Medical costs and adherence in patients receiving aqueous versus pressurized aerosol formulations of intranasal corticosteroids

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ABSTRACT

Intranasal corticosteroid (INS) formulations have different sensory attributes that influence patient preferences, and thereby possibly adherence and health outcomes. This study compares health care use and costs and medication adherence in matched cohorts of patients with allergic rhinitis (AR) using a chlorofluorocarbon-propelled pressurized metered-dose inhaler (pMDI) or aqueous intranasal corticosteroid (A-INS). Florida Medicaid retrospective claims analysis was performed of enrollees aged ≥12 years with at least 1 year of continuous enrollment before their initial AR diagnosis, 1 year for continuous enrollment before their index INS claim, and 18 months of continuous enrollment after their index INS claim during which they received either pMDI or A-INS. pMDI and A-INS patients were matched 1:2 using propensity scores. Nonparametric analyses compared outcomes between matched cohorts at 6, 12, and 18 months of follow-up. A total of 585 patients were matched (pMDI = 195, A-INS = 390). pMDI patients were more adherent to INS, as reflected in their higher median medication possession ratio (53.2% versus 32.7%; $p < 0.0001$) and fewer median days between fills (73 days versus 111 days; $p = 0.0003$). Significantly lower median per patient pharmacy fills (34.0 versus 50.5; $p < 0.05$) and costs ($1282 versus $2178; $p < 0.01$) were observed among pMDI patients versus A-INS patients 18 months after INS initiation and were maintained when analyses excluded INS fills. Adherence to INS and health care utilization and costs following INS initiation for AR differed by type of formulation received. Our findings suggest patient preferences for INS sensory attributes can drive adherence and affect disease control, and ultimately impact health care costs.

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Allergic rhinitis (AR) is a highly prevalent chronic disease, affecting an estimated 40 million Americans,[1] which adversely affects sleep, cognitive functioning, quality of life, and workplace/school productivity, and has a considerable economic impact on the health care system and society.[2–4] Although many persons with AR do not seek medical help,[5] those who do generate substantial medical costs, estimated at $11.2 billion in the United States in 2005, with the bulk of expenditures deriving from prescription medications (60%) and outpatient care (36%).[6] In addition to these costs, the economic burden of AR also includes billions in "hidden" costs for the treatment of AR-related comorbid conditions (*e.g.*, asthma and chronic sinusitis) and indirect costs due to lost productivity.[4,7] The costs of lost workplace productivity due to AR exceed those of other common illnesses, including arthritis, asthma, diabetes, hypertension, migraine, and coronary heart disease.[8]

Based on their superior effectiveness compared with other classes of AR medications, guidelines recommend intranasal corticosteroids (INS) as a treatment for AR in general and as first-line treatment for moderate-to-severe or persistent disease.[9–11] INSs relieve the major nasal symptoms of AR—sneezing, itching, rhinorrhea, and nasal congestion—and some also reduce ocular symptoms.[9] INSs are considered relatively safe, with generally mild local adverse effects (most frequently dryness, stinging, burning, and epistaxis) in 5–10% of patients.[12] Clinically significant systemic side effects are rarely seen in patients receiving recommended INS doses.[9]

The eight INS formulations currently available in the United States have comparable efficacy and safety.[12] However, patients can distinguish between and express clear preferences for INS formulations based on their sensory attributes (*e.g.*, taste and odor).[13–20] These preferences can affect patients' self-reported willingness to adhere to INS treatment.[15,19,21–24] Because 70% of AR patients with poor symptom control fail to take their medication as prescribed,[25] optimizing INS for-

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mulations to address patient sensory preferences can encourage greater adherence, leading to improved disease control and clinical outcomes in patients with AR.[26,27]

