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Cost and Utilization Impacts of Oral Antihistamines in the California Medi-Cal Program

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ABSTRACT

Objectives: Newer oral allergic rhinitis (AR) medications, the second-generation antihistamines (SGAs) have gained widespread acceptance because of their efficacy and reduced side effects relative to first-generation antihistamines (FGAs). There are no empirical studies comparing the costs of treatment of SGAs relative to FGAs.

Methods: We analyzed data from a 20% beneficiary sample (approximately 120,000 continuously enrolled beneficiaries per year) for the Medi-Cal Fee-for-Service program during 1999 to 2000. AR medications available under Medi-Cal included three SGA medications (loratadine, fexofenadine, and cetirizine) and over 200 FGA products containing either diphenhydramine or chlorpheniramine or both. Because multiple medications were evaluated, a sample selection model was estimated using a two-stage multinomial logistic—variance components regression framework.

Results: SGA medications have significantly lower total direct health-care treatment costs per patient than FGA medications with costs ranging from $347 to $448 less ($P < 0.001$), despite higher AR medication costs. Total drug expenditures were also not significantly different for patients using SGA or FGA medications despite SGA prescriptions averaging $47 higher than FGAs. Emergency department visits, inpatient admissions and physician office visits were also significantly lower for patients using SGA medications.

Conclusions: Significant cost and utilization reductions were associated with all of the SGA medications relative to FGA drugs, despite their higher acquisition costs. If facing higher copayments for prescription AR drugs, many patients, particularly lower income patients, may choose cheaper over-the-counter (OTC) FGAs rather than SGAs. Our analysis finds this might lead to increased overall health-care treatment costs, unless Medicaid and health insurance plans subsidize OTC AR medications.

Keywords: allergy, costs, Medicaid, multinomial logit, oral antihistamines, sample selection bias.

Introduction

Allergic rhinitis (AR) impacts more than 40 million Americans annually. Estimates of the annual direct and indirect economic burden of AR illness exceed $8 billion in 2000 US dollars [1–8]. The cost of AR medications alone has been estimated to exceed $6 billion annually [5]. Workforce productivity losses constitute a substantial component of AR costs of illness, ranging from 10 to 60% of the total costs per patient in various studies [9–12].

Newer generation oral AR medications, the second-generation antihistamines (SGAs) have gained widespread acceptance because of their efficacy, minimal sedation, and reduced side effects relative to first-generation antihistamines (FGAs) such as diphenhydramine (e.g., Benadryl®) and chlorpheniramine (e.g., Chor-Trimeton®). These SGAs include loratadine (Claritin®), fexofenadine (Allegra®), cetirizine (Zyrtec®) and desloratadine (Clarinex®). Evidence-based literature reviews have found that nasal steroids are more effective and less costly than nonsedating antihistamines in the treatment of AR [1,4,5]. Nevertheless, nasal steroids are less convenient than oral medications for many patients. Although SGAs are more expensive than FGAs, the reduced rate of sedation and other medication symptoms with SGAs may improve patient functioning and reduce other AR patient health-care requirements and costs relative to FGAs [13,14]. Two recent studies have modeled the cost effectiveness of SGAs relative to FGAs [15,16]. In these studies Sullivan et al. found that switching patients from FGAs to SGAs could save $100 ($64–137) per AR sufferer, as well as provide substantial

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increases in quality-adjusted life-years to the AR patient population. Nevertheless, reduced prescription coverage for SGA medications could impact AR treatment costs and patient outcomes. Sullivan and Nichol noted that "… some of the drug savings from limiting coverage of prescription SGA may be attenuated by the cost of lost productivity and direct medical expenditures due to unintentional injuries associated with increased FGA use in addition to the increased cost of therapeutic substitutes." [16] There are no empirical studies comparing either the costs of treatment, or cost effectiveness of SGAs relative to FGAs, and only a few studies comparing treatment costs among different SGAs [17,18].

The recent availability of loratadine (Claritin®) in the nonprescription over-the-counter (OTC) market raises the question of whether AR patient health-care costs will increase or decrease as AR patients switch, or are switched to, OTC oral medications. Many health insurance and Medicaid plans do not reimburse for medications that are available OTC. Others require higher copayments or additional paperwork to obtain insurance coverage for prescriptions in that therapeutic class [19]. It is well established that prescription drug consumption is highly sensitive to price and insurance coverage [20–23]. Based on a study of Medicare recipients, Stuart and Grana report that low-income elderly without supplemental drug insurance coverage are 40% less likely to use prescription medications than higher income (>$18,000 annual income) elderly with supplemental drug coverage [24]. They also found that the odds ratio for use of prescription medications to treat cold and allergies was (1.83: 95% CI 1.24–2.69) among elderly with drug insurance coverage compared to those without.

