Meta-analysis of medical intervention for normal tension glaucoma
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CRD summary
The authors concluded that latanoprost, bimatoprost and timolol were the most effective intraocular pressure lowering agents in patients with normal tension glaucoma. However, the method of combining studies in this review appeared to be inappropriate and therefore the conclusions must be treated with some caution.

Authors' objectives
To evaluate the intraocular pressure reduction achieved by antiglaucoma drugs in patients with normal tension glaucoma.

Searching
PUBMED, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched. Reference lists of identified articles and relevant reviews were checked for further studies. Google and Yahoo search engines were used and manufacturers were contacted for additional material. Articles published in any language up to October 2008 were eligible. Search terms were reported.

Study selection
Placebo or active-controlled randomised clinical trials (RCTs) that evaluated antiglaucoma drugs (which included betaxolol, timolol, dorzolamide, brinzolamide, brimonidine, latanoprost, travoprost and bimatoprost) as monotherapy for advanced normal tension glaucoma were included. The primary outcomes of interest were absolute and relative intraocular pressure reduction.

Most included trials were single-centre single-blind studies. Trial duration ranging from three to eight weeks. Withdrawal rates ranged from 0% to 11% (where reported). Mean age (where reported) ranged from 55 to 71 years. Percentage of male participants (where reported) ranged from 31% to 70%. Mean baseline intraocular pressure ranged from 14.6 to 18.3mmHg.

Two reviewers selected studies independently.

Assessment of study quality
Study quality was assessed using the Delphi list with additional items specifically important for interpretation of intraocular pressure measurements. The scale awarded a point (range 0 to 18) for each of the criteria met by individual studies based on: method of randomisation; allocation concealment; participant blinding; investigator blinding; examiner blinding; inclusion criteria specified; exclusion criteria specified; interventions described explicitly; comedication avoided or standardised; whether point estimates and measures of variability were presented for primary outcome measures; was the period of outcome measurements equal for all groups; were times of intraocular pressure measurements equal for all groups; was information about the method of intraocular pressure measurement presented; were groups similar at baseline; was it unlikely that compliance may explain differences between groups; withdrawal rate reported; was sample size calculation reported; and was an intention-to-treat analysis performed.

Two reviewers independently assessed study quality.

Data extraction
Data were extracted in order to calculate peak, trough and diurnal curve mean absolute and relative intraocular pressure reduction and associated 95% confidence intervals (CI). Where necessary, intraocular pressure reduction measures were extracted from figures using scanning techniques and missing standard deviation estimates were calculated using standard recalculation techniques. The primary outcome assessment point was one month or the closest available time (range from 0.5 to three months).
Two reviewers performed data extraction independently. Any disagreements were resolved by discussion.

**Methods of synthesis**
Mean differences of absolute and relative intraocular pressure reduction were combined in random-effects meta-analyses on intention-to-treat basis. Publication bias was assessed using funnel plots and Egger’s test.

**Results of the review**
Fifteen RCTs (n=450) were included. The quality of included studies was generally high with an average score of 12.7 (range: 9 to 16). Four RCTs reported a sample size calculation. Sample size ranged from 9 to 62. Ten RCTs employed a crossover design.

All antiglaucoma drugs included in this review showed a statistically significant peak absolute intraocular pressure reduction relative to baseline. The trough and diurnal curve absolute intraocular pressure reduction measurements were statistically significant for timolol, brimonidine, latanoprost and bimatoprost.

A statistically significant peak relative intraocular pressure reduction was reported for timolol, dorzolamide, brinzolamide, brimonidine, latanoprost and bimatoprost. The trough and diurnal curve relative intraocular pressure reductions were statistically significant for timolol, brimonidine, latanoprost and bimatoprost.

No evidence of publication bias was found.

**Authors’ conclusions**
Latanoprost, bimatoprost and timolol were the most effective intraocular pressure lowering agents in patients with normal tension glaucoma.

**CRD commentary**
This review addressed a clear research question supported by well-defined inclusion criteria. The literature search appeared adequate: several databases were searched and there were specific attempts to identify unpublished studies, which minimised risks of publication bias. Articles published in any language were eligible for this review, which reduced risks of language bias. There were attempts to minimise bias and errors during the process by independent and duplicate assessment of study eligibility, validity and data extraction. The authors appeared to combine studies by intervention arms, including a separate placebo group, and therefore lost the power of randomisation in the meta-analysis. Comparisons between drugs were based on an indirect comparison of their effects relative to baseline rather than direct between-group comparisons in most cases. Most trials included in this review were small and did not report a power calculation, so their ability to detect differences between drugs was uncertain. In view of the limitations of the synthesis, the authors’ conclusions about the relative effectiveness of different drugs should be treated with some caution.

**Implications of the review for practice and research**
**Practice:** The authors stated that there were multiple options of effective monotherapy for normal tension glaucoma that enabled physicians to tailor an optimal strategy for individual patients.

**Research:** The authors stated that more research was needed on guidance for treatment of normal tension glaucoma patients.

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