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# Update on Prostaglandin-Related Drugs in Glaucoma Management

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## ABSTRACT

Prostaglandin-related drugs include latanoprost, unoprostone, travoprost, and bimatoprost. In addition, a fixed combination of latanoprost and timolol has recently been introduced. This article reviews the development of prostaglandin-related drugs and presents an evidence-based discussion of each drug in this class, and the clinical use of these drugs including side effects, additivity, and patient compliance issues.

## INTRODUCTION

Prostaglandin-related drugs are now used as first-line agents for the treatment of glaucoma. There are several commercially available prostaglandin-related drugs in the United States, including latanoprost, unoprostone, travoprost, and bimatoprost. Unoprostone is not marketed in Canada, although a fixed combination of latanoprost and timolol is available. Other fixed combinations of prostaglandins and beta blockers are being evaluated for clinical approval. This review will describe various available prostaglandin-related drugs, their clinical use, side effects, and additivity.

## DEVELOPMENT OF PROSTAGLANDIN-RELATED DRUGS

Prostaglandins are 20-carbon chain products of arachidonic acid, a polyunsaturated fatty acid, which is bound to phospholipids in the membrane of most mammalian cells.<sup>1</sup> Early animal studies on the ocular effects of prostaglandins demonstrated that these drugs may affect intraocular pressure (IOP). Camras and co-workers showed that the dose of prostaglandin is an important factor. High doses of PGF<sub>2</sub>α applied topically to rabbit eyes have an initial hypertensive effect lasting approximately one hour, whereas lower doses of PGF<sub>2</sub>α reduce IOP by up to 7 mm Hg with the effect lasting for as long as 20 hours.<sup>2</sup>

Study of the effects on aqueous humor dynamics demonstrated that the primary ocular hypotensive mechanism of action seen in prostaglandins is an increase in uveoscleral outflow.<sup>3</sup> Kaufman and Nilsson with their respective co-workers identified IOP lowering by an increase of uveoscleral outflow. Both investigators identified this mechanism in monkeys treated with PGF<sub>2</sub>α-IE and PGF<sub>2</sub>α tromethamine salt.<sup>3,4</sup> Toris and co-workers later used fluorophotometric techniques to confirm uveoscleral outflow as the mechanism in humans.<sup>5</sup>

## PROSTAGLANDIN-RELATED DRUGS

Prostaglandin-related drugs include the following: latanoprost, unoprostone, travoprost, and bimatoprost. Latanoprost is also available in fixed combination with timolol. The clinically available prostaglandin-related drugs are shown in Table I.

### Latanoprost

Latanoprost acts to lower IOP by increasing uveoscleral outflow. Early American and Scandinavian studies compared the efficacy and side effects of latanoprost given once a day with timolol 0.5% given twice a day for 6 months in patients with ocular hypertension or glaucoma. Latanoprost was significantly more effective than timolol in lowering IOP, with a reduction in IOP of 25% to 30% in the U.S. study (Fig. 1).<sup>6</sup> In the Scandinavian study, Alm and Sternschantz not only found that latanoprost was more effective in lowering IOP than timolol, but also that latanoprost was more effective when administered in the evening compared with in the morning.<sup>7</sup>

Latanoprost administered once a day demonstrates effective diurnal pressure control, reducing the peak IOP and amplitude of IOP fluctuation. Latanoprost effectively increases uveoscleral outflow during the day and during the evening.<sup>8</sup> In contrast, beta blockers suppress aqueous production during the day but are less effective during the evening.<sup>9</sup>

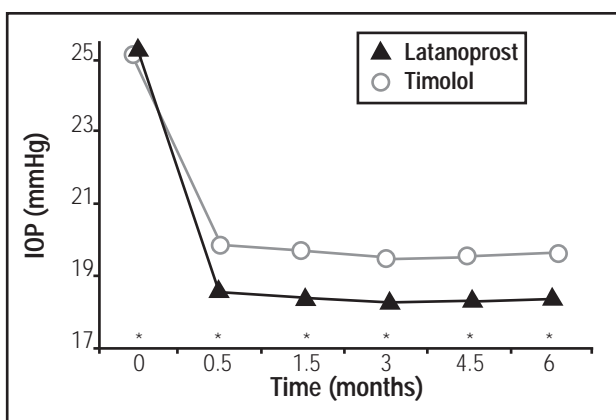
Side effects of latanoprost demonstrated in both the U.S. and Scandinavian studies included burning, stinging, blurred vision, itching, foreign body sensation, tearing, and eye pain.<sup>6,7</sup> Latanoprost caused more conjunctival hyperemia than timolol, as well as an increase in iris pigmentation in 1% to 9% of patients in the multicenter

