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Research Article

Cost-Utility Analysis of Timolol for the Treatment for Open-Angle Glaucoma

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Abstract

Objective: To present a cost-utility (cost-effectiveness) model, based upon patient preferences, for the treatment of primary open angle glaucoma.

Methods. A 21-year model, cost-utility analysis utilizing 2012 real US dollars, and societal and 3rd party insurer cost perspectives, was created. No direct patients were involved. Demographics were taken from a 2005 meta-analysis on glaucoma therapy using timolol maleate. Patient value gain was measured in QALYs (quality-adjusted life-years) and percent. Financial value gain was quantified with the cost-utility ratio in $/QALY (dollars expended per QALY gained) and net societal financial gain. All patient value and financial value gains were discounted with Net Present Value analysis at 3% annually.

Results: Topical, 0.5%, timolol therapy confers a 19.0% gain in quality-of-life (QOL) with an end-stage glaucoma vision of 20/800 bilaterally. For bilateral, end-stage vision of 20/200, timolol therapy results in a 13.4% QOL gain, while modeling end-stage vision of 20/20,000 (hand motions) results in a 29.9% QOL gain. The incremental, direct ophthalmic, medical cost for treating a primary open-angle glaucoma patient for 21 years is $7,531. When all societal costs saved by timolol therapy are included, the intervention returns a 21-year, net $440,278 to society. The 21-year, financial, return-on-investment (ROI) for glaucoma therapy is ($440,278/$7,531 =) 5,846%, an annual financial ROI of 22.5%. The average societal cost-utility ratio referent to end-stage vision of 20/800 is (-$183,449)/QALY), indicating that timolol therapy dominates no therapy. The average third party insurer cost-utility ratio for timolol therapy referent to end-stage vision of 20/800 is $3,138/QALY.

Conclusion: Timolol therapy, in a widely applicable, primary open angle glaucoma model, confers considerable patient value versus no treatment. It is highly cost-effective and has a substantial financial return-on-investment to society referent to the direct ophthalmic medical costs expended.

Keywords: Cost-Utility Analysis; Glaucoma Therapy; Modeling

Abbreviations

QALY: Quality-Adjusted Life-Year;

$/QALY: Dollars Expended Per QALY Gained;

IOP: Intraocular Pressure;

VBM: Value-Based Medicine®;

TTO: Time Tradeoff;

POAG: Primary Open Angle Glaucoma

Introduction

An information system integrating patient perceptions to quantify patient preference-based comparative effectiveness, or patient value gain (improvement in quality-of-life and/or length-of-life) of interventions across medicine is highly desirable. It facilitates use of the highest quality drugs and other interventions [1]. Concomitantly, identifying less expensive comparator interventions that confer the same or greater patient value can maximize the efficient use of scarce healthcare resources [2].

Numerous pharmacologic and surgical treatments are used for primary open angle glaucoma (glaucoma) [3,4]. Realini, Fechtner [4] have estimated 56,000 interventions can be utilized to reach maximal tolerated medical therapy. Knowing which are most beneficial is critically important.

A meta-analysis by van der Valk and colleagues [3] demonstrated the intraocular pressure-lowering effects of glaucoma drugs. Nonetheless, other relevant drug factors include: 1) vision loss prevention, 2) associated adverse events, 3) quality-of-life influences and 4) costs [1].

Several excellent papers address glaucoma drug cost-effectiveness [5-9]. Nonetheless, they are difficult to compare due to different treatment regimens, costs, utility instruments, utility respondents, and so forth.

Over 27 million different input variables can enter a cost-utility analysis [10]. Thus, few published cost-utility analyses are currently comparable [1,2]. Unfortunately, even one different input can be critical, evidenced by ophthalmologists underestimating quality-of-life diminution for macular degeneration patients by 96% to 750% [12].

Value-Based Medicine® (VBM) is the natural progression of medical practice beyond Evidence-Based Medicine [1]. VBM, cost-utility analyses integrate the highest level of interventional Evidence-Based Medicine with two important value measures: 1) patient value gain and 2) financial value gain.

Patient value gain is defined by improvement in *quality-of-life* and/or *length-of-life* conferred by interventions. Quality-of-life is numerically measured with patient utilities from patients with firsthand, health state experiences.

Financial value gain integrates the direct medical costs, as well as the direct non-medical (caregiver) costs and/or indirect medical (employment) costs returned to society versus the direct medical costs expended. Costs are integrated with patient value using the cost-utility ratio ($/QALY, or dollars expended per QALY gained).

Value-Based Medicine® standardizes cost-utility analysis with uniform inputs and outcomes [1]. It integrates all benefits, adverse events, and validated, patient-based, time tradeoff, utilities as objective quality-of-life measures [1,2,11-23].

Comparative Effectiveness Reviews. A recent comparative effectiveness review [24] was unable to identify evidence that open-angle glaucoma screening results in decreased visual impairment. A subsequent review on glaucoma therapy [25] reported: *1) "No studies of medical therapy, laser therapy* (or surgical) *therapy were identified that directly addressed outcomes related to visual impairment,* and *2) The available studies addressing the secondary outcomes of change in visual acuity and change in visual field loss are of too short a duration to answer this question, given that glaucoma is typically a slowly progressive disease that may take many years to cause clinically or statistically significant changes.* The report further states, "*Although it is logical to presume that slowing glaucoma damage would lead to preservation of vision-related quality of life and reduction in visual impairment, this link has not been demonstrated in the research literature…One specific area that would benefit from research is the association between treatment and visual impairment and/or patient-reported outcomes"* [25] The American Academy of Ophthalmology and the American Glaucoma Society vigorously disagreed with both comparative effectiveness reviews, citing QALY evidence [26].