Given this result, if drug benefit insurance coverage for SGAs is reduced or eliminated, the nonsedating antihistamines Rx-to-OTC switch will increase consumer net price and reduce SGA demand. This, in turn, will increase demand for the cheaper FGA OTC medications, such as diphenhydramine and chlorpheniramine, particularly among those AR patients with low income and/or high out-of-pocket medical expenses.

Although OTC antihistamines unquestionably reduce drug expenditures for third party payers relative to covered prescription products, there are no published studies evaluating the effects of alternative oral antihistamines on overall patient health-care costs. This study evaluates health-care resource use among patients taking different oral antihistamines to determine the effects of alternative oral AR medications on total health-care costs, after adjusting for patient treatment characteristics and treatment selection bias.

Methods

To examine the potential effects of the likely changing utilization patterns for oral antihistamines on patient health-care costs, we used data from a 20% beneficiary sample, approximately 120,000 continuously enrolled beneficiaries per year, for those California counties participating in the Medi-Cal Fee-for-Service program during the period from 1998 to 2000 when SGAs were initially introduced [25]. We focused on the three SGA medications (loratadine, fexofenadine, and cetirizine) available under Medi-Cal, and over 200 FGA products containing either diphenhydramine or chlorpheniramine or both.

The use of Medi-Cal claims history data for the period before OTC SGA availability has several advantages over other databases to assess these issues. Since the availability of OTC loratadine, it is very difficult to determine which AR medications patients are actually taking because OTC medications are seldom captured in insurance claims records. Moreover, because Medi-Cal covers generic FGA products as well as SGA products, patient usage of all AR medications is well-captured in the claims history. Finally, because Medi-Cal patients face no copayment differences between generic and brand name medications, they faced no financial incentives to use one category of AR medications rather than another. This substantially reduces the amount of potential selection bias between medications in evaluating patient's treatment costs and use of medical services.

Because SGAs were not approved on the Medi-Cal formulary until 1998, and were not all widely utilized by Medi-Cal patients until 1999, the data were restricted to the time frame from 1999 to 2000. Because total health-care costs are not observed for those patients with interrupted eligibility, the sample was restricted to those beneficiaries with continuous eligibility in each year with at least one prescription for SGA or FGA medications (45,810 patients in 1999; 46,970 patients in 2000). Because of the seasonal nature of allergy illness [26], health-care costs during every year of continuous eligibility were included in the analysis for any patients with one or more years of continuous eligibility. Repeated observations were available on roughly half of the patient sample, allowing panel

data variance components econometric estimation methods to be used.

Not all antihistamine use is for AR, although the vast majority of antihistamine users are diagnosed with AR. Because of the unreliable outpatient diagnostic indicators in claims history databases our analysis focuses on patients with any use of antihistamines, adjusting for comorbid diagnoses, rather than attempting to rely on outpatient diagnostic codes to determine which patients have AR. It should be noted that there are concerns about AR diagnostic accuracy itself. According to Szeinbach et al.[27]:

> Only 35.4% of the patients who used an oral antihistamine and were diagnosed with an allergy tested positive to the multiallergen-specific IgE test, and only 38% of the patients with records of frequent antihistamine use and who were diagnosed as allergic tested positive to the multiallergen-specific IgE test. Apparently, there are patients taking medications prescribed for allergic rhinitis who are, in fact, not allergic, which is both wasteful economically and not indicated medically.

The Medi-Cal claims history billing records have limited medical history and diagnostic information. To evaluate the relative impact on treatment costs of SGA and FGA medications we measured the incremental impact on total health-care costs per patient for each of these medications, rather than attempting to construct AR-specific treatment costs based on the unreliable diagnostic information in the claims data. We have included a number of diagnostic indicators for patient comorbidities that are likely to involve inpatient treatment, and thus be more costly and more reliable in terms of diagnostic coding in the claims data. Restricting the sample to those with definitive AR diagnosis would overweight patients with inpatient admissions, which could lead to spurious cost estimates. We excluded 3% of antihistamine patients for whom the index antihistamine was something other than FGA or SGA medications. There were no other demographic or patient history exclusion criteria.

