

APPENDIX 1A: Literature Search Strategy (Clinical)

Legend

!	Explode the search term. Retrieves the search concept plus all narrower terms.
?	Truncation symbol, single character. Retrieves plural and variant endings.
()	Proximity operator. Words must be adjacent next to each other.
(n)	Proximity operator. Words must be near each other in any order.
de	Descriptor i.e., subject heading (a controlled, thesaurus term).
ti	Search in article title.
ab	Search in article abstract.

DATABASES	LIMITS	SUBJECT HEADINGS/KEYWORDS
MEDLINE® (1951-present) BIOSIS Previews® (1969-present) ToxFile (1964 to the present) EMBASE® (1974-present)		Prostaglandins!/de [MEDLINE] OR (Prostaglandin OR Prostaglandin H Synthase)/de [BIOSIS] OR Prostaglandin!/de [EMBASE] OR Prostaglandin?/ti,ab OR (Latanoprost OR Bimatoprost OR Travaprost)/de [BIOSIS, EMBASE] OR (Bimatoprost OR AGN()192024 OR Lumigan OR Latanoprost OR Xalatan OR PHXA()41 OR XA()41 OR Louten OR Ocuprost OR Latof OR Travoprost OR AL()6221 OR AL6221 OR Travatan)/TI,AB OR RN=130209-82-4 OR RN=157283-68-6 OR TN=Xalatan OR TN=Lumigan OR TN=Travatan AND (Ocular Hypertension OR Hypertension OR Glaucoma! OR Intraocular Pressure)/de [MEDLINE]

		<p>OR (Ocular Hypertension OR Glaucoma OR Intraocular Pressure)/de [BIOSIS]</p> <p>OR</p> <p>(Intraocular Hypertension OR Glaucoma OR Intraocular Pressure OR Intraocular Pressure Abnormality OR Glaucoma, Open-Angle)/DE [EMBASE]</p> <p>OR</p> <p>(Ocular()hypotens? OR Ocular()hypertens? OR Ocular()tens? OR Intraocular OR Intra()ocular OR IOP OR Antiglaucoma OR Glaucoma)/ti,ab</p> <p>AND</p> <p>(Controlled clinical trials! OR Epidemiologic research design! OR Meta-Analysis)/de [MEDLINE]</p> <p>OR</p> <p>DT=Multicenter study OR DT=Randomized Controlled Trial OR DT=Controlled Clinical Trial OR DT=Meta-Analysis [MEDLINE]</p> <p>OR</p> <p>(Multicenter Study OR Randomized Controlled Trial OR Randomized Clinical Trial OR Randomized Trial OR Evidence-Based Medicine OR Meta-Analysis)/de [BIOSIS]</p> <p>OR</p> <p>(Major Clinical Study OR Multicenter Study OR Controlled Study! OR Randomized Controlled Trial OR Evidence Based Medicine! OR Meta Analysis)/de [EMBASE]</p> <p>OR</p> <p>(Random? OR Sham? OR Placebo? OR RCT?)/ti,ab</p> <p>OR</p> <p>(Singl?)(Blind? OR Dumm? OR Mask?)/ti,ab</p> <p>OR</p> <p>(Doubl?)(Blind? OR Dumm? OR Mask?)/ti,ab</p> <p>OR</p>
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		<p>(Tripl?)(Blind? OR Dumm? OR Mask?)/ti,ab</p> <p>OR</p> <p>(Treb?)(Blind? OR Dumm? OR Mask?)/ti,ab</p> <p>OR</p> <p>(Control?)(Study OR Studies OR Trial?)/ti,ab (Multicent? OR Multi()Cent?)(Study OR Studies OR Trial?)/ti,ab</p> <p>OR</p> <p>(Meta()Regression? OR Metaregression OR Mega()Regression?)/ti,ab</p> <p>OR</p> <p>((Systematic? OR methodologic?)(Literature()Review? OR Review? OR Overview?)/ti,ab</p> <p>OR</p> <p>(Integrative (2W)(Review? OR Overview?)/ti,ab</p> <p>OR</p> <p>(Collaborative ()(Review? OR Overview?)/ti,ab</p> <p>OR</p> <p>(Quantitative()(Review? OR Overview? OR Synthes?)/ti,ab</p> <p>OR</p> <p>(Research()(Integration? OR Overview?)/ti,ab</p> <p>OR</p> <p>(Pool?())Analy? OR Data()synthes? OR Data()extraction? OR data()abstraction? OR handsearch? OR hand()search?)/ti,ab</p> <p>OR</p> <p>(Mantel()Haenszel OR Peto</p> <p>OR</p> <p>der()simonian OR Dersimonian OR Fixed()Effect? OR Latin()Square?)/ti,ab</p> <p><i>Search performed on 17 Nov 2005</i></p>
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DIALOG® Alerts MEDLINE® BIOSIS Previews® EMBASE Alert® OVID Alerts (Jan 2006 -)		DIALOG® weekly alerts set up to capture new studies until December 2005. OVID alerts from Jan 2006 and are ongoing.
National Library of Medicine PubMed		Same MeSH headings and key words as DIALOG® MEDLINE search. Appropriate syntax for searching PubMed used.
The Cochrane Library, Issues 1-4, 2005, 1, 2006		Same MeSH headings and key words as DIALOG® MEDLINE search. Appropriate syntax for searching PubMed used.
Websites of HTA and related agencies; clinical trial registries and other databases		NICE; ECRI; National Research Register; University of York NHS Centre for Reviews and Dissemination – CRD databases

TRIAL REGISTRIES

The following trial registries were searched:

1. Clinical Study Results Org <http://www.clinicalstudyresults.org>
2. Clinical Trials Database (U.S. National Institutes of Health) <http://clinicaltrials.gov/ct/gui> (E)
3. Current Controlled Trials (Free registration)
“The metaRegister of Controlled Trials is a searchable, international database of ongoing randomised controlled trials in all areas of healthcare. At present, the mRCT also contains some completed trials. Offering access to more than 14,000 records, the mRCT is free”.
<http://www.controlled-trials.com/> (E)
4. Eli Lilly and Company Clinical Trial Registry <http://www.lillytrials.com/>
5. Forest Laboratories Clinical Trial Registry
<http://www.forestclinicaltrials.com/CTR/CTRController/CTRHome>
6. GlaxoSmithKline Clinical Trial Register <http://ctr.gsk.co.uk/disclaimer.asp>

APPENDIX 1B: Literature Search Strategy (Economic)

Legend

!	Explode the search term. Retrieves the search concept plus all narrower terms.
?	Truncation symbol, single character. Retrieves plural and variant endings.
()	Proximity operator. Words must be adjacent next to each other.
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DATABASES	LIMITS	SUBJECT HEADINGS/KEYWORDS
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	<p>(Ocular Hypertension OR Glaucoma OR Intraocular Pressure)/de [BIOSIS]</p> <p>OR</p> <p>(Intraocular Hypertension OR Glaucoma OR Intraocular Pressure OR Intraocular Pressure Abnormality OR Glaucoma, Open-Angle)/DE [EMBASE]</p> <p>OR</p> <p>(Ocular()hypotens? OR Ocular()hypertens? OR Ocular()tens? OR Intraocular OR Intra()ocular OR IOP OR Antiglaucoma OR Glaucoma)/ti,ab</p> <p>And</p> <p>(Economics OR .Costs AND Cost Analysis! OR Health Care Costs! OR Economic Value Of Life OR Economics, Medical OR Economics, Pharmaceutical OR Models, Economic! OR Markov Chains OR Monte Carlo Method OR Decision Support Techniques! OR Quality Of Life OR Quality-Adjusted Life Years OR Economics, Nursing OR Economics, Hospital)/de [MEDLINE]</p> <p>OR</p> <p>(Health Economics! OR Economic Evaluation! OR Pharmacoeconomics! OR Economic Aspect! OR Quality Adjusted Life Year OR Quality Of Life!)/de [EMBASE]</p> <p>OR</p> <p>(Economic Impact OR Economic Value OR Pharmacoeconomics OR Health Care Cost OR Economic Factors OR Economics OR Cost Analysis OR Economic Analysis OR Cost OR Cost-Effectiveness OR Cost Effectiveness OR Costs OR Quality Of Life OR Health Care Cost R Cost Savings OR Cost-Benefit Analysis OR Hospital Costs OR Medical Costs OR Quality-Of-Life)/de [BIOSIS]</p> <p>OR</p> <p>(Econom? OR Cost OR Costly OR Costing OR Costed OR Price OR Prices OR Pricing OR Priced OR Discount OR Discounts OR Discounted OR Discounting OR Expenditure OR Expenditures OR Budget? OR Afford? OR Pharmacoeconomic? OR Pharmaco(1N)Economic?)/ti,ab</p> <p>OR</p> <p>(Cost?(1N) (Util? OR Effective? OR Efficac? OR Benefit? OR Consequenc? OR Analy? OR Minimi? OR Saving? OR Breakdown OR Lowering OR Estimate? OR Variable? OR Allocation OR Control OR Illness OR Sharing OR Life OR Lives OR Affordabl? OR Instrument? OR Technolog? OR day</p>
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		<p>? OR Fee OR Fees OR Charge OR Charges)/ti,ab</p> <p>OR</p> <p>(Unit(1N)Cost OR Unit?(1N)Costs OR Drug()cost OR Drug()Costs OR Hospital()Costs OR Health(1N)Care()Costs OR Medical(1N)Cost OR Medical(1N)Costs OR Markov OR Markov OR Monte()Carlo)/ti,ab</p> <p>OR</p> <p>(Decision (1N) (tree? OR analy? OR model?)/ti,ab</p> <p>OR</p> <p>((Value OR Values OR Valuation) (2N) (Money OR Monetary OR Life OR Lives OR Cost OR Costs OR QOL OR QOLY OR QOLYS OR HRQOL OR QALY OR QALYS OR QALE OR QALES OR Quality(1N)Life OR Willingness(1N)Pay OR</p> <p>Quality(1N)Adjusted()Life()Year? OR Sensitivity()Analys?s OR Quality(1N)Adjusted()Life Expectancy OR Quality(1N)Adjusted Life Expectancies OR CE()Analysis)/ti,ab</p> <p><i>Performed on 01 Nov 2005</i></p>
<p>DIALOG[®] Alerts</p> <p>MEDLINE[®]</p> <p>BIOSIS Previews[®]</p> <p>EMBASE Alert[®]</p> <p>OVID Alerts (Jan 2006 -)</p>		<p>DIALOG[®] weekly alerts set up to capture new studies until December 2005. Ovid alerts set up in Jan 2006 and are ongoing.</p>
HEED		Appropriate keywords were used.
National Library of Medicine		Same MeSH headings and keywords as DIALOG [®] MEDLINE search. Appropriate syntax for searching PubMed used.
PubMed		
The Cochrane Library, Issues 1-4, 2005, 1, 2006		Same MeSH headings and keywords as DIALOG [®] MEDLINE search. Appropriate syntax for searching PubMed used.
Websites of HTA and related agencies; clinical trial registries and other databases		NICE; ECRI; National Research Register; University of York NHS Centre for Reviews and Dissemination – CRD databases; ISPOR International Congress Abstracts

APPENDIX 2: Relevance Assessment Forms

Level 1 Screening

Previewing only: you cannot submit data from this form

Previewing at Level 1

Refid: 1, Obstbaum, S. A., Cioffi, G. A., Krieglstein, G. K., Fennerty, M. B., Alm, A., Araie, M., Carassa, R. G., Greve, E. L., Hitchings, R. A., Kaufman, P. L., Kitazawa, Y., Pongpun, P. R., Susanna, R., Jr., Wax, M. B., and Zimmerman, T. J., Gold standard medical therapy for glaucoma: defining the criteria identifying measures for an evidence-based analysis, *Clinical Therapeutics*, 26(12), 2004, P.2102 – 2120 State: Excluded, Level 1

<p>Keywords: Adrenergic beta-Antagonists/Benchmarking/Chronic Disease /drug therapy/Evidence-Based Medicine/Glaucoma, Open-Angle/human/methods/Ophthalmology/Patient Compliance/Quality of Life/standards/therapeutic use</p> <hr/> <p>Abstract: BACKGROUND: Over the past decade, several new medical therapies have become available for the treatment of primary open-angle glaucoma (POAG). A systematic evidence-based approach for identifying an optimal therapeutic agent is lacking. OBJECTIVES: The aims of this review were to critically evaluate published treatment recommendations for POAG and, based on a systematic review of the literature, to develop criteria that would define a "gold standard" medical therapy that reflects new treatment advances and established therapeutic goals. METHODS: A MEDLINE search spanning the years 1966 to 2002 and using the search terms gold standard, drug of choice, benchmark, ophthalmology, eye and glaucoma was conducted and the results reviewed by a panel of 15 experts in the field of glaucoma. Published treatment recommendations for POAG were discussed. Criteria, anchored to medical evidence, for distinguishing a standard of medical therapy for POAG were defined. RESULTS: The terms connoting a gold standard therapy were found in only 258 of approximately 368,000 ophthalmology-related citations and 53 of almost 23,000 glaucoma citations, validating the need to define therapeutic standards. The lack of recommendations for the use of new classes of ocular hypotensive agents was acknowledged. Criteria identified to evaluate intraocular pressure (IOP)-lowering agents as gold standards included the following: efficacy in reducing IOP consistently over a 24-hour period to a level that will preserve the visual field and protect the optic nerve without inducing tachyphylaxis and tolerance, paucity of local and systematic adverse effects, promotion of patient compliance, and applicability in diverse patient populations. CONCLUSIONS: These criteria should be employed as measures for evidence-based analyses to evaluate available and future IOP-lowering medical therapies for POAG. The conceptual framework presented may be applicable to other therapeutic areas.</p> <p>Increase Font Size</p> <p>Decrease Font Size</p>	<p style="text-align: center;">Submit Data</p> <p>Relevance Assessment Form – Glaucoma Project</p> <p>Inclusion criteria</p> <p>1. Is the study a randomized controlled trial (RCT)? <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> cannot tell Clear selection</p> <p>2. Is the study reported in English? <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> cannot tell Clear selection</p> <p>3. Is the study population adult subjects (>18 years old) with raised IOP? <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> cannot tell Clear selection</p> <p>4. Is at least one intervention in the study monotherapy with a prostaglandin analogue (i.e., bimatoprost, latanoprost, travaprost, or unoprostone)? <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> cannot tell Clear selection</p> <p>5. Does the study include treatment naive patients who have received a washout period before treatment? <input type="checkbox"/> yes <input type="checkbox"/> no (comments) <input type="checkbox"/> cannot tell Clear selection</p> <p>Exclusion Criteria</p> <p>6. Does the study only evaluate patients with closed-angle glaucoma? <input type="checkbox"/> yes (comments) <input checked="" type="checkbox"/> <input type="checkbox"/> no <input type="checkbox"/> cannot tell Clear selection</p> <p>7. Is the comparator used in the study neither an IOP lowering agent nor placebo? <input type="checkbox"/> yes (comments) <input checked="" type="checkbox"/> <input type="checkbox"/> no <input type="checkbox"/> cannot tell Clear selection</p> <p>8. Is the comparator(s) used in the study another prostaglandin analogue(s)? <input type="checkbox"/> yes (comments) <input checked="" type="checkbox"/> <input type="checkbox"/> no <input type="checkbox"/> cannot tell Clear selection</p> <p>9. Comments</p> <p>Enlarge Shrink <input checked="" type="checkbox"/></p> <p>Other</p> <p>10. Is the study an economic review, economic evaluation, or cost analysis of treatment agents for open-angle glaucoma? <input type="checkbox"/> yes</p> <p>11. Does the article provide useful background information? <input type="checkbox"/> no</p> <p style="text-align: center;">Submit Data</p>
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Form took 0.65625 seconds to render

Level 2 Screening

Previewing only: you cannot submit data from this form

Previewing at Level 2

Refid: 1, Obstbaum, S. A., Cioffi, G. A., Kriegelstein, G. K., Fennerty, M. B., Alm, A., Araie, M., Carassa, R. G., Greve, E. L., Hitchings, R. A., Kaufman, P. L., Kitazawa, Y., Pongpun, P. R., Susanna, R., Jr., Wax, M. B., and Zimmerman, T. J., Gold standard medical therapy for glaucoma: defining the criteria identifying measures for an evidence-based analysis, *Clinical Therapeutics*, 26(12), 2004, P.2102 – 2120 State: Excluded, Level 1

Submit Data

Relevance Assessment Form – Glaucoma Project

Inclusion criteria

1. Is the study a randomized controlled trial (RCT)?

- yes
 no
 cannot tell

Clear selection

2. Is the study reported in English?

- yes
 no
 cannot tell

Clear selection

3. Is the study population adult subjects (>18 years old) with raised IOP?

- yes
 no
 cannot tell

Clear selection

4. Is at least one intervention in the study monotherapy with a prostaglandin analogue (i.e., bimatoprost, latanoprost, or travaprost)?

- yes
 no (comments)
 cannot tell

Clear selection

5. Does the study include treatment naïve patients who have received a washout period before treatment?

- yes
 no (comments)
 cannot tell

Clear selection

6. Does the study provide outcome data at time points ≥ 3 months from the start of the intervention?

- yes
 no
 cannot tell

Clear selection

Exclusion Criteria

7. Does the cohort include patients with closed-angle glaucoma?

- yes (comments)
 no
 cannot tell

Clear selection

8. Is the comparator used in the study neither an IOP lowering agent nor placebo?

- yes (comments)
 no
 cannot tell

Clear selection

9. Is the comparator(s) used in the study another prostaglandin analogue(s)?

- yes (comments)
 no
 cannot tell

Clear selection

10. Comments

Enlarge Shrink

Other

11. Is the study an economic review, economic evaluation, or cost analysis of treatment agents for open-angle glaucoma?

- yes

12. Does the article provide useful background information?

- yes

Submit Data

Form took 0.296875 seconds to render

APPENDIX 3: Characteristics of Included Studies

Characteristics of included studies								
Author(s), Study Countries	Length of Rx (months)	N	Comparison	Main Outcomes	Jadad Score	ITT	Industry Funded	Companion Papers or Other Notes
Alm and Stjernschantz, Scandinavia ³¹	6	267	latanoprost (2 dosage regimens) versus timolol	diurnal IOP	5	no	yes	Alm, ³² Fristom ³³
Barnebey <i>et al.</i> , US (33 centres) ³⁸	3	263	travoprost and timolol combination versus travoprost versus timolol	diurnal IOP*	4	yes	yes	none
Camras and US Latanoprost Group, US (17 centres) ³⁹	6	268	latanoprost versus timolol	diurnal IOP	5	yes	yes	none
Camras and Sheu, US (23 centres) ³⁴	6	303	latanoprost versus brimonidine	diurnal IOP	5	no	yes	Camras <i>et al.</i> abstract ³⁵
DuBiner <i>et al.</i> , US (5 centres) ⁴⁰	3	127	latanoprost versus brimonidine	IOP	5	no	yes	none
Erkin <i>et al.</i> , Turkey ⁵⁵	3	32	latanoprost versus betaxolol	IOP and ocular blood flow	2	no	NR	none
Fechtner <i>et al.</i> , study 1, US (20 centres); study 2, Europe and Israel (24 centres) ³⁶	3	1: 256 2: 288	latanoprost versus dorzolamide+timolol combination	diurnal IOP	5	yes	yes	Fechtner <i>et al.</i> abstract ³⁷
Fellman <i>et al.</i> , US (44 centres) ⁴¹	6	605	travoprost (2 concentrations) versus timolol	diurnal IOP*	5	yes	yes	none
Goldberg <i>et al.</i> , US, Australia, Europe (64 centres) ⁴²	9	573	travoprost (2 concentrations) versus timolol	diurnal IOP*	5	yes	yes	
Inan <i>et al.</i> , Turkey ⁵⁰	3	41	latanoprost versus brimonidine	IOP and ocular blood flow	2	no	NR	looked at blood flow in particular, reports IOP too
Kampik <i>et al.</i> , Europe (30 centres) ⁵¹	6	379	latanoprost versus brimonidine	diurnal IOP	2	yes	yes	none
Konstas <i>et al.</i> , Greece, US ⁴³	3	109	latanoprost versus timolol	diurnal IOP	3	no	yes	none
Lone <i>et al.</i> , India ⁵³	3	44	latanoprost versus dorzolamide	diurnal IOP	2	yes	NR	none
Martin <i>et al.</i> , Spain ⁴⁹	6	60	bimatoprost versus timolol	IOP	2	yes	no	none
Mastropasqua <i>et al.</i> , Italy ⁴⁴	12	36	latanoprost versus timolol	diurnal IOP	5	†	NR	none

Characteristics of included studies								
Author(s), Study Countries	Length of Rx (months)	N	Comparison	Main Outcomes	Jadad Score	ITT	Industry Funded	Companion Papers or Other Notes
Mishima <i>et al.</i> , Japan (35 centres) ⁴⁵	3	184	latanoprost versus timolol	IOP	3	no	NR	none
Netland <i>et al.</i> , US ⁴⁶	12	801	travoprost (2 concentrations) versus latanoprost versus timolol	diurnal IOP*	5	yes	yes	none
Niazi and Raja, Pakistan ⁵²	3	60	latanoprost versus dorzolamide	diurnal IOP	2	unclear	NR	none
O'Donoghue and UK and Ireland Latanoprost Group, UK and Ireland (12 centres) ⁵⁴	3	224	latanoprost versus dorzolamide	diurnal IOP	2	no	yes	none
Ozdemir and Ozdemir, Turkey ⁵⁶	3	60	latanoprost versus carteolol-pilocarpine combination	diurnal IOP	2	no	NR	none
Sihota <i>et al.</i> , India ⁴⁷	6	30	latanoprost versus timolol	diurnal IOP	3	yes	NR	cross-over study with each Rx for 3 months, then cross-over
Watson, Stjerschantz and UK Latanoprost Group, UK (14 centres) ⁴⁸	6	294	latanoprost versus timolol	diurnal IOP	5	no	yes	none

*Calculated by reviewers; †Mastropasqua *et al.* was intention to treat (ITT) at 6 months but not at 12 months; N=number of participants; NR=not reported.