We herein present a cost-utility analysis comparing the patient-preference-based, value gain and cost-utility (cost-effectiveness) associated with topical, 0.5% timolol therapy, one drop in each eye twice daily, for open angle glaucoma versus no therapy. A prototype for any glaucoma therapy, its results are directly comparable with VBM cost-utility analyses for virtually all glaucoma interventions and interventions across medicine [1,2].\

Methods

The assumptions in this analysis are listed in (Table 1) [1-

23,27-44]. Data obtained directly from glaucoma patients herein, other ophthalmic vision loss/glaucoma cohorts, and the evidence-based literature suggest a glaucoma cost-utility model should integrate the following assumptions listed: [1,11-23,27-44].

Table 1. Clinical Population and Assumptions.

• All participants are adults with primary open angle glaucoma (POAG).

• The mean, baseline, intraocular pressure prior to topical timolol therapy is assumed to be 25mm Hg, a common intraocular pressure in glaucoma clinical trials [27,29-32].

• The results apply to the average patients with primary open angle glaucoma, not secondary glaucomas (neovascular, uveitic, post-traumatic, pigmentary and so forth) which tend to be more asymmetric in nature.

• Timolol maleate, 0.5%, 2x in each eye daily, has been shown in a meta-analysis of clinical trials to decrease the intraocular pressure in glaucoma patients by 6.9mm Hg, or approximately 28%, [3] thus qualifying as an agent capable of achieving a "target intraocular pressure"[40].

• The average age of a glaucoma patient at baseline is 63 years [3]. The mean life expectancy at age 63 years is 21 additional years [34].

• Patient value loss associated with untreated glaucoma results primarily from diminution of quality-of-life, [14] rather than decreased length-of-life [35].

• It is uncertain whether glaucoma by itself results in earlier mortality. If so, the effect is likely negligible, but can be readily modeled if needed. It is not considered in this model [35-38].

• Adverse event data with topical timolol come from a meta-analysis [3] and studies of systemic adverse events [35].

• The mean vision of an eye with end-stage glaucoma is 20/800. For a visual acuity of 20/800 in the better-seeing eye, the corresponding utility is 0.52 [14,15,17].

• The time to end-stage glaucoma decreases with increasing intraocular pressure (Table 2) in the average POAG patient [39].

• Patient value is accrued, for the most part, when second eyes develop end-stage glaucoma, since treatment effects in a poorer-seeing are difficult to demonstrate, as per the preferences of patients with unilateral and bilateral vision loss [14,15,17].

• Progression to end-stage glaucoma in untreated POAG eyes is assumed to occur at a similar rate in each eye [33].

• Until the end of 11.2 years, the mean time of end-stage glaucoma occurrence in untreated eyes, the overall utility is better in untreated patients than in those using timolol. This occurs due to adverse events associated with use of the drug [3,32,33,36-37].

• All value and cost outcomes and costs are discounted at 3% annually with Net Present Value (NPV) analysis, as recommended by the Panel on Cost-Effectiveness in Health and Medicine [1].

• The 21-year cost of timolol 0.5% in each eye twice daily integrates an assumed 20% assumed spillage rate for the drops. (From Brown MM, Brown GC, and Spaeth GL: Improper topical self-administration of ocular medication among patients with glaucoma. Can J Ophthalmol. 1984, 19(1): 2-5.)

(FDA = Food & Drug Administration, IOP = intraocular pressure, OU = both eyes, bid = two times per day)

Table 2. Time to End-Stage Glaucoma for Untreated Eyes.

Intraocular pressure (mm Hg)	Time to end-stage glaucoma
13	31.9 years
14	30.2 years
15	28.4 years
16	26.7 years
17	24.9 years
18	23.2 years
19	21.4 years
20	19.7 years
21	17.9 years
22	16.2 years
23	14.4 years
24	12.8 years
25	11.2 years
26	9.7 years
27	8.1 years
28	6.5 years
29	5.8 years
30	5.1 years
31	4.3 years
32	3.6 years
33	2.9 years
34	2.2 years
35	1.5 years
36	0.7 years

An amalgamation of data from Jay and Murdoch39 demonstrates the theoretical time required for a person with untreated primary open angle glaucoma to progress to end-stage glaucoma (absolute visual field loss within 5o of center in 3-4 quadrants). The three anchors described by the authors are shown in bold. Intraocular pressures are extrapolated downward from 23 mm Hg at the same time interval per mm of IOP change as that encountered with pressure diminution from 28.0 mm Hg through 23 mm Hg. The upward progression time from 28 mm Hg to 32 mm Hg. comes directly from the Jay and Murdoch anchor data, while data above 32mm Hg are extrapolated at the same time interval per mm of IOP as that encountered from 28mm Hg to 32mm Hg. With this model, an untreated IOP of greater than 35mm Hg in the average glaucoma eye theoretically results in end-stage glaucoma within one year.

