Supplement to

Glaucoma TODAY

Fall 2010

CME ACTIVITY

Ophthalmic Formulations

Equivalence and Patient Care

In the next several years, most glaucoma medicines will be available as generic formulations. Learn how this development will affect patient care.

This continuing medical education activity is jointly sponsored by the Dulaney Foundation and Glaucoma Today.

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Ophthalmic Formulations

Equivalence and Patient Care

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

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STATEMENT OF NEED

Glaucoma is the second most common cause of legal blindness in the United States[1] and the leading cause of irreversible blindness in the world.[2,3] As many as half of the nearly 3 million people in the United States suffering from glaucoma may be unaware they have the disease.[1] It is well documented that, among patients who have been diagnosed and are prescribed therapy, compliance is far from optimal—which is common in chronic conditions that are largely asymptomatic (eg, hyperlipidemia, hypertension, etc). Undiagnosed and suboptimally treated glaucoma results in irreversible vision loss. Specifically, patients may lose more than 40% of their optic nerve fibers before noticing a loss of peripheral vision.[1,4]

Much data have been published in the peer-reviewed literature regarding early detection and treatment of glaucoma and related issues. There is a need among eye care professionals, however, for a comprehensive, coherent review of specific, practical, clinical considerations related to issues, such as the differences between generic and brand-name medications, side effects of therapy, and strategies to reduce adverse therapeutic effects.

Louis B. Cantor, MD, said in a recent article about generic glaucoma medications and cost savings that, although more generic availability can offer cost savings to some patients, it can also lead to confusion.[5] He also noted physicians should be sure to observe patients' reactions to differences in formulations of glaucoma therapy.
Dr. Cantor practices at the Indiana School of Medicine, Eugene and Marilyn Glick Eye Institute.

It is doubtful that generic medications enhance compliance, according to James C. Tsai, MD, from the Department of Ophthalmology and Visual Science, Yale University.[6] A 2003 study he undertook found that patients had 71 distinct reasons for noncompliance without taking cost into account.

1. Distelhorst JS, Hughes GM. Open-angle glaucoma. *Am Fam Phys*. 2003;67:1937-1944, 1950.
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TARGET AUDIENCE

This certified CME activity is designed for glaucoma specialists, general ophthalmologists, and clinical optometrists involved in the management of patients with glaucoma.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to

- Recognize the importance of patients' adherence to prescribed glaucoma therapy in medical outcomes
- Identify the key barriers to patients' adherence to prescribed glaucoma medical therapy
- Discuss the pros and cons of generic medications versus brand-name formulations
- Employ effective strategies to ensure that patients are receiving the medications prescribed and facilitate their appropriate long-term use.

METHOD OF INSTRUCTION

Participants should read the learning objectives and continuing medical education (CME) activity in their entirety. After reviewing the material, please complete the self-assessment test, which consists of a series of multiple choice questions. To answer these questions online and receive real-time results, please visit www.dulaneyfoundation.org and click "Online Courses."

Upon completing the activity and achieving a passing score of over 70% on the self-assessment test, you may print out a CME credit letter awarding 1 *AMA PRA Category 1 Credit™*. The estimated time to complete this activity is 1 hour.

ACCREDITATION/DESIGNATION STATEMENT

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

DISCLOSURE

In accordance with the disclosure policies of the Dulaney Foundation and to conform with ACCME and FDA guidelines, anyone in a position to affect the content of the CME activity is required to disclose to the activity participants: (1) the existence of any financial interest or other relationships with the manufacturers of any commercial products/devices or providers of commercial services, and (2) identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

FACULTY DISCLOSURE DECLARATIONS

Dr. Noecker discloses he has received grant/research support from Allergan, Inc., Carl Zeiss Meditec, Inc., and Lumenis, Inc. He is a consultant for Allergan, Inc., and he is on the speakers' bureaus of Allergan, Inc., Alcon Laboratories, Inc., Lumenis, Inc., and Endo Optiks.

Dr. Simmons discloses he has received grant/research support from Allergan, Inc., Alcon Laboratories, Inc., and Sun Pharmaceutical Industries, Ltd. He is a consultant for Allergan, Inc.

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

FACULTY CREDENTIALS

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Glaucoma Today and Where We Are Going

Advances in diagnostic tests and surgical and medicinal interventions enable us to better detect and treat glaucoma, but other factors still present challenges.

BY STEVEN T. SIMMONS, MD

Glaucoma is a growth industry. More than 2 million people over the age of 40 in the United States have glaucoma, and that number is expected to double in the next decade.[1] In addition, we are diagnosing glaucoma earlier in a patient's lifetime—the median age at diagnosis is 53 years[2]—and, as a result, we are following patients not for a year or two but for decades, always with the underlying goal of keeping them seeing for their entire lives.

Unfortunately, too many people are still going blind from glaucoma. According to the Glaucoma Research Foundation, one out of 10 patients will become visually handicapped because of his or her disease, and 18% of blindness in the United States is due to glaucoma.[3] These statistics were borne out in a retrospective review of a comprehensive practice, where researchers looked at the incidence of blindness in glaucoma patients who died over a 12-year period.[4] The researchers eliminated confounding causes of vision loss and isolated 106 patients with just glaucoma. They found that 15% of patients were legally blind in one or both eyes when they died. In a one-eye analysis, they found that 1% of patients per year became legally blind. I would argue that those statistics reflect what is happening in most of our practices. How can we do better?

