EXTENDED REPORT

Meta-analysis of randomised controlled trials comparing latanoprost with brimonidine in the treatment of open-angle glaucoma, ocular hypertension or normal-tension glaucoma

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Aim: To compare the efficacy and tolerability of latanoprost versus brimonidine in the treatment of open-angle glaucoma, ocular hypertension or normal-tension glaucoma.

Method: Systematic review of randomised controlled trials comparing latanoprost and brimonidine, identified by searches including Medline, Embase and Cochrane Controlled Trials Register. Two reviewers independently assessed trials for eligibility and quality and extracted data. Data were synthesised (random effects model) and expressed as the absolute mean intraocular pressure (IOP) reduction difference from baseline to end point for efficacy and relative risk for adverse events. Subgroup analysis and regression were used to explore heterogeneity according to patient characteristics, trial design and quality.

Results: 15 publications reporting on 14 trials (1784 participants) were included for meta-analysis. IOP reduction favoured latanoprost (weighted mean difference (WMD)=1.10 mm Hg (95% confidence interval (CI) 0.57 to 1.63)). Significant heterogeneity was present ($\chi^2_{13}=38.29$, $p=0.001$, $I^2=66.0\%$). Subgroup analysis showed greater WMD for studies where data were analysed from end points >6 months duration, cross-over design, open-angle glaucoma or ocular hypertension and monotherapy. Multiple regression showed no significant association of WMD with trial duration ($t_9=1.92$, $p=0.09$), trial design ($t_9=1.79$, $p=0.11$), trial quality ($t_9=-0.46$, $p=0.66$), or monotherapy or adjunctive therapy ($t_9=-2.14$, $p=0.06$). Fatigue was less commonly associated with latanoprost (RR=0.27, 95% CI 0.08 to 0.88). Publication bias was not evident on visual inspection of a funnel plot.

Conclusion: Latanoprost is more effective than brimonidine as monotherapy in lowering IOP. Brimonidine is associated with a higher rate of fatigue.

Glaucoma is the second leading cause of visual loss worldwide. It is estimated that by 2010, there will be about 60 million people worldwide with open-angle glaucoma (OAG) or angle-closure glaucoma (ACG).¹

Despite advances in laser and surgical treatments, lowering of intraocular pressure (IOP) with topical drugs remains the initial treatment of choice for most patients.² The prostaglandin analogues and α_2 -agonists are two common classes of topical anti-glaucomatous treatments that are being increasingly prescribed.³

Latanoprost (Xalatan; Pharmacia, Peapack, New Jersey, USA) is a prodrug of a prostaglandin $F_{2\alpha}$ analogue that increases aqueous outflow predominantly through the uveoscleral pathway.⁴ Brimonidine tartrate (Alphagan; Allergan, Irvine, California, USA) is a highly selective α_2 -adrenergic agonist that increases uveoscleral outflow and reduces aqueous humor production.⁵ For many patients, latanoprost is now the preferred treatment for glaucoma,⁶ and is now the most commonly prescribed ocular hypotensive in the Republic of Ireland.⁷ Despite this, several studies have suggested greater or comparable IOP-lowering efficacy or fewer adverse events with brimonidine.^{8–13} There is sufficient uncertainty to warrant a systematic review comparing these two drugs.

Two meta-analyses have compared latanoprost and brimonidine in the treatment of glaucoma, both favouring greater IOP-lowering effects with latanoprost over brimonidine. One of these did not include any head-to-head trials between the two drugs.¹⁴ The other used 1-month peak and trough IOP-lowering effects as their end point, and only included articles written in English, German, French or Dutch published up to December 2003.¹⁵ Only

two trials comparing latanoprost and brimonidine were identified.^{9, 16} In both meta-analyses, adverse events were not studied.

Given the clinical significance of glaucoma, we believe that another meta-analysis comparing the efficacy and tolerability of latanoprost versus brimonidine is warranted. This should include all randomised controlled trials (RCTs) directly comparing the two drugs, unrestricted by trial duration, outcome and language, and include the several studies that have been published since the two meta-analyses mentioned earlier. In addition to OAG and ocular hypertension (OHT), we have included normal-tension glaucoma (NTG) in the target population. This decision was made on the basis of the similarity in interventions (topical anti-glaucomatous agents) and outcome measures (IOP) in these groups.

