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Variation in Number of Doses, Bottle Volume, and Calculated Yearly Cost of Generic and Branded Latanoprost for Glaucoma

Joanna H. Queen^{1,2}, Robert M. Feldman^{1,2}, and David A Lee^{1,2}

¹Ruiz Department of Ophthalmology and Visual Science, The University of Texas Health Science Center at Houston (UTHealth) Medical School, 6431 Fannin Street, MSB 7.024, Houston, Texas 77030

²Robert Cizik Eye Clinic, 6400 Fannin Street, Suite 1800, Houston, TX 77030

Abstract

Purpose—To evaluate discrepancies in doses per bottle, bottle fill volume, and cost among branded and generic formulations of latanoprost

Design—Comparative economic analysis

Methods—This study was conducted at the Ruiz Department of Ophthalmology and Visual Science at The University of Texas Health Science Center at Houston (UTHealth). Four regionally available latanoprost formulations were measured. Number of drops per bottle and actual bottle fill volume were measured for a calculated sample size (10 bottles). Annual cost (using average wholesale price), days use per bottle, drops per milliliter, and number of bottles used per year were calculated. Data were summarized using mean and standard deviation; one-way analysis of variance and *post hoc* Tukey's studentized range test were used for comparing means among manufactures.

Results—Pfizer's branded lantanoprost, Xalatan (New York, NY), had the largest fill volume ($P<0.001$). Pfizer had the highest yearly cost at \$1,198 ($P<0.001$) whereas Akorn (Lake Forest, IL) and Bausch & Lomb (Rochester, NY) had the lowest (\$184 and \$201, respectively). Pfizer and Bausch & Lomb had the most drops per bottle (87.3 and 88.7, respectively), which was statistically more ($P<0.001$) than either Akorn or Sandoz (Princeton, NJ) (77.6 and 76.6, respectively) but there was no statistical difference among the standard deviation of drops per bottle (Levene 0.14).

Conclusions—Annual cost and number of doses per bottle, factors important to patients, vary significantly depending on manufacturer of latanoprost. Practitioners can better advise patients being aware of these differences.

Corresponding Author: David A. Lee, MD; Robert Cizik Eye Clinic, 6400 Fannin St., Suite 1800, Houston, TX, 77030; phone: 713-559-5200; fax: 713-795-0768; dlee@cizikeye.org.

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Introduction

Prostaglandin analogue topical intraocular pressure (IOP)-lowering medications (PGAs) are a class of IOP-lowering medications that work via uveal and scleral collagen breakdown to effectively increase outflow of aqueous humor via the uveoscleral pathway.¹ The once daily dosing, efficacy, and minimal systemic safety issues of PGAs^{1, 2} have made them a mainstay in the treatment of primary open angle glaucoma and ocular hypertension. Seven generic formulations of latanoprost entered the market after the termination of branded Xalatan's (Pfizer, New York, NY) patent in March 2011.

Variations in drop size and number of doses per bottle have been noted as potential inconsistencies between branded and generic medications. Issues such as bottle streaming and large drop size are also concerns with regard to medication waste, increased cost, and a patient finishing a bottle prior to the allotted time frame.³ Potential variability in how long a bottle lasts and the influence of cost of a particular generic may affect patient adherence to the prescribed regimen.⁴

Previous studies have examined similar characteristics of branded and generic topical IOP-lowering medications,⁵⁻⁷ including a recent study of branded PGAs.⁶

Materials and Methods

This comparative economic analysis was conducted at the Ruiz Department of Ophthalmology and Visual Science at The University of Texas Health Science Center at Houston (UTHealth) Medical School. Four regionally (Southeast United States) available latanoprost formulations (branded Xalatan, as well as generic latanoprost from Akorn, Lake Forest, IL; Bausch & Lomb, Rochester, NY; and Sandoz, Princeton, NJ) were investigated. All medications were purchased from a wholesaler, not from the manufacturer of the product. All purchased medications from a given manufacturer came from the same lot.

Medications were stored at 25-27°C prior to the experiment. The bottles were held at 135 degrees as the drops were collected and counted, as outlined by Fiscella et al.⁸ In an effort to avoid streaming, the bottles were squeezed with sufficient pressure to expel drops, then pressure was released between each complete drop. After the drops ceased to flow, the bottle was inverted to 180 degrees to obtain every last complete drop. The fill volume was measured in a graduated cylinder calibrated in increments of 0.1 mL. After each measurement, the cylinders were thoroughly washed using a scrub brush, rinsed with isopropyl alcohol 70%, and allowed sufficient time to air dry.