Patients have reported differences in the sensory attributes of aqueous "wet" versus aerosol "dry" pressurized metered-dose inhalers (pMDIs) INS formulations, with pMDI formulations causing significantly less medication runoff.[16] One-third of patients report medication dripping down the throat as moderately or extremely bothersome.[28] Considering the importance of this attribute in determining patient preferences, we sought to determine whether pMDI versus aqueous INS (A-INS) formulations were associated with different adherence rates and health outcomes. Chlorofluorocarbon-propelled pMDI formulations were available in the United States until July 2003, when they were removed from the market because of their potential ozone-depleting impact.[29] Accordingly, our analyses focus on use of pMDI versus A-INS before 2003. Although only A-INS formulations are available as of the end of 2011, new pMDI formulations propelled by environmentally friendly hydrofluoroalkanes are under consideration for regulatory approval in the United States.

METHODS

Florida Medicaid Data Set

Florida Medicaid provides medical coverage to >2 million underserved enrollees, approximately one-half of whom are adults. Our Florida Medicaid data set includes 12 years (1997–2009) of paid claims captured in computerized records, including patient demographics; diagnoses classified using International Classification of Diseases, 9th Revision (ICD-9) codes; medical, surgical, and diagnostic services identified by Current Procedural Terminology (CPT) codes; medications (drug name, strength, dosage form, formulation, quantity supplied, numbers of days supplied) derived from National Drug Codes (NDC) and other fields; and payment sources. Information is patient de-identified and fully compliant with the Health Insurance Portability and Accountability Act privacy rule. Previously published studies have examined patterns and outcomes of AR treatment using this data set.[30,31]

Patient Selection

Patients included in the study were aged ≥12 years who had at least one claim for AR (ICD-9, 477.0, 477.2, 477.8, or 477.9) from July 1997 through December 2001. Patients with AR symptoms due to food (ICD-9 477.1) were excluded. Eligible patients were newly diagnosed with AR (had no AR diagnosis during the 1 year or more preceding their initial AR claim). In addition, eligible patients had (a) at least 1 year of continuous enrollment preceding their index INS claim (to allow for matching of pre-INS disease severity); (b) an index INS claim that followed their initial AR diagnosis and occurred between July 1, 1998 and June 30, 2000; and (c) at least 18 months of continuous enrollment after their index INS claim. Patients who met these criteria were defined as having received pMDI if their index INS fill was for beclomethasone dipropionate (Beconase; GlaxoSmithKline, Research Triangle Park, NC and Vancenase; Schering Corporation, Kenilworth, NJ), budesonide (Rhinocort; AstraZeneca, Wilmington, DE), or triamcinolone acetonide (Nasacort; Sanofi-Aventis, Bridgewater, NJ) and they did not receive any A-INS formulations during the 18 months after initiation of pMDI. Patients who received A-INS had an index INS fill for beclomethasone dipropionate monohydrate (Beconase AQ; GlaxoSmithKline and Vancenase AQ; Schering Corporation), budesonide (Rhinocort AQ; AstraZeneca) or triamcinolone acetonide (Nasacort AQ; Sanofi-Aventis), and did not receive any pMDI formulations after initiation of A-INS. We excluded from analysis patients who received flunisolide (Nasarel and Nasalide; Ivax Laboratories, Miami, FL) or fluticasone propionate (Flonase; GlaxoSmithKline) because no pMDI formulations with the same chemical structures existed to compare with these A-INS formulations.

Because our claims data date from July 1, 1997, the earliest possible date for an index INS claim in patients with at least 1 year of continuous enrollment before that claim was July 1, 1998. June 30, 2000 was selected as the last date an index INS claim could occur so that comparison of pMDI and A-INS use during the 18-month follow-up period would not be affected by the ban on chlorofluorocarbon-propelled pMDI formulations, which went into effect on July 1, 2003.[26]

Data Analysis

Propensity Score Matching. Propensity score matching was used to minimize potential selection bias and to control for imbalances in characteristics between groups. Propensity scores for each patient were derived using a logistic regression model to predict the probability of group membership using six covariates: age at initial AR diagnosis (±6 months), sex, race/ethnicity, Charlson Comorbidity Index 1 year before initial AR diagnosis, presence of asthma (ICD-9, 493) or atopic dermatitis (ICD-9, 691.8) during the year before the index INS claim, and presence of asthma or atopic dermatitis during the 18 months after the index INS claim.