MATERIALS AND METHODS

Selection

All randomised and quasi-randomised controlled trials directly comparing topical latanoprost and brimonidine in the treatment of OAG (primary or secondary), OHT or NTG as defined by the investigators were included. Studies needed to have measured efficacy, tolerability or both in humans. Comparisons between combinations of latanoprost and other anti-glaucomatous agent(s) and brimonidine with the same anti-glaucomatous

Abbreviations: ACG, angle-closure glaucoma; IOP, intraocular pressure; IOPR, intraocular pressure reduction; OAG, open-angle glaucoma; OHT, ocular hypertension; NTG, normal-tension glaucoma; RCT, randomised controlled trial; WMD, weighted mean difference

agent(s) were accepted. There were no age or sex limitations. Trials with treatment duration <1 month for either intervention were excluded.

Literature search

We comprehensively searched Medline via Ovid (1966–March week 2, 2006), Embase via Embase.com (1980–week 11, 2006), the Cochrane Central Register of Controlled Trials in the Cochrane Library (CENTRAL, Issue 1, 2006) and Scientific Citation Index Expanded (1945–March 2006; appendix A). The strategy included populations (OAG, OHT or NTG), interventions (latanoprost and brimonidine) and publication type (randomised or quasi-randomised controlled trials). In addition, Current Controlled Trials, ClinicalTrials.gov, CenterWatch and the United Kingdom National Research Register were searched. There were no limitations on language, date or publication status.

References of included publications were reviewed until no further relevant studies were found. Authors were contacted to clarify duplications and trial methods, and to identify further relevant trials. When duplication was confirmed, only the most complete trial was included.

Data extraction

Two reviewers (ATF and SER) independently screened combined search results to determine trial eligibility and extract data on to a standardised form. Authors of trial, sample size, location, design, interventions, patient characteristics, baseline and endpoint values, trial quality (allocation concealment, blinding, measurement bias, completeness of follow-up and intention-to-treat analysis) and adverse events were recorded. Disagreements were resolved by discussion or consensus involving a third reviewer (JCC) when required.

Outcome measures

For efficacy, the mean IOP reduction (IOPR) from baseline to end point was determined. Daily mean values were analysed, given the tendency for IOP to fluctuate throughout the 24-h cycle.¹⁷ For three trials,^{9 11 12} IOP at its peak effect after drug administration was used because daily mean values were not reported.

For tolerability, adverse events were analysed in the following subgroups: itch/discomfort, hyperemia, eyelid disorder, visual disturbance, conjunctival disorder, keratopathy, dry eye, hypertrichosis, increased iris pigmentation, fatigue and headache.

Quantitative data synthesis and analysis

Extracted data were pooled for summary estimates using Review Manager 4.2.7 (The Cochrane Collaboration). Continuous outcomes were expressed as weighted mean difference (WMD), with values >0 favouring latanoprost, and dichotomous outcomes as relative risk (RR), with values <1 favouring latanoprost. Both outcomes were reported with 95% confidence intervals.

For studies that only reported absolute values for IOP at baseline and end point, the IOPR and standard deviation (SD) of the IOPR (SD_{IOPR}) were calculated as follows:

$$IOPR = IOP_{baseline} - IOP_{end\ point}$$

$$SD_{IOPR} = \sqrt{(SD_{baseline}^2 + SD_{end\ point}^2 - 2\rho SD_{baseline}SD_{end\ point})}$$

where

$$\rho \text{ (correlation coefficient)} = \frac{[(\sigma_{pre}^2 + \sigma_{post}^2) - \sigma_{\Delta}^2]}{2\sigma_{pre}\sigma_{post}}$$

and was calculated from trials with known SD_{IOPR} .

