Meta-analysis of the effect of latanoprost and brimonidine on intraocular pressure in the treatment of glaucoma

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Authors' objectives
To indirectly quantify and compare the intraocular pressure (IOP)-lowering effects of latanoprost and brimonidine eye drops at baseline and after 3 and 6 months in the treatment of primary open-angle glaucoma.

Searching
The authors searched MEDLINE and EMBASE (1992 to May 1999) using the search terms 'ophthalmic', 'glaucoma', 'clinical trial', and either 'latanoprost' or 'brimonidine'. References from the retrieved articles were searched for additional studies. The search was restricted to English language publications.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) in which IOP was measured at baseline (IOP greater or equal to 20 mm Hg) and at 3 and 6 months follow-up.

Specific interventions included in the review
Interventions included latanoprost and brimonidine eye drops, placebo or other active treatment.

Participants included in the review
Adult patients with primary open-angle glaucoma. Patients with secondary glaucoma, organic disease (such as a cardiovascular or respiratory condition that would complicate the study outcome), or who used combination drug therapy for glaucoma (such as brimonidine plus timolol) were excluded from the review.

Outcomes assessed in the review
Intraocular pressure (IOP) measured by tonometry using any standard instrument.

How were decisions on the relevance of primary studies made?
Two reviewers made decisions on the relevance of primary studies. Discrepancies were resolved by discussion and unresolved disputes were resolved by a third reviewer.

Assessment of study quality
Included studies were evaluated for quality using the method described by Jadad et al (see Other Publications of Related Interest no.1). Studies received a score between 0 (lowest) and 5 (highest). Studies with a score greater than 2 were considered to be of acceptable quality and studies with a score between 0 and 2 were considered to be low quality. The authors do not state who, or how many of the authors, performed the quality assessment.

Data extraction
Two reviewers performed the data extraction. Discrepancies were resolved by discussion and unresolved disputes were resolved by a third reviewer.

Data were extracted for the categories of: study identification and year of publication, country, number of patients who received all study treatments, drugs compared, time of IOP measurement, and quality score.

Methods of synthesis
How were the studies combined?
Data were combined using random-effects models modified for single groups. Because of the lack of RCTs that directly compared latanoprost with brimonidine, the model assumed an indirect comparison through the use of active controls and placebo.

As a proxy for success rates, area under the curve (AUC) was calculated for the proportion of patients who achieved a normal IOP (< 20 mm Hg).

**How were differences between studies investigated?**

The authors tested for statistical heterogeneity.

Quality scores (QS) were correlated with study outcomes (SO) and sample size (SS) using Spearman's p to detect the presence of any bias in the results due to the size or quality of the trials included.

**Results of the review**

Nine RCTs published in 8 articles were included in the review with 2,152 participants (597 received latanoprost, 571 received brimonidine and the remainder received either timolol or betaxolol).

Quality scores ranged from 2 to 5 for all studies included in the meta-analysis.

At 3 months, latanoprost and brimonidine reduced IOP by 8.4 and 6.5 mm Hg, respectively (P = 0.004 latanoprost versus brimonidine).

At 6 months, latanoprost and brimonidine reduced IOP by 8.0 and 6.2 mm Hg, respectively (P = 0.045 latanoprost versus brimonidine).

At 3 months, approximately 83% of patients who received latanoprost were successfully treated (AUC 0.834) whereas 68% of patients who received brimonidine were successfully treated (AUC 0.675; P < 0.001).

At 6 months, approximately 82% of patients who received latanoprost were successfully treated (AUC 0.817) whereas 72% of patients who received brimonidine were successfully treated (AUC 0.715; P < 0.001).

Testing for heterogeneity revealed no statistically significant difference between either variances or effect sizes and no correlation was found between SS, QS and SO at either end point (3 or 6 months).

**Cost information**

In one U.S. study, the daily cost for latanoprost and brimonidine in 1999 was $0.92 and $0.90 respectively.

**Authors' conclusions**

The authors state that this indirect comparison of data from the available randomised clinical trials showed latanoprost to be statistically significantly superior to brimonidine in reducing IOP in adults with primary open-angle glaucoma.

**CRD commentary**

This was a good review. The authors have clearly stated the research question and inclusion and exclusion criteria. The literature search appears to be thorough although there is no mention of searches for unpublished and grey literature and the searches were restricted to the English language.

The authors have reported how the articles were selected, and who performed the selection and data extraction. The quality of the included studies was formally assessed and discussed in the review. The authors did not state who performed the quality assessment.

The data extraction is reported in tables and discussed in the text of the review. The studies were combined in a statistical meta-analysis where possible and heterogeneity was assessed. Although no heterogeneity was discovered, a
random-effects model was used for the analyses.

A possible conflict of interest may be the funding of this review provided by a contract with Pharmacia and Upjohn Inc., the company who market latanoprost (Xalatan).

The authors conclusions appear to follow from the results but, as the authors themselves state, these should be viewed with caution since the results were not obtained from direct comparisons of the two treatments.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors state that additional long-term, head-to-head comparisons of the efficacy, safety and cost of latanoprost and brimonidine are needed to support and supplement these findings. Further research should also assess adverse effects and costs, and assess the use of these treatments in children.

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