

# Practical Considerations for Topical Ocular Hypotensive Agents

Understanding the differences between these medications may improve patients' satisfaction, their compliance, and clinic flow and minimize adverse effects.

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*This month's installment of "Residents and Fellows" is brought to us by members of the Duke University Glaucoma Service. Dr. Chak and colleagues break down the basics of glaucoma medications—mechanism of action, indications, and side effects. Being knowledgeable about the differences between these medications can improve patients' satisfaction, their compliance, and clinic flow while minimizing adverse effects. We hope you enjoy this submission and look forward to any suggestions for future topics.*

*—Sumit "Sam" Garg, MD, section editor*

**H**aving detailed knowledge of the topical medications available for IOP reduction is key as physicians strive to provide patient-centered care. Appreciating the clinical profile of each drug may enhance patients' satisfaction and compliance as well as clinic flow, because IOP-lowering drops are frequently prescribed in an ophthalmologic office. Varying prescription coverage plans, IOP goals, patient tolerance, ocular surface disease, and preexisting medical comorbidities must all be considered.

For instance, if a patient had effective IOP control with latanoprost monotherapy but has symptomatic ocular surface disease from high cumulative benzalkonium chloride (BAK) exposure, what alternative therapies without BAK are available for this patient? In another scenario, what is the difference between the following timolol-based medications: Timoptic (Aton Pharma), Timoptic-XE (Aton Pharma), Istalol (Ista Pharmaceuticals), and Betimol (Vistakon Pharmaceuticals)?

## **QUICK REFERENCE**

A quick reference chart summarizing the cost, efficacy, and tolerability of drops is provided in the Table, stratified by class of agent.<sup>1-16</sup>

## **Hypotensive Lipids**

Hypotensive lipids, commonly referred to as prostaglandin analogues, are known for their effective IOP reduction, convenient every night dosing (apart from Rescula [Novartis Ophthalmics], dosed twice daily), flat diurnal IOP curves, and very low tachyphylaxis rates. Put simply, these compounds are derivatives of prostaglandin F<sub>2α</sub> and thus bind to the prostaglandin F receptor (FP), initiating a molecular transduction cascade that alters matrix metalloproteinase (MMP) expression. MMPs remodel the extracellular matrix in the ciliary muscle and sclera, leading to increased uveoscleral outflow as well as trabecular meshwork outflow. The lipophilicity of these molecules helps them penetrate the corneal epithelium.

Because FP receptors are also present in the muscular walls of blood vessels, patients may develop conjunctival hyperemia from vascular dilatation. Additionally, these medications bind adjacent prostaglandin E receptor sites (EP1), producing inflammatory byproducts that further contribute to conjunctival hyperemia. Given their proinflammatory properties, there is some concern that these drugs may exacerbate uveitis or macular edema.<sup>17</sup>

