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Review on Cost of Anti-Glaucoma Formulation Available in India

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The objective of the present work was to determine cost per annum of various glaucoma formulation to patients and plot changes in trends of cost these formulations over years. Main purpose of this study is to provide patients and health care providers with calculated yearly costs of topical glaucoma medications in India. A price per ml model was used to eradicate difference due to pack size of formulation of different brands. And average prices per ml of all studied brands were used to present data of particular drug formulation. Daily recommended drops were also taken into consideration to obtain cost of formulation to patient per year. And results indicated that cost of glaucoma treatment in India per annum to patient varied from as low as 193.3 INR to as high as 6616.72 INR in year 2015, quite similar to that in 2005 wherein cost per annum to patient varied from 191.55 INR to 5879.12 INR. Beta blockers were reported to be the most economical group of glaucoma medications while prostaglandin analogues and its combinations were reported to be expensive group of glaucoma medications. And the study concluded that cost of glaucoma drug therapy varies from few hundred to several thousand rupees in India. And although price per annum of glaucoma medication in India remains to be significantly less compared to other developed countries, steep rising cost first line drugs like timolol maleate over the years forecasts risings concern to patient in India.

Keywords: Cost of medications; Beta Blocker; Glaucoma; Prostaglandins; Timolol Maleate.

Glaucoma is a chronic, progressive condition that is projected to affect approximately 76 million people worldwide in 2020, with the number expected to rise to almost 112 million in 2040[1]. Notably, glaucoma is the second leading cause of blindness worldwide and the leading cause of treatable blindness [2]. In 2010, the worldwide percentage of blindness due to glaucoma was 6.6%, and the contribution of glaucoma to blindness in adults aged e”50 years was 8.5% as of 2015, with a global projection of >11 million cases of bilateral blindness by 2020 [3]. Glaucoma medication plays a significant role in the treatment of patients with glaucoma, leading to increase burden of cost both to individuals, and society. In spite of substantial clinical and economic burden associated with glaucoma, studies evaluating the long-term costs of existing treatments are limited. Thus, cost-effectiveness studies are important because they allow a comparison between

different alternatives in terms of both their costs and their results. These data may be useful in selecting medications for glaucoma therapy.

Glaucoma is a complex disorder that comprises a group of heterogeneous optic neuropathies characterized by a progressive degeneration of the optic nerve head and visual field defects [3]. The cause of glaucoma generally is failure of the eye to maintain an appropriate balance between the amount of internal (intraocular) fluid produced and the amount that drains away. Just as a basketball or football requires air pressure to maintain its shape, the eyeball needs internal fluid pressure to retain its globe-like shape and ability to see.

There are about 67 million patients of glaucoma worldwide, out of which 14 million glaucoma patients in India alone, of whom 6.7 million will become blind in both eyes [4]. Globally, it is estimated that there are 38 million persons who are blind, Glaucoma is the second leading cause of vision loss in the world [5]. When calculated with above figures, almost 10 in 100 people will be suffering from glaucoma and 1 in 1000 will be blinded due to lack of proper treatment of glaucoma. And if such is the scenario, then India will be the most affected than any other countries in world. Effective intervention to prevent blindness from glaucoma is quite difficult, particularly in developing countries, where its early detection and management pose great problems [5]. Thus likely future scenario is therefore that glaucomatous blindness will continue to increase globally [5].

It has been reported that patients with advanced glaucoma suffer from reduced mobility [6], and are at higher risk of falling [7], and are also at an increased risk of causing or being involved in automobile accident [8]. Most patients with glaucoma are unaware of their visual field defects until the disease enters a late stage [9]. Recent evidence suggests that glaucoma affects the entire visual pathway [10].

Although it is noteworthy that no race is exempted from getting glaucoma [11]. But prevalence of glaucoma varies widely across the different ethnic groups and is significantly higher in blacks (4.7%) than in the white population (1.3%) [12]. Most common risk factors for glaucoma includes age, race, family history, thin cornea, myopia and oxidative stress [13]. Amongst all other factors family history of glaucoma is estimated to account for a risk of 1-10 folds among the first-degree relatives of an affected individual [14]. Estimated overall prevalence of glaucoma is 16% in those over the age of 70 amongst blacks compared to 6% and 3% respectively in Caucasians and Asians respectively [15].