APPENDIX 4: Evidence Tables

Table 1A: Trial characteristics of Alm and Stjernschantz study					
Author, Year, Location	Study Design, Treatment Duration, Study Duration	Participants	Intervention(s)	Outcomes	Funding Source(s) and Conflicts of Interest
Alm and Stjernschantz, 1995; Sweden; this study also reported in: Alm, 1995; and Fristrom, 1996; Fristrom was report of 31 patients enrolled from his centre in larger trial	Double-masked, randomized, multi-centre, parallel-group design comparing 2 treatment regimes of 0.005% latanoprost and 1 of 0.5% timolol; study conducted in 13 Scandinavian eye clinics; treatment duration for each patient 6 months; study duration not reported	<p>267 adults; Baseline characteristics</p> <ul style="list-style-type: none"> • males 116 (43%), females 151 (57%) • age, mean 67 years, range 40 to 85 years • race, 99.6% white • diagnoses of ocular hypertension, 46%; OAG, 34%; capsular glaucoma, 16%; mixed, 3%; pigmentary, 0.4% • bilateral treatment: 171 patients (64%). <p>Inclusion criteria</p> <ul style="list-style-type: none"> • age >40 years • newly diagnosed unilateral or bilateral OAG, capsular glaucoma, pigmentary glaucoma, or ocular hypertension (IOP \geq22 mm Hg pre-study) • little or no prior glaucoma treatment • if bilateral prescription required, eligibility must be fulfilled for both eyes. <p>Exclusion criteria</p> <ul style="list-style-type: none"> • use of topical β-blocker within 6 months or >3 months in past • history of acute angle-closure glaucoma • severe trauma • intraocular surgery or laser within 6 months • contact-lens use • history of severe dry eye syndrome • ocular inflammation within 3 months • cannot use β-blockers because of systemic disease • investigator thought monotherapy would be insufficient. 	<p>Washout period after previous treatment</p> <ul style="list-style-type: none"> • 2 weeks for adrenergic agonists • 5 days for pilocarpine or carbonic anhydrase inhibitors. <p>All patients used drops 2 times daily. Only affected eyes treated. Three treatment groups</p> <ul style="list-style-type: none"> • latanoprost group 1: latanoprost 0.005% once daily in morning \times 3 months, then afternoon \times 3 months; for other daily dose, used drops containing only vehicle (n=89) • latanoprost group 2: latanoprost 0.005% once daily in afternoon \times 3 months, then morning \times 3 months; for other daily dose, used drops containing only vehicle (n=94) • timolol 0.5% 2 times daily (n=84). 	<p>Visits conducted at baseline, and at 2, 6, 12, 18, and 26 weeks. Examinations done at 0800, 1200, and 1600 at baseline, 12 weeks, and 26 weeks. Examinations at 0800 only at 2, 6, and 18 weeks.</p> <p>Outcomes assessed: IOP via Goldman tonometry, conjunctival hyperemia. With bilateral treatment, mean IOPs calculated. Diurnal IOPs (average of IOPs at 0800, 1200, 1600) reported at 3 and 6 months. Diurnal IOP after 6 months of treatment used to compare efficacy of 2 drugs.</p>	<p>1st author is consultant to Pharmacia; 2nd author employed by Pharmacia. Both authors deny proprietary interest in development and marketing of latanoprost.</p>

IOP=intraocular pressure; mm Hg=millimetres of mercury.

Table 1B: Results of Alm and Stjernschantz study

Results		AEs, Including Serious AEs	Withdrawals and Dropouts; ITT Analysis (Yes or No)	Limitations Described by Study Authors	Study-Quality Measures
Primary: Change in IOP (from Baseline)	Secondary				
<p>Diurnal IOP: mean±SE (number of patients) and change from baseline</p> <ul style="list-style-type: none"> • latanoprost 1 <ul style="list-style-type: none"> ○ baseline 24.8±0.4 (89) ○ 3 months 17.1±0.3 (80) ○ 6 months 16.2±0.3 (84) ○ change at 3 months 7.7 ○ change at 6 months 8.6 • latanoprost 2 <ul style="list-style-type: none"> ○ baseline 25.5±0.3 (94) ○ 3 months 16.4±0.3 (85) ○ 6 months 17.7±0.3 (85) ○ change at 3 months 8.9 ○ change at 6 months 7.8 • timolol <ul style="list-style-type: none"> ○ baseline 24.6±0.4 (84) ○ 3 months 17.3±0.3 (78) ○ 6 months 16.9±0.3 (79) ○ change at 3 months 7.3 ○ change at 6 months 7.7 <p>Both drugs reduced IOP significantly</p> <ul style="list-style-type: none"> • lowest reduction, timolol at 6 months (26%) • greatest reduction, latanoprost in afternoon (35%) • IOP reduction for L1 at 6 months versus timolol p<0.01 • IOP reduction for L2 at 3 months versus timolol p<0.01 • IOP reduction observed at 2 weeks usually preserved throughout 6 months with little loss of effect 	<p>% patients with different degree of increase in conjunctival hyperemia at last examination for 175 patients treated with latanoprost and 82 patients treated with timolol (latanoprost/timolol):</p> <ul style="list-style-type: none"> • no increase (68.6/84.1) • barely detectable or 0.5 (26.3/9.8) • mild or 1.0 (5.1/6.1) • for 2 patients, reported as AE. <p>Hyperemia graded from standard photographs, from 0 (no) to 3 (severe) in 0.5 increments. These numbers differ in Alm, n=NR</p> <ul style="list-style-type: none"> • no increase (60.8/72.6) • barely detectable (27.1/22.6) • mild (11.0/4.8) • mild to moderate (1.1/0). <p>% patients with increased conjunctival hyperemia compared to baseline</p> <ul style="list-style-type: none"> • latanoprost 31.4 • timolol 15.9. 	<p>Ocular AEs [latanoprost (n=183)/timolol (n=84)]</p> <ul style="list-style-type: none"> • ocular discomfort (8/4) • corneal punctate erosions (2/1) • blurred vision (2/0) • hyperemia (2/0) • disc hemorrhage (3/3) • increased iris pigmentation (5/0) • conjunctivitis (1/2) • other (2/3). <p>Cardiac AEs (latanoprost/timolol) 2/0.</p> <p>Serious AEs</p> <ul style="list-style-type: none"> • latanoprost group (11/183) <ul style="list-style-type: none"> ○ double vision ○ back pain or meningioma ○ pancreatic cancer ○ breast-cancer metastases ○ esophageal tumour ○ deep venous thrombosis ○ leg venous thrombosis ○ angina ○ vitreous hemorrhage ○ arrhythmias ○ central retinal-artery thrombosis ○ central retinal-vein thrombosis • timolol group (2/84) <ul style="list-style-type: none"> ○ retinal-vein occlusion ○ visual-field deterioration. 	<p>267 patients enrolled; 248 remained at study conclusion (Alm reports 252 completed). Reasons for withdrawal (number of patients: latanoprost/timolol/total)</p> <ul style="list-style-type: none"> • centre withdrew after hearing about iris pigmentation (2/3/5) • IOP not controlled (1/1/2) • repeated corneal abrasions (1/0/1) • retinal-artery embolus (1/0/1) • central retinal-vein thrombosis (1/0/1) • increased iris pigmentation (1/0/1) • decreased visual acuity secondary to diabetes mellitus (1/0/1) • burning sensation of tongue (1/0/1) • headache (0/1/1). • cancer metastasis (1/0/1). <p>No ITT analysis. Withdrawals and dropouts excluded in efficacy comparison.</p>	<p>none described</p>	<p><i>Jadad score 5/5.</i> <i>Allocation concealment adequate.</i></p>

AE(s)=adverse event(s); IOP=intraocular pressure; ITT=intent to treat analysis; NR=not reported.

Table 2A: Trial characteristics of Barnebey *et al.* study

Author, Year, Location	Study Design, Treatment Duration, Study Time Span	Participants	Intervention(s)	Outcomes	Funding Source(s) and Conflicts of Interest
Barnebey <i>et al.</i> , 2005; US (Washington, Texas, Oregon)	<p>Double masked, randomized, multi-centre, parallel-group design comparing travoprost+ timolol solution with travoprost and timolol.</p> <p>Study conducted at 33 sites by 33 investigators.</p> <p>Treatment duration for each patient: 3 months.</p> <p>Study time span NR</p>	<p>263 adults (258 completed at least 1 visit on therapy and were considered in ITT analysis).</p> <p>Baseline characteristics</p> <ul style="list-style-type: none"> • males 126 (49%); females 132 (51%) • age mean 63±11.2 years; range 31 to 91 • white 165 (64%), black 60 (23%), Hispanic 31 (12%), Asian, 2 (1%) • diagnoses of ocular hypertension 80 (31%); OAG 174 (67%); pigmentary glaucoma 2 (1%); pseudoexfoliation glaucoma 2 (1%) • differences among 3 study groups NS. <p>Inclusion criteria</p> <ul style="list-style-type: none"> • age ≥18 years • OAG or ocular hypertension confirmed on multiple visits over 6-month period • able to discontinue all ocular hypotensive medications at time of screening • met mean IOP (mm Hg) entry criteria in ≥1 eye on 2 visits • baseline IOP ≥26 at 0800, ≥24 at 1000, ≥22 at 1600 • second visit ≥26 at 0800. <p>Exclusion criteria</p> <ul style="list-style-type: none"> • mean IOP >36 mm Hg at any visit • other forms of glaucoma • severe, chronic, or progressive eye disease • recent therapy with investigational agent • hypersensitivity to study medications • eye surgery within 6 months or laser within 3 months • VA worse than 0.6 logMAR score • cup-to-disc ratio >0.8 • severe central visual-field loss (defined) • asthma, COPD, angina, renal • pregnant, lactating, no contraception. 	<p>Washout period after previous treatment</p> <ul style="list-style-type: none"> • 2 weeks for α- and β-adrenergic agonists • 4 weeks for β-adrenergic blockers, PGAs, dorzolamide+ timolol fixed combinations • 5 days for miotics and carbonic anhydrase inhibitors. <p>All patients used drops twice daily. Dose was 1 drop per eye. Unclear if unaffected eyes treated. Patients randomized 1:1:1 in 1 of 3 treatment groups</p> <ul style="list-style-type: none"> • travoprost 0.004%+ timolol 0.5%: study medication 1 drop once daily in morning with 1 drop of vehicle in afternoon (n=82) • travoprost 0.004%: study medication 1 drop once daily in morning with 1 drop of vehicle in afternoon (n=84) • timolol 0.5%: study medication 1 drop twice daily in morning and afternoon (n=92). 	<p>Visits conducted at 2, 6, and 12 weeks post-randomization. Assessed at each visit</p> <ul style="list-style-type: none"> • IOP via Goldman tonometry at 0800, 1000, and 1600 • ocular hyperemia at 0800, 1000, and 1600 • pulse and BP at 0800 and 1000 • logMAR and slit-lamp examination at 0800. <p>Assessed at 6 and 12 weeks: iris or lash photographs. Assessed at study conclusion: dilated fundus examination.</p>	<p>Study supported by Alcon Research Ltd. 3 of 7 authors employed by Alcon Research Ltd.</p>

BP=blood pressure; COPD=chronic obstructive pulmonary disease; IOP=intraocular pressure; ITT=intent to treat [analysis]; logMAR=logarithm of minimum angle of resolution; mm Hg=millimetres of mercury; NR=not reported; NS=not significant; OAG=open-angle glaucoma; PG=prostaglandin; US= United States; VA=visual acuity.

Table 2B: Results of Barnebey *et al.* study

Results		AEs, Including Serious AEs	Withdrawals and Dropouts; ITT Analysis (Yes or No)	Limitations Described by Study Authors	Study-Quality Measures
Primary: Change in IOP (from Baseline)	Secondary				
<p>Mean IOP decreases from baseline at 3 months in mm Hg (\pmSD)</p> <ul style="list-style-type: none"> • travoprost+timolol [n=82] <ul style="list-style-type: none"> ○ 0800: 11.5 (3.9) ○ 1000: 10.4 (4.0) ○ 1600: 8.8 (4.2) • travoprost [n=84] <ul style="list-style-type: none"> ○ 0800: 9.1 (4.3) ○ 1000: 8.7 (3.8) ○ 1600: 7.7 (3.8) • timolol [n=92] <ul style="list-style-type: none"> ○ 0800: 8.5 (3.5) ○ 1000: 8.1 (3.8) ○ 1600: 6.8 (4.1). <p>Although travoprost-alone and timolol-alone data presented, differences between them are not calculated. Patients on travoprost+timolol had significantly greater IOP decreases than those on travoprost alone or timolol alone.</p>	<p>Ocular hyperemia</p> <ul style="list-style-type: none"> • travoprost+timolol: 12 patients (14.1%) • travoprost: 10 (11.6%) • timolol: 1 (1.1%). <p>Other outcomes showed no clinically relevant, treatment-related changes</p> <ul style="list-style-type: none"> • pulse and BP • logMAR and slit lamp • iris or lash photographs • dilated fundus examination. 	<p>Safety analysis included all 263 initially enrolled, including those who did not have on-therapy visits. Ocular hyperemia reported under secondary results. Other types of AEs (travoprost+timolol/travoprost/timolol) (%):</p> <ul style="list-style-type: none"> • discomfort 7.1/2.3/6.5 • pruritis 2.4/2.3/1.1 • dry eye 2.4/2.3/2.2 • photophobia 4.7/1.2/0 • FB sensation 2.4/2.3/1.1 • hair disorder 4.7/1.2/0 • keratitis 2.4/1.2/0 • blurred vision 1.2/0/2.2 • lid disorder 1.2/2.3/0 • pain 0/3.5/0 • headache 2.4/0/1.1. 	<p>Of 258 patients considered in efficacy analysis (all had 1+on-therapy visit), 248 returned for 12-week visit (96%). Reason for dropouts not reported.</p> <p>ITT analysis: yes.</p>	<p>none described.</p>	<p><i>Jadad score</i>4/5. <i>Allocation concealment</i> adequate.</p>

AE(s)=adverse event(s); BP=blood pressure; IOP=intraocular pressure; ITT=intent to treat [analysis]; logMAR=logarithm of minimum angle of resolution; SD=standard deviation.

Table 3A: Trial characteristics of Camras and Sheu study

Author, Year, Location	Study Design, Treatment Duration, Study Time Span	Participants	Intervention(s)	Outcomes	Funding Source(s) and Conflicts of Interest
Camras and Sheu, 2005 for US Latanoprost-Brimonidine Study Group, leader author from Nebraska	<p>Randomized, multi-centre, parallel-group design with masked evaluators comparing latanoprost 0.005% once daily with brimonidine tartrate 0.2% twice daily.</p> <p>Study conducted at 23 sites.</p> <p>Treatment duration for each patient: 6 months.</p> <p>Study time span NR.</p>	<p>303 adults baseline characteristics</p> <ul style="list-style-type: none"> • males 147 (49%); females 154 (51%) • age mean 63 years; range 24 to 88 • white 207 (69%); black 75 (25%), other 19 (6%) • diagnoses of ocular hypertension 149 (49%); POAG 141 (46%); exfoliation glaucoma 5 (2%); mixed 3 (1%); other 3 (1%) • bilateral eyes affected, 212 patients (70.4%) • baseline mean diurnal IOP 24.7 mm Hg • medical therapy pre-study: none 61 (20%); latanoprost 61 (20%); brimonidine 26 (15%); other (mainly β-adrenergic blockers) 135 (45%). <p>Inclusion criteria</p> <ul style="list-style-type: none"> • age \geq18 years • POAG or ocular hypertension • naïve to glaucoma therapy or on topical monotherapy treatment • best corrected VA 20/80 or better • IOP of study eye(s) \geq22 mm Hg. <p>Exclusion criteria</p> <ul style="list-style-type: none"> • closed or barely open anterior chamber angle or history of acute angle closure • history of laser trabeculoplasty within 3 months • history of ocular surgery or infection within 3 months • hypersensitivity to study medications • other eye disorders that investigators thought prevented participation • α-adrenergic agonist contraindications • systemic medications affecting IOP • pregnancy, lactation, no contraception • investigational medication within 1 month. 	<p>Washout period after previous treatment:</p> <ul style="list-style-type: none"> • 2 weeks for adrenergic agonists • 4 weeks for β-adrenergic antagonists and PGAs • 5 days for cholinergic agonists and carbonic anhydrase inhibitors. <p>At baseline visit, eligible patients stratified according to previous glaucoma therapy (latanoprost, brimonidine, other, none) and then randomized.</p> <p>Two treatment groups</p> <ul style="list-style-type: none"> • latanoprost 0.005% once daily at 0800 (n=152) • brimonidine 0.2% twice daily at 0800 and 2000 (n=151). <p>Patients requiring bilateral IOP-reducing therapy treated in both eyes</p> <ul style="list-style-type: none"> • only eyes meeting all inclusion and exclusion criteria included in statistical analyses • mean values used when both eyes eligible • treated but excluded eyes used in safety analyses, not efficacy. 	<p>Visits conducted at 0.5, 3, 6, and 6.5 months after screening and baseline visits. Assessed at every visit, IOP measured with Goldman applanation tonometry at 0800, 1000, 1200, and 1600 (except week 2, only at 0800)</p> <ul style="list-style-type: none"> • VA • slit-lamp examination • other ocular findings • BP, pulse • AEs. <p>Assessed less often</p> <ul style="list-style-type: none"> • visual field • ophthalmoscopy. 	<p>Study supported by Pharmacia Corp. (NY), manufacturer of latanoprost ophthalmic solution 0.005% (Xalatan[®]) and by unrestricted university grant from Research to Prevent Blindness (RPB), Inc., which is non-government agency that “relies on bequests and selective appeals to interested individuals, corporations and private foundations to support its research effort.”</p> <p>First author was Pharmacia consultant and is now RPB, Inc. investigator.</p> <p>Second author was Pharmacia (Canada) employee when study conducted.</p>

AE(s)=adverse event(s); BP=blood pressure; IOP=intraocular pressure; mm Hg=millimetres of mercury; NR=not reported; OAG=open-angle glaucoma; US=United States; VA=visual acuity.

Table 3B: Results of Camras and Sheu study

Results		AEs, Including Serious AEs	Withdrawals and Dropouts; ITT Analysis (Yes or No)	Limitations Described by Study Authors	Study-Quality Measures
Primary: Change in IOP (from Baseline)	Secondary				
<p>Mean IOP decreases from baseline at 6 months in mm Hg [ITT analysis]:</p> <ul style="list-style-type: none"> • latanoprost (n=152) <ul style="list-style-type: none"> ○ 0800: 5.7 ○ 1000: 5.2 ○ 1200: 5.4 ○ 1600: 6.5 ○ diurnal:* 5.8. • brimonidine (n=151) <ul style="list-style-type: none"> ○ 0800: 2.8 ○ 1000: 5.4 ○ 1200: 5.0 ○ 1600: 3.1 ○ diurnal:* 3.3. <p>All values at 6 months significantly lower than baseline values (p<0.001). IOP decrease at 6 months for latanoprost versus brimonidine:</p> <ul style="list-style-type: none"> • latanoprost>brimonidine at 0800, 1600, diurnal (p<0.001) • latanoprost>brimonidine at 1200 (p=0.08) • latanoprost versus brimonidine at 1000 (NS). <p>*Diurnal IOP was mean of measurements at 0800, 1200, and 1600.</p>	<p>Mean reduction of diurnal IOP values from baseline to 6 months (p<0.001)</p> <ul style="list-style-type: none"> • latanoprost, 22.6% • brimonidine, 12.8%. <p>Percentage of patients achieving pre-specified mean diurnal IOP reductions after 6 months treatment (latanoprost/brimonidine)</p> <ul style="list-style-type: none"> • IOP reduction≥10% 86/66 • IOP reduction≥25% 44/13 • IOP reduction≥40% 8/0 • p<0.001 for each difference between groups. 	<p>All treated eyes included in safety analysis. 189/303 patients reported ≥1 AE (62.4%). Serious AEs (none judged related to study medications) latanoprost: 7 brimonidine: 10. Ocular AEs (most common)</p> <ul style="list-style-type: none"> • latanoprost, n=152 <ul style="list-style-type: none"> ○ red eye (15) ○ eye irritation (12). • brimonidine, n=151 <ul style="list-style-type: none"> ○ eye irritation (14) ○ conjunctival disorder unspecified (11) ○ painful red eye (10) ○ allergic conjunctivitis (4). 	<p>Patient numbers:</p> <ul style="list-style-type: none"> • randomized, 303 • assessed at 3 months, 275 • assessed at 6 months, 250. <p>Withdrawals due to AEs described</p> <ul style="list-style-type: none"> • latanoprost, 4 (3%) • brimonidine, 23 (15%) <ul style="list-style-type: none"> ○ 67% external ocular ○ 20% CNS (fatigue, dizziness, somnolence, mental impairment, or headache). <p>ITT analysis: yes. Included all patients who received study medications and had ≥1 IOP evaluation after treatment. Last-observation-carried-forward used to impute missing data.</p> <p>Per-protocol analysis conducted including all patients who provided data at baseline and month 6.</p>	<p>none described</p>	<p><i>Jadad score 5/5. Allocation concealment adequate.</i></p>

AE(s)=adverse event(s); CNS=central nervous system; IOP=intraocular pressure; ITT=intent to treat [analysis]; NS=not significant.