Patient Value Assumptions

1) **The diagnosis of glaucoma causes a decrease in patient quality-of-life,** as measured by validated, reliable time tradeoff utility analysis.[1,10-23]. Utilities most highly correlate with central vision, rather than the underlying cause of vision loss, [16] and appear unaffected by most comorbidities [18]. Vision utilities were obtained from over 1,000 standardized interviews with ocular disease patients [1,11-23]. A glaucoma diagnosis alone, with bilateral good vision and full fields, reduces mean quality-of-life by 3% (from 1.00 to 0.97) on a scale with anchors of 1.00 (bilateral 20/20 vision permanently) and 0.00 (death) [14,15,17]. This reduction in quality-of-life occurs primarily due to apprehension about vision loss in the future [17].

2) **Glaucoma drug therapy decreases quality-of-life due to drug-associated adverse events**

Decision analysis (TreeAge Pro Healthcare 2012, TreeAge Software, Inc., Williamstown, MA) integrated timolol-related adverse event utilities [31,32,35]. Thus, the mean timolol-use utility was 0.9452 (Figure). Adverse event utilities were taken from the *Time Tradeoff Utility Database*, a Center for Value-Based Medicine, 50,000+ compendium of: 1) peer reviewed, literature-validated, primary, patient-based, time tradeoff (TTO) utilities, and 2) patient-based, peer-reviewed literature, comparator, TTO utilities [1,2,11-23].

3) **The quality-of-life associated with glaucoma appears to depend more upon central visual acuity than visual field loss**

- **Primary visual field data.** We examined one hundred sixty (160) patients with open-angle glaucoma. Each underwent visual field testing and time tradeoff utility analysis by the researchers (JDS, GCB). These patients were categorized into four cohorts based upon visual fields: 1) no or minor visual field defects, fields predominantly full in each eye (n=50/160=31%), 2) visual field defects, but with a field > 20° across in each eye (n=42/160=26%), 3) visual field < 20° across in one eye (n=53/160=43%), and 4) visual field < 20° across in both eyes (n=15/160=9%).

  Linear regression revealed no significant difference in utility across the field categories (p=0.08). As well, a comparison of Cohort 1 mean utility (0.92) vs. Cohorts 3 & 4 mean utility (0.89) revealed no significant difference (p=0.44). A post-hoc power calculation revealed, with a two-tailed alpha of 0.05, 50 patients in each cohort had a 91% power to detect a 15% utility difference.

- **From the literature**. Parrish and associates [27] noted that Esterman binocular visual field loss correlated poorly with global quality-of-life. Jampel and colleagues [28] found that Esterman visual fields did not correlate well with time tradeoff utilities (p = 0.14).

  Coleman and colleagues [36] noted an associated between visual filed loss and fractures in older women, though Magacho and associates [37] and Gupta and associates [38] noted a significant correlation between glaucoma quality-of-life and central vision, but not visual fields. Because of the relative paucity of correlations between visual fields and global quality-of-life, and fields with utilities, [27,28,37,38] and because of the strong correlation between central vision and utilities, [11-23] we chose to correlate patient, preference-based, quality-of-life in our model primarily with central vision.

  Paletta Guedes and colleagues, [45] however, noted a correlation between visual fields and utilities, although the authors stated the correlation was weak. It is very possible future data will confirm the data from Paletta Guedess et al [45] and disclose a convincing correlation between glaucoma visual fields and patient-based quality-of-life, especially with marked field loss. Our model can readily integrate this aspect depending upon further study. Our conservative analysis herein may thus bias against the patient value gain and cost-effectiveness associated with glaucoma therapy. Nonetheless, without multiple primary analyses supporting visual field loss and quality-of-life loss, we chose to base our model at this point in time on central visual acuity.

4) **Untreated glaucoma results in severe vision loss**

- **End-stage glaucoma.** The ingenious study by Jay

and Murdoch [39]. Demonstrated the mean length of time it takes for the average untreated glaucoma patient to progress to end-stage glaucoma, defined by absolute field loss extending to within five degrees of fixation in 3-4 quadrants. We equated this to 20/800 vision, but also included 20/200 and 20/20,000 (hand motions) vision in the sensitivity analysis. We also want to emphasize that individual patients may progress either faster or slower.

- **Intraocular pressure and end-stage glaucoma.** Jay and Murdoch [39] identified untreated glaucoma patients presenting with mild glaucomatous field defects and end-stage disease. They then correlated these clinical pictures with respective ages. Patients with a mean intraocular pressure (IOP) of 23mm Hg and early field defects averaged 58.4 years in age, while those with end-stage disease and mean 23mm Hg IOP averaged 72.8. Thus, they surmised a mean 14.4 year to progress from very mild to end-stage glaucoma at 23mm Hg. With a mean, baseline, 28 mm Hg IOP, the average person with early glaucoma was 64.2 year of age, while end-stage patients averaged 70.7 years. The time from untreated early to end-stage glaucoma at 28mm Hg was thus 6.5 years. At over 30mm Hg, which we conservatively estimated as 33mm Hg, untreated glaucoma progressed from mild to end-stage disease in 2.9 year [39]. Again, these data suggest average times of progression.

  Extrapolation. The numbers and intervals to end-stage glaucoma were extrapolated upward and downward based upon the three mean, anchor interval, IOP cohorts (Table 2) [39]. We use this important information for untreated glaucoma since are unaware of randomized clinical trials that have allowed people to deteriorate to end-stage glaucoma in the control arm.

5. **Baseline intraocular pressure.** In multiple glaucoma clinical trials, [3,29-32] the baseline intraocular pressure was approximately 25mm Hg. Thus, our model used this as a mean baseline intraocular pressure.