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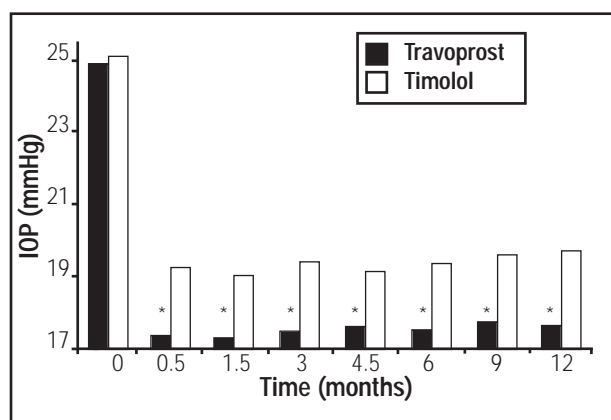
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Table I Prostaglandin-related drugs			
Prostaglandin Monotherapy Drugs			
Drug	Brand Name	Concentration	Dosing
Latanoprost	Xalatan	0.005%	QHS
Unoprostone *	Rescula	0.15%	BID
Travoprost	Travatan	0.004%	QHS
Bimatoprost	Lumigan	0.03%	QHS
Prostaglandin-Containing Fixed Combinations			
Fixed Combinations	Brand Name	Concentration	Dosing
Latanoprost-Timolol †	Xalacom	0.005%/0.5%	QHS
Travoprost-Timolol ‡	Extravan	0.004%/0.5%	QHS
Bimatoprost-Timolol ‡	Ganfort	0.03%/0.5%	QHS
* Not available in Canada			
† Not available in U.S.			
‡ Currently in clinical trials			



**Fig. 1** Comparison of effects on IOP (measured at 8:00 to 9:00 am) of latanoprost 0.005% given once daily and timolol 0.5% given twice daily for 3 to 6 months to patients with elevated IOP. Asterisks denote a significant ( $P < 0.001$ ) further reduction of IOP produced by latanoprost compared with timolol. (Adapted with permission from: Camras CB. Comparison of latanoprost and timolol in patients with ocular hypertension and glaucoma: a six-month, masked, multicenter trial in the United States. *Ophthalmology* 1996; 103: 138-174.)



**Fig. 2** Mean IOP at 10 am after administration of travoprost and timolol. The intraocular pressure was significantly lower after travoprost compared with timolol at each visit and at all time points. Asterisks indicate statistically significant differences between the timolol and travoprost groups. (Adapted with permission from: Netland P, Landry T, Sullivan E, et al. Travoprost compared with latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. *Am J Ophthalmol* 2001; 132: 472-484.)

trials. Increased iris pigmentation was seen most commonly in hazel or greenish brown irides and appears to be due to stimulation of melanin synthesis within iridial melanocytes, rather than an increase in the number of melanocytes.<sup>10</sup> The other significant side effect of latanoprost reported in clinical trials is hypertrichosis of the eyelashes.<sup>11</sup> Iris pigmentation and hypertrichosis may be more noticeable in patients treated with latanoprost in one eye.

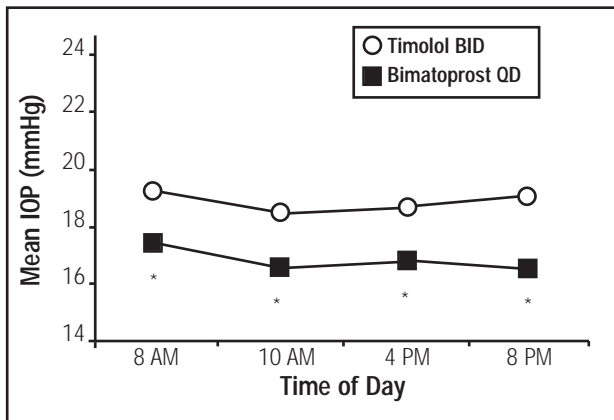
### Unoprostone

Unoprostone is a 22-carbon synthetic docosanoid prostaglandin analog that increases uveoscleral outflow.