A 1:2 nearest neighbor matching was performed whereby the pMDI and A-INS groups were randomly ordered and the first pMDI patient selected was matched to the two A-INS patients with the closest

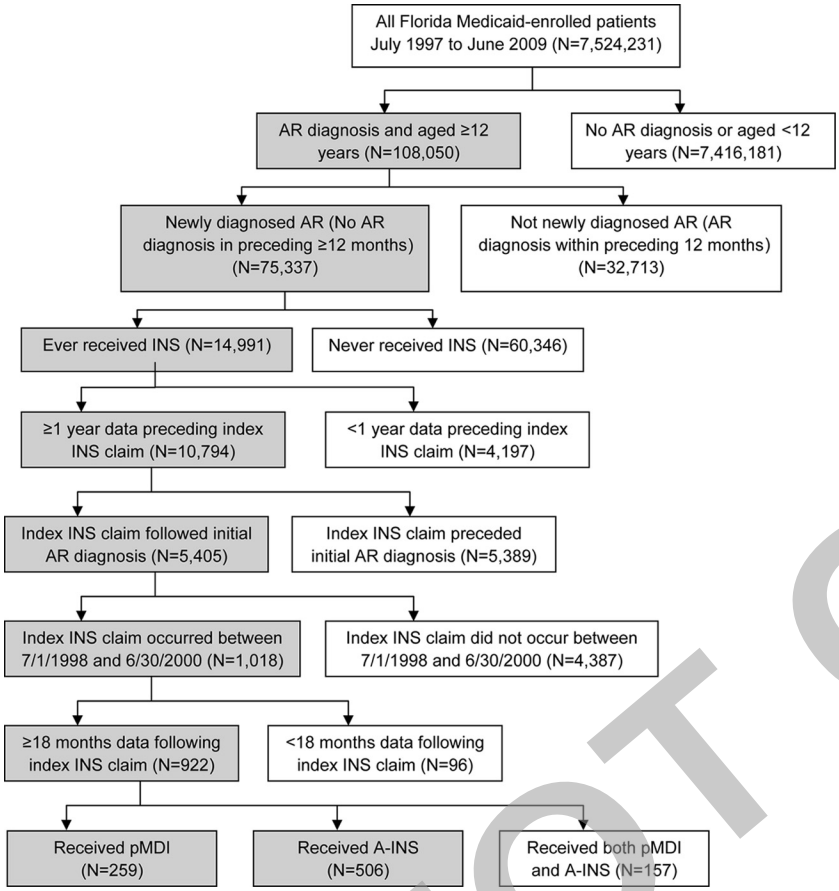

Figure 1. *Sample identification. A-INS, aqueous intranasal corticosteroid; AR, allergic rhinitis; INS, intranasal corticosteroid; pMDI, pressurized metered-dose inhaler.*

propensity scores. In selecting the appropriate number of propensity score–matched controls (A-INS patients) to cases (pMDI patients), we considered the trade-offs among bias, efficiency, and precision.[32] Although bias is minimized in a 1:1 matching scheme (because the case that is most similar to the index subject is selected), both important information and precision of the estimated treatment effect can be lost.[32] Our propensity score matching scheme was guided by a recent study that examined the impact of the number of matched controls in the context of nearest neighbor propensity score matching. The authors recommend using either a 1:1 or 1:2 matching scheme in studies similar to ours, although a 1:2 match may offer greatest precision without a commensurate increase in bias.[32]

Analysis of Group Differences. Chi-square and Wilcoxon signed-rank tests were used to compare, respectively, categorical and median values between groups. Although groups were not matched on oral antihistamine use before INS initiation, we compared the median number of pharmacy fills for oral antihistamines and the proportion of oral antihistamine fills to total pharmacy fills, during the 12 months before INS initiation between the matched cohorts as a proxy for AR severity.

