Meta-analysis of alpha2-adrenergic agonists versus carbonic anhydrase inhibitors as adjunctive therapy
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CRD summary
The review concluded that brimonidine provided greater intraocular lowering efficacy than topical anhydrase inhibitors as adjunctive therapy to beta blockers or prostaglandin analogues in patients with glaucoma or ocular hypertension. The review was unable to rule out the possibility of publication bias and there was substantial heterogeneity in the overall analyses so the authors' conclusions should be considered tentative.

Authors' objectives
To compare the efficacy of alpha 2 adrenergic agonist (brimonidine) with topical carbonic anhydrase inhibitors (dorzolamide and brinzolamide) in reducing intraocular pressure when used as adjunctive therapy to beta-blockers or prostaglandin analogues.

Searching
PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to June 2010. There were no language restrictions. Search terms were reported. Reference lists of retrieved studies and reviews were checked. Google Scholar and Yahoo search engines were used. Manufacturers were contacted for additional materials.

Study selection
Randomised controlled trials (RCTs) with more than 85% of participants diagnosed with primary open-angle glaucoma or ocular hypertension were eligible for the review. Follow-up needed to be one month or more. Trials were required to have a washout period using prostaglandin analogues or beta blockers. Eligible comparisons were brimonidine versus dorzolamide and/or brinzolamide administered in combination with beta-blockers or prostaglandin analogues. The outcome of interest was intraocular pressure reduction.

In the included studies, the mean age of participants ranged from 56 to 73 years and just over half of the participants were women (where reported). Most participants had primary open angle glaucoma; other patients were diagnosed with ocular hypertension or other conditions. Mean baseline intraocular pressure ranged from 17 to 25mmHg. Treatments used during the run-in period included timolol, latanoprost, travoprost, other prostaglandin analogues and beta blockers. The interventions used for maintenance included 0.1% to 0.2% brimonidine twice or three times daily, 0.2% brimonidine combined with 0.5% timolol, 2% dorzolamide or 1% brinzolamide twice or three times daily and 2% dorzolamide combined with 0.5% timolol. Duration of treatment ranged from one to six months. Adverse events were reported.

Three reviewers independently selected studies for the review.

Assessment of study quality
Studies were assessed for quality with the five-point Jadad scale; criteria included allocation concealment, blinding, intention-to-treat analysis and withdrawals. Studies were considered adequate if they scored 3 points or more.

Three reviewers assessed studies for quality.

Data extraction
Data were extracted to enable presentation of mean differences in intraocular pressure and relative risks (RRs) for adverse events, with corresponding 95% confidence intervals (CIs). Where data were not available in this format, mean differences and relative risks were calculated.

Three reviewers performed the data extraction. Disagreements were resolved by discussion.

Methods of synthesis
Study results were combined in meta-analyses and summary effect measures – weighted mean differences (WMDs) or relative risks, with corresponding 95% CIs – were calculated using a Mantel-Haenszel fixed-effect model where there was no significant heterogeneity or a DerSimonian and Laird random-effects model where there was significant heterogeneity. Outcomes were assessed on an intention to treat basis. Heterogeneity was assessed using the $X^2$ test (p<0.1 indicated significant heterogeneity) and the $I^2$ value. Subgroup analyses were stratified by type of run-in medication, type of carbonic anhydrase inhibitor and quality scores. Publication bias was assessed by funnel plots.

Results of the review
Eleven RCTs (1,493 patients) were included in the review. Nine trials had a prospective parallel group design and two had a prospective crossover design. Six trials scored 3 or more on the Jadad scale and five trials scored 1 or 2. Only one trial was open label.

Efficacy, peak intraocular pressure (eight trials): Compared to carbonic anhydrase inhibitors, brimonidine significantly reduced total peak intraocular pressure (WMD 0.99, 95% CI 0.45 to 1.53; significant heterogeneity $I^2=73\%$) when used as adjunctive therapy to beta blockers (WMD 0.85, 95% CI 0.42 to 1.29) or prostaglandin analogues (WMD 1.04, 95% CI 0.08 to 2.0) and when only adequate quality trials were compared (WMD 1.41, 95% CI 1.14 to 1.68). Significant associations were also found between brimonidine and dorzolamide but not between brimonidine and brinzolamide.

Efficacy, trough intraocular pressure (seven trials): There was no evidence of a significant difference between brimonidine and carbonic anhydrase inhibitors in reducing trough intraocular pressure (WMD 0.20, 95% CI -0.34 to 0.75; significant heterogeneity $I^2=63\%$). Subgroup analyses indicated that brimonidine used as adjunctive therapy to beta blockers and compared to dorzolamide significantly reduced trough intraocular pressure but brimonidine was less effective when compared with brinzolamide (results reported in the paper). There was no evidence of a significant difference between interventions when used as adjunctive therapy to prostaglandin analogues or when only trials of adequate quality were compared.

Efficacy, diurnal mean intraocular pressure (nine trials): Compared to carbonic anhydrase inhibitors, brimonidine significantly reduced diurnal mean intraocular pressure (WMD 0.62, 95% CI 0.07 to 1.18; significant heterogeneity $I^2=78\%$) and when brimonidine was compared with dorzolamide (WMD 0.83, 95% CI 0.36 to 1.29). There was no evidence of significant differences in the other subgroup comparisons.

Safety: Compared to carbonic anhydrase inhibitors, brimonidine was associated with significantly fewer episodes of ocular burning (RR 0.26, 95% CI 0.17 to 0.40; no significant heterogeneity; four trials) and dysgeusia (RR 0.20, 95% CI 0.11 to 0.37; no significant heterogeneity; five trials). There was no evidence of significant differences in rates of other adverse events between groups.

There was no evidence of publication bias from inspection of funnel plot symmetry.

Authors' conclusions
Brimonidine provided greater intraocular lowering efficacy than topical anhydrase inhibitors as adjunctive therapy to beta blockers or prostaglandin analogues in patients with open angle glaucoma or ocular hypertension who have inadequate pressure control with beta-blockers or prostaglandin analogues.

CRD commentary
The review addressed a clear research question supported by appropriate inclusion criteria. Relevant sources were searched for studies. There were no language restrictions. No specific attempts were made to identify unpublished studies so publication bias could not be ruled out. Appropriate methods for study selection, data extraction and study quality assessment minimised the chance of reviewer error and bias. A valid tool was used for quality assessment. The included studies varied in quality; approximately half were considered adequate.

Synthesis of the studies in meta-analyses may not have been appropriate as participants in one multi-arm study seemed to be counted twice in the forest plots. Methods to assess heterogeneity and publication bias were appropriate. Significant heterogeneity was appropriately explored in subgroup analyses.

The review was unable to rule out the possibility of publication bias and there was substantial heterogeneity in the overall analyses so the authors' conclusions should be considered tentative.
Implications of the review for practice and research
The authors did not state any implications for practice or further research.

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