Peer-to-peer advice to help boost your prescribing prowess.

Supported by an unrestricted grant from Bausch + Lomb
DEAR OPTOMETRIC COLLEAGUES:

Welcome to the 2018 edition of our annual Clinical Guide to Ophthalmic Drugs. Herein, we provide updates on our collective clinical experiences and heavily season them with pertinent excerpts from the literature.

This guide is intended to bring solid, scientifically accurate and clinically relevant information to our optometric colleagues. If you want to understand how the three of us treat, and what factors led us to develop these methods, you’ll find it explained here. The methods and opinions represented are our own. We recognize that other doctors may use alternative approaches. That is true in all of health care. But this three-doctor writing team has logged over 75 combined years of clinical optometry, and we bring that ‘real-world’ spirit to the discussions that follow. Know that, above all, we are doctors who are genuinely concerned for our patients’ well-being and who endeavor to provide them the best of care, and we write from that perspective.

The two topics of greatest interest and need for most eye physicians right now are glaucoma and dry eye disease. We have devoted considerable energy to thoroughly and comprehensively discuss them within these pages. Both are making the headlines these days. In dry eye, the role of omega-3 supplementation—long considered a staple of therapy in dry eye disease—has been challenged by a major study showing no benefit. We will cover this more completely in our dry eye chapter.

The situation is more positive in glaucoma. We’re always excited to have new and improved approaches to reduce intraocular pressure. Vyzulta (latanoprostene bunod ophthalmic solution 0.024%) was approved in November 2017, and the following month, rho-kinase inhibitor Rhopressa (netarsudil ophthalmic solution 0.02%) was approved. These new medicines complement our glaucoma armamentarium.

A third new product of note derives from the glaucoma world but has found a new indication. Lumify (brimonidine tartrate ophthalmic solution 0.025%), a redness reliever OTC eye drop that works on the venule tissues through a totally different mechanism of action, is now available, and should completely eclipse the old tetrahydrozaline-containing drops.

We are grateful that Bausch + Lomb and Review of Optometry have partnered with us for more than two decades to produce this important resource, as we endeavor to bring our profession the most up-to-date clinical information available to enhance patient care.

With best wishes,

Randall K. Thomas, OD, MPH, FAAO
Ron Melton, OD, FAAO
Patrick M. Vollmer, OD, FAAO

Disclosure: Drs. Melton and Thomas are consultants to, but have no financial interests in, the following companies: Bausch + Lomb/Valant and Icare. Dr. Vollmer has no financial interests in any company.

Note: The authors present unapproved and “off-label” uses of specific drugs in this guide.
My rookie year in practice has been fascinating, terrifying and exhilarating, all at the same time. I believe this effect holds even truer if you are a solo practitioner, as I am. After officially being in private practice a little more than a year, I realize I do not have all (or even most) of the answers. But I can speak from experience about what I have learned so far about growing an eye care practice and moving forward in a competitive environment. Here is my advice:

• Stop referring your patients out. Aside from some posterior pathology and cataract surgeries, I have only referred out one case to ophthalmology at the time of this writing. Examples of cases that I have not referred out include: Pseudomonas infection, other peripheral and central corneal ulcers, corneal lacerations, herpes simplex keratitis, multiple herpes zoster ophthalmicus cases with severe anterior chamber reactions, preseptal cellulitis, an eye swollen completely shut by bullous impetigo (misdiagnosed as shingles by the PCP), thermal and chemical burns, and many more. I choose not to refer these cases out, not because I am overly confident (I lost some sleep at night initially) but because the patients came to me specifically to help them. Additionally, ophthalmology is a surgical discipline. None of the cases above warrant surgical procedures, nor did ophthalmology have any more access to the medicines used to treat the cases listed above (even the compounded antibiotics used to treat Pseudomonas).

• Embrace corticosteroids. I prescribe topical or oral steroids on a daily basis. I can confidently say that their short-lived side effects (particularly with Lotemax) are negligible compared to the enormous benefits they can provide to your patients. Not only should you fully embrace your ability to prescribe these agents, you also should prescribe them aggressively early on in the inflammatory process. Tentatively prescribing steroids at suboptimal dosages will not bring your patient disease resolution. Out of all the cases I have treated, I have yet to have one patient not drastically improve while on corticosteroids.

• Befriend your urgent care centers. No secret here—urgent care hates “treating” eye-related emergencies. When the prescribed antibiotics failed to make patients’ ocular inflammation better (antibiotics do absolutely nothing for
FIRST-YEAR IMPRESSIONS

ADVICE TO NEW GRADS

Advice for new optometric graduates could fill a textbook, but it also can be succinct; we opt for the latter.

- Buy used equipment, and slowly upgrade to state-of-the-art as finances prudently allow.
- Do all you reasonably can to keep your overhead low.
- Get help and advice on all topics and concerns—don’t go it alone! Don’t be afraid to ask other successful professionals (even outside of eye care) their advice. Their success was for a reason. Model them—then improvise.
- Regarding the nightmare of insurance, every ophthalmology office has a resident authority in this area. Choose an excellent ophthalmologist to work with for surgical referrals, and in reciprocal benefit, obtain help from their insurance expert. Also, be aware that there are billing/insurance third-party companies available, many compatible with your EHR.
- You are well trained and your basic clinical knowledge is at a peak. Use this asset to keep and care for any and all patients who present to your office. Refer out with great restraint. Never in your life will you have a greater opportunity to solidify your clinical skills than during your first few years in practice.
- Remember, referring out carries a high potential for patient loss at a time when you are working to grow your practice. You have the same access to drugs that other doctors do. Your patient came to you for help. Give it to them.
- Chat with (in person or by phone) older, benevolent providers in your area to get their advice about any and every aspect of your business. But choose your advisors wisely. Tread carefully!
- Let your patients know you truly care about them. Rigorously adhere to the Golden Rule; such behavior will always be appreciated and rewarded.
- Be available to your patients. When a patient calls your office, you should have a number where you (or a colleague with whom you have developed a co-sharing of call responsibilities) can be reached. This is paramount.
- Dress for success. Wear nice, professional clothing, and a sharp, white lab coat that bears your name. Be proud to be an OD!
- Develop relationships with urgent care centers, pharmacy-based quick-care centers and primary care physicians. These centers and PCPs have extremely limited knowledge of eye and vision problems, and would be relieved to have someone willing to help them. Set up a time to take these colleagues to lunch, and carry business cards that make you easily accessible. Many health care providers do not realize the scope of practice and wealth of knowledge optometrists have. And always send a succinct letter documenting your findings and appreciation for any referrals.
- Assuming you have a sound skill set, use your deep courage to step up to the plate. Your professional growth will astound you.
- The first time we do anything, there is a level of uncertainty, uneasiness and anxiety. When treating a condition for which some of these emotions or concerns arise within you, simply get the patient’s contact number and let them know you will be calling them in a day or two to check on them. A personal phone call to a patient makes them realize how compassionate and caring you are.
- You are not a salesperson; you are a doctor. Put your whole heart into what is absolutely best for your patients, and the revenue will follow.
- Of the big instruments/equipment (beyond the basics), you will need to acquire the following, in this order:
  1. Pachymeter
  2. Humphrey visual field unit
  3. High-quality optical coherence tomography device
  4. Icare tonometer
  5. Retinal camera
  6. Slit-lamp camera
  7. Meibography unit
  8. LipiFlow

These are but a few of many practice management pearls that can be enormously helpful to a willing practitioner. Ponder these and their potential merit thoroughly, and have the determination and courage to pursue them based on your interests and the character of the practice you hope to build.

- Always send a follow-up letter.

If another provider refers to you, all they care about is that you treated/addressed the referred issue. If you don’t send a succinct, brief follow-up letter (don’t send the entire EHR exam), the referrer has no way to document that you did anything at all. This leaves no motivation to have referrals sent your way in the future.

inflammation), those cases would wind up in my office several days later.

Now, after months of frequenting their clinics, many urgent care eye cases now are referred directly to my practice without any initial treatment at all.

- Befriend MDs and other healthcare providers. To be perfectly honest, I was met with some initial resistance here. That being said, please don’t get nervous around these folks.

Medical/nursing/PA schools instruct their candidates to refer to ophthalmology. To make matters worse, a very low percentage of all these cases ever require surgery, essentially overburdening our surgical colleagues and delaying patient care.

While many primary providers are certainly well-versed in the physiology of numerous organs, the eye is just not one of them. Make yourself available and remind them of all the services you provide.

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future. By the way, many EHRs already have such templates available.

- Remind your patients of all the medical services you offer. Devote 20 seconds at the end of each patient encounter to letting them know you treat myriad ocular emergencies.
- Be available to your patients around the clock. I’m not sure that strictly being available during business hours represents the best of patient care. Everyone knows most conditions and emergencies happen after business hours! If your patient can’t find a way to contact you, their care could be significantly delayed. Develop a way to be reached at any time.
- Don’t recommend a product or service a patient doesn’t need. While the financial aspects of consumerism are beneficial, no one wants to be upsold on something that won’t benefit them. Talk with your patients to figure out what is most conducive to serving their needs. Patients will tell you that they appreciate this, and are much more likely to trust your advice in the future, and recommend family members and friends.
- Be patient. I think that this is the single most important piece of advice I can give a new graduate. Some days you will be slow. Don’t let these lulls in patient care get you down! Spend this time reading journals or getting out in the community to introduce yourself, rather than fretting over when you will see your next appointment. I often (unfortunately) compare myself to my other colleagues who see more than 30 patients a day, although many of those individuals have been in practice for decades and have established patient bases.

Control what you can control, and your practice will prosper. If you can commit to doing your best for all your patients, perhaps you’ll look back fondly on the days when you still got a short break for lunch.

Patrick Vollmer, OD, is owner of a practice in Shelby, NC.

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**Evolving Technology to Aid Your Practice**

- **ePA Solutions Help Streamline Prior Authorizations for Providers.**

  Electronic prior authorization (ePA) is the automated process of exchanging patient health and medication information, enabling health care providers to initiate PA requests after a rejection at the pharmacy or prospectively in their e-prescribing workflow.

  Services such as CoverMyMeds and PARx Solutions partner with electronic health records (EHRs), health care providers, payers and pharmacies to initiate, transmit and track the status of PA requests within the clinical workflow, helping patients to more quickly receive the medications they need for therapy.

  For example, health care providers can initiate and manage ePA requests using CoverMyMeds in an online portal or at the point of prescribing through one of the 500-plus EHR vendors integrated with the company’s technology. Health care providers can receive electronic determinations, often within minutes, and create renewals from previously submitted requests.

  In addition, PARx says its streamlined, user-friendly, full-service approach is free to prescribers, combines web-based technology and personalized support, and uses a universal approach across all health plans.

- **App for Calculating Plaquenil Dosing Undergoes Revisions.**

  Hydroxychloroquine (HCQ) retinopathy (HCR) is a potentially blinding disease. Once HCR is detected, the disease often continues to progress, even when the medication is stopped. As such, primary prevention by appropriate dosing of HCQ (brand name Plaquenil) is the best way to minimize the risk of HCR. Studies show that about half of Plaquenil patients are overdosed.1

  Two somewhat competing approaches to calculating appropriate dose exist:1

  - **Calculating Ideal Body Weight (IBW):** Assumes that HCQ is stored mostly in lean tissue
  - **Using Actual Body Weight (ABW):** Assumes that the drug is distributed evenly in muscle, skin and fat

  In an effort to solve the dilemma, a team of Massachusetts Eye and Ear ophthalmologists developed a free smartphone app—DoseChecker—that blends the two approaches. The app became available in the App Store in September 2017. Users enter the patient’s height and weight, and the app calculates the proper HCQ dose.

  However, the app deviated from current American Academy of Ophthalmology (AAO) screening recommendations for calculating optimal daily dosage, which is leading to a software revision in progress.2 The AAO now recommends that all patients using HCQ keep daily dosage less than 5mg/kg actual body weight—not ideal body weight. Older recommendations once advised calculating dosage as 6.5mg/kg ideal body weight, but that conclusion was based on 50-year-old studies about HCQ and fat-using animals, according to an article in the April 2018 issue of EyeNet.3

  When the revised app is available, it is expected to be endorsed by the AAO to simplify the calculation of daily HCQ dose and schedule of tablets needed to provide a proper weekly dose.1

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GLAUCOMA

DON’T LOSE SIGHT OF GLAUCOMA

Screening should always be on the radar of an attentive optometric physician. With a multitude of diagnostic and therapeutic tools at our disposal, patient referral should be a rarity.

Glaucoma seldom progresses quickly, so take the time to make a careful diagnosis and thoughtful decisions regarding therapy prior to treatment. Diagnosis and management of glaucoma should be a welcomed opportunity in our offices and clinics, where referral should be exceedingly rare.¹ ¹

Let’s start with some best practices and reminders for a proper diagnostic glaucoma evaluation.

¹ Carefully observe the optic nerve head. This is the foundation for the rest of the glaucoma workup. Many times glaucomatous optic neuropathy will be missed because a “normal” intraocular pressure (IOP) lured the clinician into complacency. However, low-tension glaucoma can be found in a sizable minority of patients, so analyze the optic nerve with close attention to the neuroretinal rim tissue.

² Perform tonometry (and at different times of the day). While the prevalence of glaucoma increases with higher IOP, absolute diagnosis should almost never be made from a single pressure reading alone. It is good practice to get at least three different readings, with at least one reading in the early morning, given the circadian variability of IOP.

Large-scale population studies have determined that the mean IOP is around 15.5mm Hg. Two standard deviations on either side of this value approximate

THE OPTIC DISC

While ancillary testing in glaucoma workups can be helpful, remember that glaucoma is a disease of the optic nerve.

The typical optic nerve head is slightly oval and more vertically oriented. Within the disc lies the optic cup, a paler, central depression devoid of any ganglion cell axons with visibility of the lamina cribrosa.

The tissue that lies between the cup and the edges of the disc is referred to as the neuroretinal rim. Subtle changes to the rim can result in significant changes in a patient’s visual field, so carefully scrutinize this tissue.

Remember that the size of the disc and the cup are typically closely related; a larger disc will usually have a larger cup.

This optic nerve head, while considerably cupped, honors the ISNT rule, and therefore is highly likely physiologic cupping.
a normal range to be between 10mm Hg and 21mm Hg.

Traditionally, IOP had been thought to peak in the early morning hours, but research has revealed that IOP is highest during the sleep cycle. Normal diurnal variation is less than 3mm Hg; fluctuations greater than 6mm Hg necessitate a more attentive and closer follow-up.

• **Check central corneal thickness.** Having a pachymeter readily available is crucial to establishing a true IOP. We regularly see referrals for a glaucoma evaluation in patients who have an IOP in the mid-to-upper 20s, with 0.2 or 0.3 central cups and corneal thicknesses of 620µm to 640µm. These patients commonly have a normal workup. If all optometrists would simply measure the central corneal thickness (CCT) in these pseudo-ocular hypertensives (with semi-annual follow-ups), it would be an immense service to patients and our profession.

Author’s Note: Be advised that this is not an exhaustive list of the topical beta blockers. Several less commonly used drugs have been omitted for space.

<table>
<thead>
<tr>
<th>TOPICAL GLAUCOMA DRUGS</th>
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<tr>
<td><strong>BRAND NAME</strong></td>
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<td>Beta Blockers</td>
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<td>Simbrinza</td>
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<td>Rho Kinase Inhibitors</td>
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<td>Rhopressa</td>
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relatively meaningless.

