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Ophthalmic medication price variation across the United States: Anti-inflammatory medications

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Abstract

Background: Cost-related nonadherence to medication can impact ophthalmic treatment outcomes. We aimed to determine whether medication prices vary between US cities and between different types of pharmacies within one city.

Methods: We conducted a phone survey of eight nationwide and five independent pharmacies in five cities across the United States: Boston, Massachusetts; Charlotte, North Carolina; Denver, Colorado; Detroit, Michigan; and Seattle, Washington. A researcher called each pharmacy asking for price without insurance for four common anti-inflammatory ophthalmic medications: prednisolone acetate, prednisolone sodium phosphate, difluprednate (Durezol™), and loteprednol etabonate (Lotemax™).

Results: Prednisolone sodium phosphate price could only be obtained by a small subset of pharmacies (45.2%) and was excluded from additional analysis; however, preliminary data demonstrated lower cost of prednisolone sodium phosphate over prednisolone acetate. Three-way analysis of variance revealed no interaction between pharmacy type (chain *versus* independent), city, and drug ($F = 0.40$, $p = 0.92$). A significant interaction was identified between pharmacy type and drug ($F = 5.0$, $p = 0.008$), but not city and pharmacy type ($F = 0.66$, $p = 0.62$) or city and drug ($F = 0.27$, $p = 0.97$). Average drug prices were lower at independent pharmacies compared with chain pharmacies for difluprednate (US$211.36 *versus* US$216.85, $F = 1.09$, $p = 0.297$) and significantly lower for loteprednol etabonate (US$255.49 *versus* US$274.86, $F = 14.7$, $p < 0.001$). Prednisolone acetate was cheaper at chain pharmacies, but not statistically significantly cheaper (US$48.82 *versus* US$51.61, $F = 0.34$, $p = 0.559$).

Conclusions: Medication prices do not differ significantly between US cities. High variation of drug prices within the same city demonstrates how comparison shopping can provide cost savings for patients and may reduce cost-related nonadherence.

Keywords: cost-related nonadherence, medication cost, ophthalmology, price variation, uveitis

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Introduction

Retail pharmacies in the United States dispensed over 4 billion prescriptions in 2017,[1] costing third-party payers and patients approximately US$397 billion.[2] Much of these medication costs are undescribed, as specific pricing agreements for drugs are considered trade secrets and often reflect a complicated series of rebates and discounts between manufacturers, wholesalers, and pharmacies.[3] This lack of price transparency and lack of price fixation results in widely varying drug prices across different cities in the same state,[4] and even between pharmacies located in the same city.[5] While the Health Care Cost Institute observed a spending rise in all medical service categories (inpatient, outpatient, professional, and prescription drugs) between 2012 and 2016, spending on prescription drugs increased most dramatically, growing at least 10% more than any other service.[6]

The high financial burden of medication prices can lead to cost-related nonadherence (CRN), with adults skipping doses, taking less medication than prescribed, or delaying prescription refills to save money.[7,8] Uninsured patients and patients with lower income are particularly vulnerable to CRN,[7,9,10] which may lead to poorer health outcomes and increased future healthcare costs.[8] Medication adherence is similarly crucial in ophthalmology and nonadherence has been well described in the glaucoma literature with an estimated 40% of nonadherent glaucoma patients citing cost as a prohibitory factor[11,12] placing these patients at higher risk of visual field defects.[13,14]

Uveitis, characterized by inflammation of the uvea (iris, ciliary body, retina, and choroid), is a common cause of vision loss affecting between 10% and 25% of blindness cases worldwide.[15–17] Roughly 35% of patients with uveitis will experience significant visual loss or legal blindness as a result of this disease.[17,18] Use of corticosteroids for treatment of uveitis has been described since 1950[19] and is still considered first-line for uveitis therapy due to high efficacy and rapid onset of action.[18] Despite the significant risk for vision loss and medical therapies available, a 2012 study by Castiblanco and Huang[20] found that 24% of patients with uveitis still report challenges with medication nonadherence citing cost as a significant factor. Patients with uveitis face steep financial challenges[21,22] with one study estimating drugs to account for 22% of total uveitis treatment cost.[21] However, there has been a paucity of research exploring the cost-related burden of uveitis treatment.

