. Clinical advances in ocular allergy. Rev Ophth. 2015 April;22(4):50-60.

Orally-Administered Medicines

There are many times when a clinical challenge is best met with an oral medicine. Let's explore how valuable this route of administration can be.

Because oral therapy is sometimes required to restore health and protect vision in our patients, it is important to have firm knowledge of these medicines. So let's take a clinical, practical look at how to engage oral medicines in the care of our patients.

We'll start with the most useful: antibiotics.

Oral Antibiotics

As more and more *Staph*. species become methicillin-resistant, it's important that when we prescribe an oral antibiotic, we use one that is capable of eradicating common bacterial pathogens.

Even more elementary is the realization that some ocular pathogens produce the enzyme penicillinase, which neutralizes the bactericidal effect of the penicillins. For this reason, we never prescribe any of the standard penicillins. (There are excellent "penicillinase-resistant" penicillins, such as dicloxacillin, but they are generally recommended to be taken four times a day, which limits their practical use.)

To that end, there are only two oral antibiotics that we commonly prescribe: the first-generation cephalosporin, cephalexin, known by its original brand name Keflex, and a synthetic penicillin, amoxicillin (with clavulanic acid), known by its original brand name Augmentin; both are available generically.

• ***Cephalexin***. Because the first-generation cephalosporins share about a 0.1% risk of cross-reactivity with the penicillins, a history of true IgE allergy (i.e., respiratory distress/skin rash, not a GI problem, etc.) to penicillin would generally preclude the use of Keflex. This medicine is prescribed as 500mg BID for one week. It can be taken with meals.

• ***Augmentin***. Augmentin is a

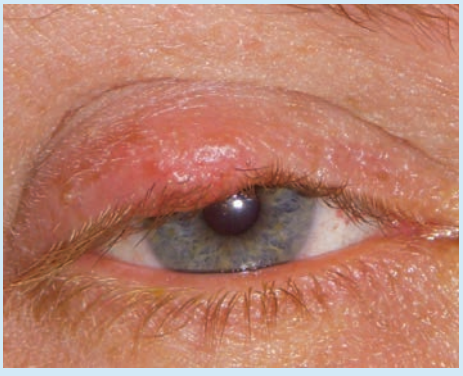
Common Drugs for Common Conditions

This category may be best divided into acute care vs. chronic care uses.

Orals for Acute Care

• Probably the most common reason to prescribe an antibiotic is for acute internal hordeola. (Aggressive use of warm compresses should accompany the use of the antibiotic in this instance.)

• Prednisone is another commonly used oral medication in acute care. We use it in advanced cases of contact dermatitis or as augmentative care for shingles.



Internal hordeolum.

• For acute angle-closure, use acetazolamide along with a topical beta-blocker, brimonidine and pilocarpine.

• An antiviral is essential in the care of herpes zoster affliction and the spectrum of herpes simplex ocular expression.

• For chlamydial conjunctivitis, we always prescribe oral azithromycin.

Orals for Chronic Care

• Looking at chronic care intervention, the limelight shines upon doxycycline. Doxycycline is not curative but rather supplemental therapy for meibomian gland dysfunction and rosacea blepharitis, and therefore it can play a significant role in dry eye disease, with or without rosacea.

combination of synthetic penicillin (amoxicillin) with clavulanic acid. Because bacterial penicillinase can dampen the efficacy of penicillin, we would never prescribe amoxicillin alone. However, combining these two chemical entities greatly enhances its clinical efficacy.

Changes and Challenges in Pain Medications

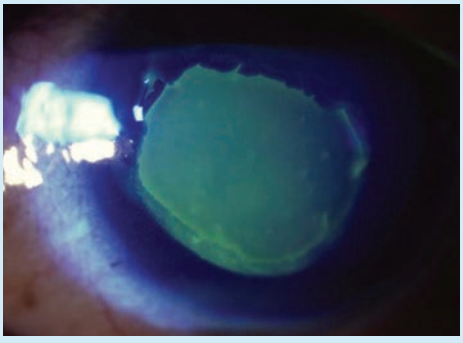
For the most part, this group of medicines is quite old, and all are generic. The biggest news in this category is the schedule change for hydrocodone. It had always been a Schedule III drug, but that changed in October 2014 when the FDA moved it to Schedule II. Historically, oxycodone had Schedule II all to itself; now it shares that category with its slightly less efficacious sister. The reason for this is pitiful: it is by far the most prescribed medicine in the United States, and has been egregiously overused and abused.

Moving hydrocodone to Schedule II does two things:

1. It cannot be called in; a written prescription, either by hand or via electronic health record, is required.

2. Hydrocodone cannot be refilled by phone; again, a written prescription must be generated. The idea is simply to make it more difficult to prescribe and therefore diminish its massive overprescribing.

Here's a classic example of why patients (a) should never go to an emergency department with a foreign body or corneal abrasion, and (b) why there has been further sequestration of hydrocodone: It has been our observation on numerous occasions that non-optometrists treat these conditions with an antibiotic and hydrocodone, and advise the patient to see an eye doctor the following day for follow-up evaluation. The patient would likely be better cared for if these healthcare providers substituted a topical cycloplegic and/or a topical generic NSAID drop for the hydrocodone!



A painful corneal abrasion calls for some type of analgesia, either Tylenol or hydrocodone.

Interestingly, OTC acetaminophen (Tylenol) and ibuprofen work quite well, so there is rarely a need to venture into the "controlled substance/opioid" category. Our approach to pain (usually for a bad abrasion, a recurrent corneal erosion or someone who just can't tolerate pain) is to ask the patient, "What do you usually use for pain?" and we simply recommend taking that approach in this instance, as well.

On the rare occasions that we do feel an opioid analgesic is merited, we prescribe hydrocodone (Vicodin and Lortab are the time-honored brand names) in the standard dosage: one or two tablets PO every to six hours as needed for pain. The standard strength is 5mg hydrocodone combined with either 325mg or 500mg acetaminophen. We generally direct that 10 to 12 tablets be dispensed, along with "no refill" annotated (although these prescriptions can't be refilled now anyway).

Oxycodone, most commonly known by the brand name Percocet, is reserved for severe pain. Like hydrocodone, oxycodone is combined with acetaminophen to enhance efficacy. The prescription would read: *Percocet – Take 1 or 2 tablets PO Q 4 to 6 hours PRN pain.* Even though Percocet is available generically, the brand name is easier to write. Just sign the prescription under the space marked "generic allowed."

All in all, oral medicines to control pain are simple. Don't hesitate to write for them when needed. For optometrists, these are rare occasions.

There are two commonly used concentrations of Augmentin: 500mg and 875mg. Very generally speaking, we use the lesser concentration for smaller bodies and the higher concentration for normal to larger-sized people. (The subjective threshold might be around 120lb., but that's a very general guideline.)

Physicians we know reserve Augmentin for more severe infections, as do we. Its caveat in practical use is a tendency to cause nausea and vomiting, but the overall greater good for the patient is the primary concern, which is eradicating a serious infection.

We almost always prescribe Keflex for conditions requiring antibiotic use; however, when Augmentin is used, such as for some patients with moderate to severe dacryocystitis, it is prescribed BID for one week, taken with meals.

For penicillin-allergic patients, consider either an oral fluoroquinolone, such as levofloxacin (the original brand-name, Levaquin, is now generic) prescribed as 500mg QD for one week, or Bactrim or Septra (trimethoprim/sulfamethoxazole), one to two double-strength (DS) tablets BID for one week.

For patients with suspected MRSA infection (such as health care workers or patients who have failed a prior antibiotic), we would select the trimethoprim/sulfamethoxazole, which is the drug of choice for such infections.[1] (As an alternative, cephalexin appears to be just as effective as trimethoprim/sulfamethoxazole for MRSA infection in uncomplicated, nonpurulent cellulitis.[2]) Prescribe trimethoprim/sulfamethoxazole for most adults as two double-strength tablets/capsules BID for one week. (Note that "double-strength" is in fact the standard dosing strength of this medicine.)

However, when a patient is truly

allergic to sulfa, then we consider doxycycline at its acute therapeutic dosage of 100mg BID for seven to 10 days. (*See "Understanding Sulfur Allergies," below.*)

Because many antibiotics can dampen the efficacy of birth control pills, it is prudent to consult with a female patient's ob/gyn prior to prescribing.

Oral Steroids

• ***Prednisone.*** Optometrists must remember that steroids should be readily used, not feared—at least for short-term use (less than a week). Further, after a single week of prednisone therapy, it can just be stopped, not tapered. Tapering is important when stepping down protracted steroid therapy (>10 days); and the higher the dose and the longer the treatment, the more critical the tapering process becomes.

There are a few precautions and fewer contraindications to the use of prednisone. First, let's look at the common precautions:

—*Peptic ulcer disease.* If a patient has gastrointestinal ulcerative disease, then our GI colleagues advise us to co-prescribe a proton (hydrogen) pump inhibitor, such as omeprazole (OTC Prilosec or Prevacid) 20mg daily, to protect the GI lining during prednisone therapy. Note that the risk of GI problems increases when prednisone is combined with an NSAID.

—*Diabetes.* Our endocrinology colleagues advise us not to be concerned about hyperglycemia (which will occur) for such short-term therapy. They remind us that patients with Type 2 diabetes mellitus are often out of control from time to time, so the concern is not so great. Patients with Type 1 diabetes mellitus are often very knowledgeable about adjusting their insulin

Understanding Sulfur Allergies

Sulfur, sulfa, sulfonamide, sulfite and sulfate—what's the difference? And if a patient is "sulfur-allergic," should drugs such as trimethoprim sulfate or polymyxin B sulfate be avoided? Should such patients be wary of sulfite preservatives?

The short answer is "no."

But, to provide a comprehensive explanation, here are some more specific answers:

• "The term 'sulfa-allergy' is misleading and dangerous, and should not be used. An allergy to a sulfonamide antibiotic may imply cross-reactivity with other sulfonamide antibiotics, but does not imply cross-reactivity with non-antibiotic sulfonamides or other drugs containing sulfhydryl or sulfate groups … Allergy to sulfonamides also does not imply cross-reactivity with sulfite preservatives, sulfates or elemental sulfur."

• "The term, sulfonamide, applies to a sulfone group connected to an amine group. All antibiotic sulfonamides are arylamines."

"Many commonly used drugs, such as thiazide diuretics … and celecoxib, contain a sulfonamide moiety, but none contain the arylamine group. While it has been long considered that allergic cross-reactivity may exist between sulfonamide antibiotics and other sulfonamide drugs, this is actually unlikely because of the structural differences."

• "In patients who have an allergic reaction to one drug, allergic reactions to other drugs, even if entirely unrelated, occur more commonly."

• "The evidence therefore suggests that non-antibiotic (non-arylamine) sulfonamide drugs need not be considered as contra-indicated in those with a history of hypersensitivity to antibiotic (sulfonylarylamine) sulfonamides. This conflicts with the product information of many drugs."

• "Sulfur is a natural element that exists in many forms. There are many substances which have names stemming from 'sulfur' such as sulfites (preservatives in food and drugs) and sulfates (common compounds found in drugs, soaps and cosmetics). Some patients who have suffered from hypersensitivity reactions to sulfonamide antibiotics are unfortunately labeled 'sulfur-allergic.' This term creates confusion for the patient and often for health professionals."

Do note that sulfacetamide and sulfamethoxazole (combined with trimethoprim as Bactrim and Septra) are both sulfonyl arylamines (i.e., antibiotics), and are likely to share allergenicity. Note that Plaquenil is hydroxychloroquine sulfate, and therefore is a non-arylamine sulfonamide. No cross-reaction with a sulfonamide antibiotic would be expected.

Lastly, allergy to shellfish is not a contraindication to using povidone-iodine (Betadine Ophthalmic Prep Solution).

Smith WB, Katelaris CH. 'Sulfur allergy' label is misleading. Aust Prescr. 2008 Feb;31(1): 8-10.

History of Sulfa Allergy

"When patients report a 'sulfa allergy,' the clinician should determine whether the patient developed a reaction to a sulfonamide antibiotic or a sulfonamide non-antibiotic drug; the latter category includes carbonic anhydrase inhibitors such as acetazolamide. The important distinction is that sulfonamide antibiotics have structurally different substituents at the N1 and N4 position that may elicit a severe hypersensitive response, even to the point of anaphylaxis, whereas non-antibiotic sulfonamides lack that structural configuration and, accordingly, are less likely to cause severe reactions. Moreover, cross-reactivity between sulfonamide antibiotics and non-antibiotics is extremely rare."

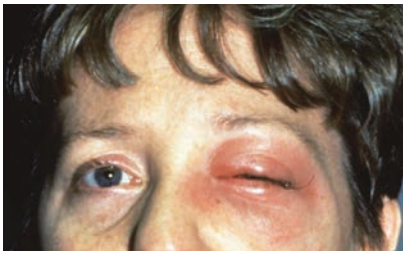
Chak G, Patel R, Allingham RR. Acetazolamide: Considerations for systemic administration. EyeNet. 2015 March;19(3):37.

on a "sliding scale," so they should be advised that they will experience a spike in their blood glucose levels, and to use a sliding scale to adjust their insulin dosage.

—*Pregnancy*. We always call the patient's obstetrician so we can put our heads together prior to prescribing any medicine. Remember, life is a team sport!

—*Active tuberculosis*. This disease is a contraindication for steroids, as is a patient's request to not be prescribed prednisone. Just about all patients with active tuberculosis are very aware of their condition. Again, consult with the patient's tuberculosis physician for guidance.

Dosage of prednisone generally depends upon the severity of the condition and, to a lesser degree, the patient's weight. For an average adult patient, we would likely prescribe 40mg for three to four days. For children, we generally prescribe 20mg QD for three to four days.



We treated this patient's painful herpetic keratoconjuctivoblepharitis with an oral antiviral, which resulted in complete healing.

Orbital pseudotumor (idiopathic orbital inflammatory disease) requires a high initial dosage, 60mg to 80mg to start, and then tapered over a course of several weeks.

This is also true for patients who are highly suspicious for giant cell arteritis, who may require 80mg to 100mg per day while waiting for the temporal artery biopsy to be performed. If the biopsy is positive, usually ultra-high dose prednisone is prescribed: 1,000mg intravenous methylprednisolone (Solu-Medrol) is infused daily for three days, followed by several days of high-dose oral prednisone. This is done either outpatient, or inpatient in a hospital setting. By the way, even these high doses are well tolerated by most patients.

For maximum tolerability, we ask that patients take oral prednisone with a meal. Dosages of 40mg or less are taken as a single dose. We begin to divide dosages at 60mg or higher (e.g., 30mg BID, etc.). As a general rule, if the condition is inflammatory, a rapid improvement in signs and symptoms will occur.

Another approach is to prescribe a Medrol Dosepak (Pfizer and generic). These come in 4mg, 5mg or 10mg blister-packs that are portioned for a six-day course; that is, the patient takes six tablets the first day, five tablets the second day, four the third day, and so on until the six-day course is completed. However, we generally prescribe the 10mg individual tablets at a targeted dosage, such as: *Take 4 tabs PO QD x 3 days*. If we do opt for a dose-pack, we generally prescribe either the 4mg or 5mg pack.

We've prescribed oral prednisone hundreds of times and have yet to have a patient develop a significant problem. Occasionally, a patient may complain of insomnia, anxiety or depression; reassure them that

Idiopathic Intracranial Hypertension

To be technically correct, increased intracranial hypertension is the proper name used to describe when increased intracranial pressure (ICP) is indeed idiopathic. The common term pseudotumor cerebri is more properly used when the cause of the increased ICP is known.

By far, the most common cause of pseudotumor cerebri is secondary to the use of a tetracycline-type drug or 13-cis-retinoic acid (Accutane). Perhaps a better designator would be just simply "intracranial hypertension."

Acetazolamide has been shown to be both effective and well tolerated in the management of increased intracranial hypertension. A recent study that "compared the effects of acetazolamide plus a low sodium, weight-reduction diet against placebo plus the diet, showed that acetazolamide combined with weight loss not only improved vision, but also lowered cerebrospinal fluid pressure, reducing papilledema grade, and improved quality of life significantly more than weight loss alone."

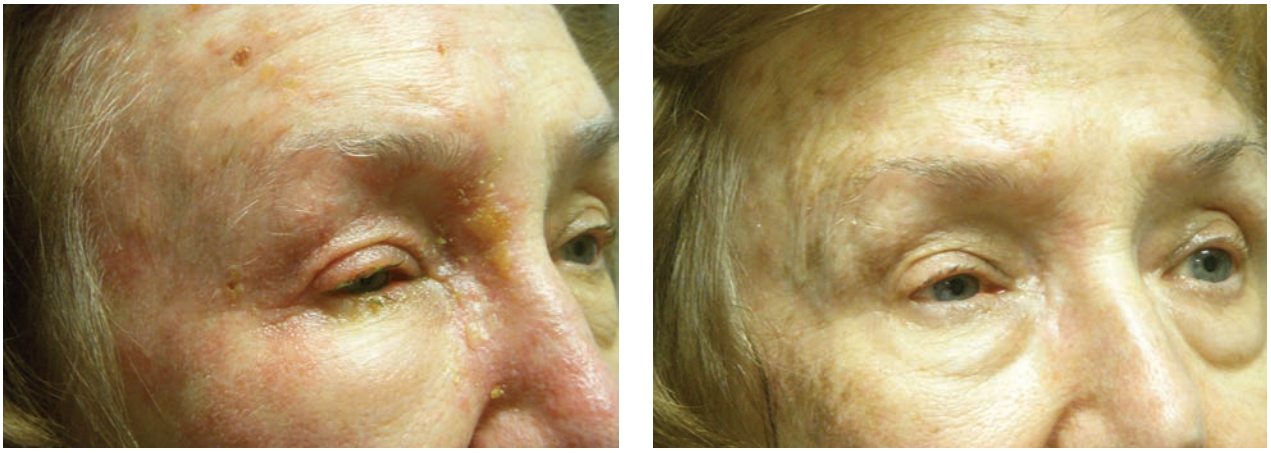
"Our patients on acetazolamide plus diet lost twice as much weight as those in placebo plus diet. The effects of acetazolamide and weight loss were independent, so it looks like we have two independent treatments. The benefit of acetazolamide occurs primarily during the first four to six weeks of treatment, while diet has a more gradual onset."

"To be effective, weight loss only has to be in the 5% to 10% range, and it can be a long-term solution to idiopathic intracranial hypertension."

Acetazolamide confers a great clinical benefit in managing this enigmatic disease. Initial therapy is 500mg twice daily. We recommend Diamox Sequels (Duramed) because they are even better tolerated than the more quickly absorbed tablets. Dosage can be increased to 4g per day, based on need and tolerability. Once the headache and papilledema have resolved, reduce the dosage. Therapy may need to be extended for a few months while weight loss occurs.

Idiopathic intracranial hypertension is largely a disease married to excess weight, mainly occurring in women of childbearing age. This is a disease best cared for as a partnership between the optometrist and the neurologist.

Weiner G. Managing idiopathic intracranial hypertension: The evidence builds. EyeNet. 2015 Feb;19(2):29-30.



This patient presented with second division shingles. In addition to standard oral antiviral treatment, such patients may well benefit from oral prednisone to help control inflammation and pain.

these will be short-lived because the therapy is short-lived. If there are ever any questions, call and speak with the patient's primary care provider.

Oral Antivirals

Possessing both high efficacy and high safety characteristics, all three oral antivirals—acyclovir, valacyclovir and famciclovir—are superb for the treatment of herpes simplex and varicella zoster disease. As with all medicines, the sooner the therapy is started, the greater the likelihood of an optimal outcome.

The dosage for treating active herpes simplex keratitis is typically 400mg of acyclovir five times a day for seven to 10 days, or valacyclovir (Valtrex and generic) 500mg TID for seven to 10 days, or famciclovir (Famvir and generic) 250mg TID for seven to 10 days.

All three of these antivirals clinically perform identically. The difference is in the bioavailability, which is why valacyclovir and famciclovir can be used less frequently than acyclovir; however, acyclovir is the least expensive of the three and therefore is the option we most commonly choose.

Such oral therapy effectively treats all expressions of acute herpes simplex disease. If the patient has a history of chronic, recurrent disease, then the literature guides us to prescribe either acyclovir 400mg BID or valacyclovir 500mg daily for many years.[3] This prophylactic intervention decreases the risk of recurrent disease by about 50%, and even should disease recur, the clinical expression for these patients is significantly muted.[4]

For shingles, we simply double the dosages recommended for herpes simplex disease; that is, acyclovir 800mg five times daily for seven to 10 days, etc.

The oral antivirals are very safe, generically available and wonderfully effective. The only real precaution is their use in patients with marked reduction in kidney function, since these drugs are renally excreted.[5] We've never encountered a patient with renal disease who needed an antiviral, but when that day comes, we'll consult the patient's physician for dosing guidance.

Lastly, note that acyclovir also comes as a liquid suspension containing 200mg/teaspoon (i.e., 200mg/5ml). This is excellent for children or for adults who have difficulty swallowing pills, tablets or capsules.

Oral CAIs

Acetazolamide (Diamox and generic) is our most common choice in the class of carbonic anhydrase inhibitors (CAIs), and is helpful in treating acute angle-closure cases or idiopathic intracranial hypertension (formerly known as pseudotumor cerebri), as well as postoperative cystoid macular edema and central serous chorioretinopathy. (*See "Idiopathic Intracranial Hypertension," page 10.*) However, for longer-term care, methazolamide (Neptazane and generic) is generally better tolerated.

For further prescribing information, consult the text (or electronic edition) of "Drug Facts and Comparisons" (www.factsandcomparisons.com). ■

1. Hsiao CH, Chuang CC, Tan HY, et al. Methicillin-resistant Staphylococcus aureus ocular infection: a 10-year hospital-based study. Ophthalmology. 2012 Mar;119(3):522-7.
2. Miller LG, Daum RS, Creech CB, et al; DMID 07-0051 Team. Clindamycin versus trimethoprim-sulfamethoxazole for uncomplicated skin infections. N Engl J Med. 2015 Mar 19;372(12):1093-103.
3. Miserocchi E, Modorati G, Galli L, Rama P. Efficacy of valacyclovir vs. acyclovir for the prevention of recurrent herpes simplex virus eye disease: A pilot study. Am J Ophthalmol. 2007 Oct;144(4):547-51. Epub 2007 Aug 9.
4. Young RC, Hodge DO, Liesegang TJ, Baratz KH. Incidence, recurrence, and outcomes of herpes simplex virus eye disease in Olmsted County, Minnesota, 1976-2007: the effect of oral antiviral prophylaxis. Arch Ophthalmol. 2010 Sep;128(9):1178-83.
5. Munar MY, Singh H. Drug dosing adjustments in patients with chronic kidney disease. Am Fam Physician. 2007 May 15;75(10):1487-96.

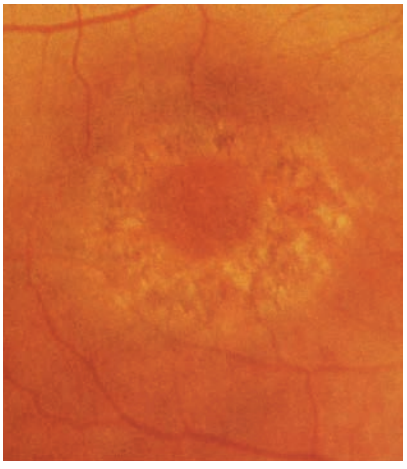
Perspective on Plaquenil

Long-term use of hydroxychloroquine puts patients at risk for retinotoxicity. The startling news is that a large minority of this population is overdosed.