Keep in mind that a physiologically thin cornea appears to be an independent risk factor for glaucomatous optic neuropathy, which needs to be factored into risk assessment.

- Evaluate the neuroretinal rim. Remember the ISNT rule? It goes like this: inferior > superior > nasal > temporal. Let’s refresh:

  In a normal optic nerve head, the inferior tissues are usually the thickest, followed by superior rim tissues, then nasal rim, with the temporal rim being the thinnest. This is not a bulletproof concept, but it is a good general guide.

From the Literature

AGEING ALONE CAN EXACERBATE PROGRESSION IN GLAUCOMA PATIENTS

It stands to reason that natural quantitative loss of optic nerve fibers over time can contribute to glaucomatous optic neuropathy. An article in Ophthalmology (December 2015) gives important insights into the impact of natural aging on visual field compromise in the setting of glaucoma progression, per these excerpts:

- “Age-related loss of neuroretinal parameters may explain a large proportion of the deterioration observed in treated patients with glaucoma and should be carefully considered in estimating rates of changes.”
- “Because there is accumulating evidence that aging in otherwise healthy subjects also results in statistically significant change, often with patterns resembling those in glaucoma, the clinical assessment of glaucomatous progression can be challenging.”
- “The effect of IOP variability on ONH parameters is probably related to changes in laminar position and prelaminar tissue compression.”
- “Because mean deviation (MD) is age adjusted, it is likely that the absence of normal aging effects with this parameter allows better estimates of glaucoma-related damage than with the neuroretinal parameters.”
- “Our findings indicate that aging in healthy control subjects leads to a significant reduction of neuroretinal parameters and may explain a large proportion of the deterioration observed in patients with treated glaucoma. Furthermore, both cross-sectional and longitudinal studies of healthy subjects show patterns of regional loss similar to those in patients with glaucoma, suggesting that age-related regional susceptibility may be accelerated in glaucoma. Because several previous longitudinal studies of structural progression of glaucoma lacked a control population, the observed changes were attributed to glaucoma, perhaps overestimating the rate of change in treated glaucoma. Therefore, without an understanding of the significant normal age-related changes, there could be errors in rate estimates and the diagnostic accuracy of glaucoma-related progression.”

Thankfully, there are many metrics and parameters to guide us in clinical decision making beyond the visual field. However, this article serves to make us more analytical in evaluating changes in the visual fields. Remember, in order to establish true progression, we would have to do three or four fields about every six to 12 months. This is why it’s so challenging and minimally productive to micromanage the visual field component of the comprehensive glaucoma assessment.

disc ratios, the focal rim tissue can be healthy and well-perfused with no pathology present. Erosion of rim tissue, if found, is usually seen at the inferotemporal (macular vulnerability zone) or superotemporal areas. This is secondary to the relatively sparse glial tissue support in this area. Remember, larger optic nerves will have larger cup-to-disc ratios.

- **Look at the patient’s history.** Glaucoma tends to run in families. When we see patients who have glaucoma or who are labeled as high-risk glaucoma suspects, we always ask about siblings, as they can have a higher risk of developing glaucoma that increases with age. We urge our patients to encourage siblings to also seek an optometric glaucoma evaluation. Such screenings have been shown to yield additional diagnoses.

- **Check blood pressure in-office.** Carefully assess the patient’s systemic conditions, especially hypertension. Particularly in low-tension

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**TIMOLOL EYE DROPS FOR MIGRAINE HEADACHE?**

Acute migraine headaches may be reduced in intensity or stopped altogether with beta blocker eye drops. While the daily use of beta-blocker pills has been proven effective in preventing chronic migraine headaches, they have been unsuccessful in treating acute, sudden-onset migraines. Beta-blocker eye drops, however, are absorbed more quickly than pills by tear duct drainage onto the nasal mucosa, achieving therapeutic plasma levels “within minutes.”


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**CENTRAL CORNEAL THICKNESS**

In a large study using manometric methods to record intraocular pressure, 44% of normal-tension glaucoma patients would have been reclassified as having primary open-angle glaucoma (POAG), while 35% of patients diagnosed with ocular hypertension would have been reclassified as normal after CCT was taken into account.

To a statistically significant degree, researchers have determined that African-Americans tend to have thinner CCT measurements than Asians, Caucasians and Hispanics. This leads to a considerable underestimation of true IOP.

Importantly, CCT is a predictor of the extent of glaucomatous damage in patients.


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**CUP-TO-DISC ASYMMETRY IN GLAUCOMA**

A study in the August 2017 *Ophthalmology* described the prevalence of vertical cup-to-disc ratio (vCDR) asymmetry in US adults and assessed the utility of vCDR asymmetry in the glaucoma diagnosis. The researchers concluded:

- vCDR asymmetry was predictive of prevalent glaucoma, although the positive predictive value remained low even at high degrees of asymmetry.
- vCDR asymmetry should initiate a more comprehensive glaucoma workup, especially in individuals with additional risk factors, but it is not appropriate as a screening metric for glaucoma.

GLAUCOMA CARE

STUDY COMPARES FIRST-LINE MEDICATIONS FOR PRIMARY OPEN-ANGLE GLAUCOMA

This article in Ophthalmology (January 2016) definitively confirms what clinicians have witnessed over the last decade: All the prostaglandins work similarly.1 Some quotes from this article provide unique insights:

- “The objective of this article is to assess the comparative effectiveness of first-line medical treatments for lowering IOP in patients with POAG orocular hypertension through a systematic review and network meta-analysis and to provide relative rankings of these treatments. By using a systematic review and network meta-analysis, we estimated the pairwise comparative effectiveness of 14 first-line IOP-lowering drugs used in patients with POAG or ocular hypertension.”

- “Drugs in the prostaglandin class were more efficacious than drugs in other classes, although the within-class differences were generally small. Bimatoprost 0.01% is no more effective than latanoprost or travoprost in lowering IOP at three months. Brimonidine lowered IOP more than apraclonidine; and unoprostone and betaxolol lowered IOP the least.”

- “In conclusion, we found that all active first-line drugs are effective compared with placebo and that prostaglandins were more efficacious in lowering IOP at three months than beta-blockers, alpha-agonists, or carbonic anhydrase. Bimatoprost, latanoprost and travoprost are among the most efficacious drugs, although the within-class differences were small and may not be clinically meaningful. All factors, including side effects, patient preferences and cost, should be considered in selecting a drug for a given patient.”

This final statement is a clinically practical admonishment. A key factor the authors failed to mention is frequency of administration. While cost is a pre-eminent factor, ease of use is similarly so. We find topical timolol to be cheap, simple and safe (in non-asthmatic patients), which is why we often start there in select patients. It is most definitely our go-to second-line drug when target IOP is not achieved with a prostaglandin. Now, with the availability of Vyzulta (Bausch + Lomb), we anticipate using it first line since studies show IOP reductions of 7 mm Hg to 9 mm Hg and outperformance of latanoprost.

24-2 OR 10-2: WHICH IS BETTER?

Researchers studied the association between quality of life (QOL) and visual function as measured by 24-2 and 10-2 VFs in patients with primary open-angle glaucoma. They also tested the hypothesis that patients with vision-related QOL disproportionate to their 24-2 VF status may exhibit 10-2 damage overlooked by the 24-2 test. Here are some of the findings:

- 50% of all ganglion cells were within 8 degrees of fixation.
- 90% of the visual cortex involved 10 degrees of the central VF.
- 24-2 did not sufficiently sample the central VF.
- Using only 24-2VF “may underestimate the extent, location, and implication of VF loss.”
- Macular damage can occur early in glaucoma in the macular vulnerability zone (MVZ).
- Macular glaucoma as measured by the 10-2 VF was “a strong, frequently unmeasured, explanatory variable in vision-related quality of life.”

patients, many asthmatics can use a topical beta-blocker successfully. However, we never prescribe one before soliciting the primary care physician for clearance and written documentation attesting to such. (As an aside, we also find ourselves communicating more often with rheumatologists, since many of these specialists have a proclivity to overdose patients taking hydroxychloroquine. Sending a copy of the EMR documentation attesting to such.

- Analyze the retinal nerve fiber layer (RNFL) and macular ganglion cell layers. While in no way is optical coherence tomography (OCT) absolutely diagnostic, the added benefits of such testing can be immensely helpful in tracking glaucoma progression. In addition to standard RNFL scans and a quick ganglion cell layer evaluation, analysis of the macula can potentially give the clinician additional information.

The latest literature suggests that very early glaucomatous damage can involve the macula, specifically the inferotemporal portion of the ganglion cell layers, referred to as the macular vulnerability zone. As always, the more information you collect, the more confident you can be in your decisions as you follow the disease over time.

- Perform perimetry (repeat, if any doubt). Ultimately, glaucoma is a disease that affects the visual field. Humphrey VF 24-2 SITA Fast testing remains our assessment of choice. One test result, especially in a naive-to-VF test patient, can be confusing unless it is either normal or it is abnormal but corresponds to the optic nerve head assessment. The problem is that many initial (and some subsequent) VF results are “noisy” and fruitless.

Remember that central VF loss can occur early in glaucoma. Where a 24-2 VF has only four central test points, a 10-2 VF has 44 central points. While routine 10-2 testing is not considered practical, strongly consider it when one or two central defects are seen on the 24-2 VF.

Once a repeatable visual field defect is present, following the patient over time is best done with serial VFs. Nerve fiber layer analyzers are more helpful in staging risk or helping to detect early glaucoma, whereas serial VFs are optimal for following patients with established VF defects.

know your type of glaucoma

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<thead>
<tr>
<th>Type</th>
<th>Intraocular Pressure</th>
<th>Optic Nerve</th>
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<tbody>
<tr>
<td>Primary Open Angle Glaucoma</td>
<td>Elevated</td>
<td>Glaucmatous</td>
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<tr>
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<tr>
<td>Normal Pressure Glaucoma</td>
<td>Normal/Low</td>
<td>Suspicious</td>
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</tbody>
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The definition of glaucoma has evolved. Once thought to be exclusively a disease of high intraocular pressure, we now know that glaucomatous optic neuropathy can occur in 25% to 40% of patients with normal IOPs. Don’t let a normal IOP distract you from careful nerve head observation and potentially delayed treatment.

Our perspective on corneal hysteresis

A number of researchers have tried to determine whether corneal hysteresis (CH)—a biomechanical property relating to the eye’s ability to absorb and respond to pressure—is an independent risk factor for glaucoma. Some studies have determined that low CH is associated with optic nerve and visual field damage in glaucoma, and risk of structural and functional glucoma progression. One recent study supports the association as a risk factor for developing glaucoma, but the authors note that it was likely not a factor in therapeutic decision-making.

We are of the same mind as the author of a 2016 Glaucoma Today article, who wrote at the time that he was unconvinced that CH was a valuable measurement for managing glaucoma: He noted the following:

- “A cornea has several features that might alter hysteresis such as hydration status, thickness, curvature, and IOP. The shape of the force-time curve of the air puff could also change the hysteresis results.”

- “A large correlation study found that corneal hysteresis is influenced by age, corneal thickness, and IOP.” This presents a problem for measuring and interpreting a result, because so many different factors interact.”

- “I remain unconvinced at this time that hysteresis is of value in the management of glaucoma.”

While glaucoma specialists continue to study the potential of this technology, we personally have found our tried-and-true methods amply sufficient for assessing ocular pressure.

Look at the angle. When performing gonioscopy, use a four-mirror lens. After administering an anesthetic drop, this procedure can be done relatively quickly. While the non-contact Van Herick assessment is helpful, it may not be as sensitive or specific as gonioscopy. This technique is especially important in moderate to high hyperopia if progressive nuclear sclerotic cataract is further narrowing the iridocorneal angle.

Most patients with pigment dispersion syndrome or pseudoexfoliation are at higher risk for increased intraocular pressure due to clogging of the trabecular meshwork by biological debris. Screening for pigment dispersion can be accomplished by careful examination of the corneal endothelium and retroillumination of the non-dilated iris to look for radial (or splotchy) iris transillumination defects.

Pseudoxefoliation can be missed if the pupil is not pharmacologically dilated, as deposits on the face of the lens may be obscured. Qualifying and quantifying such debris in the angle is vital, especially in the setting of increasing IOP.

It is also important to annotate the pigmentation of the angle tissues when contemplating laser trabeculoplasty. Pigment absorbs the laser energy to enable a positive therapeutic response. If little or no pigmentation can be found in the trabecular meshwork tissues, the patient likely won’t experience a useful therapeutic response from the procedure. On the other hand, heavily pigmented angles tend to result in decreased IOP lowering effects. Gonioscopy should be performed to rule out causes such as angle recession or neovascularization.

Consider trabeculoplasty earlier. Laser trabeculoplasty is more effective in phakic than in pseudophakic eyes. We typically repeat gonioscopy every five years or sooner with unexplained increasing IOP.

OCT in structural diagnosis
A November 2016 study in AJO investigated the role of spectral-domain optical coherence tomography (SD-OCT) in the structural diagnosis of glaucoma. The researchers wrote:

- “Evaluation of structural changes is the initial, fundamental step in glaucoma diagnosis. Structural changes serve as the primary sign of glaucoma likelihood; they provide the basis of initial glaucoma diagnostic indication as to whether patients will undergo further examination or treatment.”
- “In reality, clinicians exercise discretion in accepting OCT results or not based on their impressions gained from clinical examinations. Thus, the diagnostic role of OCT should be examined within the context of the process of clinical decision making.”

To summarize the diagnostic evaluation:
1. Carefully study the optic nerve with slit lamp-enabled ophthalmoscopy.
2. Note the IOP.
3. Check CCT.

Beyond these three maneuvers, take a careful family history, obtain RNFL measurements and baseline VFs, and perform gonioscopy. Lastly, check blood pressure, especially in the setting of low-tension glaucoma. By doing all these things, you will reduce the chance of missing glaucoma.

THERAPEUTIC PERSPECTIVES
Currently, lowering IOP is the only proven treatment for glaucoma. Knowing when to initiate therapy is the Holy Grail of patient management. Equally competent doctors have different thresholds and philosophies but, by and large, there is no rush to treat because glaucoma is usually a slowly progressive neuropathy.

The decision to treat requires much care, contemplation and comprehensive assessment. Also, don’t forget that we are not treating a condition or disease; we are treating a person, so involving patients in the decision-making process is appropriate. Also remember: This publication is a drug guide, not a textbook. We assume a significant level of knowledge on the part of the reader. There can be exceptions to everything said herein, and every patient has to be cared for in a highly individualized manner.

Let’s now look at glaucoma medications we have in our armamentarium.

FIRST-LINE THERAPY
With few exceptions, a prostaglandin or timolol remain the frontrunners in treating patients with glaucoma. Since its initial release in 1996, latanoprost (Xalatan) paved the way for prostaglandins as first-line
therapy to treat glaucoma. Prostaglandins lower intraocular pressure by elevating the presence of extracellular metalloproteinases that break down the collagen matrix, thereby enhancing uveoscleral outflow of aqueous. This class of drugs commonly reduces baseline pressures by 25% to 33%.

Prostaglandins also have an excellent diurnal effect. However, the difference in morning vs. evening instillation of a prostaglandin is somewhere in the vicinity of 1mm Hg, so good adherence in the morning is much preferred to poorer adherence in the evening. Additionally, prostaglandins’ long duration of action can be seen for up to 72 hours, which is convenient in less compliant patients.