6. **Selection of topical timolol maleate.** Per the American Academy of Ophthalmology, Preferred Practice Pattern for open-angle glaucoma, [40] therapy should decrease pre-treatment intraocular pressure to a "target pressure" at least 25% lower. The pre-treatment IOP of 25mm Hg is brought down by 6.9mm Hg to a mean 18.1mm Hg by the topical, β-adrenergic blocker, 0.5% timolol maleate, a 28% decrease [3]. Nonetheless, the model is applicable to any POAG intervention, pharmacologic, laser or surgical.

7. **Central vision maintenance.** Patient value gain from glaucoma therapy occurs primarily from lengthening time of good vision before an eye progresses to end-stage glaucoma (Table 3).

molol Therapy, 21-Year Model
nd-stage glaucoma Va = 20/800, a utility of 0.52[14,15,17])

Treatment	IOP (mm Hg)	Utility after start of topical timolol	Years to end-stage POAG	Utility with bilateral end-stage POAG	Years of central vision loss before death	Quality-of-life gain
None	25.0	1.00	11.2	0.52	9.8	NA
Timolol	18.1[3]	0.9452	23.0	0.9452	None	19.0%

(Va = vision, IOP = intraocular pressure, timolol = timolol maleate, 0.5% OU bid, NA = not applicable, POAG = primary open angle glaucoma)

8. **Bilateral end-stage glaucoma.** We assumed that, with bilateral, baseline IOP of 25mm Hg, both eyes develop end-stage glaucoma at 11.2 years without treatment [39]. Untreated glaucoma data from Wilson [33] strongly support the premise that end-stage disease occurs primarily bilaterally, at similar times with similar incidences [39].

9. **Model time frame.** The weighted averages of 7,145 patients in 24 glaucoma therapy clinical trials, [3] shows the mean and median age of someone entering a glaucoma clinical trial are both 63 years. The US life expectancy for a 63-year-old is 21.0 years, our model time frame [34]. We assumed that glaucoma and glaucoma therapy do not affect life expectancy [35].

10. **Adverse events.** Adverse events are shown in the Figure. Decision analysis demonstrates the mean glaucoma utility for patients who use topical timolol is 0.9452 (Figure).

11. **Patient-based, quality-of-life preferences (utilities). [**14,15,17] When end-stage glaucoma is modeled with a vision of 20/800, the associated utility is 0.52. End-stage, 20/200 vision correlates with a utility of 0.62, and 20/20,000 (hand motions) with a 0.35 utility.

    The time tradeoff utility instrument utilized herein numerically measures preferences by asking patients what proportion of their remaining life they would be theoretically willing to trade in return for normal health (vision) for the remainder [1]. The proportion of time traded is subtracted from 1.0 to yield the utility for that condition. For example, if a patient expects to live 20 more years and is willing to trade 4 of those years in return for normal vision permanently, the resultant utility is (1.0 – 4/20 =) **0.8**. Because people can prefer to trade something of value (time of life) for a better health state, or prefer to trade no

time and remain in the same health state, utilities are often called *patient preferences*.

People accrue patient value with time according to the formula: QALY accrual = (utility x years lived at that utility). Thus, a person with a utility of 0.8 who lives three years at that utility accrues (3 x 0.8 =) **2.4 QALYs**. By comparing the QALY accrual without therapy and with therapy (or with one intervention versus another), the QALY gain associated with a therapy can be ascertained.

12. **Model variants.** The model can be used to perform *average* cost-utility analyses comparing treatment to no treatment, or *incremental* cost-utility analyses comparing one therapy with others [1]. Our timolol versus no therapy model is an average cost-utility analysis [1].

Figure. Decision Analysis Integrating Adverse Events Associated with Topical Timolol Therapy for Glaucoma

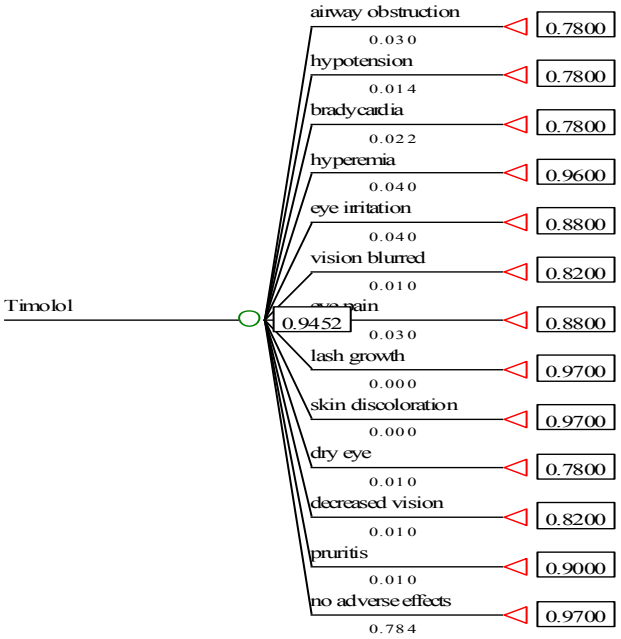

Figure. Decision analysis arm reveals the adverse events associated with using 0.5% timolol maleate twice daily in each eye.[31,32,35] The incidence of each adverse event is located beneath the respective arm on the right, while the utility associated with each adverse event is located within the rectangle on the far right. Utilities are taken from the *Time Tradeoff Utility Database* (Whitemarsh Press, 2015), a validated compendium of 50,000+ time tradeoff utilities obtained from patients referent to diseases they have personally experienced. (Airway obtruction data from Müskens RP, Nightengale JA, Bunce C, Wormald R. β blockers for glaucoma and excess risk of airways obstruction: population based cohort study. BMJ 2002;325:1396–7.)

