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REVIEW

# Latanoprost in the treatment of glaucoma



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**Abstract:** Prostaglandins are approved by the European Glaucoma Society guidelines as first-line treatment for glaucoma. This review focuses on latanoprost, an ester prodrug of prostaglandin (PG) $F_{2\alpha}$, which was the first of the currently available topical $PGF_{2\alpha}$ analogs to be launched for glaucoma or ocular hypertension and which still accounts for the majority of prescriptions. It is better absorbed than the parent compound through the cornea, and peak concentration of the active drug is in the aqueous humor 1–2 hours after topical dosing (15–30 ng/mL). Metabolism occurs mainly in the liver. Latanoprost (0.005%) has been very well studied in clinical trials and meta-analyses that show it to be generally as effective as the other PG analogs (bimatoprost, travoprost, and tafluprost) and more effective than timolol, dorzolamide, and brimonidine. Latanoprost has good short- and long-term safety and tolerability profiles. In common with other prostaglandins, it lacks systemic effects, but can cause ocular adverse events such as conjunctival hyperemia, pigmentation of the iris, periocular skin or eyelashes, hypertrichosis, and ocular surface effects or irritation. Latanoprost is significantly better tolerated than either bimatoprost or travoprost. Patients treated with latanoprost have better compliance and persist with therapy longer than those that are given other drugs. An improved formulation of latanoprost without the preservative benzalkonium chloride has recently been developed. It is as effective as conventional latanoprost, has a lower incidence of hyperemia, and can be stored at room temperature. In conclusion, latanoprost has the best efficacy–tolerability ratio of the PG analogs available for glaucoma treatment, and has good compliance and persistence. These factors should be improved further by the recent development of preservative-free latanoprost.

**Keywords:** prostaglandin, intraocular pressure, ocular hypertension, hyperemia, glaucoma, latanoprost

## Introduction

One of the major risk factors for the development and progression of glaucoma is elevated intraocular pressure (IOP).[1,2] Topical prostaglandins (PGs), with their powerful ocular hypotensive effect (which is mainly the result of increasing uveoscleral outflow), are therefore an important treatment option for glaucoma.[3]

PGs/prostamides are approved as the first-line treatment for glaucoma in the European Glaucoma Society guidelines.[4] The main reasons for this choice include their IOP-lowering efficacy, their lack of relevant systemic side effects, their requirement for only once-daily dosing, and their good overall tolerability profile.

This review focuses on the use of latanoprost, an ester prodrug of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), in the management of glaucoma. Latanoprost was the first of the currently available topical $PGF_{2\alpha}$ analogs to be launched for glaucoma treatment, and it

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still accounts for the majority of PG-analog prescriptions due to its good efficacy–tolerability profile. It was also the first PG analog to have generics developed, and an improved formulation has recently been produced without benzalkonium chloride (BAK).

Publications to be considered for inclusion in this review were selected in PubMed using the search terms "latanoprost", "glaucoma/drug therapy*[MeSH]", "meta-analysis[publication type]", "comparative study[publication type]", and "patient compliance[MeSH]". More recent studies that were yet to be indexed were identified from ad hoc searches and the author's own database.

## Prostaglandins

PGs were initially isolated from prostate tissue in 1935.[5] They are now known to be produced by almost all nucleated cells. They are a family of lipid compounds that are derived enzymatically from essential fatty acids,[6] with each one containing 20 carbon atoms, including a 5-carbon ring. They act locally as autocrine or paracrine mediators with a wide range of effects throughout the body.

### Effects of prostaglandins in ophthalmology and development for glaucoma treatment

Several PGs are naturally synthesized in the iris and ciliary body and are released following trauma to the eye.[7] One of the PGs that is released is $PGF_{2\alpha}$, which is now known to cause a powerful reduction in IOP. Animal studies have shown that this hypotensive activity is mainly due to an enhanced uveoscleral outflow, with minor effects on trabecular outflow and aqueous flow.[3] One potential mechanism behind this enhanced outflow is the regulation of matrix metalloproteinases and remodeling of the extracellular matrix, which changes the permeability of tissues associated with the outflow pathways resulting in alterations in outflow resistance and/or outflow rates.[3]

