# Rank order of IOP medications

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A SYSTEMATIC review published by Li et al[1] in the journal of the American Academy of Ophthalmology included 20,275 participants from 114 randomised controlled trials (RCT). The aim of the RCTs was to determine the effectiveness of single topical medical treatment using four medication classes (excluding miotics) when compared with placebo or another single active topical medical agent.

To be included in this systematic review, at least 60 per cent or more of the participants in each trial needed to be diagnosed with primary open angle glaucoma (POAG) or ocular hypertension (OHT). Studies were excluded if combination treatment or surgical intervention was utilised; there were fewer than 10 participants in each group and/or fewer than 28 days of follow-up after randomisation.

All medical treatments were more effective than placebo in lowering IOP. At three months, the mean reductions in IOP, ranked from the most to the least-effective topical agent, are listed in Table 1.

As shown in Table 2, prostaglandin analogues were more effective in lowering IOP when compared to other drug classes. There was no statistically significant difference in efficacy between the different prostaglandin analogues, including bimatoprost, travoprost, latanoprost or tafluprost.

Levobunolol was more effective when compared to other beta-blockers. The mean difference in IOP between timolol 0.5% or timolol < 0.5% was small and not statistically significant. Interestingly, brimonidine was more effective at lowering IOP than

**Rank order**

1. Bimatoprost 0.03%
2. Latanoprost
3. Travoprost
4. Bimatoprost 0.01%
5. Levobunolol
6. Tafluprost
7. Timolol
8. Brimonidine
9. Carteolol
10. Levobetaxolol
11. Apraclonidine
12. Dorzolamide
13. Brinzolamide
14. Betaxolol
15. Unoprostone

▲ Table 1. Ranking from most-effective to least-effective

| Medication class | Preparations | Mean reduction in IOP (mmHg) at 3 months (95 per cent CI) |
|---|---|---|
| Prostaglandin analogues | Bimatoprost 0.03%<br>Latanoprost 0.005%<br>Travoprost 0.004%<br>Bimatoprost 0.01%<br>Tafluprost 0.0015%<br>Unoprostone 0.15% | 5.77 (5.04 – 6.50)<br>4.85 (4.24 – 5.46)<br>4.83 (4.12 – 5.54)<br>4.74 (1.91 – 3.19)<br>4.37 (2.94 – 5.83)<br>1.91 (1.51 – 2.67) |
| Beta-blocker | Levobunolol 0.25%<br>Timolol 0.25%, 0.5%, 0.1%<br>Carteolol 1%<br>Levobetaxolol 0.5%<br>Betaxolol 0.25%, 0.5% | 4.51 (3.85 – 5.24)<br>3.70 (3.16 – 4.24)<br>3.44 (2.42 – 4.46)<br>2.56 (1.52 – 3.62)<br>2.24 (1.59 – 2.88) |
| Alpha 2 agonist | Brimonidine 0.2%<br>Apraclonidine 0.5% | 3.59 (2.89 – 4.29)<br>2.52 (0.94 – 4.11) |
| Carbonic anhydrase inhibitors | Dorzolamide 2%<br>Brinzolamide 1% | 2.49 (1.85 – 3.13)<br>2.42 (1.62 – 3.23) |

▲ Table 2. Mean reduction (including 95 per cent confidence interval) in IOP in mmHg for all IOP-lowering medical treatments included in the study

apraclonidine and its performance was better than carteolol, betaxolol and levobetaxolol, which are beta-blockers. Unoprostone and betaxolol were the least effective in lowering IOP.

The study ranks the relative efficacy of IOP-lowering medications and therefore can be used to guide clinical decision-making for medical treatment of POAG. However, it should not be considered a solitary reference for choice of medication that should be used for treatment of POAG.

The following factors must be considered when prescribing medical therapies, including mode of action, adverse effects, contraindications, the patient's systemic health conditions, existing risk factors, extent of damage present and current rate of progression, predicted life expectancy, level of compliance and financial burden of treatment.

## Prostaglandin analogue

Prostaglandin analogue is usually selected as the first line medical treatment of POAG due to its superior efficacy when compared to other medication classes, convenient once-daily dosing and hence better tolerability and compliance and minimal systemic contraindications. The topical adverse effects include

conjunctival hyperaemia, periorbital skin pigmentation, hypertrichosis, iris pigmentation and heterochromia.

In addition, there have been reports of patients who developed anterior uveitis after receiving latanoprost. Although the risk is small, it should be used with caution in patients with co-existing intraocular inflammation including uveitis due to the risk of developing cystoid macular oedema (reversible), and in patients with a history of herpetic infection due to the increased risk of reactivation of herpetic eye disease.

## Beta blockers

Beta-blocker is the next best IOP lowering medication in terms of efficacy. When compared to prostaglandin analogues, it has a short onset of action (30 minutes) and is therefore beneficial for rapid IOP reduction such as in acute angle closure attack. However, beta-blocker has more systemic contraindications and higher risk of adverse effects when compared to prostaglandin analogues.