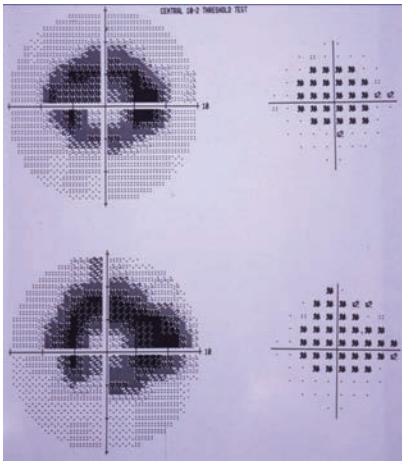
Hydroxychloroquine sulfate, better known by its original brand name Plaquenil (Sanofi-Aventis), is a widely used medicine to treat rheumatoid arthritis, systemic lupus erythematosus and, on occasion, other nonspecific collagen-vascular disorders. It is well known that hydroxychloroquine has the potential to cause irreversible damage to the macular tissues and that such damage is almost always the result of overdosage. Given this reality, it is important that the optometric community understand the following points concerning this drug:

1. The most commonly prescribed dosage of hydroxychloroquine is two 200mg tablets daily. This is a relatively safe dosage for patients who weigh >135lbs; however, it is an overdosage for small people, especially those under 5'3" in height who weigh <135lbs. Basically, the smaller the body, the greater the risk, as there is simply less tissue mass to distribute the medicine.

2. The risk of retinotoxicity is cumulative and increases considerably after seven to 10 years of continuous use. Looking at both daily and cumulative dosage is critical to properly assessing risk. Note that renal disease and, to a lesser extent, hepatic disease, can further increase the risk for toxic levels of hydroxychloroquine. While this should be taken into account by the prescribing physician, we need to be a second set of eyes for the sake of our patients because: "Prescribing health care providers may be unfamiliar with the ocular adverse effects of long-term use, or with the patient characteristics associated with high risk for macular toxic effects, or may not appreciate the usefulness of preemptive screening before vision is lost."[1]



This is a classic presentation of "bull's eye" maculopathy—a very sad, and very preventable, expression of permanent vision loss from HCQ toxicity.



This is the classic ring scotoma of this same patient. Such fields should never exist!

3. We've witnessed many times over the years that a sizable minority of patients is overdosed. So when an article was published in 2014 stating that half of this study population was overdosed, it didn't surprise us.[1] But it's deeply perplexing that a number of rheumatologists and dermatologists who prescribe hydroxychloroquine seem

oblivious to the critical importance of individualized dosing.

Dose Appropriately, Avoid Retinotoxicity

The centerpiece of optometric responsibility is to assess the appropriate dosage, because it's exceedingly rare for properly dosed patients to develop retinotoxicity. In fact, one authoritative retinal subspecialist stated in 2002 that, "under circumstances of proper dosing, screening could be rationally discontinued."[2]

Beyond such preventive intervention, it's imperative that appropriate special tests be accomplished by the optometrist. Essentially, this means a 10-2 visual field with a white target and a spectral-domain optical coherence tomography (SD-OCT), as the older-generation OCTs do not have the requisite resolution needed.

Both of these tests need to be performed at regular intervals. The exact temporal spacing of these cannot be firmly recommended because the frequency of testing depends to a significant degree on the risk assessment by the optometrist. In many cases, however, testing is done annually.

Interestingly, the 10-2 test can be more sensitive than the SD-OCT. In about 10% of patients, there can be significant defects in the 10-2, yet the SD-OCT may be entirely normal! The correlation of the 10-2 with the SD-OCT parafoveal thinning or inner segment/outer segment (IS/OS, also known as the ellipsoid zone) line disruption is associated with visual field loss.

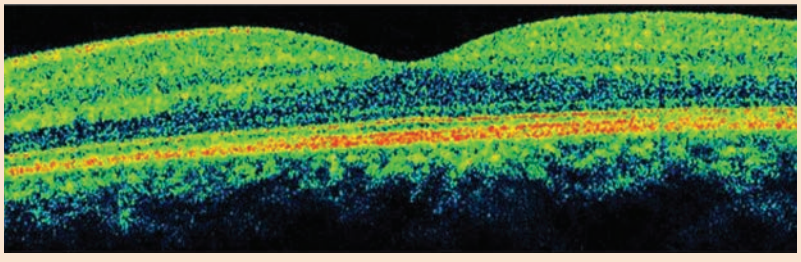
The earliest visual field changes seen in the pattern deviation probability plots of the 10-2 may be only a couple of isolated parafoveal scotomas. We all need to be keenly aware of these visual field patterns. If ever in doubt, repeat the 10-2 in a few weeks, but do not prematurely stop the hydroxychloroquine. 10-2 testing may be sufficient for initial screening (when SD-OCT is not available) because SD-OCT change is unlikely if a repeatable field shows no losses at all. Note that fundus changes are a late finding of toxicity.

Of note, multifocal electroretinography (ERG) testing and/or fundus autofluorescence testing are also used for screening, but are used less often. If choosing between these two tests, autofluorescence is preferred because multifocal ERG is too variable for widespread clinical use.

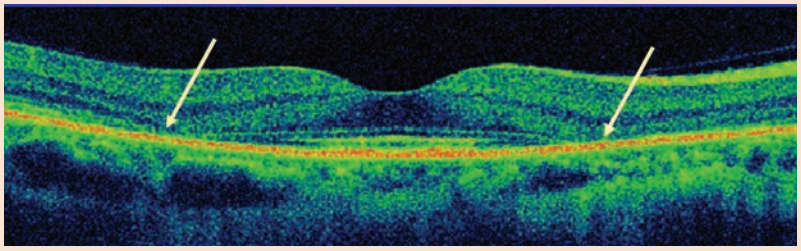
Testing for Plaquenil Toxicity

- "Interpretation of the visual field test often is difficult, because too low of a threshold for identifying important field changes potentially subjects a patient to stopping a drug that is helping them systemically, whereas too high of a threshold will fail to identify signs of retinal damage."
- "Traditional interpretation of SD-OCT for determination of toxicity is qualitative, with hydroxychloroquine toxicity manifested as a loss or disruption of perifoveal photoreceptor EZ, and relies on trained graders identifying what are often subtle findings." This "ellipsoid zone" (EZ) represents the inner segment/outer segment junction of the photoreceptors. This layer lies just beneath the outer limiting membrane. The parafoveal tissues (2° to 8° from the foveola) have the lowest threshold for tissue thinning and compromise. "The advantage of this evaluation is that it is specific for toxicity, but it requires training, and even with trained graders, lacks sensitivity."
- "OCT images can be examined to identify the presence of paracentral EZ disruption, and if present, this seems to be a quite specific finding of toxicity."
- "Our data suggest that the combination of SD-OCT and Humphrey Visual Field 10-2 testing can be used as a screening tool to identify patients with possible hydroxychloroquine toxicity. Additional testing and the consistency of the evidence can then be used to decide whether to recommend that hydroxychloroquine be discontinued."

Cukras C, Huynh N, Vitale S, et al. Subjective and objective screening tests for hydroxychloroquine toxicity. Ophthalmology. 2015 Feb;122(2):356-66.



Compare this OCT image of the normal retinal anatomy to the one below.



Here is a clear case of parafoveal compromise of the inner segment/outer segment (ellipsoid zone; yellow arrows), which is pathognomonic for HCQ toxicity.

Doctor, please feel free to remove this sheet, copy it to your letterhead and use it for referrals.

Hydroxychloroquine (Plaquenil) Evaluation

Patient Name _____ D.O.B. _____

Referring Physician _____

Consultant Optometrist _____

Date _____/_____/_____

Plaquenil dose _____ mg _____ Number of years taking HCQ _____

Acuity Right 20/_____ Left 20/_____ Patient's Weight _____ lbs.

Estimated Ideal Weight _____ lbs.

Fundus exam Normal _____ Other _____

_____

Macular Visual Field Testing (10-2) ☐ Normal _____ Other _____

_____

SD-OCT ☐ Normal _____ Other _____

_____

Recheck Annually _____ Other _____

Comments:

Thank you very much for entrusting us with the eye care of your patient.

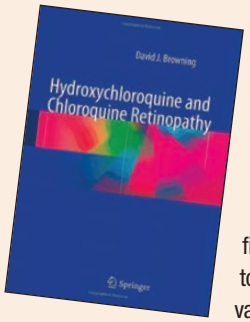
Assessing Toxicity

It is generally recommended to use both a subjective (10-2 white target) and an objective (SD-OCT) test when assessing for toxicity. If there is any sort of maculopathy at baseline, obtain documenting retinal photographs. Further, such baseline macular changes can make future diagnosis of early hydroxychloroquine changes more difficult to detect. There is no medical reason to take photos of a perfectly healthy retina because we all know what perfectly healthy retinae look like.

When retinal compromise is ophthalmoscopically evident, egregious and predictable toxic damage has occurred. Stopping the hydroxychloroquine at this stage is absolutely imperative. When the classic bull's eye maculopathy occurs, even when the medicine has been stopped, there can still be progression of retinopathy for at least three years. If toxicity is detected early,

Highlights from *Hydroxychloroquine and Chloroquine Retinopathy*

Here are select, paraphrased take-aways from the textbook "Hydroxychloroquine and Chloroquine Retinopathy" by David J. Browning, MD, PhD:



• A daily dose of hydroxychloroquine of 6.5mg/kg based on ideal body weight is associated with a very low risk of retinopathy or other toxicity.

Chloroquine is approximately twice as toxic as hydroxychloroquine on a weight basis. This certainly explains why chloroquine is rarely ever used in contemporary medical care.

• More than 10 non-ocular side effects of these medicines have been reported. Of these, gastrointestinal upset is the most common, occurring in approximately 12% of persons who take these drugs.

• The prevalence of hydroxychloroquine toxicity among properly dosed patients is much less than 1%.

• If all persons were properly dosed according to ideal body weight, such that prevalence of retinopathy dropped to much less than 1%, it would be difficult to support universal screening. It follows that a cost-effective screening program should emphasize proper dosing based on ideal body weight.

• Most clinically serious cases of toxicity are iatrogenic, arising from overdosing based on ideal body weight, missed screening or tardy recognition of evidence of toxicity from ancillary testing.

• Fewer than 15% of patients taking these medicines without retinopathy have visual symptoms.

• Decreased visual acuity is an insensitive indicator of hydroxychloroquine toxicity; its presence implies advanced retinopathy.

• There is no treatment for hydroxychloroquine toxicity.

• The risk factors for hydroxychloroquine are: drug use; cumulative dose and its surrogate; duration of use; age; pre-existing macular abnormalities; renal dysfunction; and hepatic dysfunction.

• Indirect risk factors include: female gender and obesity. The more direct risk factor in these cases is the adjusted daily dose.

• More than 80% of patients taking hydroxychloroquine have a risk factor for retinopathy. The general principle guiding clinical practice in prescribing these medicines should be to find the smallest effective dose. Risk can always be decreased by reducing daily dose.

• The most important function of screening patients for hydroxychloroquine toxicity is to detect overdosing, which can be corrected. A subsidiary function is to detect the rare occurrence of retinopathy among properly dosed patients. For this, ancillary testing is needed because the clinical examination is insensitive. More than 10 ancillary tests have been proposed and discarded because they are too variable, not standardized, too insensitive, too sensitive, nonspecific or not reimbursed.

• Standard automated perimetry with the 10-2 visual field is widely available and understood as a screening tool for hydroxychloroquine toxicity, but is hampered by variability and subjectivity in data acquisition and clinical interpretation.

• The multifocal electroretinogram (mERG) is a sensitive test, but it has high variability and is fraught with pitfalls in technical application and interpretation.

• Fundus autofluorescence is too subjective to have high value as a widely used ancillary test, but can be helpful in certain cases.

• SD-OCT has the lowest variability of all the ancillary tests, is the most objective, is almost as sensitive as mERG and 10-2 visual fields and is more specific. It is almost as widely available as the 10-2 visual field.

• At least 12.8% of patients taking hydroxychloroquine are overdosed. Screening for overdosage is inexpensive and worthwhile.

• Screening in the United States is likely to persist for historical reasons. If screening for hydroxychloroquine toxicity is retained in properly dosed patients, a reasonable approach is to obtain a baseline examination with 10-2 visual field or SD-OCT, followed by annual follow-up with one or the other, but not both.

• The five-year gap recommended between baseline and a second screening should be abandoned as impractical.

• The trend in progressive abnormality on an ancillary test over time carries greater weight than a single abnormal test.

• Continuing work by clinicians to refine their skills in interpreting ancillary tests is worthwhile. This includes understanding variability and reproducibility of the different tests. Obtaining the correct test, but misinterpreting it, is a common problem.

For further reading, get your own copy of this valuable text here: www.springer.com/us/book/9781493905966.

there is only minimal progression.

Vision can be retained in the initial toxic stages, but as outer retinal layers succumb, there is ultimately visual compromise. This occurs at the parafoveal IS/OS line (also known as the ellipsoid zone), which lies just beneath the external limiting membrane, where toxic effects are at their zenith.[3] The actual fovea resists toxic effects, which explains why central vision loss is a late finding.[4] This explains the importance of noting "parafoveal" 10-2 defects as potentially early signs of toxicity. These areas of photoreceptor injury, as detected with 10-2 testing, occur before anatomic loss is observable.

Subsequent worsening of toxicity typically deepens established scotomata more than expanding them. Subjective variability in repeated fields suggests a need for caution in judging either progression or recovery from only one or two visual fields.[3] (This is analogous to glaucomatous visual field variability.)

Interestingly—and sadly—about 20% of patients on hydroxychloroquine did not see an eye doctor during the five-year period of this study.[1] Worse yet, 6% of high-risk patients had not seen an eye doctor during this same five-year period of time. Further, only about 70% of this high-risk population had "regular" eye visits! Worst of all, every patient in this study had medical insurance! We share this information to give you a perspective on the importance of rheumatologic and optometric oversight on this population of patients using hydroxychloroquine.

Points to Keep in Mind

The most important thing you can do as an optometrist is be attentive to the patient's dosing! This article encompasses the most up-to-date information. Use it to professionally communicate with the prescribers. They want to provide excellent care to their patients just as much as you, and don't want to be sued any more than you do!

Thoroughly document in your medical records the discussions you have with your patients and with their prescribing doctors. You cannot make the prescriber change the patient's dosing, but you can clearly document your excellent, patient-centered advice to both the prescriber and the patient.

The other obligation you have is to monitor your patients for early retinal toxicity. This is done via 10-2 visual field and SD-OCT testing, and should be conducted at appropriate temporal intervals commensurate with your assessment of the patient's risk. ■

Actual vs. Ideal Body Weight: Implications for Toxic Dosing Assessment

• "Ideal body weight rather than actual body weight should be used in dosing calculations for short, obese patients. However, a subtlety often overlooked is the need to calculate dosing based on actual, not ideal, body weight in the asthenic [thin] patient. For example, in a patient of height 5' 7" and weight of 130lbs who is taking the standard dosage of 400mg per day of hydroxychloroquine, the ideal body weight from the National Heart, Lung and Blood Institute table is 153lbs—but this weight should not be used for calculating dosing in this particular patient. If one were to do so, the result would be 5.8mg/kg per day, a typically nontoxic dose. Instead, it is correct to use the actual body weight for this asthenic patient. Doing so yields an adjusted daily dose of 6.8mg/kg per day, a potentially toxic dose that would indicate a need for the ophthalmologist [or optometrist] to intervene and advise the internist to reduce the dose."

• "Doses >6.5mg/kg/d are referred to as 'potentially toxic,' not because lower doses cannot be associated with maculopathy, but because of the acknowledged higher risk of doses in this range."

• "Checking for toxic dosing is the single action by an ophthalmologist [or optometrist] most likely to reduce the occurrence of hydroxychloroquine toxicity…"

Being aware of body habitus, and giving rational thought to this concept of body weight and height is just plain common sense, but the optometrist needs to be keenly attentive to the patient's height, weight and adiposity, or lack thereof. This is critical knowledge.

Browning DJ. Impact of the revised American Academy of Ophthalmology guidelines regarding hydroxychloroquine screening on actual practice. Am J Ophthalmol. 2013 Mar;155(3):418-428.

Rule of Thumb for Calculating "Ideal" Body Weight

Women: 100lbs + 5lbs for each inch >5 feet

Men: 110lbs + 5lbs for each inch >5 feet

Using these simple formulas can provide a quick assessment of proper dosing. Also, bear in mind that "lowering the current dose in a long-term patient does not remove cumulative risk from past exposure." This is a critical point and one that merits the careful attention of the optometrist.

Marmor MF. Efficient and effective screening for hydroxychloroquine toxicity. Am J Ophthalmol. 2013 Mar;155(3):413-4.

1. Nika M, Blachley TS, Edwards P, et al. Regular examinations for toxic maculopathy in long-term chloroquine or hydroxychloroquine users. JAMA Ophthalmol. 2014 Oct;132(10):1199-208.
2. Browning DJ. Hydroxychloroquine and chloroquine retinopathy: screening for drug toxicity. Am J Ophthalmol. 2002 May;133(5):649-56.
3. Marmor MF, Hu J. Effect of disease stage on progression of hydroxychloroquine retinopathy. JAMA Ophthalmol. 2014 Sep;132(9):1105-12.
4. Mititelu M,Wong BJ, Brenner M, Bryar PJ, et al. Progression of hydroxychloroquine toxic effects after drug therapy cessation. JAMA Ophthalmol. 2013 Sep;131(9):1187-97.

A Fresh Look at Dry Eye Disease

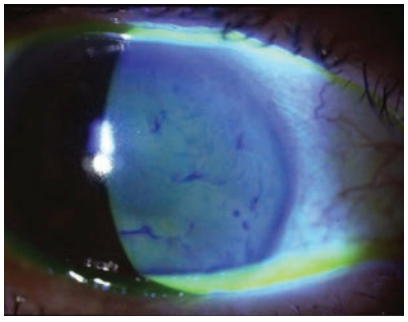
Nearly all cases of dry eye disease can be managed in the optometric office. This requires thorough evaluation and effective treatment.

First of all, dry eye is a true *disease* and should be fully acknowledged as such. Worse, it is a chronic disease, like rheumatoid arthritis, and requires years or decades of attentive care.

Dry eye disease is epidemic in nature and is a condition that most all optometrists see, and often see several times daily. So, one consistent concept that we all need to remember is to be more attentive and proactive in interacting with our patients. We should all begin asking each patient a few simple questions:

- "Do your eyes ever bother you?"
- "Do your eyes bother you after working on a computer or after reading?"
- "Does your vision vary throughout the day?"
- "Do your eyes ever burn or feel dry, sandy or gritty?"
- "Do you rub your eyes?"
- "Do you use eye drops or feel the need to use eye drops?"

Well, you get the idea. Ask pointed questions to your patients in order to determine if they have dry eye disease. This determination is vital to meeting our patients' needs. Many times, patients just don't think to bring such symptoms to the attention of their eye doctor. Perhaps they think such symptoms are just a normal part of life, or that there is nothing that can be done; perhaps they don't realize that their optometrist provides medical care services. We have indeed seen many patients with dry eye disease over the years who came to our group MD/OD practices and wound up seeing one of us, and they were very well pleased with the optometric care they received.



Assess the cornea and conjunctiva without fluorescein, and then with it to evaluate the tear film breakup time.

A Thorough Evaluation

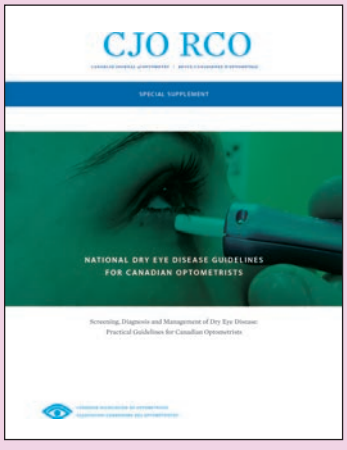
A fundamental element of dry eye disease is that it mostly centers on a deficiency of the lipid layer of the precorneal tear film.[1] The pathological epicenter in dry eye disease resides in meibomian gland

Comprehensive Dry Eye Guidelines

Superb, comprehensive guidelines have been developed by our optometric colleagues in Canada.

Consider this: "Given the high prevalence and variability of symptoms, almost every adult presenting for a primary care examination should be considered to be a DED suspect until proven otherwise."

For more, download "Screening, Diagnosis and Management of Dry Eye Disease: Practical Guidelines for Canadian Optometrists" here: http://opto.ca/sites/default/files/resources/documents/cjo_dry_eye_supplement_2014.pdf.

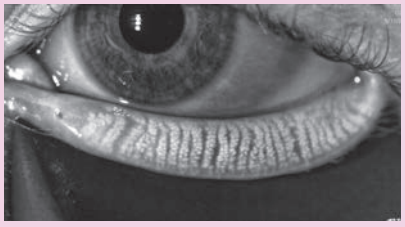


Meibography: OCT for MGD

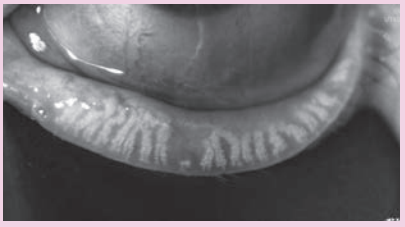
Just as OCT has revolutionized posterior pole evaluation, so will meibography for meibomian gland disease. Because atrophy or dysfunction of the meibomian glands is the main cause of dry eye disease, it seems so intuitive to assess the structure of these glands.

This sequence of photographs clearly shows how helpful assessing the meibomian glands is via meibography. Comparing normal, moderate loss and advanced loss is easily done.

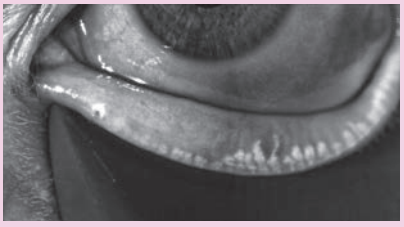
We foresee the day when meibography is part of the comprehensive ocular assessment.



Normal meibomian glands



Moderate gland dysfunction



Severe gland dysfunction

dysfunction, and so the clinical evaluation needs to include examination of both the ocular surface and the eyelid tissues.[2]

Our clinical evaluation includes:

• Careful slit lamp assessment of the lacrimal lake (height, volume, and quality); the puncta; the eyelid margins, especially noting any pouting or capping of the meibomian gland orifices; and the meibomian glands themselves as seen on the tarsal conjunctivae.

• Firmly pressing on the meibomian glands for 15 seconds can help determine if there is any "non-obvious" meibomian gland dysfunction, as evidenced by the expressed meibum, or lack thereof. Normal secretions should be relatively clear, not turbid. Of course, there should be some expressed liquid, or there may be a blocked orifice, or even meibomian gland atrophy.

• We also study the cornea and conjunctivae without, then with, fluorescein stain; and we evert the eyelids. Following fluorescein staining and tear film break-up time evaluation, rose bengal or lissamine green staining can help distinguish mild from moderate to severe disease.

These simple, straightforward clinical maneuvers help give us a good feel for how to stage our patients' dry eye disease—mild, moderate or severe.

A Simple Treatment Approach

Given that treatment needs to be individualized to the patient, our typical treatment regimen for dry eye disease is also straightforward:

• **Omega fatty acids.** Start all dry eye patients on some sort of fish oil (preferably with gamma linolenic

Commonly Used Lipid-based Artificial Tears

Brand Name	Manufacturer	Lipid	Lubricants	Preservative
Refresh Optive Advanced	Allergan	castor oil	carboxymethylcellulose, glycerin, polysorbate 80	Purite (stabilized oxychloro complex)
Refresh Optive Advanced Preservative Free	Allergan	castor oil	carboxymethylcellulose, glycerin, polysorbate 80	none
Retaine MGD	OcuSoft	glycerol	light mineral oil, mineral oil	none
Soothe XP	Bausch + Lomb	light mineral oil, mineral oil	polysorbate 80	polyquarternium-1
Systane Balance	Alcon	mineral oil	propylene glycol	polyquarternium-1

acid), but any good quality fish oil supplement is a step in the right direction. We generally recommend taking 2,000mg per day with breakfast.

• **Lipid-based tear.** Recommend a lipid-based artificial tear—such as Soothe XP (Bausch + Lomb), Systane Balance (Alcon), Refresh Optive Advanced (Allergan) or Retaine MGD (OcuSoft)—to be used initially at least four times daily. If there is significant ocular surface staining, perhaps a preservative-free, lipid-based product such as Retaine MGD (OcuSoft) might be best.

