Prostaglandin analogues for ophthalmic use: a cost-effectiveness analysis

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ABSTRACT • RÉSUMÉ

Background: The objective of this study was to perform an economic analysis of the cost-effectiveness of prostaglandin analogues for the treatment of increased intraocular pressure (IOP). Prostaglandin analogues for ophthalmic use are more costly than alternative agents for the lowering of IOP. An important policy decision is whether to support continued open listing of these agents or to restrict them to limited use status.

Methods: The cost-effectiveness of prostaglandin analogues was assessed using a decision analytic model. Latanoprost was compared with timolol, dorzolamide, and brimonidine, and travoprost was compared with timolol separately. The effectiveness data used for this economic analysis were the number of millilitres of mercury of IOP reduction compared with baseline and the incidence of adverse events resulting in a withdrawal of the patient from the study. Sensitivity analyses were conducted to assess the robustness of the study results.

Results: Compared with latanoprost, dorzolamide was not a cost-effective strategy. Compared with brimonidine, latanoprost provided a higher IOP reduction with an incremental cost-effectiveness ratio of $16.17 (base case), but the additional IOP reduction with latanoprost was obtained at a cost higher than the average cost per millimetre of mercury reduction obtained with brimonidine. Compared with timolol, latanoprost and travoprost had a positive incremental cost-effectiveness ratio of $34.48 and $39.06, respectively.

Interpretation: For the first-line treatment of glaucoma and elevated IOP, latanoprost is a more cost-effective strategy than dorzolamide and brimonidine. Latanoprost and travoprost are more effective than timolol but also more expensive. For those for whom timolol is not contraindicated, it would be preferable, from a cost-effectiveness standpoint, to initiate treatment with timolol and reserve the prostaglandin analogues as an alternative treatment or as add-on therapy for patients not achieving a clinical response with timolol. Better treatment compliance associated with these analogues improves their cost-effectiveness.

Contexte : La présente étude a pour objet d'effectuer sur le plan économique une analyse rentabilité des analogues de la prostaglandine servant au traitement de la haute pression intraoculaire (PIO). Utilisés en ophtalmologie, ces analogues sont plus dispendieux que les autres agents visant à réduire la PIO. Il importe de décider stratégiquement s'il faut continuer d'inclure ces agents dans la liste non exclusive ou de les inscrire dans la liste des agents à usage limité.

Méthodes : L'évaluation coût-efficacité des analogues de la prostaglandine a été faite selon le modèle d'analyse décisionnelle. L'on a comparé le latanoprost avec le timolol, le dorzolamide et la brimonidine, ainsi que le travoprost avec le timolol séparément. Les données d'efficacité utilisées pour cette analyse économique ont été le nombre de millimètres de mercure de réduction la PIO comparativement aux données de base ainsi que l'incidence des effets indésirables entraînant le retrait du patient de l'étude. Des analyses de sensibilité ont permis d'évaluer la solidité des résultats de l'étude.

Résultats : Comparativement au latanoprost, le dorzolamide n'était pas une stratégie rentable. Comparativement à la brimonidine, le latanoprost a permis de réduire davantage la PIO avec un taux de rentabilité accru de 16,17 $ (hypothèse de base), mais la réduction additionnelle de la PIO avec le latanoprost a été obtenue à un coût plus haut que le coût moyen de la réduction par millimètre de mercure obtenue avec la brimonidine. Comparativement au timolol, le latanoprost et le travoprost ont eu un taux positif de rentabilité accrue de 34,48 $ et 39,06 $ respectivement.

Interprétation : Pour le traitement de première intention du glaucome et de la haute PIO, le

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latanoprost présente une stratégie plus rentable que le dorzolamide et la brimonidine. Le latanoprost et le travoprost sont plus efficaces mais aussi plus dispendieux. Pour les personnes auxquelles le timolol n'est pas contre-indiqué, il serait préférable, du point de vue rentabilité, d'entreprendre le traitement avec le timolol et de garder les analogues de la prostaglandine comme thérapie optionnelle ou ajoutée pour les patients pour qui le timolol ne donnent pas de résultats cliniques. Une meilleur observance du traitement associée avec ces analogues en améliore la rentabilité.