Non-selective beta-blocker acts on beta-1 and beta-2 receptors while cardioselective beta-blocker acts on beta-1 receptors. Blockage of beta-2

# Clinical Quiz

**Associate Professor Mark Roth**

BSc(Pharm) BAppSc(Optom) PGCertOcTher NEWENCO FAAO OAM

A 48-YEAR-OLD, Caucasian woman presents with a long-standing, large, right inferiotemporal, oval, conjunctival lesion. The lesion is 6 mm in diameter and 3 mm thick, with associated dilated blood vessels. There is a yellow-white corneal line adjacent to lesion and one prominent follicle and hair in the centre of the mass. The patient is asymptomatic.

**What is your diagnosis?**
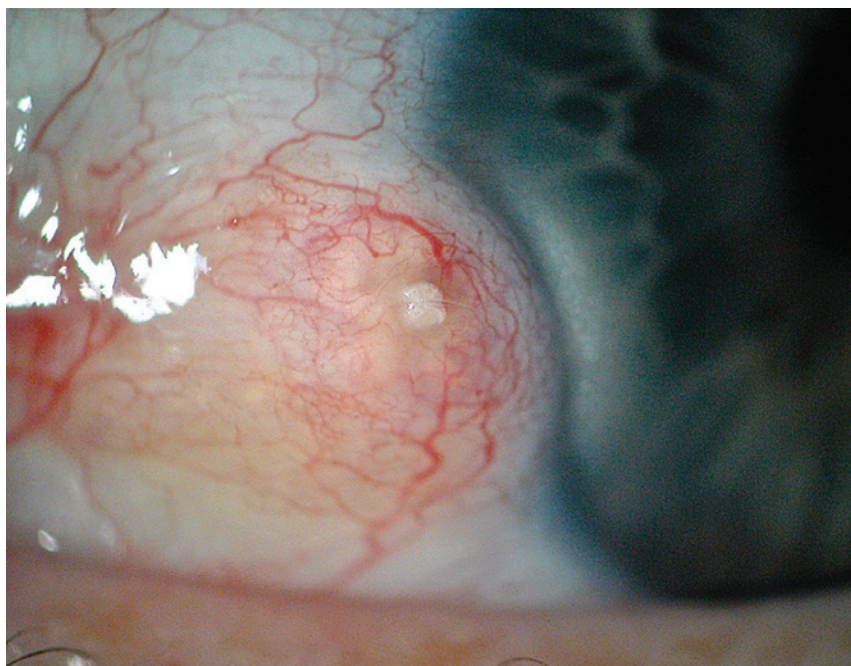


▲ Conjunctival lesion   Image: Associate Professor Mark Roth

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# IOP medications

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receptor is problematic in patients with asthma and chronic obstructive pulmonary disease. Selective beta-blockers may also cause bradycardia, hypotension and hypoglycaemia.

### Alpha 2s and CAIs

Alpha-2 agonists are contraindicated in patients taking monoamine oxidase inhibitor. Carbonic anhydrase inhibitors (CAI) are contraindicated in patients with sulfonamide allergies and patients with corneal graft and endothelial dystrophies as they may exacerbate corneal decompensation. Both CAIs and alpha-2 agonist require two to three times daily dosing, which reduces compliance.

### Limitations

IOP is the primary and most common outcome to quantify the effectiveness of topical medical therapies in the literature. IOP is the only known modifiable risk factor for treatment of glaucoma and IOP reduction correlates with preservation of visual field. The extent of damage to the optic nerve

head, the rate of retinal ganglion cell atrophy and degree of neuroretinal rim degeneration cannot be calculated and quantified easily.

The effect of the medication on the patient's quality of life is even more difficult to quantify and requires long-term follow-up. In contrast to IOP, visual field is a more meaningful outcome measure to quantify the effectiveness of treatment because it correlates with the patient's quality of life such as driving. However, only 20 per cent of randomised controlled trials included in the systemic review reported visual field as an outcome measure.

The extrapolation of visual field result is also difficult due to the heterogeneity associated with different reporting methods and relatively short follow-up time of three months. It will be interesting to see studies which have visual field results as an outcome when evaluating the effectiveness of topical IOP-lowering medication.

It is worth noting that this study does not consider the role of fixed/unfixed combination agents in the treatment of POAG. Combination agents are generally used when single agents are inadequate for reaching the

target IOP. They may be considered as first-line treatment when the extent of existing glaucomatous damage is profound. Fixed combination therapy is more cost-effective and offers the convenience of once or twice-daily dosage which maximises compliance and adherence. Fewer drops also mean reduced exposure of the ocular surface to preservatives and less risk of toxicity.

It has been published that fixed combination of latanoprost 0.005% and timolol 0.5% is statistically more effective in lowering IOP when compared to monotherapy.[2] However, there is no clear evidence demonstrating the superiority of fixed combination agents. Therefore, it will be interesting to see where combination agents fit in the rank order of topical IOP-lowering medications for the treatment of POAG. The other fact to keep in mind is that unlike single active agents, the dosing regimen and treatment times of fixed combination agents cannot be optimised.  ▲

1. Li T, Lindsley K, Rouse B, et al. Comparative effectiveness of first-line medications for primary open-angle glaucoma. *Ophthalmology* 2016; 123: 1: 129-140.
2. Polo V. Treatment of glaucoma with the fixed combination of latanoprost 0.005% and timolol 0.5%. *European Ophthalmic Review* 2009; 3: 2: 33-36.