**TABLE. QUICK REFERENCE CHART FOR IOP-LOWERING DROPS**

| Name, US only (manufacturer)               | % IOP reduction | Generic/brand               | AWP cost (mL)                              |
|--|-----------------|-----------------------------|--|
| Lumigan 0.01% (Allergan)                   | 28-33           | Brand                       | 268.86 (5 mL)                              |
| Lumigan 0.03%                              |                 | Discontinued                |  |
| Travoprost 0.004%                          | 29-31           | Generic                     | 127.50 (2.5 mL)                            |
| Travatan Z 0.004% (Alcon)                  |                 | Brand                       | 104.05 (2.5 mL)                            |
| Latanoprost 0.005%                         | 28-35           | Generic                     | 88.30 (2.5 mL)                             |
| Xalatan 0.005% (Pfizer)                    |                 | Brand                       | 142.90 (2.5 mL)                            |
| Zioptan 0.0015% (Akorn)                    | 27-31           | Brand                       | 124.55 (30)                                |
| Rescula (unoprostone) 0.15% (Sucampo)      | 14-15           | Brand                       | 129.49 (5 mL)                              |
|  |                 |                             |  |
| Timolol maleate gtt 0.25%, 0.5%            | 26-27           | Generic                     | 27.75 (10 mL), 32.35 (10 mL)               |
| Timoptic (maleate) 0.25%, 0.5% (Aton)      |                 | Brand                       | 142.22 (5 mL), 153.9 (5 mL)                |
| Istalol (maleate) 0.5% (Bausch + Lomb)     |                 | Brand                       | 137.02 (2.5 mL)                            |
| Betimol (hemihydrate) 0.25%, 0.5% (Akorn)  |                 | Brand                       | 73.26 (5 mL), 167.84 (10 mL)               |
| Timolol maleate GFS 0.25%, 0.5%            |                 | Generic                     | 124.79 (5 mL), 136.79 (5 mL)               |
| Timoptic-XE maleate gel 0.25%, 0.5% (Aton) |                 | Brand                       | 166.39 (5 mL), 182.33 (5 mL)               |
| Timoptic in OcuDose 0.25%, 0.5% (Valeant)  |                 | Brand                       | 341.81 (60), 389.77 (60)                   |
| Betagan (levobunolol) 0.5% (Allergan)      |                 | Brand                       | 105.98 (10 mL)                             |
| Levobunolol HCl 0.25%, 0.5%                |                 | Generic                     | 14.06 (5 mL), 47.01 (10 mL)                |
| Ocupress (carteolol) 1%                    |                 | Discontinued                |  |
| Optipranolol (metipranolol) 0.3%           |                 | Discontinued                |  |
| Betoptic-S (betaxolol) 0.25% (Alcon)       |                 | Brand                       | 224.16 (10 mL)                             |
| Betaxolol 0.5%                             | 20-23           | Generic                     | 63.41 (5 mL)                               |
|  |                 |                             |  |
| Alphagan P 0.1%, 0.15% (Allergan)          | 18-25           | Brand                       | 218.33 (10 mL), 239.80 (10 mL)             |
| Brimonidine tartrate 0.15%, 0.2%           |                 | Generic                     | 211.83 (10 mL), 32.60 (5 mL)               |
| lopidine 0.5%, 1% (Alcon)                  |                 | Brand                       | 145.68 (5 mL), 24.21 (0.1 mL)              |
| Apraclonidine HCl 0.5%                     |                 | Generic                     | 86.77 (5 mL)                               |
|  |                 |                             |  |
| Azopt (brinzolamide) 1% (Alcon)            | 17-23           | Brand                       | 186.42 (10 mL)                             |
| Trusopt 2% (Merck)                         | 17-22           | Brand                       | 92.04 (10 mL)                              |
| Dorzolamide 2%                             |                 | Generic                     | 66.75 (10 mL)                              |
| Trusopt 2% PF                              |                 | Not yet available in the US |  |
|  |                 |                             |  |
| Combigan 0.2-0.5% (Allergan)               | 28              | Brand                       | 120.38 (5 mL)                              |
| Cosopt 2%-0.5% (Akorn)                     |                 | Brand                       | 168.89 (10 mL)                             |
| Cosopt PF (Akorn)                          |                 | Brand                       | 102.72 (60)                                |
| Dorzolamide HCl-timolol maleate            | 30              | Generic                     | 122.49 (10 mL)                             |
| Simbrinza 1-0.2% (Alcon)                   | 21-35           | Brand                       | 111.48 (8 mL)                              |
| Travoprost and timolol                     |                 | Not yet available in the US |  |
|  |                 |                             |  |
| Pilopine HS gel 4% (Alcon)                 |                 | Brand                       | 109.50 (4 g)                               |
| Isopto carpine 1%, 2%, 4% (Alcon)          |                 | Brand                       | 89.28 (15 mL), 91.32 (15 mL), 95.7 (15 mL) |
| Pilocarpine HCl 1%, 2%, 4%                 |                 | Generic                     | 93 (15 mL), 95.13 (15 mL), 99.69 (15 mL)   |

Abbreviations: AWP, average wholesale price; BAK, benzalkonium chloride; BDB, benzododecinium bromide; SOC, stabilized oxylchloro complex.

| Preservative                 | Tolerability |
|------------------------------|--------------|
| BAK 0.02%                    | +++          |
| BAK 0.005%                   | +++          |
| BAK 0.15                     | +++          |
| SofZia ionic buffered system | ++++         |
| BAK 0.02                     | +++          |
| BAK 0.02                     | +++          |
| Preservative free            | ++++         |
| BAK 0.015%                   |              |
|                              |              |
| BAK 0.01%                    | +++          |
| BAK 0.01%                    | +++          |
| BAK 0.005%                   | +++          |
| BAK 0.01%                    | +++          |
| BDB 0.012%                   | +++          |
| BDB 0.012%                   | +++          |
| Preservative free            | ++++         |
| BAK 0.004%                   | +++          |
| BAK 0.004%                   | +++          |
| BAK 0.005%                   | +++          |
| BAK 0.004%                   | +++          |
| BAK 0.01%                    | +++          |
| BAK 0.01%                    | +++          |
|                              |              |
| Purite 0.005% (SOC)          | +++          |
| Polyquad 0.001%; BAK 0.005%  | ++           |
| BAK 0.01%                    | +            |
| BAK 0.01%                    | +            |
|                              |              |
| BAK 0.01%                    | +++          |
| BAK 0.0075%                  | ++           |
| BAK 0.0075%                  | ++           |
|                              |              |
|                              |              |
| BAK 0.005%                   | ++           |
| BAK 0.0075%                  | ++           |
| Preservative free            | +++          |
| BAK 0.0075%                  | ++           |
| BAK 0.003%                   | ++           |
|                              |              |
|                              |              |
| BAK 0.008%                   | +            |
| BAK 0.01%                    | +            |
| BAK 0.01%                    | +            |