Table 4A: Trial characteristics of Camras and US Latanoprost Study Group

Author, Year, Location	Study Design, Treatment Duration, Study Time Span	Participants	Intervention(s)	Outcomes	Funding Source(s) and Conflicts of Interest
<p>Camras and US Latanoprost Study Group, 1996; lead author from Nebraska, centres from 12 other states</p>	<p>Double-masked, randomized, multi-centre, parallel-group design comparing latanoprost 0.005% once daily with timolol 0.5% twice daily.</p> <p>Study conducted at 17 sites.</p> <p>Treatment duration for each patient: 6 months.</p> <p>Study time span not reported.</p>	<p>268 adults</p> <p>Baseline characteristics</p> <ul style="list-style-type: none"> • males 114 (43%); females 154 (57%) • age mean 62 years; range 30 to 90 • white 185 (69%), black 65 (24%), Hispanic 16 (6%), Asian 1 (1%) • family history of glaucoma or ocular hypertension 95 (35%) • diagnoses of ocular hypertension 170 (63%); POAG 84 (31%); exfoliation 5 (2%); pigmentary dispersion 4 (2%); different diagnosis in each eye 5 (2%). <p>Inclusion criteria</p> <ul style="list-style-type: none"> • POAG, ocular hypertension, exfoliation syndrome, or pigmentary dispersion syndrome • at least 1 eye with IOP ≥ 22 mm Hg while on ≤ 1 ocular hypotensive drug • with 1 affected eye, treatment for other eye would be with study drops or no treatment • projection that IOP of affected eye(s) would be effectively controlled for 6 months. <p>Exclusion criteria, e.g.,</p> <ul style="list-style-type: none"> • age <40 years • pregnant, considering pregnancy, lactating • eye diseases such as advanced glaucoma at risk of progression during washout period, narrow angles or peripheral anterior synechiae, other types of glaucoma, and active eye disease • contraindications to β-blockers • inability to adhere to protocols, history of non-compliance, unreliability. 	<p>Washout period after previous treatment</p> <ul style="list-style-type: none"> • 2 weeks for adrenergic agonists • 3 weeks for β-adrenergic antagonists • 5 days for cholinergic agonists and carbonic anhydrase inhibitors. <p>All patients used drops twice daily. Dose of 1 drop per eye. Patients treated in 1 or both eyes.</p> <p>Two treatment groups</p> <ul style="list-style-type: none"> • latanoprost 0.005%: 1 drop once daily in afternoon at 2000 hours with 1 drop of vehicle at 0800 in morning (n=128) • timolol 0.5%: 1 drop twice daily at 0800 in morning and 2000 in afternoon (n=140). 	<p>Visits conducted at 0.5, 1.5, 3, 4.5, and 6 months. Baseline and 6 months patients assessed at 0800, 1200, and 1600. Other visits, only at 0800.</p> <p>Assessed at every visit</p> <ul style="list-style-type: none"> • IOP measured with Goldman applanation tonometry • conjunctival hyperemia • slit-lamp examination • AEs. <p>Assessed less often</p> <ul style="list-style-type: none"> • visual fields • BP • pulse • iris colour • blood • urine. <p>If both eyes of patient treated, mean IOP value for both eyes used for analysis.</p>	<p>Study sponsor: Pharmacia Pharmaceuticals, Sweden, manufacturer of latanoprost ophthalmic solution 0.005% (Xalatan[®]).</p> <p>Lead author is consultant to Pharmacia Ophthalmics and Alcon Laboratories. Reference states that no author has proprietary interest in development or marketing of any drug in this study or any competing drug.</p>

AE(s)=adverse event(s); BP=blood pressure; IOP=intraocular pressure; mm Hg=millimetres of mercury; OAG=open-angle glaucoma; US=United States.

Table 4B: Results of Camras and US Latanoprost Study Group

Results		AEs, Including Serious AEs	Withdrawals and Dropouts; ITT Analysis (Yes or No)	Limitations Described by Study Authors	Study-Quality Measures
Primary: Change in IOP (from Baseline)	Secondary				
<p>Mean IOP decreases from baseline at 6 months in mm Hg (±SD) at 0800h, 12 hours after last dose (not ITT analysis)</p> <ul style="list-style-type: none"> • latanoprost 6.7(3.4) • timolol 4.9 (2.9). <p>Data for other assessments (0.5, 1.5, 3, and 4.5 months) only presented in figure but looked similar to 6-month data.</p> <p>Authors report both medications caused significant change in IOP from baseline throughout therapy (p<0.001).</p> <p>Authors report latanoprost was significantly more effective hypotensive agent than timolol (p<0.001).</p>	<p>Conjunctival hyperemia mean grade at 6 months (±SD)</p> <ul style="list-style-type: none"> • latanoprost [n=128]: mean grade 0.4 (0.4) • timolol [n=140]: mean grade 0.3 (0.3). <p>Hyperemia graded from standard photographs: 0 (none) to 3 (severe) in increments of 0.5.</p> <p>Iris pigmentation increased in 1 (definite) and 3 (possible) cases among patients on latanoprost.</p> <p>Other ocular outcomes (VA, slit-lamp examination) unchanged by either drug in follow-up visits.</p> <p>Heart rate did not change in latanoprost group but dropped significantly in timolol group (from 75 to 71 beats per minute at 6 months; p<0.001).</p> <p>BP and laboratory values did not change for patients on either drug over time.</p>	<p>Ocular AEs overall</p> <ul style="list-style-type: none"> • latanoprost, 20 AEs in 10 patients (8%) • timolol, 17 AEs in 16 patients (11%). <p>No serious ocular AEs.</p> <p>Ocular AEs between treatments were NS (except at 4.5-month visit when 20% of latanoprost patients and 13% of timolol patients had ocular symptoms; significance level not reported).</p> <p>Specific ocular AEs occurring ≥1 time in 6 months for latanoprost/timolol, as % of patients</p> <ul style="list-style-type: none"> • burning 13/10 • stinging 12/6 • blurred vision 6/10 • pruritis 11/5 • foreign body sensation 11/4 • tearing 9/2 • dry eye 4/8 • eyelid pain or discomfort 3/7 • others <10 combined. <p>Systemic AEs overall</p> <p>Serious: latanoprost 8 patients (6%); timolol 10 patients (7%).</p> <p>Two serious AEs may have been secondary to eye treatment (both patients on timolol): shortness of breath, arrhythmia with syncope.</p> <p>Other: latanoprost 23 patients (16.4%); timolol 18 patients (14.1%).</p>	<p>268 patients enrolled; 248 completed study [latanoprost 118/128 (92.2%); timolol 130/140 (92.8%)].</p> <p>Dropouts by reason (latanoprost/timolol)</p> <ul style="list-style-type: none"> • inadequate IOP control (0/4) • ocular reasons, e.g., allergic conjunctivitis (2/2) • systemic medical reasons, e.g., palpitations, rash, ulcer symptoms (4/3) • non-medical reasons, e.g., moved, lost to follow-up (4/1). <p>ITT analysis: no. Per-protocol analysis conducted. 50 patients had ≥1 IOP value excluded because of protocol violations. Authors state that calculations, including IOP values, did not change significance of results.</p>	<p>none described</p>	<p><i>Jadad score: 5/5.</i></p> <p><i>Allocation concealment adequate.</i></p>

AE(s)=adverse event(s); BP=blood pressure; IOP=intraocular pressure; ITT=intent to treat [analysis]; mm Hg=millimetres of mercury; NS=not significant; SD=standard deviation; US=United States; VA=visual acuity.

Table 5A: Trial characteristics of DuBiner *et al.* study

Author, Year, Location	Study Design, Treatment Duration, Study Time Span	Participants	Intervention(s)	Outcomes	Funding Source(s) and Conflicts of Interest
<p>DuBiner <i>et al.</i>, 2001; US (Georgia, Massachusetts, South Dakota) for Brimonidine versus Latanoprost Study Group</p>	<p>Randomized, multi-centre, double-masked, parallel-group design comparing latanoprost 0.005% once daily with brimonidine tartrate 0.2% twice daily.</p> <p>Study conducted at 5 sites.</p> <p>Treatment duration for each patient: 3 months.</p> <p>Study time span not reported.</p>	<p>127 adults</p> <p>Baseline characteristics</p> <ul style="list-style-type: none"> • males 52 (41%); females 75 (59%) • age mean 61 years; range 37 to 86; <65 years 73 (57%); ≥65 years 54 (43%) • white 88 (69%); black 30 (24%); Hispanic 9 (7%) • diagnoses of ocular hypertension 34 (27%); OAG 93 (73%) • ocular hypotensive treatment naïve 55 (43%), on treatment 72 (57%) • differences between groups NS. <p>Inclusion criteria</p> <ul style="list-style-type: none"> • age ≥18 years • bilateral OAG or ocular hypertension • no previous treatment with either study drug • IOP 22 to 34 mm Hg in each eye • corrected VA >20/100 in each eye • visual field testing within 3 months. <p>Exclusion criteria, e.g.,</p> <ul style="list-style-type: none"> • patient has significant illness that would affect study • contraindication to α-adrenergic agonists or PGAs • ocular disease • eye or laser surgery within 3 months • hypersensitivity to study medications • pregnancy or lactation. 	<p>Washout period after previous treatment</p> <ul style="list-style-type: none"> • 4 days carbonic anhydrase inhibitors • 4 days parasympathomimetics • 2 weeks sympathomimetics • 2 weeks topical α-agonists • 4 weeks topical β-blockers and combination drugs. <p>Two treatment groups</p> <ul style="list-style-type: none"> • latanoprost 0.005% once daily between 1900 and 2100 in afternoon and placebo once daily between 0700 and 0900 in morning (n=61) • brimonidine 0.2% twice daily between 0700 and 0900 in morning and between 1900 and 2100 in afternoon (n=66). <p>Treatment dose 1 or 2 drops of study drug or placebo twice daily. All patients treated in both eyes.</p>	<p>Visits conducted 1 and 3 months after baseline visit. Assessed at every visit</p> <ul style="list-style-type: none"> • IOP measured with Goldman applanation tonometry between 0900 and 1100, 120±30 minutes after study medications used • VA • slit-lamp examination • AEs. <p>Primary outcome measure % of patients achieving ≥20% reduction in IOP (mean of both eyes) from baseline to month 3, including analysis as to treatment-naïve or previously treated.</p> <p>Secondary outcome measures</p> <ul style="list-style-type: none"> • mean IOP reduction • clinical success (investigator recommended patient continue medications) • patient satisfaction assessed via questioning at 3-month visit. 	<p>Study funded by unrestricted grant from Allergan, Inc. (Irvine CA), makers of brimonidine tartrate 0.2% (Alphagan®). Authors denied proprietary interest in either study drug.</p>

AE(s)=adverse event(s); IOP=intraocular pressure; mm Hg=millimetres of mercury; NS=not significant; OAG=open-angle glaucoma; US=United States; VA=visual acuity.

Table 5B: Results of DuBiner *et al.* study

Results		AEs, Including Serious AEs	Withdrawals and Dropouts; ITT Analysis (Yes or No)	Limitations Described by Study Authors	Study-Quality Measures
Primary: Change in IOP (from Baseline)	Secondary				
<p>Mean IOP decreases from baseline at 3 months in mm Hg (\pmSD) for all patients</p> <ul style="list-style-type: none"> • latanoprost (n=61) 6.5 (3.7); 27.0% drop • brimonidine (n=66) 6.8 (3.6) 27.8% drop. 	<p>Patients achieving \geq20% reduction in IOP from baseline to 3 months (latanoprost/brimonidine)</p> <ul style="list-style-type: none"> • all patients (%) <ul style="list-style-type: none"> ○ 1 month 75/63 ○ 3 months 74/80 • treatment-naïve patients (%) <ul style="list-style-type: none"> ○ 1 month 59/54 ○ 3 months 59/88 (p=0.001) • previously treated patients (%) <ul style="list-style-type: none"> ○ 1 month 91/68 (p=0.002) ○ 3 months 88/74. <p>Patients achieving \geq20% reduction in IOP from baseline to 3 months was primary outcome of study.</p> <p>Clinical success (investigator recommended patient continue medications)</p> <ul style="list-style-type: none"> • latanoprost 45/61(74%) • brimonidine 58/64 (91%) • difference significant at p=0.001. <p>Patients satisfied or very satisfied at 3 months</p> <ul style="list-style-type: none"> • latanoprost 52/61(85%) • brimonidine 60/64 (94%) • differences NS. 	<p>No serious AEs.</p> <p>Patients reporting treatment-related AEs (latanoprost/brimonidine) (%)</p> <ul style="list-style-type: none"> • total 15/10 (24.6/15.6) • hyperemia 7/4 (11.5/6.3) • visual disturbance 2/2 (3.3/3.1) • burning 1/1 (1.6/1.6) • eyelid edema 2/0 (3.3/0) • follicles 0/1 (0/1.6) • photophobia 1/0 (1.6/0) • dry eye 0/1 (0/1.6) • headaches 1/0 (1.6/0) • nausea 1/0 (1.6/0) • drowsiness 0/1 (0/1.6) • differences between groups NS. <p>3 latanoprost patients discontinued secondary to AEs (hyperemia, nausea, headaches).</p>	<p>127 patients enrolled; 120 completed study [latanoprost, 56/61 (92%); brimonidine 64/66 (97%)]. Efficacy analysis done on 125 patients as per-protocol analysis. Data for 5 latanoprost patients withdrawn after 1-month visit carried forward for per-protocol analysis.</p> <p>Withdrawals by reason</p> <ul style="list-style-type: none"> • latanoprost (5) <ul style="list-style-type: none"> ○ AEs (3) ○ lack of efficacy (1) ○ off medications for 1 week (1). • brimonidine (2) <ul style="list-style-type: none"> ○ consent withdrawn before 1 month-visit because of admission to nursing home (1) ○ illness (1). <p>ITT analysis: no. Per-protocol analysis for 125 patients of which 5 had last-observation-carried-forward.</p>	<p>Longer study would allow further safety assessment and investigation of unexpected and unexplained findings, e.g.,</p> <ul style="list-style-type: none"> • increase in rate of response among treatment-naïve patients on brimonidine • differences in responses to study drugs in previously treated patients. 	<p><i>Jadad score</i> 5/5 (pharmacist-generated randomization schedule, although detail not provided.)</p> <p><i>Allocation concealment</i> adequate.</p>

AE(s)=adverse event(s); IOP=intraocular pressure; ITT=intent to treat [analysis]; NS=not significant; SD=standard deviation.

Table 6A: Trial characteristics of Erkin *et al.* study

Author, Year, Location	Study Design, Treatment Duration, Study Time Span	Participants	Intervention(s)	Outcomes	Funding Source(s) and Conflicts of Interest
Erkin <i>et al.</i> , 2004; Turkey	<p>Randomized, parallel-group design with masked observers, comparing latanoprost 0.005% once daily with betaxolol 0.5% twice daily.</p> <p>Treatment duration for each patient: 3 months</p> <p>Study time span NR.</p>	<p>32 adults</p> <p>Characteristics of study group (after 1 patient excluded because of non-compliance; demographic data NR)</p> <ul style="list-style-type: none"> • males 12 (39%); females 19 (61%) • mean age 52 years <ul style="list-style-type: none"> ○ latanoprost, mean age 54.3 ○ betaxolol, mean age 49.6 ○ differences NS (p=0.2) • baseline IOPs±SD <ul style="list-style-type: none"> ○ latanoprost 23.1±2.0 ○ betaxolol 24.4±3.0 ○ differences NS (p=0.18). <p>Inclusion criteria</p> <ul style="list-style-type: none"> • primary OAG • no history of treatment for glaucoma or cataracts. <p>Exclusion criteria NR</p>	<p>Washout not reported because patients all newly diagnosed.</p> <p>Two treatment groups</p> <ul style="list-style-type: none"> • latanoprost 0.005% once daily (n=16) • betaxolol 0.5% twice daily (n=16). 	<p>Visits conducted 1 and 3 months after baseline visit. Assessed at every visit</p> <ul style="list-style-type: none"> • IOP measurement with Goldman applanation tonometry, performed by 1 masked observer • visual fields • colour Doppler imaging for blood-flow velocity performed by 1 masked observer • VA • slit-lamp examination • AEs. <p>Data from right eyes of 31 patients used for analyses.</p>	NR

AE(s)=adverse event(s); IOP=intraocular pressure; NR=not reported; NS=not significant; OAG=open-angle glaucoma; SD=standard deviation; VA=visual acuity.

Table 6B: Results of Erkin *et al.* study

Results		AEs, Including Serious AEs	Withdrawals and Dropouts; ITT Analysis (Yes or No)	Limitations Described by Study Authors	Study-Quality Measures
Primary: Change in IOP (from Baseline)	Secondary				
<p>Only data from patients' right eyes used for analysis.</p> <p>Mean decrease in IOP±SD at 3 months</p> <ul style="list-style-type: none"> • latanoprost 5.2±3.5 (p=0.001) • betaxolol 3.3±2.3 (p=0.001) • latanoprost effect>betaxolol effect (p=0.03). <p>These values presented in text; different numbers appear in Table 1 of Erkin <i>et al.</i></p>	<p>Visual-field analyses: changes from baseline for patients on both medications NS.</p> <p>Changes in blood-flow velocity in retrobulbar vessels for patients on both medications (measured using CDI)</p> <ul style="list-style-type: none"> • NS with respect to baseline • NS with respect to each other. 	NR	32 patients enrolled; 31 completed study (1 latanoprost patient excluded because of non-compliance). ITT analysis: no. 1 patient excluded because of non-compliance not considered in analysis.	Operator of CDI could have erred in measurement. Several authors' comments on short study period.	<i>Jadad score 2/5. Allocation concealment unclear.</i>

AE(s) =adverse event(s); CDI=colour Doppler imaging; IOP=intraocular pressure; ITT=intent to treat [analysis]; NR=not reported; NS=not significant.