• **Reduce acute inflammation.** Based upon studies as recent as December 2014, a one-month course of topical corticosteroid should be sufficient to quickly suppress ocular surface inflammation, an off-label but effective approach.[3,4] Accordingly, we start the patient on Lotemax Gel drops QID for two weeks then BID for two more weeks. (In the two studies referenced, not a single patient had a significant increase in intraocular pressure.) Certainly the IOP can increase with any steroid, but there is a reduced likelihood of an IOP increase with loteprednol—and even if the IOP does increase, by the time it goes up, you are already tapering or have stopped the steroid. We have prescribed this off-label treatment hundreds of times, and we concur with the findings in these peer-reviewed articles. (*See "Effect of Loteprednol on MGD," page 20.*)

• **Debride the lid margin.** Depending upon the status of the meibomian gland orifices, we may gently scrape along the top of the lower eyelids, as this has been shown to facilitate meibum flow into the tear layer.[5] This procedure is simply accomplished by using a golf club spud to scrape along the meibomian gland orifices. No anesthesia is required, and there is no

Our Dry Eye Management Algorithm

All therapy—dry eye included—should be individualized to the patient. That said, here is our usual approach to dry eye management.

Two Weeks	Two Weeks	Indefinitely
Lipid-Based Artificial Tear Four to six times a day as needed	**Lipid-Based Artificial Tear** Three to four times a day as needed	**Lipid-Based Artificial Tear** Two to four times a day as needed
Loteprednol gel 0.5% * Four times a day	**Loteprednol gel 0.5%** Two times a day (Consider punctal plugs if needed)	**Discontinue loteprednol gel 0.5%** If symptoms break through or continue, then pulse dose loteprednol gel three times a day for one week, or consider loteprednol once daily as needed.

The risk of increased IOP with loteprednol is uncommon at high dosage and rare at low dosage.[4]
Our experience has been that if an increase in IOP is going to occur, it will do so at the initial one-month follow up, and not later.

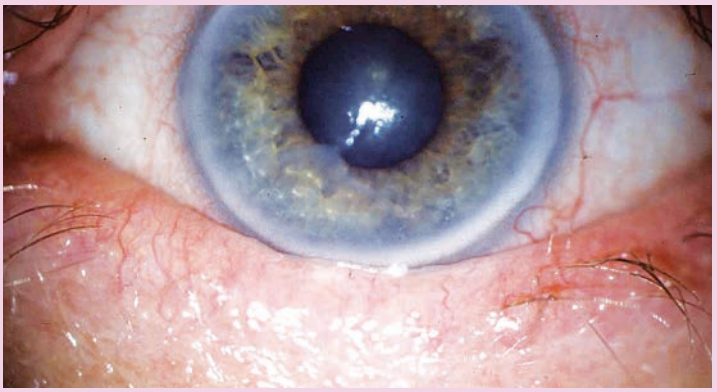
Omega-3 essential fatty acids (derived from fish and/or flaxseed oil) can be initiated at any stage, based on clinical judgment.

*Alternatively, instill loteprednol ointment daily at bedtime for two weeks, then M-W-F for two weeks.
Loteprednol therapy for inflammation due to dry eye disease is considered an "off-label" use.

Effect of Loteprednol on MGD

Primary interventions addressing meibomian gland dysfunction (MGD) have become a key element in gaining ultimate control of dry eye disease. When a patient presents with signs and/or symptoms of dry eye disease, quickly attending to these complaints is appropriate and proper. Eyelid hygiene and suppression of ocular surface inflammation are two key elements that can be easily and safely employed to help gain symptomatic control.

Maintaining control long term is addressed via meibomian gland expression, oral omega fatty acid supplementation and/or a three- to four-month regimen of 50mg of oral doxycycline.



In addition to warm compresses and lid scrubs, topical loteprednol has also been shown to reduce inflammation in meibomian gland dysfunction.

A recent article investigated the off-label use of topical loteprednol, along with eyelid scrubs and warm compresses, on MGD. The following quotes and in-context paraphrases from the December 2014 *American Journal of Ophthalmology* substantiate the dry eye management protocols we have been espousing for over a decade. This randomized controlled trial was not supported by any drug company.

• "Eyelid management, including warm compresses and lid scrubs, has been known to be a conservative and traditional treatment modality for MGD. It is thought to improve meibomian gland function and ocular comfort by melting and releasing the abnormally modified meibum. However, eyelid scrubs with warm compresses alone are insufficient to modulate the inflammatory process in moderate and severe MGD. Thus, eyelid management needs to be supported by additional treatment to achieve satisfactory and quick responses."

• "Using a generalized estimating equations model, there were statistically significant differences in expressibility, the ocular irritation symptoms score and the MGD stage, demonstrating the superior efficacy of topical loteprednol etabonate for improving these parameters."

• "The current study confirms that, compared with eyelid scrubs with warm compresses alone, additional application of topical loteprednol etabonate significantly decreases the concentrations of inflammatory tear cytokines … These results were consistent with noticeably improved TBUT [tear film breakup time], corneal and conjunctival fluorescein staining, lid margin abnormality, meibum quality, expressibility, ocular irritation symptoms, and the MGD stage."

• "[One] month of treatment is enough for topical loteprednol to control those cytokines. Relative to results with eyelid scrubs with warm compresses alone, stabilization of the ocular surface by topical loteprednol was demonstrated by significant improvements of tear film breakup time and fluorescein staining scores."

• "Considering the lipid profiles of MGD, it is possible that loteprednol etabonate can penetrate into the abnormally modified meibum in the diseased meibomian gland. Therefore, it could exert anti-inflammatory effects, not only in the conjunctiva and cornea, but also in the meibomian gland. This is consistent with our findings that loteprednol etabonate improved the ocular surface integrity and decreased eyelid inflammation."

• "In the case of keratoconjunctivitis sicca with a moderate inflammatory component, the use of 0.5% topical loteprednol etabonate four times daily for one month is beneficial with regard to clinical outcomes … Therefore, we propose that one month treatment with topical loteprednol etabonate and proper eyelid management can be an acceptable initial treatment of moderate and severe MGD."

• "In summary, we evaluated the efficacy and safety of topical loteprednol etabonate in conjunction with eyelid scrubs with warm compresses for the treatment of moderate and severe MGD. Based on the results of this study, we conclude that topical loteprednol etabonate can provide greater anti-inflammatory effects and clinical benefits through the regulation of inflammatory tear cytokines without serious adverse events."

These observations substantiate the safety and efficacy of short-term off-label use of loteprednol in gaining initial control of symptomatic dry eye disease. This study used the original suspension formulation of 0.5% loteprednol. It may be that using the newer gel-drop formulation of loteprednol could give equivalent results used just TID.

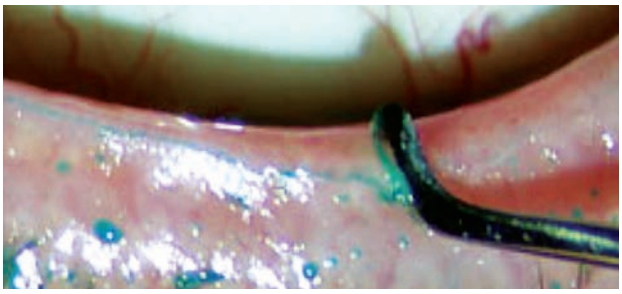
Another option could be to use the gel-drop formulation QID for two weeks, and then BID for two weeks. Yet another option could be to use the gel-drop QID for two weeks, then switch to the 0.2% loteprednol drop (Alrex, Bausch + Lomb) BID for an additional four weeks.

Lastly, we hope that reading these excerpts from the peer-reviewed literature would encourage all optometrists to consider subscribing to one or two such journals (www.ophsource.com). Such reading is vastly superior to any lecture, including ours.

Lee H, Chung B, Kim KS, et al. Effects of topical loteprednol etabonate on tear cytokines and clinical outcomes in moderate and severe meibomian gland dysfunction: randomized clinical trial. Am J Ophthalmol. 2014 Dec;158(6):1172-1183.

ICD-9 code for this procedure, which takes only a few seconds to perform.

• **Suppress long-term inflammation.** The method we most commonly employ for recurring or enduring low-grade inflammation is the off-label approach of pulse-dosing loteprednol.



To debride the lower lid margin, gently wipe a golf club spud repeatedly across the lid margin to remove debris.

Here is a very common scenario we encounter: Following an initial course of four weeks of loteprednol along with use of a lipid-based tear and fish oil supplementation and other interventions we have mentioned above, most patients do quite well.

However, after a few weeks to months, some patients have a recurrence of their symptoms. At this point we coach these patients to use their Lotemax Gel drops TID for one week and stop. The literature endorses this off-label pulse dosing, and we have found it to be highly clinically effective and cost-effective.[6] (If there was no IOP increase during the initial month of therapy, there most likely will not be any IOP increase with a mere week of pulse dosing. If you have any doubt, just check the patient's IOP on the next follow-up visit.) It has been our experience that patients generally need pulse dosing once or twice a year for recurrent symptoms. Now that we have learned the efficacy and safety of this approach, we are completely comfortable with continuing this therapy long-term as needed.

We always try such robust interventions initially, and then default to Restasis for those few patients who continue to have symptoms following four weeks of Lotemax therapy and who truly need modest, long-term suppression of inflammation.[7]

Almost all cases of dry eye disease can be successfully managed in

Dry Eye Pointers from the Experts

• "The two major types of dry eye disease are aqueous deficiency and evaporative dry eye." Regarding distinguishing between these two types of dry eye disease: "The reality is that it is pretty hard to tell. There's no sure-fire test."

• Since perhaps one in 10 patients with dry eye disease may have Sjögren's disease, "These patients often complain of dry mouth, fatigue, and joint pain. The clinician should always inquire about these symptoms in assessing dry eye patients."

• For moderate to severe cases of dry eye, "Start with a steroid four times a day for two weeks, then taper to twice a day for two weeks. No more than two to four weeks of treatment is recommended."

• "If you're going to use punctal plugs, put in the largest plug possible because it is more likely to stay in."

Karmel M. A quick guide to dry eye. EyeNet. 2014 June;18(6):41-6.

Depression and Dry Eye: Is There a Link?

People with dry eye disease are about three times more likely to have anxiety and/or depression. "Perhaps the treatment of dry eye disease, then, would also benefit from treatment of depression and/or anxiety," a new study says.

The benefit of such complementary treatment has yet to be determined, but is a plausible concept. Perhaps proper management of dry eye disease could help, to some degree, with concurrent depression and/or anxiety.

van der Vaart R, Weaver MA, Lefebvre C, Davis RM. The association between dry eye disease and depression and anxiety in a large population-based study. Am J Ophthalmol. 2015 Mar;159(3):470-4.

Update on Oral Supplements for Dry Eye

Fish oils come in different forms and qualities; and the amounts of their essential fatty acid constituents of EPA and DHA can vary. As a general guideline, the higher quality fish oil supplements have an EPA + DHA content of roughly 850 to 1,500mg per daily dose.

Omega-3 fatty acids, especially DHA, have morphological, functional and protective roles in the retina.[1] The xanthophyll macular pigments lutein and zeaxanthin (L and Z) are thought to absorb harmful wavelengths of blue light as well as have antioxidant properties. These carotenoids are most concentrated in the inner retinal layers of the macula.[2]

Although dosages of 10mg for lutein and 2mg for zeaxanthin were studied in AREDS 2, no one knows the exact daily needs of L and Z by the human body. As these are "supplements," we would need to know the dietary and nutritional intake of each and every patient in order to properly quantify this supplemental need, if any, for a given patient. This reality is often lost in the conversation regarding appropriate supplemental recommendations.

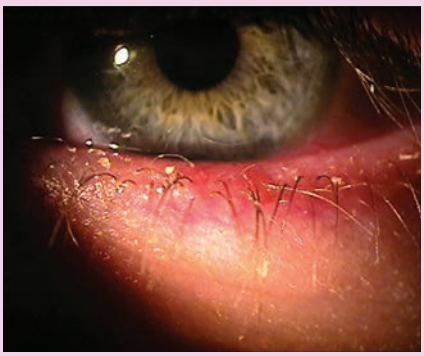
1. SanGiovanni JP, Agron E, Clemons TE, Chew EY. Omega-3 long-chain polyunsaturated fatty acid intake inversely associated with 12-year progression to advanced age-related macular degeneration. Arch Ophthalmol 2009;127(1):110-112.
2. Lectures by Dr. J. Pizzimenti and Dr. L. Capogna. February 2015.

the optometric office. Such success hinges on the clinical interest and attentiveness of the doctor. As a general rule, such therapeutic interventions are fairly intense for the first month, but long-term maintenance of comfort is accomplished when patients consistently comply with use of the fish oil and lipid-based artificial tears (with or without punctal plugs). For the exceedingly challenging patient, don't forget the benefit of employing Lacrisert (hydroxypropyl cellulose inserts, Bausch + Lomb).

It is well established that "inflammation" is central to the pathogenesis of dry eye disease, so it is imperative that suppression of inflammation be the goal of first order. Once this primary goal is reached, all other interventions can then be addressed. ■

1. Foulks GN. The correlation between the tear film lipid layer and dry eye disease. Surv Ophthalmol. 2007 Jul-Aug; 52(4):369-74.
2. Nichols KK, Foulks GN, Bron AJ, et al. The international workshop on meibomian gland dysfunction: executive summary. Invest Ophthalmol Vis Sci. 2011 Mar 30;52(4):1922-9.
3. Lee H, Chung B, Kim KS, et al. Effects of topical loteprednol etabonate on tear cytokines and clinical outcomes in moderate and severe meibomian gland dysfunction: randomized clinical trial. Am J Ophthalmol. 2014 Dec;158(6):1172-1183.
4. Sheppard JD, Donnenfeld ED, Holland EJ, et al. Effect of loteprednol etabonate 0.5% on initiation of dry eye treatment with topical cyclosporine 0.05%. Eye Contact Lens. 2014 Sep;40(5):289-96.
5. Korb DR, Blackie CA. Debridement-scaling: a new procedure that increases meibomian gland function and reduces dry eye symptoms. Cornea. 2013 Dec;32(12):1554-7.
6. Stevenson W, Chauhan SK, Dana R. Dry eye disease: an immune-mediated ocular surface disorder. Arch Ophthalmol. 2012 Jan;130(1):90-100.
7. Food and Drug Administration. Draft Guidance on Cyclosporine. June 2013. Available at: www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358114.pdf.

Battle Against Blepharitis



Common conditions beckon ever-improving technologies. Thankfully, the modern world has found numerous upgrades from baby shampoo to use as an eyelid cleanser. Prepackaged "eyelid scrubs" are a major advance and work well. Now there are solutions containing hypochlorous acid: Avenova (hypochlorous acid 0.01%, NovaBay Pharmaceuticals; previously known as i-Lid Cleanser) and HypoChlor Spray and Gel (hypochlorous acid 0.02%, OcuSoft). Avenova is prescription only and HypoChlor is available OTC.

These cleansers are non-toxic, non-sensitizing and non-irritant formulas that can be applied to a cotton pad for eyelid cleaning.

Eye Whitener on the Horizon

Topical vasoconstrictor drops (i.e., "get the red out") are the most commonly purchased eye drops. However, dry eye disease is very likely the most common cause of chronic red eyes, and chronic use of vasoconstrictor drops can actually cause more redness over time. (We need public service announcements advising Americans to see an optometrist for red eyes and ocular discomfort!)

Let's just deal with this self-treatment epidemic in the best way we can. Like the old saying goes, "If you can't beat 'em, join 'em."

Within the next year or two, an over-the-counter "eye whitener" could revolutionize self-treatment of chronic red eye. The product will be a 0.025% brimonidine eye drop. It is reported to work in about one minute with maximum effect at five minutes, and lasts for about eight hours. Best of all, preliminary studies report no rebound redness.

Stay tuned. More on this next year…

New Dry Eye Drug in the Pipeline

Lifitegrast, which was recently granted priority review by the FDA, is a new integrin antagonist that is poised to be the next advance in helping treat patients with dry eye disease. Of course, we cannot know the real performance of any new drug until it is used in widespread clinical practice on patients, but so far lifitegrast looks promising.

In a Phase III clinical trial, lifitegrast met the primary endpoint for improving patient-reported symptoms of dry eye (compared with placebo), although it did not meet a second endpoint—inferior corneal staining. (The secondary endpoints were descriptive only and were consistent with improvement in symptoms and lack of improvement in signs.)

Lifitegrast works by blocking the chronic inflammation mediated by T-cells that is central to many forms of dry eye disease. It appears to have a relatively rapid time of onset of two to four weeks and was tested twice daily, but may need to be used BID for several months to achieve maximum control of symptoms.

Once approved, lifitegrast will be packaged in a unit-dose container. We are eagerly anticipating this new product's approval and hope that it offers improvement of both dry eye signs and symptoms. (We will have much more knowledge about lifitegrast when next year's *Clinical Guide to Ophthalmic Drugs* is published.)

Sheppard JD, Torkildsen GL, Lonsdale JD, et al; OPUS-1 Study Group. Lifitegrast ophthalmic solution 5.0% for treatment of dry eye disease: results of the OPUS-1 phase 3 study. Ophthalmology. 2014 Feb;121(2):475-83.

Sjögren's Syndrome and Dry Eye

"Although common, SS [Sjögren's syndrome] is under-recognized in clinical practice, largely as a result of its diverse presentation, leading to a significant delay in diagnosis. This delay is of great clinical significance because patients with SS are likely to have reduced quality of life as a result of pain, fatigue, depressed mood and cognitive symptoms," according to a recent study in *Ophthalmology*.

Other important points from this article:

- "Sjögren's syndrome is a multisystem autoimmune disease characterized by lymphocytic infiltration of exocrine glands and other organs."
- "Lymphoma is one of the most serious complications of SS, and the primary source of increased mortality resulting from this disease. Multiple studies consistently have identified SS as an independent risk factor for non-Hodgkin's lymphoma."
- "We recommend assessing the presence of SS in patients with clinically significant dry eye because dry eye precedes the occurrence of these manifestations."

Optometry has a unique opportunity to help potential SS patients by being keenly attentive to the history, and care, of patients with dry eye disease. So, be sure to query patients, particularly women, about pain, fatigue, depressed mood and cognitive symptoms.

Simply write down the words "Sjögren's syndrome" for your SS suspects, and encourage them to ask their personal physician to pursue a diagnostic evaluation. It is our duty and responsibility to be especially attentive to this cohort of possible SS patients, and to provide guidance and encouragement to them.

Getting these SS-suspicious patients to competent care may be critical to their longevity and quality of life.

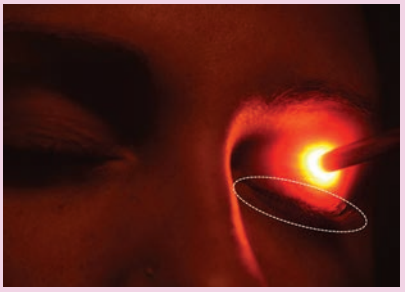
Akpek EK, Mathews P, Hahn S, et al. Ocular and systemic morbidity in a longitudinal cohort of Sjögren's syndrome. Ophthalmology. 2015 Jan;122(1):56-61.

Novel Assessment of 'Morning Dry Eye'

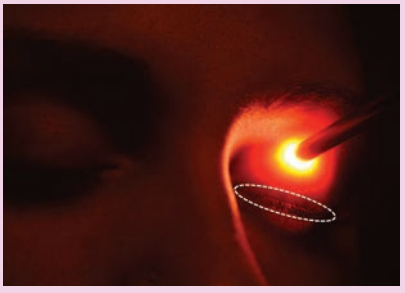
Many patients complain of a sandy, gritty, dry feeling to their eyes upon awakening; this is referred to as "morning dry eye."

Besides nocturnal lagophthalmos, many of us simply do not completely close our eyes during sleep. How else could sleeping under a ceiling fan cause ocular surface desiccation if the eyelids are indeed fully sealed?!

Optometrists Caroline Blackie and Donald Korb have found a simple way, published recently in *Eye and Contact Lens*, to assess the presence of incomplete eyelid closure. They demonstrate that using a Finoff transilluminator to transmit light through the upper eyelid can reveal subtle light points through the tiny gaps at the interface of the upper and lower eyelids. This clinically documents a route of ocular surface exposure, which is rationally linked to morning symptoms of dry eye.



A negative lid-light evaluation: no transilluminated light emanates from the keratinized lid margins (within the ellipse). The evaluation score is zero.



A positive lid-light evaluation: The amount of transilluminated light emanating from the keratinized lid margins is mild in the nasal region (a score of 1) and moderate in the central region (a score of 2).

The examination technique is this: with the patient semi-reclined (the headrest can give stability and comfort to this posture), have the patient gently close the eyes as if going to sleep. Raise the chair to a height that makes it easy for you to view the eyelid closure status. Then gently place (barely make contact) the transilluminator at the superior junction of the tarsal plate near the superotemporal region of the upper eyelid. Now simply observe for any light "leaking" from between the eyelids. (A head-fixed magnifying loupe may enhance your view.)

Therapeutic interventions for such documented "non-closure" can be tiered: have the patient use Lotemax preservative-free ophthalmic ointment for a week, followed by either gentle eyelid taping thereafter, or GenTeal gel or any other preservative-free OTC ophthalmic artificial tears, ointments, or a combination of the above.

We encourage doctors to begin performing this "Korb-Blackie lid-light evaluation" on all their patients who present with morning symptoms of dry eye. It may well provide the answer as to why some patients have these symptoms when waking.

A concurrent complexity to these morning dry eye symptoms may be a patient with a negative lid-light finding. This subset of patients may have entrapment and sequestration of an abundance of pro-inflammatory cytokines and subsequent downstream inflammatory mediators bathing the ocular surface during the sleep cycle. It is for these patients with a negative lid-light test that we would not hesitate to prescribe a one- or two-week course of Lotemax ointment at bedtime to gain symptomatic control.

Following this treatment, traditional therapeutic interventions such as a lipid-based artificial tear along with enduring use of fish oil may well keep the patient asymptomatic. Nocturnal gel or ointment lubrication may or may not need to be continued.

Blackie CA, Korb DR. A novel lid seal evaluation: the Korb-Blackie light test. Eye Contact Lens. 2015 Mar;41(2):98-100.

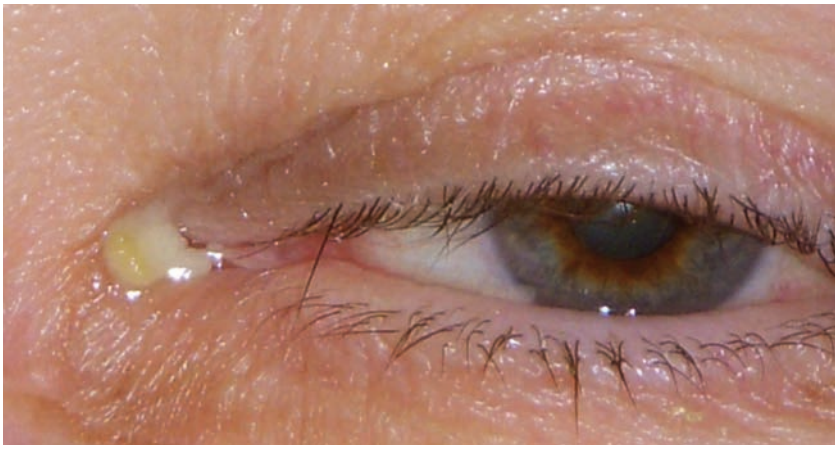
Eye Care Antibiotics

For killing pathogens, choosing the right drug is important—but ensuring frequent instillation is even more important.

Pure bacterial infection is relatively uncommon in the epidemiological perspective of the acute red eye—less common than other causes of conjunctivitis or keratitis.[1] Unless you see mucopurulent discharge, you'd be hard pressed to render a diagnosis of acute bacterial conjunctivitis.

Remember that the epidemiology of the acute red eye is primarily one of inflammation. So, keep this prevalence and incidence in the forefront of your mind to steer you in the proper diagnostic direction.

Here is a comprehensive review, in alphabetical order, of the antibiotics used in eye care.



Mucopurulent bacterial conjunctivitis in a relatively uninflamed eye, which simply calls for a topical antibiotic. However, if the eye in such an infection is injected (which it often is), use an antibiotic/steroid combination to address both the infection and the secondary inflammation.

