

Delivery of Ipratropium and Albuterol Combination Therapy for Chronic Obstructive Pulmonary Disease: Effectiveness of a Two-in-one Inhaler Versus Separate Inhalers

Elizabeth Chrischilles, PhD; Daniel Gilden, MS; Joanna Kubisiak, MPH; Linda Rubenstein; and Hemal Shah, PharmD

Objective: To determine whether a combined formulation consisting of ipratropium and an inhaled β_2 agonist (2-in-1 therapy) leads to lower respiratory-related healthcare use and charges and improved compliance compared with treatment with separate ipratropium and β_2 -agonist inhalers (separate inhaler therapy).

Study Design: Retrospective inception cohort study.

Patients and Methods: Healthcare use, charges, and treatment compliance were examined for adults age 38 years or older who initiated ipratropium therapy on or after July 1997, based on health claims data for United Healthcare enrollees from 5 health plans from July 1997 through December 1998. A total of 428 patients received 2-in-1 therapy, and 658 patients received separate inhaler therapy. To adjust for disease severity and other confounders, the following were determined for the preinitiation period: age; sex; use of oral steroids, antibiotics, or albuterol; respiratory-related healthcare use; and respiratory diagnoses. Compliance was defined as not interrupting or discontinuing therapy during the follow-up period.

Results: After adjusting for baseline covariates, 2-in-1 therapy users had a significantly lower risk of emergency department use or hospitalization (relative risk = 0.58, 95% confidence interval [CI] = 0.36, 0.94), lower mean monthly healthcare charges ($P = .015$), shorter hospital stays (2.05 vs 4.61 days, $P = .040$), and greater likelihood of compliance (odds ratio = 1.77, 95% CI = 1.46, 2.14).

Conclusion: A single inhaler containing both ipratropium and albuterol can increase compliance and decrease respiratory morbidity and charges over and above the effects achieved with separate inhalers for these 2 agents.

(*Am J Manag Care* 2002;8:902-911)

be added as needed, or as a standing dose.¹ In randomized, controlled trials, it has been demonstrated that lung function is improved^{1,4} and the number of exacerbations, number of hospital days, and total treatment charges are reduced³ when ipratropium is used to treat patients with COPD. It is possible to achieve combined ipratropium and albuterol therapy either by using separate inhalers for each drug (separate inhaler therapy) or by using a single inhaler that provides both ipratropium (21 μg of ipratropium bromide per inhalation) and albuterol (120 μg of albuterol sulfate per inhalation, equivalent to a 100- μg albuterol base) (2-in-1 therapy). An important question is whether 2-in-1 therapy improves compliance compared with separate inhaler therapy and, as a result of improved compliance, reduces COPD exacerbations and the related need for healthcare resources.⁵ The purpose of this study was to determine the impact of 2 different treatment regimens for COPD on healthcare utilization, charges, and compliance with therapy. Individuals initiating therapy with a combined ipratropium/albuterol prescription in the form of Combivent inhalation aerosol (2-in-1 therapy, Boehringer Ingelheim, Ridgefield, Conn) were compared with individuals initiating therapy with separate ipratropium (Atrovent inhalation aerosol, Boehringer Ingelheim, Ridgefield, Conn) and albuterol prescriptions (separate inhaler therapy).

© Medical World Communications, Inc.

Patients with chronic obstructive pulmonary disease (COPD) often are required to use multiple inhalers. The American Thoracic Society guidelines recommend 2 to 6 puffs of ipratropium every 6 to 8 hours daily for mild to moderate continuing symptoms. For those requiring additional relief, 1 to 4 puffs of a β_2 agonist 4 times per day may

From the University of Iowa, Iowa City, Iowa (EC, LR); Jen Associates, Inc, Cambridge, Mass (DG, JK); and Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, Conn (HS).

This work was supported by an unrestricted grant from Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, Conn.

Address correspondence to: Elizabeth Chrischilles, PhD, Department of Epidemiology, College of Public Health, 200 Hawkins Drive, C21J GH, Iowa City, IA 52242. E-mail: e-chrischilles@uiowa.edu.