Cost per year ranged widely depending on the class of medication and recommended daily dosing [16]. While other problems like inefficiencies in actual patient usage of drops, wasting, or accidental administration of more than the prescribed dose can increase cost of glaucoma medication of patients. Thus based on wasting due to various reasons in a significant portion of the glaucoma patient population actual cost per day will differ from the calculated cost per day. A spectrum of cost for individual medications highlights the importance of considering the cost effectiveness of glaucoma medical management. Drug efficacy, tolerability, medication response, medical compliance, dosing regimens, and formulary coverage are factors that may justify a decision to prescribe a more costly medication.

Differences in yearly cost exist among topical glaucoma medications [17]. The daily cost of glaucoma medications in China ranged much more wildly than developed countries [18]. It is calculated to cost approximately £380 per patient per annum [19], with an estimated £300 million spent in the UK in 2002 for treatments of glaucoma patients [20]. A cost effectiveness analysis estimates an average annual cost for standard therapy in treatment of glaucoma at USD 398 per patient in France [21]. While another study which performed cost analysis covering Denmark, Germany, Italy, Ireland, and Spain reported annual direct cost of glaucoma medication ranged from €429 to €523 [22]. Thus, blindness related glaucoma has a wide impact on the developed European societies in terms of costs.

Direct annual medication cost of glaucoma may be dependent on choice of type and category of drug prescribed by doctor. As average cost of generic timolol in USA ranged from 0.38-0.50 USD per day and beta-blocker products were reported to be about twice as costly, ranging from 0.88- 1.11 per day US dollars. The prostaglandin analogues ranged from US dollars 0.90-1.25 USD per day [23]. Combination therapy can also be deciding cause for cost as it is reported in few studies that combination

therapy of timolol plus dorzolamide was less costly than separate bottles of a topical beta-blocker and a topical carbonic [23].

Due to lack of accurate and decisive method and inclusion of various tangible factors for determination of daily cost for drugs used in glaucoma, results for cost per day to patient could vary based on method and sampling techniques used. For example according to study carried out in year 2003 average cost of generic timolol in USA ranged from 0.38-0.50 USD per day [23]. While another study reported daily cost of the beta-adrenergic blockers studied ranged widely, from $0.43 to $1.04 [24] . Thus, there is a need for harmonious method for determination of daily and annual cost to glaucoma patient.

METHODOLOGY

Various studies throughout the world have used different techniques to obtain prices of different glaucoma drugs within country (Rylander and Vold, 2008) and comparison in-between two countries [25] and across globe [26]. There is no single technique to obtain prices of all glaucoma drugs at one place. So, for study we sought prices borne by the patient for various glaucoma interventions. As there is no unanimous data source that captures prices patients pay for ophthalmic medications and other ophthalmic interventions within India, we used various data sources, including prices published by government entities on publicly available websites, academic publications, drug-pricing databases, and reference prices books like drug today, drug update ,CIMS etc .If we could not locate data from any of these sources, we contacted drug manufacturer to sought prices of drugs over years .

Cost in maximum retail price (MRP) in India of 11 molecule and its 29 different formulation based on strength & combination divided into 7 groups of antiglaucoma formulation as were studied over time span from 10 years from 2005 to 2015 to obtain cost per year of therapy of glaucoma medication to patients and change in cost of therapy over these 10 years. Drugs, formulations, strengths that were not available initial in year 2005 but where available during later years were

Table 1. List of all equation used for calculating cost & differences in cost of various antiglaucoma formulation

Equation 1 Price per ml of Brand (INR/ml)	Price per ml of a brand = (Maximum retail price of Formulation in INR/pack size in ml) For example, price of Levobunolol - 0.5% for Betagan (Allergan) for 5 ml is 53 INR than its Price per ml = 53/5= 10.6 INR/ml
Equation 2 Average Price per ml of Formulations (INR/ml)	Average price per ml of a formulation = (Sum price of all brands (INR/ml)/Sum of total brands) For example, price per ml of Levobunol 0.5 % brand one is 10.6 INR/ml and for brand two is 9.8 INR/ml than Average price per ml of a Levobunol 0.5% = (10.6+9.8)/2 = 10.2 INR/ml.
Equation 3 Rate difference of glaucoma formulations over years	((Average Price per ml of Formulations of 2nd year - Average Price per ml of Formulations of 1st year) *100/ Average Price per ml of Formulations of 1st year)
Equation 4 Glaucoma medication per day use (ml)	Per day use (ml) = (daily recommended dose in number*average drop size of eye drops) But Average Drop size for ophthalmic solution is 0.04ml So, Per day use (ml) = (daily recommended dose*0.04)
Equation 5 Glaucoma medication Cost per day (INR)	Glaucoma medication Cost per day (INR) = Glaucoma medication per day use (ml)*rate per ml (INR)
Equation 6 Glaucoma medication Cost per Annum (INR)	Cost per year (INR) = - Glaucoma medication cost per day (INR)*365 Where 365 represents total number of days in 1 year.
Equation 7 - Difference in cost per annum of Glaucoma medication over years	Difference in cost per annum in percentage = ((Cost per Annum (INR) of year 2015- Cost per Annum (INR) of year 2005)/ Cost per Annum (INR) of year 2005*100