The medication possession ratio (MPR) measures the percentage of time a patient is in possession of medication, with higher values indicating greater adherence. MPR was calculated as the ratio between the number of days of supply and the total number of days between the first and last fills plus the last fill's days of supply. Group differences in median MPR and median number of days between INS fills were examined over the 18-month follow-up.

Because health care use and cost data are usually not normally distributed, statistical analyses were based on the median number and cost of inpatient stays, outpatient visits, pharmacy fills, and total health care claims at 6-, 12-, and 18-month follow-up for the two matched groups. However, we also present the mean values for these outcomes for descriptive purposes. We also examined group differences in the proportion of oral antihistamine to total pharmacy fills during the 18-month follow-up.

RESULTS

Sample Characteristics

We identified a total of 765 patients aged ≥12 years newly diagnosed with AR who had initiated *de novo* pMDI (n = 259) or A-INS (n = 506) between July 1998 and June 30, 2000 and had at least 18 months of data following initiation of INS treatment (Fig. 1). The propen-

Table 1 **Patient characteristics after matching**

Characteristic	pMDI (n = 195)	A-INS (n = 390)	p Value
Female, *n* (%)	162 (83.1)	302 (77.4)	0.112
Race/ethnicity, *n* (%)			
White non-Hispanic	69 (35.4)	138 (35.4)	1.00
Black	39 (20.0)	78 (20.0)	
Hispanic	33 (16.9)	66 (16.9)	
Other	54 (27.7)	108 (27.7)	
Charlson Comorbidity Index before initial AR diagnosis, *n* (%)			
0 (minimal)	136 (69.4)	270 (69.2)	0.972
1 (moderate)	51 (26.2)	105 (26.9)	
2+ (severe)	8 (4.1)	15 (3.9)	
Age at initial AR diagnosis, *n* (%)			
12–17 yr	16 (8.2)	30 (7.7)	0.527
18–35 yr	67 (34.4)	130 (33.3)	
36–50 yr	56 (28.7)	92 (23.6)	
51–64 yr	30 (15.4)	73 (18.7)	
≥65 yr	26 (13.3)	65 (16.7)	
Allergy-related comorbidity, *n* (%)			
Asthma before index INS claim	36 (18.5)	50 (12.8)	0.070
Asthma after index INS claim	38 (19.5)	61 (15.6)	0.242
Atopic dermatitis before index INS claim	3 (1.5)	1 (0.3)	0.110
Atopic dermatitis after index INS claim	3 (1.5)	9 (2.3)	0.795
Oral antihistamine use before index INS claim			
No. of fills, median	2.0	2.0	0.458
Proportion of total pharmacy fills, % (*n**)	5.2 (321)	5.3 (684)	0.754

**Represents number of fills.*
A-INS = aqueous intranasal corticosteroid; AR = allergic rhinitis; INS = intranasal corticosteroid; pMDI = pressurized metered-dose inhaler.

sity score-matched pMDI (n = 195) and A-INS (n = 390) cohorts had similar baseline characteristics (Table 1).

Adherence

Median MPR was significantly higher in the pMDI cohort compared with the A-INS cohort (53.2% versus 34.7%; p = 0.0002). pMDI patients had significantly fewer median days between INS fills than A-INS patients (73 days versus 111 days; p = 0.0003).

Health Care Use and Costs

Health care use and costs for the pMDI and A-INS cohorts are shown in Tables 2 and 3, respectively. At 18 months after INS initiation, there were no significant group differences in median inpatient stays and outpatient visits (Table 2). However, significantly fewer median pharmacy fills occurred at 6-, 12- and 18-month follow-up in the pMDI versus A-INS cohort. Analysis of pharmacy fills for medication claims exclusive of INS confirmed that the difference in number of pharmacy fills between the cohorts was attributable to greater use of non-INS medications among A-INS patients versus pMDI patients. Oral antihistamines accounted for a significantly lower proportion of total pharmacy fills among patients who received pMDI compared with those who received A-INS (6.0% versus 7.2%; $p < 0.0001$).