Drugs were identified by NDC codes. Category of services is provided in the Medi-Cal data dictionary. Comorbidities were identified through ICD-9 coding, mostly for inpatient claims, but also for outpatient claims where available. All of the data elements are described in [25]. All costs were adjusted to 2000 US dollars using the medical care component of the Consumer Price Index (CPI) provided by US Bureau of Labor Statistics (http://www.bls.gov). Because they reflect the actual transactions, contractual amounts reimbursed by Medi-Cal were used to calculate treatment costs, rather than provider billing amounts. Medi-Cal receives substantial confidential discounts from published or list prices for all types of medical services, particularly drugs. By federal law Medi-Cal (Medicaid) receives the lowest nationally available price for all prescription medications. Long-term care costs were excluded from the analysis.

Although Medi-Cal patients face minimal and identical copayments regardless of medication choice, it is well-known that medication treatment selection can be nonrandom, reflecting both patient and provider characteristics and propensities [28–30]. To further complicate empirical analysis, patients can discontinue prescription medications, or switch from one medication to another during an AR treatment episode for a variety of reasons including patient-perceived lack of treatment efficacy, medication side effects, convenience, provider and/or patient detailing, etc. To adjust for both observable and unobservable cofactors explaining differences in treatment we developed a sample selection model of treatment choice using repeated observations on many of the patients in a variance-components panel data framework to adjust for any patient-specific and provider-specific characteristics impacting treatment costs [31,32].

Because multiple medications were available, the standard binary choice sample selection model framework was expanded to a multinomial choice framework with four treatment choices: loratadine, fexofenadine, cetirizine or FGA using the methodology developed by Lee and described by Maddala [31,33]. The sample selection model is based on a two-stage multinomial logistic variance components regression framework. In the first stage, medication treatment choice is estimated as a function of patient characteristics using a multinomial logistic probability estimator. Then selection bias coefficients, λ_{ij} are calculated for each medication choice i and patient j using the formula:

$$\lambda_{ij} = \varphi(\Phi^{-1}(F_i(z_{ij}y)))/F_i(z_{ij}y) \qquad (1)$$

where $\varphi(.),\Phi(.)$ represent the standard normal probability density and distribution functions, respectively; $F_i(z_{ij}y)$ is the multinomial logistic probability of treatment choice i, given observable patient characteristics z_{ij} and estimated logistic probability parameters y. Because of the independence of irrelevant alternatives structure of the multinomial logistic estimation model, λ_{ij} will be invariant to the number of alternative medication choices [31].

The second-stage variance components regression estimator for health-care costs is:

$$H_{ij} = \delta_{ij}[Xj\ \beta + \eta_i + \alpha\lambda_{ij} + u_{ij}] \quad (2)$$

where H_{ij} is total annual health-care costs for patient j using medication i, δ_{ij} is an indicator variable that equals 1 if patient j is observed to choose medication i and is zero otherwise, Xj is a vector of observable characteristics explaining annual health-care costs, η_i is the incremental effect of medication i on treatment costs, and α is the estimated coefficient on the sample selection bias coefficient vector λ_{ij}. u_{ij} is the linear regression error term. u_{ij} will be heteroskedastic for several reasons. First, using estimated values for λ_{ij} creates heteroskedastic errors [29]. Second given the small number of available explanatory factors in the data set, there are potential individual-specific omitted explanatory variables.

The advantage of a fixed effects variance components model is that any omitted characteristics that are patient-specific can be adjusted for in the estimation procedure as part of the patient-specific error component (e.g., patient medical history, prior treatment costs, preference for treatment, sociodemographics, etc.). Because the Medi-Cal claims data have only a very limited set of demographic (age, sex, race/ethnicity) and comorbidity measures (ICD-9 codes from the claims records) to use as explanatory factors, it is important to utilize this capability of panel data estimation to adjust for potential confounders that we are unable to capture in the data.

Given the repeated annual observations on many patients in the sample, a random effects model for the regression error terms would be feasible if omitted unobservable explanatory factors were not correlated with the observable explanatory characteristics [32]. Because this is not a plausible assumption for these data, we chose a fixed-effects error specification for the patient-specific variance components. Rather than explicitly characterizing the error covariance structure, we used an SPSS 12.0 macro to adjust the linear regression parameter estimates in Equation 2 for generalized heteroskedasticity (http://www.spss.com) [34].

In addition to looking at total medical costs, we looked at specific categories of medical expenditures per AR patient, including: emergency department expenditures, drug expenditures, outpatient expenditures, inpatient expenditures and other medical care expenditures. The same sample selection estimation model and correction for variance components (Equations 1–2) and same sets of explanatory variables were used in each of the expenditure subcategory analyses.