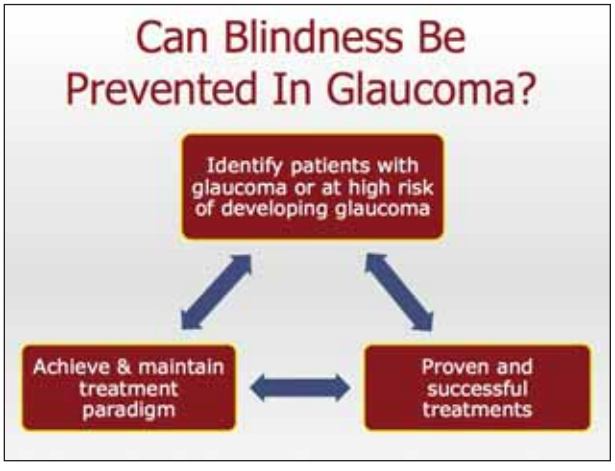

Figure 1. Preventing blindness from glaucoma requires a three-pronged approach.

> "As early as the 1960s, researchers reported the IOPs of glaucoma patients fluctuate more than the IOPs of normal patients."

FUNDAMENTAL GOALS

Improved glaucoma care involves a three-pronged effort (Figure 1). First, we must get better at identifying patients who have glaucoma or who are at risk of developing glaucoma. Population studies suggest that as many as half of all glaucoma cases have not been diagnosed.[5-7] Part of the problem is that we continue to focus too much on IOP for a diagnosis rather than on the structure and function of the optic nerve. We now have technology that enables us to look at structure and identify functional changes earlier. It is imperative that we adopt that technology.

Second, we must develop proven and effective therapies, and third, we must achieve and maintain our treatment paradigm. Numerous NIH studies over the last 2 decades have shown that we have the therapies we need to effectively treat glaucoma. We also have redefined the risk factors for glaucoma (Table 1), and in doing so, we have improved our therapies.

STUDIES SUPPORT AGGRESSIVE THERAPY

In the first 3 years of the Early Manifest Glaucoma Trial (EMGT), the rates of progression in treated versus untreated patients differed significantly.[8] In the

TABLE 1. RISK FACTORS FOR THE DEVELOPMENT AND PROGRESSION OF GLAUCOMA

Ocular factors[1,2]

- IOP (mean, short-term fluctuation, long-term fluctuation)
- Central corneal thickness
- Optic nerve structure (cup-to-disc ratio)
- Disc hemorrhage
- Other ocular disorders

Nonocular factors

- Age
- Race
- Family history/genetic predisposition
- Vascular disease (diastolic perfusion pressure, vasospastic disease)

1. Wilson MR. Primary open-angle glaucoma and risk factors. In: Higginbotham EJ, Lee DA, eds. *Clinical Guide to Glaucoma Management.* Woburn, MA: Butterworth-Heinemann; 2004:3-9.
2. Medeiros FA, Sample PA, Zangwill LM, et al. Corneal thickness as a risk factor for visual field loss in patients with preperimetric glaucomatous optic neuropathy. *Am J Ophthalmol.* 2003 Nov;136:805-813.

latter 4 years, however, progression rates were surprisingly similar, which leads to the conclusion that treatment works, but if the treatment is not aggressive enough, progression will occur (Figure 2). During the Collaborative Initial Glaucoma Treatment Study (CIGTS), patients were treated aggressively, either medically or surgically, and over a 10-year period, the majority of patients did not progress (Figure 3).[9] This study suggests that blindness from glaucoma is truly preventable.

More recently, researchers followed 250 glaucoma patients for 5 years or more to identify risk factors for disease progression.[10] They concluded that, for every 1 mm Hg of increased pressure, a patient had a 19% increased risk of progression. There is more to pressure, however, than just mean pressure.

IMPACT OF IOP FLUCTUATION

As early as the 1960s, researchers reported the IOPs of glaucoma patients fluctuate more than the IOPs of normal patients.[11] Anecdotally, I recall a man with pigmentary glaucoma who was recruited for the CIGTS. In the morning, his pressures ranged from 35 mm Hg to 40 mm Hg, but by the time he left the office at noon, his pressures were less than 18 mm Hg. If we had only seen that man every day after work, he never would have shown an elevated pressure. Pressure fluctuations, especially in untreated glaucoma patients, can be dramatic.

We also know pressures in treated patients fluctuate more than we think they do or expect them to, and that people whose pressures fluctuate more get worse.[12,13] In an analysis of data from the Advanced Glaucoma Intervention Study (AGIS), investigators found that pressure fluctuation was more important than mean pressure in disease progression.[14]

OBSTACLES TO CONTROLLING IOP

Achieving and maintaining target pressures can be challenging, and we all know it is easier to undertreat glaucoma than it is to overtreat it. Researchers who per-

(Continued on page 14)

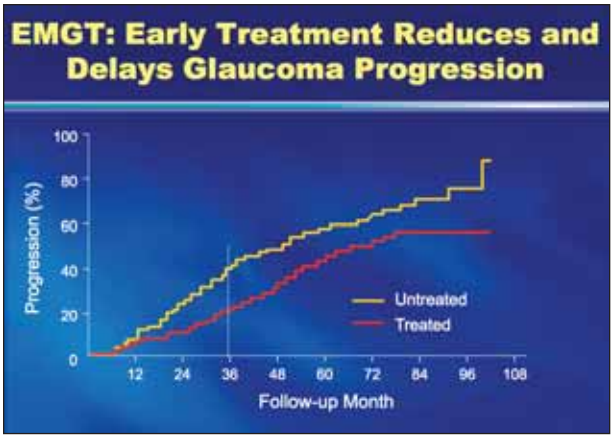

Figure 2. In the latter 4 years of the EMGT, progression rates were similar in both groups, suggesting that treatment alone, if not aggressive enough, may not stop progression.