Discovery of the effect of PGs on IOP led to the development of PG analogs as a potential glaucoma treatment. Initial research focused on $PGF_{2\alpha}$. The initial steps included esterification of the carboxylic acid of $PGF_{2\alpha}$ to improve corneal penetration and reduce side effects.[8] One of the most promising of these prodrugs of $PGF_{2\alpha}$ was the isopropyl ester form. However, despite having excellent pharmacokinetic properties, it still caused unacceptable foreign-body sensation and conjunctival hyperemia.[9,10] Modification of the omega chain of this molecule led to improved selectivity for PGF receptors and a greatly improved tolerability profile.[11] This molecule was subsequently known as latanoprost and underwent clinical development as a treatment for glaucoma. Later studies in knock-out mice showed that intact PGF and $PGE_3$ receptors were necessary for IOP reduction.[12,13]

### Latanoprost

Latanoprost (0.005%) was launched in 1996 and was the first of the currently available topical $PGF_{2\alpha}$ analogs on the market for glaucoma treatment. Later introductions included travoprost (0.004%), bimatoprost (0.03%), and, most recently, tafluprost (0.0015%). Latanoprost still accounts for approximately 65% of PG-analog prescriptions.

### Pharmacokinetics

Latanoprost is an esterified prodrug of $PGF_{2\alpha}$ and, as such, is more lipophilic than the parent compound.[11] This means that it is better absorbed through the cornea, where it is undergoes hydrolysis to latanoprost acid. In adult humans, peak concentration of the active drug was detected in the aqueous humor 1–2 hours after topical dosing and amounted to 15–30 ng/mL.[14] In the systemic circulation, the peak concentration occurred after 5 minutes and reached a level of 53 pg/mL. The elimination half-life was 2–3 hours from the eye and 17 minutes from the circulation. The median peak plasma concentration and area under the concentration-time curve after adult dosing were found to be higher in infants less than 3 years old than in older subjects, primarily due to lower body weight and smaller blood volume; but latanoprost acid was rapidly eliminated in all age groups.[15]

Metabolism mainly occurs in the liver where latanoprost acid undergoes beta-oxidation to 1,2-dinor and 1,2,3,4-tetranor latanoprost acid, the main metabolites of latanoprost.[14] The majority of the dose is excreted via the urine (88%) with the remainder being recovered in the feces.

The reduction in IOP seen with latanoprost begins after 3–4 hours, reaches a maximum after 8–12 hours, and is maintained for at least 24 hours.[16]

### Efficacy

Latanoprost has been very well studied, with numerous publications of clinical trials, meta-analyses, and reviews.[17] Initial studies showed once-daily topical latanoprost (0.005%) to be safe and effective in the short- and long-term treatment of glaucoma or ocular hypertension. A review of three masked multicenter Phase III studies in 829 patients with elevated IOP in Scandinavia, the USA, and the UK showed that 6 months treatment with latanoprost reduced IOP by 35%, if given in the evening, and by 31%, if given in the morning.[18] Conjunctival hyperemia and darkening of the

iris color were the only notable side effects. Subsequently, darker and longer eye lashes were also reported.[19] Later open studies conducted over 2 years reported that the reduction in IOP was maintained during long-term treatment and no other clinically significant side effects developed.[20,21] Similarly good results were reported in 5-year studies, although the main focus was on safety and tolerability.[22–24]

## Latanoprost versus other prostaglandins

### Bimatoprost

Latanoprost has been extensively compared with bimatoprost in randomized controlled trials. One of the largest of these involved 411 patients with open-angle glaucoma or ocular hypertension treated for 12 weeks with latanoprost, bimatoprost, or travoprost.[25] At the end of the study, there was a significant ($P<0.001$) reduction in 8 am IOP in all groups. The estimated mean reduction was 8.6±0.3 mmHg with latanoprost and 8.7±0.3 mmHg with bimatoprost. The adjusted differences in mean IOP reductions at 8 am also showed equivalence between latanoprost and bimatoprost (0.13 mmHg; 95% confidence interval [CI] 0.84–0.58). No significant differences were observed between the two treatments in IOP reduction at noon, 4 pm, and 8 pm, or in changes in mean diurnal IOP levels. A subsequent study in 48 patients with open-angle glaucoma also failed to find statistically significant differences between latanoprost and bimatoprost in IOP reductions at 8 am, 10 am, 1 pm, 4 pm, 8 pm, 11 pm, and 3 am after 8 weeks of treatment.[26]

One double-blind, crossover study focused on circadian IOP in 44 patients with open-angle glaucoma or ocular hypertension.[27] After 1 month, latanoprost and bimatoprost were equally effective in reducing IOP, with no significant differences between them, and the authors concluded that they were both powerful agents in controlling around-the-clock IOP. A more recent crossover study assessed IOP reduction in 54 patients with angle-closure glaucoma treated with latanoprost or bimatoprost for 6 weeks.[28] At the end of treatment, mean IOP was reduced by 8.4±3.8 mmHg with latanoprost and 8.9±3.9 mmHg with bimatoprost, with no significant differences between the groups.