As further validation of the estimates, we used ordinal regressions on subcategories of medical service utilization counts to determine whether the pattern of medical utilization for emergency care visits, inpatient care, and physician office visits was similar to that found for medical expenditure categories. For this analysis ordinal regression methods are superior to count models, such as the Poisson regression or the negative binomial regression methods, because of the required rigid relationship between mean and variance in count models, and the requirement that utilization differences preserve cardinality. Ordinal regression methods merely require that "more services" reflect higher service intensity without imposing cardinality of service counts. Because medical utilization and service visits differ substantially in time, complexity and cost, it is inappropriate to use cardinal counts for them. Moreover, even if cardinality is empirically correct, the ordinal regression models will generate unbiased estimates. Both the ordinal link logit and ordinal link probit models were estimated, and the first-stage selection bias correction factors were included in the ordinal regressions to adjust for nonrandom AR drug treatment selection.

Results

Medical Cost and Service Utilization Differences for Patients Using Different AR Medications

Table 1 provides the descriptive characteristics for the sample population. The patients were 38% male, 10% African Americans, 12% Hispanic, and 42% other nonwhite. Total annual health-care expenditures (excluding long-term care costs) per patient averaged $3800, with drug expenditures (both AR and all other medications) averaging more than half of total health-care expenditures.

As shown in Table 2, only 16% of the patient sample used more than one AR medication type, and essentially all of these multiple medication patients used only two medications. In the first analysis we restrict attention to the 84% of patients with only one medication type. We then extended the results to include patients with multiple medications.

Table 3 shows the first-stage multinomial logistic estimates for the sample. The estimates use a fixed effects error component estimation approach to account for additional unobservable patient-level characteristics. Most of the covariates are highly significant, with males, African Americans, and

Table 1 Patient descriptive characteristics

Descriptive statistics	1999			2000		
	N	Mean	SD	N	Mean	SD
Total health-care spending (adjusted by medical CPI)	45,810	3,737	8,398.66	46,970	4,055	9,016.08
FGA medication spending	45,810	6.43	18.57	46,970	5.31	15.19
SGA medication spending	45,810	86.59	139.45	46,970	115.39	168.32
Sex (1 = Male)	45,810	38.9%	0.49	46,970	37.7%	0.48
African American	45,810	9.8%	0.30	46,970	9.7%	0.30
Hispanic	45,810	12.8%	0.33	46,970	11.1%	0.31
Other non-white	45,810	41.4%	0.49	46,970	42.5%	0.49
Age squared	45,810	3,168.04	2,471.77	46,970	3,777.54	23,208.44
Age	45,810	49.77	26.28	46,970	50.87	25.58
Asthma prescriptions filled	42,725	0.31	0.46	43,751	0.33	0.47
Diagnosis of COPD	42,725	5.3%	0.22	43,751	5.3%	0.22
Diagnosis of congestive heart failure	42,725	3.9%	0.19	43,751	3.5%	0.18
Diagnosis of hyperlipidemia	42,725	6.1%	0.24	43,751	6.6%	0.25
Diagnosis of hypertension	42,725	19.2%	0.39	43,751	19.2%	0.39
Diagnosis of stroke	42,725	5.5%	0.23	43,751	4.6%	0.21
Diagnosis of cardiovascular disease	42,725	47.7%	0.50	43,751	51.5%	0.50
Diagnosis of emphysema	42,725	0.5%	0.07	43,751	0.5%	0.07
Diagnosis of diabetes	42,725	11.5%	0.32	43,751	12.1%	0.33
Diabetes prescriptions filled	42,725	13.4%	0.34	43,751	14.4%	0.35
Diagnosis of cancer	42,725	2.0%	0.14	43,751	2.0%	0.14
Diagnosis of sinusitis	42,725	8.7%	0.28	43,751	7.9%	0.27
Drug expenditures	45,810	1,975	3,837.02	45,790	2,294	3,841.65
Outpatient expenditures	30,821	596	3,863.36	29,319	637	4,769.24
Long-term care expenditures	1,133	514	4,796.92	1,131	432	4,590.30
Inpatient expenditures	1,938	176	2,770.03	2,125	166	2,748.66
Other medical care expenditures	14,835	477	53.55	13,865	524	56.70

COPD, chronic obstructive pulmonary disease.

younger patients more likely to use FGA medications, whereas other nonwhite ethnic groups were less likely than whites or Hispanics to use FGA. Fexofenadine, loratadine, and cetirizine were all more likely to be used in 2000 than FGA medications. Existing comorbidities are highly significant in predicting AR medication choice. The Table 3 multinomial logit results are used primarily to generate the selection bias coefficients for the second-stage cost regressions and ordinal utilization count regressions. As such the coefficient estimates do not have direct policy significance. Nevertheless, the finding that specific observable characteristics are significantly related to medication choice indicates that a correction for selection bias needs to be considered in this case.