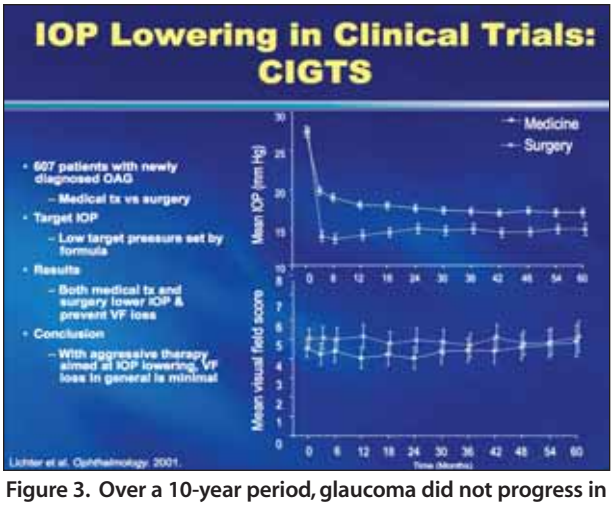

Figure 3. Over a 10-year period, glaucoma did not progress in the majority of patients in the CIGTS who were treated aggressively.

The Making of Generic Medicines

As more ophthalmic drugs become available as generics, what we know about generic requirements will help us make informed decisions when prescribing for glaucoma.

BY ROBERT J. NOECKER, MD, MBA, AND STEVEN T. SIMMONS, MD

According to IMS Health, generic drugs now represent 75% of all dispensed prescriptions in the United States. The US Department of Health and Human Services Office of the Inspector General reports that, under Medicare Part D and state Medicaid drug plans, more than 50% of dispensed drugs are generic, and generics are substituted at the pharmacy at least 85% of the time.

Until recently, most drugs prescribed in ophthalmology were branded. Now, we are seeing an increase in generic formulations of ophthalmic drugs (Table 1). Next year, latanoprost (Xalatan; Pfizer, Inc.), the most widely used glaucoma medication,[1] will be available in generic form.

Whereas, previously, we knew what to expect from each brand, now there is uncertainty about exactly what our patients are receiving when they use generics and the effects of these drugs. This situation gives rise to numerous questions: Is there a difference in the way a generic drop is formulated? Are the active ingredients different? Is the pH different? What about the vehicle? In this continuing medical education supplement, we will address these and other related questions.

FROM BRANDED TO GENERIC

Pharmaceutical manufacturers invest expertise, time, and money to bring a drug to market. First, they must find the proper molecule and develop a drug. Then they must perform clinical trials to prove efficacy and safety. After the FDA approves a drug, the manufacturer must invest in sales and marketing efforts to increase awareness of it and institute postmarketing surveillance and patent protection strategies. For its efforts, the company has exclusivity for 17 years from the time of the initial FDA application, after which time, the market opens up to generic versions of the branded product.

To gain FDA approval to manufacture a generic drug, a company must submit an abbreviated new drug application. The generic drug must

- Contain the same active ingredients as the innovator drug (although inactive ingredients may—and do—vary)
- Be identical in strength, dosage form, and route of administration
- Have the same indications for use
- Be bioequivalent
- Meet the same batch requirements for identity, strength, purity, and quality
- Have a similar shelf life
- Be manufactured under the same FDA good manufacturing practice regulations required for innovator products.

The generic drug maker is not required to repeat animal and clinical research on ingredients or dosage forms that are already approved for safety and efficacy.

As we know, the active ingredients in most ophthalmic preparations comprise only a small percentage of what is in the bottle. Most of the solution is the vehicle. As noted in "Generic and Innovator Drugs: A Guide to FDA Approval Requirements":

"Generally, a drug product intended for topical use shall contain the same inactive ingredients as the reference listed drug. … However, an applicant may seek approval of a drug product that differs from the reference listed drug provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety of the proposed drug product."[2]

We all use generic drugs. They have their place, but typically, little additional information is available on efficacy, tolerability, loss of control for chronic diseases, and patients' perceptions and confidence. In some situations, we can feel

TABLE 1. OPHTHALMIC DRUGS AVAILABLE IN GENERIC FORM

- Beta-blockers (timolol, levobunolol, carteolol, betaxolol)
- Alpha-adrenergic agonist (brimonidine 0.15%, 0.2%)
- Topical carbonic anhydrase inhibitor (dorzolamide)
- Parasympathomimetic (pilocarpine)
- Fixed combination (dorzolamide/timolol)
- Oral carbonic anhydrase inhibitor (acetazolamide, methazolamide)
- Prostaglandin analogue (available outside the United States)

fairly confident prescribing a generic drug—an antibiotic for a relatively short period, for example—but if we are prescribing therapy for a chronic condition, this lack of information could be problematic.

