Efficacy and safety of prostaglandin analogues in patients with predominantly primary open-angle glaucoma or ocular hypertension: a meta-analysis

CRD summary
This review, based on 15 variable quality RCTs, found that prostaglandin analogues (bimatoprost, latanoprost and travoprost) were equivalent in efficacy in reducing intra-ocular pressure in patients with predominantly open-angle glaucoma or ocular hypertension. Multiple sources of potential bias mean that the reliability of the authors’ conclusion is uncertain.

Authors' objectives
To assess the efficacy and adverse effects of prostaglandin analogues in patients with predominantly open-angle glaucoma or ocular hypertension

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science were searched, with no language restrictions, up to May 2008. Search terms were not reported. Conference abstracts were searched on the Greynet.org website. Bibliographies of published systematic reviews and the American Academy of Ophthalmology guidelines were scanned. Authors of trials were contacted for clarification where necessary.

Study selection
Randomised controlled trials (RCTs) that evaluated bimatoprost, latanoprost or travoprost in head-to-head comparison were eligible for inclusion. Included trials had to be of at least three months duration. Trials were excluded if they compared prostaglandins with other glaucoma treatments, employed cross-over designs, or were dose-finding trials.

Outcomes were elevated intra-ocular pressure, response rates, and adverse events.

In included trials, the mean age of patients ranged from 52 to 71 years; the overall gender balance included slightly more females than males. Prostaglandin analogue doses were 0.03% for bimatoprost, 0.005% for latanoprost and 0.004% for travoprost. Open-angle glaucoma was the predominant type of glaucoma amongst patients in 13 trials, but ocular hypertension was also apparent in the populations of ten trials. Trials varied in duration from three to 12 months.

Three reviewers independently assessed articles for eligibility, resolving discrepancies by consensus

Assessment of study quality
The quality of included trials was assessed by considering randomisation, allocation concealment, intention to treat, and blinding.

Three reviewers independently assessed validity, resolving discrepancies by consensus

Data extraction
Means, sample sizes and standard deviations of intra-ocular pressure were extracted from relevant interventions to allow calculation of mean difference and 95% confidence intervals (CIs). Numbers of events and sample sizes were extracted for response rates and adverse events to allow calculation of risk ratios and 95% confidence intervals. Trial duration was also extracted as a co-variate, along with data on trial quality. Data were inferred making standard assumptions when p values were presented without variances; 0.5 was imputed into zero cells to allow calculation of risk ratios when event rates were zero.

Three reviewers independently extracted data resolving discrepancies by consensus

Methods of synthesis
Mean differences (intra-ocular pressure) and relative risks (response rate and adverse events) were synthesised using the method of DerSimonian and Laird (random-effects model with weighting by inverse variance). A meta-regression was
performed to explore the impact of trial duration on the difference between latanoprost and bimatoprost in intra-ocular pressure. For the intra-ocular pressure synthesis, a difference of 1.5mmHg was used as a margin of equivalence when interpreting the pooled effect and associated 95% confidence intervals. Heterogeneity was quantified using $I^2$.

**Results of the review**

Fifteen RCTs allowed multiple head-to-head comparisons of the three outcomes, except the comparison of travoprost and bimatoprost for conjunctival hyperemia (for which there was only one trial). There were six three-arm trials and nine two-arm trials, with one trial excluded due to unknown sample sizes.

Trial quality was extremely variable. Three trials fulfilled all five methodological criteria assessed; the remainder failed at least one criteria and three failed four of the five criteria. This meant that most of the trials were of moderate to low quality.

**Intra-ocular pressure**: Based on the authors' definition of equivalence (95% CIs within 1.5mmHg of zero) for intra-ocular pressure: travoprost was equivalent to latanoprost (WMD -0.24mmHg, 95% CI -0.87 to 0.38; nine RCTs; $I^2=56\%$); travoprost was equivalent to bimatoprost (WMD 0.88Hgmm, 95% CI 0.13 to 1.63; eight RCTs; $I^2=56\%$); and latanoprost was equivalent to bimatoprost (WMD 0.73mmHg, 95% CI 0.1 to 1.37; eight RCTs; $I^2=47\%$). No trials showed a difference that demonstrated equivalence, although heterogeneity was high. The authors reported that trial duration did not explain this heterogeneity ($\beta$ coefficient -0.21, 95% CI -0.33 to 1.09).

**Response rates**: Response rates were defined differently in different trials (details provided). Only the comparison of travoprost with bimatoprost illustrated a significant effect, with higher event rates for bimatoprost (RR 0.82, 95% CI 0.71 to 0.95).

**Adverse events**: Travoprost was associated with a higher rate of conjunctival hyperaemia than latanoprost (RR 5.71, 95% CI 1.18 to 18.02; six RCTs; $I^2=97\%$), but bimatoprost was associated with a higher rate than latanoprost (RR 1.59, 95% CI 1.02 to 2.48; five RCTs; $I^2=74\%$). Heterogeneity was extreme for these analyses.

**Authors’ conclusions**

Prostaglandin therapy had similar efficacy effects (response rates and lowering intra-ocular pressure), but different hyperaemia effects.

**CRD commentary**

This review addressed a clear research question with replicable inclusion criteria. The search for studies had high sensitivity. Methods were used to minimise bias in study selection and data extraction, with multiple reviewers working independently.

Trial quality was predominantly moderate to low, with variable definition of response. Appropriate methods were used to pool results, although the sensitivity of the results to the authors' definition of equivalence was untested. Heterogeneity was high, especially for adverse events. Given the number of multi-arm trials, a mixed treatment comparison that compared all the treatments may have been more informative.

The low quality of the evidence-base, high heterogeneity and unknown sensitivity to the assumption of equivalence were potential sources of bias that contribute uncertainty to the reliability of the authors’ conclusions.

Three of the authors disclosed financial links with Pfizer Ltd (manufacturers of latanoprost and funders of the review).

**Implications of the review for practice and research**

**Practice**: The authors stated that policy makers may base their selection of a particular drug on cost or considerations other than efficacy.

**Research**: The authors did not state any implications for further research.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.