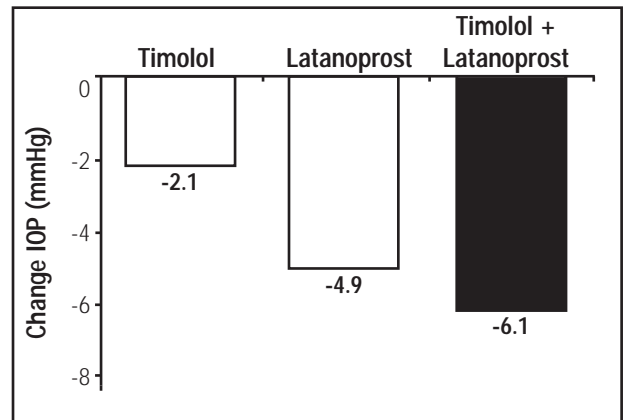
It is bound to the FP receptor; however, it does not have as high an affinity as other PG agonists.<sup>12</sup> The ocular hypotensive effect is relatively weak in comparison to other PG analogs as it lowers IOP by only 15% to 20%.<sup>13,14</sup> Unoprostone is administered twice a day.

Aung and co-workers compared the additive effect of unoprostone on patients already receiving latanoprost and found that there was no additional decrease in IOP.<sup>15</sup> In their patients pretreated with unoprostone who then received latanoprost as adjunctive therapy, however, they demonstrated an additional IOP lowering of 1.9 mm Hg.

Day and co-workers demonstrated no statistical difference in the reduction of IOP from baseline when



**Fig. 3** Diurnal mean intraocular pressure at month 6 after treatment with timolol and bimatoprost. The differences between timolol and bimatoprost were statistically significant ( $P < 0.001$ ), demonstrating that IOP reduction is greater after bimatoprost compared with timolol throughout the day. (Adapted with permission from: Brandt JD, VanDenburgh AM, Chen K, et al. Comparison of once- or twice-daily bimatoprost with twice-daily timolol in patients with elevated IOP: a 3-month clinical trial. *Ophthalmology* 2001; 108: 1023-1031.)



**Fig. 4** Fixed combination of latanoprost and timolol compared with individual components. Compared with latanoprost, the fixed combination gave an additional 1.2 mmHg lower IOP ( $P = 0.046$ ). (Adapted with permission from: Diestelhorst M, Almegard B. Comparison of two fixed combinations of latanoprost and timolol in open angle glaucoma. *Graefes Arch Clin Exp Ophthalmol* 1998; 236: 577-581.)

unoprostone in combination with timolol was compared with the fixed combination timolol and dorzolamide.<sup>16</sup> Notably, there was neither a change from baseline nor a difference in conjunctival hyperemia between the two groups as revealed by anterior segment photography.

Unoprostone has an excellent side effect profile. Aung and co-investigators reported the incidence of hyperemia in the latanoprost group was twice that of the unoprostone group, favoring unoprostone as a better-tolerated medication.<sup>17</sup> Unoprostone therapy has been associated with a low incidence of iris pigmentation compared with other prostaglandin-related drugs.<sup>18</sup>

### Travoprost

Travoprost is a pro-drug that is hydrolyzed by esterases in the cornea to the biologically active free acid that lowers IOP.<sup>19</sup> It is administered once daily at night. This drug is a potent F prostaglandin receptor agonist, which has a prolonged duration of action.<sup>20</sup>

In clinical trials, the IOP-lowering effect of travoprost was greater than timolol and equal or greater than that of latanoprost.<sup>21-23</sup> Figure 2 shows the mean IOP lowering effect of travoprost compared to timolol. Clinical trials also showed that travoprost reduced IOP significantly more in African-American patients compared with Caucasian patients.<sup>21,24</sup> Side effects of travoprost were similar to those of latanoprost and included burning, stinging, blurred vision, itching, foreign body sensation, tearing, and eye pain; there was, however, a higher incidence of hyperemia reported with travoprost.<sup>19,21-23</sup>

### Bimatoprost

Bimatoprost is a potent ocular hypotensive drug that reduces IOP by approximately 30%. This drug is significantly more effective than timolol in lowering IOP (Fig. 3).<sup>25</sup> As with travoprost, bimatoprost does seem to produce a higher incidence of hyperemia than with latanoprost.<sup>26</sup> Dosing is once daily.