Table 4 provides the variance components regression results adjusting for treatment selection bias. FGA is the omitted (default) treatment choice category. It can be seen that all of the SGA medications have significantly lower total health-care treatment costs per patient than FGA medications with total

Table 2 Allergic rhinitis medication use

(A) Number of different medications used

Number of antihistamine medications used: 1999–2000

No.	Frequency	Percent
1	77,729	83.8
2	13,089	14.1
3	1,826	2.0
4	136	0.1
Total	92,780	100.0

(B) Medication cost* and frequency of use

	Number and percentage of patients using various AR medications				
	1999			2000	
	Prescription cost ($)	Frequency	Percent	Frequency	Percent
Fexofenadine	229	5,497	12	6,984	15
Cetirizine	202	6,363	14	8,727	19
Loratadine	178	16,290	36	18,478	39
First-generation antihistamines	26	19,891	43	16,233	35

*Prescription costs exclude confidential rebates to the Medi-Cal program.

Table 3 Multinomial logistic parameter estimation of medication choice*

N = 92,780	Parameter estimates†			
Choice of AR medication	FGA	Fexofenadine	Cetirizine	Loratadine
Intercept	665.36	–217.24	–441.1	–61.193
	(0.00)	(0.00)	(0.00)	(0.15)
Sex	0.148	–0.03	0.106	0.015
	(0.00)	(0.35)	(0.00)	(0.51)
African American	0.245	–0.119	–0.153	–0.035
	(0.00)	(0.05)	(0.01)	(0.42)
Hispanic	–0.007	–0.223	–0.131	–0.242
	(0.86)	(0.00)	(0.02)	(0.00)
Other race	–0.375	–0.603	–0.464	–0.489
	(0.00)	(0.00)	(0.00)	(0.00)
Age	–0.043	0.042	–0.029	–0.031
	(0.00)	(0.00)	(0.00)	(0.00)
Year	–0.332	0.108	0.221	0.031
	(0.00)	(0.00)	(0.00)	(0.15)
Asthma medication	–0.648	–0.381	–0.397	–0.304
	(0.00)	(0.00)	(0.00)	(0.00)
COPD diagnosis	0.309	0.112	–0.011	0.075
	(0.00)	(0.08)	(0.87)	(0.13)
CHF diagnosis	0.312	0.063	0.042	0.023
	(0.00)	(0.42)	(0.58)	(0.70)
Lipid diagnosis	–0.163	–0.009	0.01	0.006
	(0.00)	(0.88)	(0.85)	(0.89)
Hypertension diagnosis	0.057	–0.098	–0.05	–0.048
	(0.04)	(0.01)	(0.19)	(0.10)
Stroke diagnosis	0.103	0.113	0.079	0.025
	(0.03)	(0.08)	(0.21)	(0.62)
CVD medication	–0.178	–0.086	–0.091	–0.149
	(0.00)	(0.02)	(0.02)	(0.00)
Emphysema diagnosis	0.145	–0.218	–0.083	–0.067
	(0.28)	(0.27)	(0.67)	(0.64)
Diabetes diagnosis	0.004	–0.114	–0.08	–0.043
	(0.93)	(0.06)	(0.17)	(0.34)
Diabetes medication	0.123	0.099	0.132	0.068
	(0.00)	(0.08)	(0.02)	(0.11)
Cancer diagnosis	–0.039	–0.164	–0.033	–0.091
	(0.58)	(0.11)	(0.73)	(0.22)
Sinusitis diagnosis	–1.101	–0.344	–0.509	–0.284
	(0.00)	(0.00)	(0.00)	(0.00)

*Fixed-effects error component parameter estimates are omitted because of space limitations.
†*P*-value for the null hypothesis in parentheses below each coefficient estimate.
CVD, cardiovascular disease.

paid medical costs ranging from $347-$448 less than with FGA ($P < 0.001$), despite the higher AR medication costs. Expenditure differences among the three SGA medications were not significant.