Some discrepancies have been reported in other studies, however, with bimatoprost being significantly more effective than latanoprost at certain time points. An older study in 232 patients with glaucoma or ocular hypertension found that bimatoprost reduced IOP significantly more than latanoprost at noon ($P=0.021$), but not at 8 am (primary efficacy parameter), 4 pm, or 8 pm after 3 months of treatment.[29] In another double-blind study, no statistically significant differences in IOP reduction were seen between latanoprost (20%–31%) and bimatoprost (26%–34%) at any time point measured on day 14 or 29 in 64 patients with open-angle glaucoma or ocular hypertension.[30] However, on day 29, bimatoprost had a significantly ($P=0.0378$) larger area under the curve for IOP reduction. Similarly, in a 7-week double-blind crossover study in 44 patients with open-angle glaucoma, bimatoprost was significantly more effective than latanoprost regarding diurnal curve IOP only at 6 pm ($P=0.008$ after Bonferroni correction), but not at 2 am, 6 am, 10 am, 2 pm, or 10 pm.[31] The mean 24 hour IOP was also significantly ($P=0.01$) lower with bimatoprost (16.7±2.4 mmHg) than latanoprost (17.3±2.8 mmHg). Significant between-group differences in mean IOP reduction in favor of bimatoprost were seen at 8 am ($P\leq0.033$), but not at noon or 4 pm, in a 3-month double-blind trial in 60 patients with normal tension glaucoma.[32] In contrast to these findings, a 6-month study involving 269 patients with glaucoma or ocular hypertension showed bimatoprost to be significantly ($P<0.004$) more effective than latanoprost in reducing IOP at all time points measured (8 am, noon, and 4 pm).[33]

Recent studies have evaluated the effects of latanoprost on central corneal thickness, which allows for a more accurate estimate of IOP.[34,35] Central corneal thickness was significantly ($P<0.001$) reduced by latanoprost (−14.95±5.04 µm) and bimatoprost (−17.00±6.23 µm) after a mean follow-up of 17 months in 69 patients with glaucoma or ocular hypertension.[36] The duration of treatment had no effect, with a lack of significant difference being seen in patients treated for ≤6 months as well as those treated for >6 months.

In summary, the considerable amount of data available indicates that latanoprost is equally as effective as bimatoprost. Some studies have shown small advantages for bimatoprost at certain time points, although there appears to be no consistency in these findings. There is some evidence to suggest that bimatoprost is hydrolyzed to its free acid, a potent PG F receptor agonist, in sufficient levels in the aqueous humor to account for at least some of its ability to reduce IOP.[37]

### Travoprost

As with bimatoprost, a considerable number of randomized controlled trials have compared travoprost and latanoprost. In a 12-week trial in 411 patients with open-angle glaucoma or ocular hypertension, the estimated mean reduction in 8 am IOP at the end of treatment was 8.6±0.3 mmHg with latanoprost and 8.0±0.3 mmHg with travoprost.[25] The

adjusted differences in mean 8 am IOP reductions also showed no significant difference between latanoprost and travoprost (0.56 mmHg; 95% CI 0.15–1.26) as did all secondary efficacy parameters. Similarly, a 1-month double-blind crossover study in 44 patients with open-angle glaucoma or ocular hypertension showed no statistically significant difference between latanoprost and travoprost in circadian IOP reduction.[27] A study in 48 patients with open-angle glaucoma reported no significant differences in efficacy on overall diurnal IOP between latanoprost and travoprost (and bimatoprost that was also included in the study), but significantly greater IOP reductions at 8 am and 10 am, but not at 1 pm, 4 pm, 8 pm, 11 pm, and 3 am, after 8 weeks of treatment with travoprost versus latanoprost or bimatoprost.[26] A more recent double-blind study in 302 patients with open-angle glaucoma or ocular hypertension found no statistically significant differences in IOP values after 6 weeks' treatment with travoprost (16.1 mmHg) or latanoprost (16.4 mmHg).[38] The pooled changes in IOP from baseline after 1, 2, 4, and 6 weeks of treatment did, however, show a significant difference in favor of travoprost (−8.3 mmHg versus −7.5 mmHg; $P$=0.009). IOP was measured at 5 pm, 20 hours after drug administration. In 69 patients with glaucoma or ocular hypertension, central corneal thickness was significantly ($P$<0.001) reduced by both latanoprost (−14.95±5.04 µm) and travoprost (−15.73±3.25 µm) after a mean follow-up of 17 months.[36]