.....
METHODS

An inception cohort study was conducted using a claims database for United Healthcare enrollees from 5 health plans spanning the period from July 1996 through December 1998. The 5 plans included in the study were chosen because of their geographic diversity. One is located in the southern United States, 2 are located in the northeastern United States, and 2 are located in the midwestern United States. The health plans selected have a common benefit structure and have fairly open formularies. Other United Healthcare health plans have more restrictive formularies.

Subjects

Subjects were eligible for inclusion in the study cohort if they were age 38 years or older, had at least 12 months of continuous plan eligibility, had an eligible respiratory condition, and were new users of ipratropium either as 2-in-1 or separate inhaler therapy.

Eligible respiratory conditions were COPD (*International Classification of Diseases, 9th Revision* [ICD-9] codes 490-492 and 496) and asthma (ICD-9 code 493). We assumed that a patient treated with ipratropium who had only an asthma code nevertheless was possibly being treated for COPD as well, because of the known ambiguities of diagnosis coding in this age group.⁶ To determine the sensitivity of our results to this assumption, we conducted sensitivity analysis in which only subjects with a COPD code and no asthma diagnosis code were included.

New users were subjects whose first month of either 2-in-1 or separate inhaler therapy use was preceded by at least a 3-month baseline period with eligibility for benefits and no claims for ipratropium in either formulation. In addition, individuals initiating separate inhaler therapy also were required to have concurrent use of albuterol either in the month during which they initiated ipratropium therapy or the prior month. Anyone who used both ipratropium two-in-one therapy and separate inhaler therapy was excluded (n = 128). Study outcomes were measured in the follow-up period. Each subject's follow-up period began in the month after prescription initiation and ended with their last eligible month or the end of the database. Individuals without at least 3 months of follow-up time because of proximity to the end of the study period or because of a loss of eligibility were excluded.

The use of 2-in-1 therapy was not observed in this population until July 1997. Therefore, to control for

variable follow-up periods, those who initiated therapy with ipratropium before July 1997 were excluded. At the time of the study, claims data were available through December 1998.

Baseline Measures

The following measures were assessed during the baseline period to determine factors related to disease severity and to identify other confounding variables: age; sex; the use of oral steroids, albuterol, and antibiotics; and the presence of a respiratory-related emergency department (ED) visit, hospitalization, outpatient visit, or diagnosis. Respiratory-related ED visits, hospitalizations, and outpatient visits included only medical encounters that were specifically for COPD, asthma, emphysema, chronic bronchitis, acute bronchitis, or pneumonia, as determined by an ICD-9 diagnosis code listed in the primary diagnosis data field in a physician or facility claim. Emergency department and hospital use was assessed during the 3-month period before initiation of therapy and was intended as a measure of recent acute exacerbation. In contrast, the respiratory diagnoses from the entire baseline period were included and were intended as a measure of having a chronic respiratory problem.

Outcome Measures

Study outcomes included the first respiratory-related ED visit or hospitalization as a measure of acute exacerbation; total monthly charges for respiratory-related care, excluding medication charges; average monthly provider-claimed charges for respiratory medications; and compliance measures. To examine the effect of 2-in-1 therapy versus separate inhaler therapy initiation on costs of respiratory medications, average monthly charges (the amount the provider claimed for the service) were compared between treatment groups for the following categories of respiratory medications: oral bronchodilators, anticholinergic inhalation aerosols, methylxanthines, salmeterol, cromolyn/nedocromil inhalation, leukotriene modifiers, inhaled corticosteroids, and oral corticosteroids. Additionally, average monthly charges submitted for all respiratory medications and average monthly charges submitted for all inhalers containing albuterol or ipratropium were compared between groups.

Measures of Respiratory Medication Use

To assess compliance, measures of therapy interruption and therapy discontinuation were constructed. A subject was considered compliant if

there was no therapy interruption or discontinuation during follow-up, determined as follows. Starting with the month of ipratropium initiation and extending until either the end of the database or the end of an individual's eligibility, each month was categorized according to whether or not a subject was receiving prescriptions for both ipratropium and albuterol. If an individual had multiple prescriptions filled in 1 month, the additional prescriptions were allowed to extend coverage to subsequent months equal to the additional quantity. For example, if an individual had 2 pre-

scriptions filled in 1 month, the month in which the prescriptions were filled and the month after would be considered covered months. Furthermore, prescriptions filled on the fifteenth of the month or later counted towards coverage for the current month and the month following.