It is estimated that the number of Canadians afflicted with vision loss will increase from 67 900 blind and 319 000 visually impaired persons in 2001 to 120 000 and 600 000, respectively, in 2026. These translate into an increase of 86% in the number of Canadians with significant vision loss.[1] Since glaucoma is the second most important cause of visual disability in Canada, after age-related macular degeneration, cost-effective therapeutic options and correct policy decisions for therapeutic eye care in Canada are extremely important challenges over the next 20 years. Once these conditions have been diagnosed, they must be monitored and treated for the remainder of the patients' lives.

Although not always associated with glaucoma, high intraocular pressure (IOP) is recognized as the most important risk factor contributing to the development and progression of glaucoma.[2] Elevated IOP is, however, neither necessary nor sufficient to cause glaucoma, since for an estimated 90% of patients with elevated IOP (>21 mm Hg) glaucoma never develops.[3] Conversely, normal or low tension glaucoma occurs in individuals without high IOP, but these patients still benefit from IOP reduction.[4] A number of studies have demonstrated that lowering IOP levels helps to prevent optic nerve damage and glaucoma-related blindness, and even a 1 mm Hg change in IOP has been associated with clinically significant differences.[5–8] Approaches to reduce IOP include either pharmacotherapy or surgery.

Pharmacotherapy is usually the first line of treatment for elevated IOP and chronic open-angle glaucoma. There are currently 5 major classes of drugs used to manage glaucoma and elevated IOP:[2,9]

- Beta-adrenergic antagonists
- Adrenergic agonists
- Carbonic anhydrase inhibitors
- Cholinergics (acetylcholine receptor agonists)
- Prostaglandin analogues

Prostaglandin analogues are the newest class of glaucoma medication to be introduced into the Canadian market (Table 1). There are currently 3 approved in Canada for the treatment of patients with elevated IOP or glaucoma (Table 1). These include latanoprost (Xalatan, Pfizer Canada Inc, Kirkland, Que.), travoprost (Travatan, Alcon Canada Inc, Mississauga, Ont.), and bimatoprost (Lumigan, Allergan Inc, Irvine, Calif.). They are indicated for the reduction of IOP in patients who have open-angle glaucoma or ocular hypertension. Most drug programs sponsored by provincial and territorial governments provide unrestricted coverage for these drugs (open listing), with the exception of Ontario and New Brunswick, where coverage is restricted (i.e., there is a requirement to fulfill specific clinical criteria before approval is obtained for reimbursement). This review was prepared by the Canadian Agency for Drugs and Technologies in Health in conjunction with the University of Ottawa Eye Institute.

The objective of this economic evaluation was to estimate the cost-effectiveness of prostaglandin analogues for ophthalmic use compared with other medications used for the treatment of glaucoma in Canada.

Methods

Economic evaluation

A cost-effectiveness analysis is a type of economic evaluation that considers the outcome of health interventions measured in natural (health) units and the cost of these interventions. Cost-effectiveness analyses were performed using the change in IOP from baseline as the main outcome. The target population was adult patients (>18 years) with raised IOP who were being treated with a prostaglandin analogue or another glaucoma medication currently available in Canada.

Treatment comparators for the economic analysis were those retained in the clinical review to be published in detail elsewhere. Low-dose travoprost (0.0015%) was not considered, since this dose is not approved for use in Canada. The treatment comparators were latanoprost, travoprost, timolol, brimonidine, and dorzolamide. In accordance with the clinical data available, cost-effectiveness analyses were performed for the following sets of comparators:

- Latanoprost vs. brimonidine
- Latanoprost vs. dorzolamide
- Latanoprost vs. timolol
- Travoprost vs. timolol

There was no eligible study on bimatoprost to be included in the cost-effectiveness analysis.

This economic analysis was performed from the perspective of a public third-party payer (Ministry of Health) and conducted in the framework of a decision analytic model

Table 1—Single-agent prostaglandin analogues for glaucoma treatment currently available in Canada*

Generic name	Trade name (manufacturer)	Ophthalmic solution	Format	Cost per unit	Approved dosage
Latanoprost	Xalatan (Pfizer Canada Inc)	0.005%	2.5 mL	$26.00	Once daily
Travoprost	Travatan (Alcon Canada Inc)	0.004%	2.5 mL	$26.50	Once daily
Bimatoprost	Lumigan (Allergan Inc)	0.03%	2.5 mL	$26.00	Once daily

*Cost and dosing information obtained from the online Ontario Drug Benefit Formulary effective from April 4, 2006.