Side effects, while minimal, include iris color darkening, increased eyelid pigmentation, hypertrichosis and conjunctival hyperemia. Another side effect, superior eyelid sulcus deepening, can be dramatic in some patients.

Prostaglandins can be contraindicated in patients with a history of uveitis, herpes simplex and aphakia (due to the slight increased risk of macular edema).

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NO SINGLE VF DIAGNOSES

Do not make the mistake of relying on a single VF to diagnose glaucoma. Depending on the level of patient risk, do your due diligence to repeat the fields in a few weeks to months, looking for defect repeatability. Also, remember that glaucomatous VF defects are most commonly arcuate and nasal in shape. Patients can have irregularities in their fields that are not glaucomatous and, depending upon the pattern, may or may not necessitate other routes of investigation.

Once a diagnosis of glaucoma is firmly established, initiation of drop therapy is the next step. Note: never make a change in medical therapy based on the results of a single visual field test, as it is established that repeating VF testing three to four times is necessary before one can confirm true progression of aVF.

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TOP LEFT: Since the inferior and superior neural tissues have the least robust glial tissue support, they are most prone to sustain loss. Here the loss of neuroretinal rim is manifested as clinical “notching,” a hallmark observation in many glaucoma patients.

MIDDLE LEFT: This optic nerve sustained severe loss of neural tissue, thus showing a C/D ratio of 0.8.

BOTTOM LEFT: Side effect of prostaglandins include periorbital fat atrophy that gives rise to marked deepening of the superior lid sulcus, which can result in ptosis and enophthalmos; beyond the obvious cosmetic concerns, such altered lid/orbital anatomy can make applanation tonometry challenging.

TOP RIGHT: This optic nerve head was judged to be 0.1 by a previous doctor, but a careful look will show a very thinned neuroretinal rim in a shallow cup. Note also the peripapillary atrophy.

BOTTOM RIGHT: Because this patient’s IOP was 16mm Hg, we surmise the prior eye doctor failed to carefully study the optic nerve head. Note the pronounced inferior erosion of the neuroretinal rim, which manifested as a superior hemispheric visual field defect.
Generic latanoprost is a commonly prescribed glaucoma drop, and for many patients, it may be the best initial option because of cost. However, choosing the right medicine is highly complicated due to diverse and ever-changing marketing promotion. In some situations, a brand-name-protected product can be less expensive, especially with a coupon.

As well, different insurance companies have different drug formularies. To help you navigate this dynamic landscape, turn to the GoodRx, Micromedex and UpToDate web sites to help you in your decision-making.

In our patients, the 0.01% formulation of Lumigan (bimatoprost, Allergan) is much better tolerated with less hyperemia than the 0.03% (which is generically available), yet there is four times as much benzalkonium chloride (BAK) in the lesser-concentrated formula. We feel that this suggests that BAK is not as offensive as commonly touted. In fact, we have found that the 0.01% formulation with the higher BAK concentration has better corneal penetration.

That said, for patients sensitive to BAK, Travatan Z (travoprost, Novartis) is preserved with SofZia. And for those rare individuals who truly need a preservative-free option, Zioptan (tafluprost, Akorn) nicely meets this need. The main downside is that, like latanoprost and trifluridine, Zioptan has to be stored under refrigeration at the pharmacy.

Timolol, a non-selective beta-blocker, lowers IOP by decreasing aqueous humor production. It was the first topical beta-blocker to be used as an ocular hypotensive for glaucoma in the United States, and for decades was considered the gold standard by which all other glaucoma drops were compared. Timolol typically lowers pressures 25% from baseline.

**ASSESSING THE NARROW ANGLE!**

- “Often, at cocktail parties, glaucoma specialists get together and say, ‘What’s wrong with the general ophthalmologists? They’re missing a lot of angle closure.’ And I usually say, ‘Well, what’s wrong with us that we haven’t been teaching them gonioscopy?’”
- “...there are a lot of cases that come from optometry where they have been referred for high pressure, and no assessments of the angle were performed.”
- Always “do gonioscopy in a completely darkened room [...]. There should be no light through the pupil.”


**QUOTABLE**

“PRIMARY OPEN-ANGLE GLAUCOMA (POAG) IS A CHRONIC, PROGRESSIVE OPTIC NEUROPATHY IN ADULTS IN WHICH THERE IS A CHARACTERISTIC ACQUIRED ATROPHY OF THE OPTIC NERVE AND LOSS OF RETINAL GANGLION CELLS AND THEIR AXONS.”

A VICTORY FOR VYZULTA

The first new glaucoma medication in quite some time, latanoprostene bunod ophthalmic solution, 0.024% (LBN) was FDA approved in November 2017, more than 20 years after Xalatan made its debut in 1996.

LBN is the first IOP-lowering agent with a novel dual mechanism of action. Once in the eye, resident esterases cleave the molecule into latanoprost acid and butanediol mononitrate, which is further metabolized, yielding nitric oxide that appears to relax the smooth muscles of the trabecular meshwork. This outcome enhances aqueous outflow. The IOP-lowering effects were up to 7mm Hg to 9mm Hg.

In a 28-day trial head-to-head trial (VOYAGER) against latanoprost, LBN demonstrated superior diurnal reductions in IOP from baseline. Four concentrations of LBN (0.006%, 0.012%, 0.024% and 0.040%) were compared with Xalatan. All demonstrated a higher IOP reduction than Xalatan, with the high concentrations of LBN (0.024% and 0.040%) showing the greatest IOP reduction from baseline. Because the two higher concentrations of LBN ended up having similar clinical efficacy (probably due to receptor saturation), the 0.024% dose was selected for further clinical evaluation. In the study, Vyzulta led to an additional IOP reduction of 1.2mm Hg.

Vyzulta is a prostaglandin analog indicated for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension. Note that it is not indicated for “elevated” IOP, thus acknowledging that many patients have normal pressure glaucoma or are glaucoma suspects. Like latanoprost, the drop is stored long-term under refrigeration until dispensed to the patient. Approved for once-daily use (in the evening) and recommended for people over age 16, Vyzulta’s main side effect is conjunctival hyperemia (about 6%). It is preserved with 0.02% BAK (just like latanoprost) and comes in a 7.5mL bottle filled to 5mL volume.

Since it is established that every millimeter reduction in IOP significantly decreases the risk of glaucoma progression, we perceive using this new medicine in at least four clinical situations:

1. First line in an attempt to drive IOP as low as possible.
2. Patients in whom target IOP is nearly achieved with any of the older generation prostaglandins. We could easily add a beta-blocker once daily, but this would require the acquisition of another topical preserved eye drop that might not be necessary.
3. Certainly, if the patient has asthma or is a beta-blocker nonresponder, Vyzulta might achieve target IOP.
4. When a prostaglandin and a beta-blocker come close but do not achieve target IOP, replacing the prostaglandin with Vyzulta might meet treatment goals.

We are pleased to have a new, dual-mechanism, single-molecule drug available that can help us achieve further IOP reduction and provide optic nerve protection, as well as potentially delay the need to add a second or third drug.

Unlike the dosing of prostaglandins, it is important to dose this drop in the morning. Remember, beta-blockers act on the sympathetic nervous system, which is greatly downregulated during our sleeping hours. There is no proven benefit of dosing this drop in the evening or more than once a day.

Perhaps the greatest asset of generic timolol is its cost—under $10 for a 5mL bottle—so you likely won’t find a better price point on the market. This is important, as cost is a well-recognized reason for patient noncompliance. For patients who need a preservative-free beta-blocker, Timoptic (Bausch + Lomb) in ocudose (a unit-dose container) is available, though not generically.

ADJUNCTIVE THERAPY

If we prescribe a prostaglandin for initial therapy, and it works well but doesn’t achieve the proposed target range of IOP reduction, we would consider switching to Vyzulta before adding a beta-blocker as adjunctive therapy (assuming no contraindications). If a second drug was needed, we would have the patient instill one drop of the beta-blocker in the affected eye in the morning, and one drop of the prostaglandin in the evening. This combined therapy usually achieves target IOP.

If the beta-blocker is contraindicated (e.g., in a patient with asthma), our next preferred drop is the alpha-2 selective adrenergic agonist 0.2% brimonidine. While 1% apraclonidine demonstrates a more rapid...
Every Millimeter Counts

- “...the risk reduction could be about 19% per mm Hg, confirming results from the EMGT [Early Manifest Glaucoma Trial] and Canadian Glaucoma Study, and showing that IOP reduction is highly effective, and that every mm Hg of pressure counts... These results [...] should also serve as a stimulus to the pharmaceutical industry to continue development of new and even more potent drugs.”

- “...elevated IOP is a strong risk factor for glaucoma progression, with the HR [hazard ratio] increasing by 11% for every 1mm Hg of higher IOP.”

NEW GLAUCOMA CLASS OF DRUG

The trabecular meshwork is finally getting some overdue attention. A new class of drugs known as rho kinase (ROCK) inhibitors is focused on enhancing conventional outflow.

Netarsudil ophthalmic solution 0.02%, marketed under the brand name Rhopressa (Aerie Pharmaceuticals), was FDA approved in December 2017 for lowering elevated IOP in patients with open-angle glaucoma or ocular hypertension. The solution is to be used once daily. Findings from a Phase II trial comparing netarsudil to latanoprost revealed that IOP reductions were similar, and in all enrolled patients netarsudil was 1mm Hg less effective than latanoprost.1 The most frequently reported adverse event with netarsudil was conjunctival/ocular hyperemia, with an incidence of about 52%.1

These rho kinase inhibitors represent a new class of IOP-lowering agents to help many glaucoma patients try to achieve target IOP. As of the time of publishing, we have not yet had access to Rhopressa to be able to assess its utility in clinical patient care.

This drug class is available as a solution (generic dorzolamide) and a suspension (Azopt [brinzolamide, Novartis]). Only Azopt and Simbrinza (Novartis) are glaucoma suspensions, which have to be shaken before instillation.

**COMBINATION DROPS**

Many glaucoma patients are treated with multiple drops during the duration of their disease. Three combination drops are on the market: Cosopt (0.5% timolol with 0.2% dorzolamide, Akorn), Combigan (0.5% timolol with 0.2% brimonidine, Allergan) and Simbrinza (0.2% brimonidine with 1% brinzolamide suspension).

Simbrinza—the only suspension combination drug available to treat glaucoma—must be shaken before use. Unlike the other combination glaucoma drops, Simbrinza does not contain a beta-blocker. So, for an asthmatic patient or one who is nonresponsive to beta-blockers, Simbrinza might be an ideal add-on to a prostaglandin drug, once trials of brinzolamide and brimonidine are found to be efficacious.

If first-line therapy with a prostaglandin just misses target IOP, it is possible that switching to Vyzulta, or adding once-daily timolol, generic dorzolamide or generic brimonidine alone might get the IOP to target, so employing a more expensive combination drug might not be necessary.

Cosopt is unique in that it is generically available as a bottled product and also as a brand-name-protected, preservative-free unit-dose product. The carbonic anhydrase inhibitors, which reduce IOP about 15% by suppressing aqueous production, are approved as TID-dosed products (similar to brimonidine), yet they are mainly used twice daily in general clinical care. Dorzolamide is an ophthalmic solution (original brand name Trusopt) and brinzolamide is an ophthalmic suspension (original brand name Azopt).

When we need to prescribe one, we dose the medication twice daily—in early morning and about eight hours later (as with brimonidine), since effectiveness wanes after about eight hours.

**FINAL THOUGHTS**

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

Glaucoma therapy with a beta-blocker is often reserved until we need a 5mm Hg to 6mm Hg reduction in IOP or when we believe that cost is a factor in patient compliance. A 5ml bottle of timolol is widely available for under $10. Be mindful that we have found that prostaglandins generally reduce intraocular pressure by about 30%, whereas nonselective beta-blockers reduce IOP by about 25%. That’s a separation of only about 1mm Hg to 3mm Hg. Do not lose sight of the fact that beta-blockers remain an excellent choice for reducing IOP.

Initial therapeutic interventions generally are not complicated. However, if the patient is a prostaglandin nonresponder or has active asthma, establishing a therapeutic plan becomes more like a chess game, involving considerable thought and trials until target IOP is achieved.

Glaucoma should be readily embraced by more optometric offices and clinics. While the disease remains a leading cause of blindness worldwide, blindness from glaucoma in developed countries is relatively uncommon. Optimal care necessitates appropriate ancillary testing when needed, treatment initiation when indicated and a close observation of the optic nerves at follow-up visits to prevent vision loss. As medical practitioners of the eye, it seems appropriate that we should be first-line providers for the majority of glaucoma patients.
What does “off-label” really mean? The answer: little or nothing. Allow us to explain.

It is outrageously expensive to get drugs approved for their true therapeutic intent, and the idea is to get the drug to market as quickly and as inexpensively as possible. So, pharma companies choose the easiest path to approval—not necessarily the one that best showcases the drug’s capabilities. Once approved, doctors can and do find other uses and we, collectively, determine its proper role in the therapeutic toolbox.

It is indeed a game—a very high-stakes game—but it should not be this way. “Conjunctivitis” and “postoperative care” are two common targets for a new drug approval purely because they are the easiest to get through, even though these conditions may have nothing to do with the true clinical intent for the new drug.

Here are a few examples corroborating this candid perspective.

The early-generation fluoroquinolones were approved to treat conjunctivitis and keratitis. The fourth-generation fluoroquinolones and the bi-halogenated quinolone besifloxacin are FDA-approved only for treatment of conjunctivitis, but are commonly and effectively used “off-label” to treat bacterial keratitis.

Years ago, a drug known as Vexol (rimexolone, Novartis) was the only topical steroid FDA-approved for postoperative care, but it never gained intended traction. Interestingly, Pred Forte (prednisolone acetate 1%, Allergan), which is widely used for this purpose, does not have a specific indication for postoperative care.

Lotemax suspension (loteprednol etabonate 0.5%, Bausch + Lomb) has a litany of anti-inflammatory indications; however, the newer drug delivery system for loteprednol, known as Lotemax gel, is only FDA approved for postoperative care, as this was simply the easiest path to approval; however, it’s the exact same molecule.

The FDA indication is only a starting point for a drug’s career, and often a poor one at that. We doctors determine the proper use of any drug based on the scientific literature.

ON THE RECORD ABOUT ‘OFF-LABEL’ THERAPY

“We recall seeing a pediatrician a few years ago with acute epidemic keratoconjunctivitis. She was miserable and in full-panic mode. We explained to her that the Betadine treatment we would recommend was off-label. She laughed and said, ‘Ninety percent of what I do is off-label; let’s get on with it!’”
Both alpha-agonists and topical carbonic anhydrase inhibitors are FDA-approved for three-times-a-day administration, yet they are most commonly used twice daily, which is an off-label use albeit reasonable and efficacious for most patients.

Oracea (doxycycline, Galderma Laboratories) is a relatively new prescription drug containing 30mg of standard doxycycline and 10mg of time-released doxycycline. This is the only FDA-approved drug to treat rosacea. Regular doxycycline is not specifically labeled for rosacea. These drugs are clinical equivalents, but the brand-name, on-label drug is very expensive, while standard doxycycline is relatively inexpensive. So, treating rosacea blepharitis with regular doxycycline is off-label; yet over the decades we have used it ad infinitum for this very purpose, as do legions of dermatologists.