Table 7A: Trial characteristics of Fechtner *et al.* study

Author, Year, Location	Study Design, Treatment Duration, Study Time Span	Participants	Intervention(s)	Outcomes	Funding Source(s) and Conflicts of Interest
<p>Fechtner <i>et al.</i>, 2004; US (New Jersey, Pennsylvania) and Finland; on behalf of Cosopt versus Xalatan Study Groups. Study also reported in Fechtner <i>et al.</i>, 1999 (abstract)</p>	<p>2 studies with identical designs: randomized, double-masked, multi-centre, parallel-group comparing latanoprost 0.005% with dorzolamide+2%/timolol 0.5% solution. Study 1 conducted at 20 sites in US. Study 2 conducted at 24 sites in 11 countries in Europe and Israel. Treatment duration for each patient: 3 months. Study time span: NR.</p>	<p>Study 1: 256 adults Study 2: 288 adults.</p> <p>Baseline characteristics, study 1</p> <ul style="list-style-type: none"> • males 47%; females 53% • mean age 62.9 years • white 67%; black 22%, other 11% • mean daytime diurnal IOP 25.9 mm Hg. <p>Baseline characteristics, study 2</p> <ul style="list-style-type: none"> • males 43%; females 57% • mean age 62.7 years • white 98%; black 2% • mean daytime diurnal IOP 25.0 mm Hg. <p>Diagnoses for groups combined: ocular hypertension 31%; OAG 68%; pigmentary glaucoma 1%.</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • age ≥18 years • bilateral OAG or ocular hypertension • IOP ≥24 mm Hg at 0800. <p>Patients could be included whether they were on ocular hypotensive treatment and regardless of its effectiveness.</p> <p>Exclusion criteria</p> <ul style="list-style-type: none"> • VA worse than 20/80 in both eyes • history or evidence of acute or chronic angle closure glaucoma • history or evidence of intraocular surgery or trauma within 6 months • intraocular laser within 3 months • contraindications to study medications. 	<p>Washout period after previous treatment</p> <ul style="list-style-type: none"> • 3 weeks for topical β-blockers, carbonic anhydrase inhibitors, latanoprost, brimonidine, apraclonidine • 1 week for epinephrine, dipivefrin • 72 hours for pilocarpine, carbachol, aceclidine. <p>Patients stratified according to iris colour.</p> <p>2 treatment groups</p> <ul style="list-style-type: none"> • latanoprost 0.005% once daily at 2200 (0800 dose was placebo) • dorzolamide 2%+timolol 0.5% twice daily between 0700 and 0900. <p>Treatment dose 1 drop. All patients treated both eyes at 0800 and 2200.</p>	<p>Visits conducted 1, 2, and 3 months after baseline visit. Assessed at every visit</p> <ul style="list-style-type: none"> • IOP measured with Goldman applanation tonometry at 0800, 1000, 1400, and 1600 • VA. <p>Diurnal IOP average of 0800, 1000, 1400, and 1600 values. All analyses performed using data from worst eye of each patient as assessed at hour 0 on day 1 (if both equal, right eye used). Performed at pre- and post-study visits</p> <ul style="list-style-type: none"> • visual fields. 	<p>Studies funded by Merck Research Labs (NJ), manufacturer of Cosopt™. Lead author receives support from unrestricted grant from RPB, Inc. RPB, Inc. is non-government agency that “relies on bequests and selective appeals to interested individuals, corporations and private foundations to support its research effort.” 2 authors have acted as paid consultants for Merck and have had studies funded by Merck. 3 authors are Merck employees.</p>

IOP=intraocular pressure; mm Hg=millimetres of mercury; NR=not reported; OAG=open-angle glaucoma; US=United States; VA=visual acuity.

Table 7B: Results of Fechtner *et al.* study

Results		AEs, Including Serious AEs	Withdrawals and Dropouts; ITT Analysis (Yes or No)	Limitations Described by Study Authors	Study-Quality Measures
Primary: Change in IOP (from Baseline)	Secondary				
<p>Mean decreases from baseline at 3 months in mm Hg for daytime diurnal IOP</p> <ul style="list-style-type: none"> • study 1 <ul style="list-style-type: none"> ○ latanoprost 7.2 ○ combination 7.2. • study 2 <ul style="list-style-type: none"> ○ latanoprost 7.2 ○ combination 7.9. <p>Detailed data not presented numerically in publication (presented graphically). Authors report that differences between responses to 2 medications were</p> <ul style="list-style-type: none"> • study 1 -0.04 (95% CI -0.85, 0.77) • study 2 -0.57 (95% CI -1.31, 0.16). 	<p>VA and visual-field data analyzed. Findings were NS, so data not presented in paper.</p>	<p>No serious AEs.</p> <p>Study 1, reported AEs by number of patients (latanoprost/combination)</p> <ul style="list-style-type: none"> • any 53/52 • drug-related 23/34 • ocular stinging 7/23* • ocular itching 4/2 • blurred vision 2/3 • conjunctival hyperemia 2/0 • taste perversion 2/10 (differences between groups statistically significant p<0.05). <p>Study 2, reported AEs by number of patients:(latanoprost/combination)</p> <ul style="list-style-type: none"> • any 24/32 • drug-related 13/17 • ocular stinging 2/10 (differences between groups statistically significant p<0.05) • ocular itching 2/1 • blurred vision 3/1 • conjunctival hyperemia 4/2 • taste perversion 0/2 <p>No cases of irreversibly increased iris pigmentation observed (authors state this is more typical after latanoprost use >6 months)</p>	<p>Study 1: 256 patients randomized; 238 (93%) completed study [latanoprost 123/128 (96%); combination 115/128 (90%)].</p> <p>Reasons for withdrawal, number of patients (latanoprost/combination)</p> <ul style="list-style-type: none"> • AE 3/8 • lack of efficacy 1/1 • protocol deviation 1/2 • withdrew 0/1 • lost 0/1. <p>Study 2: 288 patients randomized; 276 (94%) completed study [latanoprost 137/143 (96%); combination 134/145 (92%)].</p> <p>Reasons for withdrawal, number of patients (latanoprost/combination)</p> <ul style="list-style-type: none"> • AE 0/8 • lack of efficacy 2/0 • protocol deviation 2/0 • withdrew 1/3 • lost 1/0. <p>ITT analysis: yes. “All patients treated, last observation carried forward” (APT-LOCF).</p> <p>Study 1: 13 patients not analyzed and had no complete measurements beyond day 1.</p> <p>Study 2: 7 patients not analyzed and had no complete measurements beyond day 1.</p>	<p>Longer studies needed to compare tolerability between medications and to observe iris-pigmentation changes.</p>	<p><i>Jadad score 5/5. Allocation concealment adequate.</i></p>

AE(s)=adverse event(s); IOP=intraocular pressure; ITT=intent to treat [analysis]; NS=not significant; VA=visual acuity.

Table 8A: Trial characteristics of Fellman *et al.* study

Author, Year, Location	Study Design, Treatment Duration, Study Time Span	Participants	Intervention(s)	Outcomes	Funding Source(s) and Conflicts of Interest
<p>Fellman <i>et al.</i> and Travoprost Study Group 2002; US (Texas). Study group lists investigators from many sites in US and several in Canada</p>	<p>Double masked, randomized, multi-centre, parallel-group design comparing 3 treatments: timolol and 2 regimes of travoprost. Study conducted at 44 sites. Treatment duration for each patient: 6 months. Study time span NR.</p>	<p>605 adults initially enrolled; 11 did not have on-therapy data so were excluded from ITT analysis. Baseline characteristics of patients with on-therapy data (n=594)</p> <ul style="list-style-type: none"> • males 293 (49%); females 301 (51%) • mean age 63.7 years; range 21 to 91; <65 years 274 (46%); ≥65 years 320 (54%) • white 488 (82%); black, 63 (11%), Asian 4 (1%), other 9 (6%) • diagnoses of ocular hypertension 196 (33%); OAG 382 (64%); pigmentary glaucoma 14 (2%); pseudoexfoliating glaucoma 2 (<1%) • differences among groups NS, including baseline IOPs. <p>Inclusion criteria</p> <ul style="list-style-type: none"> • age ≥21 years • OAG or ocular hypertension with or without pseudoexfoliation or pigment dispersion component • IOP measurement of 24 to 36 mm Hg in 1+ eye (same eye) at 2 eligibility visits. <p>Exclusion criteria</p> <ul style="list-style-type: none"> • IOP >36 mm Hg in either eye • VA worse than 0.60 logMAR • cup-to-disc ratio >0.80 or severe central-field loss in either eye • gonioscopy-measured angle grade <2 • eye diseases • ocular trauma or surgery within 6 months • laser surgery within 3 months • women of childbearing potential • systemic diseases, e.g., cardiac, respiratory, renal, hepatic • history of hypersensitivity to study medications • glucocorticoid or NSAID use. 	<p>Washout period after previous treatment</p> <ul style="list-style-type: none"> • 5 days carbonic anhydrase inhibitors and miotics • 2 weeks sympathomimetics and topical α-agonists • 3 weeks for topical β-blockers and PGs. <p>Patients randomized by site. 3 treatment groups</p> <ul style="list-style-type: none"> • travoprost 0.0015% once daily in afternoon and matching placebo (vehicle) in morning (n=202) • travoprost 0.004% once daily in afternoon and vehicle in morning (n=201) • timolol 0.5% twice daily (n=202). <p>Treatment dose 1 drop per eye. All patients treated both eyes. 4% to 6% of patients on stable oral beta-blockers before study and continued during study. 433 patients previously treated for glaucoma.</p>	<p>Visits conducted at baseline, and at 0.5, 1.5, 3, 4.5, and 6 months. Examinations done at 0800, 1000, and 1600 at 0.5-, 3-, and 6-month visits. Examinations done at 0800 and 1000 at 1.5- and 4.5-month visits. Outcomes assessed at every visit</p> <ul style="list-style-type: none"> • IOP via Goldman tonometry • ocular hyperemia and flare or cell assessment • VA (logMAR scale) • biomicroscopy • pulse and BP. <p>Outcomes assessed less frequently</p> <ul style="list-style-type: none"> • iris or lash photographs (1.5, 3, 4.5, and 6 months) • blood, urine, dilated fundus examination, cup-to-disc ratio, and visual fields (6 months). 	<p>Study funded by Alcon Research, Ltd., manufacturers of travoprost (Travatan®). Lead author and members of Travoprost Study Group compensated for their contributions to study, but denied proprietary interest in any products mentioned in publication. 5 of 8 listed authors employed by Alcon Research, Ltd.</p>

BP=blood pressure; IOP=intraocular pressure; logMAR=logarithm of minimum angle of resolution; mm Hg=millimetres of mercury; NR=not reported; NS=not significant; OAG=open-angle glaucoma; US=United States; VA=visual acuity.

Table 8B: Results of Fellman *et al.* study

Results		AEs, Including Serious AEs	Withdrawals and Dropouts; ITT Analysis (Yes or No)	Limitations Described by Study Authors	Study-Quality Measures
Primary: Change in IOP (from Baseline)	Secondary				
<p>Efficacy data taken from patients' eye with higher baseline mean IOP. Mean IOP decreases from baseline to 6 months in mm Hg [ITT analysis]</p> <ul style="list-style-type: none"> • travoprost 0.0015% <ul style="list-style-type: none"> ○ 0800: 7.2 ○ 1000: 6.6 ○ 1600: 6.0. • travoprost 0.004% <ul style="list-style-type: none"> ○ 0800: 7.1 ○ 1000: 6.6 ○ 1600: 6.5. • timolol <ul style="list-style-type: none"> ○ 0800: 6.8 ○ 1000: 6.3 ○ 1600: 5.2. <p>P=0.0001 for all time points. Mean IOP significantly lower for both doses of travoprost versus timolol. Travoprost 0.0015% superior to timolol at 9 of 13 visits; travoprost 0.004% superior to timolol at 10 of 13 visits (and equal to timolol at other 3 visits). Differences between groups for concomitant treatment or previous treatment for glaucoma all NS.</p>	<p>No significant differences among groups for</p> <ul style="list-style-type: none"> • VA • inflammatory cells or aqueous flare • visual fields • ocular signs • fundus parameters • cup-to-disc ratio • visual fields • laboratory values. <p>Patients in timolol group had decreases in pulse (p=0.0001) and systolic BP (p=0.0022).</p>	<p>No serious AEs. No cases of CME. Ocular hyperemia</p> <ul style="list-style-type: none"> • travoprost 0.0015%, 60/202 (29%) • travoprost 0.004%, 87/201 (43%) • timolol, 18/202 (9%). <p>Changes in iris colour:</p> <ul style="list-style-type: none"> • travoprost 0.0015%, 0/202 • travoprost 0.004%, 2/201 (1%) • timolol, 0/202. <p>Reported ocular AEs: (number of patients on travoprost 0.0015%/number of patients on travoprost 0.004%/number of patients on timolol)</p> <ul style="list-style-type: none"> • pruritis (7/12/5) • pain (3/12/1) • VA decrease (9/10/9) • keratitis (6/9/4) • foreign body sensation (4/6/2) • dry eye (3/6/4) • blurred vision (6/5/6) • discomfort (5/5/9). 	<p>14 patients withdrew secondary to treatment-related AEs (8/14 secondary to ocular hyperemia)</p> <ul style="list-style-type: none"> • travoprost 0.0015%, 3/202 (1.5%) • travoprost 0.004%, 9/201 (4.5%) • timolol, 2/202 (1.0%). <p>ITT analysis: yes (defined as including all patients with ≥1 assessment on therapy). 11 patients did not have on-therapy data so were excluded from ITT analysis (n=594). Safety analysis done on all patients who received study treatment. Last observation carried forward used to impute missing data in ITT data set (patients who received ≥1 treatment and completed ≥1 on-study visit)</p>	<p>CME may not have been seen because of stringent selection criteria for study patients. Generalization may be an issue with wider use.</p>	<p><i>Jadad score 5/5. Allocation concealment adequate.</i></p>

AE(s)=adverse event(s); BP=blood pressure; CME=cystoid macular edema; IOP=intraocular pressure; ITT=intent to treat [analysis]; mmHg =millimetres of mercury; NS=not significant; VA=visual acuity.

Table 9A: Trial characteristics of Goldberg *et al.* study

Author, Year, Location	Study Design, Treatment Duration, Study Time Span	Participants	Intervention(s)	Outcomes	Funding Source(s) and Conflicts of Interest
Goldberg <i>et al.</i> , 2001; Australia, Portugal, Norway, US	Double masked, randomized, parallel-group design comparing 2 concentrations of travoprost with timolol. Study conducted at 64 sites in Australia, Belgium, Finland, France, Germany, Iceland, Ireland, Italy, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, UK. Treatment duration for each patient: 9 months. Study time span NR.	<p>573 adults</p> <p>Baseline characteristics</p> <ul style="list-style-type: none"> • males 49.7%; females 50.3% • age <65 years 51.7%; age ≥65 years 48.3% • white 97.9% • diagnoses of OAG 54.7%; ocular hypertension 38.6%; pigmentary glaucoma 1.6%; pseudoexfoliation glaucoma 5.1% • no significant differences in baseline characteristics among patients in 3 groups. <p>Inclusion criteria</p> <ul style="list-style-type: none"> • OAG or ocular hypertension • after wash-out of previous medications (≥5 days) <ul style="list-style-type: none"> ○ IOP 24 to 36 mm Hg at 0900 in ≥1 eye ○ IOP 21 to 36 in same eye at 1100 and 1600 on 2 eligibility visits. <p>Exclusion criteria</p> <ul style="list-style-type: none"> • extensive, e.g., <ul style="list-style-type: none"> ○ best-corrected VA worse than 0.60 logMAR in either eye ○ cup-to-disc ratio >0.80 ○ severe central-field loss ○ angle grade <2 ○ ocular trauma or surgery within 6 months or ocular infection, inflammation, laser surgery within 3 months ○ severe inflammatory eye disease ○ significant or progressive retinal disease ○ severe ocular pathology ○ underlying medical conditions preventing use of topical β blocker or topical prostaglandin, or β-blocker or prostaglandin hypersensitivity. 	<p>Drops instilled in both eyes.</p> <p>Low-dose travoprost group</p> <ul style="list-style-type: none"> • 0900: travoprost vehicle • 2100: travoprost 0.0015%. <p>Higher-dose travoprost group</p> <ul style="list-style-type: none"> • 0900: travoprost vehicle • 2100: travoprost 0.004%. <p>Timolol group:</p> <ul style="list-style-type: none"> • 0900: timolol 0.5% • 2100: timolol 0.5%. 	<ul style="list-style-type: none"> • IOP measured with Goldman applanation tonometry <ul style="list-style-type: none"> ○ 0900, 1100, and 1600 at baseline and week 2, month 3, month 9 ○ 0900 and 2300 at month 1.5, month 4.5, month 6. • best-corrected VA • monitoring for AEs <ul style="list-style-type: none"> ○ ocular hyperemia ○ ocular flare ○ ocular signs using slit lamp ○ dilated fundus examination ○ visual fields ○ iris colour ○ pulse, BP, AEs. 	study supported by Alcon Research Ltd. (Texas), manufacturer of travoprost

AE(s)=adverse event(s); BP=blood pressure; IOP=intraocular pressure; logMAR=logarithm of minimum angle of resolution; mm Hg=millimetres of mercury; OAG=open-angle glaucoma; UK=United Kingdom; US=United States; VA=visual acuity.

Table 9B: Results of Goldberg *et al.* study

Results		AEs, Including Serious AEs	Withdrawals and Dropouts; ITT Analysis (Yes or No)	Limitations Described by Study Authors	Study-Quality Measures
Primary: Change in IOP (from Baseline)	Secondary				
<p>Mean IOP decreases from baseline (mm Hg)* [ITT analysis]</p> <ul style="list-style-type: none"> • travoprost 0.0015% <ul style="list-style-type: none"> ○ 3 months: 7.9 (reported range 7.1 to 8.3) ○ 6 months: 8.2 (reported range 8.1 to 8.2) ○ 9 months: 8.0 (reported range 7.9 to 8.3). • travoprost 0.004% <ul style="list-style-type: none"> ○ 3 months: 8.6 (reported range 8.0 to 8.9) ○ 6 months: 8.8 (reported range, 8.7 to 8.9) ○ 9 months: 8.3 (reported range 8.0 to 8.5). • timolol <ul style="list-style-type: none"> ○ 3 months: 7.3 (reported range 6.3 to 7.9) ○ 6 months: 7.9 (reported range 7.8 to 7.9) ○ 9 months: 7.1 (reported range 6.4 to 7.6). <p>Mean [peak and trough drug activity] IOP (mm Hg) decreases from baseline [ITT analysis]:</p> <ul style="list-style-type: none"> • travoprost 0.0015% [9 a.m.; 4 pm] <ul style="list-style-type: none"> ○ 3 months: 8.1; 7.5 ○ 6 months: 8.2; NR ○ 9 months: 8.3; 7.8. • travoprost 0.004% [9 a.m.; 4 pm]: <ul style="list-style-type: none"> ○ 3 months: 8.7; 8.5 ○ 6 months: 8.9; NR ○ 9 months: 8.5; 8.0. • timolol [11 AM; 9 a.m.][†] <ul style="list-style-type: none"> ○ 3 months: 7.4; 7.8 ○ 6 months: 7.8; 7.9 ○ 9 months: 7.4; 7.6. <p>For travoprost 0.004% versus timolol, all changes statistically significant at all visits ($p \leq 0.0001$).</p> <p>Significance of travoprost 0.0015% versus timolol difference NR (though implied as NS).</p>	<p>No clinically significant treatment differences in change from baseline for</p> <ul style="list-style-type: none"> • VA • ocular flare • ocular signs • fundus parameters • cup-to-disc ratios • visual fields • pulse (BP NR). 	<p>AEs by study group</p> <ul style="list-style-type: none"> • travoprost 0.0015% (n=190): 104 • travoprost 0.004% (n=197): 117 • timolol (n=186): 29. <p>Types of AEs (low-dose travoprost/high-dose travoprost/timolol) (%)</p> <ul style="list-style-type: none"> • hyperemia 25.8/32.5/7 • Stinging or burning or pruritis 11.1/13.7/3.8 • iris discolouration 5.3% of 0.0015% group • all other AEs occurred in <5% of patients in each group • no CME reported • no serious AEs. 	<p>16 patients withdrew secondary to treatment-related ocular AEs</p> <ul style="list-style-type: none"> • travoprost 0.0015%, 4/190 (2.1%) • travoprost 0.004%, 9/197 (4.6%) • timolol, 3/186 (0.5%). <p>1 patient excluded from ITT analysis because of lack of data.</p> <p>3 analyses performed</p> <ul style="list-style-type: none"> • safety (n=573): all patients who received study medication • ITT (n=572): all patients with study medication who completed ≥ 1 study visit • per-protocol (n=507): as above plus satisfied all inclusion and exclusion criteria <ul style="list-style-type: none"> ○ 1 patient excluded because of lack of data ○ 65 patients excluded because of protocol violations (e.g., non-qualifying IOP, inadequate washout, contraindicated medications, dosing errors). 	<p>none described</p>	<p><i>Jadad score</i> 5/5. <i>Allocation concealment</i> adequate.</p>

AE(s)=adverse event(s); BP=blood pressure; CME=cystoid macular edema; IOP=intraocular pressure; ITT=intent to treat [analysis]; mmHg =millimetres of mercury; NR=not reported; NS=not significant; VA=visual acuity; *calculated by reviewers as mean of mean IOP values at reported time points; [†]reviewer’s comment: peak and trough timolol data reported are opposite to what is expected.