Ideally, an IOP-lowering drop binds prostaglandin FP receptors with a high affinity and EP1 with a low affinity. The agents currently available stratify as follows:

- FP receptor affinity: travaprost > bimatoprost > latanoprost > unoprostone<sup>18</sup>
- EP1 receptor affinity: bimatoprost > latanoprost > travaprost > unoprostone<sup>18</sup>

With a working understanding of the pharmacology as well as the drug features listed in the table, the clinician can select the hypotensive lipid that is most appropriate for a patient.

### $\beta$ -Blockers

$\beta$ -blockers suppress aqueous production by inhibiting cyclic adenosine monophosphate or cAMP production in the ciliary epithelium via a G-protein coupled receptor. The agents are thus most effective in a setting of high sympathetic tone.

$\beta$ -blockers have been prescribed since the 1970s and because they were generally well tolerated (with notable exceptions described later), they were long considered first-line glaucoma therapy. There is considerable variability in the metabolism and efficacy of this class of drugs within the population. Timolol, for instance, is metabolized by the cytochrome P450 2D6 enzyme, or CYP2D6, and phenotypic variability of this enzyme due to genetic polymorphism produces variable responses.

Moreover, topical  $\beta$ -blockers can have significant side effects upon systemic absorption. Specifically, there is a risk of bronchospasm in patients with asthma or chronic obstructive pulmonary disease, adverse cardiac effects in patients with bradycardia or history of second- or third-degree heart block, negative effects on lipid profiles (raising triglycerides and lowering high-density lipoprotein cholesterol), and exacerbation of myasthenia gravis.

Unintended ocular effects of topical  $\beta$ -blockers may include tachyphylaxis as well as a crossover IOP-lowering effect on the fellow eye (problematic if the fellow eye is hypotonous). Tachyphylaxis is defined as a decreased response to a drug due to compensatory receptor upregulation of the agonist. This may occur anytime from days to 1 year after the initiation of therapy. If tachyphylaxis is suspected, the clinician may place the patient on a  $\beta$ -blocker holiday and recheck the IOP in 2 to 4 weeks to discern if reduced IOP control is due to a decreased drug response or the progression of disease. Patients on concurrent systemic  $\beta$ -blocker

therapy have also been found to have reduced IOP-lowering effect with topical timolol (by a mean of 25%),<sup>19</sup> likely due to drug tolerance.

Pharmacologic strategies to circumvent the issue of systemic absorption have included (1) lowering drug concentration (eg, timolol 0.25%); (2) creating a selective  $\beta$ -blocker, betaxolol, which is safe for patients with coexistent glaucoma and pulmonary disease, though less effective in IOP reduction than timolol or levobunolol<sup>20</sup>; (3) selecting a  $\beta$ -blocker with intrinsic sympathomimetic activity, carteolol, which exerts less effect on both cardiovascular function and lipid profiles than other nonselective  $\beta$ -blockers; and (4) creative drug formulations that improve ocular bioavailability and decrease systemic absorption. The gel vehicle versions Timoptic-XE and Timoptic-GFS decrease plasma concentration compared to timolol solutions and avoid BAK by using benzododecinium bromide 0.012% (another quaternary ammonium compound) as the preservative.

Istalol, formulated with potassium sorbate to enhance ocular bioavailability and halve the BAK concentration found in timolol maleate, is as effective as Timoptic. Betimol (timolol hemihydrate) replaces the maleate salt buffer with phosphate buffer for increased tolerability; in a multicenter trial, Betimol was as effective as Timoptic in controlling IOP.<sup>21</sup> Levobunolol contains a viscosity agent to create a longer-lasting medication with similar potency and side effect profile but without the problem of corneal anesthesia. It may be an alternative  $\beta$ -blocker for those with a timolol allergy.<sup>20</sup>

### $\alpha$ -Adrenergic Agonists

Two main medications exist in this class: brimonidine and apraclonidine. Activation of presynaptic  $\alpha_2$  receptors inhibits norepinephrine release at presynaptic terminals, and with decreased norepinephrine available for postsynaptic  $\beta$  receptors on the ciliary epithelium, aqueous production is decreased.  $\alpha_2$  agonists (specifically brimonidine 0.15% twice daily, both eyes) have also been found to increase uveoscleral outflow and produce a vasomodulatory effect on normal-tension glaucoma patients with retinal vascular dysregulation by normalizing autoregulation.<sup>22</sup>