Topamax (topiramate, Janssen Pharmaceuticals) has indications for the treatment of seizure disorders and the prevention of migraine headaches, yet it is heavily used to treat obesity, bipolar disorder and some forms of eating disorders, among others.

There is no FDA-approved drug for the treatment of acute adenoviral infection, yet, based on sound rationale, we have successfully used off-label Betadine 5% (povidone-iodine ophthalmic solution, Novartis) numerous times over the years for this very purpose. We recall seeing a pediatrician a few years ago with acute epidemic keratoconjunctivitis. She was miserable and in full-panic mode. We explained to her that the Betadine treatment we would recommend was off-label. She laughed and said, “Ninety percent of what I do is off-label; let’s get on with it!” This exemplifies the clinical virtue of off-label drug use. By the way, she was much better at her two-day follow-up visit, and was extremely appreciative of our help.

It should now be abundantly evident that off-label use of many medicines can render a significant therapeutic benefit to many patients. As stressed above, such off-label use needs to be underpinned by a scientific rationale, preferably discussed in the professional literature and should demonstrate an expected clinical outcome.

PRUDENT AND EFFECTIVE OFF-LABEL USE

Here are examples of intelligent, rational and patient-centric off-label uses of medications in eye care:

- Using an alpha-adrenergic receptor blocker, such as brimonidine 0.1%, 0.15% or 0.2%, or a topical carbonic anhydrase inhibitor, such as dorzolamide or brinzolamide, twice daily instead of the FDA-approved TID.
- Using a fourth-generation fluoroquinolone or the bi-halogenated besifloxacin to treat a corneal ulcer when these medicines are only FDA-approved to treat bacterial conjunctivitis.
- Using Pred Forte in postoperative care, when it is not FDA-approved for such.
- Using Lotemax gel or ointment to treat dry eye disease, when its FDA-approved indication is for postoperative care. The literature consistently endorses a corticosteroid in the short term to treat dry eye disease, yet such is not FDA approved.
- Using Alrex to treat dry eye disease when its only FDA-approved indication is for treating ocular allergy.
- Betadine 5% sterile ophthalmic prep solution is intended to be used to sterilize the ocular surface prior to surgery or intravitreal injection. However, its off-label use to treat epidemic keratoconjunctivitis is the only effective approach to quickly and inexpensively quell this virulent adenoviral affliction. Betadine for this purpose is especially
get on with it. Don’t allow yourself to
nial, patient-centered judgment—and
reviewed literature; use sound, ratio-
tis is caught in the early, actively rep-
effective when the keratoconjunctivi-
be hampered by bureaucratic guide-
WHAT THE EXPERTS SAY
The Alliance of Specialty Medicine
released a position statement regard-

THE GREATEST OFF-LABEL STORY EVER TOLD
The year was 2005. Genentech was prepping a new drug called Lucentis that
looked to revolutionize treatment of the wet form of age-related macular
degeneration (AMD) the following year. This would be the first time that eye
doctors could bring back some vision that patients had lost to AMD. Everyone
knew it would be a blockbuster. But then...

Bascom Palmer retina specialist Philip Rosenfeld, MD, published a study
showing that the same company’s drug Avastin, commonly used for the intra-
venous cancer therapy, could be reformulated into an intravitreal dose and
used for AMD, with results comparable to Lucentis. At a fraction of the cost:
about $50 vs. $2,000. Lucentis did just fine in the marketplace—some MDs do
prefer the on-label, factory-fresh Lucentis instead of working with a compounding
pharmacy to obtain Avastin for ocular use. But Avastin was the revolution
within the revolution.

A recent retrospective review of Medicare payments for anti-VEGF therapy
in eye care documents the savings attributable to Avastin from 2008 to 2015
at $17.3 billion. That figure represents a $13.8 billion savings to Medicare and
$3.5 billion savings to patients, the article states. But the real number is even
greater. “This amount underestimated the actual cost-savings to Medicare pro-
viders since approximately 30% of Medicare-eligible recipients received care
within Medicare Advantage plans and were not included in this analysis,” says
the article. Also, since anti-VEGF drugs are used to treat more than just AMD,
and Avastin has been used in eye care for 13 years while this study only looked
at the years 2005 to 2013, surely the savings are even higher than the already
eye-popping number of $17 billion.

Now, think of who had to allow this. Retina subspecialist MDs, a very conser-
ervative group of clinicians, had to be comfortable with the idea of going outside
the FDA system. Medicare had to allow this as a reimbursable expense. And in
one high profile case, the Veterans Administration even condoned the use of
Avastin, knowing how much money this could save, which they could then put
to better use for America’s vets.

Yes, it was a little risky, since it was an injectable drug. An outbreak of endo-
phthalmitis due to poor sterilization methods at one compounding pharmacy
did cause serious infections in a small number of patients. But the vast majority
of patients treated with Avastin have been well served by their doctor’s deci-
dion to do so.

Keep that story in mind the next time you reach for your Rx pad.

1. Rosenfeld, PJ, Moshefigh, AA, Puliafito, CA. Optical coherence tomography findings after an
intravitreal injection of bevacizumab (avastin) for neovascular age-related macular degeneration.
of bevacizumab for the treatment of exudative age-related macular degeneration. Am J Ophthalmol
[ePub ahead of print.]

effective when the keratoconjunctivi-

The bottom line: follow the peer-
reviewed literature; use sound, ration-
ol, patient-centered judgment—and
get on with it. Don’t allow yourself to

WHAT THE EXPERTS SAY
The Alliance of Specialty Medicine
released a position statement regard-
ing off-label use of medical products,
states in part: “Physician-directed
applications, also known as ‘off-label
uses,’ are an integral component of
the art and science of medical prac-
tice, particularly for specialty physi-
cians.”

The Alliance of Specialty Medicine
maintains that a specialty physician
may prescribe or administer any le-
gally marketed product for an off-la-
bel use within the authorized practice
of medicine where the physician ex-
cercises appropriate medical judgment
and it is in the best interests of the
patient.

It says further that specialty physi-
cians are limited as to what we can
say in educational settings because of
regulations surrounding teaching on
off-label medicines, and that we
must educate our colleagues the best
we can within forums that allow us
to discuss off-label usage.

Our take: Within the guidelines
and perspectives set forth above,
we simply want our optometric
colleagues to feel completely com-
fortable doing what is best to serve
patients with FDA-approved medi-
cines using the most effective drugs
available. DG

1. Physician-Directed Applications: A Position
Statement of the Alliance of Specialty Medicine.
Available at: www.specialtydocs.org/files/
Alliance_Off-label_Statement_5.2.14.pdf (last
accessed February 27, 2017).
For many decades after dry eye was first named in the 1950s, the focus of diagnosis and treatment remained on the aqueous component of the tears produced by the lacrimal glands. This initially made sense because dry eye was first identified in a group of Sjögren’s patients. However, as far back as 1977, McCulley and Sciallis published findings of dry eye in a group with no evidence of lacrimal dysfunction. These patients presented with reduced tear film breakup time, superficial punctate keratitis, symptoms of dryness and stagnated meibomian secretions. McCulley and Sciallis named this condition meibomian dysfunction.

Their discovery is what we now know as meibomian gland dysfunction (MGD). McCulley and Sciallis also showed that if one squeezed out the meibomian gland contents, the tear film normalized and patient symptoms improved significantly. Despite this study and the hundreds that followed, all of which repeatedly evidenced that healthy meibomian gland physiology was critical to the health of the ocular surface, it took until 2011 for the scientific community to conclude that MGD was the leading cause of dry eye.

Today, we use meibography to stage the degree of meibomian gland atrophy and make a critical diagnostic assessment. We believe the diagnostic tools LipiView and LipiScan—a combination system from TearScience, now part of Johnson & Johnson Vision—represents the pinnacle of managing and preventing dry eye disease secondary to MGD. In addition, the company’s Meibomian Gland Evaluator can help assess gland secretions during a slit lamp exam and its LipiFlow device aids in restoring function to obstructed glands.

A wealth of hands-on clinical experience and the latest wisdom from the literature are changing the way we think about, and treat, this all-too-common condition.

Note that this patient has a scant lacrimal lake volume.

Corneal break up with fluorescein dye is useful in quantifying the expression of tear film integrity.

Though TearScience has led the charge...
in developing technology for MGD, other methods of assessing gland structure are available. Some topographers have meibography capabilities, and a white light transilluminator is available if you do not have access to imaging technology. And, of course, since many patients present to us at an advanced, symptomatic level of ocular surface disease, precorneal tear film breakup time and vital dye staining further quantify the extent of tissue compromise.

Unsurprisingly, we have found that about 90% of dry eye is related to MGD, and that up to 70% of our clinical population has MGD. We hypothesize that the following reasons are why MGD is so prevalent: poor blink function due to unrelenting use of digital technology, poor dietary hygiene and behaviors that actively stress the tear film, e.g., contact lens wear, cataract and refractive surgeries, and chronic use of preserved topical eye drops. Fortunately, lifestyle and blinking patterns can be addressed with education. For patients who wear contact lenses, need to undergo surgery or use preserved topical medications daily, the meibomian glands can be routinely assessed and treated as needed.

TREATING DRY EYE: AS EASY AS 1-2-3

There are three somewhat fluid stages of intervention we can use to prevent the escalation of dry eye disease, each discussed in detail below.

ENGAGING DIVERSE APPROACHES

TREATING DRY EYE: AS EASY AS 1-2-3

There are three somewhat fluid stages of intervention we can use to prevent the escalation of dry eye disease, each discussed in detail below.

PERSPECTIVE ON DRY EYE TESTING

We share the sentiments expressed in this editorial piece from 2017 about diagnostic approaches to dry eye. While it may not come from the peer-reviewed literature, its practical insights ring true to our ears, as busy clinicians who feel comfortable diagnosing dry eye without the need for additional testing.

- “None of the currently available methods for testing—Schirmer’s, validated questionnaires, tear osmolarity, tear breakup time, Sjögren’s, MMP-9—are definitive.”
- “Having a numeric value to attach to dry eye became less useful when the generated number did not support the patient’s experience or exam.”
- “It was challenging trying to explain treatment plans to my patients in part based on numbers that did not make sense.”
- “Reimbursements for dry eye testing, which admittedly can vary wildly between insurance plans and geographic regions, were regularly less than the cost of the test.”
- “In the end, I base my treatment decisions on the patients’ symptoms and on a thorough slit lamp exam with staining.”
- “The best use of our patients’ resources is to give them an accurate diagnosis and a treatment that will make a noticeable difference in their dry eye disease.”
- “There is no value in spending money on a battery of tests that tell patients what they (and you) likely already know—that they have dry eyes—instead of on something that could help them mitigate or cure the problem.”
- “My patients are happier because they are using their money to address the problem, not just test it to death.”

The bottom line is this: When the tear film and eyelids fail to protect the ocular surface from exposure to desiccating stress, a cascade of events is triggered. If the exposure to desiccating stress becomes chronic, the ocular surface commonly exhibits signs and symptoms of dry eye. These are variable and frequently manifest independently, especially in the earlier stages of dry eye disease. Short-term management may involve lipid tear supplements and suppression of inflammation with loteprednol, but long-term rehabilitation requires that the eyelid function (primarily and including meibomian gland function) and patient behavior be optimized to reduce exposure to desiccating stress.

Engaging these diverse approaches can be highly variable, depending on the decade of patient presentation as well as the degree of disease severity.

The rationale behind this three-tiered approach is that we find that most patients present when their dry eye disease has advanced to the degree that several of these staged interventions may be required to help re-establish comfort and enhanced quality of life. Oftentimes, we, as clinicians, are forced to engage in tertiary care first to quiet the ocular surface and then work back up the continuum of interventions.

The key to patient care is to understand the pathophysiology of dry eye disease so that appropriate steps can be taken, either concurrently or sequentially, to care for the patient. Let’s take a closer look at these staged interventions.

PRIMARY INTERVENTIONS

Start with these, as they tend to be the easiest, cheapest and most broadly applicable.
Blink function. Educating patients about the importance of blinking is critical and easy to accomplish. Apps are available that teach proper blinking exercises, and we encourage our dry eye patients to avail themselves of these. For example, Donald Korb Blink Training can be downloaded for free from iTunes or Google Play. We also proactively share this education with patients at risk of meibomian gland disease (e.g., computer users, contact lens wearers, patients using preserved topical medications daily and those preparing for cataract and refractive surgeries).

Our guidance is for patients to perform these blinking exercises four times daily—at breakfast, lunch, dinner and bedtime, as this simple maneuver helps many individuals. We recommend the orbicularis squeeze for five seconds, with a brief break before repeating the cycle for a full minute. One respected colleague shared anecdotally that having patients set hourly alarms on their smartphone or smartwatch during the work day to remind them to stop and do blink exercises is as effective as using an app.

Oral supplementation. While the eye care community has historically espoused omega-3 supplementation to help with dry eye disease, there has been little Level 1 evidence to solidly support this intervention. Now, with the publication of the DREAM Study, published in the April 13 issue of the Journal of the American Medical Association - Internal Medicine, a clear-eyed view of restasis and chronic dry eye disease. JAMA Intern Med. 2018;178(2):181-2.

online edition of the *New England Journey of Medicine*, we have (for better or worse) authoritative Level 1 science showing little or no evidence of a clinically meaningful effect of 3,000mg of a triglyceride-based fish oil. However, since the study’s recent publication, a number of prominent ophthalmologists specializing in dry eye, some of whom have lead research showing the benefits of omega-3 supplementation, have raised concerns about the methodology of the study and the choice of a potentially active placebo.

They have noted, among other issues, that the manufacturer of the active dry eye therapy was not disclosed in the study, that study participants were permitted to use a wide variety of dry eye therapies concurrently and change therapies during the study, and that it’s not known whether re-esterified forms of omega-3 therapies were used, which many dry eye experts have pointed out is essential for maximum absorption and bioavailability.

Critics have also expressed reservations that the controls received olive oil with fish essence, which are known anti-inflammatories and which may have included an active ingredient, given the improvements observed in controls. Yet, we were able to uncover that the olive oil was 68% oleic acid, an omega-9 fatty acid considered to be neutral with respect to inflammation control. And, though the study olive oil had a small amount of alpha-linolenic acid (ALA), a plant-based omega-3, the total dose was 30mg, while our recommended omega-3 dosage of EPA and DHA for patients is 3,000mg, or about 1,000 times that delivered by the placebo. Furthermore, ALA conversion to EPA and DHA is not known to be efficient.

Dry eye experts have also pointed out that both groups in the study had statistically significant improvements in OSDI symptom scores, which somewhat contradicts early press reports indicating that the study found omega-3 supplementation failed to yield a beneficial response.

Whether we are at the end of an era in which such supplementary intervention has a significant role in the care of patients with dry eye disease remains to be seen. We would like to see another study replicating these findings before we would be fully comfortable abandoning a therapeutic intervention that for many years has appeared to work. A discussion of the report can be read on our website: www.eyeupdate.com.

### LIPIFLOW TREATMENT FOR CONTACT LENS WEARERS

Thermal pulsation of the eyelids could be a major benefit to thousands of patients struggling with contact lens comfort. A study in *Clinical Ophthalmology* found that a single LipiFlow treatment extended contact lens wearing time by approximately 4 hours per day. Clin Ophthalmol. 2018;12:169-183.