Table 10A: Trial characteristic of Inan *et al.* study

Author, Year, Location	Study Design, Treatment Duration, Study Time Span	Participants	Intervention(s)	Outcomes	Funding Source(s) and Conflicts of Interest
Inan <i>et al.</i> , 2003; Turkey	Randomized, parallel-group, open-label design with masked evaluators comparing latanoprost 0.005% once daily with brimonidine tartrate 0.2% twice daily. Main outcome retrobulbar blood flow velocity using CDI. Treatment duration for each patient: 3 months. Study time span NR.	<p>41 consecutive adults enrolled.</p> <p>Baseline characteristics</p> <ul style="list-style-type: none"> • diagnoses of POAG 30 (73%); ocular hypertension 11 (27%) • prior treatment: topical β-blockers 10/41 (24%); none 31/41 (76%). <p>Characteristics reported for completers (n=38)</p> <ul style="list-style-type: none"> • males 16 (45%); females 22 (55%) • mean age 62.2 years; range 48 to 73. <p>Inclusion criteria</p> <ul style="list-style-type: none"> • POAG (defined as IOP >21 mm Hg measured on 2+ occasions and glaucomatous or disc changes) or ocular hypertension (defined as IOP >24 mm Hg with normal optic disc and visual fields) • refractive errors between -3.50 and +3.50 diopters. <p>Exclusion criteria</p> <ul style="list-style-type: none"> • history of ocular trauma or ocular surgery • laser trabeculectomy within 6 months • optic nerve drusen • diabetic retinopathy • visual-field loss not due to glaucoma • use of specific systemic drugs, e.g., α-blockers or ophthalmic drugs • chronic systemic disease. 	<p>Washout period after previous treatment</p> <ul style="list-style-type: none"> • 3 weeks for β-blockers. <p>2 treatment groups</p> <ul style="list-style-type: none"> • latanoprost 0.005% once daily in afternoon (n=23); of these, 18 patients had OAG and 5 had ocular hypertension • brimonidine 0.2% twice daily (n=18); of these, 12 patients had OAG and 6 had ocular hypertension. 	<p>Measurements done between 0900 and 1100.</p> <p>Baseline examination</p> <ul style="list-style-type: none"> • IOP measured with Goldman applanation tonometry • CDI • VA • slit-lamp examination • gonioscopy • fundal examination • BP and pulse. <p>Right eyes used for IOP and CDI assessment.</p>	<p>Study funding NR. All authors deny proprietary interest in any product mentioned in publication.</p>

BP=blood pressure; CDI=colour Doppler imaging; mm Hg=millimetres of mercury; NR=not reported; OAG=open-angle glaucoma; VA=visual acuity.

Table 10B: Results of Inan *et al.* study

Results		AEs, Including Serious AEs	Withdrawals and Dropouts; ITT Analysis (Yes or No)	Limitations Described by Study Authors	Study-Quality Measures
Primary: Change in IOP (from Baseline)	Secondary				
<p>Mean IOP decreases from baseline at 3 months in mm Hg (%):</p> <ul style="list-style-type: none"> • latanoprost 6.2 (26.9%) • brimonidine 5.5 (23.6%). <p>Both drugs significantly decreased IOP. Difference in reductions between drugs NS.</p>	<p>Perfusion pressure increases (mm Hg)</p> <ul style="list-style-type: none"> • latanoprost 5.9 • brimonidine 5.9. <p>No changes observed in</p> <ul style="list-style-type: none"> • BP and pulse. 	<p>3 patients in latanoprost group withdrawn because of allergic symptoms (conjunctival hyperemia, burning, tearing) and headache.</p>	<p>41 patients enrolled and 38 patients completed: 3 patients withdrawn because of AEs (all in latanoprost group). ITT analysis: no.</p>	<p>Patients with OAG and ocular hypertension not divided into 2 groups, which might have allowed different observations of blood-flow changes.</p>	<p><i>Jadad score 2/5. Allocation concealment not applicable. Study open-label for patients.</i></p>

AE(s)=adverse event(s); BP=blood pressure; IOP=intraocular pressure; ITT=intent to treat [analysis]; mm Hg =millimetres of mercury; NS=not significant; OAG=open-angle glaucoma.

Table 11A: Trial characteristics of Kampik *et al.* study

Author, Year, Location	Study Design, Treatment Duration, Study Time Span	Participants	Intervention(s)	Outcomes	Funding Source(s) and Conflicts of Interest
<p>Kampik <i>et al.</i>, 2002; Germany, Spain, UK, Finland</p>	<p>Randomized, multi-centre, parallel-group design with masked evaluators comparing latanoprost 0.005% once daily with brimonidine tartrate 0.2% twice daily in patients not controlled on current treatment. Study conducted at 30 eye clinics. Treatment duration for each patient: 6 months. Study time span NR.</p>	<p>379 adults Baseline characteristics</p> <ul style="list-style-type: none"> • males 154 (41%); females 225 (59%) • mean age 64.5 • diagnoses of POAG 284 (75%); ocular hypertension 64 (17%), exfoliation glaucoma 15 (4%), mixed (eyes differed) 10 (3%), diagnosis NR, 6 (2%) • mean IOP at baseline 22.8 mm Hg • number of previous ocular medications 1, 219 (58%); 2, 129 (34%); 3, 26 (7%); 4, 5 (1%) • differences between groups NS except pre-study diagnoses: more patients with ocular hypertension randomized to latanoprost (40 versus 24; p=0.027). <p>Inclusion criteria</p> <ul style="list-style-type: none"> • age ≥18 years • unilateral or bilateral primary open-angle glaucoma, exfoliation glaucoma, or ocular hypertension • current mono or dual therapy • IOP ≥21 mm Hg with current therapy • only eyes fulfilling inclusion criteria included as study eyes, although both eyes could be treated. <p>Exclusion criteria</p> <ul style="list-style-type: none"> • previous treatment with latanoprost or brimonidine • current or history of acute angle closure • argon-laser trabeculoplasty • other ocular surgery within 3 months • current use of contact lenses • ocular inflammation or infection within 3 months • problems having applanation tonometry done • hypersensitivity to study medications • ongoing treatment with α-adrenoreceptor agonists • pregnancy, lactation, inadequate contraception • inability to adhere to protocol. 	<p>Washout period after previous treatment</p> <ul style="list-style-type: none"> • 2 weeks for adrenergic agonists • 4 weeks for β-adrenergic antagonists • 5 days for cholinergic agonists and carbonic anhydrase inhibitors. <p>2 treatment groups</p> <ul style="list-style-type: none"> • latanoprost 0.005% once daily in afternoon at 2200 (n=187) • brimonidine 0.2% twice daily at 0800 and 2200 (n=192). 	<p>Visits conducted at 0.5, 3, and 6 months after baseline visit. Patients assessed at 1000 and 1700 at 3 and 6 months (measured before 1200 at 0.5-month visit). Baseline examination</p> <ul style="list-style-type: none"> • IOP measured with Goldman applanation tonometry • VA and refraction • slit-lamp examination for cells and flare • gonioscopy • conjunctival hyperemia • fundal examination. <p>Mean diurnal IOP was mean of 1000 and 1700 measurements. If both eyes used, mean IOP calculated.</p>	<p>Study supported by Pharmacia Corp. (NJ), manufacturer of latanoprost ophthalmic solution 0.005% (Xalatan®). Authors' conflicts of interest NR.</p>

IOP=intraocular pressure; mm Hg=millimetres of mercury; NR=not reported; NS=not significant; OAG=open-angle glaucoma; UK=United Kingdom; VA=visual acuity.

Table 11B: Results of Kampik *et al.* study

Results		AEs, Including Serious AEs	Withdrawals and Dropouts; ITT Analysis (Yes or No)	Limitations Described by Study Authors	Study-Quality Measures
Primary: Change in IOP (from Baseline)	Secondary				
<p>Mean diurnal IOP decreases from baseline at 6 months in mm Hg (\pmSD) (%) [ITT analysis]</p> <ul style="list-style-type: none"> • latanoprost, n=187: 7.1 (3.3) (28%) • brimonidine, n=188: 5.2 (3.5) (21%) • both drugs significantly decreased IOP ($p < 0.001$) • IOP-reduction difference of 1.9 mm Hg favoured latanoprost ($p < 0.001$). <p>Patients reaching IOP \leq 18 mm Hg at 6 months</p> <ul style="list-style-type: none"> • latanoprost 57% • brimonidine 33%. <p>Patients reducing mean IOP \geq 30% at 6 months</p> <ul style="list-style-type: none"> • latanoprost 42% • brimonidine 22% • $p = 0.006$. <p>Patients reducing IOP \leq 15% at 6 months (non-response)</p> <ul style="list-style-type: none"> • latanoprost 12% • brimonidine 32% • $p = 0.036$. 	NR	<p>4 serious AEs reported (number of patients):</p> <ul style="list-style-type: none"> • latanoprost: dehydration (1) • brimonidine: severe bronchitis (1), head injury secondary to collapse (1), earlobe cancer (1) • none believed to be due to ocular hypotensives. <p>Ocular AEs occurring in >2 patients (latanoprost/brimonidine) (number of patients)</p> <ul style="list-style-type: none"> • total 62/95 • irritation 10/22 • allergic reaction 0/16 • conjunctivitis or blepharitis 9/12 • conjunctival hyperemia 11/11 • hypertrichosis 6/0 • corneal changes except keratitis 2/6 • disturbed vision 3/5 • keratitis 3/4 • eyelid disorder 3/3 • increased IOP 1/3. <p>No statistical difference between groups.</p> <p>Systemic AEs occurring in >3 patients (latanoprost/brimonidine)</p> <ul style="list-style-type: none"> • total 23/56 • dry mouth 2/10 • headache 4/8 • fatigue or drowsiness 0/5 • respiratory symptoms 4/4 • dizziness or vertigo 1/4 • influenza-like symptoms 2/2 <p>More AEs in brimonidine group ($p = 0.005$).</p>	<p>379 enrolled; 327 completed; withdrawals by group after starting medications (4 patients withdrew before starting medications):</p> <ul style="list-style-type: none"> • latanoprost 5 • brimonidine 43. <p>Reasons for withdrawal where >1 patient affected (patient numbers; latanoprost/brimonidine)</p> <ul style="list-style-type: none"> • ocular allergic reaction 0/14 • IOP not controlled 2/13 • consent withdrawn 0/5 • ocular irritation 1/2 • non-drug reasons (e.g., rash, insomnia, lost to follow-up) 1/8. <p>ITT analysis: yes.</p> <p>4 patients withdrawn before using medications excluded from analyses. All other withdrawn patients included in analyses for 6 months with last available IOP measurement carried forward included.</p>	NR	<p><i>Jadad Score 2/5. Allocation concealment not applicable. Study open-label for patients.</i></p>

AE(s)=adverse event(s); IOP=intraocular pressure; ITT=intent to treat [analysis]; mmHg =millimetres of mercury; NR=not reported; SD=standard deviation.

Table 12A: Trial characteristics of Konstas *et al.* study

Author, Year, Location	Study Design, Treatment Duration, Study Time Span	Participants	Intervention(s)	Outcomes	Funding Source(s) and Conflicts of Interest
Konstas <i>et al.</i> , 2004; Greece, US (South Carolina)	Randomized, multi-centre, parallel-group design with masked observers comparing latanoprost 0.005% once daily with timolol 0.5% twice daily in patients with exfoliation glaucoma. Study conducted at 6 sites in Greece. Treatment duration for each patient: 3 months. Study time span: 12 months (dates NR).	<p>109 consecutive adults enrolled. Characteristics of enrolled population NR. Characteristics of study completers (n=103)</p> <ul style="list-style-type: none"> • males 46 (45%); females 57 (55%) • mean age 69.8 years • white 103 (100%) • diagnoses of exfoliation glaucoma 73 (71%); exfoliation syndrome 30 (29%) • baseline diurnal IOP 24.8 mm Hg • differences between groups NS. <p>Inclusion criteria</p> <ul style="list-style-type: none"> • exfoliation glaucoma or ocular hypertension and exfoliation syndrome (glaucoma precursor) in 1+ eye • IOP 22 to 36 mm Hg on 2 measurements within 1 hour at baseline • VA in study eye 0.3 on Snellen eye chart or better • IOP controllable on monotherapy and safe to undergo washout • contralateral eye IOP controllable on no drug, study medication, or with surgery. <p>Exclusion criteria, e.g.,</p> <ul style="list-style-type: none"> • unable to have reliable tonometry • conjunctivitis (infectious or non-infectious) • keratitis or uveitis • hypersensitivity to study medications • surgery in study eye • projected decrease in VA or visual fields • non-glaucoma retinal or optic disease • pregnant, lactating, no contraception • significant medical or psychiatric illness • using systemic β-blockers • opposed to darkening iris or increased eyelash growth. 	<p>Washout period after previous treatment</p> <ul style="list-style-type: none"> • 4 weeks for β-adrenergic antagonists, PGAs (no detail provided). <p>All patients used drops twice daily. Dose 1 drop per eye. 2 treatment groups</p> <ul style="list-style-type: none"> • latanoprost 0.005%: study medication once daily at 2000 hours with placebo (artificial tears) at 0800 (n=51) • timolol 0.5%: study medication twice daily at 0800 and 2000 (n=52). <p>If both eyes eligible for study, 1 eye chosen at random for analysis.</p>	<p>After baseline, patients assessed at 2 and 6 weeks, and 3 months. Diurnal assessment at 0800, 1000, 1400, and 2000 performed at baseline and 3 months. Assessed at every visit</p> <ul style="list-style-type: none"> • IOP measured with Goldman applanation tonometry • VA • slit-lamp biomicroscopy • stereoscopic-fundus evaluation • AEs. <p>Visual fields assessed at outset.</p>	<p>Clinical sites supported by grant from Pharmacia Hellas, Greece. The 1 author from US denied receiving study funding for himself.</p>

AE(s)=adverse event(s); IOP=intraocular pressure; mm Hg=millimetres of mercury; NR=not reported; NS=not significant; US=United States; VA=visual acuity.

Table 12B: Results of Konstas *et al.* study

Results		AEs, Including Serious AEs	Withdrawals and Dropouts; ITT Analysis (Yes or No)	Limitations Described by Study Authors	Study-Quality Measures
Primary: Change in IOP (from Baseline)	Secondary				
<p>Mean IOP decreases from baseline at 3 months in mm Hg (\pmSD) (latanoprost/timolol)</p> <ul style="list-style-type: none"> • diurnal: 7.5(2.7)/6.4(2.8); p=0.03 • 0800: 8.5(2.9)/6.0(2.8); p<0.0001 • 1000: 8.6(3.2)/8.1(3.0); p=0.38 • 1400: 7.4(3.1)/6.0(3.1); p=0.02 • 2000: 5.6(2.8)/5.5(3.2); p=0.76. <p>Both drugs significantly decreased IOP at all time points, compared with baseline (p<0.0001). Differences between decreases from 2 drugs NS except at 0800 (p<0.0001), although reductions showed non-statistical trend in favour of latanoprost.</p>	NR	<p>Ocular AEs occurring >2 times (number of events) (latanoprost/timolol)</p> <ul style="list-style-type: none"> • total 33/22 (p=NR) • conjunctival hyperemia 8/1 • corneal superficial punctuate epitheliopathy 3/5 • stinging 3/4 • dry-eye sensation 2/4 • itchiness 4/2 • foreign body sensation 3/3 • burning on administration 2/2 • hypertrichosis 3/0. <p>No statistical difference between groups except for conjunctival hyperemia where p=0.01.</p> <p>Systemic AEs (number of events) (latanoprost/timolol)</p> <ul style="list-style-type: none"> • total 4/4 • dyspnea 0/2 • insomnia exacerbation 0/1 • increased fatigue 0/1 • headaches 1/0 • URI 1/0 • hypoglycemia 1/0 • elevated systolic BP 1/0. 	<p>109 patients enrolled; 103 (94.5%) completed; 6 patients withdrew. Reasons for withdrawal (patient numbers; latanoprost/timolol)</p> <ul style="list-style-type: none"> • poor IOP control 0/1 • ocular intolerance 1/0 • floaters 1/0 • bradycardia 0/1 • lost to follow-up 2 (group NR). <p>ITT analysis: no</p>	<p>Study slightly under-powered. Study did not cover 24 hours so night-time IOPs inadequately assessed.</p>	<p><i>Jadad score 3/5. Allocation concealment not applicable. Study open-label for patients.</i></p>

AE(s)=adverse event(s); BP=blood pressure; IOP=intraocular pressure; ITT=intent to treat [analysis]; mm Hg=millimetres of mercury; NR=not reported; NS=not significant; SD=standard deviation; URI=upper respiratory infection.

Table 13A: Trial characteristics of Lone *et al.* study

Author, Year, Location	Study Design, Treatment Duration, Study Time Span	Participants	Intervention(s)	Outcomes	Funding Source(s) and Conflicts of Interest
Lone <i>et al.</i> , 2003; India	<p>Randomized, double-masked, parallel-group design comparing latanoprost 0.005% once daily with dorzolamide 2% 3 times daily.</p> <p>Aside from abstract, no wording about patients being randomized and no reason to believe there was blinding. Treatment duration for each patient: 3 months. Study time span NR.</p>	<p>44 adults Baseline characteristics NR. Authors state “the results of the study were not significantly altered with regards to the age, sex, iris colour, or diagnosis (ocular hypertension or glaucoma).” Mean baseline IOP 29.0 mm Hg.</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • age ≥40 years • OAG, ocular hypertension, pigmentary glaucoma, or exfoliation glaucoma • IOP ≥22 mm Hg on previous treatment • investigators’ expectation that IOP would remain adequately controlled on monotherapy for 3 months with no eye damage. <p>Exclusion criteria</p> <ul style="list-style-type: none"> • previous treatment with latanoprost or carbonic anhydrase inhibitor • narrow angles or peripheral anterior synechiae • ocular surgery or laser trabeculoplasty within 6 months • problems with tonometry • active eye disease other than those included • hypersensitivity to study medications • oral drugs affecting IOP • pregnancy or lactation • history of non-compliance or unreliability. 	<p>Washout period after previous treatment</p> <ul style="list-style-type: none"> • 2 weeks for adrenergic agonists • 3 weeks for β-adrenergic antagonists • 5 days for cholinergic agonists. <p>2 treatment groups</p> <ul style="list-style-type: none"> • latanoprost 0.005% once daily at bedtime (n=22) • dorzolamide 2% 3 times daily (n=22). 	<p>Visits conducted at 2 and 4 weeks , and 3 months after baseline visit.</p> <p>At each visit</p> <ul style="list-style-type: none"> • IOP measured with Goldman applanation tonometry at 1100 and 1600 • VA and refraction • slit-lamp examination • abnormalities of conjunctivae, cornea, lids, and iris. 	NR

IOP=intraocular pressure; NR=not reported; OAG=open-angle glaucoma; VA=visual acuity.

Table 13B: Results of Lone *et al.* study

Results		AEs, Including Serious AEs	Withdrawals and Dropouts; ITT Analysis (Yes or No)	Limitations Described by Study Authors	Study-Quality Measures
Primary: Change in IOP (from Baseline)	Secondary				
Mean diurnal IOP decreases from baseline at 3 months in mm Hg (\pm SD) <ul style="list-style-type: none"> • latanoprost 6.8 (3.1) • dorzolamide 4.7(2.4). 2.1 mm Hg difference “highly significant” (p=NR). Diurnal IOP was mean of 1100 and 1600 readings.	NR	AEs reported (number of patients) (latanoprost/ dorzolamide) <ul style="list-style-type: none"> • total 5/6 • ocular discomfort 1/2 • conjunctival hyperemia 1/1 • superficial punctuate keratitis 1/1 • uncontrolled IOP 2/2. No systemic AEs reported.	NR. ITT analysis: yes (no withdrawals reported).	none described	<i>Jadad score 2/5. Allocation concealment unclear.</i>

AE(s)=adverse event(s); IOP=intraocular pressure; ITT=intent to treat [analysis]; mmHg =millimetres of mercury; SD=standard deviation.

Table 14A: Trial characteristics of Martin *et al.* study

Author, Year, Location	Study Design, Treatment Duration, Study Time Span	Participants	Intervention(s)	Outcomes	Funding Source(s) and Conflicts of Interest
Martin <i>et al.</i> , 2005; Spain	Randomized, observer-masked, parallel-group design comparing bimatoprost 0.03% once daily and timolol maleate 0.5% twice daily. Study conducted at 1 eye clinic. Treatment duration for each patient: 6 months. Study time span NR.	<p>60 consecutive adults who met inclusion criteria. Baseline characteristics NR except mean IOP 24.1 mm Hg.</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • age >18 years • ocular hypertension, primary open-angle glaucoma, pigmentary glaucoma, or pseudoexfoliative glaucoma in 1+ eye • IOP \geq22 mm Hg at enrolment and 24 to 34 after wash-out at 0900 examination, flare <10 photons/millisecond, and normal macular thickness (<220 μm) • VA \geq0.1 in study eye • capacity to follow protocol. <p>Exclusion criteria</p> <ul style="list-style-type: none"> • anomaly impeding tonometry • eye infection or inflammation • allergy to study medications • macular or retinal pathology • diabetes mellitus • fertile women with unreliable contraception • other chronic eye medications • intraocular surgery within 6 months or laser surgery within 3 months • severe visual-field defects • enrolment in another trial within past 3 months. 	<p>Washout period after previous treatment</p> <ul style="list-style-type: none"> • 6 weeks for PGs • 4 weeks for topical β-blockers • 3 weeks for α-agonists • 1 week for carbonic anhydrase inhibitors. <p>2 treatment groups</p> <ul style="list-style-type: none"> • bimatoprost 0.03% once daily at 2100 (n=30) • timolol 0.5% twice daily at 0900 and 2100 (n=30). <p>Treatment dose NR.</p>	<p>Visits conducted post-baseline at 2 weeks and 1, 2, 3, and 6 months. No details about what examinations done at each visit.</p> <p>Primary outcome was hypotensive efficacy using Goldman applanation tonometry IOP measurements.</p> <p>Secondary outcomes</p> <ul style="list-style-type: none"> • changes in macular thickness using optical coherence tomography • anterior flare using laser flare meter. 	Partly financed by grant from Instituto de Salud Carlos III. Additional funding NR. Authors deny commercial interest in products mentioned in publication.

mm Hg =millimetres of mercury; NR=not reported; PG=prostaglandin; VA=visual acuity.