(Fig. 1). For the base-case analysis, the time horizon was restricted to 3 months, in accordance with the most frequent endpoint found in the clinical data available. For each treatment, the decision tree included 3 endpoints:

- Withdrawn because of adverse effects
- Persistent with treatment
- Nonpersistent with treatment

Effectiveness

The effectiveness of compared treatments was taken from the literature. For each treatment comparison, the effectiveness data used for the cost-effectiveness analyses were restricted to the results of studies that compared the 2 treatments and were retained in the clinical review.

The effectiveness data used for this economic analysis were the number of millimetres of mercury of IOP reduction compared with the baseline, as well as the incidence of adverse events resulting in a withdrawal of the patient from the study. For patients who withdrew for this reason, it was assumed that they would not benefit from the treatment.

Ocular hyperemia and all other ocular adverse events were not considered in the cost-effectiveness equation because these events typically resolve without treatment. If the events were severe enough to cause a treatment discontinuation, their probabilities were factored into the analyses as withdrawals due to adverse events.

For the base-case analyses, all patients were considered to be persistent with their treatment. (Persistence refers to the long-term continuation of treatment, which is one dimension of treatment adherence.) The impact of nonpersistence was estimated in sensitivity analyses.

Costs

In accordance with the adopted Ministry of Health perspective, costs considered in the evaluation are those of the medications used to reduce IOP and those of physician visits for the initial prescribing of treatment and for the handling of adverse events.

Costs of medications were estimated using amounts reimbursed by the Ontario Drug Benefit Formulary,[10] to which the pharmacist dispensing fee was added. The cost per day was then calculated by estimating the number of millilitres per bottle and adjusting for each product with the specific number of drops per millilitre and the usual daily frequency of administration. The number of drops per millilitre was taken from the study by Fiscella et al.[11] It was assumed that all patients received treatment for both eyes.

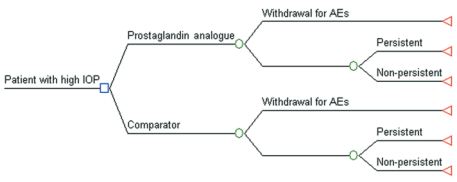

Fig. 1—Decision analysis tree. (IOP, intraocular pressure; AE, adverse effect.)

For each treatment, the fee for an initial visit with an ophthalmologist was added. For the base-case analysis, it was assumed that the 2 different initial fees (consultation or specific assessment) were paid using a 50:50 ratio. For patients experiencing adverse events requiring treatment withdrawal, a repeat consultation fee was added. The amounts of ophthalmologists' fees were taken from the current Ontario Schedule of Benefits for Physician Services.[12] For patients who were withdrawn because of adverse events, it was assumed that they would not benefit from the discontinued treatment, which would reduce the average efficacy of this treatment, but that they had to incur the cost of 1 bottle of medication.

Complementary analyses

Data comparing latanoprost with timolol at 6 and 12 months were available, as were data for the comparison of travoprost to timolol at 6 months. Cost-effectiveness analyses were performed using these longer-term data.

Contrary to what is observed in a clinical trial, in current practice the patients' adherence to their treatment represents a significant issue. This was considered in sensitivity analyses in which the impact of patients' persistence on the cost-effectiveness was estimated. Levels of persistence associated with each glaucoma medication were obtained from the literature and used for these analyses. For patients who were not persistent, it was assumed that they would not benefit from the treatment and that, on average, they would have consumed the medication for half of the time horizon.

Sensitivity analyses

Sensitivity analyses were performed to evaluate the robustness of the base-case results in light of the uncertainty of some parameters. Difference in IOP reduction between comparators was varied with the value of the 95% confidence interval (CI). The cost of treatment was varied by ±25%, to take potential wastage into account.

Data analysis

The decision tree, cost-effectiveness analyses, and sensitivity analyses were performed with the TreeAge Pro 2006 Suite software (v. 1.2, TreeAge Software Inc, Williamson, Mass.). Probabilistic sensitivity analyses were performed with the Crystal Ball software (v. 7.2.2, Decisioneering Inc, Denver, Colo.).

Results

As a result of the systematic literature search, a total of 22 studies[13–33] were included in the clinical effectiveness analysis and 5[34–38] in this cost-effectiveness review. Table 2 summarizes the study characteristics of research reporting clinical outcomes.