Because all exogenous variables are included in both the first- and the second-stage estimation equations, the model is identified through nonlinearities in the Mills ratio selection terms. Although this can raise issues of multicollinearity, examination of the collinearity diagnostics showed that the variance inflation factors are mostly less than 2, and always less than 20. Given the high levels of significance and large patient sample size, multicollinearity is not a problem for these estimates.

As expected, treatment costs increase with age and year of observation. Health-care costs were significantly greater for African Americans and lower for Hispanics and other ethnic groups (white was the omitted race/ethnicity category). Indicators of either diagnosis or medication use for comorbidities were all highly significant. Since the fixed effects variance components model adjusts for other unobservable patient-specific characteristics including medical history, additional comorbidities and patient and provider medication preferences, the results are robust. To determine whether these results also hold for AR patients on multiple medication types, the selection model on total health-care costs was re-estimated using a five-choice logistic probability framework, with multiple medications representing an additional fifth treatment choice category. Treatment costs for FGA medications were significantly higher than the three SGA medications as a group ($P < 0.05$), although the pairwise difference between FGA and each separate SGA treatment cost did not reach statistical significance (results available from authors on request).

The fact that all of the Table 4 selection bias coefficients (lambdas) were significant indicates that unobservable factors were significantly correlated

Table 4 Total health-care costs variance components regression dependent variable: total health-care spending (adjusted by medical CPI)

Parameter	Estimate	Parameter significance	95% CI	
			Lower bound	Upper bound
Intercept	–601,848	0.00	–819,738	–38,3957
Sex	578.44	0.00	429.69	727.19
African American	550.11	0.00	287.45	812.78
Hispanic	–1902.23	0.00	–2137.49	–1666.96
Other race	–657.11	0.00	–826.85	–487.38
Age squared	0.04	0.00	0.03	0.05
Age	–34.84	0.00	–40.60	–29.08
Year	304.33	0.00	195.61	413.05
Asthma medication	923.69	0.00	778.91	1068.48
COPD diagnosis	2583.71	0.00	2316.52	2850.89
CHF diagnosis	2898.99	0.00	2596.48	3201.50
Lipid diagnosis	575.36	0.00	343.12	807.60
Hypertension diagnosis	820.52	0.00	662.48	978.56
Stroke diagnosis	1954.21	0.00	1700.49	2207.93
CVD medication	1408.45	0.00	1244.52	1572.38
Emphysema diagnosis	2474.91	0.00	1698.74	3251.07
Diabetes diagnosis	1767.80	0.00	1532.78	2002.81
Diabetes medication	655.18	0.00	411.38	898.98
Cancer diagnosis	2186.38	0.00	1802.91	2569.84
Sinusitis diagnosis	405.19	0.00	138.26	672.12
Fexofenadine	–346.80	0.00	–568.68	–124.91
Cetirizine	–447.97	0.00	–649.21	–246.73
Loratadine	–378.04	0.00	–523.96	–232.11
Mlambda A*	1546.57	0.00	1180.75	1912.39
Mlambda Z*	371.65	0.02	57.99	685.31
Mlambda C*	–303.55	0.09	–658.20	51.10
Mlambda F*	227.60	0.00	122.60	332.59

*Multinomial selection bias correction factor: A, fexofenadine; Z, cetirizine; C, loratadine; F, first-generation antihistamine.
CHF, congestive heart failure.
N = 92,780.

with both the choice of AR medications and the costs associated with AR treatment. In fact, when the lambdas were excluded from the model estimation, the results were still significant, but the magnitude of the cost savings associated with SGA medications were only about half of what was estimated in the Table 4 results (results available from authors on request). On the other hand, when we estimated the model using ordinary least squares (ignoring patient-specific unobservables and heteroskedasticity) the results were very similar to the Table 4 results. This implies that correcting for selection bias is important for these data, but correcting for heteroskedasticity is not.

To determine which specific medical service costs decrease with use of SGA medications, the selection bias correction model was rerun on medical cost subcategories. Table 5 provides the cost parameter estimates for each SGA medication (relative to FGA) for drug expenditures, inpatient costs, outpatient costs, and other medical service costs (which include durable medical equipment, home health, lab and diagnostic tests, etc.). It can be seen that the reductions in inpatient, outpatient, and other medical service costs are significant for patients using SGA drugs. Furthermore, drug expenditures are not significantly different for patients using SGA and FGA medications despite the fact that FGA medications averaged $3 per prescription and SGA medications averaged $50 per prescription. The increases in AR medication costs were offset by reductions in other medication expenditures for SGA patients, particularly emergency department costs and other medical costs.