Table 2. Average Price per ml of Formulations (INR/ml) 1st Year

No	Drug category	Drug percentage in w/v	Brand (year)	Pack	Price in INR(Year)	Price in INR per ml	Average rate per ml in INR
1	Para sympathomimetic (Cholinomimetic)	Pilocarpine-0.5%	Carpine	1ml	15.00 (2005)	15.00	15.00
2		Pilocarpine-2%	Carpo Miotic	5ml	32.00 (2005)	6.40	5.53
			Locarp	5ml	25.00 (2005)	5.00	
			Pilagan	5ml	32.66 (2005)	6.53	
			Pilocar	5ml	32.00 (2005)	6.40	
			Pilodrops	5ml	19.95 (2005)	3.99	
			Pilomax	5ml	20.00 (2005)	4.00	
			Pilopress	5ml	32.00 (2005)	6.40	
3		Pilocarpine gel 0.5%	LocarpOpthalmic Gel	5gm	85.94 (2005)	17.19	17.19
4	Non selective alphaagonist	Dipivefrine HCl-1%	Propine	5ml	50.65 (2005)	10.13	10.13
5	BETA BLOCKER	Timolol maleate-0.25%	Glucomol	5ml	17.05 (2005)	3.41	3.276
			Iotim	5ml	15.85 (2005)	3.17	
			Lopres	5ml	15.55 (2005)	3.11	
			Oclean	5ml	17.00 (2005)	3.40	
			Oculan	5ml	13.50 (2005)	2.70	
			Ocupress	5ml	17.00 (2005)	3.40	
			Ocutim	5ml	16.40 (2005)	3.28	
			Teemol	5ml	12.90 (2005)	2.58	
			Teoptic	5ml	15.60 (2005)	3.12	
			Timolen	5ml	16.00 (2005)	3.20	
			Timolet	5ml	19.00 (2005)	3.80	
			Timolo	5ml	20.00 (2005)	4.00	
			Timopress	5mla	17.10 (2005)	3.42	
6		Timolol maleate-0.5%	Glucotim	5ml	28.00 (2005)	5.60	5.21
			Nyolol	5ml	29.50 (2005)	5.90	
			Teemol	10ml	30.00 (2005)	3.00	
			Timdus	10ml	31.00 (2005)	3.10	
			Timolet P	5ml	45.00 (2005)	9.00	
			Gluchek	5ml	25.00 (2005)	5.00	
			Glunil	5ml	24.50 (2005)	4.90	
7		Timolol maleate unit dose 0.5%	Iotim Unims	6X0.3ml	23.15 (2005)	12.86	12.86