Azithromycin

There are three macrolide antibiotics: azithromycin, clarithromycin and erythromycin. The two most commonly used in eye care are azithromycin (orally and topically) and erythromycin (topical ointment). These share a common allergenicity.

• ***Topical azithromycin***. The topical form of azithromycin 1% is known by the brand name AzaSite (Akorn). Its approved indication in eye care is for treatment of bacterial conjunctivitis. Because of its highly viscous delivery vehicle (DuraSite), it has a convenient dosing schedule of twice a day for two days, then daily for five more days. (While azithromycin may also have a very limited role in the amelioration of eyelid disease, it pales in comparison to the efficacy of a combination antibiotic/steroid such as Zylet, TobraDex or generic Maxitrol.)

• ***Oral azithromycin***. Oral azithromycin is the drug of choice in treatment of adult inclusion (chlamydial) conjunctivitis, which is pathognomonically characterized by the presence of giant follicles in the inferior forniceal conjunctiva, usually unilaterally. Given as a single dose of 1,000mg, oral azithromycin is chlamydiacidal in almost all cases. It is available generically and by the brand name Zithromax (Pfizer) in 250mg and 500mg tablets, and as a pre-packaged 1,000mg oral suspension.

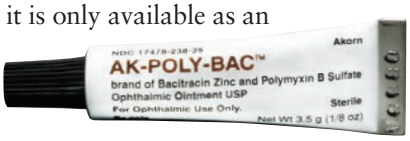
Bacitracin

Available since 1948, bacitracin remains a highly efficacious bactericidal drug against gram-positive bacterial pathogens. It is only available in ointment form, which limits its practical clinical use to the treatment of staphylococcal blepharitis and as augmentation

to topical therapies when treating severe bacterial conjunctivitis and/or keratitis. Bacitracin ointment is best instilled at bedtime because of ointment-associated blur.

Bacitracin/Polymyxin B

Bacitracin is almost exclusively gram-positive bactericidal—including methicillin-resistant *Staph. aureus* (MRSA) isolates—so combining it with polymyxin B, which is almost exclusively gram-negative bactericidal, produces a highly effective, nontoxic combination antibiotic. The drawback is that it is only available as an



ophthalmic ointment, which limits its clinical usefulness. However, some doctors treat children's eye in-

A Simple, Two-Tiered Approach to Topical Antibiotics

Mild to Moderate Bacterial Infection

When we encounter a mild to moderate bacterial infection, we commonly prescribe the generic version Maxitrol (Alcon), commonly known as NeoPolyDex, a combination of neomycin, polymyxin B and dexamethasone.

While we're not huge fans of neomycin, we have zero fear of it. It is indeed an excellent broad-spectrum antibiotic, but it's not effective against *Pseudomonas*, which is why it is combined with the excellent gram-negative bactericidal polymyxin B. We also have little use for dexamethasone, but this combination drug is cheap (the cash price was about $10 five years ago and is about $25 currently) and works excellently. We have never prescribed NeoPolyDex for more than a week because of the slight possibility of a mild aminoglycoside toxic reaction from the neomycin and the risk of increased intraocular pressure from the dexamethasone. Our perspective on the use of this combination antibiotic: Kill the bacteria, and concurrently kill the inflammation! This drug is so simple, so inexpensive and so effective—for short-term use.

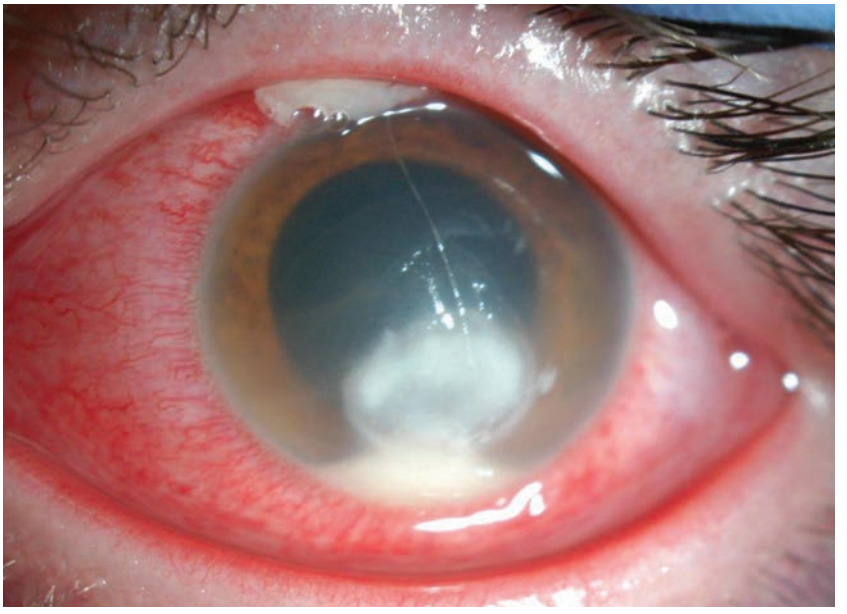
Severe Infection

For more severe infections, we may use a pure antibiotic such as Besivance (besifloxacin 0.6%, Bausch + Lomb) or gentamicin, and perhaps an ophthalmic ointment such as Polysporin (bacitracin/polymyxin B) or Neosporin (neomycin/polymyxin B/bacitracin) at bedtime.

In even rarer cases, we may consider prescribing an oral antibiotic along with these other measures, but these instances are truly rare.

Topical Antibiotic Drugs

BRAND NAME	GENERIC NAME	MANUFACTURER	PREPARATION	PEDIATRIC USE	BOTTLE/TUBE
Fluoroquinolones					
Besivance	besifloxacin 0.6%	Bausch + Lomb	suspension	≥ 1 yr.	5ml
Ciloxan	ciprofloxacin 0.3%	Alcon, and generic	sol./oint.	≥ 1 yr./ ≥ 2 yrs.	5ml, 10ml/3.5g
Moxeza	moxifloxacin 0.5%	Alcon	solution	≥ 4 mos.	3ml
Ocuflox	ofloxacin 0.3%	Allergan, and generic	solution	≥ 1 yr.	5ml, 10ml
Vigamox	moxifloxacin 0.5%	Alcon	solution	≥ 1 yr.	3ml
Zymaxid	gatifloxacin 0.5%	Allergan, and generic	solution	≥ 1 yr.	2.5ml
Aminoglycosides					
Tobrex	tobramycin 0.3%	Alcon, and generic	sol./oint.	≥ 2 mos.	5ml/3.5g
Garamycin	gentamicin 0.3%	Perrigo, and generic	sol./oint.	N/A	5ml/3.5g
Polymyxin B Combinations					
Polytrim	polymyxin B/trimethoprim	Allergan, and generic	solution	≥ 2 mos.	10ml
Polysporin	polymyxin B/bacitracin	generic	ointment	N/A	3.5g
Neosporin	polymyxin B/neomycin/gramicidin	generic	solution	N/A	10m
	polymyxin B/neomycin/bacitracin	generic	ointment	N/A	3.5g
Other Antibiotics					
AzaSite	azithromycin 1%	Akorn	solution	≥ 1 yr.	2.5ml
Ilotycin	erythromycin 0.5%	Perrigo, and generic	ointment	≥ 2 mos.	3.5g
Bacitracin	bacitracin 500u/g	Perrigo	ointment	N/A	3.5g



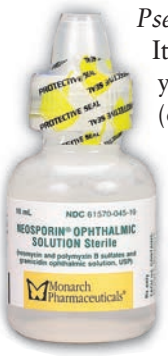
If a patient presents with a bacterial corneal ulcer, begin frequent instillation of a newer fluoroquinolone. If the ulcer is central or large (>2mm), then use fortified vancomycin or fortified tobramycin.

fections by smearing this ointment on the eyelids, where body temperature melts the ointment and allows adequate ocular surface application of the drug. (Such a principle can be applied to all ointment formulations for patients of all ages.)

When used to treat bacterial keratitis or a severe bacterial conjunctivitis, this combination medicine can be applied at bedtime to nicely augment daytime eyedrops.

Bacitracin/Polymyxin B/ Neomycin

Neomycin, an aminoglycoside, is inherently broad spectrum with the notable exception of *Pseudomonas* species. It is a terrific drug, yet its use is avoided (out of proportion) because of its slight potential to cause a type 4 delayed hypersensitivity reaction to the eye surface and eyelid tissues. This annoying reaction, which is not a serious concern, is reported to occur in about 10% of patients, and is one reason this triple antibiotic ophthalmic is minimally used.[2]



If such a delayed reaction occurs, simply stop the antibiotic and instruct the patient to use cool compresses. Or, replace the antibiotic with a steroid to suppress the inflammatory process. Once the neomycin combination is discontinued, the reaction will subside in a few days. Again, this is an annoyance, not a crisis.

This triple antibiotic was originally known as Neosporin, and is available in both solution (which contains gramicidin in place of bacitracin) and ointment forms. (By the way, when this drug is combined with a corticosteroid, such neomycin reactions are either muted or rarely seen.)

Besifloxacin

Besifloxacin 0.6% is available as Besivance (Bausch + Lomb) suspension. This unique bi-halogenated chlorofluoroquinolone is a highly effective, broad-spectrum topical antibiotic. It is our drug of choice when treating moderate to severe conjunctival or corneal infections.

For severe infectious processes, we dose besifloxacin hourly (while awake) for one to three days, then taper the dose to every two hours for a few more days, then to four times a day for a few more days. Depending upon the severity and character of the infectious process, we may adjunctively prescribe Polysporin or Neosporin ointment at bedtime.

Cephalexin

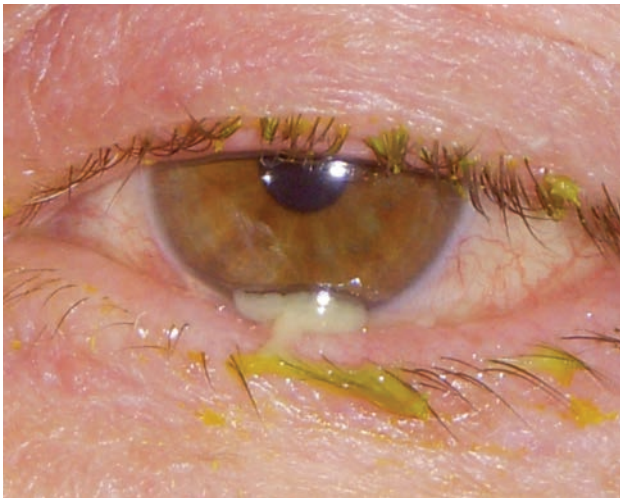
This is the "go-to" oral antibiotic we prescribe for almost all moderate to advanced cases of acute eyelid infections. It is prescribed at 500mg by mouth twice a day for one week. We always urge aggressive use of warm soaks along with antibiotic use for lid infections.

This first-generation cephalosporin shares about a 0.1% cross-allergenicity with the penicillins, so if a patient has had a severe reaction to penicillin, then avoid first-generation cephalosporins. For those very rare patients who do have a true allergy to penicillin, there are plenty of other options:

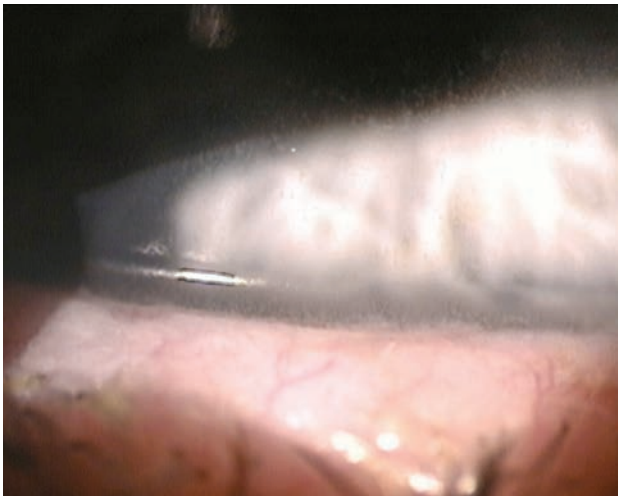
- Second- or third-generation cephalosporins
- Sulfamethoxazole/trimethoprim (Bactrim or Septra)
- One of the fluoroquinolones
- Doxycycline
- One of the macrolides

Ciprofloxacin

This early-generation fluoroquinolone is still a drug of choice against



A typical bacterial conjunctivitis showing mucopurulent discharge.



However, not all bacterial infections present with obvious discharge. Check the lacrimal lake for microparticulant debris.

Pseudomonas species. It remains a good drug for general external eye bacterial infections, and is close in efficacy to the fourth-generation fluoroquinolones.

However, ciprofloxacin is a somewhat unstable solution that precipitates out when treating corneal ulcers and gives a fine powder-like appearance to the ulcer bed, which is of no clinical significance.

Doxycycline

Other than doxycycline, tetracycline and minocycline are the other two drugs in the tetracycline class. But unlike tetracycline (which is rarely used), doxycycline (which is available only for oral use) can be taken with meals.

It is a drug of choice for treating MRSA eyelid and other skin infections, and is dosed at 100mg twice a day for seven to 10 days. Doxycycline can be used to treat chlamydial infections at 100mg twice a day for two weeks. In most of these cases, we prefer the simpler dosing of oral azithromycin; however, if the chlamydial species proves resistant to azithromycin, we consider using the longer course of the oral doxycycline.

By far, the greatest utility of doxycycline is in the treatment and management of meibomian gland disease, rosacea blepharitis, dry eye, pterygia and recurrent corneal erosion. These five conditions comprise a sizable chunk of those seen in routine practice. Doxycycline is used in low doses and for extended periods of time for these conditions.

As a general rule, we prescribe 50mg of doxycycline daily for one to six months, depending upon the patient's specific condition.

Some finer points:

• For dry eye disease and meibomian gland dysfunction, we find that doxycycline provides a more robust and quicker onset of action than do fish or flaxseed oils.

• For patients with severe dry eye disease, we may begin with doxycycline for a couple of months before converting them over to omega fatty acids for maintenance care.

• For recurrent corneal erosion and for inflamed pterygia, we typically prescribe doxycycline 50mg daily for about six to eight weeks along with Lotemax gel (loteprednol 0.5%, Bausch + Lomb) three to four times a day for six to eight weeks.

• For rosacea blepharitis, we prescribe doxycycline for about two to four months, along with eyelid scrubs once daily and Lotemax gel four times a day for one month, then twice a day for one month. For enduring care, eyelid hygiene and warm soaks usually keep most of these rosacea blepharitis conditions in check.

Erythromycin

• *Topical erythromycin.* Ophthalmic erythromycin is a soothing, non-toxic, weakly bacteriostatic ointment. Like its oral counterpart, it is rarely ever used as first-line treatment for anything, but often as second-line treatment for

many things. We never use this ointment for active disease treatment because of its relatively poor

antimicrobial spectrum of activity.

However, erythromycin is useful for "soft" overnight prophylaxis when indicated, such as for corneal abrasions and marked exposure keratitis, among others.

• ***Oral erythromycin***. The oral form (dosed at 250mg to 500mg BID or QID, depending on disease severity and the weight of the patient) can be very helpful in the treatment of blepharoconjunctivitis in children under the age of 10. However, QID dosing of erythromycin is impractical in young children; for this reason clarithromycin, and especially azithromycin, have replaced erythromycin as the macrolide of choice for this purpose. Doxycycline is preferable for patients over age 10 with this condition.

Erythromycin is not a high-use medication, either topically or orally.

Gatifloxacin

Topical gatifloxacin 0.5% is available as Zymaxid (Allergan) solution, and is a fairly effective fourth-generation fluoroquinolone for bacterial conjunctivitis. Although it is still a useful medicine, all fourth-generation fluoroquinolones are exhibiting increasing bacterial resistance. Like all topical antibiotic medicines, use it more

Antibiotic Resistance and Endophthalmitis

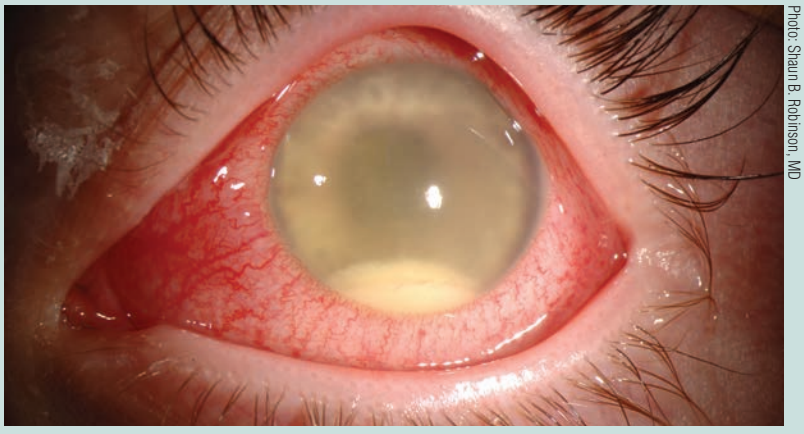


Photo: Shaun B. Robinson, MD

1."Moxifloxacin resistance rates of coagulase-negative *Staphylococcus* [this speaks almost exclusively to staphylococcal epidermidis], the cause of approximately 70% of endophthalmitis in cataract surgery, are increasing. The mean resistance rates for moxifloxacin against coagulase-negative *Staphylococcus* endophthalmitis specimens at a large university center over the past six years were almost 60%. This is up from 0% in the early 1990s."—*JAMA Ophthalmology*, November 2014[1]

2. "Recent studies suggest that repeated short courses of postinjection topical antibiotics not only do not decrease the risk of endophthalmitis but also may actually increase antibiotic resistance among conjunctival flora."—*American Journal of Ophthalmology*, March 2014[2]

3. "Use of only povidone-iodine [Betadine Sterile Ophthalmic Prep Solution] at the time of intravitreal injections without topical antibiotics appears to have the lowest risk of contributing to the widespread problem of increasing antibiotic resistance."—*American Journal of Ophthalmology*, March 2014[2]

4. "Numerous studies have evaluated the efficacy of third- and fourth-generation fluoroquinolones against endophthalmitis isolates and noted the increasing resistance of bacteria to these agents." Interestingly, "the fourth-generation fluoroquinolones evaluated did not provide much greater coverage than the earlier generation fluoroquinolones."

There is "a significant trend toward decreasing microbial resistance against aminoglycosides"; indeed, "the efficacy of aminoglycosides has been well documented in endophthalmitis."—*Ophthalmology*, August 2014[3]

5. "For topical agents, the MIC_{90} value … is considered the gold standard measurement of antibiotic efficacy."—*Review of Optometry*, April 2014[4]

1. Schimel AM, Alfonso EC, Flynn HW Jr. Endophthalmitis prophylaxis for cataract surgery: are intracameral antibiotics necessary? JAMA Ophthalmol. 2014 Nov;132(11):1269-70.
2. Hsu J, Gerstenblith AT, Garg SJ, Vander JF. Conjunctival flora antibiotic resistance patterns after serial intravitreal injections without postinjection topical antibiotics. Am J Ophthalmol. 2014 Mar;157(3):514-8.
3. Gentile RC, Shukla S, Shah M, et al. Microbiological spectrum and antibiotic sensitivity in endophthalmitis: a 25-year review. Ophthalmology. 2014 Aug;121(8):1634-42.
4. Mangan RB. Don't let dangerous pathogens resist arrest. Rev Optom. 2014 April;151(4):42-47.

Antimicrobial Resistance

• "The high prevalence of fluoroquinolone-resistant organisms among ocular and nasal flora in our patient population raises concern with regard to the usefulness of topical fluoroquinolones as the best first-line agent in the setting of ophthalmic prophylaxis and for empiric use in acute ophthalmic infectious processes."

• *Staph.* epidermidis was the most common pathogen in this study.

• 97% of all isolates were sensitive to gentamicin.

• Fluoroquinolone resistance ranged from 32% to 40%.

Alabiad CR, Miller D, Schiffman JC, Davis JL. Antimicrobial resistance profiles of ocular and nasal flora in patients undergoing intravitreal injections. Am J Ophthalmol. 2011 Dec;152(6):999-1004.

frequently initially (i.e., every one to two hours) until the condition comes under control. Then reduce its use to four times a day for a few more days until the condition is resolved.

Gentamicin (and Tobramycin)

These old, generic aminoglycosides are some of the most highly efficacious antibiotic eyedrops available. The reason: These medicines are not used systemically (because of ototoxicity issues), and therefore are relatively protected from the bacterial resistance that comes from primary care use. It is the widespread systemic use of an antibiotic that tends to fast-forward its resistance.

While these drugs have a reputation for their potential to be corneotoxic, we have never experienced such in our practices. With most medicines, the key is to "get in and get out" as quickly as possible. We can't imagine a situation in which these aminoglycosides ever would be used for more than seven to 10 days, which may be why we've never seen a toxic response (severe corneal infection is one case where these will be used longer than 10 days).

If such a response were to occur, simply stop the offending medicine and try a different drug, such as trimethoprim/polymyxin B or Besivance. Consider adding artificial tears for a few days to help restore the ocular surface to normal.

Levofloxacin

• ***Topical levofloxacin.*** This so-called third-generation fluoroquinolone came in two concentrations: levofloxacin 0.3% as Quixin and levofloxacin 1.5% as Iquix. But both have been discontinued in the US.

• ***Oral levofloxacin.*** The oral form is known by the original brand name Levaquin (Janssen Pharmaceuticals), but is also available generically.

Levofloxacin is a superb oral antibiotic, and is very convenient to take as one 500mg tablet daily for seven to 10 days. But, even the generic form of levofloxacin is more expensive than other first-tier generic options, and so it is not our first choice.

For acute eyelid infections, we commonly prescribe cephalexin (Keflex, or generic) at 500mg twice a day for one week. However, if the patient is truly penicillin-allergic, then oral levofloxacin may be an excellent alternative.

Moxifloxacin

Topical moxifloxacin 0.5%, available as Moxeza (Alcon) and Vigamox (Alcon), has been perhaps the most popular of the fourth-generation fluoroquinolones and has served the public well. But, like all the classic fluoroquinolones, it has developed significant bacterial resistance. Both varieties function very similarly. But

Evolving Fluoroquinolone Resistance

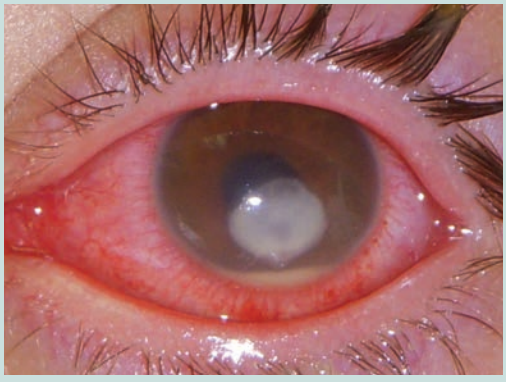
"Fourth-generation fluoroquinolones are significantly more expensive than generic traditional antibiotic eyedrops such as gentamicin sulfate and polymyxin B sulfate/trimethoprim, which have been shown to cover endophthalmitis isolates at least as well … Given the frequent and increasing resistance, subtherapeutic penetration and higher cost compared with other antibiotic eyedrops, the widespread perioperative and periprocedural use of fourth-generation fluoroquinolone antibiotic eyedrops should be reevaluated."

Schimel AM, Miller D, Flynn HW. Evolving fluoroquinolone resistance among coagulase-negative Staphylococcus isolates causing endophthalmitis. Arch Ophthalmol. 2012 Dec 1;130(12):1617-8.