Table 14B: Results of Martin *et al.* study

Results		AEs, Including Serious AEs	Withdrawals and Dropouts; ITT Analysis (Yes or No)	Limitations Described by Study Authors	Study-Quality Measures
Primary: Change in IOP (from Baseline)	Secondary				
<p>Decrease in mean IOP at 6 months in mm Hg</p> <ul style="list-style-type: none"> • bimatoprost 10.6 • timolol 7.5 • difference at 6 months statistically significant (p=0.003). <p>From 1 month on, mean IOPs lower for bimatoprost than timolol (p≤0.004). Data from 1 eye per patient used in analyses.</p> <p>Authors do not report how single eye chosen in cases where both eyes treated. Authors do not report proportion of included subjects with both versus 1 eye treated.</p>	<p>No inter- or intra-group differences in macular thickness detected (p=0.790).</p> <p>No inter- or intra-group differences in anterior chamber flare detected (p=0.143).</p>	<p>No AEs reported for timolol patients.</p> <p>Bimatoprost (n=30)</p> <ul style="list-style-type: none"> • conjunctival hyperemia 4 • eyelash growth 2 • hyperpigmentation around eyes 1. 	<p>No withdrawals.</p> <p>ITT analysis: yes (no withdrawals).</p>	<p>Authors noted that small sample size limited findings, e.g.,</p> <ul style="list-style-type: none"> • possible differences in macular thickness (estimated n=2,891 per group needed) • possible differences in anterior chamber inflammation (estimated n=209 per group needed). 	<p><i>Jadad score 2/5.</i></p> <p><i>Allocation concealment unclear.</i></p>

AE(s)=adverse event(s); IOP=intraocular pressure; ITT=intent to treat [analysis]; mm Hg =millimetres of mercury.

Table 15A: Trial characteristics of Mastropasqua *et al.* study

Author, Year, Location	Study Design, Treatment Duration, Study Time Span	Participants	Intervention(s)	Outcomes	Funding Source(s) and Conflicts of Interest
Mastropasqua <i>et al.</i> , 1999; Italy	Double masked, randomized, parallel-group design comparing latanoprost 0.005% once daily with timolol 0.5% twice daily in patients with pigmentary glaucoma. Study conducted at 1 eye clinic. Treatment duration for each patient: 12 months. Study time span NR.	<p>36 adults</p> <p>Baseline characteristics</p> <ul style="list-style-type: none"> • males 21 (58%); females 15 (42%) • mean age 46.0; range 35 to 58 • family history of glaucoma or ocular hypertension 9 (28%) • authors state differences between groups are NS regarding age, gender, race, family history of glaucoma, iris colour, and previous treatment. <p>Inclusion criteria, e.g.,</p> <ul style="list-style-type: none"> • prior diagnosis of bilateral pigmentary glaucoma • IOP \geq21 mm Hg on diurnal curve when on no therapy and typical glaucomatous defects (on field analysis) • stable visual field-defects and IOP \leq21 with no more than 1 type of therapy on screening examination. <p>Exclusion criteria</p> <ul style="list-style-type: none"> • systemic treatment that could interfere with ocular hydrodynamics • pregnant or considering pregnancy • ocular medications aside from glaucoma • glaucoma susceptible during washout • intraocular surgery or laser • conditions making tonometry difficult • ocular inflammation within 3 months • contraindication to β-blockers • history of non-compliance or unreliability. 	<p>Washout period after previous treatment</p> <ul style="list-style-type: none"> • 2 weeks for adrenergic agonists • 3 weeks for α- and β-adrenergic antagonists • 5 days for cholinergic agonists and carbonic anhydrase inhibitors. <p>All patients used drops twice daily. Dose was 1 drop per eye. Patients treated in both eyes.</p> <p>2 treatment groups</p> <ul style="list-style-type: none"> • latanoprost 0.005%: study medication once daily in afternoon at 2000 hours with placebo (vehicle) only at 0800 (n=18) • timolol 0.5%: study medication twice daily at 0800 and 2000 (n=18). 	<p>Visits conducted at 0.5, 3, 6, and 12 months. Assessed at every visit</p> <ul style="list-style-type: none"> • IOP measured with Goldman applanation tonometry measured at 0800, 1200, 1600, and 2000 • conjunctival hyperemia • slit-lamp examination • AEs • BP and pulse. <p>Mean diurnal IOP was average of 4 daily IOP measurements. Assessed less often</p> <ul style="list-style-type: none"> • visual fields • tonography • anterior segment (colour photograph) • gonioscopy. 	<p>Study funding NR. Authors stated that they had no proprietary interest in development or marketing of products named in publication.</p>

AE(s)=adverse event(s); BP=blood pressure; mm Hg =millimetres of mercury; NR=not reported; NS=not significant.

Table 15B: Results of Mastropasqua *et al.* study

Results		AEs, Including Serious AEs	Withdrawals and Dropouts; ITT Analysis (Yes or No)	Limitations Described by Study Authors	Study-Quality Measures
Primary: Change in IOP (from Baseline)	Secondary				
<p>Mean diurnal IOP decreases from baseline in mm Hg (\pmstandard error) [ITT analysis]</p> <ul style="list-style-type: none"> • 3 months <ul style="list-style-type: none"> ○ latanoprost 6.1 (3.0) ○ timolol 5.2 (2.9). • 6 months <ul style="list-style-type: none"> ○ latanoprost 6.0 (4.5) ○ timolol 4.8 (3.0). • 12 months <ul style="list-style-type: none"> ○ latanoprost 5.9 (4.6) ○ timolol 4.6 (3.1). <p>Both eyes used in analyses. Both medications caused significant change in IOP from baseline throughout therapy ($p < 0.001$). Latanoprost was significantly more effective hypotensive agent than timolol at 3, 6, and 12 months ($p < 0.001$).</p>	<p>No changes seen</p> <ul style="list-style-type: none"> • gonioscopy • visual fields. 	<p>No serious AEs occurred. Ocular AEs (number of patients) (latanoprost/ timolol)</p> <ul style="list-style-type: none"> • total 24/35 • blurred vision 2/2 • dry eye 3/8 • foreign body sensation 3/7 • ocular discomfort* 3/6 • conjunctival hyperemia 5/3 • photophobia 1/1 • pruritis 2/4 • tearing 2/4 • increased iris pigmentation 3/0[†]. <p>*Includes burning, stinging, and eye pain. [†]Definite in 1, suspected in 2.</p> <p>Conjunctival hyperemia increase over baseline in number of patients at 12 months (latanoprost/ timolol)</p> <ul style="list-style-type: none"> • no increase 13/15 • 0.5 increment increase 3/1 • 1.0 increment increased 2/2 • >1.0 increment increase 0/0. <p>Hyperemia graded from photographs (0 to 3 in 0.5 increments; 0=none, 1=mild, 2=moderate, 3=severe).</p> <p>Systemic AEs</p> <ul style="list-style-type: none"> • timolol group had significantly decreased pulse over 12 months. 	<p>36 patients enrolled; 34 completed study; 1 withdrawal from each group</p> <ul style="list-style-type: none"> • latanoprost: lost to follow-up • timolol: inadequate IOP control. <p>ITT analysis</p> <ul style="list-style-type: none"> • at 6 months, yes • at 12 months, no (both withdrawals occurred before 12-month visit). 	<ul style="list-style-type: none"> • trabecular pigmentary changes may not have been seen because study too short or disease of patients too advanced • changes in eyelashes might have been under-estimated because drug treatment was bilateral • small sample size meant low incidence of complications would not likely occur. 	<p><i>Jadad score 5/5. Allocation concealment adequate.</i></p>

AE(s)=adverse event(s); IOP=intraocular pressure; ITT=intent to treat [analysis]; mmHg =millimetres of mercury.

Table 16A: Trial characteristics of Mishima *et al.* study

Author, Year, Location	Study Design, Treatment Duration, Study Time Span	Participants	Intervention(s)	Outcomes	Funding Source(s) and Conflicts of Interest
Mishima <i>et al.</i> , 1996; Japan	Double masked, randomized, parallel-group design comparing latanoprost 0.005% once daily with timolol 0.5% twice daily. Study conducted at 35 centres. Treatment duration for each patient: 3 months. Study time span NR.	184 adults enrolled. Baseline characteristics <ul style="list-style-type: none"> • males 87 (49%); females 91 (51%) • mean age 56.8; range 22 to 81 • mean IOP 23.1; range 20 to 32 • previous IOP-lowering medications 107 (60%) • differences between groups NS. Inclusion criteria <ul style="list-style-type: none"> • POAG or ocular hypertension. Exclusion criteria <ul style="list-style-type: none"> • intraocular surgery or laser within 12 months • severe ocular trauma, contact lenses, corneal infection, or uveitis within 6 months • contraindication to β-blockers, e.g., asthma, COPD, heart failure • cerebrovascular, hepatic, renal, or metabolic diseases • women of childbearing potential • allergy to benzalkonium chloride. 	Washout period after previous treatment <ul style="list-style-type: none"> • 4 weeks for topical β-blockers or systemic carbonic anhydrase inhibitors • 2 weeks for topical epinephrine or other medications. All patients used drops twice daily. Number of drops NR. 2 treatment groups <ul style="list-style-type: none"> • latanoprost 0.005%: study medication once daily in morning, with placebo in afternoon (n=89) • timolol 0.5%: study medication twice daily morning and afternoon (n=95). 	Visits conducted post-baseline at 2, 4, 8, and 12 weeks. Assessed at every visit <ul style="list-style-type: none"> • IOP measured with Goldman applanation tonometry at 0900 before drug administered* • horizontal pupil diameter • subjective and objective symptoms • compliance. Assessed at baseline and study conclusion <ul style="list-style-type: none"> • visual fields • VA • ophthalmthscopy • gonioscopy • blood and urine. *0900 described as trough reading for both drugs.	Study funding NR. Authors deny financial or proprietary interest in products mentioned.

COPD=chronic obstructive pulmonary disease; IOP=intraocular pressure; NR=not reported; NS=not significant; OAG=open-angle glaucoma; VA=visual acuity.

Table 16B: Results of Mishima *et al.* study

Results		AEs, Including Serious AEs	Withdrawals and Dropouts; ITT Analysis (Yes or No)	Limitations Described by Study Authors	Study-Quality Measures
Primary: Change in IOP (from Baseline)	Secondary				
<p>Mean IOP decreases from baseline in mm Hg (%) at 3 months for n=163 (latanoprost/timolol 80/83)</p> <ul style="list-style-type: none"> • latanoprost 6.3 (26.8) • timolol 4.3 (19.0). <p>Both medications caused significant change in IOP from baseline throughout therapy (p NR).</p> <p>Latanoprost significantly more effective ocular hypotensive agent than timolol at all time points. (p=0.001).</p>	NR	<p>No serious AEs occurred.</p> <p>Ocular and systemic AEs (by number of reports) (latanoprost/ timolol)</p> <ul style="list-style-type: none"> • total 33/23 • conjunctival hyperemia 13/8 • smarting 10/11 • pruritis 1/0 • discharge 1/0 • allergic conjunctivitis 1/0 • conjunctival follicles 1/0 • blepharitis 2/1 • blurred vision 1/0 • lacrimation: 1/0 • cells in anterior chamber 1/0 • bradycardia 0/2 • arrhythmia 0/1 • headache 1/0. <p>Ocular and systemic AEs (by number of patients)</p> <ul style="list-style-type: none"> • latanoprost 22/87 (25%) • timolol 17/91 (19%). <p>Slight but significant pulse reduction in timolol group (p<0.01).</p>	<p>Patient numbers</p> <ul style="list-style-type: none"> • enrolled 184 • safety analysis 178 (6 patients withdrew before follow-up) • efficacy analysis 163 (15 more withdrew because of AEs or protocol violations). <p>ITT analysis: no, analysis based on 163 patients remaining after withdrawals.</p>	none described	<p><i>Jadad score 3/5.</i></p> <p><i>Allocation concealment adequate.</i></p>

AE(s)=adverse event(s); IOP=intraocular pressure; ITT=intent to treat [analysis]; mm Hg =millimetres of mercury; NR=not reported.

Table 17A: Trial characteristics of Netland *et al.* study

Author, Year, Location	Study Design, Treatment Duration, Study Time Span	Participants	Intervention(s)	Outcomes	Funding Source(s) and Conflicts of Interest
<p>Netland <i>et al.</i> and Travoprost Study Group, 2001; US (Tennessee and Texas). This study group lists investigators from many sites in US and several in Canada.</p>	<p>Double masked, randomized, multi-centre, parallel-group design comparing 4 treatments: 2 concentrations of travoprost, latanoprost, and timolol. Treatment duration for each patient: 12 months. Study time span NR.</p>	<p>801 adults randomized Baseline characteristics (n=787 in ITT analysis)</p> <ul style="list-style-type: none"> • males 392 (50%); females 395 (50%) • mean age 64.3 years; range 22 to 94 • white 566 (72%); black 177(22%), Asian 6 (1%), other 38 (5%) • diagnoses of ocular hypertension 247 (31%); OAG 530 (67%); pigmentary glaucoma 6 (1%); pseudoexfoliating glaucoma 4 (<1%) • mean IOP at baseline 25.5 mm Hg • differences among groups NS. <p>Inclusion criteria (1 or both eyes)</p> <ul style="list-style-type: none"> • OAG or ocular hypertension with or without pseudoexfoliation or pigmentary glaucoma • IOP measurement <ul style="list-style-type: none"> ○ 24 to 36 mm Hg in same eye(s) at 0800 at both eligibility visits ○ 21 to 36 mm Hg in same eye(s) at 1000 and 1600 at both eligibility visits ○ ≤36 mm Hg at all times. <p>Exclusion criteria, e.g.,</p> <ul style="list-style-type: none"> • IOP >36 at any 1 measurement in any eye during eligibility phase • VA worse than 0.60 logMAR • eye diseases (within 3 months): trauma, infection, inflammation • intraocular surgery within 6 months • history of hypersensitivity to study medications • women of childbearing potential • systemic diseases, e.g., cardiac, respiratory, renal, hepatic • glucocorticoid or topical ocular NSAID use. 	<p>Washout period after previous treatment</p> <ul style="list-style-type: none"> • 3 days with no ocular hypotensives • 5 days carbonic anhydrase inhibitors and miotics • 2 weeks α- and α/β agonists • 3 weeks β antagonists and PGs. <p>Chronic glucocorticocoid treatment decreased ≥4 weeks and intermittent glucocorticoid treatment decreased before 1st eligibility visit.</p> <p>4 treatment groups</p> <ul style="list-style-type: none"> • travoprost 0.0015% at 2000 and matching placebo (vehicle) at 0800 (n=205) • travoprost 0.004% once daily at 2000 and matching placebo (vehicle) at 0800 (n=200) • latanoprost 0.005% once daily at 2000 and matching placebo (vehicle) at 0800 (n=196) • timolol 0.5% twice daily at 0800 and 2000 (n=200). 	<p>Visits conducted at baseline, and at 0.5, 1.5, 3, 4.5, 6, 9, and 12 months. Examinations done at 0800, 1000, and 1600 at 0.5, 3, 6, and 12 month visits. Examinations done at 0800 and 1000 at 1.5, 4.5, and 9 month visits. Outcomes assessed at every visit</p> <ul style="list-style-type: none"> • IOP via Goldman tonometry • ocular hyperemia and flare or cell assessment • VA • biomicroscopy • pulse and BP. <p>Outcomes assessed less frequently</p> <ul style="list-style-type: none"> • iris photographs (1.5, 3, 4.5, 6, 9, and 12 months) • endothelial photographs, pachymetry, blood and urine (6 and 12 months) • dilated fundus and automated perimetry (12 months). 	<p>Study funded by Alcon Research, Ltd., manufacturers of travoprost (Travatan®). Lead author denied proprietary interest in products mentioned in publication. 10 of 11 listed authors employed by Alcon Research, Ltd.</p>

BP=blood pressure; IOP=intraocular pressure; ITT=intent to treat [analysis]; logMAR=logarithm of minimum angle of resolution; mm Hg =millimetres of mercury; NR=not reported; NS=not significant; NSAID=non-steroidal anti-inflammatory drug; OAG=open-angle glaucoma; PG=prostaglandin; VA=visual acuity.

Table 17B: Results of Netland *et al.* study

Results		AEs, Including Serious AEs	Withdrawals and Dropouts; ITT Analysis (Yes or No)	Limitations Described by Study Authors	Study-Quality Measures
Primary: Change in IOP (from Baseline)	Secondary				
<p>Mean IOP decreases in mm Hg from baseline at 3/6/12 months (n=787; ITT analysis)</p> <ul style="list-style-type: none"> • travoprost 0.0015% (n=202) <ul style="list-style-type: none"> ○ 0800: 7.7/7.2/7.0 ○ 1000: 6.9/7.0/6.5 ○ 1600: 6.4/6.2/6.0. • travoprost 0.004% (n=197) <ul style="list-style-type: none"> ○ 0800: 8.0/7.6/7.1 ○ 1000: 7.3/7.3/6.9 ○ 1600: 6.7/6.5/6.6. • latanoprost (n=193) <ul style="list-style-type: none"> ○ 0800: 7.8/7.7/7.5 ○ 1000: 7.1/7.3/7.1 ○ 1600: 6.7/6.5/6.3. • timolol (n=195) <ul style="list-style-type: none"> ○ 0800: 6.9/6.7/6.3 ○ 1000: 6.1/5.8/5.5 ○ 1600: 5.3/5.1/4.7. <p>Efficacy data taken from patients' worst eye. Travoprost (both doses) IOP reduction equal to latanoprost except at 0.5-month visit where travoprost was superior. Mean IOP significantly lower for both doses of travoprost versus timolol.</p>	<p>No significant differences from baseline or among groups for</p> <ul style="list-style-type: none"> • VA • inflammatory cells or aqueous flare • visual fields • ocular signs • fundus parameters • cup-to-disc ratio • laboratory values • corneal thickness • endothelial cell count • BP. <p>No clinically significant changes in pulse rate, BP or laboratory values between groups.</p>	<p>No serious AEs or CME reported. Most common AEs by % of patients (travoprost 0.0015%/ travoprost 0.004%/ latanoprost/timolol)</p> <ul style="list-style-type: none"> • VA decrease (6/9/5/10) • pain (3/8/4/2) • discomfort (5/8/3/8) • pruritis (4/8/6/2) • foreign body sensation (2/7/3/1) • cataract (5/7/3/4) • dry eye (2/5/1/2) • keratitis (2/4/2/3) • blepharitis (1/4/4/1) • blurred vision (1/3/5/3) • surgical or medical procedure (11/10/13/12) • hypertension (6/7/4/5) • infection (4/6/5/7). <p>% of patients with increased ocular hyperemia</p> <ul style="list-style-type: none"> • travoprost 0.0015%: 38.0 • travoprost 0.004%: 49.5 • latanoprost: 27.6 • timolol: 14.0. <p>Mean hyperemia score <1 for all measurements. Hyperemia graded using photographs, scale 0 to 3 in 0.5 increments, where 0=none, 1=mild, 2=moderate, 3=severe. Changes in iris colour (%)</p> <ul style="list-style-type: none"> • travoprost 0.0015%: 4.9 • travoprost 0.004%: 3.0 • latanoprost: 5.1 • timolol: 0. 	<p>Patient numbers</p> <ul style="list-style-type: none"> • 801 randomized • 787 in ITT analysis: 14 excluded secondary to lack of on-treatment data <ul style="list-style-type: none"> ○ travoprost 0.0015%=3 ○ travoprost 0.004%=3 ○ latanoprost=3 ○ timolol=5. • 760 in per-protocol analysis: 27 additional patients excluded secondary to protocol violations* <ul style="list-style-type: none"> ○ travoprost 0.0015%=7 ○ travoprost 0.004%=13 ○ latanoprost=8 ○ timolol=13. <p>*Violations included</p> <ul style="list-style-type: none"> • non-qualifying IOP • too little time between medications and IOP measurement • contraindicated concomitant medications • improper dosing or non-compliance • violations not attributed to specific patient groups. <p>ITT analysis: yes (defined as including all patients with ≥1 assessment on treatment).</p>	<p>none described</p>	<p>Jadad score 5/5. Allocation concealment adequate.</p>

AE(s)=adverse event(s); BP=blood pressure; CME=cystoid macular edema; IOP=intraocular pressure; ITT=intent to treat [analysis]; mmHg =millimetres of mercury; VA=visual acuity.