SYSTEMIC GENERICS: EFFICACY AND TOLERABILITY

Systemic generics are not required to be tested for therapeutic equivalency to the parent branded formulation, and although the FDA asserts generic drugs are as safe and effective as their branded counterparts, that is not always the case in clinical practice, as we have seen from reports in the literature.

For example, clinicians have reported loss of therapeutic control with variations of generic preparations of levothyroxine for hypothyroid patients.[3,4] Other reports have implicated generic formulations for reduced seizure control in epileptic patients, citing differing plasma and serum concentrations between branded and generic drugs.[5-7] We have also learned that sustained-release generic antidepressants may have different absorption rates than branded products, owing to differences in the coatings or the size of the granules in the pills.[8,9] There have been reports of symptom relapses with certain generic anti-anxiety drugs.[10]

Regarding tolerability, there have been reports of increased side effects when patients were switched from branded systemic products to some generic drugs. These have included

- Increased reflux symptoms with the generic proton pump inhibitor omeprazole (possibly due to differences in pill coating)[11]
- Doubling of adverse effects in elderly patients (ages 75+)[12]
- Increased headaches and gastrointestinal problems[10]
- Increased side effects in patients using generic antiepileptic drugs.[13]

Although these effects are now documented, they could not have been predicted, owing to the lack of advance information from clinical trials. The situation becomes even more complicated when you consider that several different companies may be manufacturing their own generic formulations of a branded drug, with differences that may not be apparent on the package insert. At any given time, a retail pharmacy or insurance plan could be dispensing any one of these formulations, with the potential for differing efficacy or side effects. (See "Barriers to Control of the Medical Regimen.")

PATIENTS' PERCEPTIONS AND CONFIDENCE

Patients' perceptions of generic drugs vary from noncommital to suspicious. Some patients ask for generic preparations to save money, but others are wary of generics. Patients who are most skeptical or anxious about switching to a generic preparation are usually those who have tried several medicines before finding one that works for them.

Studies have shown that switching to a generic drug may affect a patient's confidence. When generic antihypertensives were given to patients between the ages of 50 and 80, one-third said it was more difficult to keep track of their medicine because the shape and size of the pill changed.[14] Another third were concerned about the drug's efficacy, and 15% reported having new or more side effects with the generic. Regardless of whether or not the side effects were real, that was their perception.

In another report involving patients 50 years of age or older who were switched to generic drugs, 72% were satisfied, but the rate of medication mistakes by patients using generics increased (15.5% vs 7.7%).[11] These data contradict our thinking that compliance increases when cost decreases. In fact, those of us who prescribe topical ophthalmic medicines have found other factors will influence compliance.

In the next section, we discuss the impact of excipients in ophthalmic medications. ■

BARRIERS TO THE CONTROL OF THE MEDICAL REGIMEN

A generic version of an individual branded drug may be produced by several manufacturers, each with a different formulation, resulting in refill-to-refill variability in the consistency and bioavailability of the active ingredient. Drop size and bottle fill also may vary, causing the drug to be depleted before the refill date. In addition, bottles themselves may come from different sources with different properties and pliability.

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When a Vehicle Is Not Just a Vehicle

Although considered inactive ingredients, excipients in topical ophthalmic preparations are not necessarily benign.

BY ROBERT J. NOECKER, MD, MBA, AND STEVEN T. SIMMONS, MD

Generic ophthalmic drops must contain the same active ingredients and have the same indications for use as their branded counterparts. They must be identical in strength, dosage form, and route of administration. They must be bioequivalent, meaning the rate and extent of drug absorption must be the same, and they must be manufactured to the same FDA standards as the branded drugs.

What is important to remember, however, is that they are not required to be tested for bioequivalence or therapeutic equivalency to the parent branded formulation. In addition, excipients—preservatives, pH adjusters, antioxidants, thickening agents, buffers, and tonicity adjusters—may differ from those in the innovator product, even though they account for more than 95% of what goes into the eye (Table 1). In this article, we look at some of these ingredients and their effects.

TABLE 1. PERCENTAGES OF EXCIPIENTS IN COMMONLY PRESCRIBED GLAUCOMA DROPS

Drug	Active Ingredient	Excipients
Timolol	0.5%	99.5%
Latanoprost	0.005%	99.995%
Bimatoprost	0.03%	99.97%
Brimonidine	0.1%, 0.15%	99.9%, 99.85%
Dorzolamide/timolol FC	2%/0.5%	97.5%

OVERVIEW OF PRESERVATIVES

Since the 1950s, the FDA has required that multidose bottles of ophthalmic drops contain a preservative. Although the main goal is to kill microbial contaminants, some surfactant preservatives also help the more lipophilic drugs, such as the prostaglandin analogues, stay in solution. Three types of preservatives are used in ophthalmic drops:

- Detergent (eg, benzalkonium chloride [BAK]), which causes bacterial cell death by interrupting the lipid component of cell membranes
- Oxidizing (eg, Purite; Allergan, Inc.), which alter the lipid membrane of microbes by penetrating the membrane and altering the DNA, protein, and lipid components of bacterial cells
- Ionic-buffering systems (eg, Sofzia; Alcon Laboratories, Inc.), which act in a manner similar to oxidizing preservatives.

