

COMPOUNDED GLAUCOMA MEDICATIONS

Could this therapeutic strategy solve some problems?

BY LAUREN SEO AND NATHAN RADCLIFFE, MD



Patients with glaucoma who require three or four topical agents for pressure control are in a tough spot. On top of wrestling with what is likely to be an aggressive disease, they face challenges with regard to the tolerability of, compliance with, and the cost of multiagent topical therapy. Could compounded medications address these problems?

ity of, compliance with, and the cost of multiagent topical therapy. Could compounded medications address these problems?

COMPOUNDING OPTIONS

Two compounding pharmacies, Ocular Science and Imprimis Pharmaceuticals, recently began offering multiagent compounded glaucoma therapies in the United States. For the four main molecules in use today and available generically, several two-molecule fixed-ratio combinations have been studied, and several others have been approved outside the United States. In Mexico, Krytan Tek (Ophea) combines timolol maleate 0.5%, dorzolamide hydrochloride 2%, and brimonidine tartrate 0.2%. Although the portfolios of Ocular Science and Imprimis differ, both offer combination drops containing all four major classes of glaucoma therapy: prostaglandin analogue, β -blocker, carbonic anhydrase inhibitor, and α -adrenergic agonist.

TOLERABILITY

Two types of side effects are associated with the use of topical glaucoma drops: those attributable to the active ingredients and those attributable to the preservatives.^{1,2} Fixed-combination therapies reduce the amount of preservatives required by putting two active ingredients into a bottle containing a single preservative load, but many patients on a fixed combination still use more than one bottle of eye drops, which can increase their exposure to preservatives. Meanwhile, patients who adhere to prescribed therapy involving four bottles of eye drops will receive roughly 30 times the volume of preservatives than they would if all their agents came in just one bottle.

Skeptics accurately point out the lesser amount of data available for compounded glaucoma therapies than for currently available brand-name products, but the former do have potential advantages. For example, Imprimis offers preservative-free fixed-combination agents. Although the four-drop therapy from Ocular Science contains benzalkonium chloride (BAK) as a preservative, the concentration is 0.001%—much lower than in typical generic preparations. In total, Ocular Science's compounded formulation would expose a patient to 0.002% BAK ($0.001\% \times 2 \text{ doses} = 0.002\%$), whereas using the same agents in separate bottles would amount to an exposure of 0.06%, a 30-fold increase ($[\text{latanoprost with } 0.02\% \text{ BAK} \times 1 \text{ dose}] + [\text{timolol with } 0.01\% \text{ BAK} \times 2 \text{ doses}] + [\text{dorzolamide with } 0.0075\% \text{ BAK} \times 2 \text{ doses}] + \text{brimonidine with } 0.005\% \text{ BAK} = 0.06\%$).

ADHERENCE AND EFFICACY

Many patients use all four classes of pressure-lowering agents, and there are no solid data comparing the efficacy of combination single-bottle therapies and multibottle regimens. It is well known, however, that patients using four separate bottles of IOP-lowering drops are likely to skip doses and to administer their drops improperly.³⁻⁵ Confusion over the application of eye drops is ubiquitous. Even seemingly intuitive techniques such as using cap color as a drop identifier can be derailed, because the



AT A GLANCE

- Many glaucoma patients use all four classes of IOP-lowering agents, a challenging regimen in terms of tolerability, compliance, and cost.
- Compounded multiple-molecule therapies offer a potential solution to these problems, but more data are required to guide clinical care.

patient or caregiver can inadvertently screw the cap from one bottle on the next.

Independent data are not available on the efficacy of compounded agents, either alone or compared with agents in separate bottles. To determine the benefit of a compounded quadruple-therapy agent, Ocular Science is performing a prospective randomized trial of patients on three or four topical agents who are using at least three different bottles. Subjects are being randomized (1:1) either to remaining on their current therapy or to switching to a four-agent fixed-combination drop in the evening (containing a prostaglandin analogue) and a three-agent fixed-combination drop in the morning. Investigators will evaluate outcomes such as IOP, ophthalmic signs and symptoms, and compliance.