Less selective, apraclonidine has a much greater affinity for  $\alpha_1$  receptors; therefore, it is more likely to produce vasoconstriction, pupillary dilation, and lid retraction. Although apraclonidine lowers IOP effectively, one-third of patients are afflicted with

follicular conjunctivitis, contact blepharitis-dermatitis, and tachyphylaxis. Brimonidine has significantly fewer adverse effects given its selective profile for  $\alpha_2$  receptors (30 times more selective than apraclonidine).<sup>20</sup> Purite and polyquad formulations were designed to reduce topical irritation while enhancing penetration of the drug through the cornea.<sup>20</sup> The clinician should be aware that brimonidine has been shown to have a crossover effect on the untreated eye.<sup>19</sup>

All  $\alpha_2$  agonists can cause central nervous system depression if they cross the blood-brain. As such, they are contraindicated in children aged 2 years and under and should be used with caution in children up to 10 years of age. It is also imperative that one ask if patients use monoamine oxidase inhibitors or tricyclic depressants, as  $\alpha_2$  agonists place such patients at risk for hypertensive and hyperthermic crises.

### Carbonic Anhydrase Inhibitors

Again, there are two main topical medications in this class: brinzolamide and dorzolamide. Both topical carbonic anhydrase inhibitors (CAIs) selectively inhibit carbonic anhydrase isoenzymes (CA-II >> CA-IV >> CA-I); for instance, dorzolamide inhibits CA-II:CA-IV at a ratio of 38:1.23 CA-II is located in secretory ciliary epithelial cells, and CAIs suppress aqueous humor secretion to lower IOP. One of the benefits of CAIs is their efficacy across a 24-hour period, including at night when sympathetic tone is low.

Brinzolamide has been shown to have a four-fold higher affinity for CA-II than dorzolamide, but clinically, both drops lower IOP effectively.<sup>23</sup> Because Azopt (brinzolamide; Alcon) is more comfortable than Trusopt (dorzolamide; Merck) for most patients given that the former has a pH of 7.5 whereas the latter has a pH of 5.6, Azopt is preferable when it comes to pediatric patients and anyone else for whom ocular discomfort reduces compliance.<sup>24</sup> All CAIs should generally be avoided in sulfallergic patients.

### PROS AND CONS OF BAK

The preservative BAK protects drops against contamination from microorganisms and prevents decomposition of drugs at recommended storage temperatures. Although it also enhances the ocular penetration of a drug by breaking cell-cell junctions in the corneal epithelium, BAK has been shown to produce dose-response cytotoxicity

affecting conjunctival and corneal cell survival. The preservative is known to induce necrosis at 0.05% to 0.1% concentration, to cause apoptosis at 0.01% concentration, and even to arrest cellular growth at just 0.0001% (the lowest concentration among BAK-preserved drops is 0.004%) by altering cell membranes and lysing cytoplasmic structures.<sup>25</sup> Because the effect of the preservative is nonselective, human ocular surface cells can also absorb this detergent. Patients who have long-term topical administration of BAK may manifest with an unstable tear film from goblet cell loss,<sup>26</sup> dry eye disease, chronic conjunctival inflammation, and even corneal endothelial cell loss.<sup>27</sup> In animal studies, BAK has been found to cause neurotoxicity to the mouse cornea on *in vivo* imaging,<sup>28</sup> and it may induce apoptosis of trabeculocytes in rabbit studies.<sup>29</sup> Physicians are well served to continue looking for alternative preservatives to minimize toxicity in long-term drop users.

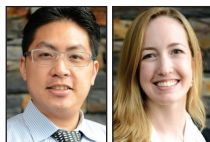
## STORAGE

Storage of IOP-reducing eye drops can be subdivided into opened versus unopened. With the exception of those that are recommended to be refrigerated until opened (latanoprost, Xalatan, and Zioptan) and then used within 4 weeks (Zioptan) or 6 weeks (latanoprost), all other IOP-lowering drops can be stored at room temperature whether opened or unopened. The drugs should generally be kept away from direct heat, moisture (eg, do not store in the bathroom), and sunlight/ultraviolet light exposure if possible. When unopened, Cosopt PF (Akorn Pharma) and Timoptic Ocusol (Valeant) should be stored in their protective foil packaging and should be used within 15 days and 30 days, respectively, after the foil is opened.

## CONCLUSION

There is a wide array of topical ocular hypotensive agents to choose from in the United States. Keeping in mind the patient's needs, his or her means, and the clinical target will guide the clinician in choosing what is most appropriate for any patient. ■

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