The overall results from randomized controlled studies therefore show that latanoprost is as effective as travoprost. Further evidence is available from meta-analyses that will be discussed later in the review.

### Tafluprost

Only two studies have so far been published comparing latanoprost with tafluprost. The first of these was a randomized double-blind Phase II trial comparing latanoprost with tafluprost treatment for 42 days in 38 patients with open-angle glaucoma, exfoliation glaucoma, or ocular hypertension.[39] There was no significant difference between the treatments, with maximum IOP reduction occurring after 7 days and being maintained on day 42 and day 43. A subsequent randomized double-blind Phase III study was considerably larger, enrolling 533 patients with open-angle glaucoma or ocular hypertension.[40] Treatment was given with latanoprost or tafluprost for 24 months. Both treatments substantially reduced IOP, with a 7.7 mmHg decrease with latanoprost and 7.1 mmHg decrease with tafluprost after 24 months. The effect of latanoprost was somewhat larger, but non-inferiority of tafluprost over all diurnal IOP measurements was shown with analysis of variance and almost reached with analysis of covariance (upper limits of the 95% CIs 1.38 and 1.52, respectively). The non-inferiority limit was 1.5 mmHg. In this study, there were 18 discontinuations for lack of efficacy on tafluprost compared with only three on latanoprost.

Overall, the relatively restricted amount of data currently available suggests no clinically significant difference in efficacy between latanoprost and tafluprost, although more studies are required.

### Results of meta-analyses

A number of recent meta-analyses of randomized controlled trials have compared latanoprost with bimatoprost and travoprost in patients with glaucoma or ocular hypertension (Table 1);[41–49] to date, only one meta-analysis has included a comparison with tafluprost (Table 1).[50]

One of the largest of these analyses was performed by Eyawo et al, in 2009,[41] who assessed randomized single- or double-blind head-to-head comparisons of latanoprost, bimatoprost, and travoprost of at least 3 months' duration. Data were included from a total of 15 studies (up to 12 months' duration), five of which had more than two treatment arms. Thus, nine trials compared latanoprost and travoprost (n=1,098), eight compared travoprost and bimatoprost (n=714), and eight compared latanoprost and bimatoprost (n=943). The IOP-lowering effect at study conclusion was expressed by the weighted mean difference across groups. This was −0.24 mmHg (95% CI −0.87–0.38) for travoprost versus latanoprost and 0.73 mmHg (95% CI 0.10–1.37) for latanoprost versus bimatoprost. Response rates were also compared between studies that had similar definitions of response; three trials comparing latanoprost to bimatoprost found a pooled relative risk of 0.98 (95% CI 0.76–1.26, $P$=0.87) and two comparing travoprost to latanoprost found a pooled relative risk of 1.15 (95% CI 0.99–1.33, $P$=0.07). A study specifically designed to identify the nonresponder rate during latanoprost treatment found that only 14 of 340 newly diagnosed patients failed to respond to latanoprost.[51]

Another large analysis was conducted in 2010 and involved 2,943 patients treated with latanoprost, bimatoprost, travoprost, or timolol in 18 studies.[42] A mixed treatment comparison was used to assess the relative efficacy of the treatments in terms of absolute on-treatment IOP at 3 months. Latanoprost and bimatoprost produced significantly ($P$<0.05) lower on-treatment IOP compared with timolol. There was no significant difference between latanoprost and bimatoprost.