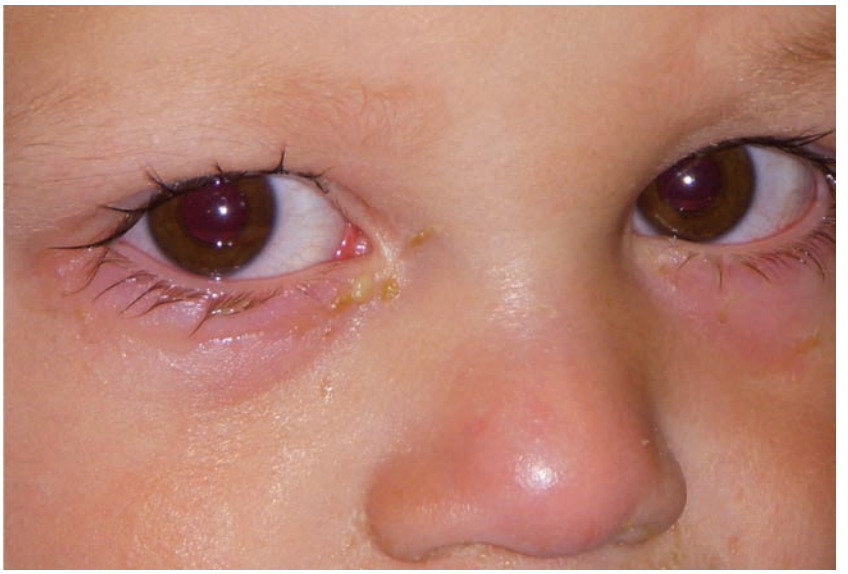
Antibiotics for Corneal Keratitis

"Corneal infectious keratitis and ulceration are ocular emergencies that require topical antibiotics as a therapeutic mainstay. At the initial examination, it is unclear whether we are dealing with one or more organisms, and if any resistance to antibiotics exists. Hence, a shotgun approach is preferred with a broad-spectrum antibiotic that covers both gram-positive and gram-negative organisms. Newer fluoroquinolones, such as besifloxacin, can be used as monotherapy with frequent applications around the clock, depending on the severity of the corneal infection."

However, if the focus of infection is central or large, then fortified vancomycin and fortified tobramycin is used.



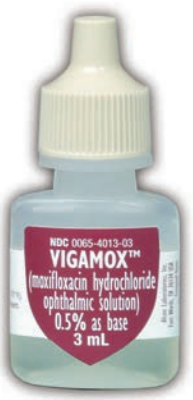
John T. Corneal clarity: A battle of biblical proportions. Ophth Management. 2014 Dec;18(12):18-19.



This baby has a low grade bacterial infection, most likely from a blocked nasolacrimal system. Prescribe generic Polytrim along with massage over the medial canthus.

Moxeza has a xanthan gum base, which allows it prolonged contact time and thus a slight reduction in dosing frequency.

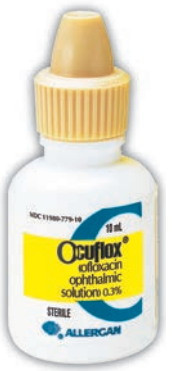
In spite of this evolving class resistance, moxifloxacin appears to remain a satisfactory choice for bacterial conjunctivitis; personally, we would choose Besivance or fortified antibiotics (vancomycin or tobramycin) for bacterial keratitis because of their documented enhanced efficacy.



An attribute of Vigamox is that it is preservative-free, thus reducing the potential for a toxic or allergic response. Also, do inform patients that the drop has a slight yellow color to avoid the misconception that the medicine has "gone bad."

Ofloxacin

Although it is now a minimally used, second-generation fluoroquinolone antibiotic, ofloxacin 0.3% is still a reasonable option for bacterial conjunctivitis—primarily because it is an inexpensive generic drug. It is also available as brand-name Ocuflox (Allergan).



Sodium Sulfacetamide

Topical sodium sulfacetamide, a workhorse of the 1960s and 1970s, has long ago gone by the wayside, chiefly because of a high resistance rate and the number of sulfa-allergic patients. But it still pops up from time to time, usually prescribed by older physicians, urgent care centers and emergency departments.

The reasons we end up seeing a subset of these folks in our offices are because of a wrong diagnosis (most common) or ineffectiveness of the drug.

Trimethoprim

• ***Topical trimethoprim***. Because of its efficacy against primarily the gram-positive spectrum—including MRSA—trimethoprim is found only in combination with other drugs. Thus, it is combined with polymyxin B to make it a truly broad-spectrum topical combination antibiotic. This combination was originally known as brand name Polytrim (Allergan), but is widely available generically. Note that trimethoprim itself is not a sulfa drug, although it also inhibits the production of bacterial folic acid.

Beyond the excellent therapeutic efficacy of this topical combination, it also has the advantage of being packaged in a 10mL bottle, allowing the patient to get more drug for the purchase price. It has minimal toxic potential, so we like to prescribe this combination along with bandage contact lens therapy if there is significant epithelial compromise, as in a corneal abrasion.

• ***Oral trimethoprim***. Systemically, trimethoprim is combined with sulfamethoxazole and known by its original brand names of Bactrim or Septra. This is one of the drugs of choice for MRSA infections. Like levofloxacin, it's an option when a patient is truly penicillin-allergic.

The signatura (*sig*.) is two "DS" tablets twice a day for seven to 10 days. (The standard strength is "double strength," thus the DS designation.) Note that the added sulfamethoxazole is a sulfonamide, so be sure to inquire about true sulfa allergy prior to prescribing. ■

1. Collier SA, Gronostaj MP, MacGurn AK, et al. Estimated Burden of Keratitis—United States, 2010. Morbidity and Mortality Weekly Report (MMWR). Centers for Disease Control and Prevention. 2014 Nov 14;63(45):1027-30.
2. Wilson FM. Adverse external ocular effects of topical ophthalmic medications. Surv Ophthalmol. 1979 Sep-Oct;24(2):57-88.

Corticosteroids

The key to success in suppressing inflammation: select an appropriate topical steroid medicine and have the patient use it frequently.

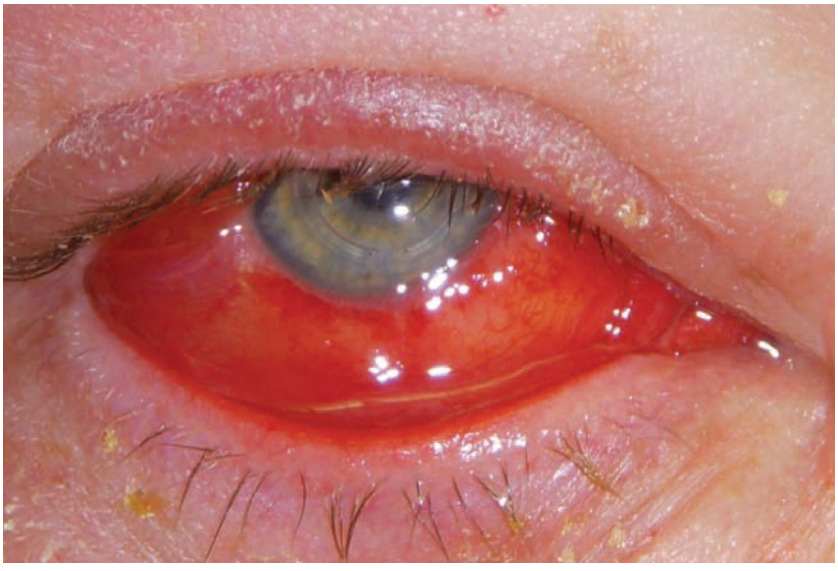
The sight-saving, quality-of-life-enhancing benefits of oral and topical corticosteroids are still not optimally embraced because of antiquated teaching that stresses their thorns, not their roses.

To be sure, improper use of steroids can cause damage; however, this reality is commonly overshadowed by their enormous benefit!

While there is a plethora of indications for the use of topical steroids, there is only one contraindication: epithelial herpetic infection. There is also only one precaution: uncertainty of the diagnosis. This "precaution" bears explanation. It's possible to have an *Acanthamoeba* or fungal keratitis that is difficult to diagnose, especially in the early stages. Using a steroid—even a combination antibiotic/steroid—could cause the condition to worsen; however, these are exceedingly rare presentations.

An essential element in disease management is proper follow-up. Seeing patients in a timely manner is critical so that if your initial treatment turns out to be ineffective, close follow-up allows you to catch it sooner. Then you can refine your diagnosis and alter the therapy.

We've seen many cases of therapeutic error in which the patient simply did not return to the initial prescriber for timely follow-up, but instead sought care from another doctor. Had the patient returned to the initial prescriber, the diagnostic error and subsequent erroneous treatment could have been easily managed. We've also seen instances in which the initial prescriber did not schedule a follow-up visit, thus the patient simply decided to go elsewhere.



This patient presented with an acute allergic reaction to an unknown chemical. He was given lavage, cold compresses and topical steroid eye drops.

Here is an example of what to do to avoid such an unfortunate scenario: Let's say we see a patient with a typical corneal lesion that could be Thygeson's or herpetic. Because the majority of acute eye presentations that we see are inflammatory in nature, we're inclined to initiate therapy with a steroid. However, in this type of situation, we would tell the patient something like this: "This medicine should help your eye get better quickly; however, the diagnosis of your condition is not completely clear, and there is a chance your eye could actually worsen on this medicine. It is important that you let me see you again in a couple of days. I will be glad to work you in anytime." We believe this truly caring, straightforward conversation is crucial for optimum patient care and rapport.

Two Keys to Clinical Success with Red Eye

1. Make an accurate diagnosis! When this simply isn't possible, then try to determine if the condition is primarily infectious or primarily inflammatory. You'll find that many, if not most, such cases are likely inflammatory in nature.

2. Since neither life nor medical care is perfect, we must properly manage occasional diagnostic and/or therapeutic uncertainty. Here's how: Tell the patient that their condition is not clear-cut, and that the best course of action is to try Drug X. We tell the patient that the medication should improve the condition over two to three days. We further explain that if the condition does not improve, and most certainly if it worsens, to let us know right away. We generally see patients back in three to five days anyway, but our patients know we care about them, and that we will see them right away if there are problems.

On those rare occasions when we are more concerned, we get a telephone number where the patient can be reached, and we call daily to see how they are doing. For an added measure of comfort, we give the patient a means to contact us directly. Again, these are uncommon scenarios, but handling those who do present in this manner is simply the right thing to do.

If you are in a group practice or have a call-sharing arrangement with area colleagues, this method for patient care can be even easier. By the way, when patients know they are supported and truly cared for, litigation is less likely. But more than that, it is just the right thing to do.

All this is called "patient management" and it is far more than disease management. (This not only applies to steroid treatment, but to the treatment of any eye condition.)

Maximum Efficacy Steroids

The key to success in suppressing inflammation is to select an appropriate topical steroid medicine and have the patient use it frequently until control is achieved, then tapering can begin as indicated.

The two most efficacious topical ophthalmic corticosteroids are Durezol emulsion (difluprednate 0.05%, Alcon) and Pred Forte (prednisolone acetate 1%, Allergan)—but not generic prednisolone acetate! (More on this below.)

• ***Durezol***. Durezol is an emulsion and does not need to be shaken before instillation. We use it as our "big gun" to treat advanced cases of iritis and episcleritis. Durezol's longer duration of action permits less frequent dosing than with prednisolone formulations, but provides equal efficacy.[1] So, we dose it every two hours initially, rather than hourly.

But, along with Durezol's increased efficacy comes an increased risk of significant IOP elevation, especially in children.[2] So be sure to monitor IOP attentively.

• ***Pred Forte***. Prednisolone acetate 1% also has good anti-inflammatory efficacy.[3] Pred Forte is a workhorse and, like Durezol, is used primarily to treat significant cases of anterior uveitis and episcleritis, and other severe ocular inflammatory conditions.

Topical Corticosteroid Drugs

BRAND NAME	GENERIC NAME	MANUFACTURER	PREPARATION	BOTTLE/TUBE
Maximum Strength Steroids				
Durezol	difluprednate 0.05%	Alcon	emulsion	5ml
Lotemax gel	loteprednol etabonate 0.5%	Bausch + Lomb	gel-drops	5g
Lotemax ointment	loteprednol etabonate 0.5%	Bausch + Lomb	ointment	3.5g
Pred Forte	prednisolone acetate 1%	Allergan, and generic	suspension	5ml, 10ml, 15ml
generic prednisolone sodium phosphate	prednisolone sodium phosphate 1%	generic	solution	5ml, 10ml, 15ml
Vexol	rimexolone 1%	Alcon	suspension	5ml, 10ml
Moderate and Lesser Strength Steroids				
Alrex	loteprednol etabonate 0.2%	Bausch + Lomb	suspension	5ml, 10ml
Flarex	fluorometholone acetate 0.1%	Alcon	suspension	5ml, 10ml
FML	fluorometholone alcohol 0.1%	Allergan	suspension	5ml, 10ml, 15ml
FML ointment	fluorometholone alcohol 0.1%	Allergan	ointment	3.5g
Pred Mild	prednisolone acetate 0.12%	Allergan	suspension	5ml, 10ml

Because it is a suspension, instruct your patients to shake it well prior to each instillation.

Some pharmacists will dispense generic prednisolone acetate, even when you have prescribed "Dispense as written." Although the generics are considerably less expensive, they are also less effective.[4] When the maximum effect is required, nothing surpasses brand-name Pred Forte and Durezol.

High Efficacy Steroids

Next in clinical efficacy are Lotemax gel (loteprednol 0.5%, Bausch + Lomb), generic prednisolone sodium phosphate 1% solution (original brand name Inflamase Forte), and generic prednisolone acetate 1%. Dexamethasone, either the solution or suspension form, is also in this category.

• ***Lotemax gel.*** Lotemax gel is a non-settling eyedrop that does not require shaking before instillation. Don't be confused because it's called a "gel"—when dispensed from its dropper bottle, it becomes a viscous liquid. (*See "Lotemax Gel vs. Lotemax Ointment," right.*)

We often use Lotemax gel as an "off label" treatment for our dry eye patients, but we also use it to treat many other chronic, recurrent, inflammatory conditions such as stromal herpes simplex keratitis, Thygeson's SPK, uveitis, inflamed pingueculae and pterygia, etc.

While loteprednol may not be quite as efficacious as prednisolone and Durezol, it has significantly less propensity to cause unwanted side effects of subcapsular cataracts and increased IOP. In Phase III studies, for instance, only two out of 409 patients on Lotemax gel had an increase in intraocular pressure greater than 10mm Hg.[5] In addition, loteprednol 0.5% suspension was shown to be as effective as prednisolone acetate for post-op cataract surgery inflammation, and with less effect on IOP.[6]

• ***Prednisolone sodium phosphate 1%.*** This generic steroid is an excellent choice when a potent, relatively inexpensive steroid is needed. Because this is a solution, it does not require shaking; so it may be an especially good choice for older people with arthropathies for whom shaking a bottle can be a challenge. It's also good for soft contact lens wearers because it won't precipitate on the lens as much as other drops.

• ***Prednisolone acetate 1%.*** Generic prednisolone acetate suspension is a reasonable choice for mild to moderate acute inflammatory conditions, especially if cost is a concern—but not in the setting of advanced iritis and episcleritis, as discussed above.

• ***Others.*** Rimexolone 1% (Vexol, Alcon) and dexamethasone 0.1% (Decadron solution [Merck] and Maxidex suspension [Alcon]) are fine products, but are no longer commonly used.

Moderate Efficacy Steroids

Moderate efficacy steroids in common usage are fluorometholone 0.1% suspension and Alrex

Lotemax Gel vs. Lotemax Ointment

Patients, practitioners and pharmacists may mix up these two medicines, so let's set the record straight.

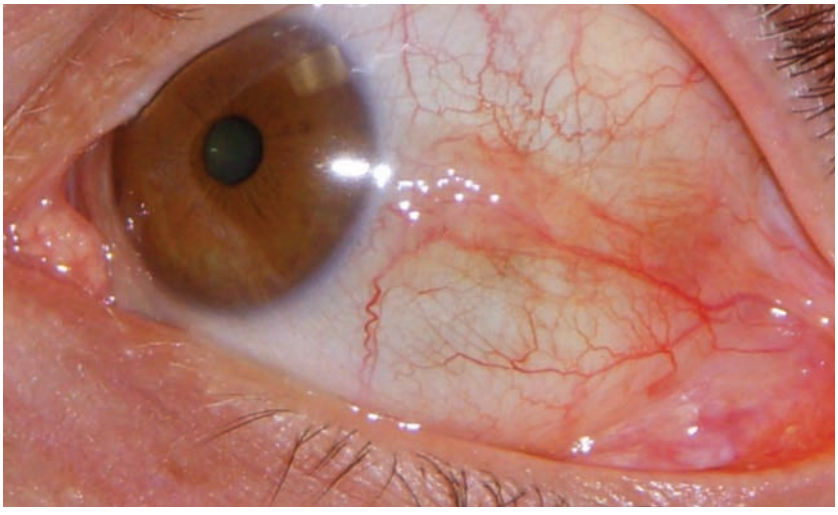
• **Lotemax gel.** Though called a gel, this comes in a dropper bottle, like a solution. However, inside the bottle, it is indeed a highly viscous, semisolid gel formulation. But, through a process called adaptive viscosity, it becomes a liquid when squeezed out of the dropper. And, upon instillation in the eye, the formulation loses its gel structure altogether as the polycarbophil polymer interacts with the electrolytes in tears. Still, the drop is rather thick upon instillation, and will cause a moment of initial blur until the gel fully converts into a liquid. We advise patients to allow the drop to spread out on the ocular surface for four to five seconds before blinking, so that the initial blink does not displace the drop onto the eyelid.

Because of the nature of this unique gel, the steroid does not settle out of the vehicle, so it does not require shaking. (It is best to tip the bottle back and forth just once to make sure the drug enters the tip of the dropper prior to instillation, but no actual shaking is necessary.) Also, unlike with suspensions, this delivery system provides a perfectly uniform dose at every instillation.

• **Lotemax ointment.** This preparation comes in a 3.5g tube and contains inactive ingredients of white petrolatum and mineral oil. Because it is an ester-based corticosteroid and also because it is a preservative-free preparation, it may provide a safety advantage over fluorometholone ointment.

Lotemax ointment is indicated for the treatment of postoperative inflammation and pain, but is also applicable in many other cases in which an ointment is useful for suppression of inflammation.

1. Marlowe ZT, Davio SR. Dose uniformity of loteprednol etabonate ophthalmic gel (0.5%) compared with branded and generic prednisolone acetate ophthalmic suspension (1%). Clin Ophthalmol. 2014;8:23-9.
2. Comstock TL, Paterno MR, Singh A, et al. Safety and efficacy of loteprednol etabonate ophthalmic ointment 0.5% for the treatment of inflammation and pain following cataract surgery. Clin Ophthalmol. 2011;5:177-86.



This inflamed pingueculum should be treated with a topical steroid. Once the inflammation is under control, then the ocular surface must be kept properly lubricated to prevent further inflammatory expression.

(loteprednol 0.2%, Bausch + Lomb) suspension, both of which must be shaken prior to instillation.

• ***Fluorometholone 0.1%.*** There are two derivatives of fluorometholone 0.1% suspension—the alcohol (FML, Allergan, and generic) and the acetate (Flarex, Alcon, and generic). The acetate moiety gives the fluorometholone molecules some additional anti-inflammatory effectiveness over the alcohol moiety.[7]

Fluorometholone is available generically and is thus reasonably inexpensive. (However, there have been sporadic reports of fluorometholone not being available in various parts of the country. When prescribing, be sure to check with your pharmacy for availability.) While fluorometholone has less tendency to increase intraocular pressure than other ketone steroids, we are not nearly as comfortable using it long-term as we are with the ester-based loteprednol.

FML Forte (fluorometholone 0.25%, Allergan) is not recommended because fluorometholone 0.1% represents the top of the dose response curve—meaning that the 0.25% formulation is no more efficacious than the 0.1%. Moreover, the 0.25% concentration has a greater tendency to raise IOP.[8]

• ***Alrex.*** For allergic eye disease, prescribe a topical steroid when itching is accompanied by clinical signs of conjunctival injection, chemosis or eyelid swelling. In these instances, Alrex (or even Lotemax gel) is the answer. We typically dose Alrex (or Lotemax gel) QID for one week, then BID for one month.

Beyond awareness of the various delivery systems (suspensions, solutions, emulsions, gels and ointments), knowing the clinical efficacy of these drugs is important.

Steroid Ointments

The ophthalmic ointments enjoy a wide array of clinical indications. There are three corticosteroid medicines that merit frequent clinical use in the ointment formulation:

• ***Lotemax ointment.*** Lotemax ophthalmic ointment (loteprednol 0.5%, Bausch + Lomb) is the only ester-based steroid ointment available. It is indicated for postoperative inflammation and pain, but also has many "off-label" clinical uses: dry eye, allergy, corneal trans-

Tips for Tapering

Ever had a challenge tapering a patient off a topical corticosteroid? Steroids are wonderful for short-term therapy, but carry intrinsic risks when used long-term.

Here are a couple of thoughts: You can usually get patients down to three or two times a day, or even once daily, before a relapse occurs. Of course, now you have to increase the dosage again and try a longer, slower taper. Try adding a topical NSAID, such as Prolensa (bromfenac, Bausch + Lomb), daily as you begin the next step-down of the corticosteroid. This may offer enough supplemental anti-inflammatory support to enable the continuation of the steroid taper. Or, try the oral NSAID route: prescribe Celebrex (celecoxib, Pfizer) 100mg per day for a few weeks.

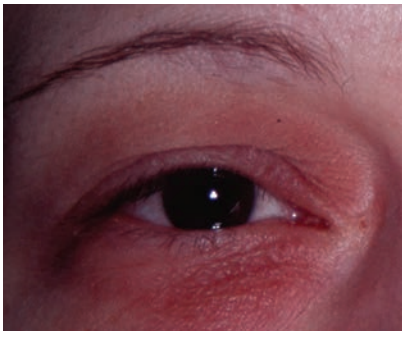
There are instances when long-term steroid use is indicated. Some patients who have had corneal transplants, stromal immune corneal disease, chronic uveitis or recalcitrant dry eye disease may be kept on low-dose steroids for life. While older ketone-based steroids have been used for long-term therapy in the past, we would recommend ester-based loteprednol 0.5% gel once daily for these protracted dosing schedules. (The ketone-based steroids seem to work well in this low-dose approach, yet it stands to reason that loteprednol, being an ester-based steroid, is preferable because of its enhanced safety profile.) Some patients just require one drop of steroid daily to maintain control of their condition.

plant protection, blepharitis, giant papillary conjunctivitis, chronic uveitis, stromal immune herpetic keratitis, Thygeson's SPK, RCE, augmentation of steroid eyedrop therapy in acute advanced uveitis or episcleritis, contact dermatitis and other inflammatory conditions.

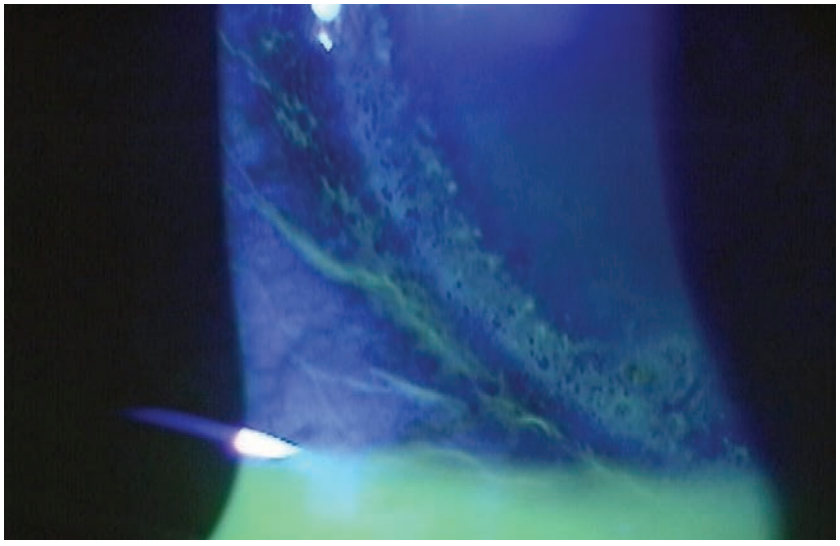
• ***FML ointment.*** FML ophthalmic ointment (fluorometholone 0.1%, Allergan) is used much the same as Lotemax ointment. It is indicated for inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe, and any of the "off label" uses mentioned above. The only very minor difference is to keep a little bit closer watch on the patient for steroid-related adverse effects.