Screen usage recommendations. Excessive screen use, either by choice or necessity, has become a way of life. Thus, educating patients on the impact of digital media use is essential. When patients understand why an activity isn’t healthy, they are more apt to engage in behaviors to avoid meibomian gland disease, especially when accompanied by rosacea blepharitis, a four-month course of oral doxycycline can help jump-start the clinical response.

Moving on to orally administered doxycycline, at 50mg per day for three to four months, this drug has been shown to enhance meibomian gland function. Thus, for those patients with more advanced meibomian gland disease, especially when accompanied by rosacea blepharitis, a four-month course of oral doxycycline can help jump-start the clinical response.
mitigate the negative effects. We proactively tell our intensive screen users to consciously and purposefully look up and away from the screen every few minutes and to blink several times.

**Avoiding desiccating stress.** Encourage patients to minimize exposure to ceiling fans, forced air drafts from home or car heating and air-conditioning systems. Patients can also minimize low-humidity environments by using a humidifier whenever possible.

**Application of warm soaks.** Applying warm soaks using a clean washcloth, uncooked white rice in a stocking (warmed in the microwave) or a commercially available device such as a Bruder mask, can be beneficial to enhance meibomian gland function. Patients frequently tell us that their eyes feel better following such use. The limiting factor is that patients rarely make time to use warm soaks consistently.

**Moisture-preserving eyewear.** Dry eye does not exist in 100% humidity, so anything one can do to increase the ambient humidity of the ocular surface is a step in the right direction. Moisture “goggles” have vastly improved over the years and offer us another methodology to preserve, protect and enhance ocular surface health.

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**DRY EYE THERAPY**

**A NEW TREATMENT FOR CHRONIC RED EYE**

It is widely known that millions of people purchase over-the-counter “get the red out” eye drops every year. Most of these purchases are made by individuals suffering from dry eyes, chronic allergy, blepharitis and/or exposure to smoke (e.g., tobacco, marijuana). Though tetrahydrozaline-containing eye drops have been shown to whiten eyes, they must be used chronically, which typically leads to the development of protracted and rebound hyperemia.

Now, a newly approved venule-based vascular constrictor should quickly replace tetrahydrozaline over time. This over-the-counter drop, Lumify (brimonidine tartrate opthalmic solution 0.025%, Bausch + Lomb), is a revolutionary agent that quickly “whitens” eyes, with effects lasting several hours and without reports of rebound hyperemia.

This low-dose brimonidine is a 0.025% solution with approximately a 10-fold dilution of 0.2% brimonidine. Our impression is that people with idiopathic, untreated or undertreated secondary chronic redness might use Lumify once daily in the morning, primarily on the days when their eyes are noticeably red. Since the drop, which could be used again in the afternoon or evening if needed, is not by prescription, it is our job to make patients aware of this newer-generation, more effective and longer-lasting topical vasoconstrictor.

We would never recommend such a medication as first-line therapy since redness is a secondary result of a primary problem such as dry eyes. Always try to remedy any primary conditions first, and, if other rational therapies do not relieve the redness, Lumify should be called in to handle the job.

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Here, in just 20 seconds, this patient’s eyes appear whiter.
While they might not make much of a fashion statement, they are much more visually acceptable now than they were years ago. Ziena Eyewear and 7eye by Panoptx feature contemporary, moisture-preserving eyeglass designs on their websites for your review and analysis.

SECONDARY INTERVENTIONS

Options in this class tend to be more focused on addressing a specific component of dry eye pathogenesis, such as reduced tear volume or meibomian gland obstruction.

Lipid-based artificial tears and lubricating ointments. Since a healthy lipid layer is critical in most all cases of dry eye disease, we start nearly all of our patients on a lipid-based artificial tear. We generally recommend either Soothe XP (Bausch + Lomb) or Systane Balance (Alcon), as both drugs were invented by Donald Korb, OD, a world-recognized expert in the area of MGD. When we need a preservative-free product, we recommend OcuSoft’s Retaine MGD. Patients are generally encouraged to use artificial tears at least four times a day, although patients rarely use them as often as recommended.

A study published in the Journal of Pharmacology and Therapeutics reported the following:

- “Lipid based therapies […] are an attractive alternative to water-based artificial tears because they more closely mimic the composition of the tear film. Lipid-based therapies not only relieve patient symptoms immediately after topical administration, but may also directly improve the lipid tear film structure and thickness component in ocular surface disease, resulting in enhanced tear film stability.”
- “Oil-in-water emulsions reduce the signs and symptoms of all types of dry eye, but are particularly recommended for lipid-deficient dry eye patients.”

- “The favorable tolerability profile and efficacy of lipid-based therapies in improving both signs and symptoms of dry eye make them a promising therapeutic option in the management of DED.”

Meibomian gland expression.

Physical/mechanical evacuation of the meibomian glands is essential. This can be done effectively only in the office. Perform manual glandular expression the old-fashioned way, using the Mastrota Meibomian Paddle (OcuSoft), the butt end of a pair of jewelers’ forceps or even a cotton swab to enable adequate trans-eyelid pressure.

If expression is attempted by pressing on the lids with the globe as a backstop, sufficient pressure cannot be applied and the IOP might become pathologically high. Some advocate for heating the lids prior to expressing the glands, possibly to make the expression process a little easier. However, there are two limitations to this process: the meibomian glands cannot be adequately heated from the outside since the meibomian glands reside in the posterior portion of the eyelids, and the highly vascularized nature of the tissue in this area means that, once the heat source is removed, the tissue rapidly returns to body temperature, negating the effect.

The gold standard for performing this highly therapeutic maneuver is the LipiFlow, which heats the meibomian glands from the tarsal conjunctival side (as opposed to the epidermal side) of the eyelid, while protecting the cornea. LipiFlow is cleared by the FDA for the safe and effective direct treatment of meibomian gland disease by addressing obstruction.

Another unique aspect of the device is that during the 12 minutes of highly specific heating, a compressive function simultaneously mechanically expresses the glandular contents. As a result, the newly formed meibum mimics natural physiology, resulting in a healthier lipid layer and enhanced tear film function. Another device, the MiBo ThermoFlo (MiBo Medical Group), delivers emissive heat to the meibomian glands.

Debridement of lower lid margins.

It is well-established that meibomian gland obstruction is a weak link in the chain of lipid production, excretion and incorporation into the tear film. Thus, anything that enhances this process is virtuous. One effective and simple procedure that can be performed at the slit lamp is to take a
golf club spud and gently scrape back and forth, four or five times, along the top of the lower eyelids. We do this at each follow-up visit. The procedure helps to open/de-obstruct the meibomian gland orifices and smooth the surface of the lower eyelids—particularly if there is any debris on the mucocutaneous border—and enhance the backward flow of meibum into the tear film. A topical anesthetic is not necessary for this effective 15-second procedure, which currently has no CPT code. Since meibomian gland expression devices are not yet ubiquitous due to cost, many clinicians will need to perform in-office expression, enhanced by pre-expression warm soaks.

Consider intranasal stimulation. With this new approach, a handheld intranasally inserted device uses electrical impulses to stimulate the trigeminal nerve and tear production. This procedure may be helpful to select patients, but as of press time, we had no clinical experience with this technique.

TERTIARY INTERVENTIONS

These options will be among the most effective in reducing dry eye symptoms and may require greater skill by the clinician to perform.

Topical anti-inflammatory drops. As previously mentioned, untreated MGD invariably leads to a cascade of events resulting in ocular surface inflammation. The most efficacious, and least expensive, intervention to suppress ocular surface inflammation is through the use of a topical corticosteroid.

Because the ester-based steroid loteprednol has become our drug of choice in such settings, we prescribe Lotemax gel-drops QID for two weeks, then BID for two more weeks. Our clinical experience reveals that the inflammatory component of dry eye disease is controlled within about four weeks for most patients.

A subset of patients may need to “pulse-dose” Lotemax QID for a week, once or twice a year, should there be any breakthrough symptom recurrence. A smaller subset of patients may require once-daily Lotemax on an ongoing basis.

As patient-centric doctors, we always attempt to use the least amount of cost-valued medicine possible to meet the care needs of our patients. We have found that Lotemax gel drops are vastly less expensive than any of the BID prescription “dry eye” drops and have far superior anti-inflammatory properties.

One of the key benefits of short-term pulse-dosing of a topical corticosteroid is its ability to induce long-term cessation of DED. As an example, the TFOS DEWS II Management and Therapy Report reported the following:

“Fifty-three patients with Sjögren syndrome were treated with topical nonpreserved 1% methylprednisolone four times a day for two weeks, and then re-evaluated and tapered off the medication until they demonstrated no corneal fluorescein staining or symptoms. Most patients were in a disease-free state for a relatively long period (57 weeks) after the first pulse therapy, and eleven individuals (21%) experienced recurrence of either symptoms or signs. After the second pulse therapy, a disease-free period of 72 weeks was observed and only 1.9% of patients had recurrence. No serious complications (such as IOP elevation or cataract formation) were encountered during the entire follow-up period.”

Furthermore: “A recent retrospective safety study, listing 77 published studies, concluded that topical treatment with loteprednol etabonate has minimal effect on IOP when used in treatment of a wide range of ocular surface and intraocular inflammatory disorders, including ocular allergy, DED, anterior uveitis, penetrating keratoplasty, endothelial keratoplasty, and postoperative pain and inflammation following ocular surgery.”

What more could a clinician ask for?

Punctal plugs. Once loteprednol has been used for at least two weeks, the bulk of ocular surface inflammation usually has been suppressed. At this juncture, consideration of punctal occlusion is quite reasonable. It is important to use a steroid first, as the “plug first and steroid second” treatment regimen could actually worsen symptoms by further concentrating proinflammatory cytokines in the already hyperosmotic tear film.

Autologous serum. The concept of using a patient’s blood-derived serum for topical drop application is not new. While a somewhat cum-
dersome process, use of autologous serum is a reasonable approach for patients suboptimally helped with other more common interventions. The drops may need to be used QID for many weeks; however, they are not to be used as simple monotherapy. Autologous serum drops are best used to supplement more comprehensive care.

**Lacriscert.** These dissolvable pellets of hydroxypropyl cellulose can provide a time-released supplemental enhancement to the tear volume. Because of their somewhat challenging insertion and cost, they are not used first-line, but some of our patients have been helped by Lacrisert more than any other intervention. Go to [www.lacrisert.com](http://www.lacrisert.com) for more details on this prescription hydration device.

**Amniotic membrane devices.** These devices can be remarkably beneficial for non-healing epithelial defects, including recalcitrant SPK. It takes some practice to insert the devices, requiring a technique similar to large-diameter contact lenses. Amniotic membranes dissolve over several days to a couple of weeks, and can play a beneficial role in resolving stubborn SPK.

**Scleral rigid contact lenses.** While these lenses have a learning curve to properly fit, they can be a lifesaver, as many patients have been helped by these devices when other approaches have failed. As such, we encourage all ODs to become adept at providing care with these lenses.

**WHY SYMPTOMS AND SIGNS DON’T ALWAYS AGREE**

Why is there discordance between symptoms and signs in patients with dry eye disease?

- There is “growing evidence that part of the dry eye population may show signs of dysfunctional somatosensory pathways, indicating neuropathic ocular pain.”
- Patients with chronic pain syndromes (CPSs) had 30% greater symptoms than signs. Important CPSs are irritable bowel syndrome, fibromyalgia, chronic pelvic pain and osteoarthritis.
- Many patients with itchy eyes also have dry eyes. “Patients with atopy or allergy have a sensitized ocular surface because of inflammatory processes influencing corneal nerves, which can lead to symptoms of dry eye even when the homeostasis of the ocular surface is minimally compromised.”

**QUOTABLE**

“**MOST DRY EYE PATIENTS ARE SUCCESSFULLY MANAGED USING A VARIETY OF PRIMARY, SECONDARY AND TERTIARY INTERVENTIONS. THE KEY IS TO FOCUS ON MEIBOMIAN GLAND FUNCTION ENHANCEMENT, SINCE MANY TERTIARY CARE MANEUVERS CAN BE PREEMPTED OR DECREASED IN FREQUENCY.**”

Most dry eye patients are successfully managed using a variety of primary, secondary and tertiary interventions. The key is to focus on meibomian gland function enhancement, since many tertiary care maneuvers can be preempted or decreased in frequency.

Symptomatic eye disease is epidemic and will only become more prevalent in our screen-addicted world. It’s our duty to arm ourselves with the knowledge, instrumentation and drug therapies to meet this clinical challenge.

Lastly, remember to assess each patient as an individual, since no algorithm can uniformly meet the needs of everyone. Bottom line: if we can adequately enhance meibomian gland function, we may not have to wait until patients present with dry eye discomfort to intervene. **DG**

The eye is vulnerable to damage from intraocular and ocular surface inflammation. Untreated, inflammation may lead to temporary, or even permanent, vision loss. Steroids suppress cellular infiltration, collagen deposition, fibroblast proliferation and scar formation. They stabilize cell membranes and block phospholipase A2—a critical initial step in the inflammatory cascade of the arachidonic acid pathway.

Topical corticosteroids derive from two different molecular classes: ketones and esters. Ketone-based steroids (e.g., dexamethasone, prednisolone, fluorometholone) have a higher propensity over time for unwanted side effects compared with ester-based steroids (e.g., loteprednol). Our bodies have limited means to actively degrade the ketone molecules, whereas esters are rapidly broken down by innate physiological esterases into inert substances shortly after providing effective anti-inflammatory action. Loteprednol has been shown to greatly lower the risk for increased intraocular pressure, with no reports of cataract formation. For either category, the risks associated with short-term topical use are minimal.

Remember: Suppressing ocular inflammation early in the disease process substantially decreases the potential for tissue damage. Uncontrolled intraocular inflammation carries far more risks than appropriate steroid therapy.
To be clear, improper use of steroids (and contact lenses) can have unwanted and damaging results for your patient. While there are plenty of indications for the use of topical steroids, there is only one contraindication: epithelial herpetic infection. There is also only one precaution: uncertainty of diagnosis. To explain, it’s possible, for example, to have an *Acanthamoeba* or fungal keratitis that is difficult to diagnose, especially in the early stages. The use of a steroid—even a combination antibiotic/steroid—could cause the condition to worsen; however, such presentations are exceedingly rare. When prescribing steroids, the initial dosage must be sufficiently frequent to achieve symptomatic relief and expedite remission. In our practices, we suppress inflammation by “hammering” it with corticosteroids out of the gate. This approach

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**TOPICAL CORTICOSTEROID DRUGS**

<table>
<thead>
<tr>
<th>BRAND NAME</th>
<th>GENERIC NAME</th>
<th>MANUFACTURER</th>
<th>PREPARATION</th>
<th>BOTTLE/TUBE</th>
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<td>emulsion</td>
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<td>Allergan and generic</td>
<td>suspension</td>
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quickly controls the inflammatory cascade, after which an appropriate tapering schedule (if necessary) can be executed.

In all cases of disease management, proper follow-up is paramount. Education of patients and open discussions minimize patient misconceptions and concerns about a given condition or therapy, and strengthen doctor-patient trust. This, in turn, reduces the likelihood of patients seeking unwarranted second opinions that delay care.