8		Timolol maleate gfs 0.5%	Timolet-Gfs	3ml	60.00 (2005)	20.00	20.00
9		Betaxolol-0.5%	Glucoptic	5ml	30.00 (2005)	6.00	5.95
			Iobet	5ml	30.90 (2005)	6.18	
			Nopres	5ml	30.00 (2005)	6.00	
			Optipress	5ml	29.25 (2005)	5.85	
			Betapress	5ml	29.00 (2005)	5.80	
			Ocubeta	5ml	29.33 (2005)	5.87	
10		Betaxolol-0.25%	Optipres-S	5ml	29.25 (2005)	5.85	5.83
			Bulol	5ml	29.05 (2005)	5.81	
11		Levobunolol-0.5%	Betagan	5ml	53.00 (2005)	10.60	10.20
			Levob	5ml	49.00 (2005)	9.80	
12	Carbonic anhydrase inhibitor (CAI)	Dorzolamide-2%	Dortas	3ml	180.00 (2005)	60.00	49.52
			Dorzox	5ml	195.25 (2005)	39.05	
13	Alpha 2 agonist	Brimonidine-0.2%	BrimodinDps	5ml	100.25 (2005)	20.05	26.35
			Alphagan	10ml	300.04 (2005)	30.00	
			Iobrim	5ml	145.00 (2005)	29.00	
14		Brimonidine-0.15%	Brimodin P	5ml	120.00 (2005)	24.00	24.00
15		Brimonidine-0.10%	Brimochek	5ml	140.00 (2010)	28.00	27.30
			Brimosun-Ls	5ml	133.00 (2010)	26.60	
16		Apraclonidine-0.5%	Alfadrops	5ml	40.00 (2005)	8.00	8.00
17		Apraclonidine-1%	Alfadrops Ds	2ml	40.25 (2005)	20.12	20.12
18	Prostaglandin Analogue	Latanoprost-0.005%	9pm Eye Drops	2.5ml	320.75 (2005)	128.30	121.20
			Latoprost	2.5ml	285.50 (2005)	114.20	
			Xalatan	2.5ml	N.A. (2005)	—	
19		Bimatoprost-0.03%	Lumigan	3ml	595.00 (2005)	198.33	198.3
20		Travoprost-0.004%	Lupitros	3ml	150.00 (2012)	50.00	75.33
			Travo	3ml	302.00 (2012)	100.67	
21	Beta blocker + Cholinomimetic	Timolol 0.5% + pilocarpine 2%	Timolet Plus	5ml	75.00 (2005)	15.00	15.00
22	Beta blocker + Alpha 2 agonist	Timolol 0.5% + brimonidine tartrate 0.15%	Betabrim	5ml	150.00 (2008)	30.00	30.00
23	Beta blocker + Carbonic anhydrase inhibitor (CAI) inhibitor (CAI)	Dorzolamide 2%+timolol maleate 0.5%.	Misopt	5ml	220.00 (2007)	44.00	44.50
			Ocudor-T	5ml	225.00 (2007)	45.00	
24	Beta blocker + Prostaglandin	Latanoprost 0.005%+ timolol 0.5%	Laprost Plus	3ml	220.00 (2008)	73.33	100.67
			Latim	2.5ml	N.A. (2008)	—	
			Latocom	2.5ml	320.00 (2008)	128.00	

Table 3. Average Price per ml of Formulations (INR/ml) 2nd Year

No	Drug category	Drug percentage in w/v	Brand (year)	Pack	Price in INR(Year)	Price in INR per ml	Average Rate per mlin INR
1	Para sympathomimetic (Cholinomimetic)	Pilocarpine-0.5%	Carpine	1ml	15.00 (2015)	15.00	15.00
2		Pilocarpine-2%	Locarp	5ml	25.00 (2015)	5.00	6.05
			Pilagan	5ml	32.66 (2015)	6.53	
			Pilocar	5ml	51.95 (2015)	10.39	
			Pilodrops	5ml	19.95 (2015)	3.99	
			Pilomax	5ml	20.00 (2015)	4.00	
			Pilopress	5ml	32.00 (2015)	6.40	
3		Pilocarpine gel 0.5%	LocarpOpthalmic Gel	5gm	89.52 (2015)	17.90	17.90
4	Non selective alpha agnoist	Dipivefrine hcl-1%	Propine	5ml	50.65 (2015)	10.13	10.13
5	BETA BLOCKER	Timolol maleate-0.25%	Glucomol	5ml	17.05 (2015)	3.41	3.31
			Iotim	5ml	19.90 (2015)	3.98	
			Oclean	5ml	17.00 (2015)	3.40	
			Oculan	5ml	13.50 (2015)	2.70	
			Ocupress	5ml	17.03 (2015)	3.41	
			Ocutim	5ml	16.40 (2015)	3.28	
			Teoptic	5ml	15.60 (2015)	3.12	
			Timolen	5ml	16.00 (2015)	3.20	
6		Timolol maleate-0.5%	Glucotim	5ml	28.00 (2015)	5.60	8.45
			Nyolol	5ml	34.10 (2015)	6.82	
			Timolet	5ml	61.00 (2015)	12.20	
			Timdus	10ml	31.00 (2015)	3.10	
			Timolet P	5ml	48.20 (2015)	9.64	
			Lopres	5ml	56.00 (2015)	11.20	
			Glucotim -La	5ml	45.00 (2015)	9.00	
			Timoblu	5ml	42.00 (2015)	8.40	
			Optilax	10ml	22.00 (2015)	2.20	
			Tily	5ml	40.00 (2015)	8.00	
			Timolet-Od	5ml	84.00 (2015)	16.80	
7		Timolol maleate unit dose 0.5%	Iotim Unims	6X0.3ml	23.15 (2015)	12.86	12.86
8		Timolol maleate gfs 0.5%	Timolet-Gfs	3ml	82.00 (2015)	27.33	27.33
9		Betaxolol-0.5%	Iobet	5ml	38.80 (2015)	7.76	6.47
			Nopres	5ml	30.00 (2015)	6.00	
			Optipres	5ml	34.50 (2015)	6.90	
			Ocupres-B	5ml	29.05 (2015)	5.81	
			Ocubeta	5ml	29.33 (2015)	5.87	
10		Betaxolol-0.25%	Optipres-S	5ml	29.25 (2015)	5.85	5.83
			Bulol	5ml	29.05 (2015)	5.81	
11		Levobunolol-0.5%	Betagan	5ml	53.00 (2015)	10.60	10.20
			Levob	5ml	49.00 (2015)	9.80	
12	Carbonic anhydrase inhibitor (CAI)	Dorzolamide-2%	Dortas	3ml	195.00 (2015)	65.00	51.89
			Monosopt	5ml	246.00 (2015)	49.20	
			Ocudor	5ml	195.25 (2015)	39.05	
			Dorzox	5ml	271.50 (2015)	54.30	