"Interruption" was de-fined as at least a 1-month break in prescription coverage that was followed by subsequent use of both ipratropium and albuterol. "Discontinuation" was de-fined as a break of at least 2 consecutive months of prescription coverage without subsequent use of both ipratropium and

albuterol. Examination of the refill patterns supported this approach in that regularly occurring gaps of a month or more were not observed. In other words, refill patterns were consistent with the premise that prescriptions were intended to cover a single month. The observed number of days for which medication was supplied (30 days or fewer for 97% of claims) and the dispensed quantity of medication (200 inhalations or fewer for 99% of claims) also support this premise. The one exception was that multiple dispensing events for albuterol in a month can lead to a projection of multiple months of accumulated drug supply (the average number of albuterol dispensing events per month was 1.62 versus 0.9 for ipratropium-containing canisters). This leads to an underestimate of treatment interruptions for the separate inhaler therapy group. Hence, the compliance comparisons reported are conservatively biased against finding a difference between the 2-in-1 and separate inhaler therapies. An additional measure of compliance

Table 1. Baseline Patient Demographic Information and Medical Utilization Characteristics*

Characteristic	No. (%) in Prescription Treatment Group		P*
	Separate Inhaler Therapy (n = 658)	2-in-1 Therapy (n = 428)	
Mean age, y	59.3	63.4	<.001
Female	355 (54)	226 (53)	.711
Age categories, y			
<55	247 (38)	118 (28)	<.001
55-64	175 (27)	73 (17)	<.001
65-74	153 (23)	167 (39)	<.001
75+	83 (13)	70 (16)	.083
History of diagnoses before ipratropium initiation			
COPD (ICD-9 code 496)	365 (55)	237 (55)	.975
Asthma (ICD-9 code 493)	277 (42)	139 (32)	.001
Emphysema (ICD-9 code 492)	112 (17)	85 (20)	.236
Chronic bronchitis (ICD-9 codes 490-491)	287 (44)	164 (38)	.083
Acute bronchitis (ICD-9 code 466)	210 (32)	142 (33)	.664
Pneumonia (ICD-9 codes 480-486)	184 (28)	98 (23)	.063
Baseline [†] respiratory-related medical utilization			
Hospitalization/ED visit	150 (23)	70 (16)	.01
Outpatient visit	244 (37)	136 (32)	.073
Baseline [†] prescription use			
Albuterol	226 (34)	68 (16)	<.001
Oral steroids	180 (27)	79 (18)	<.001
Antibiotics	262 (40)	154 (36)	.204

COPD indicates chronic obstructive pulmonary disease; ED, emergency department; ICD-9, *International Classification of Diseases, 9th Revision*.

*P values were obtained from chi-square tests for all dichotomous variables and from a t test for the continuous age variable.

[†]Baseline measures were assessed during the 3-month period before either combined or dual therapy initiation.

was the average monthly number of canisters filled containing albuterol and/or ipratropium during the follow-up period.

Statistical Methods

Chi-square analysis was used for univariate analysis of categorical variables. Change in the incidence of hospitalizations before and after initiation of ipratropium therapy was estimated by using generalized estimating equation techniques for log-linear models. Cox proportional hazards survival analysis models controlled for baseline covariates when risks of ED use or hospitalization were compared between the therapy groups. Compliance analysis used multivariate logistic regression weighted by months of follow-up. Multivariate ordinary least-squares regression was used for the continuous-charge and length-of-stay variables. Analyses of dollar amounts used log-transformed dollars as the dependent variable.

.....
RESULTS

Subjects

The total number of enrollees age 38 years or older in the 5 plans was 420 421, of whom 33 147 had eligible respiratory conditions and at least 12 months of continuous coverage. Of these, 1086 people initiated treatment during or after July 1997 (428 subjects initiated 2-in-1 therapy, 658 initiated separate inhaler therapy).