NEED FOR FOLLOW-UP
Acute conjunctivitis rarely presents in textbook fashion. More often than not, the eye will just show signs of nonspecific inflammation. While this shouldn’t dampen your willingness to treat with topical steroids, having the patient return to you in a timely manner will illuminate ineffective treatments or misdiagnosed conditions. When you elect to see the patient back sooner rather than later, you position yourself to confirm your diagnosis or alter treatment if necessary. If you are truly concerned, call the patient in a couple of days to check on the therapy’s progress. Patients love having their doctors call to check on them.

As one example, let’s say you see a patient with typical lesions that could be Thygeson’s superficial punctate keratopathy or herpetic eye disease. Since most red eyes are inflammatory in nature, we are inclined to initiate therapy with a steroid.

However, in the uncertainty of a diagnosis, we would tell the patient something like this: “This medicine should help your eye get better quickly; however, at this time the diagnosis of your condition is not completely clear, and there is a chance your eye could 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.” As previously mentioned, this caring conversation is crucial for optimal patient care and rapport.

All of this falls under the heading of “patient management” and is far more than just disease management. Trying to manage the disease without managing the patient will often result in frustration for both the doctor and patient. (This not only applies to corticosteroid treatment, but to the treatment of any eye condition.)

OBSERVATIONS ON WHY ANTIBIOTICS ARE OVERPRESCRIBED
During our many years in clinical eye care practice, we have identified the following reasons why many doctors overprescribe antibiotic agents:

1. Many eye care providers neglect to stay abreast of current research and, consequently, get stuck in habitual practices and become therapeutically complacent.
2. Clinically differentiating between different types of conjunctivitis can be challenging. This leads providers to prescribe antibiotics “just in case” there is an underlying infection.
3. The patient perception that antibiotics are a harmless cure-all for their ailments leads many patients to frequently request prescriptions “to be safe.” To improve patient satisfaction and address potentially relentless requests, providers submit to these unfounded petitions.

QUOTABLE
“Most cases of acute conjunctivitis are nonbacterial in origin, and even among those with a bacterial cause, antibiotics have only a modest benefit in reducing symptom duration. The complications of acute conjunctivitis are so rare that there is no evidence from systematic reviews that antibiotics reduce rates of complications.”

Steroid molecules are lipophilic in nature. Their inability to dissolve in solutions makes the majority of corticosteroids on the market available only in suspension form. But ophthalmic suspensions separate over time, causing the active ingredients to settle at the bottom. To ensure homogenous distribution, patients must vigorously shake the bottle prior to instillation. Otherwise, the patient risks subtherapeutic dosing, rendering less than desirable outcomes despite full compliance with drops.

Even when the bottle is shaken as directed, the particles still have a tendency to agglomerate, especially as the particle size of the drug increases. This causes dosage inconsistencies, and potential frustrations from the doctor and the patient.

In 2008, the FDA approved difluprednate ophthalmic emulsion 0.05% to treat inflammation and pain associated with ocular surgery. The drop was formulated as a stable oil-in-water emulsion, giving optimum dose consistency, while eliminating the need for shaking. In clinical trials, the drop showed therapeutic dose consistency far surpassing generic prednisolone acetate suspension 1% and branded prednisolone acetate suspension 1% in cataract surgery.

Durezol’s excellent drug uniformity and decreased dosing suggests increased compliance and more predictable results vs. other steroids in its class.

Durezol is often used as the heavyweight (prednisolone acetate 1%, Allergan) and Pred Forte (prednisolone acetate 1%, Novartis) and Durezol emulsion (difluprednate 0.05%, Novartis) and Pred Forte.

Don’t let ocular inflammation linger by hesitantly prescribing topical steroids. Corticosteroids must be dosed early and often, with an appropriate tapering schedule when needed.

Clinically, we have found the two most efficacious topical ophthalmic steroids in the last several years to be Durezol emulsion (difluprednate 0.05%, Novartis) and Pred Forte (prednisolone acetate 1%, Allergan).

Durezol. Introduced in 2008, Durezol is often used as the heavyweight recognition as a popular postoperative drug. Clinically, we prefer it over Pred Forte for several reasons: We have found it to be more effective, it does not need to be shaken prior to instillation and it does not need to be dosed as often as Pred Forte, thereby increasing patient compliance.

Durezol’s glucocorticoid binding affinity for the active metabolite difluprednate was found to be 56 times stronger than prednisolone.2 A derivative of prednisolone, the drug’s structural modifications to have a stronger binding affinity and a more consistent potency compared with its counterpart.

As a general rule, the more powerful the drug, the more potential for adverse side effects. Durezol is no exception, as it can be associated with elevated IOP. Thus, standard of care practices must be engaged, with frequent follow-ups to monitor the condition and check IOP.

Pred Forte. While not as clinically effective as Durezol, prednisolone acetate 1% possesses impressive anti-inflammatory efficacy. Its widespread use in ocular inflammatory conditions is most notably embraced postoperatively as well as in anterior uveitis cases. Remind your patients to

**KEEP IT LOCAL WITH LOTEMAX**

A number of years ago, researchers examined the clinical efficacy of loteprednol etabonate 0.5% in rabbit corneas.1 After instillation, the researchers assessed tissue structures in the eye. The cornea was found to have the highest ratio of metabolite to loteprednol etabonate 0.5%, followed by a much lesser concentration in subsequent tissues posteriorly. Strikingly, the aqueous humor concentration of the drug was 100 times lower than the concentration found in the cornea.

By keeping high levels of the drug out of the aqueous humor, the trabecular meshwork was less affected, and the propensity to increase IOP was considerably less than other topical steroids.

Of equal significance, when the drug was absorbed systemically, it was rapidly excreted through bile and urine.

The prompt de-esterification of Lotemax gel and its ability to be expelled promptly with any systemic absorption should make the prescribing doctor confident in applying its use in patient care.

vigorously shake the bottle before instillation because the drop is a suspension.

Some pharmacists will dispense generic prednisolone acetate, even when you have indicated “dispense as written.” Although less expensive, the generics are considerably less effective.3 When maximum efficacy is required, Durezol is our drug of choice.

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 in solution or suspension form, is also in this category. Of note, we have found that generic prednisolone sodium phosphate 1% solution does not penetrate transcorneally as effectively as the acetate moiety, but has the advantage of not requiring shaking.

Lotemax gel. Perhaps one of the most commonly used drugs among the corticosteroid class is loteprednol etabonate 0.5% (Lotemax gel, Bausch + Lomb). An ester-based steroid, its propensity to raise IOP is substantially less than its ketone-based counterparts.

Lotemax is highly lipophilic—10 times greater than dexamethasone—thereby increasing its efficacy and penetration across cell membranes. Additionally, loteprednol etabonate 0.5% undergoes rapid de-esterification to an inactive metabolite after exerting its effect, minimizing the risks of drug toxicity while maintaining good clinical efficacy.

Lotemax gel is a non-settling eye drop that does not require shaking before instillation. Though labeled as a gel, it becomes a viscous liquid once on the ocular surface (see “Lotemax Gel vs. Lotemax Ointment”).

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 (no shaking is necessary), 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 once to make sure the drug enters the tip of the dropper prior to instillation, but no actual shaking is necessary.) Also, unlike suspensions, this delivery system provides a perfectly uniform dose at every instillation.1

• Lotemax ointment.2 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 fluoromethonol 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.
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 the patient down to three or two times a day, or even once daily before a relapse occurs. If a relapse does happen, you have to increase the dosage frequency again and try a longer, slower taper.

In addition, try adding a topical NSAID such as Prolensa (bromfenac, Bausch + Lomb) or Iluva (napafenac ophthalmic suspension, Novartis) once daily, or generic diclofenac or ketorolac QID as you begin the 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: 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. Some patients require one drop of steroid daily to maintain control over their condition.

While older ketone-based steroids have been used for long-term therapy in the past, we would recommend ester-based loteprednol 0.5% gel off-label 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.)

Though Lotemax gel can seem cost prohibitive for patients without drug coverage, most eligible commercially insured patients pay no more than a $25 co-pay for their first prescription through the Access Program, and eligible refills at Walgreens and other participating independent pharmacies. Discounted pricing is also available for eligible uninsured patients, according to Bausch + Lomb's website.

As well, Novartis offers various coupons for Durezol (difluprednate). And when there is no getting around cost issues for the patient, generic FML (fluorometholone 0.1%, Allergan) is another option. In addition, consulting www.goodrx.com can turn up the best local prices.

MODERATE EFFICACY STEROIDS

The two most common topical steroids in this category are fluorometholone 0.1% suspension and Alrex suspension (loteprednol 0.2%, Bausch + Lomb), both of which must be shaken prior to instillation.

Fluorometholone 0.1%. There are two derivatives of fluorometholone 0.1% suspension: alcohol (FML, Allergan; and generic) and acetate (Flarex, Novartis; and generic). The acetate moiety gives the fluorometholone molecules some additional anti-inflammatory effectiveness over the alcohol moiety.

Fluorometholone alcohol is available generically, so it is relatively inexpensive. While fluorometholone has less likelihood of raising IOP than other ketone steroids, we are not nearly as comfortable using it long-term as we are using ester-based loteprednol.
CORTICOSTEROID USE

Since the lowest effective dose should be used in all cases, FML Forte (fluorometholone 0.25% ophthalmic suspension) is not recommended because the 0.1% concentration represents the top of the dose response curve—meaning that 0.25% is no more efficacious than 0.1%.

Alrex. An ester-based corticosteroid, Alrex is an excellent off-label treatment option in cases when a patient needs long-term therapy. We often use Alrex in our patients with allergic eye disease when clinical signs of conjunctival injection, chemosis or eyelid swelling accompany itching. In such cases, Alrex (or even Lotemax gel) will best help subdue the patient’s condition. 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. Three corticosteroid medicines that merit frequent clinical use are:

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:

- Difluorprednate 0.05%
- Prednisolone acetate 1%
- Loteprednol 0.5%
- Rimexolone 1%
- Fluorometholone acetate 0.1%
- Dexamethasone 0.1%
- Fluorometholone alcohol 0.1%
- Loteprednol 0.2%
- Prednisolone 0.125%
- Hydrocortisone 1%

works well for periocular dermatitis conditions. Triamcinolone 0.1% cream, which became generic many years ago, has been our favorite medication to treat contact blepharo-dermatitis. It comes in 15g and 30g tubes, each costing about $10 in most markets. We have treated hundreds of periocular contact dermatitis patients with this drug with consistent, superb, clinical outcomes.

Be sure to tell the patient that the statement “Not for Ophthalmic Use” is on the side of the tube, but that the medication is perfectly fine to use as prescribed. We explain to patients that triamcinolone is frequently used by retina subspecialists for FDA-approved injection into the eye, so if some of the triamcinolone cream gets into patients’ eyes, it’s nothing to be concerned about. Doctors should be cautioned to use this approach only for short-term relief, as long-term use can result in skin atrophy and, in some cases, elevated IOP (which we have never seen).

Corticosteroids are the most essential and highly prescribed drugs 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 eye care. It is imperative that all doctors of optometry embrace this reality and become comfortable using these essential drugs in order to effectively care for patients with inflammatory eye disease.

Topical nonsteroidal anti-inflammatory drugs (NSAIDs), employed sparingly in the clinical setting, are mainly approved to treat pain and inflammation associated with cataract surgery, although some off-label uses exist. Additional therapy can be used to maintain mydriasis during cataract surgery and decrease pain in photorefractive keratectomy patients.1,2

INDICATIONS
NSAIDs primarily ameliorate pain on the ocular surface. When used together, NSAIDs and corticosteroids have beneficial therapeutic effects on postoperative cystoid macular edema (CME) formation. Generally, topical NSAIDs are prescribed in combination with maximal-efficacy steroids to treat postoperative CME.

Dosing ranges from QD to QID, and recommended dosing limits should be followed to minimize side effects. It may also be prudent to comanage surgical patients with cataract surgeons. Duration of use should be limited to two weeks with the exception of CME cases, for which we'll prescribe one month of a topical NSAID with a potent steroid. Note that chronic use of NSAIDs can retard corneal epithelial healing, and lead to, in very rare cases, corneal melting and perforation.3

MORE RECENT DRUGS
Newer to the topical NSAID space are Ilevro (nepafenac ophthalmic suspension 0.3%, Novartis) and Prolensa (bromfenac ophthalmic solution 0.07%, Bausch + Lomb). FDA-approved for post-op inflammation and pain, the drugs are dosed QD.4,5

Ilevro, a prodrug, is highly permeable to the cornea and rapidly hydrolyzed to amfenac in the aqueous.4,5 Prolensa, structurally similar to amfenac, contains a bromine atom, making it highly lipophilic, which increases corneal penetration and duration of action.6 Since NSAIDs are fundamentally acidic, Prolensa is buffered to a pH of 8.3 for added comfort with instillation.4 Amfenac is a potent inhibitor of COX-1/COX-2 isoenzymes. Once-a-day dosing is also an option due to the increased nepafenac concentration from 0.1% to 0.3%.

Other NSAIDs include: Acular LS (ketorolac tromethamine ophthalmic solution 0.4%, Allergan), Acuvail (ketorolac tromethamine ophthalmic solution 0.45%, Allergan), Bromsite (bromfenac ophthalmic solution 0.075%, Sun Pharma) and Voltaren (diclofenac sodium topical gel 1%, Endo Pharmaceuticals).

As with all medical therapy, the availability of once-daily dosing increases patient compliance, and the right formulations are key to ensuring appropriate concentrations with each instillation.6

Patients with ocular allergies make up a large portion of clinical encounters in daily practice. Nearly one-third of the population is affected by allergic disease, with an estimated 40% to 80% of individuals manifesting ocular involvement. And yet, allergic eye disease is often misdiagnosed as allergic rhinitis or sinusitis, since the conditions frequently coexist, according to the American Academy of Allergy, Asthma and Immunology. As a result, sinus inflammation is routinely diagnosed, treated and managed, while ocular allergies are not.

As in all cases of an allergic response, exposure to an allergen prompts the immune system to overreact and produce immunoglobulin E (IgE) antibodies that bind to mast cells. Ongoing exposure leads to the release of chemical mediators that cause the symptoms of allergy and cascade of local inflammation—a process known as mast cell degranulation. Allergic eye disease, an IgE-mediated common condition responds well to therapy. Start symptom suppression right away and let resolution guide your decisions, but don’t miss coexisting dry eye.

IDENTIFYING COMMON TRIGGERS

The two most prevalent allergens—pollen and animal dander—cycle throughout varying seasons. In the spring, grass and tree pollen aeroallergens are most common; in the fall, ragweed is more predominant. Meanwhile, indoor pets can be the cause of allergic eye disease year-round.

The symptoms of ocular allergy are usually itching, redness and tearing. Without itching, the patient likely does not have allergic eye disease.

Allergists suggest that patients suffering from chronic and cyclical signs and symptoms caused by allergic disease should be tested to identify the offender. Treatment is found through medicine, environment control (avoidance) or allergy injections/sublingual drops.

The next time your patient presents with a long-standing history of repeatable allergic patterns, consider the role of an allergist to further assist your management.

response and type I hypersensitivity reaction, presents in various forms, from a persistent itch to a potentially sight-threatening corneal ulcer (vernal keratoconjunctivitis). For seasonal allergic conjunctivitis, the treatment protocols are straightforward: antihistamines/mast cell stabilizers or corticosteroids. Though the therapeutic options are essentially the same, perennial allergic conjunctivitis follows a more indolent course, often requiring more attentive and persistent care by the attending doctor.