13	Alpha 2 agonist	Brimonidine-0.2%	Alphagan	10ml	300.04 (2015)	30.00	25.28
			Iobrim	5ml	106.50 (2015)	21.30	
			Brimodin	5ml	129.50 (2015)	25.90	
			Brimopress	5ml	111.05 (2015)	22.21	
			Brimodin-Ls	5ml	135.00 (2015)	27.00	
			Albrimlst	5ml	N.A. (2015)	—	
14		Brimonidine-0.15%	Brimosun-P	5ml	198.00 (2015)	39.60	33.76
			Brimodin P	5ml	169.00 (2015)	33.80	
			Brimocom	5ml	199.50 (2015)	39.90	
			Rimonid	5ml	137.00 (2015)	27.40	
			Alphagan-P	5ml	210.16 (2015)	42.03	
			Britiblu	5ml	99.00 (2015)	19.80	
15		Brimonidine-0.10%	Brimochek	5ml	141.40 (2015)	28.28	27.44
			Brimosun-Ls	5ml	133.00 (2015)	26.60	
16		Apraclonidine-0.5%	Alfadrops	5ml	40.25 (2015)	8.05	8.05
17		Apraclonidine-1%	Alfadrops	2ml	40.00 (2015)	20.00	20.00
18	Prostaglandin Analogue	Latanoprost-0.005%	9pm Eye Drops	2.5ml	441.00 (2015)	176.40	114.85
			Ioprost	2.5ml	199.00 (2015)	79.60	
			Ioptame	2.5ml	263.75 (2015)	105.50	
			Lacoma	5ml	229.00 (2015)	45.80	
			Laprost	3ml	230.00 (2015)	76.67	
			Latodrops	3ml	275.00 (2015)	91.67	
			Latoprost	2.5ml	345.00 (2015)	138.00	
			Xalatan	5ml	1142.00 (2015)	228.40	
			Latochek	2.5ml	229.00 (2015)	91.60	
19		Bimatoprost-0.03%	Lumigan	3ml	595.00 (2015)	198.33	126.17
			Xyprost	3ml	265.00 (2015)	88.33	
			Ganfort	5ml	N.A. (2015)		
			Xyprost-Tm	3ml	330.0 (2015)	110.00	
			Careprost	3ml	324.00 (2015)	108.00	
20		Travoprost-0.004%	Lupitros	3ml	164.50 (2015)	54.83	119.10
			Travo	3ml	302.00 (2015)	100.67	
			Xovatra	2.5ml	450.00 (2015)	180.00	
			Lupitr0s-T	3ml	180.00 (2015)	60.00	
			Xovatra-T	2.5ml	500.00 (2015)	200.00	
			Tralvost	3ml	N.A. (2015)		
21	Beta blocker + Cholinomimetic	Timolol 0.5% + pilocarpine 2%	Tily-P	3ml	69.00 (2015)	23.00	21.58
			Timolet Plus	5ml	122.00 (2015)	24.40	
			Iotim-Plus Ed	5ml	86.75 (2015)	17.35	
22	Beta blocker + Alpha 2 agonist	Timolol 0.5% + brimonidine tartrate 0.15%	Betabrim	5ml	185.00 (2015)	37.00	37.33
			Globrim-T	5ml	135.00 (2015)	27.00	
			Iotim -B	5ml	240.00 (2015)	48.00	
23	Beta blocker + Carbonic anhydrase inhibitor (CAI)	Dorzolamide 2%+timolol maleate 0.5%.	Dorzox T	5ml	302.50 (2015)	60.50	56.83
			Misopt	5ml	300.00 (2015)	60.00	
			Ocudor-T	5ml	250.00 (2015)	50.00	
24	Beta blocker + Prostaglandin	Latanoprost 0.005%+ timolol 0.5%	Laprost Plus	3ml	235.00 (2015)	78.33	113.30
			Latim	2.5ml	369.15 (2015)	147.66	
			Latochek-T	2.5ml	250.00 (2015)	100.00	
			Latocom	2.5ml	318.00 (2015)	127.20	