For studies that only reported standard errors (SEs), SD was calculated by the formula $SD = SE \times \sqrt{n}$. Six trials contained at

least a component of crossover design.^{11 12 17–21} For these trials, only the initial parallel phase was analysed. To minimise unit-of-analysis error, the sample size analysed in each arm was the true sample size divided by two.

For continuous data (IOP), the sample size was based on intention-to-treat analysis or last observation carried forward only if the authors of the trial clearly stated that this was the process used. Otherwise, available case analysis was used. For dichotomous data (adverse events), available case analysis was undertaken irrespective of how the original trialists explored the data to avoid imputing data.

Intertrial statistical heterogeneity was explored using the Cochran Q test, with calculated I^2 indicating the percentage of the total variability in effect estimates among trials that is due to heterogeneity rather than chance.²² Results for efficacy and tolerability were calculated using a random effects model. This assumes that each study estimates different but related treatment effects, and is more conservative than a fixed effects model in the presence of heterogeneity.²²

Subgroup analyses were determined a priori and included duration (<6 months, ≥6 months), study type (parallel v crossover), peak versus trough IOP readings, glaucoma type (OAG/OHT v NTG) and monotherapy versus adjunctive therapy. For trials in which end points were reported at more than one duration, only the longest duration was analysed.

Regression models exploring heterogeneity were performed with SAS statistical software V.8. A priori determined covariates included trial duration analysed, trial design (parallel v crossover), trial quality (allocation concealment) and treatment (monotherapy v adjunctive therapy). Publication bias was assessed by visually inspecting a funnel plot.

RESULTS

Literature search

A total of 16 publications (15 trials) met the eligibility criteria for the systematic review. These were published in 10 different journals, written in English, except one (Portuguese),²³ and included 1824 participants. One trial²³ had insufficient information for statistical analysis, leaving 15 publications (14 trials) and 1784 participants for meta-analysis^{8–13 16–21 24–26} (fig 1). Seven of these acknowledged direct financial support from a pharmaceutical company.^{9 11 12 16 20 21 24} No unpublished data were identified.

Efficacy

All trials reported greater IOPR for latanoprost than brimonidine, except for those by Simmons and Samuelson¹¹ (WMD = −1.17, 95% confidence interval (CI) −2.78 to 0.44) and DuBiner *et al*⁹ (WMD = −0.30, 95% CI −1.58 to 0.98). The pooled summary estimate for all 14 trials favoured latanoprost, and was significant (WMD = 1.10, 95% CI 0.57 to 1.63). Significant heterogeneity was present ($\chi^2_{13} = 38.29$, $p = 0.001$, $I^2 = 66.0\%$), reflecting quantitative heterogeneity in the difference of treatment effect.

Subgroup analyses

The pooled summary estimate for trials where data were analysed from end points >6 months duration (WMD = 1.64, 95% CI 0.92 to 2.36) was greater than that for end points <6 months in duration (WMD = 0.76, 95% CI 0.12 to 1.39; fig 2). After subgrouping by trial design, the WMD was greater with crossover design (WMD = 1.48, 95% CI 0.66 to 2.31) than parallel design (WMD = 0.97, 95% CI 0.24 to 1.71) but still retained significance in each favouring latanoprost. Participants with OAG or OHT (WMD = 1.10, 95% CI 0.48 to 1.72) responded similarly to those with NTG (WMD = 0.97, 95% CI 0.02 to 1.93). The WMD was greater when both drugs were prescribed as monotherapy (WMD = 1.56, 95% CI 0.90 to 2.23) than as an adjunct to other

Figure 1 Flow chart showing the process of identification of randomised controlled trials (RCTs) for inclusion in the systematic review. In all, 8 trials were multicentre, 7 single-centre; 11 were parallel in design and 4 crossover. Follow-up ranged between 2 and 12 months. All trials compared latanoprost 0.005% eye drops once daily directly with brimonidine 0.2% twice daily, nine as monotherapy and six as adjuvant therapy. Of the data available on sex, 864 (48.3%) of participants were men and 923 (51.7%) were women. Mean ages ranged from 52 to 77 years. Of the data available on type of glaucoma, 1299 (72%) participants had open-angle glaucoma, 390 (22%) had ocular hypertension, 64 (4%) had normal-tension glaucoma and 60 (3%) had other or mixed glaucoma (table 1). Mean baseline intraocular pressure (IOP) ranged from 15.5 to 26.4 mm Hg (latanoprost) and from 15.5 to 26.5 mm Hg (brimonidine), with good comparability between the two intervention groups in each trial (only one trial²⁶ had a mean baseline IOP difference >0.4 mm Hg).