Itching is the definitive hallmark of ocular allergy. Patients should be asked: “Is itching or burning your main symptom?” Typically, their response can isolate your next step. If your patient is unable to decide which symptom distresses them the most, treatment with an ester-based steroid drop typically solves both complaints. Preferred options include Alrex (loteprednol etabonate 0.2%, Bausch + Lomb) and Lotemax (loteprednol etabonate 0.5%, Bausch + Lomb).

If patients report itching as their predominant symptom, therapy is directed toward one of two paths, discussed below.

**SYMPTOMS ONLY**
If the anterior segment exam shows minimal or unremarkable signs of allergic conjunctivitis (e.g., conjunctival chemosis, conjunctival injection, eyelid edema and/or papillae), treatment with a combination antihistamine/mast cell stabilizer is the ideal clinical choice. To date, there are six drugs in this class to choose from:

- **Alcaftadine** (Lastacaft, Allergan)
- **Azelastine** (Optivar, Meda Pharmaceuticals; generic available)
- **Bepotastine** (Bepreve, Bausch + Lomb)

**AN UPDATE ON PREVALENCE**
According to the published findings from a series of studies conducted by the International Study of Asthma and Allergies in Childhood (ISAAC) starting two decades ago, allergic conjunctivitis has shown a worldwide trend in increasing prevalence. This upsurge has been attributed to climate changes, pollution, increased pollen and a heightened immunological sensitivity in response to environmental changes, among other factors. About 40% of patients who suffer from allergies reportedly experience some form of ocular symptomology (itching, chemosis, redness). Of equal significance are the documented negative impacts of ocular allergies on patient quality of life, confirming the importance of early therapeutic intervention.
Epinastine (Elestat, Allergan; generic available)
Ketotifen (Zaditor, Alcon; many generics available. This drop is OTC.)
Olopatadine—branded (Pazeo/Pataday/Patanol, Novartis) and generic 0.1% olopatadine
Cetirizine (Zerviate, Nicox/Akorn)

Of these, all are rated pregnancy category C except for Lastacaft, which is dosed QD. After two weeks of BID therapy, consider reducing instillation to QD for maintenance dosing. Remember, as with any treatment, the lowest effective dose is always desired. In our experience, once the inflammation

OLOPATADINE: HISTORICAL GOLD STANDARD OF ALLERGY TREATMENT
The first dual-action antihistamine/mast cell stabilizer to transform ocular allergy therapy was olopatadine 0.1% (Patanol, Novartis). In 1996, the FDA approved Patanol for the treatment of signs and symptoms of allergic conjunctivitis. The drug is highly selective for the H1 receptor, and has been shown in studies to possess anti-inflammatory properties, as well the ability to inhibit the release of leukotrienes, cytokines and adhesion molecules. Olopatadine 0.1% was the first topical drop for allergic conjunctivitis approved for BID dosing, far surpassing the second-generation antihistamines, which, in their time, had advanced to QID.

In 2010, olopatadine 0.2% (Pataday) became available with comparable efficacy and improved patient satisfaction for relief of ocular symptoms for up to 18 hours. Five years later, olopatadine 0.7% (Pazeo) made its market debut with efficacy surpassing 24-hour ocular itching relief while maintaining a similar safety profile to lesser concentrations that came before it.


WHEN THE ITCHY EYE IS ALSO DRY
Most patients with allergic conjunctivitis also suffer from dry eye and hyperemia, even if the dryness has not elicited symptoms of burning. Specifically, the likelihood of allergic conjunctivitis patients also having dry eye is more than twice that of patients without symptoms of itch, and the chance of these patients also experiencing redness is more than seven times that of patients with non-itchy eyes.¹

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


Some people rub their itchy eyelids to the point of epidermal abrasion. Topically applied Lotemax, FML or triamcinolone ointment could have prevented this. Now an antibiotic/steroid ointment is needed to restore tissue health.

Some people rub their itchy eyelids to the point of epidermal abrasion. Topically applied Lotemax, FML or triamcinolone ointment could have prevented this. Now an antibiotic/steroid ointment is needed to restore tissue health.

• Epinastine (Elestat, Allergan; generic available)
• Ketotifen (Zaditor, Alcon; many generics available. This drop is OTC.)
• Olopatadine—branded (Pazeo/Pataday/Patanol, Novartis) and generic 0.1% olopatadine
• Cetirizine (Zerviate, Nicox/Akorn)

Of these, all are rated pregnancy category C except for Lastacaft, which is pregnancy category B. Notwithstanding other fine differences, all of the antihistamine subtype 1 receptor blockers nicely suppress ocular itching. As well, all are dosed initially BID (except Pazeo, Pataday and Lastacaft, which are dosed QD).

After two weeks of BID therapy, consider reducing instillation to QD for maintenance dosing. Remember, as with any treatment, the lowest effective dose is always desired. In our experience, once the inflammation
is brought under control, less pharmaceutical intervention is needed to maintain suppression of symptoms. Then again, some patients still require a second additional drop later in the afternoon.

Perhaps the best news for the consumer was the loss of patent protection for Zaditor (Novartis). Since 2007, ketotifen has been available generically and over the counter. In addition to Zaditor, several brand name OTC ketotifen preparations are available, including Alaway (Bausch + Lomb), Refresh Eye Itch Relief (Allergan) and others. All come in 5ml bottles, except for Alaway and TheraTears Eye Itch Relief (Akorn), which come in 10ml bottles.

When a prescription medication is preferable, 5ml bottles of Alrex and Bepreve are only $10 copays for the first Rx and refills through the Bausch + Lomb Access program at Walgreens and other participating independent pharmacies during

### OCULAR ALLERGY MEDICINES

<table>
<thead>
<tr>
<th>BRAND NAME</th>
<th>GENERIC NAME</th>
<th>MANUFACTURER</th>
<th>PEDIATRIC USE</th>
<th>BOTTLE SIZE(S)</th>
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<tr>
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<td>3 yrs</td>
<td>5ml, 10ml</td>
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<td>5ml</td>
<td>BID</td>
</tr>
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</table>

| **Chronic Care Products** |                                     |                          |               |                |        |
| Alocril             | nedocromil sodium 2%                | Allergan and generic     | 3 yrs         | 5ml            | BID    |
| Alomide             | lodoxamide tromethamine 0.1%        | Alcon                    | 2 yrs         | 10ml           | QID    |
| Crolofem            | cromolyn sodium 4%                  | Bausch + Lomb and generic| 4 yrs         | 10ml           | QID    |
allergy season (between February 15 and June 15, and August 1 through October 31); they are only $15 co-pays for the first Rx and refills filled outside of the program’s participating pharmacies during allergy season. Also consider consulting www.goodrx.com to find the best available price in your area.

SYMPTOMS AND SIGNS
Whenever possible, therapy for ocular allergies should be prophylactic. Therefore, in the setting of allergic conjunctivitis, initiate therapy early in the process, make sure it is sufficient to suppress the patient’s signs and symptoms, and have the patient continue for long enough to prevent conversion into a chronic disease. The basis of treating any allergic eye disease remains the same: quell the inflammation early to avoid potential late complications.

In individuals presenting with symptoms of allergy along with classic anterior segment findings, a topical, ester-based corticosteroid is a wonderful option. We recommend Alrex or off-label use of Lotemax gel (loteprednol 0.5%, Bausch + Lomb). Additionally, the generic, ketone-based corticosteroid FML ophthalmic suspension (fluorometholone 0.1%, Allergan; and generic) is a viable therapy, although we have found it has a higher propensity to increase IOP compared with its ester-based loteprednol counterparts. (Also of interest, FML, though generic, is often more expensive than the varying concentrations of loteprednol once a Bausch + Lomb coupon has been applied).

Frequency of instillation is tailored to the severity of the patient’s signs and symptoms. Typically, we prescribe a steroid drop Q2H for two days, then QID for one week, followed by BID for one more week. Once the signs of allergic eye disease are subdued, consider switching your patient to an antihistamine/mast cell stabilizer for ongoing symptomatic regulation.

AN EQUAL-OPPORTUNITY DISEASE
While once considered to be a “disease of affluence,” allergic conjunctivitis is now clearly recognized around the world, with increasing prevalence in countries with sustained growth and developing urban populations. Doctors should bear in mind that, while the disease is not life-threatening, the persistent symptoms experienced by those who suffer from ocular allergies can have a profound impact on productivity and quality of life.

Remember, allergy is an expression of inflammation. In addition to the therapeutic strategies listed above, don’t forget to discuss with patients palliative options such as daily cold compresses. Telling your patients to place their allergy drops in the refrigerator until it’s time to instill the drop can add additional relief. DG


AN OUNCE OF PREVENTION...
Avoidance is one of the best ways to prevent common eye allergies. Other tips from the Asthma and Allergy Foundation of America include:
- Don’t touch or rub the eye(s).
- Wash hands often with soap and water.
- Use a vacuum with a HEPA filter to reduce exposure to allergens.
- Wash bed linens and pillowcases in hot water and detergent to reduce allergens.
- Use allergen covers (encasements) for pillows, comforters, duvets and mattresses, and consider using them for box springs.
- Keep pets out of the bedroom to reduce pet dander allergen in bedding.
- Wear sunglasses and a wide-brimmed hat to help keep pollen from getting into the eyes.
- Close windows during high-pollen and mold seasons. Run the air conditioner in the car and at home, and consider using a HEPA filter.


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The herpes virus can manifest in a wide range of ocular conditions, from a mild vesicular lid lesion to an aggressive retinitis. Clinicians should be aware that the virus can affect every ocular tissue and treat the patient accordingly.

**HERPES SIMPLEX**

The herpes simplex virus (HSV), characterized by its ability to remain latent in the nervous system, can impact individuals of all ages. By adulthood, almost all of the population has herpes simplex antibodies, with the majority of people having had exposure by age five. HSV, a DNA virus largely spread by close personal contact, is primarily broken down into two types: herpes simplex I (oral/facial/ocular) and herpes simplex II (genital); HSV can also cross-infect between type 1 and type 2.1

In the setting of periocular skin disease, the patient may have confined prodromal symptoms such as mild pain, tingling, itching or burning before the lesion potentially progresses to the following stages: macule, papule, vesicle, encrustation and healing (without scarring). Only after skin lesions are encrusted is the primary disease no longer contagious.

It is well known that herpes simplex disease tends to recur. With a prevalence of 150 per 100,000 people in western countries, patients have a 1% global lifetime risk of developing herpes simplex keratitis (HSK). Furthermore, 40% of patients will have between two to five relapses in their lives; an additional 11% will experience between six and 15 relapses.2

A reactivation from the ophthalmic branch of the trigeminal ganglion may result in HSK. In those who exhibit relapsing HSK, the three primary presentations of keratitis—epithelial, stromal and endothelial—can occur in isolation, combination or succession.

With HSK, the patient will often present with unilateral injection and a mild, watery discharge. It is imperative to remember that, early on, corneal lesions may not present in their classic dendrite formation. When caught at the start of the infection process, HSK may appear merely as a superficial punctate keratitis secondary to dry eye. However, these primarily coarse punctate lesions form unilaterally (with the exception of children with atopic disease who may get bilateral...
Antiviral Agents

Other Faces of HSV Expression

We are all familiar with the typical clinical manifestations of primary herpes simplex expression, but there are two other presentations to recognize: herpes gladiatorum and eczema herpeticum. While both are dermatologic in nature and share a similar clinical presentation, unique differences exist between them.

Herpes Gladiatorum

This form is seen almost exclusively in high school or college wrestlers. The athlete develops a spontaneous primary infection, engages in wrestling activity and transmits the virus via vigorous skin-to-skin contact. Note that while spontaneous primary HSV expression is generally unilateral, this condition (as well as eczema herpeticum) can be much more diffusely dispersed. A patient history is critical to diagnosis, and both primary and gladiatorum forms are treated either with acyclovir 400mg, five times a day for seven to 10 days; valacyclovir 500mg, three times a day for seven to 10 days; or famciclovir 250mg, three times a day for seven to 10 days. Because of the easier dosing schedule of valacyclovir and famciclovir (TID), we generally prescribe one of these two drugs. Check with www.goodrx.com to find where this medicine is the least expensive in your area.

Eczema Herpeticum

This is somewhat of an opportunistic infection, in that it is almost always seen in patients with eczema, a subset of atopic disease. As with gladiatorum, it has a rather disseminated expression that does not respect laterality. The face and neck are most commonly involved, and younger and gladiatorum forms are treated either with acyclovir 400mg, five times a day for seven to 10 days; valacyclovir 500mg, three times a day for seven to 10 days; or famciclovir 250mg, three times a day for seven to 10 days. Because of the easier dosing schedule of valacyclovir and famciclovir (TID), we generally prescribe one of these two drugs. Check with www.goodrx.com to find where this medicine is the least expensive in your area.

Herpes Zoster Virus

The varicella virus (chickenpox) is the initial or primary infection of the herpes zoster virus (HSV) disease process. Herpes zoster, better known as “shingles” to the general public, is the reactivation of the varicella virus and is seen most commonly in the sixth to seventh decades of life. When an individual is initially exposed to chickenpox, the virus becomes latent in the sensory ganglion of the trigeminal nerve. If the disease is reactivated, the virus will travel down the neural pathways to its respective afferent peripheral nerves and dermatome (an...
area of skin that is mainly supplied by a single spinal nerve).

A shingles outbreak is always unilateral, and will not cross the midline of the patient, thus making it one of the most recognizable disease processes in medicine. The recurrence of the zoster virus is rather low—less than 6%—as additional outbreaks could lead to the patient to become immunocompromised.6

Up to 30% of patients will develop a herpes zoster outbreak in their lifetimes. The prevalence of HZV is well-documented to have increased over the past decade.7 Each year, nearly one million Americans develop shingles—with the face being the second most common site of infectious development, after the trunk.8 Fortunately, due to the advent of the childhood Varivax vaccine (live varicella virus, Merck), which came to market in 1995, generations of people will never have shingles because they will never contract chickenpox.

This, however, is a double-edged sword. Prior to the Varivax vaccine, children with chickenpox in various stages of contagion came into contact with adults during the course of daily living, boosting the adult population’s immunity against the varicella zoster virus. Since Varivax, such immune-stimulation has diminished each year. Thus, we face another 30 to 50 years of increasing occurrence of shingles in those underexposed patients who have not had sufficient exposure to boost their immunity against it. As such, clinicians need to be ready to competently care for this expanding population.

*Herpes zoster ophthalmicus* (HZO) is present in up to 25% of all zoster outbreaks, and occurs when the virus affects the first branch of the trigeminal nerve (V1, or the ophthalmic branch).9 A long-held clinical belief has been that, if the tip of the nose is involved (Hutchinson’s sign, indicating involvement of the nasociliary nerve that innervates corneal and intracocular tissues), the eye is, too. With the first branch innervating the structures of the eye, it is easy to see why nearly every ocular tissue can be affected by a viral reactivation.

Ocular involvement of HZO presents as an inflammatory keratitis, uveitis, conjunctivitis or a combination of all three. Uveitic involvement manifests as inflammatory cells in the anterior chamber, corneal involvement as stromal inflammation and conjunctival involvement as unilateral injection, to varying degrees. An elevated intraocular pressure may occur if the trabecular meshwork is inflamed. Should the IOP be sufficiently elevated, a temporary reduction can be accomplished with a topical beta-blocker such as timolol and/or the alpha-adrenergic agonist brimonidine, for a few days. Conjunctival injection will accompany these scenarios to some degree.