Although the groups did not differ in median 18-month inpatient or outpatient costs, total health care costs were significantly lower among pMDI patients versus A-INS patients. This difference was largely attributable to significantly lower median pharmacy costs in the pMDI cohort versus A-INS cohort. Significantly lower pharmacy costs for the pMDI cohort were observed at all follow-up periods, with the largest reduction occurring at 18 months.

DISCUSSION

Patient preferences regarding the sensory attributes of different INSs may play an important role in determining adherence and influencing health care outcomes. To our knowledge, this is the first study in which different sensory attributes of INS formulations have been associated with substantial and statistically significant differences in health care use and costs. We found that newly diagnosed patients with AR who

Table 2 **Comparison of health care resource use in pMDI and A-INS matched cohorts over 18 mo**

Type of Service	pMDI (n = 195)			A-INS (n = 390)			p Value*
	n	Mean (SD)	Median	n	Mean (SD)	Median	
Inpatient stays							
6 mo	4	1.3 (0.5)	1.0	4	3.3 (2.2)	3.0	0.250
12 mo	9	1.8 (1.6)	1.0	9	3.8 (4.0)	2.0	0.094
18 mo	15	1.9 (1.6)	1.0	15	3.5 (4.6)	2.0	0.071
Outpatient visits							
6 mo	190	9.7 (10.7)	6.0	345	10.4 (8.4)	8.3	0.096
12 mo	194	17.0 (19.7)	10.0	376	17.7 (13.8)	13.8	0.282
18 mo	194	23.9 (28.0)	16.0	383	24.5 (20.4)	18.3	0.484
Pharmacy fills							
6 mo	195	20.3 (16.6)	15.0	390	22.5 (14.7)	19.5	0.039
12 mo	195	37.0 (32.6)	25.0	390	41.5 (28.5)	35.0	0.026
18 mo	195	53.7 (50.3)	34.0	390	59.8 (42.6)	50.5	0.041
Non-INS pharmacy fills							
6 mo	193	18.9 (16.5)	13.0	385	21.0 (14.5)	18.5	0.042
12 mo	193	35.6 (32.4)	23.0	385	39.9 (28.1)	34.0	0.029
18 mo	194	52.0 (50.2)	31.5	388	57.9 (42.2)	49.0	0.043

**Based on comparison of median values for pMDI vs A-INS.*
A-INS = aqueous intranasal corticosteroid; INS = intranasal corticosteroid; pMDI = pressurized metered-dose inhaler.

received pMDI had 33% fewer median pharmacy fills (34.0 versus 50.5; $p < 0.05$) and 41% lower median costs ($1282 versus $2178; $p < 0.01$) compared with A-INS recipients 18 months after INS treatment initiation. These differences were attributable to less use of non-INS medications among pMDI patients.

Differences observed between groups in pharmacy use and costs may reflect better disease control achieved by pMDI patients attributable to superior adherence to INS. Continuous use of AR medication is more effective than on-demand therapy, particularly for patients with moderate-to-severe intermittent symptoms and those with persistent AR.[33] Clinically meaningful improvement in AR symptoms is not typically realized until 1–2 weeks after initiation of INS.[33] As continuous INS use attenuates the inflammatory process,[34] some also recommend continuous use of INS for patients with seasonal allergies during the weeks before and throughout the pollen season.[33] Patients with perennial AR who use oral antihistamines continuously also have significantly improved symptoms as well as lower use and costs of AR-related rescue medications compared with patients using on-demand oral antihistamines.[35] These data support the contention that improved symptom control achieved by more consistent AR therapy can lead to reduced AR-related pharmacy use and costs.