A 2015 comparison study of glaucoma medication prices between the United States and Canada found the price of glaucoma therapy varies widely by country and by drug type (brand *versus* generic), noting a fourfold increase in price for medications purchased in the United States.[23] Subsequent multinational studies have further highlighted the high cost of ophthalmic medications in the United States, compared with the same medications in international markets.[24–26] Price comparison studies have used publicly available databases to determine US drug prices, specifically the Average Wholesale Price (AWP) and Medicare databases. However, the AWP has long been criticized as a controversial tool for determining accurate medication pricing, as the AWP is set by drug manufacturers and has been demonstrated to overestimate the price of medications by as much as 20%.[3,27] Also, using aggregate Medicare prices may not reflect potential price variations within the United States.

Interestingly, a study by Popovic and colleagues[28] demonstrated the existence of a large price variation for multiple glaucoma drugs within one city (Ontario, Canada). Priluck and Havens[29] found similar variation in drug prices within US states and even greater variation between US states in their study of topical prostaglandin analogs, which the authors hypothesized was due to geographic variation and availability of regional supplemental plans. However, no study to date has performed a regional analysis of medication price variation across the United States.

While topical corticosteroids are indicated for a wide range of uses in ophthalmology, our study compared the price variation of four common anti-inflammatory ophthalmic medications used in the chronic management of uveitis. We compared both independent and chain pharmacies across the United States to determine how drug prices may vary within a city and how prices vary across different cities in the United States.

Methods

This pharmacy phone survey study was approved by the University of Colorado Institutional Review Board (IRB #18-0468) and no consent was required. We selected five cities in five different geographic regions in the United States with similar total population sizes, obtained from the US 2017 Census[30]: Boston, Massachusetts (population 685,094); Charlotte, North Carolina (population 859,035); Denver, Colorado (population 704,621); Detroit, Michigan (population 673,104); and Seattle, Washington (population 724,745). Phone calls were completed to eight nationwide chain pharmacies and five independent pharmacies in each city between March and July 2018. A pharmacy was selected for inclusion as a 'chain pharmacy' if it was owned by one of eight pharmacy chains identified before study initiation and then, using a digital map, a marker was placed to estimate the city center and the five closest branches were contacted.

During the call, the researcher asked for the no-insurance price or 'cash price' of two generic and two brand-name topical corticosteroids used in the treatment of uveitis: prednisolone acetate, 1% ophthalmic suspension (5 mL); prednisolone sodium phosphate, 1% ophthalmic suspension

(5 mL); difluprednate (Durezol™), 0.05% ophthalmic emulsion (5 mL); and loteprednol etabonate (Lotemax™), 0.5% ophthalmic suspension (5 mL). For standardization purposes, the researcher declined any offered pharmacy coupons or in-store discount program. Pharmacies which were unable to be reached or unable to provide medication prices after three phone attempts were excluded, and the researcher contacted an alternate pharmacy within the same nationwide chain or an alternate independent pharmacy. Of note, an attempt was made to obtain medication prices for Medicare and Medicaid insurance coverage; however, without a prescription and proof of insurance, no pharmacies were able to provide this information. A boxplot analysis was conducted to identify any significant outliers. For each of the 15 outliers identified – prices which were greater than 1.5 times the interquartile range from the box – an additional call was placed to the pharmacy to ensure accuracy of prices. Statistical analysis was performed using SPSS Statistics Version 24 (IBM, Armonk, New York).

Results

A total of 319 prices were collected from chain pharmacies ($n = 126$) and independent pharmacies ($n = 86$). We stratified our dataset according to our three independent variables: drug, city, and type of pharmacy (chain *versus* independent). A majority of pharmacies did not carry prednisolone sodium phosphate (58.6%) and were unable to provide a price. Of the pharmacies which were able to provide a price for prednisolone sodium phosphate, 21 pharmacies were only able to provide prices for a 10-mL bottle, which we reduced by half to approximate the price of a 5-mL bottle, the bottle size for the other three medications.

Simple statistics (mean, standard deviation, minimum, and maximum) were computed for all groups (Table 1). Due to low response rate and subsequent small sample size, prednisolone sodium phosphate was excluded from further analysis. We conducted a three-way analysis of variance (ANOVA) to determine the effects of city, drug, and type of pharmacy. Drug prices were determined to be normally distributed as assessed by Shapiro–Wilk's test of normality ($p > 0.05$).

