Systematic review of intraocular pressure-lowering effects of adjunctive medications added to latanoprost
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CRD summary
This review found that adjunctive medications added to latanoprost (0.005%) decreased intra-ocular pressure in patients with primary open-angle glaucoma or ocular hypertension, especially with timolol (0.5% once daily). The limitations of the data and review methods, particularly the flaws in the analysis, mean that the findings of the review are unlikely to be reliable and should be interpreted with caution.

Authors' objectives
To evaluate the intra-ocular pressure-lowering effects of adjunctive medications added to latanoprost in patients with primary open-angle glaucoma or ocular hypertension.

Searching
PubMed, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched to October 2008 for relevant published articles; search terms were reported. Reference lists of retrieved articles were searched for additional studies. The Internet search engines Google and Yahoo were also searched, and manufacturers of the medications were also contacted for additional studies. There were no language restrictions.

Study selection
Randomised controlled trials (RCTs) of patients with primary open-angle glaucoma or ocular hypertension that received one adjunctive intra-ocular pressure-lowering drug with latanoprost (0.005%), given once daily for at least one month (after an initial run-in phase of latanoprost treatment for at least two weeks), were eligible for inclusion. Included trials could compare adjunctive medications with active comparators or placebo. Trials were excluded if: more than 15% of patients did not have primary open-angle glaucoma or ocular hypertension; prostaglandin analogues were added; only short-term results were reported.

Eligible outcomes included absolute and relative reductions in intra-ocular pressure at peak and/or trough (defined as maximum and minimum intra-ocular pressure-lowering effects of the adjunctive treatments).

The majority of the patients in the included trials were diagnosed with primary open-angle glaucoma, ranging from 75 to 100% of the patients in each trial. The mean age of the included patients ranged from 54 to 69 years, with 47% being male. The adjunctive medications were compared with each other used alongside 0.005% latanoprost in the trials were: timolol (0.5%); carteolol (2%); nipradilol (0.25%); bunazosin (0.01%); dorzolamide (1% or 2%); brinzolamide (1%); and brimonidine (0.15% or 0.1%). The length of run-in with 0.005% latanoprost ranged from one month to six months. The outcome measures evaluated were absolute and relative intra-ocular pressure reductions, with baseline ranges of 16.2mmHg to 23.3mmHg.

It was unclear how many reviewers performed the study selection.

Assessment of study quality
Methodological quality was assessed by two reviewers using the Delphi list to which items relevant for the interpretation of intra-ocular pressure measurements were added. The 18-item assessment included the analysis of randomisation, allocation concealment, blinding, outcome measurements, compliance, withdrawals and the use of intention-to-treat analyses. The trials were awarded a score out of a maximum of 18 points.

Data extraction
Where possible, two reviewers extracted the mean (with standard deviation) absolute and relative intra-ocular pressure changes from baseline. The moments of expected peaks and troughs of intra-ocular pressure were calculated according to the definition by the American Academy of Ophthalmology.
The standard time point of measurement was one month or the closest time point after that, to a maximum of three months. If data were not reported, estimates were made from any available figures or calculated where necessary using other information (endpoint standard deviations were calculated using sample sizes and standard errors or the baseline standard deviation, or the p-value and sample size).

The outcome measures were assessed using intention-to-treat analyses, from all randomised patients who received a minimum of one dose of active treatment after providing a valid baseline measurement.

The reviewers recorded data taken one month after initiation of adjunctive therapy (following the latanoprost-only run-in period).

Methods of synthesis
Pooled absolute and relative changes in intra-ocular pressure were calculated with 95% confidence intervals (CIs) using the DerSimonian and Laird random-effects model. Potential publication biases were explored using funnel plots and the Egger test for publication bias.

Results of the review
Nine RCTs were included in the review (n=410 patients). The size of the trials ranged from 16 to 36 patients. The included trials were judged to be of high quality with a mean quality score of 15.3 (range 13 to 17). Where reported, withdrawals ranged from 0 to 20%, but in the majority of trials the withdrawals were 0 to 6.3%.

The mean absolute intra-ocular pressure reductions observed for the adjunctive medications (added to latanoprost 0.005% once daily) were: timolol (0.5% once daily) at trough 3.3mmHg (95% CI 2.1 to 4.5) and at peaks 4.4mmHg (95% CI 3.5 to 5.4); timolol (0.5% twice daily) at trough 2.4mmHg (95% CI 2.0 to 2.8) and at peak 2.7mmHg (95% CI 2.2 to 3.2); brimonidine (0.1 to 0.15% twice daily) at trough 2.6mmHg (95% CI 1.9 to 3.3) and at peak 3.8mmHg (95% CI 2.5 to 5.2); dorzolamide (2% twice daily) at trough 2.6mmHg (95% CI 1.7 to 3.4) and at peak 3.1mmHg (95% CI 2.6 to 3.6); and brinzolamide (1% twice daily) at trough 2.8mmHg (95% CI 1.5 to 4.1) and at peak 1.8mmHg (95% CI 1.2 to 2.3).

Visual appraisal of funnel plots and the Eggers test showed no evidence of publication bias.

Authors’ conclusions
For patients with primary open-angle glaucoma or ocular hypertension, intra-ocular pressure was significantly reduced with the use of 0.005% latanoprost with the adjunctive medications brimonidine (1% twice daily), dorzolamide (2% twice daily), brinzolamide (0.1/0.15% twice daily) and timolol (0.5% once/twice daily). The use of 0.5% timolol once daily represented the most effective adjunctive medication.

CRD commentary
The review addressed a clear question and criteria for study inclusion were stipulated. Appropriate databases were searched, but as the review was restricted to published studies, there was a risk of publication bias. Although the authors evaluated publication bias, the small number of included trials meant that these tests were unlikely to be reliable. Steps were taken during most parts of the review process to minimise errors and bias, but were not explicitly reported for the selection of studies.

The included trials were all small, evaluated a wide range of medications, and few results could be pooled. It was unclear what the comparators in the included trials were from the trial details; the reviewers appeared to have pooled the mean differences in treatment arms for each type of adjunctive medication. Even with pooling of trial results, the maximum number of results for one treatment arm for comparison was still small (27 patients). There were no attempts to evaluate statistical heterogeneity across the results. The degree to which the adjunctive medications conferred additional benefits to patients was not clear.

Although the authors’ conclusions are based on the evidence presented, the limitations of the data and review methods, particularly the flaws in the analysis, mean that the findings of the review are unlikely to be reliable.
Implications of the review for practice and research

**Practice**: The authors stated that for patients with untreated high intra-ocular pressure advance glaucoma, or those who require a low target intra-ocular pressure, benefits may be attained by combining latanoprost with adjunctive medications.

**Research**: The authors stated that a randomised trial in which single dosing of timolol is directly compared with timolol given twice daily as an adjunctive therapy for patients with low responsiveness to latanoprost is required to further assess the efficacy of timolol.

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