treatments (WMD = 0.58, 95% CI -0.04 to 1.19). The overlapping 95% CIs of each of the four subgroup pairings indicates no significant difference between them.

Trial quality

Trial quality was inconsistently reported (table 2). We were confident of adequate allocation concealment in only seven trials,^{9 12 13 17 24 25} double blinding in four trials^{9 12 20 21} and intention-to-treat analysis in five trials.^{11 16 17 24 25} Withdrawals ranged from 0% to 19%.

Regression

After adjustment for other covariates, there was no significant association of WMD of IOPR with trial duration ($t_9 = 1.92$, $p = 0.09$; fig 3), trial design ($t_9 = 1.79$, $p = 0.11$), trial quality

($t_9 = -0.46$, $p = 0.66$), or monotherapy or adjunctive therapy ($t_9 = -2.14$, $p = 0.06$).

Ocular haemodynamics

Three trials (four papers) reported on ocular haemodynamics. Latanoprost was found to considerably increase ocular blood flow,^{18 23} peak systolic velocity of the ophthalmic artery¹⁰ and ocular perfusion pressure.¹⁹ Brimonidine did not significantly alter these parameters.

Tolerability

None of the adverse events showed a significant difference between the treatment arms, except for fatigue (RR = 0.27, 95% CI 0.08 to 0.88, $p = 0.03$). In all, 11 of 211 (5%) (brimonidine) versus 3 of 247 (1%) (latanoprost) participants from three trials^{16 20 26} complained of fatigue (table 3).

Table 1 Characteristics of trials included in the review

Trial	n	Location	Multicentre (number)	Design	Duration analysed (months)	Latanoprost (dosing time)	Brimonidine (dosing time)	Adjuvant	Sex (%M/%F)	Mean age (years)	Treatment naive*	Glaucoma type			
												OAG	OHT	NTG	Other/mixed
Akman <i>et al</i> ⁸	80	Turkey	N	Parallel	3	22:00	08:00, 20:00	Y (3rd line)†	41/59	58	N	80	0	0	0
Camras <i>et al</i> ¹⁴	303	USA	Y (23)	Parallel	6	08:00	08:00, 20:00	N	49/51	63	Y (61) N (242)	141	149	0	11
De Figueiredo and De Figueiredo ²³	40	Brazil	N	Parallel	2-3	19:00-20:00	07:00-08:00, 19:00-20:00	N	47/53‡	52	Y	40	0	0	0
Dubiner <i>et al</i> ⁷	127	USA	Y (5)	Parallel	3	19:00-21:00	07:00-09:00, 19:00-21:00	N	41/59	61	Y (55) N (127)	93	34	0	0
Garcia-Sanchez <i>et al</i> ¹⁵	334	Europe	Y (34)	Parallel	6	08:00	08:00/20:00	Y (2nd line)§	45/55	65	N	230	80	0	15
Inan <i>et al</i> ¹⁰	41	Turkey	N	Parallel	3	Nightly	bd	N	42/58	62	Y (41) N (41)	30	11	0	0
Kampik <i>et al</i> ¹⁶	379	Europe	Y (30)	Parallel	6	20:00	08:00, 20:00	N	41/59	65	N	284	64	0	31
Simmons and Samuelson ¹¹	40	USA	Y (8)	Parallel	1**	22:00	08:00, 20:00	Y (3rd line)††	30/70	63	?	39	1	0	0
Simmons <i>et al</i> ¹²	115	USA	Y (14)	Parallel ⁵	1 ⁶	20:00	08:00, 20:00	Y (2nd line)‡‡	41/59	66	N	96	16	0	3
Sodhi <i>et al</i> ¹³	181	India	N	Parallel	12	od	bd	Y (?) line	74/26	61	N	181	0	0	0
Wallock <i>et al</i> ¹⁸	67	UK	N	Parallel	3	od	bd	N	7/7	77	Y	35	0	32	0
Liu <i>et al</i> ^{18, 19}	32	Taiwan	N	Crossover	1§§	21:00	09:00, 21:00	N	72/28	64	Y (25) N (25)	0	0	32	0
Orzalesi <i>et al</i> ¹⁷	20	Italy	N	Crossover	1*¶¶	21:00	08:00, 20:00	N	45/55	63	Y (20) N (20)	10	10	0	0
Stewart <i>et al</i> ²⁰	33	USA	Y (?)	Crossover	1.5 ⁹	20:00	08:00, 20:00	N	52/48	60	?	22	11	0	0
Stewart <i>et al</i> ²¹	32	USA	Y (?)	Crossover	1.5 ⁹	Nightly	08:00, 20:00	Y (2nd line)***	41/59	62	N	18	14	0	0