Clinical outcomes

The probability of withdrawal due to adverse events and the reduction in IOP for each comparison analysed are sum-

marized in Table 3. For the primary analysis, differences in IOP reduction were those assessed at 3 months, whereas probability of withdrawal due to adverse events were those reported in the clinical studies and are not associated with a specific time frame. CIs for the average reduction in IOP were estimated using the same weights associated with each study that were used for the estimation of the mean difference in IOP in the clinical review.

Costs

The pharmacist dispensing fee and the different ophthalmologist fees are summarized in Table 4. Costs per day were estimated for each medication analysed. The data used for these estimations are summarized in Table 5.

Incremental cost-effectiveness analyses—base case

For each treatment comparison, an incremental cost-effectiveness ratio was calculated. This is the ratio of the differences in costs and the differences in outcomes of the compared interventions. It represents the additional cost for each unit of additional outcome. Details of these cost-effectiveness analyses are summarized in Table 6. Compared with timolol, latanoprost and travoprost had a positive incremental cost-effectiveness ratio of $34.48 and $39.06, respectively. This means that each additional millimetre of mercury of IOP reduction obtained with latanoprost or travoprost would cost $34.48 and $39.06, respectively, over a 3-month period. Compared with brimonidine, latanoprost had a ratio of $16.17. Latanoprost was more effective and less costly than dorzolamide.

Complementary analyses

For some treatment comparisons, data on the reduction in IOP at 6 and 12 months were available (Table 7), and from these data incremental cost-effectiveness ratios were also calculated (Table 8).

Persistence with treatment

Compliance with glaucoma medications has been estimated in many different studies. In 12 of these, treatment compliance with a prostaglandin analogue was compared with compliance with other glaucoma medications.[36,37,39–49] All of these studies focused on the persistence dimension of compliance and were either based on chart review data or on data from administrative claims databases. In all of them, persistence with the prostaglandin

Table 2—Characteristics of studies reporting clinical outcomes

Study country	Rx length, mo	*n*	Comparison	Main outcomes*	Jadad score†	ITT	Industry -funded
Scandinavia[13]	6	267	Latanoprost (2 dosage regimens) vs. timolol	Diurnal IOP	5	No	Yes
USA (20 centres)[14]	3	256	Latanoprost vs. dorzolamide/timolol combination	Diurnal IOP	5	Yes	Yes
Europe/Israel (24 centres)[14]	3	288	Latanoprost vs. dorzolamide/timolol combination	Diurnal IOP	5	Yes	Yes
USA (17 centres)[15]	6	268	Latanoprost vs. timolol	Diurnal IOP	5	Yes	Yes
Greece, USA[16]	3	109	Latanoprost vs. timolol	Diurnal IOP	3	No	Yes
Italy[17]	12	36	Latanoprost vs. timolol	Diurnal IOP	5	‡	NR
Japan (35 centres)[18]	3	184	Latanoprost vs. timolol	IOP	3	No	NR
USA[19]	12	801	Travoprost (2 concentrations) vs. latanoprost vs. timolol	Diurnal IOP§	5	Yes	Yes
India[20]	6	30	Latanoprost vs. timolol	Diurnal IOP	3	Yes	NR
UK (14 centres)[21]	6	294	Latanoprost vs. timolol	Diurnal IOP	5	No	Yes
Turkey[22]	3	32	Latanoprost vs. betaxolol	IOP & ocular blood flow	2	No	NR
Turkey[23]	3	60	Latanoprost vs. carteolol–pilocarpine combination	Diurnal IOP	2	No	NR
USA (23 centres)[24]	6	303	Latanoprost vs. brimonidine	Diurnal IOP	5	No	Yes
USA (5 centres)[25]	3	127	Latanoprost vs. brimonidine	IOP	5	No	Yes
Turkey[26]	3	41	Latanoprost vs. brimonidine	IOP & ocular blood flow	2	No	NR
USA (44 centres)[27]	6	605	Travoprost (2 concentrations) vs. timolol	Diurnal IOP§	5	Yes	Yes
Spain[28]	6	60	Bimatoprost vs. timolol	IOP	2	Yes	No
Pakistan[29]	3	60	Latanoprost vs. dorzolamide	Diurnal IOP	2	NC	NR
UK & Ireland (12 centres)[30]	3	224	Latanoprost vs. dorzolamide	Diurnal IOP	2	No	Yes
Europe (30 centres)[31]	6	379	Latanoprost vs. brimonidine	Diurnal IOP	2	Yes	Yes
India[32]	3	44	Latanoprost vs. dorzolamide	Diurnal IOP	2	Yes	NR
USA (33 centres)[33]	3	263	Travoprost/timolol combination vs. travoprost vs. timolol	Diurnal IOP§	4	Yes	Yes
USA, Australia, Europe (64 centres)[34]	9	573	Travoprost (2 concentrations) vs. timolol	Diurnal IOP§	5	Yes	Yes