Baseline characteristics of the 2 study groups are displayed in **Table 1**. Two-in-One and separate inhaler therapy users were equally likely to have a prior COPD diagnosis (55% of subjects). Two-in-One therapy users were on average 4 years older than users of separate inhaler therapy. Those using separate inhalers were significantly more likely to have baseline asthma and pneumonia diagnoses, and to have used albuterol and oral steroids. Baseline respiratory-related hospitalizations and outpatient vis-

Table 2. Hazard Ratios and 95% Confidence Intervals From Cox Proportional Hazards Model of Time Until First Emergency Department Visit or Hospitalization

Independent Variable	Parameter Estimate	Standard Error	Chi-square Test	P	Adjusted* Hazard Ratio	95% Confidence Interval
2-in-1 therapy [†]	-0.538	0.243	4.88	.027	0.58	0.36, 0.94
Baseline respiratory hospitalization/ED visit	0.553	0.245	5.09	.024	1.74	1.08, 2.81
Baseline respiratory outpatient visit	0.057	0.234	0.06	.809	1.06	0.67, 1.67
Baseline albuterol use [‡]	-0.001	0.238	0.00	.998	1.00	0.63, 1.59
Baseline oral steroid use [‡]	-0.051	0.248	0.04	.836	0.95	0.58, 1.54
Baseline antibiotic use [‡]	0.396	0.224	3.14	.077	1.49	0.96, 2.31
History of COPD [§]	0.090	0.239	0.14	.705	1.10	0.69, 1.75
History of asthma [§]	0.437	0.224	3.78	.052	1.55	1.00, 2.40
History of emphysema [§]	0.114	0.265	0.19	.667	1.12	0.67, 1.88
History of chronic bronchitis [§]	0.209	0.226	0.86	.355	1.23	0.79, 1.92
History of acute bronchitis [§]	0.283	0.218	1.69	.193	1.33	0.87, 2.03
History of pneumonia [§]	0.132	0.227	0.34	.562	1.14	0.73, 1.78
Female	-0.311	0.213	2.14	.144	0.73	0.48, 1.11
Age 55-64 [¶]	0.037	0.289	0.02	.898	1.04	0.59, 1.83
Age 65-74 [¶]	0.192	0.287	0.45	.504	1.21	0.69, 2.12
Age 75+ [¶]	0.189	0.346	0.30	.586	1.21	0.61, 2.38

COPD indicates chronic obstructive pulmonary disease; ED, emergency department.

*Adjusted for all other variables in the table.

[†]Estimate is for 2-in-1 therapy relative to separate inhaler therapy. In other words, separate inhaler therapy is the reference group to which 2-in-1 inhaler therapy is being compared, adjusted for all other variables.

[‡]Reference group is nonusers of the particular drug (ie, albuterol, oral steroids, or antibiotics) during the baseline period.

[§]Reference group is individuals without a history of the particular diagnosis.

^{||}Reference group is males.

[¶]Reference group is individuals under age 55 years.

its were more frequent among the separate inhaler therapy users. All analyses presented are adjusted for baseline differences in these covariates.

Risk of Emergency Department Visit or Hospitalization

Overall, in both groups the incidence of ED visits or hospitalization declined from 2.30 to 1.09 per 1000 person-days on initiation of ipratropium therapy ($P < .001$). **Table 2** presents the multivariate survival analysis results. After adjusting for baseline covariates, 2-in-1 therapy users were at significantly less risk of having an ED visit or hospitalization than separate inhaler therapy users (relative risk [RR] = 0.58, 95% confidence interval [CI] = 0.36, 0.94). An

ED visit or hospitalization for a respiratory-related condition in the baseline period was the only other factor significantly associated with an increased risk for ED use or hospitalization in the follow-up period (RR = 1.74, 95% CI = 1.08, 2.81). Furthermore, among those with at least 1 hospitalization, the adjusted mean length of a hospital stay was significantly lower among 2-in-1 therapy users than among separate inhaler therapy users (2.05 days vs 4.61 days, $t = 2.08$, $P = .040$).