ECONOMICS

Some eye care providers are surprised to learn that patients using several generic medications are often on the hook for more than \$100 per month in copayments, particularly if they are using three or more drops. Unfortunately, generic price gouging is a real phenomenon, as documented by *The New York Times* for other areas of medicine.⁶ Ophthalmology may be particularly susceptible to this phenomenon, because smaller markets can be less efficient, and because glaucoma patients tend to be more isolated, making them less aware of what the appropriate price of an eye drop should be.

Many providers also are not aware that each pharmacy sets its own price for an eye drop irrespective of the price charged by the manufacturer. It can therefore be an individual pharmacy rather than a generic manufacturer that is gouging patients. In addition, a pharmacy benefit manager can set a copayment higher than the cash cost of a drug, meaning that insured patients in some situations would pay less for a medication if they used cash—particularly for generics.⁷

Another factor is e-prescribing. When practices send prescriptions directly to the requested pharmacy, it is harder for patients to shop around, thus limiting competition and market efficiency.

Depending on a patient's financial situation, combining all glaucoma medications in a single bottle might save him or her a significant amount of money. The website goodrx.com lists cash prices for latanoprost ranging from \$19 to \$84, \$10 to \$15 for brimonidine, and \$20 to \$42 for timolol-dorzolamide, resulting in a maximum out-of-pocket cost between \$49 and \$141. The cost listed currently for a quadruple-therapy from Ocular Science is \$40. Imprimis lists, for a 2-month supply, \$78 for preservative-free latanoprost and \$158 for the preservative-free four-agent drop. Both companies include direct shipping to patients in their pricing.

IN THE NEWS

On September 7, 2017, Allergan issued a press release regarding lawsuits that Allergan USA has filed against Imprimis Pharmaceuticals, Prescriber's Choice, and Sincerus Florida. Allergan USA alleges that those companies are unlawfully manufacturing and selling unapproved new drugs and violating the Lanham Act and state law by engaging in false and misleading advertising and promotion of their unapproved new drugs. The suits have been filed in the US District Court for the Central District of California.

Commenting on the lawsuits, the company issued the following statement:

"Biopharmaceutical companies like Allergan have a duty to put the safety of their patients first. This commitment is the cornerstone of our manufacturing, marketing and advertising of our FDA-approved products. Today, we have brought suit against companies that we believe stand in stark contrast to that commitment. Imprimis Pharmaceuticals, Inc., Prescriber's Choice, Inc., and Sincerus Florida, LLC do not follow the established compounding regulations, engage in false and misleading advertising, and ultimately, put patients and physicians at risk by selling unapproved new drugs."

On September 11, 2017, Imprimis responded to Allergan's press release. A portion of the statement reads, "Imprimis will aggressively defend itself against Allergan's frivolous lawsuit and will take action against Allergan to protect its good name, never yielding to Allergan's tactics to limit patient choice and drive up the cost of ophthalmic therapies to Americans. Allergan, one of the most powerful Big Pharma companies in the world, has filed this lawsuit against one of the smallest pharmaceutical companies in the world, to snuff out any competition to its high drug price strategies. Allergan, a true Goliath, is bent on ensuring that Americans continue to pay the highest possible prices for its drugs."

—Gillian McDermott, Editor-in-Chief





“Combining all glaucoma medications in a single bottle might save [a patient] a significant amount of money.”

SAFETY

Although topically delivered compounded therapies have not been associated with adverse outcomes, recently, 12 patients developed endophthalmitis after an intravitreal injection of compounded bevacizumab,⁸ and many others developed devastating adverse events after compounded intraocular injections following cataract extraction.⁹ These events are worrisome, but a study of almost 400,000 intravitreal injections did not find a difference in endophthalmitis rates between compounded and commercially available injections.¹⁰ More importantly, infection risks for topical glaucoma therapy are orders of magnitude lower than for intravitreal injections and intracameral injections following cataract extraction.