Studies show that preservatives in topical glaucoma drops can affect dry eye symptomatology and Ocular Surface Disease Index scores,[1,2] allergy rates,[3] tear breakup time,[4] and ocular surface toxicity.[5,6]

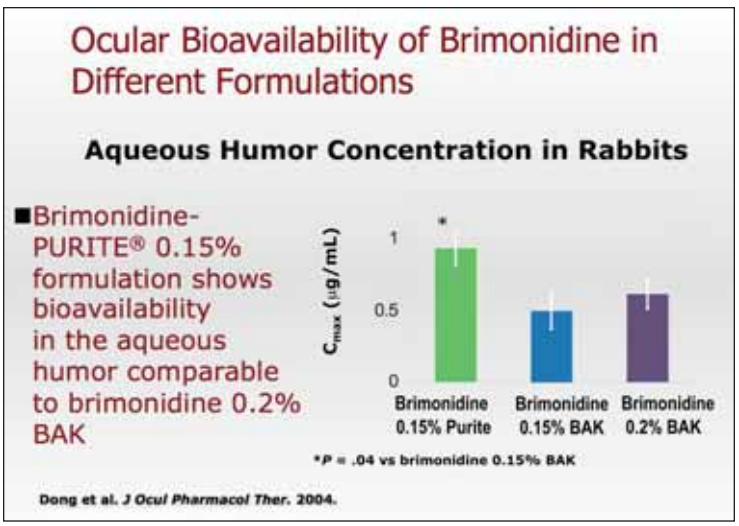

Figure 1. Brimonidine-Purite 0.15% achieved a higher anterior chamber concentration than when it was preserved with BAK at a slightly acidic pH.

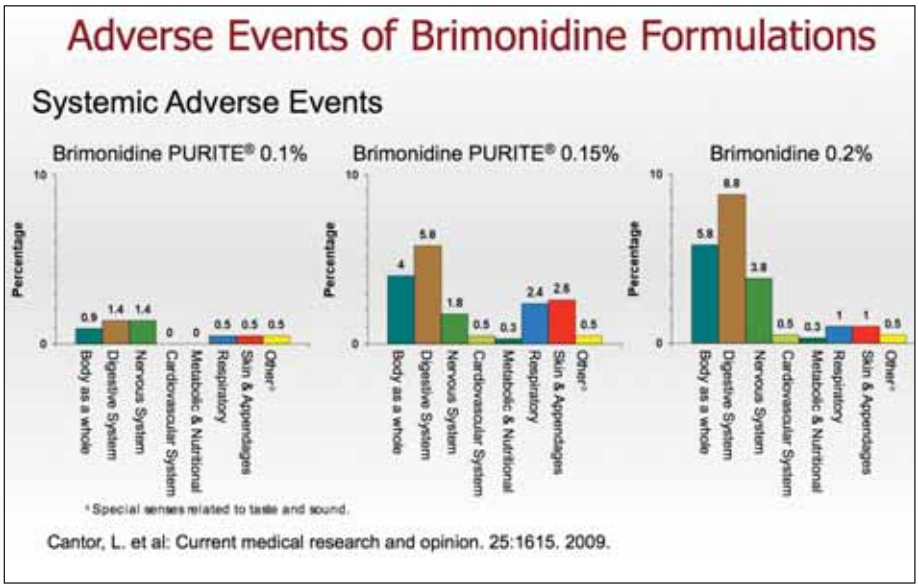

Figure 2. As the concentration of brimonidine has been reduced, the incidence of systemic and ocular side effects has improved.

COMPLEXITIES OF pH

The pH of a topical ophthalmic drop is an important driver that must be manipulated for the active ingredient and the therapeutic concentration. pH affects how well a drug penetrates the cornea and whether or not the active ingredient stays in solution. pH also affects comfort because the lower the pH, the more acidic a drop will be and the more likely it is to sting.

A question we sometimes hear is: Why is brimonidine now 0.1% when the original formulation was 0.2%? The short answer is: because the manufacturer was able to improve the efficacy and safety of brimonidine by reformulating the product. The science behind that change in formulation is more complex than merely replacing BAK with Purite.

With BAK, it is difficult to raise the pH of a brimonidine solution beyond the upper 6s, while with Purite, the pH can be raised to close to 7.8. By changing the preservative and raising the pH, it was possible to improve the penetration of brimonidine through the cornea and increase its concentration in the aqueous (Figure 1).

As Figure 1 shows, brimonidine in Purite at 0.15% achieved a much higher anterior chamber concentration than when it was preserved with BAK at a slightly acidic pH.[7] As the concentration of brimonidine has been reduced from 0.2% to 0.15% to 0.1%, with each reformulation, the incidence of systemic and ocular side effects has significantly improved (Figure 2) while maintaining efficacy.[8]

VISCOSITY AGENTS

Viscosity agents provide increased contact time to improve absorption into the eye, and increased retention time increases systemic safety. Viscosity agents may affect the ability of an active ingredient to stay in solution, and they stabilize the interaction with the tear film, which will affect tolerability.

A classic example of a viscosity agent's impact is the gel-forming solution of timolol (Timoptic XE; Merck & Co., Inc.). In clinical trials, the manufacturer was able to show fewer systemic side effects and equal efficacy with minimal dosing.[9] The gel kept the timolol on the eye longer, so it could be delivered into the eye and reduce nasal/lacrimal absorption.