Healthcare Charges

The parameter estimates and standard errors from multivariate regression models of average monthly charges (excluding medications) associated with respiratory-related medical diagnoses after initiation of ipratropium therapy are displayed in **Table 3**. Two-in-One therapy users had significantly lower total average monthly charges. After transformation back to normal dollars, the predicted average monthly charge was \$261 for separate inhaler therapy and \$215 for 2-in-1 therapy, an adjusted mean difference in total monthly charges of \$46 per person per month. This estimate was unchanged in models that also controlled for baseline respiratory charges. When categories of charges were examined, the greatest differences between groups were seen for inpatient facilities (\$5.96 per month higher adjusted average monthly charges for separate inhaler therapy; $P < .10$) and physician services (\$4.14 higher for separate inhaler therapy; $P < .05$).

Table 3. Results from Multiple Linear Regression Predicting Log-Transformed Average Monthly Total Charges Associated With Respiratory Diagnoses

Independent Variable	Parameter Estimate*	Standard Error	T	P
Intercept	0.067	0.063	1.06	.290
2-in-1 therapy [†]	-0.124	0.051	-2.44	.015
Baseline respiratory hospitalization/ED visit	0.251	0.064	3.92	<.001
Baseline respiratory outpatient visit	0.470	0.055	8.62	<.001
Baseline albuterol use [‡]	0.357	0.057	6.25	<.001
Baseline oral steroid use [‡]	0.036	0.061	0.59	.558
Baseline antibiotic use [‡]	0.023	0.052	0.44	.658
History of COPD [§]	0.732	0.053	14.03	<.001
History of asthma [§]	0.206	0.052	3.92	<.001
History of emphysema [§]	0.682	0.065	10.48	<.001
History of chronic bronchitis [§]	0.273	0.051	5.34	<.001
History of acute bronchitis [§]	-0.049	0.053	-0.94	.349
History of pneumonia [§]	0.215	0.057	3.80	<.001
Female	0.064	0.049	1.33	.184
Age 55-64 [¶]	0.199	0.065	3.08	.002
Age 65-74 [¶]	0.397	0.064	6.18	<.001
Age 75+ [¶]	-0.075	0.080	-0.95	.344

COPD indicates chronic obstructive pulmonary disease; ED, emergency department.

*Adjusted for all other variables in the table.

[†]Estimate is for 2-in-1 therapy relative to separate inhaler therapy. In other words, separate inhaler therapy is the reference group to which 2-in-1 inhaler therapy is being compared, adjusted for all other variables. After transforming back to normal dollars, the predicted average monthly charge was \$261 for separate inhaler therapy and \$215 for 2-in-1 therapy, for an adjusted mean difference in total monthly charges of \$46 per person per month.

[‡]Reference group is nonusers of the particular drug (ie, albuterol, oral steroids, or antibiotics) during the baseline period.

[§]Reference group is individuals without a history of the particular diagnosis.

^{||}Reference group is males.

[¶]Reference group is individuals under age 55 years.

Charges for Respiratory Medications

Table 4 presents the unadjusted and adjusted average monthly charges submitted during the follow-up period for respiratory medications, according to study group. Separate inhaler users submitted adjusted mean charges that were \$13.97

Table 4. Comparison by Treatment Group of the Average Monthly Charges Submitted for Respiratory Medications After Initiation of Ipratropium Therapy

Category of Respiratory Medication	Monthly Charges (\$)			
	Unadjusted		Adjusted*	
	Separate Inhaler Therapy	2-in-1 Therapy	Separate Inhaler Therapy	2-in-1 Therapy
Oral bronchodilators	0.90	0.84	1.79	1.78
Quick relief bronchodilator inhalers	11.49	2.54	9.48	4.68 [†]
Anticholinergic inhalation aerosols	12.85	7.60	11.46	10.28
Methylxanthines	1.55	1.97	2.46	2.67 [†]
Salmeterol	3.09	1.22	3.28	2.91 [†]
Cromolyn/nedocromil inhalation	6.95	4.51	6.51	5.73
Leukotriene modifiers	0.17	0.14	1.16	1.15
Inhaled corticosteroids	1.70	0.73	2.24	2.11 [†]
Oral corticosteroids	0.48	0.39	1.45	1.41
All respiratory medications	39.19	19.93	42.87	28.90 [§]
All medications containing albuterol and ipratropium	25.18	10.90	23.97	15.66 [†]

*Adjusted for baseline respiratory emergency department visits and hospitalization; baseline outpatient visits; baseline respiratory charges; baseline use of albuterol, oral steroids, and antibiotics; history of chronic obstructive pulmonary disease, asthma, emphysema, acute or chronic bronchitis, and pneumonia; age; and sex.