No significant three-way interaction was identified between our three independent variables: city, type of pharmacy, and drug ($p = 0.919$). No significant two-way interactions were identified between city and type of pharmacy ($p = 0.622$) or city and drug ($p = 0.974$). However, a statistically significant two-way interaction was detected between type of pharmacy and drug when combining city data ($p = 0.008$). Post hoc Bonferroni pairwise comparison demonstrated a statistically significant decrease in average medication prices for loteprednol etabonate obtained at independent pharmacies, compared with average price at chain pharmacies (US$255.49 *versus* US$274.86, respectively) resulting in a mean cost savings of US$19.37 ($F = 14.7$, $p < 0.001$). Similarly, the mean drug price of difluprednate was cheaper at independent pharmacies compared with chain pharmacies (US$211.36 *versus* US$216.85), but did not result in a statistically significant price difference (US$5.49, $F = 1.09$, $p = 0.297$). Surprisingly, the reverse trend was seen for prednisolone acetate which was, on average, more expensive at independent pharmacies (US$51.61 *versus* US$48.82) but also did not reach statistical significance ($F = 0.34$, $p = 0.559$). Pairwise comparisons for the simple main effect of drug on medication price yielded statistically significant results for all three drugs ($p < 0.001$ for all groups).

Discussion

This study is the first of its kind to compare prices of ophthalmic corticosteroid drops across different cities of the United States and examine how drug prices vary between US cities in different geographical regions as well as between different types of pharmacies within the same city. Our study of 98 pharmacies in five cities across the United States demonstrated no significant difference in medication prices based on city. However, drug prices did differ significantly between chain and independent pharmacies. Mean price of generic drugs (prednisolone acetate, prednisolone sodium phosphate) was significantly cheaper compared with brand drugs (difluprednate, loteprednol etabonate), which reflects similar results found in a 2018 study by Popovic and colleagues.[28]

Chain versus *independent pharmacies*

Upon inspection of the overall means and standard deviations listed in Table 1, prednisolone acetate and prednisolone sodium phosphate – the generic medications – were slightly more expensive at independent pharmacies *versus* chain pharmacies. In our analysis, however, the mean cost difference

Table 1. Descriptive statistics (mean, standard deviation, minimum, and maximum) of medication prices in five major US cities, grouped by drug and city.

City	Mean price (US$)	SD	Min	Max	Mean price (US$)	SD	Min	Max
Prednisolone acetate (*n* = 97)								
	Chain pharmacy (*n* = 37)				**Independent pharmacy (*n* = 25)**			
Boston	44.82	9.09	35.50	56.69	48.59	13.49	33	60
Charlotte	48.52	9.56	36	64.99	50.55	3.76	45	55.32
Denver	51.30	9.65	35.50	65	66.30	43.42	50	85.32
Detroit	47.61	10.44	35.50	65	49.20	10.38	45	55
Seattle	51.18	9.51	35.50	64.99	43.41	15.24	25	65.44
Total	48.82	9.43	35.50	65	51.61	13.10	25	85.32
Prednisolone sodium phosphate (*n* = 28)								
	Chain pharmacy (*n* = 17)				**Independent pharmacy (*n* = 11)**			
Boston	34.99	5.78	29.50	42.77	33.82	5.38	30	42.77
Charlotte	35.04	5.83	29.50	41.70	39.60	6.10	31.63	41.7
Denver	35.52	7.58	31.21	46.87	42.95	–[a]	42.95	46.87
Detroit	31.50	–[a]	31.50	31.5	37.50	–[a]	37.5	31.50
Seattle	35.00	5.20	32	41	31.25	1.77	30	41
Total	34.93	5.45	29.50	46.87	36.62	5.75	30	46.87
Difluprednate (*n* = 98)								
	Chain pharmacy (*n* = 37)				**Independent pharmacy (*n* = 25)**			
Boston	207.09	31.31	140.99	233.00	210.39	23.06	190.00	239.95
Charlotte	220.29	16.09	206.57	239.99	201.84	17.32	190.03	230.00
Denver	221.31	16.59	206.57	247.32	222.19	29.32	185.00	258.70
Detroit	212.83	10.08	206.57	233.00	208.94	21.32	183.00	239.00
Seattle	221.45	16.69	207.00	248.00	213.46	31.48	175.00	258.70
Total	216.85	19.08	140.99	248.00	211.36	23.80	175.00	258.70
Loteprednol etabonate (*n* = 98)								
	Chain pharmacy (*n* = 37)				**Independent pharmacy (*n* = 25)**			
Boston	268.60	22.51	225.00	298.99	256.79	24.96	225.00	279.95
Charlotte	272.71	7.16	266.01	283.00	251.07	37.67	197.83	300.00
Denver	278.84	15.41	265.94	304.63	258.42	46.44	223.00	332.92
Detroit	275.17	12.50	266.00	300.99	247.10	20.83	219.48	269.00
Seattle	277.94	15.59	265.95	304.63	264.05	27.01	225.00	292.56
Total	274.86	15.05	225.00	304.63	255.49	30.50	197.83	332.92