? value unknown; bd, twice daily; F, female; M, male; n, number of units of analysis ("eyes" randomised); N, no; NTG, normal-tension glaucoma; OAG, open-angle glaucoma; od, once daily; OHT, ocular hypertension; Y, yes.

*Sums may be less than n if authors excluded some withdrawals in this analysis.

†Both arms also received Timolol/dorzolamide combination 0.5%/2% (07:30/19:30).

‡Proportion in all nine arms.

§The latanoprost group received fixed combination latanoprost 0.005%/Timolol 0.5% (08:00), the brimonidine group received the unfixed combination of brimonidine 0.2% and timolol (0.5%) (08:00/20:00).

¶Patients not achieving clinical success (1.5% intraocular pressure reduction at 1 month) were crossed over to other treatment at 1 month.

**Total trial duration 6 months. Analysed end point at 1 month before crossover of patients not achieving clinical success.

††Both arms also received a topical β -blocker and either dorzolamide or pilocarpine.

‡‡Both arms also received a topical β -blocker.

§§Duration of treatment arm. Entire duration of trial was 3 months.

¶¶Duration of treatment arm. Entire duration of trial was 5 months.

***The latanoprost group received latanoprost 0.005%/Timolol 0.5% (nightly), the brimonidine group received brimonidine 0.2% and timolol (0.5%) (08:00/20:00).

Review: Latanoprostvs brimonidine
 Comparison: 01 latanoprostvs brimonidine
 Outcome: 25 IOPR (all trials by duration) Xadj

Figure 2 Trials subgrouped by duration analysed. IOPR, intraocular pressure reduction; WMD, weighted mean difference.

Table 2 Trial quality assessment

		Blinding		Measurement				Withdrawals (%)	ITT analysis or last observation carried forward
	Allocation concealment adequate	Patient	Investigator	Equipment	Examiners*	Average of 3 readings in study eye?	Washout†		
Trial									
Akman <i>et al</i> ⁶	NS	N	Y	GAT	Same	Y	NS	11	NS
Camras <i>et al</i> ²⁴	Y	N	Y	GAT	Different	Y	Y	19	Y
De Figueiredo and De Figueiredo ²³	N (alphabetical)	NS	NS	NS	Same	NS	Y	NS	NS
DuBiner <i>et al</i> ⁶	Y	Y	Y	GAT	Different	NS	Y	6	N
Garcia-Sanchez <i>et al</i> ²⁵	Y	N	Y	GAT	Different	Y	Y	12	Y
Inan <i>et al</i> ¹⁰	NS	N	Y	GAT, colour Doppler ultrasound	Same	NS	Y	7	NS
Kampik <i>et al</i> ¹⁶	NS	N	Y	GAT	Different	Y	Y	13	Y
Simmons and Samuelson ¹¹	NS	N‡	Y	Applanation tonometry	Different	NS	NS	0§	Y
Simmons <i>et al</i> ¹²	Y	Y	Y	NS	Different	NS	NS	7 ¹⁵	N
Sodhi <i>et al</i> ³	Y	N ¹⁴	Y	GAT	NS	NS	NS	6	N
Waldock <i>et al</i> ²⁶	NS	N	Y	GAT	Same	Y	NS	7¶	N
Liu <i>et al</i> ^{8, 19}	Y (random number table)	N	Y	GAT, Ocular blood flow tonometer	Same	Y	Y	22	NS
Orzalesi <i>et al</i> ¹⁷	Y (list of random numbers)		Y	GAT and hand-held tonometer	Different (2)	NS	Y	0	Y
Stewart <i>et al</i> ²⁰	NS	Y	Y	GAT	Different	N	N**	3††	N
Stewart <i>et al</i> ²¹	NS	Y	Y	GAT	Different	N	N ¹⁷	9	N