• ***Triamcinolone 0.1% cream.*** This is a dermatologic preparation that works well for periocular dermatitis conditions. Triamcinolone 0.1% cream, which became generic long ago, has been our favorite medicine for many years to treat contact blepharodermatitis. It comes in 15g and 30g tubes, each costing less than $10 in most markets.

Be sure to tell the patient that on the side of the tube is the statement "NOT FOR OPHTHALMIC USE," but that the medication



A classic case of contact dermatitis. Prescribe triamcinolone 0.1% cream.



Microcystic edema is a marker for tissue inflammation and is easily suppressed with topical corticosteroid therapy.

is perfectly fine to use as you have prescribed. We explain that triamcinolone, also known by the brand name Kenalog, is frequently used by retina subspecialists for FDA-approved injection into the eye. In other words, if some of the triamcinolone cream gets into the patient's eyes, it's nothing to worry about.

Corticosteroids are the most essential and highly prescribed medicines in the treatment of ocular inflammation of any stripe. Their widespread clinical usage confirms that ocular inflammation is the most common clinical manifestation seen in eyecare.

It is so important that all doctors of optometry come to terms with this reality and strive to become very comfortable caring for patients with inflammatory eye disease. ■

1. Foster CS, Davanzo R, Flynn TE, et al. Durezol (Difluprednate Ophthalmic Emulsion 0.05%) compared with Pred Forte 1% ophthalmic suspension in the treatment of endogenous anterior uveitis. J Ocul Pharmacol Ther. 2010 Oct;26(5):475-83.
2. Slabaugh MA, Herlihy E, Ongchin S, van Gelder RN. Efficacy and potential complications of difluprednate use for pediatric uveitis. Am J Ophthalmol. 2012 May;153(5):932-8.
3. Leibowitz HM, Ryan WJ Jr, Kupferman A. Comparative anti-inflammatory efficacy of topical corticosteroids with low glaucoma-inducing potential. Arch Ophthalmol. 1992 Jan;110(1):118-20.
4. Roberts CW, Nelson PL. Comparative analysis of prednisolone acetate suspensions. J Ocul Pharmacol Ther. 2007 Apr;23(2):182-7.
5. US Food and Drug Administration. Center for Drug Evaluation and Research. Deputy Division Director Review for NDA 202-872. 2012 Sep 27. Available at: www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202872Orig1s000MedR.pdf.
6. Lane SS, Holland EJ. Loteprednol etabonate 0.5% versus prednisolone acetate 1.0% for the treatment of inflammation after cataract surgery. J Cataract Refract Surg. 2013 Feb;39(2):168-73.
7. Leibowitz HM, Hyndiuk RA, Lindsey C, Rosenthal AL. Fluorometholone acetate: clinical evaluation in the treatment of external ocular inflammation. Ann Ophthalmol. 1984 Dec;16(12):1110-5.
8. Kass M, Cheetham J, Duzman E, Burke PJ. The ocular hypertensive effect of 0.25% fluorometholone in corticosteroid responders. Am J Ophthalmol. 1986 Aug 15;102(2):159-63.

Relative Clinical Efficacy of Topical Steroids

Here, based on our clinical experience and the comparative information we have available, we rate the relative efficacy of the topical steroids, starting with the most efficacious:

1. Difluprednate 0.05%
2. Prednisolone 1%
3. Loteprednol 0.5%
4. Rimexolone 1%
5. Fluorometholone acetate 0.1%
6. Dexamethasone 0.1%
7. Fluorometholone alcohol 0.1%
8. Loteprednol 0.2%
9. Prednisolone 0.125%
10. Hydrocortisone 1%

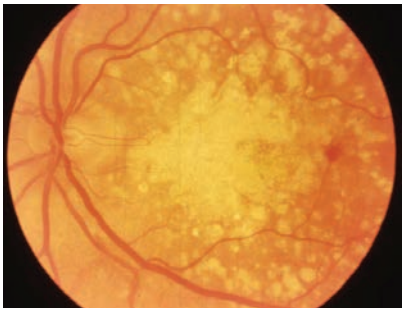
Perspectives on the Posterior Pole

Age-related macular degeneration can be an insidious disease. Fortunately, we can help patients protect themselves by recommending a healthy diet and lifestyle.

In November 2014, there was a workshop at the Institute of Medicine involving the National Eye Institute focused on dry age-related macular degeneration. Following is a summary of the salient points gathered from that meeting, as published in the March 2015 issue of *EyeNet*:[1]

• ***Dry AMD progresses to wet AMD.*** The neovascular form of AMD is a complication of the progression of dry AMD. "Any disease that causes the breakdown of Bruch's membrane and [retinal] pigment epithelium has the potential to encourage these abnormal choroidal vessels to start growing," said Frederick L. Ferris III, MD. As a result of this, slowing the progression of dry AMD is a critical goal. "So finding an effective treatment for dry AMD really is the Holy Grail of AMD treatment."

• ***Medium drusen signal AMD.*** Dr. Ferris observed that the common form of AMD is expressed as the progression from small drusen to medium drusen to large drusen, along with associated RPE pigmentary changes, eventually leading to the development of geographic atrophy. However, he said, very few small drusen progress to large drusen.



Few small drusen progress to large drusen, and most large drusen never progress to geographic atrophy.

One recent study revealed that it takes, on average, six years to progress from large drusen to geographic atrophy.[2] "The reality is that most large drusen never progress to geographic atrophy … that is a major cause of vision loss," Dr. Ferris said.

"Just about everyone will develop small drusen as part of the aging process," Dr. Ferris said. In fact, some researchers argued that small drusen really should not be classified as AMD, but rather simply be referred to as "normal aging changes." Current data support that small drusen are not a risk factor for progression to large drusen. It has been shown that it's not the little drusen that are a problem, and these patients don't need to needlessly worry by being told they have early AMD. (Dr. Ferris added, "That's not to say that these little drusen aren't important.")

But when medium-sized drusen are observed, this patient may be potentially on the way to advanced forms of AMD, most notably geographic atrophy. Patients who have medium-sized drusen in both eyes have a 50/50 chance of having large drusen in five years. To repeat, it's the medium drusen that are the hallmark of the earliest stages of AMD.

• ***Dietary factors are protective.*** It was pointed out that even in patients who have a genetic predisposition to advanced forms of AMD, if one eats well and eats the foods that one is supposed to eat, one's risk can be muted, which is exciting news.

So, what can patients do to decrease their risk for advanced AMD? "Don't smoke; follow a healthful diet rich in dark green leafy vegetables and low in fat; eat fish a few times a week; maintain a normal weight and waist size; exercise regularly; and control blood pressure and cholesterol," suggested Johanna M. Seddon, MD, ScM.

She added that "anyone who has signs of intermediate level macu-

lar degeneration in both eyes, or advanced macular degeneration in one eye, should take dietary supplements that contain lutein, zeaxanthin, vitamin C, vitamin E and zinc." Further, consumption of fish and nuts is associated with a decreased risk of progression from the intermediate forms to the advanced stages of macular degeneration.[3]

We thought these were quite interesting revelations, and are grateful to the National Eye Institute and its consulting doctors for sharing this clinically relevant knowledge. Keeping abreast of such findings enables us to more properly guide and counsel our patients. ■

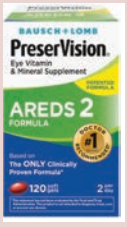
1. Doran M. Dry AMD—Advancing the pace of research. EyeNet. 2015 March;19(3):41-45.
2. Ferris FL 3rd, Wilkinson CP, Bird A, et al; Beckman Initiative for Macular Research Classification Committee. Clinical classification of age-related macular degeneration. Ophthalmology. 2013 Apr;120(4):844-51.
3. SanGiovanni JP, Chew EY, Clemons TE, et al; Age-Related Eye Disease Study Research Group. The relationship of dietary lipid intake and age-related macular degeneration in a case-control study: AREDS Report No. 20. Arch Ophthalmol. 2007 May;125(5):671-9.

Genetic Testing: AMD and AREDS2

Recent studies have advocated that genetic testing could be used for the purpose of recommending vitamin/mineral supplements for patients with AMD, and also that AREDS2 supplements offered no benefit for some patients with certain genetic characteristics.[1]

In the wake of such studies, other experts have argued that such genetic testing is not appropriate for deciding who should and who shouldn't receive nutritional supplements for AMD:

- "The combination of antioxidants and zinc, found in both the AREDS and AREDS2 supplements, remains the only beneficial formulation regardless of genotype, with no apparent indication for treatment with either antioxidants or zinc alone. Genetic testing is not recommended for initiating or determining the appropriateness of the AREDS formulation. One should not deprive patients of a therapy that has been proven to have significant public health impact on the basis of a statistically flawed, not replicated retrospective analysis of existing data."[2]
- "Improved outcomes for genotyped patients have not yet been demonstrated in a prospective clinical trial, and as a result, the costs and risks of routine genetic testing currently outweigh the benefits for patients with age-related macular degeneration."[3]



Based on these perspectives, we continue to recommend AREDS2 vitamin/mineral supplements for our patients who have clinically significant AMD.

1. Awh CC, Lane AM, Hawken S, et al. CFH and ARMS2 genetic polymorphisms predict response to antioxidants and zinc in patients with age-related macular degeneration. Ophthalmology. 2013 Nov;120(11):2317-23.
2. Chew EY, Klein ML, Clemons TE, et al. Genetic testing in persons with age-related macular degeneration and the use of the AREDS supplements: to test or not to test? Ophthalmology. 2015 Jan;122(1):212-5.
3. Stone EM. Genetic testing for age-related macular degeneration: Not indicated now. JAMA Ophthalmol. 2015 Mar 19. [Epub ahead of print]

Update on Ocriplasmin (Jetrea)

Jetrea (ocriplasmin, ThromboGenics) is an intravitreally administered treatment for symptomatic vitreomacular traction (VMT), which came to market in October 2012, and was covered in our *2013 Drug Guide*. Now with a couple of years of clinical use, more is known regarding its potential side effects.

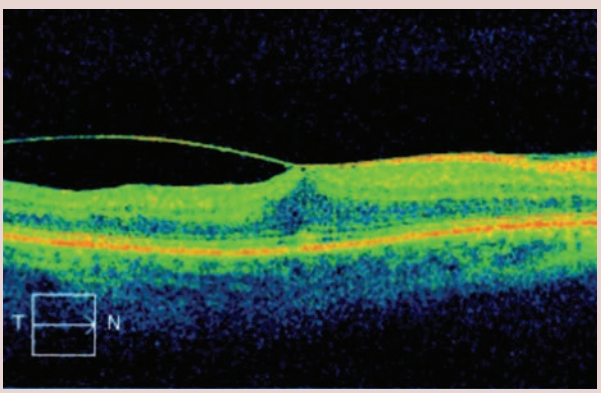
Ocriplasmin works by enzymatically cleaving fibronectin and laminin at the vitreoretinal interface. Its effectiveness is not robust, as only 26.5% of patients had VMT resolution, whereas 10.1% had resolution with a placebo injection. Macular hole closure occurred in 40% of eyes, whereas closure with placebo was 10%.

"However, since the real-world use of the drug began, there have been unfavorable anecdotal reports of visual disturbances after ocriplasmin injection, including transient but profound vision decline, raising concerns regarding its safety."[1]

"The reason for vision loss appears to involve damage to the photoreceptor outer and inner segments, suggesting that ocriplasmin may have broader substrate specificity."[2]

"Injecting an enzyme with broad substrate specificity into the eye has already revealed adverse effects."[2]

While there are many patients who have benefitted from interventional treatment with ocriplasmin, the less-than-optimum therapeutic benefit along with post-marketing realization of more extensive tissue effects has limited the embrace of this intervention. "Judicious use, thorough pretreatment discussion, and careful follow-up are needed in light of these potential adverse effects."[1]



Vitreomacular traction.

1. Kim JE. Safety and complications of ocriplasmin: ocriplasmin, ocriplasmin; oh, how safe art thou? JAMA Ophthalmol. 2014 Apr 1;132(4):379-80.
2. Beebe DC. Understanding the adverse effects of ocriplasmin. JAMA Ophthalmol. 2015 Feb;133(2):229.

Glaucoma

Selecting the proper glaucoma drug is important, but the pivotal challenge is deciding *when* to begin treatment.

About 2.5 million Americans have undiagnosed and untreated glaucoma.[1] It recently came to our attention that there are many more CE courses on glaucoma than on dry eye disease, yet our prescribing rate for glaucoma medicines is abysmal and flat! This is way beyond our understanding. If there were only three areas in which optometrists should have rock-solid expertise, it should be refractive care, dry eye disease and glaucoma.

Remember the very first time you did anything of import? You were likely nervous. We remember our fear in first performing applanation tonometry or placing a contact lens on the eye, doing gonioscopy, etc.—you get the picture. Caring for patients with glaucoma is very similar, and the learning curve (comfort curve) is very steep. We beg you to begin the process of assessing, diagnosing and treating glaucoma; you will amaze yourself.

The most challenging decision for all glaucoma doctors is when to treat. Within the next several pages, we clearly lay out the steps for both diagnosing and therapeutically managing your glaucoma and glaucoma suspect patients. We hope you will read these carefully and then confidently apply these steps directly to the care of patients in your own practice.

However, if all this encouragement doesn't lift you above the comfort threshold, then we sincerely urge you to find an optometrist in your area who does provide glaucoma services, and send your glaucoma-related patients to that colleague.

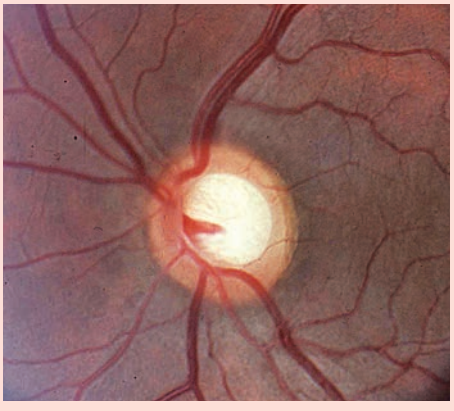
Optic Nerve Examination

All eye physicians should closely study the optic nerve—in our observation, missing subtle optic neuropathy (optic nerve head cupping) is a major cause of missed diagnosis.

Optic nerve head examination is best done via slit lamp-enabled ophthalmoscopy. The most critical observation is evaluation of the

Judging the Appearance of the Optic Nerve Head

All eye doctors are challenged in accurately assessing the optic nerve head.



- "Even among glaucoma subspecialists, a high degree of variability has been reported for optic disc assessment."
- "Ophthalmology trainees and comprehensive ophthalmologists underestimate glaucoma likelihood in one of five discs, and are twice as likely to underestimate as overestimate glaucoma likelihood."
- "Underestimating the vertical cup-to-disc-ratio and cup shape, and missing retinal nerve fiber layer defects and disc hemorrhage, were the key errors that led to underestimation."

Good grief! Conduct a thorough stereoscopic study of the optic nerve head and employ one of the advanced imaging technologies, such as OCT, GDx, HRT, etc., for the nerve fiber layer assessment. Missing a glaucoma diagnosis should be extremely rare!

O'Neill EC, Gurria LU, Pandav SS, et al. Glaucomatous optic neuropathy evaluation project: factors associated with underestimation of glaucoma likelihood. JAMA Ophthalmol. 2014 May;132(5):560-6.

anatomy of the neuroretinal rim tissues, particularly the inferotemporal and superotemporal rim tissues. There is less glial support tissue in these two critical locations, and this sets the stage for axonal loss in these two watershed areas.

This is underscored by the "ISNT" rule, which emphasizes that as a general guideline in a healthy, normal optic nerve, the *Inferior* neuroretinal rim tissues are the thickest, followed by the *Superior* rim tissues, then the *Nasal* rim tissues and, thinnest of all, the *Temporal* rim tissues.

"Oblique insertions" of the optic nerve head can complicate assessment of the entire cup-to-disc interface. A keen eye is required, as is supplemental testing, such as retinal nerve fiber layer scanning.

Central Corneal Thickness

Beyond critical study of the optic nerve head anatomy, the second area requiring critical assessment is vastly simpler: the central corneal thickness. We remain dismayed, however, that not all optometrists have a pachymeter. Knowing the central corneal thickness holds enormous risk-assessment and diagnostic value, and obtaining this in-

Topical Glaucoma Drugs

BRAND NAME	GENERIC NAME	MANUFACTURER	CONCENTRATION	BOTTLE SIZE
Beta Blockers				
Betagan	levobunolol hydrochloride	Allergan, and generic	0.25% 0.5%	5ml, 10ml 5ml, 10ml, 15ml
Betimol	timolol hemihydrate	Akorn	0.25% 0.5%	5ml 5ml, 10ml, 15ml
Betoptic-S	betaxolol hydrochloride	Alcon	0.25%	5ml, 10ml, 15ml
Istalol	timolol maleate	Bausch + Lomb	0.5%	2.5ml, 5ml
Timoptic	timolol maleate	Valeant Ophthalmics, and generic	0.25% 0.5%	5ml, 10ml, 15ml 5ml, 10ml, 15ml
Timoptic (preservative-free)	timolol maleate	Valeant Ophthalmics	0.25% 0.5%	unit-dose unit-dose
Timoptic-XE	timolol maleate	Valeant Ophthalmics, and generic	0.25% 0.5%	2.5ml, 5ml 2.5ml, 5ml
Prostaglandin Analogs				
Lumigan	bimatoprost	Allergan	0.01%	2.5ml, 5ml, 7.5ml
Travatan Z	travoprost	Alcon	0.004%	2.5ml, 5ml
Xalatan	latanoprost	Pfizer, and generic	0.005%	2.5ml
Zioptan	tafluprost	Akorn	0.0015%	unit-dose
Docosanoid Compound				
Rescula	unoprostone isopropyl	Sucampo	0.15%	5ml
Alpha Agonists				
Alphagan P	brimonidine	Allergan	0.1%,	5ml, 10ml, 15ml
generic brimonidine	brimonidine	generic	0.15%, 0.2%	5ml, 10ml, 15ml
Carbonic Anhydrase Inhibitors				
Azopt	brinzolamide	Alcon	1%	5ml, 10ml, 15ml
Trusopt	dorzolamide	Merck	2%	5ml, 10ml
Combination Glaucoma Medications				
Combigan	brimonidine/timolol	Allergan	0.2%/0.5%	5ml, 10ml
Cosopt	dorzolamide/timolol	Akorn	2%/0.5%	5ml, 10ml
Cosopt PF	dorzolamide/timolol	Akorn	2%/0.5%	unit-dose
Simbrinza	brinzolamide/brimonidine	Alcon	1%/0.2%	8ml

formation is simple, cheap and easy for ancillary staff to accomplish. Unless you reflect the IOP against the central corneal thickness, you really have no idea what the true intraocular pressure is! Nerve fiber layer analyzers and visual field analyzers are truly of value, but their data are largely ancillary to the trio of ophthalmoscopy, intraocular pressure and central corneal thickness.

Laser Trabeculoplasty in Glaucoma Care

"Effects of laser trabeculoplasty on aqueous drainage may be explained by several mechanisms, including mechanical pulling open of uveoscleral trabecular meshwork and Schlemm's canal, cellular mechanisms that stimulate cell division, and biochemical mechanisms that alter cytokines and stimulate macrophage-like capacity of trabecular-lining cells. In eyes receiving SLT, histology shows minimal mechanical damage. The intraocular pressure-lowering effect of SLT may therefore be explained by biochemical and cellular alteration instead of mechanical effects."

"The difference in pooled mean reduction in IOP by SLT treatment as compared to ALT was 0.5mm Hg, which did not reach statistical significance."

"In this meta-analysis, SLT was compared with ALT, and medication in terms of mean IOP reduction, reduction in number of medications and treatment success. SLT was found to be noninferior to ALT."

"The results of the meta-analysis provided robust evidence that SLT may be introduced into glaucoma management algorithms in two ways. First, it may be offered as a primary treatment to patients with open-angle glaucoma that is comparable to medication. Second, it may act as a treatment alternative for patients with IOP not controlled with maximally tolerated medication, apart from ALT, before invasive surgery is to be considered."

"Existing evidence suggests that repeat SLT is still efficacious in lowering the IOP. The success rate varied from 36.3% to 67% in achieving a preset target of IOP reduction in the two available studies. The success rate was 56% for a second repeat SLT (i.e., third SLT). The rate of success was lower than that of the second SLT in the same study (67%)."

"SLT was efficacious in open-angle glaucoma patients, lowering IOP from 6.9% to 35.9%, and demonstrated comparable treatment success when compared to ALT and medication among patients with maximally tolerated medication and newly diagnosed patients, respectively."

Wong MO, Lee JW, Choy BN, et al. Systematic review and meta-analysis on the efficacy of selective laser trabeculoplasty in open-angle glaucoma. Surv Ophthalmol. 2015 Jan-Feb;60(1):36-50.

Glaucoma Pearls

From the Glaucoma Society meeting in Denver, Colorado (October 2014), we gained these pearls:

- Raising the head of the bed some might decrease intraocular pressure 2mm to 3mm Hg by reducing episcleral venous pressure.
- 30% of ganglion cells reside in the central eight degrees of the visual field. There are only four points of the 24-2 that test for the central eight degrees, therefore if there is a defect in one of the four central points on the 24-2, then consider obtaining a 10-2 visual field. This triples the resolution of paracentral defect by testing at two-degree intervals rather than the 6-degree intervals of the 24-2.
- A patient has to lose about 30% of the retinal nerve fiber layer to move from the Green Zone into the Yellow Zone on nerve fiber analysis instruments.
- It is best to ask "open-ended" questions with your glaucoma patients, such as "Tell me how you are doing using your eye drops?" or "What are your thoughts about your glaucoma?"

Glaucoma Evaluation

The entire pursuit of diagnostic precision is overshadowed only by the decision of "when to watch, and when to treat"—the Holy Grail of decision-making in the care of patients with glaucoma.

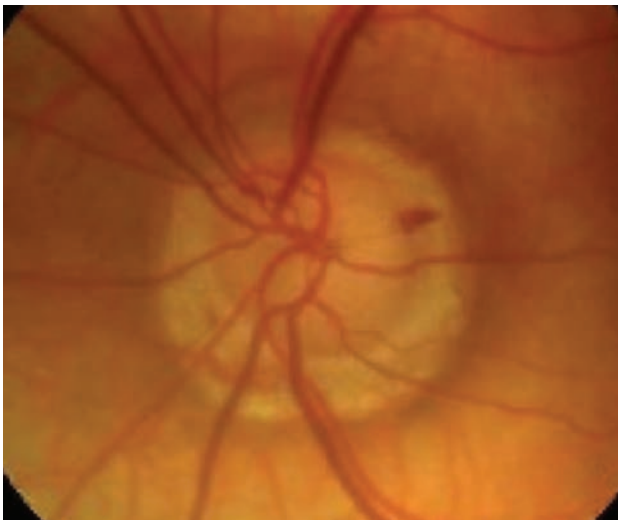
History

To maximize the validity of this decision, an exhaustive clinical evaluation must be conducted, and that evaluation should begin with the patient's family history. Glaucomatous optic neuropathy tends to run in families, but the fragility of this data is the validity of the history. Many times mom or dad are said to have had glaucoma, but indeed are/were being treated for a disease they do/did not have. Twenty or so years ago, many doctors still called a pressure over 21mm Hg "glaucoma," when in fact the patient did not have glaucoma!

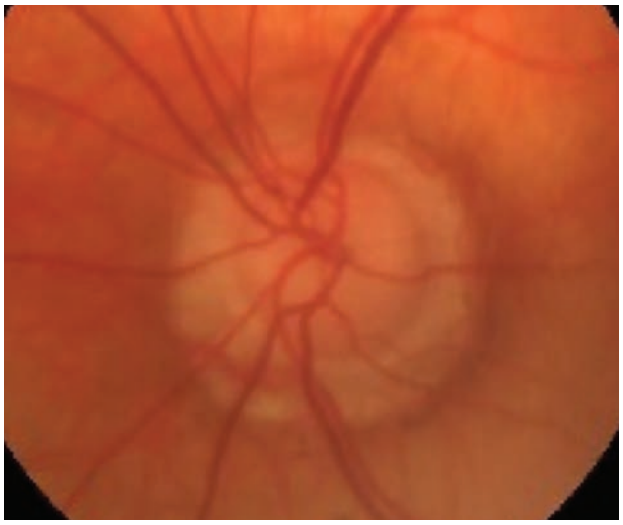
In our experience, it is the sibling history that may hold the most value. Determining the true glaucoma status of a brother or sister may assist in your decision making. When possible, try to get siblings in the office for a definitive examination. Or, if a sibling is out of the area, try to get a copy of the sibling's medical records to gather as much information as possible.