Bimatoprost is a lipid amide. Prostaglandins are derived from anandamide, which has been found to be a substrate for the cyclooxygenase-2 (COX-2) enzyme, rather than the COX-1 enzyme whose substrate is arachidonic acid, from which the lipid esters are derived.<sup>27</sup> When tested in receptor-binding assays, bimatoprost or its metabolites have been shown to stimulate the FP receptor, which may increase uveoscleral outflow and lower IOP.<sup>12</sup> It is not clear whether or not the drug is a pro-drug that is converted to a free acid.<sup>27-29</sup> Specific prostamide receptors that mediate the ocular hypotensive effect have been postulated.

### COMBINATION PRODUCTS

A combination product of latanoprost and timolol has been approved in Canada as a once-a-day drug. Fixed combinations of timolol and latanoprost have been studied for several years. Diestelhorst compared 0.5% timolol and latanoprost (0.001% or 0.005%) in fixed combination versus timolol twice daily and latanoprost daily, and reported a lower IOP with the 0.005% fixed combination than with the 0.001% combination and with either latanoprost or timolol alone (Fig. 4).<sup>30</sup>

Pfeiffer and co-workers compared the fixed combination of latanoprost and timolol with latanoprost

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and timolol monotherapies in a 6-month double-masked and 6-month open-label study.<sup>31</sup> The percent change from baseline was 12% after the fixed combination, compared with 9% after latanoprost and 5% after timolol ( $P < 0.001$  comparing the fixed combination to either latanoprost or timolol monotherapy). In a similar study, Higginbotham and co-workers found a 14% reduction of IOP compared with baseline after the fixed combination, with 9% and 1% reductions of IOP found after latanoprost or timolol monotherapy.<sup>32</sup> The IOP reduction after treatment with the fixed combination was significantly greater than the change in IOP after treatment with the individual components (timolol and latanoprost).

Diestelhorst and co-workers compared fixed combination 0.005% latanoprost and 0.5% timolol taken once daily with once-daily latanoprost 0.005% and twice-daily 0.5% timolol.<sup>33</sup> The difference in mean within-patient diurnal IOP was 1.1 mm Hg favoring the unfixed combination. The authors concluded that, although the primary efficacy endpoint was not met, the fixed combination was safe and effective and may perhaps be a convenient alternative to three instillations required with the individual components. This could result in improved compliance and lower patient costs.

Fixed combination latanoprost and timolol has also been compared to fixed combination timolol and dorzolamide.<sup>34</sup> The main outcome measure was a difference between treatment groups in the change in mean diurnal IOP from baseline to month 3. The results of the study demonstrated a 1 mm Hg difference in IOP lowering in favor of the fixed combination of latanoprost and timolol.

Latanoprost and timolol fixed combination was found to be similar in efficacy compared with administration of the individual components.<sup>35</sup> The fixed combination of travoprost and timolol produced significantly lower intraocular pressures during the day compared with travoprost or timolol alone.<sup>36,37</sup> However, the fixed combination of travoprost and timolol was similar in ocular hypotensive efficacy compared with the concomitant therapy with travoprost and timolol.<sup>37,38</sup> Although, in clinical trials, the differences of IOP reduction are small in comparisons of prostaglandin and timolol fixed combinations with concomitant administration of the individual components, fixed combinations may be associated with improved compliance associated with use of fewer bottles of medications and perhaps fewer drops per day. Fixed combination products containing travoprost and bimatoprost are currently in clinical trials.

#### CLINICAL USE OF PROSTAGLANDINS

The FDA has approved latanoprost for primary therapy for the treatment of glaucoma and ocular hypertension.

Prostaglandin-related drugs have a potent ocular hypotensive effect. Other issues regarding prostaglandin-related drugs and their clinical use include side effects, additivity and compliance.