Oral antihistamines accounted for a significantly lower proportion of total pharmacy fills among patients who received pMDI than those who received A-INS, which may reflect superior control of AR among those who received pMDI. More than one-half of patients with AR report using at least two prescription medications to manage symptoms,[36] with 40% receiving both INS and antihistamines.[36,37] Although evidence is lacking to clearly support the superiority of INS and oral antihistamine combination therapy over INS alone,[38,39] guidelines indicate INS and oral antihistamines may be combined in patients with moderate-to-severe disease who fail to achieve adequate symptom relief with monotherapy[11] and patients with severe disease are more likely to be prescribed combination AR pharmacotherapy than those with mild or moderate disease.[40]

Several limitations of this study should be mentioned. First, the retrospective nature of this analysis precludes definitive conclusions regarding causality. Second, groups may have differed on variables that were not controlled for by matching procedures. However, we note that groups were matched by medical and AR-related comorbidity, and that matched cohorts did not significantly differ in their pre-INS oral antihistamine use. Moreover, because all patients received their health care coverage through Florida Medicaid, pricing, reimbursement, policies, and incentives were similar between and within groups. Given that Medicaid patient copays for prescription medications did not vary by INS formulation, patient out-of-pocket costs are not likely to have biased refill rate results. Third, claims data may include missing, imprecise, or incorrect codes, although it is unlikely that such errors would systematically differ across cohorts. Finally, be-

Table 3 **Comparison of health care costs in pMDI and A-INS matched cohorts over 18 mo**

Type of Service	pMDI (n = 195)			A-INS (n = 390)			p Value*
	n	Mean (SD)	Median	n	Mean (SD)	Median	
Inpatient costs ($)							
6 mo	4	3600 (1304)	4093	4	18,772 (14,437)	15,348	0.125
12 mo	9	3785 (3438)	2839	9	17,102 (24,693)	7779	0.020
18 mo	15	5535 (5007)	3717	15	15,185 (30,061)	5261	0.208
Outpatient costs ($)							
6 mo	190	932 (1302)	453	345	1149 (1815)	636	0.049
12 mo	194	1729 (2534)	846	376	2002 (3436)	1169	0.234
18 mo	194	2492 (3767)	1381	383	2950 (5524)	1581	0.397
Pharmacy costs ($)							
6 mo	195	1009 (1171)	588	390	1221 (1222)	813	0.005
12 mo	195	1931 (2447)	990	390	2279 (2190)	1533	0.004
18 mo	195	2892 (3811)	1282	390	3434 (3557)	2178	0.010
Non-INS pharmacy costs ($)							
6 mo	193	955 (1165)	539	385	1159 (1218)	756	0.007
12 mo	193	1876 (2441)	908	385	2214 (2183)	1459	0.006
18 mo	194	2829 (3806)	1222	388	3354 (3550)	2115	0.011
Total health care costs ($)							
6 mo	195	2581 (4072)	1225	390	3199 (4213)	1711	0.007
12 mo	195	4852 (7939)	2511	390	5771 (7448)	3189	0.022
18 mo	195	6894 (10,104)	4398	390	8539 (11,243)	4676	0.044

**Based on comparison of median values for pMDI vs A-INS.*
A-INS = aqueous intranasal corticosteroid; INS = intranasal corticosteroid; pMDI = pressurized metered-dose inhaler.

cause study patients were Medicaid enrollees, findings are not necessarily generalizable to broader patient populations.

In summary, we found that patients treated for AR with pMDI had significantly lower costs compared with those who received prescriptions for A-INS, implying that treatment with different formulations can lead to better adherence to INS, resulting in improved disease control and reduced use of supplemental non-INS medications. Our data suggest that preferences for INS formulations among patients with AR can influence health care use and costs. Although all INS formulations available in the United States as of the end of 2011 are aqueous sprays, the anticipated introduction of new hydrofluoroalkane-propelled pMDI formulations will broaden therapeutic options for patients with AR and permit enhanced targeting based on patient preferences,[26] thereby potentially improving adherence, increasing clinical benefit and reducing costs.

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