Max: maximum price; Min: minimum price; SD: standard deviation.
[a]Standard deviation was unable to be calculated, due to low response rates in the prednisolone sodium phosphate group.

between groups for prednisolone acetate between independent and chain pharmacies was not statistically significant. However, this trend reversed in the case of the more expensive brand-name drugs, difluprednate and loteprednol etabonate. The latter finding echoes similar studies conducted by Arora and colleagues[5] and ConsumerReports.org,[31] both of which found significant cost savings using independent pharmacies. Variation in drug price (reflected as measures of standard deviation) was uniformly higher in the independent pharmacy group compared with the chain pharmacy group, possibly reflecting the independent pharmacies' individual negotiation with pharmacy benefit managers.

Prednisolone sodium phosphate: A cost-saving alternative

One of the largest challenges in this study was the low response rate of pricing for prednisolone sodium phosphate. Of the 62 pharmacies contacted – chain and independent – prices could only be obtained by 28 pharmacies (45.2%). In total, 22 pharmacies (35.4%) noted not carrying prednisolone sodium phosphate, which precluded these pharmacies from being able to quote a price. In a 20-year literature review of prednisolone acetate *versus* prednisolone sodium phosphate efficacy, Dr. Francis Sousa[32] traced the decline in use of prednisolone sodium phosphate – and the subsequent rise of prednisolone acetate – to a 1974 publication which declared prednisolone acetate as 'most effective for the suppression of corneal inflammation'. This was based on a study by Leibowitz and Kupferman[33] that showed that prednisolone acetate seemed to penetrate the intact cornea in a normal uninflamed rabbit eye better then prednisolone phosphate, thus the authors incorrectly concluded that prednisolone acetate was the superior medication. However, prednisolone phosphate and prednisolone acetate both achieved similar anterior chamber concentrations in the rabbit model of uveitis, thus suggesting that both medications would achieve similar potency in the treatment of uveitis.[32,34] Sousa contrasted this presentation with several studies from 1979 to 1990 which demonstrate 'at least equivalent bioavailability and therapeutic effectiveness' of prednisolone sodium phosphate with prednisolone acetate, arguing that prednisolone sodium phosphate demonstrated an advantage for patient compliance and uniform dosing.[32] It seems that, due to the popularity of prednisolone acetate, decrease in the demand for prednisolone sodium phosphate has driven pharmacies to stop carrying the medication – a medication which our study demonstrates as a cheaper alternative, potentially saving patients 1/3 of the price over prednisolone acetate.

A 2014 study by Sheppard and colleagues[35] conducted a comparative trial of difluprednate 0.05% *versus* prednisolone acetate 1%, when patients were directed to take half as many drops of difluprednate (4 drops of difluprednate *versus* 8 drops of prednisolone acetate). The study found noninferiority of difluprednate to prednisolone acetate using a reduced number of drops. However, our study found that the mean price of prednisolone acetate across all cities is less than one-fourth of the price of difluprednate, demonstrating that difluprednate remains more expensive than both prednisolone acetate and prednisolone sodium phosphate.

Limitations

Our study was limited by the inability to obtain further drug comparison pricing for patients with Medicaid or Medicare insurance, as pharmacies were unable to give a drug price without providing a valid prescription and Medicare/Medicaid insurance policy information. Although the phone survey was carried out in a systematic fashion, responses by individual pharmacists and technicians may have varied based on how busy the pharmacy was at the time of the phone call, especially related to pricing of prednisolone sodium phosphate, which most pharmacies were largely unfamiliar with.

To standardize medication price collection, we requested all drug prices without any coupon or discounts offered by pharmacies. While using the 'cash' or 'out-of-pocket' pharmaceutical prices avoids the potential confounding variable of inconsistently offered drug coupons, denying these discounts may also limit the generalizability of our study.

Conclusion

The Commonwealth Fund estimates that 4 million working-age adults have lost insurance coverage since 2016,[36] creating an increased need for physicians to be stewards of cost-efficient solutions for patients. While our study found similar medication pricing across cities in five different regions in the United States, the intracity price variation between

chain and independent pharmacies demonstrates the benefit of price comparison shopping for medications. Increased prescribing of older, yet cheaper medications, such as prednisolone phosphate, may also help contribute to cost savings for patients in the future if prescribing practices drive pharmacies to stock these medications.

Conflict of interest statement

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