Clinical Examination

Many factors go into the decision of if/when to initiate treatment. As we've stated, family history can be quite valuable. Then consider the baseline status of the optic nerve, the patient's overall health status, and the patient's desire to be treated—after an objective, informative discussion of the risks, benefits and



A classic nerve fiber hemorrhage, a presentation that is occasionally associated with glaucoma.



Several weeks later, the hemorrhage has resolved. Note that the peripapillary atrophy is still present.

alternatives to both treatment and non-treatment.

The comprehensive glaucoma evaluation includes:

• ***Best visual acuity.***

• ***Pupillary function.*** Is there a relative afferent pupillary defect?

• ***Anterior segment tissues.*** Is there pseudoexfoliation, pigment dispersion, endothelial guttata (which can potentially alter corneal thickness measurements and can be a relative contraindication of the use of carbonic anhydrase inhibitors because the inhibition of carbonic anhydrase in the metabolism of the corneal endothelium)?

• ***Gonioscopy to assess the iridocorneal angle.*** We typically use a four-mirror goniolens to perform these anatomic assessments. Note the patency of the anatomic angle as well as the degree of trabecular pigmentation. If laser trabeculoplasty is ever considered, it will be essential to know the degree of pigmentation because there must be a reasonable amount of pigment present to absorb laser energy. Said another way, if there is little or no angle pigmentation, laser trabeculoplasty is not a meaningful therapeutic option. (Another clinical pearl: Laser trabeculoplasty can be much more effective in a phakic patient than in a pseudophakic one).

• ***Intraocular pressure.*** The standard of care remains Goldmann applanation tonometry. Always note the time of day the measurement is taken. When practical, try to obtain three to four IOP readings prior to initiating treatment so that a more comprehensive intraocular pressure profile can be established. Knowing the IOP profile can be very useful, especially when establishing the peak IOP.

• ***Corneal pachymetry.*** Intra-

Glaucoma and Nocturnal Blood Pressure

• "Physiologic or medication-induced decreases in nocturnal blood pressure may lead to visual field progression in patients with normal-tension glaucoma."

It is well established that lower systolic blood pressure and ocular perfusion pressure are significant risk factors for the development of open-angle glaucoma, especially for those with normal to low IOP.

• "The study by Charlson et al. supports the notion that the optic nerve head, like the brain and heart, may be susceptible to the ischemic insult from drops in nighttime blood pressure, resulting in visual field progression in patients with normal-tension glaucoma."

• "Patients with normal-tension glaucoma who require aggressive blood pressure control to reduce their cardiovascular risk may be vulnerable to nocturnal hypotension and visual field progression, even when IOP is seemingly well controlled. Such patients should be carefully managed in concert with their primary care physicians. Ambulatory blood pressure monitoring may play a role in furthering physicians' understanding of normal tension glaucoma and improving their management of patients with this disease."

When you have patients with progressive visual field loss in spite of lower intraocular pressure, be sure to carefully assess their blood pressures. At the 2014 European Glaucoma Society Annual Conference, one lecturer queried the audience: "How many of you have ordered a 24-hour blood pressure study?" About 200 glaucoma specialists, out of about 1,000, raised their hands. The concept of plugging blood pressure measurements into the risk assessment of low-tension glaucoma patients is indeed evolving.

Harizman N, Vinod K. The Literature: Nocturnal systemic hypotension increases the risk of glaucoma progression. Glaucoma Today. 2014 Sept/Oct;12(5):10.

ocular pressure in a vacuum can be deceiving. The central corneal thickness must be known in order to have a meaningful understanding of the intraocular pressure. Beyond this anatomic assessment, a physiologically thin cornea is an independent risk factor for the development of glaucoma.

Pachymeters are inexpensive and every OD needs such a device to help assess risk for the development of glaucoma. For those ODs who tend to refer out glaucoma suspects, such knowledge can radically improve the sensitivity and specificity of your patient referrals.

• ***Nerve fiber layer measurement.*** Having an HRT, GDx and/or OCT is not critical, but exceedingly helpful, so these instruments are highly recommended. OCT technology is particularly informative, and is the most versatile of these technologies. We encourage all optometrists to acquire an OCT device.

One word of caution—while all the devices are generally referred to as generating "objective data," such data are only relatively objective (compared to highly subjective visual field testing). There are occasional artifacts in which the retinal nerve fiber layer appears to be thinning over time, only to have such thinning "restored" on the next scan, even when the quality index is superb! So, do not look at any parameter in isolation, but rather as a component part of the comprehensive glaucoma assessment. Always look at the big picture.

• ***Visual fields.*** These functional assessments can be complementary to the structural data. When all is said and done, the bottom line in glaucoma care is quite simple: Does the patient have a noticeable loss of the field of vision? Our goal is straightforward: The patient should not have any awareness of visual field loss prior to death. We have

The Changing Roles of Glaucoma Care Providers

There are two critical events with which all optometrists should be familiar: (1) Fewer ophthalmologists are pursuing subspecialty training in glaucoma; thus (2) more glaucoma care is being delivered by general ophthalmologists. It stands to reason that many general ophthalmologists hold little passion for glaucoma care or they likely would have pursued subspecialty training in this area.

The soil is extremely fertile for optometrists to fill this gap in office-based glaucoma care. Purely from a public health perspective, office-based glaucoma care seems to be falling into a relative void that neither optometry nor ophthalmology enthusiastically embraces. From our editorial perspective, the time is now for the optometric profession to redouble its educational intensity to train superb glaucoma doctors. We do not see ophthalmology having any interest in doing such, so it appears that by default optometry needs to step up and be the beacons of excellence in medical eye care. (This also perfectly applies to the care of patients with dry eye disease!)

Along these same lines, and underscoring this observation, is that most glaucomas are medically-managed diseases, not surgically managed ones. Following are quotes from *American Journal of Ophthalmology* (March 2014), which offer support for this position:

• "Between 2000 and 2010, the rate of laser trabeculoplasty by general ophthalmologists increased about 20%, and by glaucoma subspecialists about 9%. Optometrists in Oklahoma, Kentucky and Louisiana can now perform these simple laser procedures, thus continuing the trend of non-glaucoma subspecialists performing a large and increasing proportion of such laser procedures."

• "Incisional glaucoma surgery has increasingly become the purview of high-volume glaucoma subspecialists."

• "Ophthalmologists who do not perform incisional glaucoma surgery provide a large and growing portion of clinic-based glaucoma care."

• "A growing number of patients are referred to a glaucoma subspecialist only at the time of needing surgery. This development emphasizes the importance of systems that support excellent communication among care providers involved in glaucoma treatment."

• "It is predicted there will be an even greater separation between the providers of surgical and nonsurgical glaucoma care in the coming years. This raises concerns regarding the sustainability of access to clinic-based care for chronic diseases such as glaucoma, as competing acute-care demands for ophthalmology resources—human and otherwise—continue to mount."

In summary, the need and time for optometry to rise to the occasion is here. Let's embrace this incredible need for competent, office-based glaucoma patient care.

Campbell RJ, Bell CM, Gill SS, et al. Clinic-based glaucoma care in the era of surgical subspecialization. Am J Ophthalmol. 2014 Mar;157(3):631-9.

Topamax and Visual Field Defects

In April 2014, the manufacturer of Topamax, Janssen Pharmaceuticals, announced that "Visual field defects have been reported in patients receiving topiramate independent of elevated intraocular pressure. In clinical trials, most of these events were reversible after topiramate discontinuation."

Thus, it may be wise to perform 30-2 or 10-2 visual field testing on your patients taking Topamax just to be certain that there has been no development of asymptomatic compromise of visual field. According to a conversation with Leonard Messner, OD, at the February 2015 meeting of the North American Neuro-Ophthalmology Society, there was no consensus on an explanation for this phenomenon.

numerous patients with sizable amounts of repeatable visual field loss who are subjectively unaware of these losses. (By the way, the vast majority of these patients were in this state of unawareness when we first encountered them!)

For more than a decade now, the Swedish Interactive Threshold Algorithm (SITA) has been available (via Carl Zeiss Meditec), and this has massively shortened the time it takes to conduct visual field testing. It is the standard-of-care technology and the "universal language" of visual field analysis.

There are two options applicable to glaucoma testing: SITA-Standard and SITA-Fast. We almost exclusively employ the 24-2 SITA-Fast program, which can be done by most patients in about three minutes per eye.

In summary, if one performs these assessments and thoughtfully assimilates all the findings, a proper staging of either risk for glaucoma or the presence of the disease itself can be rendered with high sensitivity and specificity.

If the preponderance of the assessment yields a decision to lower the intraocular pressure, then the next step is to set a target pressure range and select a medicine to best achieve the goal. Because compliance is the weak link in the chain of care, and cost is often the most likely reason for poor compliance, we must consider the potential cost as well as the clinical efficacy of the medicines we choose for each patient.

First-Line Therapy

Prostaglandins

For most patients most of the time, a prostaglandin analog is the "go-to" option for first-line therapy. Thanks to the innovator drug Xalatan (latanoprost, Pfizer) going generic in 2011, as well as free-market competition, all prostaglandins are now more affordable than ever. Because there have been concerns about inconsistency with the various manufacturers of generic latanoprost, some doctors and patients are sticking with consistent formulations of brand-name Travatan Z (travoprost, Alcon), Lumigan (bimatoprost, Allergan) and Zioptan (tafluprost, Akorn). All prostaglandins function nearly identically, thus knowing which of these brand-name products is the least expensive is a kind expression of patient advocacy.[2] Also, all of these brand-name products have various coupons that enable cost reduction approaching generic prices. So, whichever way you prefer—generic or coupon-assisted pricing of brand-name products—the cost of these wonderful drugs is now more affordable.

While the prostaglandins are systemically safe, there are small barbs here and there. Remember that cold or flu-like symptoms can occur, hazel-colored irides can become darkened, gastrointestinal disorders can arise, and orbital fat can be compromised, causing enophthalmos. And, of course, as with any drug, idiosyncratic allergic reactions can occur. However, for the most part, prostaglandins perform beautifully for most patients most of the time.

Although prostaglandins perform optimally when used in the evening, many people "take their medicine" at breakfast, and so if compliance is enhanced with breakfast time administration, so be it. Our observation is that efficacy and compliance is attained or at least improved in this manner.

Two medicines of the prostaglandin class require refrigeration for long-term storage: latanoprost and Zioptan. Once dispensed to the patient, though, these medicines can be kept at room temperature.

The only representative of the prostaglandin class that is preservative-free and comes in unit-dose packaging is Zioptan. There are eight to nine drops per container, so many patients are able to double their savings by getting two days of therapy from one vial. Not many patients truly need preservative-free options, in our experience.

Beta Blockers

The beta blockers are the other first-line treatment option, in that they are about as effective as prostaglandins (25% vs. 30% to 35% reduction in IOP) and can be used once daily—

but absolutely must be instilled in the morning.[3]

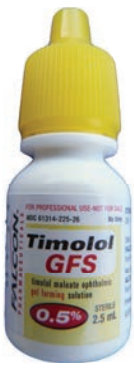
Numerous corroborating studies have found that once-daily instillation of a nonselective beta blocker (timolol and levobunolol) works as well as BID dosing.[4] But there is little benefit to nocturnal instillation of a beta blocker—none of our current glaucoma medicines exert much of an effect during sleeping as during waking periods.

Additive and Secondary Therapy

Beta Blockers

Because simpler dosing schedules typically lead to better compliance, once-daily medications are preferable. This is why we almost always add a nonselective beta blocker to a prostaglandin when the prostaglandin alone does not achieve target intraocular pressure.

We prescribe the 0.25% concentration for white patients and the 0.5% concentration for black and darkly-pigmented patients. Melanin pigments tend to bind beta blocker molecules, so in the end both types of patients receive approximately a 0.25% concentration.



We never dose these medicines BID when added to a prostaglandin. The beta blocker is dosed in the morning and, when practical, the prostaglandin is dosed in the evening. This combination, in our experience, achieves target intraocular pressure nearly 90% of the time.

Alpha Agonists

Brimonidine, an alpha adrenergic agonist, decreases IOP through enhancement of aqueous outflow and, to some degree, reduction in aqueous production.[5]

Although FDA-approved for TID instillation, brimonidine is more

Brimonidine

Remember when Alphagan 0.2% went to Alphagan P at 0.15%, then ultimately to 0.1%? It was stated that because of the side effect profile of the 0.2% concentration, the market should warmly embrace the lesser concentrations. However, when Combigan (0.2% brimonidine/0.5% timolol) was launched, those concerns were no longer mentioned. Marketing a product is indeed a peculiar dance. The prescribing optometrist needs to be highly attentive to science and extremely wary of marketing statements.

"The brimonidine 0.15% costs several times more than brimonidine 0.2%. The drug companies know that we would prefer to prescribe 0.15% because it's going to have fewer side effects with the same efficacy," according to one glaucoma subspecialist.[1]

Quoting the FDA from July of 2003 concerning brimonidine vs. Alphagan P:

- "The risk/benefit ratio of Alphagan vs. Alphagan P is essentially the same."
- "The differences in adverse events and IOP lowering ability are not clinically significant."
- "We find any differences in study results between the two products to be typical of the variability seen in clinical trials and do not find the difference in this case to be significant."[2]

Sometimes it is just difficult to know the truth. Here you see two differing perspectives on the side effect profile of brimonidine. Being therapeutic minimalists, we would prefer to use a lesser, but equally effective, concentration of any drug if cost was more or less neutral. Since the 0.2% and 0.15% concentrations of brimonidine are both generic, we would prefer the 0.15%, provided it was priced similarly to the 0.2%. Certainly, once the 0.1% concentration goes generic, we hope that its pricing will be similar to the other two concentrations.

On a somewhat positive note: "Correction of retinal vascular dysregulation may explain why topical brimonidine was superior to timolol in preserving visual field in normal tension glaucoma patients after three years of treatment, as reported in the Low Pressure Glaucoma Treatment Study."[3] This same study found that brimonidine only lowers intraocular pressure about 1mm Hg. So, perhaps the clinical benefit of brimonidine in the setting of low-tension glaucoma may be more attuned to helping with retinal vascular autoregulation than with reduction in intraocular pressure. These mechanisms are not yet fully understood. It would be interesting to enroll more patients and follow them for a longer period of time so that this speculation could be corroborated or disproved.

Do note that brimonidine *must* be used at least twice daily to be effective, whereas most patients do quite well with only once-daily timolol, particularly when dosed in the morning.

1. Roach L. The state of generic drugs. A sampling of costly and missing drugs. EyeNet. 2015 Jan;19(1):45.
2. Woodcock J. FDA Center for Drug Evaluation and Research to Terry G. Mahn, Esq [letter]. RE: Docket No. 02P-0469/CP1. May 21, 2003. Available at: www.fda.gov/ohrms/dockets/dailys/03/May03/052903/02p-0469-pdn0001-vol1.pdf
3. Feke GT, Bex PJ, Taylor CP, et al. Effect of brimonidine on retinal vascular autoregulation and short-term visual function in normal tension glaucoma. Am J Ophthalmol. 2014 Jul;158(1):105-112.

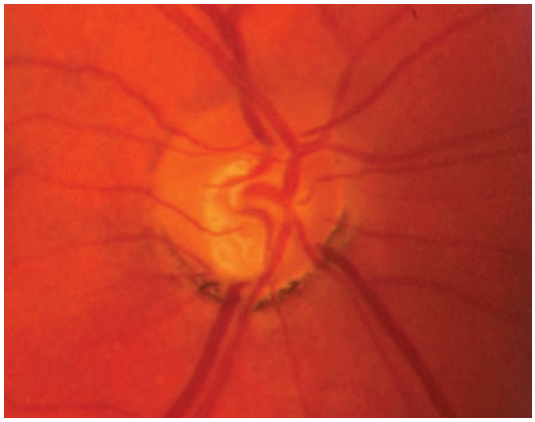
often used BID in actual practice. Because alpha agonists do little or nothing while we sleep and because trough levels occur about eight hours after instillation, it makes sense to optimize the timing of instillation during diurnal hours.[6] This is why brimonidine is perhaps best dosed shortly after waking and again about eight hours later, not near bedtime. When used as monotherapy, brimonidine is best used TID, otherwise there is often complete loss of the IOP effect after 10 to 12 hours.[7]

Brimonidine is available in three concentrations: 0.2% and 0.15% generically, and 0.1% as brand-name Alphagan P (Allergan).

All three concentrations perform very much the same. The 0.2% is an inexpensive generic, 0.15% is a relatively expensive generic, and the brand-name is the most expensive. (The combination drugs Combigan and Simbrinza contain the 0.2% brimonidine.)

For cost-related concerns, we almost always prescribe the 0.2% concentration. About 10 to 20% of patients develop a local allergic reaction to brimonidine, which is somewhat concentration-dependent.[8]

If an allergic reaction does occur, we move on to another class of drug, such as a carbonic anhydrase inhibitor (CAI), the docosanoid Rescula (unoprostone isopropyl, Sucampo Pharmaceuticals) or a combination drug containing a beta blocker with a CAI. We would use such a combination drug if we had already established efficacy with a beta blocker and needed to reduce the IOP a bit more.



Marked inferior neuroretinal rim erosion in advanced glaucoma. The inferior pigmentary peripapillary atrophy is a neutral finding.

CAIs

The topical carbonic anhydrase inhibitors are Azopt (brinzolamide 1%, Alcon) ophthalmic suspension and generic dorzolamide 2% ophthalmic solution. Both brinzolamide and dorzolamide perform similarly, yet the suspension is more comfortable upon instillation than is the solution; on the other hand, the solution does not have to be shaken before instillation as the suspension does.

Docosanoid

Unoprostone isopropyl, available as Rescula, is a somewhat enigmatic molecule in that it has many properties similar to prostaglandins and many properties dissimilar to prostaglandins. It is very safe and has hardly any known side effects, but it decreases IOP only about 3mm to 4mm Hg. It is indeed a niche drug whose efficacy is similar to the carbonic anhydrase inhibitors.

Combinations

There are three combination glaucoma drugs: Combigan (timolol 0.5% with brimonidine 0.2%, Allergan), Cosopt (timolol 0.5% with dorzolamide 0.2%, Akorn) and Simbrinza (brimonidine 0.2% with brinzolamide suspension 1%, Alcon).

For combination drugs, we have found it is best to try each of the component drugs first to be sure each component exerts a meaningful therapeutic effect before using the combination formulation. The carbonic anhydrase inhibitors reduce intraocular pressure by suppressing aqueous production, but do so by only about 15%. Like brimonidine, they are approved as TID products, yet are used twice daily in general clinical care. Dorzolamide is an ophthalmic solution and brinzolamide is an ophthalmic suspension. When we need to prescribe one of these, we dose the

medication twice daily: first dose in early morning and the second drop about eight hours later (just as we do with brimonidine).

Cosopt is unique in that it is available as a traditional bottled product and as a preservative-free unit-dose, Cosopt PF. Simbrinza is the only suspension combination drug. Its other main difference is that, unlike Cosopt and Combigan, it does not contain a beta blocker. Thus, for a patient with asthma or one who is nonresponsive to beta blockers, Simbrinza would likely be an ideal "add-on" to a prostaglandin drug, once individual trials of both brinzolamide and brimonidine are found to be efficacious.

What may be found, however, is that if the prostaglandin brought us close to target intraocular pressure, yet fell short, it is likely that adding brinzolamide or generic brimonidine alone will get the IOP to target, and using a more expensive combination drug may not be necessary.

In summary, we typically initiate glaucoma therapy with a prostaglandin, and add timolol 0.25% or 0.5% once daily (in the morning) if target intraocular pressure is not reached with the prostaglandin alone.

Be mindful that prostaglandins generally reduce intraocular pressure about 30% to 35%, whereas nonselective beta blockers reduce intraocular pressure by about 25%. That's only about 1mm to 3mm Hg separation! So, do not lose sight of the fact that beta blockers remain an excellent choice for reducing intraocular pressure.

We still regularly initiate glaucoma therapy with a beta blocker, particularly when only a 4mm to 5mm Hg reduction in IOP is needed and/or when we believe that cost is a critical factor in patient compliance. A 5ml bottle of timolol is generally available for about $5!

Taking all this together, it can be seen that initial therapeutic interventions are easy; but if the patient is a prostaglandin nonresponder and/or has active asthma, establishing a therapeutic plan becomes more like a chess game—it involves considerable strategy and therapeutic trials until target intraocular pressure is achieved. (Having ample samples on hand is tremendously helpful in augmenting these various therapeutic trials.)

Glaucoma is the only disease having its own subspecialty fellowship within ophthalmology. This is due to the highly specialized surgical procedures and intraocular devices that are often needed for treatment of advanced and end-stage disease. For the large majority of patients who thankfully do not require such specialized microsurgical interventions, glaucoma medical care should be firmly in the province of optometric physicians. ■

A Preview of Rho-Kinase Inhibitors (RKIs) for Glaucoma

While not yet approved by the FDA, the RKIs appear to show a fair amount of promise as ocular hypotensives. Here is a brief introduction to this evolving class of glaucoma drugs.

RKIs target trabecular outflow-related tissues. There may also be a secondary effect of inhibition of aqueous humor. Like the prostaglandins, these meds are to be used once daily, as they have an effect that lasts up to 60 hours.

Considerable conjunctival hyperemia is a main side effect. About 50% of patients experienced hyperemia, as compared to about 15% of patients on latanoprost. The degree of hyperemic expression was reduced in both groups over time, but the RKI continued to cause much more hyperemia than latanoprost.

Regarding clinical efficacy, the RKI decreased IOP about 6mm Hg, whereas the latanoprost reduced IOP about 7mm Hg.

As the study ran only 28 days, it is not known whether other side effects such as eyelash growth, iris pigmentary changes or lid sulcus changes could occur.

It is not known if the RKI class of medicine will be effective in prostaglandin nonresponders. Neither is it known if these two classes will be additive in their effect. The RKI class does appear to be clinically effective, and we anticipate that it will play a role in glaucoma care. Of course, it will have to be price-competitive with generic latanoprost, which could mute its market success and profitability; time will tell. We will have more to share in the 2016 *Clinical Guide to Ophthalmic Drugs*.

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1. Shaikh Y, Yu F, Coleman AL. Burden of undetected and untreated glaucoma in the United States. Am J Ophthalmol. 2014 Dec;158(6):1121-1129.
2. Parrish RK, Palmberg P, Sheu WP; XLT Study Group. A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: a 12-week, randomized, masked-evaluator multicenter study. Am J Ophthalmol. 2003 May;135(5):688-703.
3. McCannel CA, Heinrich SR, Brubaker RF. Acetazolamide but not timolol lowers aqueous humor flow in sleeping humans. Graefes Arch Clin Exp Ophthalmol. 1992;230(6):518-20.
4. Silverstone D, Zimmerman T, Choplin N, et al. Evaluation of once-daily levobunolol 0.25% and timolol 0.25% therapy for increased intraocular pressure. Am J Ophthalmol. 1991 Jul 15;112(1):56-60.
5. Toris CB, Gleason ML, Camras CB, Yablonski ME. Effects of brimonidine on aqueous humor dynamics in human eyes. Arch Ophthalmol. Dec 1995;113(12):1514-1517.
6. Tanna AP, Rademaker AW, Stewart WC, Feldman RM. Meta-analysis of the efficacy and safety of alpha2-adrenergic agonists, beta-adrenergic antagonists, and topical carbonic anhydrase inhibitors with prostaglandin analogs. Arch Ophthalmol. 2010 Jul;128(7):825-33.
7. Stewart WC, Day DG, Stewart JA, et al. 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. May 2001;131(5):631-635.
8. Sullivan-Mee M, Pensyl D, Alldredge B, et al. Brimonidine hypersensitivity when switching between 0.2% and 0.15% formulations. J Ocul Pharmacol Ther. 2010 Aug;26(4):355-60.