?, value unknown; GAT, Goldmann applanation tonometer; ITT, intention-to-treat; N, no; NS, not stated or uncertain; Y, yes.

*Unless otherwise stated, multicentre trials were assumed to have different examiners. †For trials in which all patients were treatment naive, this is reported as Yes (Y).

‡Patients masked to bottles, not to frequency (ie morning placebo not specified for latanoprost arm). §At 1 month. Unable to ascertain percentage (authors did not specify from which arms withdrawals originated). **Washout occurred before beginning the trial, but not between crossover arms.

††Insufficient information to determine whether all withdrawals were reported.

Figure 3 Weighted mean difference of intraocular pressure reduction (IOPR) versus trial duration. Diamonds represent parallel design studies. Squares represent cross-over design studies.

Publication bias

A funnel plot of all trials did not show asymmetry suggestive of publication bias.

DISCUSSION

Importance of IOP in glaucoma

The diagnosis of glaucoma depends on visual field, optic disc and retinal nerve fibre layer assessment, with less emphasis placed on IOP. Despite this, IOPR is the mainstay of treatment.² Several studies have shown this to reduce the progression of optic nerve damage and visual field loss in patients with increased IOP^{28–30} or NTG.³¹

Summary of key findings

Our meta-analysis is the first to directly compare efficacy and tolerability of topical latanoprost versus brimonidine for OHT or glaucoma. Latanoprost was found to be significantly more effective in reducing IOP, even after subgrouping by duration, trial design or glaucoma type. This advantage was not as significant as adjunctive therapy.

In six studies,^{8, 11–13, 21, 25} latanoprost and brimonidine were compared as adjuncts to either topical β -blockers (eg, timolol) or topical carbonic anhydrase inhibitors (dorzolamide). Theoretically, we can expect the reduced aqueous production effects of β -blockers and dorzolamide³² to be additive to the increased uveoscleral outflow effects of latanoprost,⁴ but have less additional benefit with brimonidine, which acts by both these mechanisms.⁵ This would suggest an even greater difference between latanoprost and brimonidine when given as adjunctive therapy rather than as monotherapy. Instead, we only found a

significant difference as monotherapy. It is possible that a ceiling effect for IOPR is responsible for the discordance between theory and evidence. An alternative explanation is the bias against latanoprost in two trials,^{21, 25} where the adjuvant timolol 0.5% was prescribed twice daily in the brimonidine group but only once daily in the latanoprost group.

Multiple regression of covariates failed to explain the significant heterogeneity in WMD of IOPR between latanoprost and brimonidine. It is possible that the variability is explained by another hidden cofactor, or more likely, by a combination of factors.

Fatigue is a recognised side effect of brimonidine³³ related to its α -adrenergic effect. Although some adverse events such as hypertrichosis and increased iris pigmentation are known side effects of latanoprost^{34, 35} but not brimonidine, the low sample size and event rates may have hidden evidence of a difference.

External validity

The decision on whether our results apply to a particular patient should be made on the basis of their potential benefit and harm and not on the eligibility criteria of the individual studies.³⁶ For example, in two of the trials, patients with IOP >30 mm Hg¹⁷ or 34 mm Hg⁸ were excluded, yet it is precisely these patients who are most likely to benefit from treatment if glaucoma is not irrevocably advanced.