Financial Value Assumptions

Direct ophthalmic medical costs [41]. The direct ophthalmic medical costs were modeled from the 2012 average, national Medicare Fee Schedule (Table 4). After an initial eye exam, two annual office visits occurred every six months throughout the 21-year model. Automated visual fields and scanning, computerized, optic disc imaging occurred biannually for 21 years. Gonioscopy was modeled annually and corneal pachymetry once.

Drug costs. VBM cost-utility analyses generally employ the ASP (Average Sales Price) for drugs. Nonetheless, the Walmart Drug Plan has been in place since 2008 and offers timolol maleate, 0.05%, in a 15cc bottle (3-month supply) for $10 (Table 4). The incremental, 21-year, drug cost for bilateral timolol therapy, assuming a 20% administration miss rate, and estimating an average of 480 drops per 15cc bottle, is $604.

Table 4. Medicare Direct Ophthalmic Medical Costs (2012 United States Real Dollars) Associated with 0.5% Timolol Maleate Therapy.

A. Timolol Maleate, 0.5%, Used Twice Daily in Each Eye3

Drug	Cost*	Drops/ ml§	Total drops per bottle	Bottles/ Year	Cost/year	21-year cost
Timolol maleate	$10/15cc	32	480	3.8	$38.02	$604

(One drop of 0.5% timolol maleate is given twice daily in each eye. The model assumes a 20% spillage rate for topical administration. (Brown MM, Brown GC, and Spaeth GL: Improper topical self-administration of ocular medication among patients with glaucoma. Can J Ophthalmol 1984; 19:2-5.)

B. Overall, 21-year, direct, ophthalmic medical costs associated with topical timolol therapy, 0.5% OU bid.

Descriptor	CPT code	Cost, 2012 U.S. real dollars/unit of service	Units/21 years	21-year cost
Eye exam, new patient	92004	145	1	145
Follow-up visits	92014	102	41	3,137
Corneal pachymetry, bilateral	76514	10	1	10
Gonioscopy, bilateral	92020	27	21	429
Automated visual field, bilateral	92083	80	42	1270
Scanning computerized imaging, bilateral	92133	46	42	730
Optic disc photographs	92250	153	21	1207
Timolol, 0.5%, one drop OU 2x/day	NA	38	21	604
TOTAL	--------	648	-------	7,531

(Note that all costs are those associated with bilateral glaucoma therapy. All costs are discounted at 3% annually, CPT = Current Procedural Terminology, OU = both eyes, bid = two times daily, NA = not applicable)

** The 2012 price for timolol 0.5%, 15cc, in the Walmart Retail Prescription Program is U.S. $10. From the Internet @ http://i.walmartimages.com/i/if/hmp/fusion /customer_ list.pdf, accessed 4-12-12. Cost assumes a 20% miss rate for the topical timolol drops (Brown MM, Brown GC, and Spaeth GL: Improper topical self-administration of ocular medication among patients with glaucoma. Can J Ophthalmol 1984; 19:2-5.)*

§ Fiscella RG, Green A, Patuszynski DH, Wilensky J. Medical therapy cost considerations for glaucoma. Am J Ophthalmol 2003;135:18-25.

All unit costs are in 2012 nominal U.S. dollars, while 21-years costs are in 2012 U.S. real dollars.

Societal Costs

Societal costs. Societal costs [1] include: 1) **direct medical costs**, encompassing direct ophthalmic medical costs expended for, and direct non-ophthalmic medical costs avoided by, glaucoma therapy, 2) **direct non-medical (caregiver) costs** saved by therapy, and 3) **indirect medical (employment) costs** gained from therapy. Other than direct ophthalmic medical costs, all costs are negative, thus accruing against the direct, ophthalmic medical costs [1].

Direct non-ophthalmic medical costs. Javitt and colleagues [42] have shown blindness is associated with increased costs from depression, injuries, greater Skilled Nursing Facility and nursing home admissions and other unidentified costs. Accruing against direct ophthalmic medical costs, they vary with end-stage vision of 20/200 or 20/800 to 20/20,000 (Table 5).

Table 5. Societal Costs (2012 U.S. Real Dollars) Over the 21-Year Model Associated with Timolol Therapy for Primary Open-Angle Glaucoma.

ITEM COSTS	COSTS (20/200 vision)	COSTS (20/800 vision)	COSTS (20/20,000 vision)
Direct ophthalmic medical costs	$7,531	$7,531	$7.531
*Direct non-ophthalmic medical costs [42]	(-$58,171)	(-$63,306)	(-$63,306)
3rd party insurer (direct medical costs, oph + non-oph [42])	(-$50,617)	(-$55,751)	(-$55,751)
*Caregiver costs [43]	(-$127,779)	-($357,457)	-($357,457)
*Nursing home costs [42]	(-$9,479)	(-25,338)	(-25,338)
*Employment costs (decreased incidence of employment and decreased wages) [44]	(-$1,708)	(-$1,708)	(-$1,708)
TOTAL, Non-ophthalmic direct medical costs	(-$197,137)	(-$447,809)	(-$447,809)
TOTAL, ALL SOCIETAL COSTS	(-$189,606)	(-$440,278)	(-$440,278)

(Base case, end-stage vision is 20/800, with sensitivity analysis assessing the costs associated with 20/200 and 20/20,000 vision.)