*Time frame for IOP measurement is within 3 months.
†Range of possible scores: 0–5.
‡ITT at 6 months but not at 12 months.
§Calculated by reviewers.
Note: Rx, treatment; mo, months; ITT, intent to treat; IOP, intraocular pressure; NR, not reported; NC, not clear.

analogue was always better than with the other comparators. In some studies, patients were considered nonpersistent if they had stopped taking any glaucoma medication, whereas in other studies patients who had switched to another medication were also considered as nonpersistent. In most, the results were estimated in terms of hazard rate ratios, which are unsuitable for inclusion in the decision tree. The study by Dasgupta et al.[41] reported results in terms of proportion of patients who were still persistent with their treatment after 2 years.

In the present study, the persistence rate, not including those patients who switched to another medication, was 77% for latanoprost, 63% for beta-blockers, 64% for carbonic anhydrase inhibitors, and 67% for brimonidine. Cost-effectiveness analyses incorporating persistence data were performed. A persistence rate of 77% was used for both latanoprost and travoprost. For timolol, the persistence rate of 63% for beta-blockers was used; for dorzolamide, the 64% rate associated with carbonic anhydrase inhibitors was used; and for brimonidine the 67% rate was used. All other parameters were the same as in the base-case analyses. The results of these cost-effectiveness analyses are summarized in Table 9. As was observed with the base-case analyses, latanoprost was a dominant strategy compared with dorzolamide, and all other incremental cost-effectiveness ratios remained positive, although inferior, to those estimated in the base case.

Table 3—Summary of clinical outcomes for the primary analysis

Comparison	Probability of withdrawal due to adverse events	Average reduction* in IOP (95% CI)
Latanoprost	19/755 (2.52%)[13,15–18,20,21]	7.36 (7.12–7.61)[16,18]
vs. timolol	21/669 (3.14%)[13,15–18,20,21]	6.11 (5.84–6.37)[16,18]
Latanoprost	12/423 (2.84%)[24,26,31]	6.15 (5.74–6.57)[25,26]
vs. brimonidine	46/423 (10.87%)[24,26,31]	5.12 (4.70–5.33)[25,26]
Latanoprost	1/127 (0.79%)[29,30]	8.43 (7.96–8.89)[29,30]
vs. dorzolamide	1/127 (0.79%)[29,30]	5.78 (5.40–6.17)[29,30]
Travoprost	18/598 (3.01%)[19,33,34]	8.11 (7.83–8.39)[33]
vs. timolol	5/588 (0.85%)[19,33,34]	6.90 (6.67–7.12)[33]

*mm Hg.
Note: IOP, intraocular pressure; CI, confidence interval.

Table 4—Pharmacist and ophthalmologist fees

Item	Cost ($)	Source
Pharmacist dispensing fee	6.54	Ontario Drug Benefit Dispensing Fees. Ontario Ministry of Health and Long-Term Care Web site (consulted January 11, 2007)
Ophthalmologist fees		Schedule of Benefits for Physician Services under the *Health Insurance Act.* Ontario Ministry of Health and Long-Term Care. January 1, 2007
Consultation	66.30	
Specific assessment	42.15	
Repeat consultation	45.85	

Table 5—Cost of ophthalmic preparations

IOP-lowering agent	Format	Cost ($)*	Dispensing fee ($)	Drops/mL†	Drops/day × 2 eyes	Cost/day ($)
Latanoprost	2.5 mL	26.00	6.54	32.0	2	0.8135
Travoprost	2.5 mL	26.50	6.54	34.5	2	0.7661
Timolol	10 mL	18.60	6.54	31.5	4	0.3192
Dorzolamide	5 mL	16.50	6.54	25.8	6	1.0716
Brimonidine	10 mL	23.10	6.54	22.2	4	0.5341

*Ontario Drug Benefit Formulary/Comparative Drug Index 39, Sept. 2005.
†Fiscella et al.[11]
Note: IOP, intraocular pressure.