In addition to medical costs, we also looked at specific categories of medical service utilization using ordinal regression to evaluate service counts. Table 6 demonstrates that the same pattern observed with costs was seen with significantly higher medical service utilization (emergency department admissions, inpatient admissions, and physician office visits) for patients using FGA medications relative to those using SGA medications ($P < 0.01$), using ordinal logit link function regression after adjusting for the same demographic and comorbidity covariates shown in Table 4. As a further sensitivity analysis check, we also re-estimated the cost regressions as two-part models using log-transformed costs in the second equations and found predicted cost differences similar to those reported in Tables 4 and 5 [35].

Finally, we briefly examined the pattern of medication switching among patients initiating any of the FGA or SGA medications during the two year

Table 5 Medical service component cost differences for SGA relative to FGA medications*

Parameter	Estimate	Parameter significance†	95% CI	
			Lower bound	Upper bound
Drug costs	n = 91,600			
Fexofenadine	−63.47	0.21	−162.78	35.83
Cetirizine	3.33	0.942	−86.8	93.45
Loratadine	−42.72	0.193	−107.1	21.66
Inpatient costs	n = 4,063			
Fexofenadine	−25.73	0.252	−69.73	18.28
Cetirizine	−41.99	0.04	−82.01	−1.98
Loratadine	−41.57	0.009	−72.94	−10.19
Outpatient costs	n = 60,140			
Fexofenadine	−17.94	0.517	−72.27	36.39
Cetirizine	−45.23	0.079	−95.67	5.21
Loratadine	−49.18	0.017	−89.57	−8.79
Emergency department costs	n = 17,421			
Fexofenadine	−29.75	0.000	−42.92	−16.57
Cetirizine	−17.92	0.002	−29.14	−6.71
Loratadine	−32.87	0.000	−41.60	−24.15
Other medical costs	n = 28,700			
Fexofenadine	−115.66	0.007	−200.36	−30.96
Cetirizine	−78.32	0.048	−155.91	−0.73
Loratadine	−76.95	0.011	−136.51	−17.39

*Regression results shown are adjusted for the same covariates and selection bias factors shown in Table 4.
†Parameter significance reflects the *t* test type-I probability for each SGA that cost category values are different from FGA treatment costs.

period. As shown in Table 7, those patients who switched medications were more likely to switch to an SGA medication than to an FGA medication. These results were also found in multinomial logit regressions, adjusting for patient demographics and comorbidities.*

Discussion

There is substantial evidence that FGA medication increases AR patient injury and accident rates primarily because of high levels of sedation [16,36–39]. This is the first evaluation of health-care treat-

Table 7 Antihistamine medications switching patterns

Switched to drug in class	Frequency	Percent
No. switch	63,420	68.36
Switched to		
First-generation antihistamines (FGA)		
Chlorphenhydramine	2,402	2.59
Diphenhydramine	3,564	3.84
Second-generation antihistamines (SGA)		
Cetirizine	2,929	3.16
Fexofenadine	2,862	3.08
Loratadine	6,943	7.48
Other medications		
Nasal steroid	7,928	8.54
Other AR medication	2,732	2.94
Total	92,780	100.00

Table 6 Medical service utilization differences for antihistamine medications

Parameter	Estimate	Parameter significance	95% CI	
			Lower bound	Upper bound
Emergency department visits	n = 17,421			
FGA medications	0.21	0.00	0.14	0.28
Fexofenadine	−0.09	0.09	−0.20	0.02
Cetirizine	−0.15	0.00	−0.25	−0.05
Loratadine	−0.24	0.00	−0.32	−0.17
Inpatient admissions	n = 4,063			
FGA medications	0.36	0.00	0.27	0.45
Fexofenadine	−0.06	0.38	−0.19	0.07
Cetirizine	−0.05	0.48	−0.17	0.08
Loratadine	0.02	0.72	−0.08	0.12
Physician office visits	n = 3,043			
FGA medications	0.46	0.00	0.25	0.674
Fexofenadine	0.15	0.34	−0.16	0.461
Cetirizine	−0.27	0.12	−0.60	0.069
Loratadine	−0.09	0.48	−0.34	0.16

Logit link ordinal regression results adjusted for the same covariates shown in Table 4.