The newer ophthalmic medicines tend to use modern artificial tear technology to control viscosity. Many of these new products are stable across a range of pH.

SEE THE WHOLE PICTURE

Formulations of glaucoma medicines matter in terms of pressure-lowering efficacy as well as the systemic and ocular safety of a product. In ophthalmic preparations, reading the label does not always tell the whole story. ■

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Generic Ophthalmics and Adverse Events

Formulation differences in generic ophthalmic drops may affect comfort and compliance and, in some cases, may induce adverse effects, as documented in the literature.

BY ROBERT J. NOECKER, MD, AND STEVEN T. SIMMONS, MD

The FDA receives few reports of adverse events about specific generic drugs, but any ophthalmologist in practice more than 10 years is likely to remember the adverse events related to the generic formulation of the topical NSAID diclofenac. Although the branded drug (Voltaren; Novartis Pharmaceuticals) had a good safety record, almost immediately after the generic formulation became available, ophthalmologists started seeing corneal complications after relatively routine ophthalmic procedures.[1-4] The first concern was that it was a class effect, but the complications were determined to be associated with the generic preparation specific to one manufacturer. The product was quickly removed from the market. No final reports were made public on what components were responsible for the corneal complications. Since then, branded diclofenac and the other generic versions of the drug have not caused those problems.

Although we have not seen such devastating adverse events in generic ophthalmic preparations in recent years, other cases of adverse events have been reported in the literature.

PRECIPITATE PROBLEMS

Prednisolone acetate is generally accepted as the gold standard in topical steroid therapy. It is a lipophilic drug, and for this reason, the branded preparation (Pred Forte; Allergan, Inc.) is specifically milled as a suspension. The particle size is consistent and well formulated. In generic preparations of prednisolone acetate, however, researchers have found serious problems related to precipitate formation. These include

- Significantly reduced concentration of active ingredient in each drop[5]
- Degraded homogeneity of suspension[6]
- Occluded bottle tips[6]

These discoveries resulted in product recalls[7] and removal of the generic formulation from formularies.[6]

> "Even though generic drug-makers are held to certain standards by the FDA, we do not know how individual patients will respond to a generic formulation."

INFERIOR IOP-LOWERING EFFICACY

We have seen some formula variations in topical drops for glaucoma. For example, researchers compared the generic with the branded gel-forming solution of timolol (Timoptic XE; Merck & Co., Inc.) and found the formulations were statistically different in their pressure-lowering efficacy at the 16-hour time. The branded drug had better efficacy and tolerability from a systemic and an ocular standpoint.[8]

Latanoprost is currently available as a generic in India and is expected to be introduced in the United States within the next year. Researchers in India found the IOP-lowering efficacy of the generic was inferior to that of the branded drug (Xalatan; Pfizer, Inc.).[9] Researchers also found the generic product had a higher pH value and higher levels of particulate matter compared to the brand. They concluded these differences could potentially affect stability, as well as the release of active drug in the eye. (See also "Pushing Tolerance Limits.")

TRIAL AND ERROR

Even though generic drug-makers are held to certain standards by the FDA, we do not know how individual patients will respond to a generic formulation. While some patients tolerate changes in their eye drops with minimal complaints, others are extremely sensitive and may notice even small changes related to preservatives, pH, tonicity, or other components. This can lead to noncompliance or adverse events.

PUSHING TOLERANCE LIMITS

By Robert J. Noecker, MD, MBA

My colleagues and I measured the amount of active drug in two generic formulations of latanoprost (trade names: 9 PM and Latoprost), which are currently available in India, and compared them with the branded latanoprost (Xalatan; Pfizer, Inc).[1] As shown in Table 1, on average, the Latoprost brand contained 97% of what was in the Xalatan, with a standard deviation of ±8.5%. The 9 PM showed about an 8% difference on average, with a standard deviation of ±7.4%. About 40% of the bottles of generic latanoprost tested were outside the 10% tolerance. In the clinical world, this amount is where we start to see differences in efficacy with many drugs. By comparison, when we looked at the branded drug, the standard deviation from bottle to bottle was about 1%.

Table 1. Percentage of Active Ingredient in Generic Latanoprost

Formulation Name	% of latanoprost compared to branded formulation	*P* value
Latoprost	97.0% ±8.5%	.37
9 PM	92.2% ±7.4%	.02

1. Hein A, Pokabla MJ, Lu D, et al. Chemical analysis of Xalatan 0.005% compared with commercially available latanoprost formulations. Poster presented at: The Annual Meeting of the American Glaucoma Society; March 4-7, 2010; Naples, FL.

Patients usually will try a drug that we prescribe. If it is uncomfortable or causes side effects, they may stop it, and often they do not report stopping until they return for follow-up. What is troubling in glaucoma therapy is that adverse events may be measurable in terms of signs, but some may present as vague systemic complaints that emerge over time.

For example, we are starting to see patients who have been successfully using the name-brand dorzolamide/timolol fixed combination (Cosopt; Merck & Co.), many of them for 10 years, who are experiencing some problems with the generic formulation. Although it is a minority of patients, for those patients, it is a problem we must address.