Sensitivity analyses

Sensitivity analyses were performed to test the robustness of the base-case and complementary analyses. Probabilistic sensitivity analyses were done with the IOP reduction using the 95% CI of the mean estimate. For each analysis, 1000 first-order Monte Carlo simulations were run using a normal distribution (Table 10). Also, univariate sensitivity analyses were performed to factor in a 25% wastage rate for when patients inappropriately used their medication. Base-case results were robust to all these sensitivity analyses. Relative to dorzolamide, latanoprost remained in all cases a dominant strategy, and a positive incremental cost-effectiveness ratio was found for all other comparisons.

Interpretation

Other studies have compared the cost-effectiveness of prostaglandin analogues with other IOP-lowering medications as first-line therapy. The study by Goldberg and Walt[34] was a cost-effectiveness analysis based on results of published studies reporting the percentage of patients with elevated IOP achieving specific individualized target IOPs. They found that the incremental cost of achieving additional success with bimatoprost compared with timolol ranged from US$800 to US$1700 (Can$960 to

Table 6—Incremental cost-effectiveness analyses

IOP-lowering agent	Cost ($)	Cost* ($)	mm Hg reduction	mm Hg reduction*	Average CER ($)	ICER ($)
Timolol	84.08	43.33	5.92	1.26	14.21	34.48
Latanoprost	127.41		7.17		17.76	
Brimonidine	104.57	22.84	4.56	1.41	22.92	16.17
Latanoprost	127.41		5.98		21.32	
Dorzolamide	150.41	–22.97	5.73	2.63	26.23	†
Latanoprost	127.43		8.36		15.24	
Timolol	83.26	40.02	6.84	1.02	12.17	39.06
Travoprost	123.28		7.87		15.67	

*Ontario Drug Benefit Formulary/Comparative Drug Index 39, Sept. 2005.
†Latanoprost dominant.
Note: IOP, intraocular pressure; CER, cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio.

Table 7—Average reduction in IOP at 6 and 12 months

Comparison	Average reduction in IOP, mm Hg, at 6 months (95% CI)	Average reduction in IOP, mm Hg, at 12 months (95% CI)
Latanoprost	7.55 (7.32–7.81)[13,15,20,21]	6.78 (6.36–7.20)[17]
vs.timolol	6.11 (5.84–6.37)[13,15,20,21]	5.74 (5.33–6.14)[17]
Travoprost	7.68 (7.47–7.89)[27]	—
vs. timolol	6.79 (6.58–7.01)[27]	

Note: IOP, intraocular pressure; CI, confidence interval.

Table 8—Incremental cost-effectiveness analyses at 6 and 12 months

Comparison	Cost ($)	Cost* ($)	mm Hg reduction	mm Hg reduction*	Average CER ($)	ICER ($)
Timolol	112.52	87.85	6.31	1.07	17.84	81.80
Latanoprost (6 months)	200.37		7.38		27.15	
Timolol	169.10	176.39	5.56	1.05	30.42	168.06
Latanoprost (12 months)	345.49		6.61		52.27	
Timolol	112.38	79.26	6.73	0.72	16.69	110.61
Travoprost (6 months)	191.64		7.45		25.73	

*Ontario Drug Benefit Formulary/Comparative Drug Index 39, Sept. 2005.
Note: CER, cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio.

Can$2040). Latanoprost was less effective and more costly than bimatoprost.

Another cost-effectiveness study done by Noecker and Walt,[50] similar to this review, had included a slightly different set of studies and had different eligibility criteria for study inclusion. These authors determined that the rank order of cost-effectiveness for the prostaglandin analogues was as follows: bimatoprost, latanoprost, travoprost.

The cost-effectiveness study by Holmstrom et al.[35] was also based on data from published clinical trials reporting the proportion of patients achieving specific IOP targets. In that study, comparing timolol, bimatoprost, and latanoprost as initial treatment but allowing add-on treatment, they found that the most cost-effective strategy was to use timolol as first-line therapy and to add bimatoprost if the target was not met.

Bernard et al.[36] performed a cost-effectiveness analysis based on a decision model populated with data from a retrospective chart review comparing latanoprost with beta-blockers and allowing for noncompliance and switch to other treatments. The incremental cost per day of IOP control when latanoprost was used as a first-line treatment compared with a beta-blocker as first-line treatment was €0.82 (Can$1.23) and €0.36 (Can$0.54) over 2 and 3 years, respectively.