Clinical implications

The greater IOPR effect of latanoprost over brimonidine that we have shown does not necessarily indicate a greater anti-glaucomatous effect with latanoprost. This is because IOP is a surrogate measure for glaucoma, and the two drugs may act through pathways independent of this mechanism. Brimonidine may neuroprotect retinal ganglion cells.³⁷ It has been shown to prolong retinal ganglion cell survival independent of its IOP-lowering effect in rats rendered ocular hypertensive.^{38, 39} Clinical trials, several of which are in progress,³⁷ are still required to definitely show a neuroprotective effect of brimonidine in human eyes.

The increased ocular haemodynamics with latanoprost but not brimonidine may be secondary to vasomotor effects on vessels supplying the optic disc.¹⁸ This may be associated with a more favourable prognosis for glaucoma.⁴⁰

None of the studies provided assessment of visual fields, the optic nerve head or retinal nerve fibre layer. Such studies are required if a definitive answer on efficacy is sought; however, these are difficult to perform, given the chronic nature of glaucoma and multiple covariates.

In addition to efficacy and tolerability, other factors such as adherence to treatment and cost are important when comparing anti-glaucomatous drugs. Latanoprost has the advantage of once-daily dosing. Two studies have shown better treatment

Table 3 Adverse events

Adverse event	Number of trials	Crude event rate		RR (95% CI)	RD (95% CI)	I ² (%)
		Latanoprost	Brimonidine			
Itch/discomfort	8	62/583	96/532	0.81 (0.40 to 1.61)	−0.02 (−0.11 to 0.06)	73.1
Hyperemia	8	66/530	46/482	1.37 (0.84 to 2.25)	0.04 (−0.02 to 0.10)	39.2
Eyelid disorder (swelling, blepharitis, laxity)	5	8/341	5/308	1.61 (0.47 to 5.48)	0.01 (−0.02 to 0.05)	10.4
Visual disturbance (photophobia, blurred vision, floaters, diplopia)	8	53/504	46/468	1.19 (0.88 to 1.61)	0 (−0.02 to 0.02)	0
Conjunctival disorder (including conjunctivitis)	2	9/313	27/260	0.16 (0.01 to 5.09)	−0.08 (−0.18 to 0.01)	82.3
Keratopathy	3	10/249	14/213	0.69 (0.24 to 1.96)	−0.03 (−0.07 to 0.01)	30.5
Dry eye	4	5/149	7/152	0.76 (0.26 to 2.27)	−0.02 (−0.05 to 0.02)	0
Hypertrichosis	1	6/182	0/145	10.37 (0.59 to 182.60)	0.03 (0 to 0.06)	NA
Increased iris pigmentation	2	6/268	0/229	5.48 (0.65 to 46.50)	0.03 (−0.04 to 0.10)	0
Fatigue*	3	3/247	11/211	0.27 (0.08 to 0.88)	−0.04 (−0.07 to −0.01)	0
Headache	4	6/362	13/327	0.43 (0.17 to 1.11)	−0.02 (−0.04 to 0.01)	0

I², intertrial statistical heterogeneity (Cochran Q test); NA, not available; RD, risk difference.

*Significant.

persistence and adherence with prostaglandins than α -agonists.^{41–42} Of the included studies, only one attempted to monitor adherence, the results of which were not reported.⁹ Latanoprost has been shown to be cheaper,⁴³ comparable⁴⁴ or more expensive⁴⁵ than brimonidine on a per-day basis.

CONCLUSION

Latanoprost, 0.005%, once daily has greater IOP-lowering effects as monotherapy than brimonidine 0.2% twice daily up to 1 year after initial treatment for OAG, OHT and NTG. There is significant variability in the IOP-lowering difference between the two drugs that is unexplained by trial duration, design, quality, and monotherapy or adjunctive therapy. Brimonidine is more commonly associated with fatigue than latanoprost. Application of our results depends on knowledge of individual patient risks and benefits.

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