A switch from a branded to a generic drug can be somewhat trial and error. For this reason, when a patient switches to a generic glaucoma therapy, we need to decrease the time between follow-up visits to ensure the new drug is performing as we expect and the patient is comfortable and compliant. Based on our clinical findings, we may decide that writing "dispense as written" on our prescriptions may be the best solution for some patients. ■

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Frequently Asked Questions

With Commentary by Robert J. Noecker, MD, MBA

During a May 2010 symposium, Dr. Noecker fielded several general-interest questions from the audience. The following responses represent his opinions.

Q—Why can't manufacturers of generic drugs exactly duplicate the brand-name drugs?

The answer, in a word, is patents. Typically, there are at least a half dozen patents associated with the average drug. To avoid patent infringement, generic drug-makers sometimes intentionally change the preservative or the pH, but the truth is, they never really know exactly how the name-brand product is manufactured.

Some manufacturers of branded drugs also produce the generic formulation. For example, Merck & Co., Inc., manufactures branded and generic Cosopt, so I trust that the generic that Merck manufactures is the same as the branded drug. Unfortunately, there is only a one in four chance of receiving that particular generic at the pharmacy, because you cannot ask for it specifically. You do not know what you will get.

Q— Manufacturers that produce generic drugs are not required to perform clinical trials. How do they determine therapeutic equivalence?

Basically, they have formulation equivalence, package insert to package insert. The amount of active ingredients in the formulation must be within 10% of what is on the label. The bottles are tested, and those data are submitted to the FDA. They also perform stability studies. They ship the product and show that, bottle to bottle, the drug is the same.

Q—Is a generic drug more likely to push the limits of that tolerance?

The active ingredients have to be ±10%. What is in the bottle is not always in the middle of the average. For dorzolamide, for example, everything will be skewed more toward the acidic end because the drug is more soluble. It is likely the generic preparation will be more acidic than the branded drug to ensure they get that 2% into solution. For other drugs, it does not matter so much. You are correct that a generic drug is more likely to be at least 10% off. In the pharmaceutical world, a 10% difference is the magic cut-off. Beyond 10%, nonequivalence issues arise.

Q— Is the same percentage of medication in the bottle from batch to batch?

Manufacturers must submit data confirming batch-to-batch consistency. They submit all the data initially, so for what is submitted to the FDA, it is consistent. Once a drug is in production, however, if a manufacturer wants to change the bottle, it can be difficult to do so. Bottle design often influences drop size, and researchers have found drop size can range from about 20 to 60 µm.[1-3] This variation is not something easily controlled at the clinical level. Patients who are using beta-blockers, for example, are more likely to have side effects if they are getting more of the drug because of a bigger drop size.

We just assume that bottles are bottles, but they are more than simple containers. That is why each company has its own unique bottle. The interactions between the drug and the packaging are complex, but in the initial data, manufacturers do have to show batch-to-batch similarities.

Q—What is your opinion of using punctal plugs to improve retention time for glaucoma patients?

One of my residents did a study last year to find out if using punctal plugs would decrease systemic side effects while increasing efficacy by increasing retention time.[4] He used punctal plugs in one eye of each patient and had them return in a month. He found about a millimeter-and-a-half improvement in IOP lowering with the use of the plugs. The short answer is: I think it is not a bad thing to do. You need to be realistic about how much you can accomplish, but it seems to decrease systemic effects. There seems to be some efficacy benefit, at least with certain drugs, in terms of increasing the retention time. ■

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Special Challenges for Glaucoma Treatment

The chronic nature of glaucoma with its slow progression and lack of early symptoms creates challenges for us in an increasingly generic world.

BY ROBERT J. NOECKER, MD, MBA, AND STEVEN T. SIMMONS, MD

Generic substitution in all of medicine is increasing. For most systemic medications, a generic formulation can at least be tested or observed to learn, for example, if seizures recur, blood pressure rises, or symptoms of thyroid dysfunction develop.

Because glaucoma is a chronic, slowly progressive disease, the endpoint is vision loss over many years, and we do not know how a generic medicine will influence this long-term outcome. It is difficult for us to determine if we need to adjust treatment, and our therapeutic goals are not easy for patients to notice.

TABLE 1. TYPICAL COPAYS FOR PRESCRIPTION DRUG PLANS

Tier	Typical Medication	Typical Copay
1	Generic	$5-$10
2	Premium	$10-$20
3	Brand	$20-$30
4	Brand	$30-$40

TABLE 2. GENERIC FIXED COMBINATION OF TIMOLOL AND DORZOLAMIDE

Cost varies by nearly 100% depending on manufacturer and location

Sandoz, Target	$97.33
Prasco, CVS	$101.99
Hi-Tech, Local	$104.92
Apotex, Walmart	$55.54

The cost of the fixed combination can vary by 100%, depending on the manufacturer and where a patient fills his or her prescription.

> "The Congressional Budget Office estimates consumers save $8 to $10 billion annually at retail pharmacies by buying generics."

Formulation of eye drops is not a trivial exercise. Most of the newer medications—prostaglandin analogues, topical carbonic anhydrase inhibitors, alpha-agonists—have stringent, specific environmental needs to keep the drugs stable, tolerable, and efficacious. As discussed previously, although generic ophthalmics have the same active ingredients as their branded counterparts, formulation differences can affect efficacy, tolerability, safety, patients' confidence, and control of the medical regimen.