Table 18A: Trial characteristics of Niazi and Raja study

Author, Year, Location	Study Design, Treatment Duration, Study Time Span	Participants	Intervention(s)	Outcomes	Funding Source(s) and Conflicts of Interest
Niazi and Raja, 2004; Pakistan	Randomized,* open-label, parallel-group design comparing latanoprost 0.005% once daily with dorzolamide 2% 3 times daily. Study conducted at 1 site. Treatment duration for each patient: 3 months. Study time span NR. *Although this term is used, there is no description of randomization. Authors state that study subjects “were equally distributed between the 2 groups.”	60 adults Baseline characteristics (n=787) <ul style="list-style-type: none"> • males 37 (62%); females 23 (38%) • mean age 56 years; range 35 to 77 • most common diagnoses <ul style="list-style-type: none"> ○ POAG 34 (57%) ○ capsular glaucoma 13 (22%) • eyes treated: both 47 (78%); 1 eye 13 (22%) • on treatment pre-study 46 (76%) • mean IOP at baseline 27.9 mm Hg • significance of differences between groups NR. Inclusion criteria <ul style="list-style-type: none"> • age ≥18 years • unilateral or bilateral POAG, capsular glaucoma, or ocular hypertension • IOP ≥21 mm Hg on previous treatment or ≥25 mm Hg witho previous treatment • investigators’ expectation that IOP would remain adequately controlled on monotherapy for 3 months with no eye damage. Exclusion criteria <ul style="list-style-type: none"> • previous treatment with latanoprost or carbonic anhydrase inhibitor • closed or barely open anterior chamber angles • current use of contact lenses • ocular surgery or laser trabeculoplasty within 3 months • ocular infection or inflammation within 3 months • hypersensitivity to study medications • condition preventing reliable tonometry. 	Washout period after previous treatment ≥ 3 weeks for all medications. 2 treatment groups <ul style="list-style-type: none"> • latanoprost 0.005% at 2200 (n=30) • dorzolamide 2% 3 times daily at 0900, 1400, and 2200 (n=30). 	Visits conducted at 0.5, 1, and 3 months after baseline visit. Patients assessed at 0900, 1100, and 1700 at baseline and 3 months. At each examination <ul style="list-style-type: none"> • IOP measured with Goldman applanation tonometry at 1100 and 1600 • VA and refraction • slit-lamp examination • abnormalities of conjunctiva, cornea, and iris. Mean IOP was mean of 3 readings.	NR

IOP=intraocular pressure; mm Hg =millimetres of mercury; NR=not reported; OAG=open-angle glaucoma; VA=visual acuity.

Table 18B: Results of Niazi and Raja study

Results		AEs, Including Serious AEs	Withdrawals and Dropouts; ITT Analysis (Yes or No)	Limitations Described by Study Authors	Study-Quality Measures
Primary: Change in IOP (from Baseline)	Secondary				
Mean diurnal IOP decreases from baseline at 3 months in mmHg (\pm SD): <ul style="list-style-type: none"> • latanoprost 8.9 (2.4) • dorzolamide 6.6 (2.1) • 2.3 mm Hg difference “highly significant” ($p < 0.001$). 	NR	AEs reported (number of patients) (latanoprost/dorzolamide) <ul style="list-style-type: none"> • total 67 in both groups • conjunctival hyperemia 11/8 • itching or dryness 9/15 • photophobia 8/6 • metallic taste 1/7 • flare or cells anterior chamber 6/3 • facial edema 0/1 • iris changes 1/0. Systemic complications reported=9 (no detail provided). No “serious systemic” AEs reported. Publication states “there were no major differences between groups.”	2 reported withdrawals due to “non-serious” AEs, both from dorzolamide group (number of patients) <ul style="list-style-type: none"> • facial edema and irritation (1) • metallic taste and nausea (1). ITT analysis: probably not; no indication that ITT used.	none described	<i>Jadad score 2/5.</i> <i>Allocation concealment none;</i> <i>study open-label.</i>

AE(s)=adverse event(s); IOP=intraocular pressure; ITT=intent to treat [analysis]; mm Hg=millimetres of mercury; NR=not reported; SD=standard deviation.

Table 19A: Trial characteristics of O'Donoghue and UK and Ireland Latanoprost Study Group

Author, Year, Location	Study Design, Treatment Duration, Study Time Span	Participants	Intervention(s)	Outcomes	Funding Source(s) and Conflicts of Interest
<p>O'Donoghue and UK and Ireland Latanoprost Study Group, 2000. Lead author from Ireland, study group from Ireland and UK.</p>	<p>Randomized, open-label, multi-centre, parallel-group design comparing latanoprost 0.005% once daily to dorzolamide 2% 3 times daily. Study conducted at 12 eye centres. Treatment duration for each patient: 3 months. Study time span NR.</p>	<p>224 adults. Baseline characteristics (n=224)</p> <ul style="list-style-type: none"> • males 130 (58%); females 94 (42%) • mean age 67 years; range 28 to 94 • white 215 (96%); black 6 (3%), Asian 2 (1%), other 1 (<1%) • diagnoses of ocular hypertension 88 (39%); POAG 120 (53%); capsular glaucoma 5 (2%); pigmentary glaucoma 2 (1%); mixed 9 (4%) • eyes treated: 2, 189 (83%); 1, 35 (17%) • on treatment pre-study 74 (32%) • mean IOP at baseline 27.2 mm Hg. <p>Inclusion criteria</p> <ul style="list-style-type: none"> • age ≥18 years • unilateral or bilateral primary POAG, capsular glaucoma, or ocular hypertension • IOP ≥21 mm Hg on previous treatment or ≥25 mm Hg without previous treatment. <p>Exclusion criteria</p> <ul style="list-style-type: none"> • previous treatment with latanoprost or carbonic anhydrase inhibitor • closed or barely open anterior chamber angles or history of angle closure • current use of contact lenses • ocular surgery within 6 months or laser trabeculoplasty within 3 months • ocular infection or inflammation within 3 months • hypersensitivity to study medications • condition preventing reliable tonometry • pregnant, lactating, or considering pregnancy • participation in a clinical trial within past month • unable to adhere to study protocol. 	<p>Washout period after previous treatment</p> <ul style="list-style-type: none"> • 1 week for adrenergic agonists • 3 weeks for β-adrenergic antagonists • 5 days for cholinergic agonists. <p>2 treatment groups</p> <ul style="list-style-type: none"> • latanoprost 0.005% once daily at 2200 (n=112) • dorzolamide 2% 3 times daily at 0900, 1400, and 2200 (n=112). <p>If both eyes eligible, both accepted as study eyes, and mean of IOP in both eyes used in analysis (n=189). In remaining 35 patients, 1 eye met inclusion criteria and was eligible.</p>	<p>Visits conducted at 2 weeks and 3 months after baseline visit. Patients assessed at 0900, 1100, and 1700 at baseline and 3 months. Mean diurnal IOP calculated by authors as mean of these 3 values.</p> <p>At each examination</p> <ul style="list-style-type: none"> • IOP measured with Goldman applanation tonometry • VA and refraction • slit-lamp examination • abnormalities of conjunctiva, cornea, and iris. <p>At baseline and 3 months</p> <ul style="list-style-type: none"> • visual fields. 	<p>Study funded by grant from Pharmacia and Upjohn, UK, manufacturer of latanoprost ophthalmic solution 0.005% (Xalatan®).</p>

IOP=intraocular pressure; mm Hg =millimetres of mercury; NR=not reported; OAG=open-angle glaucoma; UK=United Kingdom; VA=visual acuity.

Table 19B: Results of O'Donoghue and UK and Ireland Latanoprost Study Group

Results		AEs, Including Serious AEs	Withdrawals and Dropouts; ITT Analysis (Yes or No)	Limitations Described by Study Authors	Study-Quality Measures
Primary: Change in IOP (from Baseline)	Secondary				
<p>Mean diurnal IOP decreases from baseline at 3 months in mm Hg (\pmSD):</p> <ul style="list-style-type: none"> • latanoprost 8.5 (3.3) • dorzolamide 5.6 (2.6) • 2.9 mm Hg difference “highly significant” ($p < 0.001$). 	NR	<p>Ocular AEs reported in >2 patients (number of patients) (latanoprost/dorzolamide)</p> <ul style="list-style-type: none"> • total 50/57 • ocular discomfort 22/29 • eyelid rash/dermatitis 0/3 • corneal disorder 2/2 • conjunctivitis 6/5 • conjunctival hyperemia 1/2 • uncontrolled IOP 3/2 • optic atrophy or pallor 5/7 • deterioration of visual field 4/4. <p>Systemic AEs reported in >2 patients (number of patients) (latanoprost/ dorzolamide)</p> <ul style="list-style-type: none"> • total 24/42 • taste perversion 1/12 • respiratory disorders 3/6 • gastrointestinal disorders 1/8 • skin disorders 2/4 • headache or migraine 3/2 • cardiovascular disorders 2/1. <p>Serious AEs reported in 6 patients [none considered secondary to study medications] (number of patients)</p> <ul style="list-style-type: none"> • latanoprost (3) <ul style="list-style-type: none"> ○ stroke (1) ○ hospitalized for planned non-ocular surgery or procedure (2) • dorzolamide (3) <ul style="list-style-type: none"> ○ colon cancer or pulmonary edema (1) ○ hospitalized for planned non-ocular surgery or procedure (2). 	<p>224 patients enrolled, 213 included in efficacy analysis. 8 patients withdrawn: latanoprost group (3); dorzolamide group (5). Reasons for withdrawal (latanoprost/dorzolamide)</p> <ul style="list-style-type: none"> • serious AE 1/1 • non-compliance with protocol 2/2 • consent withdrawn 0/2. <p>3 additional patients withdrawn after study completion because of protocol violations (dorzolamide group). ITT analysis: no</p>	none described	<p><i>Jadad score 2/5. Allocation concealment not applicable.</i></p>

AE(s)=adverse event(s); IOP=intraocular pressure; ITT=intent to treat [analysis]; mm Hg=millimetres of mercury; SD=standard deviation.

Table 20A: Trial characteristics of Ozdemir and Ozdemir study

Author, Year, Location	Study Design, Treatment Duration, Study Time Span	Participants	Intervention(s)	Outcomes	Funding Source(s) and Conflicts of Interest
Ozdemir and Ozdemir, 2003; Turkey	Randomized,* observer-masked, parallel-group design comparing latanoprost 0.005% once daily to carteolol+pilocarpine combination twice daily. Treatment duration for each patient: 3 months. Study time span: September 2000 to January 2002. *Although this term is used, there is no description of randomization. Authors state that study subjects “were randomly divided into 2 groups and matched according to sex, race, and Dx.”	<p>60 adults (65 eyes) enrolled. Baseline characteristics (n=51 patients; 64 eyes)</p> <ul style="list-style-type: none"> • males 24 (47%); females 27 (53%) • mean age 62.4 years; range, 38 to 76 • all Caucasian • diagnoses (based on number of eyes) of ocular hypertension 11 (17%); POAG 46 (72%); pigmentary glaucoma 2 (3%); pseudoexfoliating glaucoma 5 (8%) • mean IOP at baseline 25.3 mm Hg • differences among groups NS (p>0.05). <p>Inclusion criteria</p> <ul style="list-style-type: none"> • newly diagnosed glaucoma (including pigmentary and exfoliative) or ocular hypertension. <p>Exclusion criteria</p> <ul style="list-style-type: none"> • closed or barely open anterior chamber angles, or history of acute angle closure • ocular surgery or laser trabeculoplasty within 6 months • perforating ocular trauma at any time • severe dry-eye syndrome • use of non-glaucoma ocular medications • medication affecting IOP • pregnancy, nursing, considering pregnancy • current use of contact lenses • ocular infection or inflammation within 15 months • condition preventing reliable tonometry • inability to adhere to study protocol • history of asthma or cardiac disease. 	<p>Washout not required because all patients newly diagnosed. 2 treatment groups</p> <ul style="list-style-type: none"> • latanoprost 0.005% once daily at 2100 (n=25 patients; 31 eyes) • carteolol+ pilocarpine combination: carteolol 2% administered at 0800 and 2000; pilocarpine administered at 0900 and 2100 (n=26 patients; 33 eyes). 	<p>Visits conducted at 0.5, 1, and 3 months after baseline visit. At each examination</p> <ul style="list-style-type: none"> • IOP measured with Goldman applanation tonometry at 1000 and 1600 • VA • slit-lamp examination • funduscopy • evaluation of conjunctival hyperemia and anterior chamber angle • symptoms and AEs. <p>Diurnal IOP was mean of 2 daily readings. If both eyes of a patient studied, mean IOP used.</p>	NR

AE(s)=adverse event(s); IOP=intraocular pressure; mm Hg =millimetres of mercury; NR=not reported; NS=not significant; OAG=open-angle glaucoma; VA=visual acuity.

Table 20B: Results of Ozdemir and Ozdemir study

Results		AEs, including Serious AEs	Withdrawals and Dropouts; ITT Analysis (Yes or No)	Limitations Described by Study Authors	Study-Quality Measures
Primary: Change in IOP (from Baseline)	Secondary				
<p>Mean diurnal IOP decreases from baseline at 3 months in mm Hg</p> <ul style="list-style-type: none"> • latanoprost 7.2 (28.7%) • carteolol+picolopine 7.4 (29%). <p>SD numbers removed because it was not identified that these were SDs.</p> <p>At 3 months, each treatment produced significant IOP decreases versus baseline (p<0.001).</p> <p>At 3 months, mean IOP decreases equivalent for both treatments (p=0.51).</p>	NR	<p>No serious AEs reported.</p> <p>AEs reported (number of events) (latanoprost/carteolol+picolopine)</p> <ul style="list-style-type: none"> • total 19/58 (p<0.01) • ocular discomfort 11/19* • blurred vision 1/15* • decreased VA 2/7* • decreased twilight vision 0/5* • conjunctival hyperemia 2/2 • punctate corneal erosions 1/1 • headache 1/8* • dizziness 0/1 • allergic conjunctivitis 1/0. <p>*p<0.01</p> <p>No clinically significant changes in iris colour or eyelash length, and no cells or flare in anterior chambers.</p> <p>Decreased VA and twilight vision, blurred vision, and headache more frequent in carteolol+picolopine group (p<0.05).</p>	<p>Reporting of withdrawals unclear</p> <ul style="list-style-type: none"> • 9 excluded because of lack of follow-up • 4 withdrawn before study termination. <p>Carteolol+picolopine: blurred vision (2), headache (1); latanoprost: allergic conjunctivitis (1).</p> <p>ITT analysis: no. Withdrawn patients excluded in efficacy analysis.</p>	none described	<i>Jadad score 2/5. Allocation concealment unclear.</i>

AE(s)=adverse event(s); IOP=intraocular pressure; ITT=intent to treat [analysis]; mm Hg=millimetres of mercury; NR=not reported; SD=standard deviation; VA=visual acuity.

Table 21A: Trial characteristics of Sihota *et al.* study

Author, Year, Location of Authors	Study Design, Treatment Duration, Study Time Span	Participants	Intervention(s)	Outcomes	Funding Source(s) and Conflicts of Interest
Sihota <i>et al.</i> , 2003; India	Randomized, multi-centre, cross-over design with masked evaluators comparing latanoprost 0.005% once daily to 0.5% timolol twice daily. Study conducted at 1 site. Treatment duration for each patient: 3 months on each of 2 drugs (7 months total with 1 month washout in middle). Study time span: enrolled over 3 months, dates NR.	<p>30 consecutive adults (60 eyes). Baseline characteristics:</p> <ul style="list-style-type: none"> • males 16 (53%); females 14 (47%) • mean age 59.7 years; range 44 to 76 • mean IOP at baseline 23.3±2.1 mm Hg • average cup to disc ratio 0.73±1.1 • prevalence of systemic disorders: DM 10%; hypertension 23% (all controlled with oral medications , no oral beta-blockers used). <p>All 60 eyes had dark-brown irides.</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • bilateral untreated (newly diagnosed) primary open-angle glaucoma • baseline IOP >21 mm Hg on >2 occasions • optic nerve head and visual-field changes commensurate with diagnosis of glaucoma • open angle on gonioscopy. <p>Exclusion criteria</p> <ul style="list-style-type: none"> • previous treatment for IOP control (medical, surgical, laser) • previous ocular surgery • previous ocular disorder • condition preventing reliable tonometry • hypersensitivity or contraindications to study medications • inability to adhere to study protocol • IOP >35 mm Hg. 	<p>Initial washout not required because all patients were newly diagnosed.</p> <p>Washout at time of cross-over occurred for 1 month, i.e., 4th month of trial for all patients was 1st month of treatment with 2nd IOP-lowering agent. This was considered to be period of washout.</p> <p>2 treatment groups</p> <ul style="list-style-type: none"> • latanoprost 0.005% once daily at 2200 (n=15; 30 eyes) • dorzolamide 2% 3 times daily at 0900, 1400, and 2200 (n=15; 30 eyes). <p>Patients crossed over after 1st 3 months.</p>	<p>1st set of visits conducted at 3 and 6 weeks , and 3 months after baseline visit. 2nd set of visits conducted at 3 and 6 weeks , and 3 months after washout period.</p> <p>At each examination</p> <ul style="list-style-type: none"> • IOP measured with Goldman applanation tonometry: <ul style="list-style-type: none"> ○ at baseline, 3 and 7 months: at 0700, 1000, 1300, 1600, and 2200 ○ at 3 and 6 weeks: at 1000 only. • VA and refraction • slit-lamp examination • AEs • BP and pulse. <p>IOP was mean of readings from both eyes.</p>	NR

AE(s)=adverse event(s); BP=blood pressure; DM=diabetes mellitis; IOP=intraocular pressure; mm Hg=millimetres of mercury; VA=visual acuity.

Table 21B: Results of Sihota *et al.* study

Results		AEs, Including Serious AEs	Withdrawals and Dropouts; ITT Analysis (Yes or No)	Limitations Described by Study Authors	Study-Quality Measures
Primary: Change in IOP (from Baseline)	Secondary				
<p>Mean diurnal IOP decreases from baseline at 3 months in mm Hg</p> <ul style="list-style-type: none"> • latanoprost 8.84 (37%) (p<0.01) • dorzolamide 6.75 (29%) (p=0.01). <p>Effect of drugs similar regardless of which was used 1st or 2nd.</p> <p>No effect on efficacy of either treatment regarding age, sex, presence or absence of DM, and hypertension.</p>	<p>% patients with mean IOP of ≤15 mm Hg</p> <ul style="list-style-type: none"> • latanoprost 53.3% • dorzolamide 18.3% • p<0.001. <p>Pressure reduction of ≥30% from baseline</p> <ul style="list-style-type: none"> • latanoprost 90% • dorzolamide 33% • p<0.001. 	<p>AEs reported (number of patients) (latanoprost/ dorzolamide)</p> <ul style="list-style-type: none"> • total 4/2 • mild brow ache 4/0 • foreign body sensation 0/2. <p>No significant changes in</p> <ul style="list-style-type: none"> • BP or pulse • iris pigmentation • ocular adnexa. 	<p>No withdrawals or dropouts.</p> <p>ITT analysis: yes.</p>	<p>none described</p>	<p><i>Jadad score 3/5.</i></p> <p><i>Allocation concealment not applicable.</i></p>

AE(s)=adverse event(s); BP=blood pressure; DM=diabetes mellitus; IOP=intraocular pressure; ITT=intent to treat [analysis]; mm Hg=millimetres of mercury.

Table 22A: Trial characteristics of Watson *et al.* study

Author, Year, Location	Study Design, Treatment Duration, Study Time Span	Participants	Intervention(s)	Outcomes	Funding Source(s) and Conflicts of Interest
<p>Watson <i>et al.</i> and UK Latanoprost Study Group, 1996; England and Sweden. Study group from UK</p>	<p>Double masked, randomized, multi-centre, parallel-group design comparing latanoprost 0.005% once daily with timolol 0.5 twice daily. Study conducted at 14 sites in UK. Treatment duration for each patient: 6 months. Study time span NR.</p>	<p>294 adults enrolled.</p> <p>Baseline characteristics</p> <ul style="list-style-type: none"> • males 191 (65%); females 103 (35%) • mean age 65.0 years; range 39 to 88 • white 285 (97%); black 9 (3%) • diagnoses of ocular hypertension 148 (50%); POAG 121 (41%); exfoliation glaucoma 5 (2%); pigmentary glaucoma 3 (1%); mixed 17 (6%) • mean IOP 25.3 mm Hg. <p>Inclusion criteria</p> <ul style="list-style-type: none"> • age \geq40 years • unilateral or bilateral POAG, exfoliation glaucoma, pigmentary glaucoma, or ocular hypertension • IOP \geq22 mm Hg • newly diagnosed or already on glaucoma treatment. <p>Exclusion criteria</p> <ul style="list-style-type: none"> • use of topical β-blockers within 6 months or for $>$3 months • history of acute angle closure • severe ocular trauma • intraocular surgery or laser within 6 months • history of severe dry-eyes syndrome • ocular inflammation or infection within 3 months • contact-lens use • women of childbearing potential or lactating • systemic diseases involving contraindications to β-blockers • unable to have IOP controlled on 1 drug. <p>If 2 eye eligible but both eyes needed treatment, patients excluded.</p>	<p>Washout period after previous treatment</p> <ul style="list-style-type: none"> • 2 weeks for adrenergic agonists • 5 days for cholinergic agonists and carbonic anhydrase inhibitors. <p>2 treatment groups</p> <ul style="list-style-type: none"> • latanoprost 0.005% once daily at 2000 hours with matching placebo (vehicle) at 0800 (n=149) • timolol 0.5% at 0800 and 2000 (n=145). <p>Randomization performed in block and stratified by centre.</p>	<p>Visits conducted at 2, 6, 12, 18, and 26 weeks after baseline. At baseline and 6 months, patients assessed at 0900, 1300, and 1700. Other visits, only at 0900.</p> <p>Assessed at every visit</p> <ul style="list-style-type: none"> • IOP measured with Goldman applanation tonometry • conjunctival hyperemia • slit-lamp examination • AEs. <p>Assessed less often</p> <ul style="list-style-type: none"> • visual fields • gonioscopy • ophthalmthscopy • refraction • BP and pulse • photography of face and iris • blood and urine. <p>Diurnal IOP was average of measurements at 0900, 1300, and 1700.</p>	<p>Study sponsor Pharmacia AB, Sweden, manufacturer of latanoprost ophthalmic solution 0.005% (Xalatan[®]). 2nd author employed by Pharmacia AB, Sweden. All authors deny proprietary interest in development or marketing of latanoprost.</p>

AE(s)=adverse event(s); BP=blood pressure; IOP=intraocular pressure; mm Hg=millimetres of mercury; NR=not reported; OAG=open-angle glaucoma; UK=United Kingdom.