*Additional results tables are available online at http://www.ispor.org/valueinhealth_index.asp.

ment costs for AR patients comparing SGA and FGA medications, adjusting for treatment selection bias, demographics, comorbidities, and unobservable patient-specific variance components. The analysis finds significant AR treatment cost and utilization reduction associated with each of the SGA medications relative to FGA drugs, despite their higher acquisition costs. Inpatient and outpatient costs trend lower with all SGA medications. Significant cost reductions are observed for emergency and other medical services, whereas total drug expenditures per AR patient are not significantly higher for those taking SGA medications. The results are robust, and are observed in regressions evaluating utilization of several types of medical services directly, as well as specific medical service cost component regressions.

Because all of the costs are estimated using Medi-Cal prices, the estimated cost differences are projected to be substantially larger among private sector health insurers and MCOs. Moreover, Medi-Cal receives additional confidential rebates from SGA manufacturers that make the SGA cost-savings even larger than our estimates, which are based on publicly available drug prices.

Medi-Cal (Medicaid) patients are low-income and from a relatively lower socioeconomic status compared to typical US AR patients and managed care enrollees. The Medi-Cal AR population is bimodal, with many young beneficiaries covered under the AFDC and S-CHP programs, and many older beneficiaries being jointly eligible for Medicare. Generalizability of these findings beyond the Medi-Cal or Medicaid populations should be done with caution. Nevertheless, it should be pointed out that because Medi-Cal covers prescriptions even when equivalent OTC products are available, none of the Medi-Cal AR patients had to choose therapy based on differences in AR medication costs. This means that the observed medical cost differences in this study are even less pronounced than would be observed in an AR patient population which had self-selected FGA medications because of out-of-pocket differences in medication costs. When the analyses were separately repeated for older (Medicare-eligible) and younger Medi-Cal-only AR patients, the same significant medical cost differences obtained between AR patients choosing FGA and SGA medications still obtained, implying that patient age and type of Medi-Cal eligibility did not explain the cost difference results.

Ideally, one would like to measure the actual impact of making SGA medications available OTC, rather than using data from the pre-OTC switch era. Nevertheless, it is empirically impossible (or very difficult) to evaluate the impact of this policy change in a post-OTC world, precisely because OTC medications are not tracked in third party claims data. It is difficult to know which OTC medications AR patient are taking, including Medi-Cal patients, because they are not reimbursed for OTC medications. Therefore, the cleanest way to compare the costs associated with FGA and SGA medications is using data from the immediate pre-OTC era.

Health insurers have successfully convinced drug manufacturers to move at least one SGA medication (loratadine) to OTC status. One motivation is to reduce health plan covered expenditures on AR medications by encouraging greater use of noncovered nonprescription AR medications. Nevertheless, evaluation of Medi-Cal claims data suggest that such a strategy could lead to higher health plan payments if patients substituted cheaper FGA OTC medications for more expensive SGA medications. With higher copayments for SGA drugs, many patients, particularly lower income patients, may choose cheaper OTC FGA medications rather than loratadine or other relatively expensive SGA medications. Although it is likely that the price differential between OTC diphenhydramine and OTC loratadine will diminish over time, OTC loratadine will likely never become as cheap as OTC FGA products. Current prices for OTC FGAs can be found on the internet for less than $0.02 per pill.

Our analysis finds that FGA usage may increase annual treatment costs from $347 to $448 per AR patient. Sullivan and Nichol's AR medication cost effectiveness modeling implies that careful structuring of health plan and Medicaid AR medication benefits to subsidize OTC SGAs could overcome these problems by preventing large-scale switches to OTC FGA products, without net increases in health plan expenditures [16]. Certainly OTC availability of SGA products will improve access to nonsedating AR medications for those who would not otherwise visit a physician and obtain an SGA prescription. But eliminating coverage for OTC loratadine and restricting access to other SGAs may result in increased medical expenditures as a result of inappropriate use of substitute drugs or discontinuation of drug therapy [19].

This analysis has the typical limitations of retrospective data analysis. Although we have attempted to adjust carefully for selection bias, heteroskedasticity, and other estimation issues, and found our results to be quite robust to various alternative spec-

ifications, omitted variables or model specification errors may have impacted our findings.

It is unclear whether medication compliance, additional inpatient and outpatient visits to deal with AR disease, medication symptoms, comorbidities or other factors result in higher treatment costs for FGA patients relative to SGA patients. There is evidence that optimal management of AR will decrease ER and inpatient utilization for comorbidities such as asthma [36]. The finding that patients switching medications were more likely to switch to an SGA medication than to an FGA medication suggests a preference for the newer SGA medications. Additional research with more detailed medical history information not available in claims history data is needed to determine which specific medical history and medication treatment patterns contribute to the observed increase in medical care costs for patients taking FGA medications.

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