**Negative costs in parentheses ( ) indicate dollars returned to patients, the government, and insurers from the treatment of primary open-angle glaucoma. These costs, which accrue against the direct ophthalmic medical costs, do not accrue until 11.2 years, when bilateral blindness develops.*

Direct, non-ophthalmic medical costs obviated by timolol therapy maintaining good vision long-term include those for: depression, injury, Skilled Nursing Facility admissions and other, as yet, unidentified medical costs.[42]

All costs are discounted @ 3% annually with Net Present Value Analysis.

(oph = ophthalmic, non-oph = non-ophthalmic)

Caregiver costs. Schmier and associates [43] demonstrated increasing caregiver costs correlated with decreasing vision, with costs increasing as vision decreases (Table 5). Decreased caregiver costs associated with vision preservation accrue against direct ophthalmic medical costs.

Employment costs. The mean U.S. employment rate for a cohort from age 74-84, the time of accrual of patient value for the treated glaucoma cohort is approximately 4%, with the average, annual, 2012 U.S. wage approximately $40,000.[44] This results in a mean, 21-year, incremental, salary gain of $1,708 with timolol therapy.

Statistical analyses. Microsoft Excel (Redmond, WA) with Analyse-it software (Leeds, UK) was used to compare the utility associated with timolol therapy with no therapy using the paired t-test. Linear regression was utilized to correlate gradations of visual field abnormalities with utilities. Significance was presumed to occur at $p < 0.05$.

All patient, utility data were obtained with approval of the Wills Eye Hospital and/or Manhattan Eye and Ear Institutional Review Boards. Informed consent was obtained from participants, the work was HIPAA-compliant, and all research adhered to the tenets of the Declaration of Helsinki.

Results

Patient Value Decreasing the IOP in an open angle glaucoma eye from 25mm Hg (11.2 years of good central vision) to 18.1mm Hg (23.0 years of good vision) (Table 2), results in an extension of good vision by (23.0 years–11.2 years =) **11.8** years. Since 23-years exceed the 21-year model, timolol therapy allows the average POAG patient to maintain good central vision and vision-related quality-of-life for the remainder of his or her life.

Value gain. The base case (20/800 end-stage vision) QALY gain was 2.40 over the 21-year model. This equates to a 19.0% quality-of-life gain for the average, timolol-treated, glaucoma patient ($p = 0.0015$ versus no therapy) (Table 6).

Sensitivity analysis. For 20/200 end-stage vision, timolol therapy yielded 1.78 QALYs, a 13.4% improvement in quality-of-life. With 20/20,000 end-stage vision, the QALY gain is 3.45, a 29.9% quality-of-life gain (Table 6).

Financial Value

3rd party insurer (direct medical) costs. The direct ophthalmic medical costs total $7,531 over 21 years, irrespective of end-stage vision.

Sensitivity analysis. The direct, non-ophthalmic, medical costs range from (-$58,171) when end-stage vision was 20/200 to (-$63,306) when end-stage vision was either 20/800 or 20/20,000 (hand motions) (Table 5).

Societal costs. Including all direct medical (ophthalmic and non-ophthalmic) costs, direct non-medical (caregiver) costs and indirect medical (employment) costs, the total societal cost was (-$440,278) (Tables 5,6).

Sensitivity analysis. The total societal cost was (-$189,606) with 20/200 end-stage vision and (-$440,278) with 20/20,000 vision, the latter the same as with 20/800 vision. The direct ophthalmic medical costs expended yield a 21-year, financial ROI of 5,846% (22.5%/year) referent to the societal costs gained when end-stage vision was 20/800 to 20/20,000.

Cost-Utility Ratio (CUR)

Cost-utility ratio, societal cost-perspective. The base-case (20/800 end-stage central vision) cost-utility ratio was **(-$183,449)/QALY)**, meaning $183,449 was returned to patients, insurers and society for each QALY gained (Table 6). A negative cost-utility ratio indicates timolol therapy dominated no therapy, since it conferred greater patient value and had a net positive financial return to society for the direct ophthalmic medical costs expended. For each percent gain in patient value from timolol, $23,173 was returned to society.

Table 6. Average Cost-Utilities Associated with Timolol Therapy for Open Angle Glaucoma over the 21-Year Model

Cost perspective	QALY gain	Percent patient value gain	Costs (2012 U.S. real dollars)	Cost-utility ratio ($/QALY)	Cost-value ratio (PPV, or price percent value gain)
End-stage Va = 20/200					
Third party insurer*	1.78	13.4%	7,531	4,231	562
Third party insurer§	1.78	13.4%	(-50,641)	(-28,451)	(-3,779)
Societal	1.78	13.4%	(-189,606)	(-106,520)	(-14,150)
End-stage Va = 20/800 (Base-case)					
Third party insurer*	2.40	19.0%	7,531	3,138	396
Third party insurer§	2.40	19.0%	(-55,775)	(-23,240)	(-2,936)
Societal	2.40	19.0%	(-440,278)	(-183,449)	(-23,173)
End-stage Va = 20/20,000					
Third party insurer*	3.45	29.9%	7,531	2,183	252
Third party insurer§	3.45	29.9%	(-55,775)	(-16,167)	(-1,865)
Societal	3.45	29.9%	-(440,278)	(-127,617)	(-14,725)

(Base case, end-stage vision is 20/800, with sensitivity analysis assessing the costs, cost-utility ratios and cost-value ratios associated with 20/200 and 20/20,000 vision.)