The study by Day et al.[37] was also based on data from a retrospective chart review and compared latanoprost, bimatoprost, and beta-blockers. The authors estimated IOP reduction, persistence with treatment, and cost associated with each treatment but did not calculate any cost-effectiveness ratio. Their study indicated that patients taking latanoprost had better persistence and lower IOP compared with those taking bimatoprost or beta-blockers, but beta-blockers incurred lower overall costs.

Le Pen et al.[38] performed a cost-effectiveness and a cost-utility analysis comparing travoprost, latanoprost, and timolol in advanced glaucoma in 5 European countries: Austria, France, Germany, The Netherlands, and the United Kingdom. They constructed a Markov model, which considered the probability of stable versus unstable visual acuity and 2 health states: stable glaucoma and visual field defect. The time horizon of the model was 5 years with 60 cycles of 1 month. Probabilities were taken from a study by Stewart et al.,[51] and utility values were estimated using the formula developed by Sharma et al.[52] or the utilities measured in Brown et al.[53] For the cost-effectiveness analysis, the effectiveness was defined as the time spent without disease progression. The results of the cost-effectiveness analysis indicated that travoprost dominated latanoprost in all countries except France, where an incremental cost-effectiveness ratio was found of €825 (Can$1237). Ratios for travoprost compared with timolol varied from €823 (Can$1234) to €1495 (Can$2242), depending on the country. In the cost-utility analysis, travoprost also dominated latanoprost in all countries except France, where an incremental cost-utility ratio was found of €23 948 (Can$35 922). Incremental cost-utility ratios for travoprost compared with timolol varied from €23 828 (Can$35 742) to €43 296 (Can$64 944), depending on the country.

The economic evaluation in the present study comprised many cost-effectiveness analyses that had different comparators and different time frames, and reflected different settings. Some key findings emerged from these analyses.

Compared with latanoprost, dorzolamide was not a cost-effective strategy. It was dominated by latanoprost in the base-case analysis, the complementary analyses, and all the sensitivity analyses.

Compared with brimonidine, latanoprost provided a

Table 9—Incremental cost-effectiveness analyses with persistence data

Comparison	Cost ($)	Cost* ($)	mm Hg reduction	mm Hg reduction*	Average CER ($)	ICER ($)
Timolol	78.93	40.27	3.73	1.80	21.17	22.42
Latanoprost	119.20		5.52		21.58	
Brimonidine	97.50	21.72	3.06	1.54	31.89	14.07
Latanoprost	119.23		4.60		25.91	
Dorzolamide	133.18	–14.10	3.67	2.77	36.29	†
Latanoprost	119.08		6.44		18.49	
Timolol	77.99	37.60	4.31	1.75	18.10	21.53
Travoprost	115.59		6.06		19.08	
Timolol	102.11	81.66	3.97	1.71	25.70	47.46
Latanoprost (6 months)	183.77		5.68		32.34	
Timolol	148.23	163.98	3.50	1.59	42.32	103.36
Latanoprost (12 months)	312.21		5.09		61.35	
Timolol	101.72	74.37	4.24	1.49	23.98	49.77
Travoprost (6 months)	176.09		5.74		30.70	

*Ontario Drug Benefit Formulary/Comparative Drug Index 39, Sept. 2005.
†Latanoprost dominant.
Note: CER, cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio.

Table 10—Results of probabilistic sensitivity analyses on the reduction of intraocular pressure