Table 4. Rate difference of glaucoma formulations over years

No	Drug category	Drug percentage in w/v	Average Rate perml in INR (1st Year)	Average Rate per ml in INR (2nd Year)	Ratedifference over years in INR
1	Para sympathomimetic	Pilocarpine 0.5%	15 (2005)	15 (2015)	0.00
2	(Cholinomimetic)	Pilocarpine 2%	5.531 (2005)	6.052 (2015)	0.52
3		Pilocarpine Gel 0.5%	17.19 (2005)	17.904 (2015)	0.71
4	Non selective alpha agnoist	Dipivefrine Hcl 1%	10.13 (2005)	10.13 (2015)	0.00
5	Beta Blocker	Timolol Maleate 0.25%	3.276 (2005)	3.31 (2015)	0.04
6		Timolol Maleate 0.5%	5.214 (2005)	8.45 (2015)	3.24
7		Timolol Maleate Unit Dose 0.5%	12.86 (2005)	12.86 (2015)	0.00
8		Timolol Maleate Gel forming solution 0.5%	20 (2005)	27.33 (2015)	7.33
9		Betaxolol 0.5%	5.949 (2005)	6.467 (2015)	0.52
10		Betaxolol 0.25%	5.83 (2005)	5.83 (2015)	0.00
11		Levobunolol 0.5%	10.2 (2005)	10.2 (2015)	0.00
12	Carbonic anhydrase inhibitor (CAI)	Dorzolamide 2%	49.52 (2005)	51.88 (2015)	2.36
13	Alpha 2 agonist	Brimonidine-2%	26.35 (2005)	25.28 (2015)	-1.07
14		Brimonidine 0.15%	24 (2005)	33.75 (2015)	9.75
15		Brimonidine 0.10%	27.3 (2010)	27.44 (2015)	0.14
16		Apraclonidine 0.5%	8.00 (2005)	8.05 (2015)	0.05
17		Apraclonidine 1%	20.12 (2005)	20 (2015)	-0.12
18	Prostaglandin Analogue	Latanoprost-0.05%	121.2 (2005)	114.84 (2015)	-6.40
19		Bimatoprost 0.03%	198.3 (2005)	126.17 (2015)	-72.16
20		Travoprost 0.004%	75.33 (2012)	119.1 (2015)	43.77
21	Beta blocker + Prostaglandin	Latanoprost 0.05%+Timolol maleate 0.5%	100.6 (2008)	113.29 (2015)	12.63
22	Beta blocker + Carbonic anhydrase inhibitor (CAI)	Dorzolamide 2%+Timolol Maleate 0.5%.	44.5 (2007)	56.83 (2015)	12.33
23	Beta blocker + Cholinomimetic	Timolol 0.5% Pilocarpine 2%	15 (2005)	21.58 (2015)	6.58
24	Beta blocker + Alpha 2 agonist	Timolol 0.5% + Brimonidine 0.15%	30 (2008)	37.33 (2015)	7.33

Table 5. Difference in cost per annum of Glaucoma medication over years

No.	Category	Anti-Glaucoma formulation	Number of drops per day (Recommended daily dose)	Per day use in ml	Year	Rate per ml in INR	Cost per day In INR	Cost per annum (INR)	Difference in cost per annum of anti-glaucoma formulation from year 2005 to 2015 in percentage in India
1	Para-sympathomimetic (Cholinomimetic)	Pilocarpine 0.5%	4	0.16	2005	15	2.40	876	0.00
					2015	15	2.40	876.00	
2		Pilocarpine 2%	4	0.16	2005	5.53	0.88	322.95	9.40
					2015	6.05	0.97	353.32	
3		Pilocarpine Gel 0.5%	4	0.16	2005	17.19	2.75	1003.89	4.13
					2015	17.9	2.86	1045.36	
4	Non selective alpha agnoist	Dipivefrine Hcl 1%	4	0.16	2005	10.13	1.62	591.59	0.00
					2015	10.13	1.62	591.59	
5	Beta Blocker	Timolol Maleate 0.25%	4	0.16	2005	3.28	0.52	191.55	0.91
					2015	3.31	0.53	193.30	
6		Timolol Maleate 0.5%	4	0.16	2005	5.21	0.83	304.26	62.19
					2015	8.45	1.35	493.48	
7		Timolol Maleate Unit Dose 0.5%	4	0.16	2005	12.86	2.06	751.02	0.00
					2015	12.86	2.06	751.02	
8		Timolol Maleate Gfs 0.5%	4	0.16	2005	20	3.20	1168.00	36.65
					2015	27.33	4.37	1596.07	
9		Betaxolol 0.5%	4	0.16	2005	5.95	0.95	347.48	8.74
					2015	6.47	1.04	377.85	