** Direct ophthalmic medical costs only*
§ Direct ophthalmic and direct non-ophthalmic medical costs

(20/20,000 = hand motions vision, Percent patient value gain = percent quality-of-life gain in this analysis)

(QALY = quality-adjusted life-year, $/QALY = dollars expended per QALY gained, QOL = quality-of-life)

(Costs inside parentheses are negative costs. All costs and QALY gains, Percent Value Gains and cost-utility ratios are discounted with Net Present Value analysis at a 3% annual rate.)

(Va = vision, value gain = quality-of-life gain)

Table 7. Two-Way Sensitivity Analysis of Timolol Therapy for Open Angle Glaucoma.

Cost perspective	QALY gain	Percent patient value gain	Costs (2012 U.S. real dollars)	Cost-utility ratio ($/QALY)	Cost-value ratio (PPV, or price percent value gain)
End-stage Va = 20/800 (Base-case)					
Third party insurer*	2.40	19.0%	7,531	3,138	396
Third party insurer§	2.40	19.0%	(-55,775)	(-23,240)	(-2,936)
Societal	2.40	19.0%	(-440,278)	(-183,449)	(-23,173)
End-stage Va = 20/800 (Base-case)					
Third party insurer,*50% patient value decrease	1.2	9.5%	7,531	6,276	793
Third party insurer, 50% patient value decrease§	1.2	9.5%	-10,779	-8,983	-1135
Societal, 50% patient value decrease	1.2	9.5%	-100,178	-83,482	-10545
End-stage Va = 20/80					
Third party insurer*	1.07	7.8%	7,531	7,038	966
Third party insurer§	1.07	7.8%	-11,813	-11,040	-1514
Societal	1.07	7.8%	-102,649	-95,934	-13160
End-stage Va = 20/40					
Third party insurer*	0.45	3.2%	7,531	16,736	2353
Third party insurer§	0.45	3.2%	7,531	16,736	2353
Societal	0.45	3.2%	-1,025	-2,278	-320

(Base case, end-stage vision is 20/800, with sensitivity analysis assessing the costs, cost-utility ratios and cost-value ratios associated with 20/200 and 20/20,000 vision.)

** Direct ophthalmic medical costs only*
§ Direct ophthalmic and direct non-ophthalmic medical costs

(20/20,000 = hand motions vision, Percent patient value gain = percent quality-of-life gain in this analysis)

(QALY = quality-adjusted life-year, $/QALY = dollars expended per QALY gained, QOL = quality-of-life)

(Costs inside parentheses are negative costs. All costs and QALY gains, Percent Value Gains and cost-utility ratios are discounted with Net Present Value analysis at a 3% annual rate.)
(Va = vision, value gain = quality-of-life gain)

Sensitivity analysis, societal cost-perspective. The societal CUR was (-$106,520)/QALY with 20/200 end-stage vision. For 20/20,000 end-stage vision the CUR was (-$127,617)/QALY.

Cost-utility ratio, 3rd party insurer cost perspective. The third party insurer, base-case, CUR using only direct ophthalmic medical costs was ($7,531/2.40 QALY =) **$3,138/QALY** (Table 6). When the direct non-ophthalmic medical costs were included, the CUR was **(-$28,451/QALY).**

Sensitivity analysis, 3rd party insurer cost perspective. The CUR was **$4,231/QALY** with end-stage vision of 20/200 and **$2,183/QALY** when end-stage vision was 20/20,000 (Table 6).

Two-way sensitivity analysis (Table 7). Glaucoma therapy with timolol is still highly cost-effective when patient value gain is decreased by 50%. The same is the case when the vision associated with end-stage glaucoma is 20/80 or 20/40.

Comparators. Table 8 lists interventional value gains and cost-utilities for ocular and systemic interventions. Timolol therapy compares favorably with common interventions for systemic arterial hypertension therapy, hyperlipidemia and osteoporosis.

Table 8. Third Party Insurer, Average Value Gains and Cost-Utility Ratios Associated with Ophthalmic and Non-Ophthalmic Interventions (In 2012 U.S. Real Dollars)

Intervention	Value gain	Cost-utility ($/QALY)
Major depression, SSRI therapy [2]	21.9%	$11,436
Cataract surgery, 1st eye [20*	20.4%	$2,624
Glaucoma therapy, current study end-stage glaucoma vision: 20/800	*19.0%*	*$3,151*
Cataract surgery, 2nd eye [21]*	12.2%	$3,709
Photodynamic therapy with verteporfin for neovascular AMD[2]*	8.1%	$33,970
Ca channel blockers for systemic arterial hypertension [2]*	6.3%	$11,520
Pegaptanib therapy for subfoveal neovascular AMD[2,*]	5.8%	$72,138
Statins (HMG-CoA reductase inhibitors) for hyperlipidemia*	4.0%	$74,925
Sildenafil for erectile dysfunction*	2.7%	$83,813
Bisphosphonates for osteoporosis*	0.8%	$152,000*

(AMD – age-related macular degeneration, SSRI = selective serotonin re-uptake inhibitor,

** = Center for Value-Based Medicine Pharmaceutical Value Index® data. Average cost utilities comparing treatment versus no treatment, are presented to allow comparability.)*

Discussion

Our analysis presupposes that timolol therapy prevents primary open-angle glaucoma from progressing to end-stage optic nerve damage with severe diminution in patient quality-of-life in the average, primary open angle glaucoma patient. While we suspect that marked, visual field loss is also associated with decreased quality-of-life, we remain conservative in excluding this aspect since there is no current criterion for correlating visual field data with quality-of-life. When and if it is persuasively demonstrated that visual field loss reduces quality-of-life, this can be readily integrated into our model. But with or without field loss, the model shows glaucoma therapy provides great patient value, is extraordinarily cost-effective, and yields a large net financial ROI to society. While we utilized topical timolol, any medical/surgical glaucoma therapy could be evaluated with this model format. It is also comparable to Value-Based Medicine® cost-utility models across all of medicine.