[†]*P* < .0001.

[‡]*P* < .05.

[§]*P* < .01.

higher per month than 2-in-1 therapy users for all respiratory medications combined; \$8.31 of this difference was accounted for by higher submitted charges for albuterol- and/or ipratropium-containing inhalers. This was expected because the average wholesale price (AWP) for separate inhalers (\$42.84 for 1 canister of Atrovent; \$21.41 for albuterol) exceeds that of 2-in-1 therapy (\$44.87 for Combivent).

Compliance Analysis

Multivariate logistic regression analysis of compliance (ie, having no treatment interruption or discontinuation) found 2-in-1 therapy to be significantly associated with an increased likelihood of compliance, controlling for baseline covariates (OR = 1.77, 95% CI = 1.46, 2.14) (Table 5). Of the other factors associated with higher compliance, 4 were more common among users of separate inhaler therapy (history of asthma, use of oral steroids, use of albuterol, younger age; Table 1), and 1 was more common among 2-in-1 therapy users (no baseline ED/hospital use; Table 1).

Table 6 displays the log-transformed multiple regression analysis of mean canisters of albuterol and/or ipratropium filled per month. Separate inhaler therapy users filled an adjusted average of 0.49 more canisters per month (1.41 vs 0.92 canisters per month; *P* < .0001). Because 2-in-1 therapy includes both ingredients and separate inhaler therapy includes single ingredients, equal compliance would result in twice as many canisters for the latter than for the former. The ratio of canisters filled (1.41 vs 0.92) is less than the 2-to-1 ratio expected under conditions of equal compliance, supporting lower compliance for the separate inhaler therapy group.

Sensitivity Analysis

We considered patients taking ipratropium to be eligible if they had either a COPD or an asthma diagnosis code. However, to evaluate the possibility that the higher frequency of baseline asthma diagnosis (Table 1) might account for our findings, we repeated the analyses for the subgroup of subjects with only a COPD diagnosis (ICD-9 code 496, n = 399). The 2-in-1 therapy parameter estimates were essen-

Table 5. Results From Multivariate Logistic Regression Modeling the Probability of Being Compliant With a Prescription Treatment

Independent Variable	Parameter Estimate	Standard Error	Chi-Square Test	P	Adjusted* Odds Ratio	95% Confidence Interval
Intercept	-3.978	0.144	762.91	<.001	—	—
2-in-1 therapy [†]	0.569	0.099	33.14	<.001	1.77	1.46, 2.14
Baseline respiratory hospitalization/ED visit	-0.471	0.139	11.56	<.001	0.62	0.48, 0.82
Baseline respiratory outpatient visit	0.169	0.105	2.59	.108	1.18	0.96, 1.45
Baseline albuterol use [‡]	0.499	0.108	21.37	<.001	1.65	1.33, 2.03
Baseline oral steroid use [‡]	0.336	0.115	8.51	.004	1.40	1.12, 1.75
Baseline antibiotic use [‡]	-0.439	0.109	16.36	<.001	0.65	0.52, 0.80
History of COPD [§]	0.768	0.115	44.47	<.001	2.16	1.72, 2.70
History of asthma [§]	0.331	0.104	10.19	.001	1.39	1.14, 1.71
History of emphysema [§]	1.615	0.104	242.23	<.001	5.03	4.10, 6.16
History of chronic bronchitis [§]	-0.545	0.107	26.05	<.001	0.58	0.47, 0.72
History of acute bronchitis [§]	0.224	0.105	4.56	.033	1.25	1.02, 1.54
History of pneumonia [§]	0.124	0.111	1.25	.263	1.13	0.91, 1.41
Female	0.007	0.099	0.01	.943	1.01	0.83, 1.22
Age 55-64 [¶]	-0.367	0.134	7.46	.006	0.69	0.53, 0.90
Age 65-74 [¶]	-0.313	0.127	6.11	.013	0.73	0.57, 0.94
Age 75+ [¶]	-0.339	0.165	4.21	.040	0.71	0.52, 0.99

COPD indicates chronic obstructive pulmonary disease; ED, emergency department.