Clinical Insights

Having now amassed nearly 70 combined years of intense clinical experience, we offer some perspectives for enhanced patient care, as well as some general insights.

• **Antibiotics** continue to be grossly overprescribed among all the healthcare professions. Many times, this may be due to patient demands or perhaps diagnostic uncertainty by the clinician.

• At the same time, topical **corticosteroids** continue to be underprescribed. This may be because the rare side effects are often stressed in comparison to the enormous benefits they provide. In our experience, contact lenses cause far more tissue compromise and risk to the eye than steroids!

• The epidemiology of **acute red eye(s)** is almost exclusively inflammatory in nature.

So (generally speaking), when in doubt, prescribe a steroid.

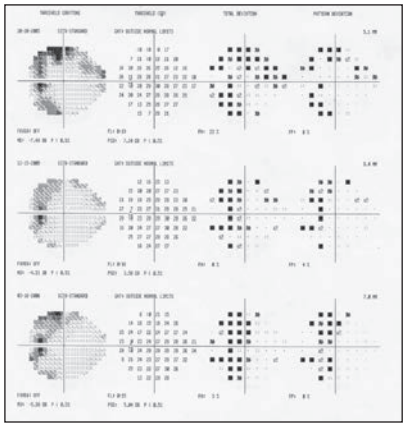
• There are several other **"when in doubt…"** maneuvers we must remember to try (in the appropriate context):

– Cycloplege
– Dilate
– Get a visual field
– Evert the eyelid
– Call for advice (don't just refer the patient)

• After a **diabetic patient**'s annual eye examination, send a succinct note to the patient's health care provider(s) Doctor-to-doctor communication is critical to optimize patient care, and for recognition of the optometric profession as a critical element in patient's overall care.

• We are **"eye doctors,"** having worked diligently to earn a doctor's degree. The term "eyecare provider" poorly represents who we are and what we do.

• Don't let **a single visual field defect** fake you out. Unless the defect can be clinically correlated, repeat the field. In most cases, the visual field defect (in the setting of optic nerve disease) can be predicted. If there is an intact neuroretinal rim, it would be unusual to see a repeatable visual field defect in the setting of glaucoma.



When in doubt, repeat the field.

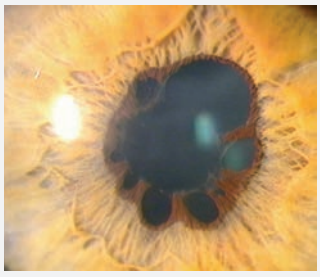
• Have a general information sheet, or simply tell your patients about **your scope of professional services**. We have seen hundreds of patients over the years who develop a floater, a trichiatic lash, a subconjunctival hemorrhage, bacterial conjunctivitis, etc., etc., who self-refer to our OD/MD practices (unbeknownst to their primary care optometrist), thinking erroneously that they needed to see an ophthalmologist. This is almost always the result of optometrists who failed to educate their patients about their scope of clinical expertise and patient care services. So be sure you consistently, honestly and forthrightly communicate with your patients at each visit.

• When any **doctor calls** your office, politely and briefly excuse yourself from the examination room to take the call. There may be times when the calling doctor will have to wait a minute or two, but "phone tag" can be ever so frustrating. Always, if at all practical, take the call from another provider.

Adverse Effects of Phenylephrine Eye Drops

Phenylephrine has the potential to affect blood pressure and heart rate; but does this potential translate into clinical significance?

A study based on eight randomized clinical trials involving more than 900 patients concluded that 2.5% phenylephrine had no meaningful effect on blood pressure or heart rate. The 10% concentration tended to raise blood pressure about 15mm Hg and increase the heart rate about five beats per minute. These changes occurred in about 10 to 20 minutes, but rates returned to baseline in less than an hour.



Iris synechia.

Summary: "Phenylephrine 2.5% leads to no clinically relevant change in blood pressure or heart rate, and the changes in blood pressure and heart rate seen with phenylephrine 10% are short-lived. Thus, phenylephrine 2.5% is safe to use in clinical routine."

With exceedingly rare exceptions, we have also found the 10% concentration to be safe and useful as well. It can be helpful in dilating "difficult-to-dilate" patients, and adjunctively with potent steroids to help break uveitic synechiae.

We actually use Paremyd, a combination dilating agent containing 0.25% tropicamide with 1% hydroxyamphetamine (HCL), which is an indirect acting sympathomimetic, to dilate most all of our patients. It gives a 5mm to 7mm pupillary dilation, and wears off more quickly than 1% tropicamide with 2.5% phenylephrine.

Stavert B, McGuinness MB, Harper CA, et al. Cardiovascular adverse effects of phenylephrine eyedrops: A systematic review and meta-analysis. JAMA Ophthalmol. 2015 Mar 19. [Epub ahead of print]

Management of Nausea and Vomiting

As primary care optometric physicians, we need to be prepared to deal with all possible nonsurgical presentations; this includes those rare presentations of patients with nausea and/or vomiting, which may occur in patients taking Augmentin, oral antivirals or other medicines, and in those in acute angle-closure, or who have an unrelated illness.

Historically, there have been two major drugs used to ameliorate these conditions: promethazine (Phenergan) and prochlorperazine (Compazine).

Promethazine is an antihistamine/antidopaminergic that has long been generic, and a mainstay of management of nausea and vomiting for decades. The usual adult dose is a 25mg tablet by mouth every four to six hours as needed. Phenergan also comes in 25mg suppositories.

Prochlorperazine, a specific antiemetic/antivertigo agent, is another medicine long used to manage nausea and vomiting. It, too, comes in 25mg tablets and suppositories, either of which can be used three to four times daily as needed.

However, Phenergan and Compazine have taken a back seat since the newer medicine Zofran (ondansetron, GlaxoSmithKline), which gained FDA approval in 1992, came to market. Now also available generically, Zofran, a "selective 5-hydroxytryptamine (5-HT3) receptor antagonist," is purely designed for the management of nausea and vomiting and has little or no affinity for any other receptor substrates.

Zofran comes in 4mg, 8mg and 24mg tablets; however, the most common dosage in the setting of clinic-based nausea and vomiting is 4mg BID (every eight hours while awake). Zofran is also made in 4mg and 8mg oral disintegrating tablets (ODTs). Either form can be of considerable help in the management of the patient with nausea and vomiting.

All three of these drugs are category B and widely used in all health care settings.

• If a **clinician error** occurs, the doctor should admit it. "Patients strongly prefer full disclosure with use of the word 'error' or 'mistake' and the doctor's taking responsibility," according to a recent editorial.[1] It's important that when errors happen, we deal with them a patient-centered, ethical manner. "Apologies—statements that acknowledge an error and its consequences, take responsibility, and communicate regret for having caused harm—can decrease blame, decrease anger, increase trust and improve relationships," a separate editorial notes.[2]

Also important, apologies can reduce the risk of medical malpractice lawsuits. "There is now greater empiric support for error disclosure, as published evidence from communication-and-resolution programs have demonstrated a significant decrease in claims, lawsuits, length of dispute, and costs."[1]

1. Lee BS, Gallagher TH. Saying "I'm sorry": error disclosure for ophthalmologists. Am J Ophthalmol. 2014 Dec;158(6):1108-1110.
2. Robbennolt JK. Apologies and medical error. Clin Orthop Relat Res. 2009 Feb;467(2):376-82.

Goodbye, Scopolamine and Enuclene

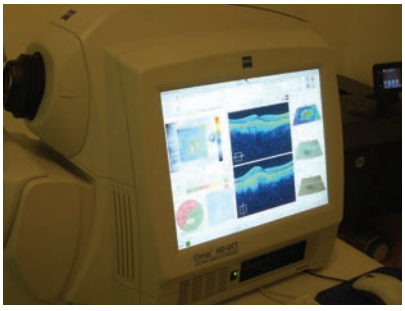
For decades, homatropine and scopolamine ophthalmic topical drops have been commonly employed in the adjunctive treatment of anterior uveitis. Now, only homatropine is available to us. For unknown reasons, the production of scopolamine has been discontinued and is no longer available. However, the loss of scopolamine is not a therapeutic disaster as 5% homatropine performs excellently.

In like manner, Enuclene (tyloxapol, Alcon), an OTC detergent with BAK used to clean and lubricate ocular prostheses, is no longer available. We now use a lipid-based artificial tear for this purpose, and pulse-dose with a topical corticosteroid eye drop as needed for tarsoconjunctival inflammation.

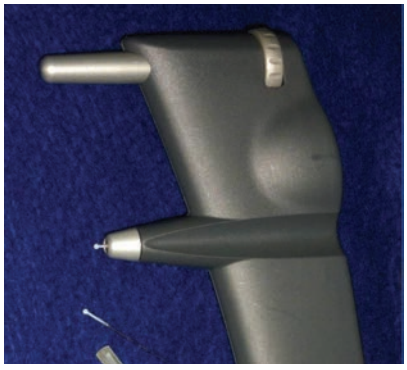
Essential Office Instruments

Beyond the phoropter, slit lamp and binocular indirect ophthalmoscope, there are some other key acquisitions that need be considered for comprehensive eye care. Following are our suggestions, in no particular order of importance:

• ***OCT***. Any OCT unit is to be prized; however, a high-definition-OCT is much preferred, mainly because it is quickly evolving toward standard of care for Plaquenil (hydroxychloroquine) retinal toxicity screening. It would be better to find other areas in your practice where costs can be reduced in order to obtain OCT technology.

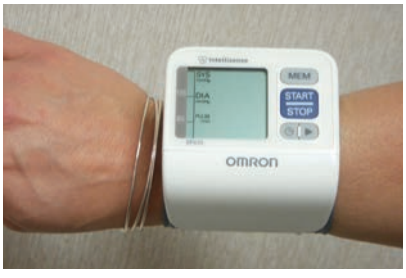


• ***Pachymeter***. We are absolutely stunned that not every OD has a corneal pachymeter. Corneal thickness assessment is a must to be able to accurately assess the risk for glaucoma. Remember that "failure to diagnose" is the foremost reason for lawsuits, and this structural assessment can be very helpful for staging risk in glaucoma suspect patients.



• ***Handheld tonometer***. Almost everyone dreads/hates the air-puff tonometer! The Icare rebound tonometer is the best upgrade currently available to replace the antiquated air-puff. We have yet to meet a single OD who is not happy with their Icare tonometer and it is a nice step up in the professional care of patients.

• ***Blood pressure device***. In like manner, optometry practices need to acquire a blood pressure device. The radially (forearm)-placed devices are inexpensive and readily available OTC at any pharmacy. The instrument is easy and simple to use, provides a huge service to your patients, and may be even life-saving. We urge you to train your staff to perform this half-minute assessment on your patients. Our arbitrary age for blood pressure assessment is 35 years and over.



• ***Golf club spud***. A golf club spud is an essential, all-around workhorse instrument for removing corneal foreign bodies and removing erosive (symptomatic) concretions on the tarsal surface of the superior eyelid.

In addition, Korb et al. have discovered that simply using this device to scrape along the top of the meibomian gland orifices can greatly facilitate meibum flow posteriorly into the lacrimal lake, thus enhancing the care of patients with dry eye disease.[1] While there is no procedure code for this simple maneuver, no topical anesthetic needs to be used, it takes only about 15 seconds per lower lid to perform, and it can be helpful in the care for your dry eye disease patients.

1. Korb DR, Blackie CA. Debridement-scaling: a new procedure that increases Meibomian gland function and reduces dry eye symptoms. Cornea. 2013 Dec;32(12):1554-7.

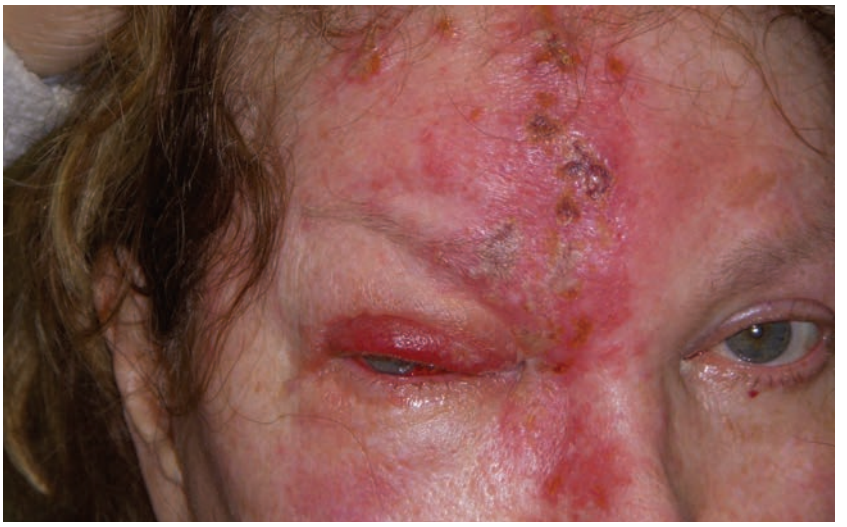
Highly Viscous Eye Medicines

There are several products that merit special instruction to the patient: AzaSite, Besivance, Lotemax Gel drop, Zirgan (in a tube). To ensure proper drug delivery with these medicines, it is important that two maneuvers occur with each instillation:

• First, with the lid still on the bottle or tube to prevent contamination, tap the bottle or tube tip a couple of times to ensure that the medicine gets into the tip.

• Second, instruct the patient not to blink for about five seconds after the instillation. This allows the eye drop or gel formulation to spread across the ocular surface.

Both of these maneuvers enhance the effectiveness of drug delivery and absorption.



A severe case of shingles that might have been prevented with the zoster vaccine.

Shingles and the Zostavax Vaccine

As a general rule, optometrists should encourage their over-50 patients to talk to their primary care providers about getting the shingles vaccine.

A common question: "Should I get the vaccine if I've already had shingles?" The answer depends on the patient. Having shingles powerfully reboots the immune system. This explains why shingles is pretty much a "once-and-done" event.

The rate of having a second bout of shingles lies somewhere around 3% to 5%. Because the vaccination reduces the risk of shingles by about 50%, this would yield a risk of about 1.5% to 2.5% in patients who have already had one outbreak. Like many aspects of life, it's a gamble.

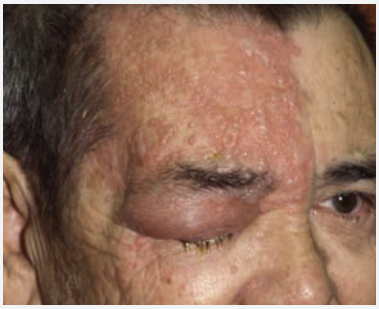
Our general practice is to not recommend Zostavax (Merck) within three to five years of a shingles episode since having such an episode is as good as or better than having the vaccine. As we age, our immunity becomes less robust, so perhaps after three to five years following a shingles episode, one might consider becoming vaccinated.

Just for perspective, we are over 50 and we have both received the Zostavax vaccine. ■

Tseng HF, Chi M, Smith N, et al. Herpes zoster vaccine and the incidence of recurrent herpes zoster in an immunocompetent elderly population. J Infect Dis. 2012 Jul 15;206(2):190-6.

Zoster Vaccine Efficacy: How Long Does it Last?

After 10 years, zoster vaccination loses most of its power, according to a recent report from the Shingles Prevention Study.[1] The investigators found that efficacy against herpes zoster incidence fell from 46% in year seven to 14% in year 10. By the eleventh year, efficacy was negligible.



These numbers suggest that a single dose of herpes zoster vaccine administered at age 60 is unlikely to confer protection for the duration of one's life. An editorial cautiously suggests "rethinking public health recommendations" and possibly endorsing a second dose of vaccine about eight years after the first.[2]

Based on these relatively dismal observations, it certainly seems reasonable to us that perhaps after eight years revaccination might well be in order. We will leave it to the CDC and the infectious disease epidemiologists to establish firm guidelines in the near future.

1. Morrison VA, Johnson GR, Schmader KE, et al; for the Shingles Prevention Study Group. Long-term persistence of zoster vaccine efficacy. Clin Infect Dis. 2015 Mar 15;60(6):900-909.
2. Whitley RJ. Editorial commentary: waning efficacy of the herpes zoster vaccine. Clin Infect Dis. 2015 Mar 15;60(6):910-1.

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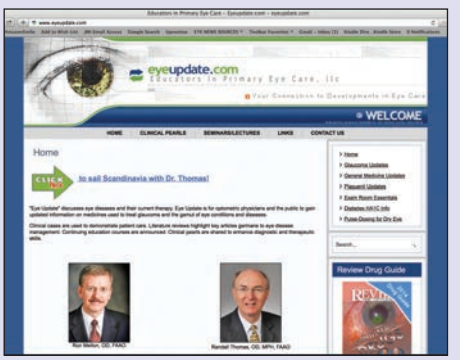
It may not be an award-winning site, but it does contain many nuggets of valuable information, clinical pearls, forms and handouts you can download, and dates/locations for our lectures.



Also, this *Clinical Guide to Ophthalmic Drugs* is posted on our home page (as well as on www.reviewofoptometry.com), and therefore readily available electronically.

Why Drug Costs are Skyrocketing

(continued from page 2)
manufacturers abandoned production, while others merged. With generics having similar active ingredients, price dictates pharmacies and managed care companies contracts, causing some manufacturers to cease or decrease production if contracts are not gained or minimal profits met.[7,8]

Staple medications—including ophthalmic drugs such as pilocarpine, phenylephrine and atropine—were classified as unapproved marketed drugs because many of these medications came to market before regulatory guidelines began. Suddenly, these drugs had to undergo the FDA's New Drug Application regulatory process, which placed a financial burden on many manufacturers.[10]

> ***"More than one out of four Americans do not fill their prescriptions because they cannot afford the cost."***—*Sen. Bernie Sanders (I-Vt.), chairman of the Senate Subcommittee on Primary Health and Aging, October 2014.*

This was the case for Teva Pharmaceutical Industries, the world's largest generic drug manufacturer. As required, Teva informed the FDA in 2012 of its intention to stop selling doxycycline in the United States. Experts believe this led to the sudden price increase. Other manufacturers have shown intentions of bringing these medications to market, but newer FDA regulations have extended time frames of drug to market approvals.[7–9]

Prednisolone, on the other hand, is manufactured by Pacific Pharma as well as Sandoz. Sandoz accounted the increase in price of prednisolone to manufacturing and supply issues, while Pacific Pharma followed a comparable price increase with profits in mind.[3]

Also, a recent (2011) FDA regulation affected many older drugs.

Another factor, although minor, for the increase in drug prices could be a lack of price controls in the marketplace. Consider the fact that for years, brand name drug companies must provide rebates to Medicaid despite the rising cost of their compounds. This is not the case for generic manufacturers, which provide no such rebates.[7]

Dealing with Reality

Price is not the only factor that matters to our patients and to us; accessibility is just as important. In an era where one in four Americans do not fill their prescriptions because of cost, the burden of safe and effective pharmacological therapeutic management is placed on the clinician. Higher prices and/or limited accessibility create clinical juggling challenges where efficacy, safety and cost might just be at odds.

It is imperative then that we discuss and develop strategies to deal with these shortfalls. At the same time, we must be aware of the risks of using substitutes and sometimes temper our hopes of obtaining our desired and predictable therapeutic clinical outcomes. ■

Dr. Gonzalez is in private practice in Dallas and serves as adjunct faculty at InterAmerican University in Puerto Rico. He tracks optometrists' patterns of adoption and usage of ophthalmic medications.

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2. International prescription drug costs containment strategies and suggestions for reform in the United States. Available at: www.bc.edu/content/dam/files/schools/law/lawreviews/journals/bciclr/26_2/07_TXT.htm. Accessed January 20, 2015.
3. Prices of generics drugs soar as mergers reduce competition. Available at: www.jacksonville.com/news/health-and-fitness/2014-07-08/story/prices-generic-drugs-soar-mergers-reduce-competition. Accessed January 20, 2015.
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7. Barlas S. Generic Prices Take Flight: The FDA Is Struggling to Ground Them. Pharmacy and Therapeutics. 2014;39(12):833-845. Available at: www.ncbi.nlm.nih.gov/pmc/articles/PMC4264670/. Accessed January, 20, 2015.
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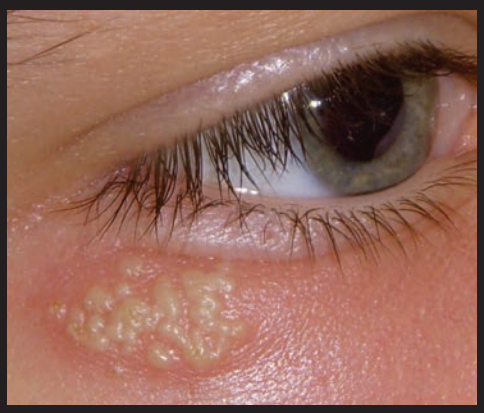

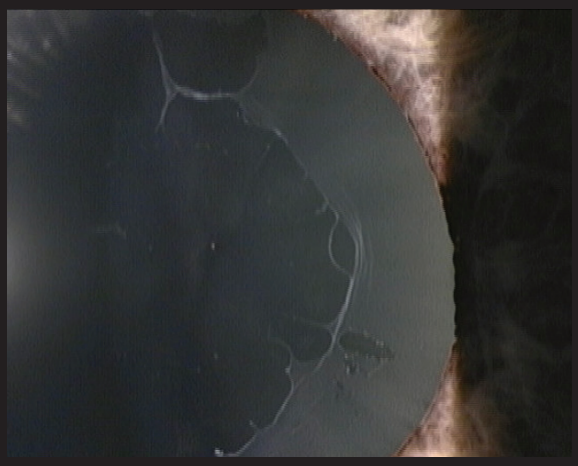

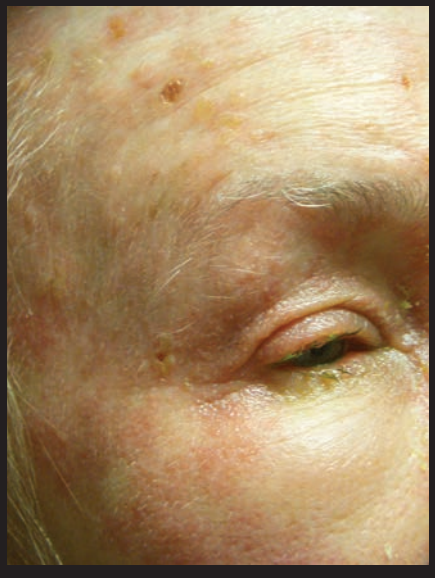

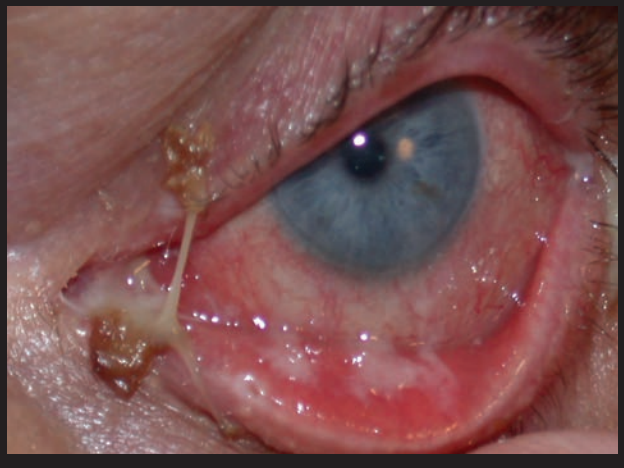

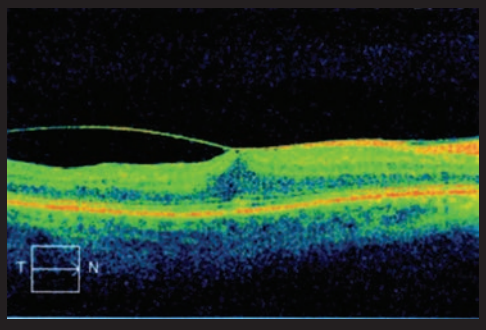
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