Sample Size

Rylander et al investigated the number of drops in branded latanoprost and reported the standard deviation (SD) ranged from 2 to 6 drops per bottle.⁹ In investigating efficacy of PGA drop instillation, Fiscella et al reported the SD of branded latanoprost as roughly 5 drops per bottle.⁸ Since glaucoma is a bilateral disease and patients apply PGA drops once a day to both eyes, on average, a 2.5 ml size of PGA can last for 45 days (8.1 bottles of medication per year). If the number of drops/bottle differs by 8 drops (4 daily dosages)

among medications, then the yearly difference is 32 daily dosages (4 daily doses for each of the 8.1 bottles per year) or approximately one month's worth of medication. Ten bottles per drug is required to detect an 8-drop difference among the drugs, assuming the SD is 5 drops and 5% significance and 80% power.

Data Analysis

The numbers of drops per milliliter were determined by dividing the fill volume measured by the number of drops in the bottle. Assuming both eyes receive the medication once daily, as per prescribing guidelines, the number of the bottles per year was calculated by dividing the number of drops per bottle by 2, then multiplying by 365.20 days (accounting for leap years). The yearly cost was calculated by multiplying the average wholesale price (AWP) by the number of bottles per year. Although the true wholesale price of a prescription may vary, especially with generic products, and the price to the patient varies greatly due to specific insurance coverage, the AWP is a common baseline wholesale price that is the same throughout the United States and has been used previously for price comparisons.^{5, 9}

Data were summarized using mean and standard deviation (SD) for each manufacturer. One-way analysis of variance (one-way ANOVA) and *post hoc* Tukey's studentized range test for comparison were used for comparing means among manufacturers. However, Levene's test for homogeneity was conducted first to compare variances among manufacturers. If heterogeneous variances were found, variance-weighted one-way ANOVA was performed using the Welch method.

All statistical analyses were performed using SAS for Windows v9.3 (SAS, Inc., Cary, NC). $P < 0.05$ was considered statistically significant for all comparisons.

Results

Fill Volume

Table 1 denotes the fill volume, number of drops per bottle, number of drops per milliliter, and costs for each manufacturer's product assuming no drops were wasted. Figure 1 demonstrates the differences among mean values and SD of this data. Kolmogorov-Smirnov testing was used to examine the normality distribution assumption for each study variable for each brand. All P values were > 0.05 .

Variations of the fill volume in a bottle were not homogenous among manufacturers. The SD for Akorn (0.11 mL; $P=0.002$ by Levene's test) was statistically significantly higher in comparison to Bausch & Lomb (0.043 mL), Sandoz (0.039 mL), and Pfizer (0.029 mL). There was a significant difference in average fill volume among the manufacturers ($P<0.001$, Welch test). The mean volume of each tested manufacturer was above the stated bottle fill volume of 2.5 mL. Pfizer had the largest average fill volume (2.9 mL), followed by Bausch & Lomb (2.7 mL), then Sandoz and Akorn (2.6 mL and 2.5 mL, respectively, not significantly different between these 2 by Tukey grouping). Of all tested manufacturers, only Akorn had any bottles containing less than the stated 2.5 mL fill, with 5 of the 10 (50%) tested bottles containing between 2.3 and 2.5 mL.

Number of Drops per Bottle

The mean number of drops per bottle were significantly different ($P<0.001$, F test from unweighted one-way ANOVA) among manufacturers. Two significantly different groups were found by the Tukey test: Pfizer (87.3 drops) and Bausch and Lomb (88.7 drops) in one group; Akorn (77.6 drops) and Sandoz (76.6 drops) in the other. Standard deviations of the number of drops per bottle were not statistically different among manufactures ($P=0.14$, Levene).

Drops per milliliter

Similarly, standard deviations of the drops per milliliter were not statistically different among manufactures ($P=0.10$, Levene). The mean number of drops per milliliter was significantly different among manufacturers. ($P<0.001$, F test from unweighted one-way ANOVA). Pfizer, Akorn, and Sandoz all had similar numbers of drops per milliliter at 30, 31, and 30, respectively. Only Bausch & Lomb had statistically more drops per milliliter at 33.1 (by Tukey grouping).

Yearly Cost

The AWP is \$142.90 for Pfizer's branded latanoprost, \$19.44 for Akron, \$24.38 for Bausch & Lomb, and \$95.00 for Sandoz. Standard deviations of the yearly cost were not homogenous among manufactures ($P=0.003$ by Levene's test). The standard deviation for Pfizer (\$54) was higher, compared to Bausch & Lomb (\$5), Akron (\$10), and Sandoz (\$25). There was a significant difference in average yearly cost among them ($P<0.001$, Welch test). Yearly cost of Pfizer's branded latanoprost was significantly more expensive than all generics at \$1,198 per year. Sandoz was second most expensive at \$907 and was significantly more expensive than the remaining 2 generics, Bausch & Lomb and Akorn (\$201 and \$184, respectively).

Discussion

Practitioners have a variety of classes of topical medications to choose from in managing their patients' elevated IOP. Increasingly over the last several years, the first-line topical agent for primary open angle glaucoma has become PGAs due to their once nightly dosing, efficacy, and often better tolerated side effect profiles.¹⁰ As the first PGA on the market, latanoprost, is available in generic, it brings with it a reprise of the discussion of differences in branded and generic products. Significant differences exist among branded and generic formulations of latanoprost in all categories tested in our study, including total volume, drops/doses per bottle, and annual cost. Patients could foreseeably get nearly a week's less use if they were given a bottle of latanoprost manufactured by Bausch & Lomb one month and Sandoz the next.