It is important to remind patients that their eyes may become red with the use of prostaglandins and that their eyelashes may grow longer. Some patients with unilateral glaucoma may be hesitant to take a medication that will cause any cosmetic asymmetry. Moreover, this reasoning applies to iris pigmentation when counseling a patient with brown/green or hazel eyes.

In addition, in patients with uveitic glaucoma, cystoid macular edema, or a history of ocular herpetic infection, a prostaglandin should be avoided if possible, and discontinued in patients who develop a uveitis or cystoid macular edema when there is no appreciable cause.<sup>39,40</sup>

Although primary monotherapy with a prostaglandin is often effective for IOP reduction, a certain percentage of patients need additional IOP lowering. The hypotensive effects of the prostaglandin-related drugs have been evaluated when used in addition to, or in fixed combination with, other hypotensive agents.

If a patient is on maximally tolerated medical therapy and has an unfavorable reaction to the once-daily prostaglandins, the excellent side effect profile of unoprostone often allows it to be well tolerated. However, its twice-daily dosing may decrease compliance. If a patient is already on a prostaglandin and is tolerating it well, unoprostone does not seem to have any additive effect.<sup>15,17</sup>

Patients who fail to respond to one prostaglandin may benefit from switching to another. Gandolfi and Cimino demonstrated that in 15 patients who did not respond to latanoprost and were switched to bimatoprost, 13 of the 15 patients had at least a 20% decrease in IOP after switching.<sup>26</sup> There was an increase in hyperemia seen in these patients, however, after switching from latanoprost to bimatoprost.

There are no known adverse interactions of prostaglandin-related drugs with other topical glaucoma medications. The different mechanism of action of prostaglandin-related drugs increases their additivity to other IOP-lowering drugs. There is additivity of effect seen with beta-blockers, carbonic anhydrase inhibitors, pilocarpine, adrenergic agents, and alpha-2 agonists.

Timolol suppresses aqueous formation, whereas prostaglandin-related drugs increase uveoscleral outflow. Adding these two medications is a frequent choice among clinicians. Alm and Rulo both demonstrated an additive effect of latanoprost to timolol with an additional 37% and 14% IOP lowering, respectively.<sup>41,42</sup> There is no definite clinical indication for use of a fixed combination of prostaglandin and beta blocker versus the use of these drugs as individual components. Clinical judgment based

on the needs of the individual patient, and compliance issues, should ultimately influence the choice of drug. It is possible that fixed combination products may be more effective in actual clinical practice compared with the clinical trial setting, due to better compliance.<sup>43</sup>

Additivity has also been shown both with oral and topical carbonic anhydrase inhibitors. Patients treated with acetazolamide 250 mg twice daily were started on latanoprost or placebo eye drops.<sup>44</sup> The addition of latanoprost yielded a 15% decrease in IOP, while placebo resulted in an upward drift of 6%.

In order to determine the additivity of topical dorzolamide and latanoprost, Kimal and co-investigators enrolled thirty patients with elevated IOP and randomly assigned them to two treatment groups; one group received latanoprost once daily for ten days (Group 1) and the other, dorzolamide three times daily for 10 days (Group 2).<sup>45</sup> After 10 days, both groups were administered either dorzolamide or latanoprost as additional treatment respectively for an additional 10 days. After 20 days, the IOP was measured and Group 1 showed additional IOP decrease of 15% after adding dorzolamide, while Group 2 demonstrated an additional decrease in IOP of 24.1% after adding latanoprost.

Susanna and co-workers determined the additivity of latanoprost in patients already taking both timolol 0.5% and dorzolamide 2%.<sup>46</sup> Of the 52 patients in the study, 9.6% were discontinued from latanoprost treatment because of side effects. The remaining 47 patients had a decrease in IOP of 16%, with 17 patients (36.3%) showing a mean IOP reduction greater than 20%, demonstrating that a prostaglandin can be effective when administered to patients treated with multiple anti-glaucoma medications.

There is also additivity when combining prostaglandins with brimonidine. In an open-label study, Lee and Gornbein demonstrated that combining brimonidine with latanoprost showed an additional decrease in IOP of 32.2%.<sup>47</sup> In this same study, addition of brimonidine to combination regimens that included latanoprost provided an additional mean decrease in IOP ranging from 15.5% to 20.1%.