Table 22B: Results of Watson *et al.* study

Results		AEs, Including Serious AEs	Withdrawals and Dropouts; ITT Analysis (Yes or No)	Limitations Described by Study Authors	Study-Quality Measures
Primary: Change in IOP (from Baseline)	Secondary				
<p>Mean diurnal IOP decreases from baseline at 6 months in mm Hg</p> <ul style="list-style-type: none"> • latanoprost (n=133) 8.5 (33.7%) • timolol (n=129) 8.3 (32.7%). <p>Both medications caused significant change in IOP from baseline (p<0.0001). At 6 months, both medications equally effective. Latanoprost showed trend to greater IOP decreases during 0900 readings at 12- and 18-week visits (p=0.04 and p<0.001 respectively).</p>	<p>No drift in IOP occurred with either treatment during 6-month period. Increased iris pigmentation</p> <ul style="list-style-type: none"> • latanoprost 15 patients (10.1%)* • timolol 2.† <p>*2 considered definite and reported as AEs, other 13 “suspicious.” †These 2 also had “suspected” iris pigmentation, later deemed to be false.</p>	<p>Ocular AEs reported by ≥5 patients (number of patients) (latanoprost/timolol)</p> <ul style="list-style-type: none"> • overall total 77/38 • foreign body sensation 10/3 • conjunctival hyperemia 14/3 • punctate epithelial erosions 13/4 • blurred or disturbed vision 7/4 • discharge 4/2 • eyelid edema or erythema 3/3. <p>Systemic AEs reported by ≥5 patients (number of patients) (latanoprost/timolol)</p> <ul style="list-style-type: none"> • overall total 34/47 • URI 8/7 • headache 1/4 • bronchitis 2/3 • shortness of breath 2/3 • ear infection or discomfort 4/2 • vertigo 2/3. <p>Serious AEs (9 total; unrelated to study medications)</p> <ul style="list-style-type: none"> • latanoprost: 1 each of angina, myocardial infarction, carotid stenosis, retinal detachment • timolol: 1 each of stroke, Herpes zoster, bronchitis, hematemesis, renal colic <p>Increased pigmentation of iris observed in 15 patients.</p>	<p>294 patients enrolled; 268 (91%) remained after 26 withdrew. Latanoprost (12 withdrew)</p> <ul style="list-style-type: none"> • poor compliance (6) • IOP not controlled (2) • local side effects (2) • shortness of breath (1) • chest pain (1). <p>Timolol (14 withdrew)</p> <ul style="list-style-type: none"> • breathing problems (2) • hypotension or bradycardia (2) • headaches (2) • ocular allergic reactions (perhaps not drug-related) (2) • productive cough (1) • self-withdrawal (1) • previously received timolol (1) • eyelid and periorbital edema (1) • lassitude and ocular symptoms (1) • allergic conjunctivitis (1). <p>Conjunctival hyperemia</p> <ul style="list-style-type: none"> • latanoprost caused statistically significantly more conjunctival hyperemia than timolol. Degree of hyperemia slight. <p>ITT analysis: no. Because of protocol violations and withdrawals, mean IOP at different time points not based on all patients.</p>	<ul style="list-style-type: none"> • Use of vehicle as latanoprost placebo (benzalkonium) may have added to eye irritation. • Iris pigmentation in latanoprost group may have been over-estimated because of classification of some changes as “suspicious” (worst view presented). 	<p><i>Jadad score 5/5. Allocation concealment adequate.</i></p>

AE(s)=adverse event(s); IOP=intraocular pressure; ITT=intent to treat [analysis]; mm Hg=millimetres of mercury; URI=upper respiratory infection.

List of Included Studies

Alm A. Comparative phase III clinical trial of latanoprost and timolol in patients with elevated intraocular pressure. *Adv Prostaglandin Thromboxane Res* 1995;23:527-32.

Alm A, Stjernschantz J. Effects on intraocular pressure and side effects of 0.005% latanoprost applied once daily, evening or morning. A comparison with timolol. Scandinavian Latanoprost Study Group. *Ophthalmology* 1995;102(12):1743-52.

Barnebey HS, Orengo-Nania S, Flowers BE, Samples J, Mallick S, Landry TA, Bergamini MV. The safety and efficacy of travoprost 0.004%/timolol 0.5% fixed combination ophthalmic solution. *Am J Ophthalmol* 2005;140(1):1-7.

Camras CB. Comparison of latanoprost and timolol in patients with ocular hypertension and glaucoma: a six-month masked, multicenter trial in the United States. The United States Latanoprost Study Group. *Ophthalmology* 1996;103(1):138-47.

Camras CB, Sheu WP. Latanoprost or brimonidine as treatment for elevated intraocular pressure: multicenter trial in the United States. *J Glaucoma* 2005;14(2):161-7.

Camras CB, UnitedStates, Latanoprost-BrimonidineStudy, Group. Efficacy and Safety of Latanoprost or Brimonidine in Patients with Ocular Hypertension or Primary Open Angle Glaucoma. *ARVO Annual Meeting Abstract Search and Program Planner* 2002; Abstract.

DuBiner HB, Mroz M, Shapiro AM, Dirks MS. A comparison of the efficacy and tolerability of brimonidine and latanoprost in adults with open-angle glaucoma or ocular hypertension: a three-month, multicenter, randomized, double-masked, parallel-group trial. *Clin Ther* 2001;23(12):1969-83.

Erkin EF, Tarhan S, Kayikcioglu OR, Deveci H, Guler C, Goktan C. Effects of betaxolol and latanoprost on ocular blood flow and visual fields in patients with primary open-angle glaucoma. *Eur J Ophthalmol* 2004;14(3):211-9.

Fechtner RD, Airaksinen PJ, Getson AJ, Lines CR, Adamsons IA. Efficacy and tolerability of the dorzolamide 2%/timolol 0.5% combination (COSOPT) versus 0.005% (XALATAN) in the treatment of ocular hypertension or glaucoma: results from two randomized clinical trials. *Acta Ophthalmol Scand* 2004;82(1):42-8.

Fechtner R, Clineschmidt C, Getson A, Adamsons I. A three-month, parallel, randomized, observer-masked, multicenter study comparing Cosopt™ to Xalatan™ in patients with elevated IOP. *Invest Ophthalmol Vis Sci* 1999;40(4):S665.

Fellman RL, Sullivan EK, Ratliff M, Silver LH, Whitson JT, Turner FD, Weiner AL, Davis AA. Comparison of travoprost 0.0015% and 0.004% with timolol 0.5% in patients with elevated intraocular pressure: a six-month, masked, multicenter trial. *Ophthalmology* 2002;109(5):998-1008.

Fristrom B. A six-month, randomized, double-masked comparison of latanoprost with timolol in patients with open-angle glaucoma or ocular hypertension. *Acta Ophthalmol Scand* 1996;74(2):140-4.

Goldberg I. Comparison of tropical travoprost eye drops given once daily and timolol 0.5% given twice daily in patients with open-angle glaucoma or ocular hypertension. *J Glaucoma* 2001;10:414-22.

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- Lone IA, Rizvi A, Ahmad SS, and Unto RA. Comparison of latanoprost and dorzolamide in patients with open-angle glaucoma. *JK Science* 2003;5(1):26-8.
- Martin E, Martinez-de-la-Casa JM, Garcia-Feijoo J, Troyano J, Larrosa JM, Garcia-Sanchez J. A six-month assessment of bimatoprost 0.03% versus timolol maleate 0.5%: hypotensive efficacy, macular thickness and flare in ocular-hypertensive and glaucoma patients. *Eye* (28 October 2005), 1-5.
- Mastropasqua L, Carpineto P, Ciancaglini M, Gallenga PE. A 12-month, randomized, double-masked study comparing latanoprost with timolol in pigmentary glaucoma. *Ophthalmology* 1999;106(3):550-5.
- Mishima HK, Masuda K, Kitazawa Y, Azuma I, Araie M. A comparison of latanoprost and timolol in primary open-angle glaucoma and ocular hypertension. A 12-week study. *Arch Ophthalmol* 1996;114(8):929-32.
- Netland PA, Landry T, Sullivan EK, Andrew R, Silver L, Weiner A, Mallick S, Dickerson J, Bergamini MV, Robertson SM, Davis AA. Travoprost compared with latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. *Am J Ophthalmol* 2001;132(4):472-84.
- Niazi MK, Raja N. Comparison of latanoprost and dorzolamide in the treatment of patients with open-angle glaucoma. *J Ayub Med Coll Abbottabad* 2004;16(1):50-3.
- O'Donoghue EP. A comparison of latanoprost and dorzolamide in patients with glaucoma and ocular hypertension: a three-month, randomized study. Ireland Latanoprost Study Group. *Br J Ophthalmol* 2000;84(6):579-82.
- Ozdemir M, Ozdemir G. Comparison of the intraocular pressure-lowering effect of latanoprost and carteolol-pilocarpine combination in newly diagnosed glaucoma. *Jpn J Ophthalmol* 2003;47(1):72-6.
- Sihota R, Saxena R, Agarwal HC, Pandey RM, Gulati V. Peak pressures: crossover study of timolol and latanoprost. *Eur J Ophthalmol* 2003;13(6):546-52.
- Watson P, Stjernschantz J. A six-month, randomized, double-masked study comparing latanoprost with timolol in open-angle glaucoma and ocular hypertension. The Latanoprost Study Group. *Ophthalmology* 1996;103(1):126-37.

APPENDIX 5: Summary

Latanoprost Trials

Prostaglandin (Dose)	Comparator	Patient Cohort	Authors
latanoprost versus timolol			
latanoprost 0.005% once daily	timolol 0.5% twice daily	assorted*	Camras and US Latanoprost Group
latanoprost 0.005% once daily	timolol 0.5% twice daily	assorted	Mastropasqua <i>et al.</i>
latanoprost 0.005% once daily	timolol 0.5% twice daily	assorted	Netland <i>et al.</i> (also under travoprost)
latanoprost 0.005% once daily	timolol 0.5% twice daily	first line	Sihota <i>et al.</i>
latanoprost 0.005% once daily	timolol 0.5% twice daily	first line	Alm and Stjernschantz
latanoprost 0.005% once daily	timolol 0.5% twice daily	assorted	Konstas <i>et al.</i>
latanoprost 0.005% once daily	timolol 0.5% twice daily	assorted (40% first line)	Mishima <i>et al.</i>
latanoprost 0.005% once daily	timolol 0.5% twice daily	assorted	Watson, Stjernschantz <i>et al.</i>
latanoprost versus brimonidine			
latanoprost 0.005% once daily	brimonidine 0.2% twice daily	second line†	Kampik <i>et al.</i>
latanoprost 0.005% once daily	brimonidine 0.2% twice daily	assorted (43% first line)	DuBiner <i>et al.</i>
latanoprost 0.005% once daily	brimonidine 0.2% twice daily	assorted (76% first line)	Inan <i>et al.</i>
latanoprost 0.005% once daily	brimonidine 0.2% twice daily	assorted (20% first line)	Camras and Sheu
latanoprost versus dorzolamide			
latanoprost 0.005% once daily	dorzolamide 2% 3 times daily	assorted	Lone <i>et al.</i>
latanoprost 0.005% once daily	dorzolamide 2% 3 times daily	assorted (24% first line)	Niazi and Raja
latanoprost 0.005% once daily	dorzolamide 2% 3 times daily	assorted (68% first line)	O'Donoghue <i>et al.</i>
latanoprost versus miscellaneous			
latanoprost 0.005% once daily	dorzolamide-timolol combination twice daily	assorted	Fechtner <i>et al.</i>
latanoprost 0.005% once daily	betaxolol 0.5% twice daily	first line	Erkin <i>et al.</i>
latanoprost 0.005% once daily	carteolol-pilocarpine combination (each administered)	first line	Ozdemir and Ozdemir
travoprost versus timolol			
travoprost 0.004% once daily	<ul style="list-style-type: none"> • timolol 0.5% twice daily • travoprost 0.004%-timolol 0.5% combination once daily 	assorted	Barnebey <i>et al.</i>
travoprost 0.0015% and 0.004% once daily	timolol 0.5% twice daily	assorted	Fellman <i>et al.</i>
travoprost 0.0015% and 0.004% once daily	timolol 0.5% twice daily	assorted	Goldberg <i>et al.</i>
travoprost 0.0015% and 0.004% once daily	timolol 0.5% twice daily	assorted	Netland <i>et al.</i> (also under latanoprost)
bimatoprost versus timolol			
bimatoprost 0.03% once daily	timolol 0.5% twice daily	assorted	Martin <i>et al.</i>

*Combined cohort of patients who were treatment naïve with those who had received prior therapy with IOP-lowering agent.

†Patients who could not use, or had failed therapy, with IOP-lowering agent.

APPENDIX 6: List of Excluded Studies

Studies Excluded at Level 2

Hypotensive efficacy in primary open-angle glaucoma and ocular hypertension: latanoprost in monotherapy vs timolol and dorzolamide in association. *Acta Ophthalmol Scand Suppl* 2000;(232):49-50. No washout

Akarsu C, Bilgili Y K, Taner P et al. Short-term effect of latanoprost on ocular circulation in ocular hypertension. *Clin Experiment Ophthalmol* 2004;32(4):373-377. Follow-up is less than 3 months

Akman A, Cetinkaya A, Akova Y A et al. Comparison of additional intraocular pressure-lowering effects of latanoprost vs brimonidine in primary open-angle glaucoma patients with intraocular pressure uncontrolled by timolol-dorzolamide combination. *Eye* 2005;19(2):145-151. Not monotherapy with PGA

Alm A, Widengard I. Latanoprost: experience of 2-year treatment in Scandinavia. *Acta Ophthalmol Scand* 2000;78(1):71-76. Not a RCT

Alm A, Villumsen J, Tornquist P et al. Intraocular pressure-reducing effect of PhXA41 in patients with increased eye pressure. A one-month study. *Ophthalmology* 1993;100(9):1312-1316. Not patients with high IOP

Alward W L. Additive efficacy of unoprostone isopropyl 0.12% (rescula) to latanoprost 0.005%. *Am J Ophthalmol* 2001;132(3):449-451. Not a RCT

Arend O, Harris A, Wolter P et al. Evaluation of retinal haemodynamics and retinal function after application of dorzolamide, timolol and latanoprost in newly diagnosed open-angle glaucoma patients. *Acta Ophthalmol Scand* 2003;81(5):474-479. Follow-up is less than 3 months

Azuara-Blanco A, Katz L J, Spaeth G L et al. Effect of latanoprost on intraocular pressure in patients with glaucoma on maximal tolerated medical treatment. *Br J Ophthalmol* 1997;81(12):1116. Not a RCT

Azuma I, Kitazawa Y, Yamamura H et al. Phase III double masked comparative study of UF-021 ophthalmic solution in primary open-angle glaucoma and ocular hypertension. *Nippon Ganka Kiyo* 1992;43(12):1432-1440. Not in English

Azuma I, Kitazawa Y, Yamamura H et al. Phase II double-masked dose-determination study of UF-021 ophthalmic solution in primary open-angle glaucoma and ocular hypertension. *Nippon Ganka Kiyo* 1992;43(12):1425-1431. Not in English

Azuma I, Masuda K, Kitazawa Y et al. Double-masked comparative study of UF-021 and timolol ophthalmic solutions in patients with primary open-angle glaucoma or ocular hypertension. *Jpn J Ophthalmol* 1993;37(4):514-525. Not monotherapy with PGA

Bernstein P. A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: a 12-week, randomized, masked-evaluator, multicenter study. *Am J Ophthalmol* 2004;137(2):387-388. Not a RCT

Brandt J D, Beiser J A, Gordon M O et al. Central corneal thickness and measured IOP response to topical ocular hypotensive medication in the Ocular Hypertension Treatment Study. *Am J Ophthalmol* 2004;138(5):717-722. Follow-up is less than 3 months

Brandt J D, VanDenburgh A M, Chen K et al. Comparison of once- or twice-daily bimatoprost with twice-daily timolol in patients with elevated IOP : a 3-month clinical trial. *Ophthalmology* 2001;108(6):1023-1031. Study cohort includes patients with closed-angle glaucoma

Bron A M, Denis P, Nordmann J P et al. Additive IOP-reducing effect of latanoprost in patients insufficiently controlled on timolol. *Acta Ophthalmol Scand* 2001;79(3):289-293. No washout

Bucci M G. Intraocular pressure-lowering effects of latanoprost monotherapy versus latanoprost or pilocarpine in combination with timolol: a randomized, observer-masked multicenter study in patients with open-angle glaucoma. Italian Latanoprost Study Group. *J Glaucoma* 1999;8(1):24-30. No washout

Camras C B. Travoprost compared with latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. *Am J Ophthalmol* 2002;133(5):732-733. Not a RCT

Camras C B. Bimatoprost vs. timolol. *Ophthalmology* 2002;109(4):627-628. Not a RCT

Camras C B, Hedman K. Rate of response to latanoprost or timolol in patients with ocular hypertension or glaucoma. *J Glaucoma* 2003;12(6):466-469. Not a RCT

Camras C B, Alm A, Watson P et al. Latanoprost, a prostaglandin analog, for glaucoma therapy. Efficacy and safety after 1 year of treatment in 198 patients. Latanoprost Study Groups. *Ophthalmology* 1996;103(11):1916-1924. Not a RCT

Camras C B, Schumer R A, Marsk A et al. Intraocular pressure reduction with PhXA34, a new prostaglandin analogue, in patients with ocular hypertension. *Arch Ophthalmol* 1992;110(12):1733-1738. Follow-up is less than 3 months

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- Carenini B, Boles Brogliatti B, Spinelli D et al. Latanoprost in monotherapy compared with Timolol and Dorzolamide in association as hypotensive agents in primary open-angle glaucoma and ocular hypertension. An open, randomized, multicentric, Italian study. *Acta Ophthalmol Scand* 1999;77(Suppl 229):53. No washout
- Carpineto P, Ciancaglini M, Zuppari E et al. The role of the uveoscleral outflow in the management of pigmentary glaucoma: a 24-month study comparing latanoprost with timolol. *Acta Ophthalmol Scand Suppl* 2000;(232):54. No washout
- Cheetham J K, Tang-Liu D, Yu Z et al. Long-term Systemic Exposure Of Lumigan In Patients With Glaucoma Or Ocular Hypertension. ARVO Annual Meeting Abstract Search and Program Planner 2002; Abstract. Not a RCT
- Chew P T, Aung T, Aquino M V et al. Intraocular pressure-reducing effects and safety of latanoprost versus timolol in patients with chronic angle-closure glaucoma. *Ophthalmology* 2004;111(3):427-434. Study cohort includes patients with closed-angle glaucoma
- Christiansen G A, Nau C B, McLaren J W et al. Mechanism of ocular hypotensive action of bimatoprost (Lumigan) in patients with ocular hypertension or glaucoma. *Ophthalmology* 2004;111(9):1658-1662. Follow-up is less than 3 months
- Cohen J S, Gross R L, Cheetham J K et al. Two-year double-masked comparison of bimatoprost with timolol in patients with glaucoma or ocular hypertension. *Surv Ophthalmol* 2004;49 Suppl 1S45-S52. Study cohort includes patients with closed-angle glaucoma
- Cohen J S, Gross R L, Sherwood M B et al. 2-Year comparison of bimatoprost with timolol in patients with glaucoma or ocular hypertension. ARVO Annual Meeting Abstract Search and Program Planner 2003; Abstract. Study cohort includes patients with closed-angle glaucoma
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