Branded latanoprost was statistically distinct from tested generics only in the total bottle fill and cost/year. It was not statistically different when looking at the number of drops per bottle, doses per bottle, days use per bottle, or number of bottles used per year. As such, though filled to a larger volume, branded latanoprost did not confer statistically longer use per bottle nor did this translate to cost savings. Pharmacies and retailers contract with

generic manufacturers to provide usually one, not multiple, generic options. Thus, a patient's prescription could be filled with a different manufacturer's latanoprost if he/she went to a different pharmacy or if their pharmacy changed generic providers.

Yearly cost of using branded latanoprost corresponds with data published by Fiscella et al.⁵ Not unsurprisingly, generic options now available are significantly less expensive. At the time of this study, examining the generic latanoprost availabilities in the Southeast United States, Bausch & Lomb appears to be the most economical (based on AWP) of available generics in regards to days of use per bottle and price. It did not differ significantly from branded latanoprost in regards to number of drops per bottle, days use per bottle, or bottles use per year but was similarly priced to the least expensive option, costing \$200 per year.

Compliance in treating glaucoma patients is a well-known problem.¹ Any additional hurdle to a patient taking their medication, be it cost or running out of their medication early, should be minimized if at all possible (particularly in light of limited coverage of early refills of prescription eye drops¹¹). If a patient being treated successfully with a PGA is interested in generic options, one potential solution could be to specify a generic manufacturer on the prescription, as one would typically do for the branded, thus improving the reliability of duration of use for that specific medication.

There were several limitations to this study. While we tested all generic lantanoprost medications available to us, we were not able test all generics available on the market. Our results can only be applied to those we tested. Also, all of the generic medications we tested have a similar bottle design; therefore, we cannot comment on the effect of bottle design. Additionally, we used AWP as a proxy for the cost comparison analysis as has been done before in previous studies.^{5, 7, 9} Prescription plan coverage is a source for drug cost variation. It is difficult to address the true cost savings/loss for the patient when comparing branded and generic medications due to the extreme range of coverage per medication per insurance plan including copayments, coupons cards, etc. In order to have a consistent comparison, we used AWP.

Annual cost and number of doses per bottle, factors important to patients, vary significantly depending on the manufacturer of latanoprost. Practitioners can better advise patients by being aware of these differences, and pharmacy managers can use this data to help select generics contracted.

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Biography

Joanna H. Queen, MD is a senior ophthalmology resident at The University of Texas Health Science Center at Houston (UTHealth). Prior training includes medical school at UTHealth and an internship at Houston Methodist Hospital. She lives with her family in Houston, Texas and is currently pursuing a fellowship in glaucoma.

Figure 1.

Boxplot of differences for branded latanoprost and generic manufacturers describing mean values and standard deviations for the different manufacturers for fill volume (top left); number of doses per bottle (top right); drops/mL (bottom left); and yearly cost (bottom right).

Table 1
Mean ($\pm$ SD) [Range] of fill volume (mL), drops/bottle, drops/mL, and yearly cost (\$) of lantanoprost for each manufacturer

Variable	Manufacturer				P Value
	Pfizer	Akorn	Bausch & Lomb	Sandoz	
Fill Volume (mL)	2.91 ($\pm$ 0.03) ^a [2.86 – 2.96]	2.50 ($\pm$ 0.11) ^c [2.30 – 2.64]	2.68 ($\pm$ 0.04) ^b [2.61 – 2.73]	2.56 ($\pm$ 0.04) ^c [2.50 – 2.60]	Levene: 0.002Welch: <0.001
Drops/Bottle	87.3 ($\pm$ 3.9) ^a [81 – 94]	77.6 ($\pm$ 4.1) ^b [70 – 84]	88.7 ($\pm$ 2.3) ^a [86 – 93]	76.6 ($\pm$ 2.07) ^b [72 – 79]	Levene: 0.14F: <0.001
Drops/mL	30.0 ($\pm$ 1.4) ^b [28 – 32]	31.0 ($\pm$ 1.2) ^b [29– 33]	33.1 ($\pm$ 0.6) ^a [32 – 34]	30.0 ($\pm$ 0.9) ^b [29 – 31]	Levene: 0.10F: <0.001
Yearly Cost (\$)	1198 ($\pm$ 54) ^a [1111 – 1289]	184 ($\pm$ 10) ^c [169 – 203]	201 ($\pm$ 5) ^a [192 – 207]	907 ($\pm$ 25) ^b [879 – 964]	Levene: 0.003Welch: <0.001

^aTukey grouping. Means with the same letter are not significantly different.

^bTukey grouping. Means with the same letter are not significantly different.

^cTukey grouping. Means with the same letter are not significantly different.