10		Betaxolol 0.25%	4	0.16	2005	5.83	0.93	340.47	0.00
					2015	5.83	0.93	340.47	
11		Levobunolol 0.5%	4	0.16	2005	10.2	1.63	595.68	0.00
					2015	10.2	1.63	595.68	
12	Carbonic anhydrase inhibitor (CAI)	Dorzolamide 2%	4	0.16	2005	49.53	7.92	2892.55	4.76
					2015	51.89	8.30	3030.38	
13	Alpha 2 agonist	Brimonidine 0.2%	4	0.16	2005	26.35	4.22	1538.84	-4.06
					2015	25.28	4.04	1476.35	
14		Brimonidine 0.15%	4	0.16	2005	24	3.84	1401.60	40.63
					2015	33.75	5.40	1971.00	
15		Brimonidine 0.10%	4	0.16	2010	27.3	4.37	1594.32	0.51
					2015	27.44	4.39	1602.50	
16		Apraclonidine 0.5%	4	0.16	2005	8	1.28	467.20	0.63
					2015	8.05	1.29	470.12	
17		Apraclonidine 1%	4	0.16	2005	20.12	3.22	1175.00	-0.60
					2015	20	3.20	1168.00	
18	Prostaglandin Analogue	Latanoprost 0.005%	2	0.08	2005	121.25	9.70	3540.50	-5.28
					2015	114.85	9.19	3353.62	
19		Bimatoprost 0.03%	2	0.08	2005	198.33	15.87	5791.23	-36.38
					2015	126.17	10.09	3684.16	
20		Travoprost 0.004%	2	0.08	2012	75.33	6.03	2199.63	58.10
					2015	119.1	9.53	3477.72	
21	Beta blocker + Prostaglandin	Latanoprost 0.005%+ Timolol 0.05%	4	0.16	2008	100.67	16.11	5879.12	12.55
					2015	113.3	18.13	6616.72	
22	Beta blocker + Carbonic anhydrase inhibitor (CAI)	Dorzolamide 2% + Timolol Maleate 0.5%.	4	0.16	2007	44.5	7.12	2598.80	27.71
					2015	56.83	9.09	3318.87	
23	Beta blocker + Cholinomimetic	Timolol 0.5% + Pilocarpine 2%	4	0.16	2005	15	2.40	876.00	43.87
					2015	21.58	3.45	1260.27	
24	Beta blocker + Alpha 2 agonist	Timolol 0.5% Brimonidine 0.15%	4	0.16	2008	30	4.80	1752.00	24.43
					2015	37.33	5.97	2180.07	

also taken into account and its cost and difference of cost of therapy to patient was considered with respect to year it was first available to 2015. Formulation of which at least 4 years of data were available where considered part of study.

A price per ml model was used to eradicate difference due to pack size of formulation of different brands. And average prices per ml of all studied brands were used to present data of particular drug formulation. Daily recommended drops was taken into consideration to obtain cost of formulation to patient per year. Following equation were considered for study. Table 1 enlist all the essential equation to calculate price and differentiate of various formulation .

RESULTS

All the results of study were represented in terms of tables obtained using calculation mentioned in table 1 .While table 2 and table 3 represents average price per ml of 24 different formulations in year 2005 and year 2015 respectively . Results represented in table 2 and table 3 are particular important of discards variation in price due to pack size of an formulation. Table 4 represents variation in cost of anti-glaucoma formulations over span of 10 years, while table 5 represents change in cost of anti-glaucoma formulations per annum to patients over span of 10 years.