We believe our model, utilizing critical data from Jay and Murdoch on the natural course of untreated POAG, [39] convincingly demonstrates glaucoma therapy prevents visual impairment. Therapy also dramatically improves quality-of-life by saving central vision. Thus, it provides answers to the doubt whether glaucoma therapy is comparatively effective.

The use of topical timolol therapy for open angle glaucoma is very cost-effective. This is especially relevant since conventional upper limits for cost-effectiveness are typically $50,000-$100,000/QALY in the U.S, ~$40,000-$60,000/QALY in the U.K., and approximately $150,000/QALY using World Health Organization criteria [1].

Our model replicates clinical glaucoma therapy by integrating the following features for the average open angle glaucoma patient: 1) the time needed for untreated eyes to progress to end-stage disease at different intraocular pressures (Table 2), [39] 2) primary and secondary evidence that mild to moderate visual field loss does not appreciably decrease quality-of-life, [27,28] 3) topical medication use decreases quality-of-life, [1] 4) lowering intraocular pressure likely preserves good vision, [29,30,39] and 5) untreated glaucoma results in end-stage vision loss concomitantly in each eye [33].

With 56,000 ways to reach maximal tolerated medical therapy [4] and 27 million cost-utility analysis input variants, [11] standardized VBM analyses (base case analysis, [47] time tradeoff utilities from patients, average national Medicare Fee Schedule, and societal and third party insurer cost perspectives) are critical to identify which glaucoma therapies provide the greatest patient value and cost-effectiveness. VBM cost-utility analyses also allow a comparison of glaucoma therapies with interventions across all medical specialties [1].

Nordhaus, [46] the respected Yale economist, estimated that

50% of the wealth created in the United States during the 20th century occurred from healthcare advances. Our data support this concept that medical interventions can provide a net financial ROI to society. With increasing cost data available, [42-44,46] model that assume healthcare interventions solely consume financial resources appears inappropriate for the 21st century.

The fact that the great majority of medical interventions improve quality-of-life and/or length-of-life is undisputed, but the financial ROI derived from interventions is less well appreciated [1]. More favorable employment for patients and unpaid caregivers (73% are unpaid [43]) freed-up for paid employment both contribute to an improved GDP (Gross Domestic Product), a measure of national wealth. The societal costs averted are returned to society, especially patients, Medicare and other insurers [47]. Thus, we concur with Beauchamp and colleagues [49] who advocate that medicine's business is the production of patient value and economic return.

An estimated, 12,000 new cases of glaucoma blindness occur in the U.S. annually [50]. If earlier glaucoma therapy prevents end-stage glaucoma in the 50% of people who don't realize they have glaucoma, [51] the 21-year, financial saving from preventing 6,000 blind cases would exceed $2.6 billion. The Medicare direct, non-ophthalmic, medical cost saving alone would be $335 million more than the direct ophthalmic medical costs. If half of the 120,000 blind glaucoma patients in the U.S [50]. were saved from progression to end-stage glaucoma, our data suggest the 21-year ROI to society would exceed $26 billion.

It is conceivable the rate of progression to end-stage glaucoma differs from Jay and Murdoch [39] data, and our extrapolation, which is close to linear. Obtaining primary, long-term, prospective, natural history data on untreated glaucoma in the current environment, however, is ethically challenging [31]. We doubt a clinical trial will be undertaken for primary open angle glaucoma with a long-term, non-treatment arm.

An end-stage vision of 20/800 seemed an appropriate base-case vision, from the author's perspectives, though Jay and Murdoch [39] did not specify this exact central vision. Their definition of end-stage glaucoma, however, coincides with the International Council of Ophthalmology definition of "profound visual loss" to "near-total blindness" requiring a long cane, hearing and other blind mobility skills.[51] This supports our base-case vision of 20/800. But even with 20/200 vision, glaucoma therapy still provides great patient value, returns considerable net dollars to society, and is highly cost-effective.

The simultaneous bilaterality of end-stage glaucoma can be argued. Nevertheless, data from Wilson [33] on untreated, end-stage glaucoma reveal that progression typically occurs in both eyes concomitantly and at a similar rate for the average person.

Conclusion

In summary, glaucoma therapy with topical timolol confers considerable patient value and is highly cost-effective. It also has a remarkable financial return-on-investment for patients and society.

Our glaucoma therapy model integrates years of good vision saved, patient-based, quality-of-life preferences for vision and visual field loss, drug adverse events, and financial resources expended for, and saved by, treatment. Using standardized costs with patient-based utilities, it emphasizes central vision, which glaucoma and other ophthalmic patients have told us is a key issue affecting their ophthalmic quality-of-life. The model allows a direct comparison of patient value gain and cost-utility associated with glaucoma therapy with interventions across all medical specialties.

Conflicts of Interest

The authors have no conflicts of interest with the information presented herein. The study received no external funding.

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