**Table 1** Summary of meta-analyses of randomized controlled trials for the effect of latanoprost and other PG analogs on IOP in patients with glaucoma or ocular hypertension

| Study | PG analogs | Other drugs assessed | Studies (n) | Patients (n) | Duration | Primary efficacy variables |
|---|---|---|---|---|---|---|
| Cucherat et al[50] | LAT (BAK-preserved and preservative-free), BIM[f] (BAK-preserved), TRA (preserved with BAK, polyquaternium-1 or sofzia), TAF (BAK-preserved) | None | 21 | Not reported | ≥2 months | Preservative-free LAT significantly more effective than TAF regarding IOP at 3 months. No significant difference between other PG analogs. |
| Orme et al[42] | LAT, BIM, TRA | TIM | 18 | 2,943 | 3 months | No significant difference between LAT and BIM in on-treatment IOP. LAT and BIM significantly more effective than TIM. No significant difference between TRA and TIM. |
| Cheng et al[43] | LAT, BIM, TRA | TIM | 9 | 1,090 | 2 weeks to 3 months | No significant difference in IOP-lowering effect from baseline between LAT, BIM, TRA, and TIM. |
| Cheng et al[44] | LAT, BIM | TIM, DOR, BRIM | 15 | 450 | 3 weeks to 2 months | No significant difference between LAT and BIM in IOP reduction from baseline at peak, trough, and diurnal assessments. |
| Eyawo et al[41] | LAT, BIM, TRA | None | 15 | 2,755 | 3–12 months | No significant differences in IOP-lowering effects at study conclusion between LAT, BIM, and TRA. |
| Aptel et al[45] | LAT, BIM, TRA | None | 8 | 1,610 | 1–6 months | Significantly greater change in IOP with BIM than LAT at 8 am, noon, 4 pm, and 8 pm after 3 months. No significant difference between LAT and TRA. |
| Cheng and Wei[46] | LAT, BIM | None | 13 | 1,302 | 1–6 months | Percentage reduction in morning IOP significantly greater with BIM than LAT at 1, 3, and 6 months. |
| Stewart et al[48] | LAT, BIM, TRA | TIM, DOR, BRIM | 11 | 386 | 1–2 months | No significant differences reported in the publication between LAT, BIM, and TRA in 24-hour IOP efficacy. |
| Denis et al[49] | LAT, BIM, TRA | None | 9 | 1,318 | 2 weeks to 12 months | No significant difference between LAT and BIM or TRA in IOP levels at the end of follow-up. |
| Van der Valk et al[47] | LAT, BIM, TRA | TIM, DOR, BRIM, BET, BRIN | 28 | 6,953 (trough) 6,841 (peak) | 1–6 months | No significant difference between LAT, BIM, and TRA in IOP change from baseline at 1 month. |

**Note:** [f]0.01% and 0.03%.
**Abbreviations:** BAK, benzalkonium chloride; BET, betaxolol; BIM, bimatoprost (0.03%); BRIN, brinzolamide; BRIM, brimonidine; DOR, dorzolamide; IOP, intraocular pressure; LAT, latanoprost (0.005%); PG, prostaglandin; TAF, tafluprost (0.0015%); TIM, timolol; TRA, travoprost (0.004%).

A somewhat smaller analysis in 1,090 patients showed no significant difference in the IOP-lowering effects from baseline of latanoprost, bimatoprost, travoprost, or timolol in studies ranging from 2 weeks to 3 months.[43] The difference in absolute IOP reduction between PG analogs and timolol ranged from 0.4–1.6 mmHg for the diurnal curve, 0.9–2.3 mmHg for the peak, and 1.3–2.4 mmHg for the trough. For latanoprost, the relative IOP reduction was 31% (95% CI 27%–34%) for the diurnal curve, 34% (95% CI 31%–37%) for the peak, and 31% (95% CI 28%–35%) for the trough. The corresponding values were 26% (95% CI 21%–30%), 28% (95% CI 24%–32%), and 27% (95% CI 23%–30%) for bimatoprost and 28% (95% CI 20%–36%), 32% (95% CI 31%–34%), and 31% (95% CI 29%–33%) for travoprost, respectively.

Another analysis by Cheng et al in 450 patients with normal tension glaucoma reported no statistically significant differences between latanoprost and bimatoprost with regard to reductions in IOP at peak, trough, and diurnal assessments (–20% at all assessments with latanoprost versus 21%, 18%, and 17%, respectively, with bimatoprost).[44]

The 24-hour IOP lowering efficacy, determined in one analysis of 386 patients, showed a statistically significant difference between monotherapy treatments with PG analogs, timolol, brimonidine, and dorzolamide ($P$=0.026).[48]

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