Netland and co-workers compared brimonidine-purite in combination with bimatoprost vs. timolol in combination with latanoprost and showed that brimonidine/bimatoprost in combination was at least as effective as timolol/latanoprost in reducing IOP.<sup>48</sup> Stewart and co-investigators showed similar IOP-lowering effects when comparing latanoprost/timolol fixed combination vs. brimonidine/latanoprost therapy.<sup>49</sup>

Pilocarpine acts by increasing trabecular outflow through contraction of the ciliary muscle; however, pilocarpine also reduces uveoscleral outflow. Despite theoretical concerns, clinical trials have shown that

prostaglandin-related drugs are additive to pilocarpine. The decrease in uveoscleral outflow with pilocarpine is not significant when combined with the much greater effect of a prostaglandin on uveoscleral outflow. Moreover, pilocarpine does not block the uveoscleral outflow effect of a prostaglandin. Toris and co-investigators added pilocarpine to latanoprost-treated eyes and, after a washout of three weeks, added latanoprost to pilocarpine.<sup>50,51</sup> Both groups showed a statistically significant decrease in IOP after combining the two medications.

Although used infrequently in clinical practice, epinephrine increases both trabecular outflow and uveoscleral outflow. Hoyng and co-workers have demonstrated additivity of dipivefrin and latanoprost.<sup>52</sup> Latanoprost added to dipivefrin reduced IOP an additional 28% and dipivefrin added to latanoprost lowered IOP by another 15%.

Several studies have compared the various prostaglandin-related drugs with each other. Comparisons with unoprostone and latanoprost demonstrate less IOP-lowering efficacy and fewer side effects with unoprostone.<sup>13,17</sup> Netland and co-workers compared travoprost with latanoprost and timolol and showed travoprost to be equal or superior to latanoprost and superior to timolol in lowering mean IOP.<sup>21</sup> Gandolfini and his team of investigators compared bimatoprost and latanoprost and concluded that bimatoprost lowered mean IOP more than latanoprost at every time point in their study and more patients reached low target pressures.<sup>53</sup> More recently, Noecker and co-workers compared bimatoprost and latanoprost, and also came to the conclusion that bimatoprost is more effective than latanoprost in lowering IOP.<sup>54</sup>

Parrish et al compared latanoprost, bimatoprost and travoprost in a 12-week study of 410 patients receiving one of the above three drugs once daily in the evening.<sup>55</sup> The primary efficacy outcome measure was change from baseline at week 12 at the 8:00 am IOP measurement (the time of peak effect). Also measured was conjunctival hyperemia before the 8:00 am IOP measurement. The study found all three to be comparable in their ability to lower IOP in patients with open-angle glaucoma and ocular hypertension. In addition, latanoprost seemed to show the least amount of hyperemia.

In a study of latanoprost, travoprost, and bimatoprost, all three drugs showed excellent 24-hour control of IOP.<sup>56</sup> In this study, no significant differences were observed among the three drugs, although the statistical power of the study was low. Evening dosing of travoprost was more effective compared with morning dosing, resulting in lower daytime intraocular pressure and a narrower range of diurnal IOP.<sup>57</sup> Bimatoprost showed significantly lower mean 24-hour control of IOP compared with travoprost; however, the differences were small and conjunctival hyperemia was statistically greater with bimatoprost.<sup>58</sup>

The three main prostaglandin-related drugs are all highly effective in lowering IOP. However, conflicting evidence over comparative efficacy exists. This emphasizes the need for continued clinical trials designed to compare these drugs. Clinical trial results must be interpreted based upon the power of the study (sample size), the patient population, and the diurnal time points measured.

Due to compliance, cost, and the side effect profile of the various medical therapies, the patient with glaucoma should be an active participant in deciding the course of therapy. Treatment must be individualized to each patient. In patients using multiple drugs, the fixed combinations may provide improved compliance due to less washout effect, more convenient dosing regimens, and possibly lower cost.

The prostaglandin-related drugs play a critical role in the medical management of glaucoma, although the differences between these drugs are not well established at this time. These drugs, as a group, are currently the most commonly prescribed drugs for medical therapy of glaucoma. Prostaglandins are clearly the most effective topical agents for lowering IOP and can be used successfully in most patients with glaucoma and ocular hypertension, either alone or added to other glaucoma medications. □

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