DISCUSSION

Apart from being first line choice of drug for glaucoma, different studies around the globe has suggested beta blockers to be the most economic drug therapy to patients [27]. As recorded in this studycost of glaucoma treatment in India per annum to patient varied from as low as 193.3INR to as high as 6616.72 INR in year 2015, quite similar to that in 2005,and the cost per annum to varied from 191.55 to 5879.12 INR. Beta blockers were reported to be the most economical group of glaucoma medications while prostaglandin analogues and its combinations were reported to be expensive group of glaucoma medications. Except timolol gel forming solution, all other beta blockers were reported to cost below 752 INR per annum to patients. While in case of prostaglandin analogues latanoprost cost per annum of was the most economical prostaglandin in year 2005 until introduction of travoprost in year 2012, but over just four years travoprost recorded substantial rise in its cost making latanoprost again most economical prostaglandin by year 2015. Irrespective of any scenario prostaglandins and its combination remained to be most expensive glaucoma medication therapy.

An unlikely noteworthy point was recorded in para-sympathomimetic group of glaucoma medication, that an higher concentration of pilocarpine (2%) in solution formulation recorded less than half the price per annum to patients compared to its lower concentration pilocarpine (0.5%) solution formulation, this trend remained constant throughout years of 2005 to 2015. Similar one instance was also recorded in Alpha 2 agonist group of medication in year 2015 where in cost per annum of Brimonidine (0.2%) was slightly less than both its counter parts of Brimonidine (0.15%) and brimonidine (0.1%). While as expected in terms of combination therapy, combination of two most economical groups of beta blockers and para-sympathomimetic presented the most cost-effective therapy while combination of prostaglandins as described above provided to be most expensive glaucoma medication therapy. And remaining other combinations provided median cost in-between highest and lowest costing combinations.

Change is cost per annum of Glaucoma therapy from 2005 and 2015 in India

Study recorded increase in cost per annum to patients of seven formulations by more than 20 percent in 10 years of 2005 to 2015. Amongst them timolol maleate solution (0.5%) recorded highest of 62.19 percent rise in price per annum to patient which was followed by 58.10, 43.87, 40.63, 36.65, and 27.71 for travoprost, combination of timolol & pilocarpine, brimonidine (0.15%), timolol maleate gel forming solution, combination of dorzolamide & timolol Maleate and combination of Timolol & Brimonidine respectively. And overall, three formulation recorded rise in its cost by between 5 to 20 percent which include Pilocarpine (2%), combination of Latanoprost &Timolol, and Betaxolol (0.5%). And five other formulation like Dorzolamide, Pilocarpine Gel, Timolol Maleate (0.25%), Apraclonidine (0.5%), and Brimonidine (0.10%) recorded rise in its annual cost to patients

of less than 5 percent in between those 10 years.

While majority of formulation recorded increase in cost per annum, formulation like Pilocarpine (0.5%), Dipivefrine, Timolol Maleate Unit Dose, Betaxolol (0.25%), and Levobunolol reported no change in price per annum to patients in India from year 2005 to 2015. And surprisingly four formulation reported fall in its price per annum over years which included Apraclonidine, Brimonidine (0.2%), Latanoprost and Bimatoprost. Amongst them Bimatoprost recorded highest -36.38 percent fall in price per annum to patient which was followed by -5.28 percent of Latanoprost, -4.06 percent of Brimonidine (0.2%), while Apraclonidine (1%) recorded only marginal fall of -0.60 percent in its price over these ten years.

When calculated by category of glaucoma formulation, betablockers are responsible for 39.21 percent rise in overall cost of glaucoma medication over 10 years of study, followed by 34.74 percentage of combination therapy. As a result, beta blockers and combination therapy are collective responsible for 73.95 percent of total of all increase in price to patient by per for glaucoma medication. While alpha 2 agonist category drug formulations were responsible for 13.42, other categories like para-sympathomimetic, Carbonic anhydrase inhibitors, Prostaglandin Analogue resulted for 12.63 percent responsible for overall increase in price of glaucoma medication.

CONCLUSION

Cost of glaucoma drug therapy varies from few hundred to several thousand rupees in India. Beta blockers were documented to be most economical therapy of glaucoma patient in India, while prostaglandins and its combinations were documented to be most expensive. Although price per annum of glaucoma medication in India remains to be significantly less compared to other developed countries, steep rising cost first line drugs like timolol maleate over the years forecasts risings concern to patient in India. As almost all the formulation for treatment of glaucoma remains to be either in solution or suspension form, it is suggested to develop other formulation of same drugs into other dosage forms like ointment, gels, and emulsions which could be provide better reduction in IOP at lower concentration than existing formulation. More focus should be given to cost effective formulation to restrict the continuous rising cost of glaucoma drug therapy in India.

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Conflict of interests

The authors declare no conflict of interest.

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