What steps are being taken to ensure the safety and quality of compounded drugs? Sterile compounding regulations are set forth by United States Pharmacopeia (USP) General Chapter <797> that can be adopted wholly by the state or supplemented with additional regulatory guidelines.¹¹ Compounding pharmacies are divided into two sectors for regulation: 503A and 503B. Any prescription from a 503A pharmacy is patient specific and written as a custom order from the prescriber. Testing is performed by a qualified analytics laboratory for initial formula potency (ie, drug concentration), sterility, and the presence of endotoxin in accordance with the sterility testing regulations of USP <71> and based upon the volume of the formula. A 503A pharmacy can gain accreditation through independent agencies that perform in-depth inspections at the facility to verify compliance with USP <797> standards. The Accreditation Commission for Health Care is a primary accreditation agency that encompasses the Pharmacy Compounding Accreditation Board, which ensures that an organization has demonstrated compliance with the highest industry standards. A pharmacy can be searched for accreditation at www.achc.org/compounding-pharmacy.html.

Also known as outsourcing facilities, 503B facilities are FDA-registered operations that must adhere to strict current good manufacturing practice guidelines. These regulations are enforced by the FDA and ensure correct design, monitoring, and control of manufacturing processes and facilities. A 503B designation allows the pharmacy to produce on a larger scale than 503A facilities, so 503B facilities are not required to dispense patient-specific medication and can take orders in sufficient quantity for office use.

Although only 503B pharmacies are required to undergo FDA inspection, 503A pharmacies are also commonly subject to discretionary FDA inspections and evaluations. Imprimis has both 503A and 503B facilities, whereas Ocular Science uses Pinnacle Compounding Pharmacy, a 503A facility.

CONCLUSION

Price gouging and high copayments, complex dosing regimens, and the poor tolerability of multiple-agent therapy have created a need for a simpler and more direct way to treat glaucoma. Compounded multiple-molecule therapies offer a potential solution to these problems, but more data are required to guide clinical care. ■

1. Pisella PJ, Pouliquen P, Baudouin C. Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. *Br J Ophthalmol*. 2002;86(4):418-423.
2. Wilson WS, Duncan AJ, Jay JL. Effect of benzalkonium chloride on the stability of the precorneal tear film in rabbit and man. *Br J Ophthalmol*. 1975;59(11):667-669.
3. Robin AL, Novack GD, Covert DW, Crockett RS, Marcic TS. Adherence in glaucoma: objective measurements of once-daily and adjunctive medication use. *Am J Ophthalmol*. 2007;144(4):533-540.
4. Robin AL, Covert D. Does adjunctive glaucoma therapy affect adherence to the initial primary therapy? *Ophthalmology*. 2005;112(5):863-868.
5. Higginbotham EJ, Hansen J, Davis EJ, et al. Glaucoma medication persistence with a fixed combination versus multiple bottles. *Curr Med Res Opin*. 2009;25(10):2543-2547.
6. Thomas K. 20 states accuse generic drug companies of price fixing. <http://nyti.ms/2vG7PzD>. Published December 15, 2016. Accessed August 30, 2017.
7. Appleby J. Filling a prescription? You might be better off paying cash. <http://cnn.it/28QjZD>. June 23, 2016. Accessed August 30, 2017.
8. Goldberg RA, Flynn HW Jr, Isom RF, et al. An outbreak of Streptococcus endophthalmitis after intravitreal injection of bevacizumab. *Am J Ophthalmol*. 2012;153(2):204-208.
9. Ballor C. Patients lose vision after routine cataract surgeries at Dallas Key-Whitman center. Dallas News. <http://bit.ly/2h13XXn>. Published April 28, 2017. Accessed September 12, 2017.
10. VanderBeek BL, Bonaffini SG, Ma L. Association of compounded bevacizumab with postinjection endophthalmitis. *JAMA Ophthalmol*. 2015;133(10):1159-1164.
11. Sterile compounding <797>. USP website. <http://d8www.usp.org/compounding/general-chapter-797>. Accessed August 29, 2017.

Nathan Radcliffe, MD

- associate clinical attending, Mount Sinai School of Medicine
- (212) 966-3901; dradcliffe@gmail.com; www.drdradcliffe.com;
- Twitter @n8radcliffe
- financial disclosure: consultant to Ocular Science

Lauren Seo

- medical student, NYU School of Medicine, New York
- lauren.seo@med.nyu.edu
- financial interest: none acknowledged