		Results of probabilistic sensitivity analyses ($)			
Comparison	Base-case ICER ($)	Mean (SD)	Med	Min	Max
Timolol vs. latanoprost (3 months)	34.48	35.13 (6.46)	34.00	22.33	90.05
Brimonidine vs. latanoprost (3 months)	16.17	17.17 (5.91)	15.87	9.08	99.33
Dorzolamide vs. latanoprost (3 months)	–8.74	–9.00 (1.34)	–8.83	–18.16	–5.86
Timolol vs. travoprost (3 months)	39.06	41.02 (10.41)	39.26	22.39	116.67
Timolol vs. latanoprost (6 months)	81.80	85.20 (18.40)	81.79	47.81	208.98
Timolol vs. travoprost (6 months)	110.61	119.04 (35.05)	111.11	59.50	321.46
Timolol vs. latanoprost (3 months) with persistence	22.42	22.52 (1.91)	22.33	18.17	31.58
Brimonidine vs. latanoprost (3 months) with persistence	14.07	14.28 (2.45)	13.85	8.86	27.11
Dorzolamide vs. latanoprost (3 months) with persistence	–5.09	–5.19 (0.51)	–5.15	–7.80	–3.94
Timolol vs. travoprost (3 months) with persistence	21.53	21.62 (1.87)	21.44	17.24	31.19
Timolol vs. latanoprost (6 months) with persistence	47.76	48.35 (4.20)	47.85	38.63	68.04
Timolol vs. latanoprost (12 months) with persistence	103.36	105.75 (17.08)	103.37	179.99	108.95
Timolol vs. travoprost (6 months) with persistence	49.77	50.07 (4.43)	49.76	39.08	71.66

Note: ICER, incremental cost-effectiveness ratio; Med, median; Min, minimum; Max, maximum.

higher IOP reduction with an incremental cost-effectiveness ratio of $16.17 (base case). Latanoprost was a more effective and more costly strategy than brimonidine, but in this case additional IOP reduction with latanoprost was obtained at a cost lower than the average cost of IOP reduction with brimonidine (incremental cost-effectiveness ratio of $16.17 and average cost-effectiveness ratio for brimonidine of $22.92). Selecting brimonidine, the less costly alternative, implies a willingness to pay $22.92 per millimetre of mercury of IOP reduction. An additional reduction in IOP obtained with latanoprost costs $16.17, which is below the willingness-to-pay amount for brimonidine. Therefore, on the basis of its incremental cost-effectiveness ratio, latanoprost could be considered as a cost-effective strategy compared with brimonidine.

Compared with timolol, latanoprost and travoprost are more effective but also more costly. As is the case in most cost-effectiveness analyses, it is difficult to judge from such incremental cost-effectiveness ratios. There are no implicit values for a 1 mm Hg reduction in IOP. In some of the cost-effectiveness analyses, the ratio was close to the average cost per 1 mm Hg of IOP reduction associated with timolol, but in some cases it was significantly higher. The implication of these findings for clinical practice could be to use timolol as a first-line strategy, reserving latanoprost or travoprost for those patients who do not achieve an appropriate clinical response with timolol or for whom timolol would be contraindicated. As indicated by Holmstrom et al.,[35] add-on treatments, which were not considered in the scope of this evaluation, could also be potential alternative strategies for patients not achieving a clinical response with timolol. Better treatment compliance associated with prostaglandin analogues improves their cost-effectiveness, as was shown in the complementary analyses.

In the cost-effectiveness analyses, it was assumed that these patients would require an additional visit to the ophthalmologist. Other assumptions could have been conceivable, but they would have been hypothetical given the nature of the data available from the clinical trials. For the cost of this additional visit to the ophthalmologist the fee for a repeat consultation was used, although other types of fee might have been appropriate.

The dosages used in this cost-effectiveness analysis were those used in the clinical trial. In clinical practice other dosages could be used, such as timolol once a day or brimonidine 3 times daily, but these were not considered.

The costs used were those from Ontario sources. The costs of medications are the same in all Canadian provinces and territories, but physicians' fees vary among jurisdictions. Although these differences are usually minimal, they should be taken into account when considering the results of this economic evaluation for other provinces/territories.

Because glaucoma is a chronic disease, patients are expected to take IOP-lowering agents for extended periods, i.e., for the duration of their life. It would have been preferable to evaluate the cost-effectiveness of the IOP-lowering agent over a longer time horizon. The results from clinical trials, however, were based on limited periods—3 months in most cases and up to 6–12 months in a few studies.

In conclusion, for the treatment of glaucoma and elevated IOP, latanoprost is a more cost-effective strategy than dorzolamide or brimonidine according to the cost-effectiveness and incremental cost-effectiveness ratio results. However, for 3 months of treatment, brimonidine costs less than latanoprost. Latanoprost and travoprost are more effective than timolol but also more expensive. For those for whom timolol is not contraindicated, it would be preferable, from a cost-effectiveness standpoint, to initiate treatment with timolol and reserve the prostaglandin analogues as an alternative treatment or as add-on therapy for patients not achieving a clinical response with timolol.

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