Treatment for ocular involvement is available in topical and oral form; now let’s look at our options.

**TOPICAL THERAPY**

Ocular HSV keratitis responds well to either Zirgan (ganciclovir gel 0.15%, Bausch + Lomb) or Viroptic (trifluridine 1%, Pfizer and generic). If the disease is confined to the epithelium, never treat with topical steroids, as that can enhance viral replication that could progress to a potentially sight-threatening geographic ulcer.

Ganciclovir 0.15% (preserved with benzalkonium chloride) is a more advanced option than trifluridine 1%, allowing for less frequent dosing, in turn decreasing risk of toxicity. Patients should instill one drop into the affected eye five times daily until the corneal ulcer heals, then one drop three times daily for a week. Remember that ganciclovir is available as a gel only. Dosed appropriately, most HSK cases resolve over the course of two weeks or less.

For patients with ocular involvement in the setting of HZO, the strategy is quite different. Typically, an aggressive approach with cyclopedia and topical steroids is deployed. We prescribe homatropine 5% BID to QID,
along with Durezol (difluprednate 0.05%, Novartis) every one to two hours for a few days until the inflammation is well controlled. Only then is tapering initiated.

Recurrent flare-ups may require maintenance therapy as a prophylactic measure. Once the inflammation is brought fully under control with Durezol, we switch the topical steroid to Lotemax gel. The sequence would be something like this: TID for one month, BID for two to four months and then once daily for several more months. The goal is to find the minimum therapeutic dosing to achieve the desired result.

It should be noted that some pharmacies in certain locations don’t always stock topical antivirals, so oral therapy can be an equally effective, and less expensive, approach.

**ORAL THERAPY**

When shingles presents as an uncomplicated skin disease accompanied by pain, erythema and vesicular expression, we recommend an oral antiviral for seven to 10 days. We find three such medications equivalent in their therapeutic effectiveness (dosed specifically for zoster disease):

- **Acyclovir 800mg** five times daily
- **Valacyclovir 1,000mg** three times daily
- **Famciclovir 500mg** three times daily

Interestingly, some research advocates the use of famciclovir over acyclovir and its prodrug valacyclovir in adults >65 years of age with or without reduced renal function. This is due to findings that valacyclovir and acyclovir carry an increased risk of central nervous system adverse reactions (agitation, confusion, encephalopathy) and acute renal failure compared with famciclovir.10,11 Moreover, in lactose-intolerant patients, valacyclovir is preferred. In children, the oral suspension form of acyclovir is a prudent option.

The three aforementioned oral antivirals are generic. Acyclovir tends to be less expensive than valacyclovir or famciclovir, but is dosed five times a day. As a quick rule of thumb, the dosage of the antiviral drug is halved to treat simplex disease.

Remember that antiviral medications are most efficacious during the early, replicative phase of the infection (initial 72 hours). This does not mean that after three days, the opportunity for medical intervention has passed, just that there is decreasing clinical efficacy with each day of delayed care. With more virulent expressions, especially in older individuals, concurrent therapy with oral prednisone (usually 40mg to 60mg/day for a week) can be valuable in decreasing pain and inflammation, and may dampen the expression of post-herpetic neuralgia.

Oral antivirals are extremely safe and effective. Their only Achilles’ heel is that they are metabolized by the kidneys. Thus, if a patient has clinically significant renal disease, the antiviral dosage must be...
A patient exhibiting HZO. Note the first division, trigeminal distribution, dermatological vesicles, the edema to the upper eye lid and the mild ocular inflammation. Treatment would include an oral antiviral and a topical corticosteroid. Oral prednisone (40mg) for a week could also be considered depending upon the pain level of the patient.

reduced. A phone consultation with the patient’s primary care physician, nephrologist or pharmacist is of utmost importance in determining optimum dosages in the setting of renal disease.

THE HERPETIC EYE DISEASE STUDY
Originally undertaken to evaluate the usefulness of oral acyclovir in stromal HSV disease, the Herpetic Eye Disease Study (HEDS)—which consisted of five randomized, placebo-controlled trials to determine the best treatment options and prophylaxis against HSV keratitis—looked at more than 700 patients with various manifestations of ocular HSV infection.12

The study concluded that:
- The placebo group had a 32% cumulative probability of ocular HSV recurrence during the first 12 months.
- Epithelial disease alone did not make future recurrences more likely, but stromal disease definitely did.
- With regards to patients who had epithelial dendrites, oral acyclovir did not reduce the rate of stromal disease.
- Oral acyclovir did not improve outcomes in stromal keratitis cases, nor did it prevent stromal involvement.
- Stromal disease was best managed with topical steroids, which did not increase the rate of recurrence.

As revealed in the Acyclovir Prevention Trial, oral acyclovir 400mg dosed BID for one year resulted in a 45% decrease in the chance of recurrence for all forms of ocular involvement. However, the effect was stopped upon discontinuation of the drug.13 This research points to the importance of potential lifetime treatment with oral acyclovir in patients who have two or more outbreaks in a year, or a recurrent disiform keratitis. Newer data show a parallel effect with a single 500mg dose of valacyclovir.

While acyclovir was used in the HEDS, it is our belief that the other antivirals would have a similar effect. We do know that a single 500mg dose of valacyclovir is equivalent to 400mg of acyclovir BID for long-term suppression therapy when needed.

SHINGLES OUTLOOK LOOKS BRIGHT—EVENTUALLY
With the advent of the childhood Varivax vaccine, generations of people will never have shingles, as they never contracted chicken pox. This leaves a sizable majority of the adult population underexposed to the virus, diminishing their immunity and increasing the prevalence of the disease for the next several decades. It is critical that this population is swiftly and effectively treated when it arises in our offices and clinics.

REGARDED AS ONE OF THE GREATEST DISCOVERIES IN MEDICINE, ANTIBIOTICS have been used since the 1940s to treat millions of patients with infections worldwide. However, antibiotics are, in a sense, victims of their own success: dosing has become widespread and over-prescribed over time. As a result, some bacteria are now resistant to antibiotics that were once highly effective.

According to a report from the Centers for Disease Control and Prevention, antibiotic resistance causes two million bacterial and fungal illnesses, and 23,000 deaths, yearly. It also results in an annual increase in direct health care costs of $20 billion, plus $35 billion in lost productivity. Though most studies on antibiotic resistance have focused on systemic antibiotics, researchers have begun to look at resistance to topical ophthalmic antibiotics.

Given this growing epidemic of antibiotic resistance across medical disciplines, researchers are under increasing pressure from the clinical world to seek out potential new drugs to treat infections.

RED EYES ARE RARELY INFECTIOUS

We have found that acute red eyes uncommonly derive from bacterial infection. The presence of mucopurulent discharge with acute red eyes is often the result of a bacterial infection. Lacking “discharge,” the acute red eye almost always results from some expression of inflammation. These inflammatory conditions require corticosteroids, not antibiotics, yet time and time again, clinicians will prescribe an antibiotic drug that does not improve the patient’s condition.

Let’s take a more in-depth look at this class of medicines. There are many antibiotics; however, only a few enjoy—or should enjoy—widespread use.

BACITRACIN

Available since 1948, bacitracin is only available in ointment form, and is strictly a gram-positive antibiotic often employed in the clinical setting of staphylococcal blepharitis. After warm compresses and lid scrubs, bacitracin can be applied to the lid margins at night before the patient goes to bed for four to six days. However, since tissue inflammation invariably accompanies staphylococcal blepharitis, we more frequently have our patients apply an antibiotic-steroid combination ointment such as generic Maxitrol (dexamethasone/neomycin/polymyxin B) here.

For true bacterial corneal infections, a broad-spectrum antibiotic is always preferred. In such cases, we dose Besivance (besifloxacin ophthalmic suspension, Bausch + Lomb) by day with Polysporin ophthalmic ointment at bedtime (bacitracin/polymyxin B), as the polymyxin B is bactericidal against gram-negative pathogens.

SMART SELECTION OF ANTIBIOTIC AGENTS

Both the topical and oral forms should be used judiciously to avoid perpetuating antibiotic resistance. Here are strategies to choose the right medicine and dose it correctly.

ANTIBIOTIC AGENTS
THE AMINOGLYCOSIDES: GENTAMICIN, NEOMYCIN AND TOBRAMYCIN

The aminoglycosides historically were a go-to drug for optometrists. However, they have taken a back seat with the advent of fluoroquinolones. Today, some clinicians may be reluctant to prescribe the aminoglycosides due to their potential to cause a type IV hypersensitivity reaction. Neomycin is broad-spectrum, but does not cover Pseudomonas, which is why it is always packaged with polymyxin B or an antibiotic effective against gram-negative organisms. In our experience, type IV delayed hypersensitivity dermatoconjunctivokeratitis reactions are exceedingly rare when the neomycin combination is used for no more than a week.

POLYMYXIN B COMBINATIONS

Combination drugs that pair polymyxin B with a complementary gram-positive agent can extend the total antibiotic coverage achieved.

Polytrim. Originally marketed by Allergan and now generically available, Polytrim (polymyxin B/trimethoprim) is an effective combination antibiotic available in solution form. Polymyxin B is active only against gram-negative bacteria. Trimethoprim is broad-spectrum against many gram-positive and some gram-negative bacteria, and works by interfering with the folic acid pathway. Note that trimethoprim itself is not a sulfa drug, although it also inhibits the production of bacterial folic acid.
In reality, though, it’s not used very often in clinical practice because new studies have found it to be suboptimal against methicillin-resistant staphylococcal epidermis species.

**Polysporin.** This drug, which combines polymyxin B with bacitracin, is available generically but only as an ophthalmic ointment. The pairing of polymyxin B’s gram-negative and bacitracin’s gram-positive action makes this an excellent, nontoxic, broad-spectrum antibiotic.

The drug is often used in pediatric eye care, and instilled along the lids and lashes, where body temperature melts the ointment and allows adequate ocular surface application of the drug. This approach obviously can be applied to patients of all ages.

In cases of bacterial keratitis or a severe bacterial conjunctivitis, Polysporin ointment can be especially useful at night for sustained antibacterial coverage.

**Neosporin.** This triple-antibiotic of neomycin, bacitracin and polymyxin B is conveniently available generically as an ophthalmic ointment and solution (the solution contains gramicidin, not bacitracin). We rarely use Neosporin in eye drop form due to the aforementioned potential type IV hypersensitivity reaction in some patients. Alternatively, we prefer generic Polytrim (trimethoprim/polymyxin B), tobramycin or Besivance (Bausch + Lomb), depending on the nature and severity of the infectious condition, as these options are much less prone to cause any type of allergic reaction.

### THE FLUOROQUINOLONES

The options in this class have some notable differences.

**Besifloxacin.** Besivance, a unique, dual-halogenated fluoroquinolone, is the only topical ophthalmic antibiotic that comes as a suspension. As with all fluoroquinolones, Besivance provides activity against DNA gyrase and topoisomerase IV. Its broad-spectrum coverage combats gram-positive, gram-negative (including *Pseudomonas*) and anaerobic organisms, as well as methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus epidermidis* (MRSE). The latest research (i.e., the ARMOR study) has demonstrated in vitro that besifloxacin and vancomycin share very low MICs against the common gram-positive ocular pathogens.2 This is important in that we know how efficacious compounded vancomycin is, and would expect similar *in-vivo* performance with Besivance.

As a suspension, this thick eye drop must be shaken prior to each use. The patient also must refrain from blinking for several seconds after instillation to allow the drop to spread out across, and remain on, the ocular surface. When properly instilled, Besivance has been shown to maintain very high concentrations on the ocular surface, with minimal systemic exposure.

An *Ophthalmology and Therapy* study finds: “Large randomized, controlled clinical trials have established the efficacy and safety of besifloxacin administered three times daily for five days for the treatment of acute bacterial conjunctivitis in both adults and children, with high rates of clinical resolution (up to more than 70% by day five) and bacterial eradication (more than 90% by day five), and a low incidence of adverse effects.”3

For severe infectious processes such as microbial keratitis, we dose Besivance 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. Practically speaking, Besivance is a white viscous drop that can bother some patients, so patients should be advised of its consistency.

**Ciprofloxacin.** Ciloxan, a second-generation fluoroquinolone, remains a drug of choice against the gram-negative *Pseudomonas* species, and remains close in efficacy to the...
fourth-generation fluoroquinolones. Note that generic forms of the drug can be less expensive for the patient.

**Moxifloxacin.** Two popular fourth-generation fluoroquinolones—topical moxifloxacin 0.5% available as Moxeza (Novartis) and Vigamox (Novartis)—function similarly. Of clinical note, Vigamox and Moxeza are the only preservative-free ophthalmic fluoroquinolone antibiotics, thus minimizing the potential for a toxic or allergic response (although such is exceedingly rare). Patients should be informed that the drop has a slight yellow color, to avoid the misconception that it has gone bad.

**Ofloxacin.** A second-generation fluoroquinolone, ofloxacin is rarely used. However, because the drug is generic, it remains a reasonable, inexpensive option for bacterial conjunctivitis. It is also available as brand-name Ocuflox (Allergan).

**Gatifloxacin.** A fairly effective fourth-generation fluoroquinolone, Zymaxid is FDA-approved to treat bacterial conjunctivitis. While useful and generically available, fourth-generation fluoroquinolones are exhibiting increasing bacterial resistance.

## SYSTEMIC AGENTS
Oral antibiotics remain wonderful options when used judiciously in patient care. Their clinical indications are vast, and can be used in short-term therapy (such as for internal hordeolum) to long-term or maintenance therapy (for meibomian gland disease and rosacea blepharitis).

For an acute internal hordeola, we prefer the first-generation cephalosporin, cephalaxin (Keflex), at 500mg BID for one week. If the condition is severe and/or the patient is large in size, 500mg QID for one week may be indicated. This predominantly gram-positive antibiotic, along with warm soaks, has been shown to improve acute hordeola in about a week. We may also prescribe generic Maxitrol ointment at night to the lid margins to use after warm compresses and lid scrubs. This will be covered in the combination drug section.

Patients tend to have allergies to antibiotics more than other classes of drugs. Always take a careful medical history to avoid the risk of an allergic reaction. If a patient has had a true anaphylactic reaction to penicillin or penicillin-like drugs such as cephalosporins, we opt for Levaquin (500mg QD) or doxycycline (200mg QD), or Bactrim DS or Septra DS (both common brand names of trimethoprim with sulfamethoxazole) prescribed as two double-strength tablets BID for one week, which is the standard, commonly prescribed dosage.

If the patient is truly allergic to penicillin and sulfa, consider oral doxycycline 100mg BID for one week, or the oral fluoroquinolone levofloxacin 500mg once daily for one week. For perspective, the risk of a cross-sensitivity reaction of a cephalosporin in a patient truly allergic to penicillin is about 0.1%—but why ever take the miniscule risk? Just prescribe an alternative class.

As well, the extremely rare occurrence of tendonitis or tendon rupture associated with oral fluoroquinolone use makes this class our last option.

Occasionally, we encounter patients who need antibiotic treatment for chronic care conditions such as meibomian gland disease or rosacea blepharitis. We prescribe doxycycline at 50mg daily for three to six months. The dichotomous nature of doxycycline (anti-infective at high dosage and anti-inflammatory at low dosage) requires customized dosing.

Though doxycycline hyclate and doxycycline monohydrate are well-tolerated, the monohydrate form appears to be a bit better tolerated. 06

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