WEIGHING THE COSTS

The major benefit of generic drugs is that they cost less than branded drugs. The Congressional Budget Office estimates consumers save $8 to $10 billion annually at retail pharmacies by buying generics. Clearly there is a tremendous financial incentive to use them.

Pricing of prescription drugs is often determined by contracts and formulary copayment tiers (Table 1). Patients covered by a prescription plan who switch from a tier 2 branded drug to a generic drug save $10 to $20. Some of the generics, such as dorzolamide/timolol fixed combination, are considered premium generics, and those typically run 85% to 90% of the cost of the branded preparation. As Table 2 illustrates, the cost of the fixed combination can vary by 100%, depending on the manufacturer and where a patient fills his or her prescription. The only $4 generics for glaucoma are timolol and pilocarpine.

Any cost analysis must also take the following factors into consideration:

- Drop size and bottle fill
- Convenience and comfort
- Impact on compliance
- Potential extra visits or procedures
- Long-term uncertainty

In a typical scenario, a patient may ask, "Doctor, is the generic as good as the branded preparation? I just got this letter from my insurer, and they say I should switch to the generic." If the patient is newly diagnosed and it is early in the disease state, we may be more inclined to suggest that he or she try the generic. We may be reluctant to suggest a switch for patients with advanced disease, particularly if they are well controlled and have tried many different medicines to get there. In our experience, when patients switch medications, it may be more difficult to regain control.

PRESCRIBING IN A GENERIC WORLD

There is no doubt we are moving toward a totally generic world, and as our patients adapt to different medicines, we must monitor efficacy and safety vigilantly. This is not to say patients should not use generic drugs, but we must monitor the effects to ensure our patients are getting the cost savings they expect without sacrificing efficacy or creating side effects and tolerability issues. ■

(Continued from page 5)

formed a surveillance study of data for 395 patients with primary open-angle glaucoma in six managed care plans found that a significant percentage of patients were undertreated.[15]

One factor that may contribute to undertreatment is poor compliance by patients, not only with therapy but also with keeping appointments. In another study, researchers found 40% percent of glaucoma patients did not keep their appointments.[16] It is difficult to treat and observe patients with a blinding disease when they do not return to our offices for follow-up.

Patients' adherence to and persistence with therapy are integral to successful glaucoma management. As many as 80% of patients do not take their medicines as prescribed.[17] In addition, one study found that nearly half of the patients who had filled a prescription for glaucoma drops discontinued therapy within 6 months, and just 37% recently had refilled their initial prescription 3 years after the first dispensing.[18]

What factors interfere with compliance? One of the most common reasons why people do not take their medicine is that they forget.[19] Another major issue is the cost of the medicine.

PREPARE FOR A REVOLUTION

As we know, cost containment is an important goal in all of health care today, and substituting generic drugs for brand-name drugs is a common cost-cutting tactic. Some of us remember when we had only branded products with which to treat our glaucoma patients, but within a couple of years, all of those medicines will have generic counterparts. That will mark the beginning of a tremendous revolution in ophthalmology, a revolution for which we must be prepared. In "The Making of Generic Medicines," we explore these issues further. ■

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Ophthalmic Formulations: Equivalence and Patient Care

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CME QUESTIONS

1. A 71-year-old patient with primary open-angle glaucoma and dry eyes treated with brimonide 0.2% had excellent IOP control using the medication b.i.d. but noticed considerable dry mouth with dosing. Which of following would be most reasonable to do?

a. Switch to brimonidine-Purite 0.1% b.i.d.
b. Increase dosing to t.i.d.
c. Switch to dorzolamide t.i.d.
d. Switch to pilocarpine 2% q.i.d.

2. A 44-year-old man with recurrent anterior uveitis used prednisolone acetate for several years to control recurrent episodes of inflammation. After the recent switch to a generic preparation, he had less control of his inflammation. What is the best course of action?

a. Have patient double his dosing indefinitely
b. Write for brand necessary preparation of prednisolone
c. Change therapy to topical nonsteroidal anti-inflammatory drug
d. Change therapy to systemic nonsteroidal anti-inflammatory drug

3. A 78-year-old man with mild primary open-angle glaucoma using timolol gel-forming solution q.a.m. with good control of IOP was switched to generic preparation. He noted increased blurred vision and more shortness of breath with exertion. His IOP also increased by several mm Hg. What is the best course of action?

a. Discuss punctal occlusion with patient
b. Switch to prostaglandin analogue q.d.
c. Suggest incisional surgery to patient
d. Increase dosing to b.i.d.

4. You recently diagnosed a 51-year-old man with primary open-angle glaucoma, and he asked you what the chances are of his becoming visually handicapped because of his glaucoma. Based on current knowledge, what will you tell him?

a. 1% to 2%
b. 3% to 5%
c. 5% to 10%
d. 10% to 15%

5. Which of the following is required for an ophthalmic generic drug to gain FDA approval?

a. Bioequivalence
b. Formulation equivalency
c. Therapeutic equivalency
d. None of these

6. Which of the following excipients in topical glaucoma drops has been found to affect ocular surface toxicity?

a. Antioxidants
b. Buffers
c. Preservatives
d. Tonicity adjusters

7. Which of the following clinical benefits could be achieved through the use of punctal plugs with topical glaucoma medications?

a. Decreased systemic absorption
b. Increased drug retention time
c. Improved IOP lowering
d. All of the above

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Ophthalmic Formulations: Equivalence and Patient Care

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