*Adjusted for all other variables in the table.

[†]Estimate is for 2-in-1 therapy relative to separate inhaler therapy. In other words, separate inhaler therapy is the reference group to which 2-in-1 inhaler therapy is being compared, adjusted for all other variables.

[‡]Reference group is nonusers of the particular drug (ie, albuterol, oral steroids, or antibiotics) during the baseline period.

[§]Reference group is individuals without a history of the particular diagnosis.

^{||}Reference group is males.

[¶]Reference group is individuals under age 55 years.

tially unchanged (though the confidence intervals were wider due to reduced power for this subgroup analysis). The adjusted RR of ED/hospital use was 0.54 (95% CI = 0.25, 1.17) for 2-in-1 versus separate inhaler therapy users. The adjusted odds ratio for compliance was 2.62 (95% CI = 1.95, 3.50) for 2-in-1 versus separate inhaler therapy. Thus, consistent with our primary analysis, after adjusting for baseline covariates, 2-in-1 therapy was associated with a lower risk of ED/hospital use and greater likelihood of compliance.

DISCUSSION

Adults who initiated combined ipratropium and albuterol therapy in a single inhaler (2-in-1 therapy) had lower healthcare charges and were less likely to make an ED visit or be hospitalized for a

respiratory-related event, and had subsequent shorter hospital stays, compared with those who initiated therapy using 2 separate inhalers (separate inhaler therapy). Compliance analyses found significantly fewer treatment interruptions and discontinuations among two-in-one therapy users. Also supporting the finding of lower compliance in the separate inhaler therapy group was the fact that the ratio of the average number of albuterol and/or ipratropium canisters dispensed per month for separate versus two-in-one therapy was less than the 2-to-1 ratio expected based on the dual-ingredient versus single-ingredient formulations. These findings are consistent with the findings of less use of acute care and lower total charges for the two-in-one therapy group. One explanation for these findings is that better synergy of therapeutic effect results from a more consistent combined use of albuterol and ipratropium in the 2-in-1 group.

Table 6. Results from Multiple Regression Model Predicting the Log-Transformed Average Monthly Number of Canisters Filled for Inhalers Containing Albuterol and/or Ipratropium After Initiation of Ipratropium Therapy

Independent Variable	Parameter Estimate	Standard Error	T	P
Intercept	0.16363	0.01862	8.79	<.0001
2-in-1 therapy*	-0.17742	0.01493	-11.88	<.0001
Baseline respiratory hospitalization/ED visit	-0.03206	0.01879	-1.71	.0880
Baseline respiratory outpatient visit	0.08276	0.01602	5.17	<.0001
Baseline albuterol use [†]	0.29581	0.01680	17.61	<.0001
Baseline oral steroid use [†]	0.01724	0.01804	0.96	.3391
Baseline antibiotic use [†]	-0.01366	0.01517	-0.90	.3679
History of COPD [‡]	0.14352	0.01532	9.37	<.0001
History of asthma [‡]	0.04307	0.01540	2.80	.0052
History of emphysema [‡]	0.27380	0.01911	14.33	<.0001
History of acute bronchitis [‡]	0.02458	0.01503	1.63	.1021
History of chronic bronchitis [‡]	-0.07297	0.01542	-4.73	<.0001
History of pneumonia [‡]	-0.00862	0.01663	-0.52	.6043
Female [§]	0.00301	0.01426	0.21	.8326
Age 55-64	0.01536	0.01899	0.81	.4186
Age 65-74	-0.00480	0.01884	-0.25	.7989
Age 75+	0.03289	0.02340	1.41	.1599

COPD indicates chronic obstructive pulmonary disease; ED, emergency department.

*Estimate is for 2-in-1 therapy relative to separate inhaler therapy. In other words, separate inhaler therapy is the reference group to which 2-in-1 inhaler therapy is being compared, adjusted for all other variables. After transformation back to a normal count of canisters, the predicted average monthly number of canisters filled for individuals using separate inhaler therapy is 1.41 and the predicted average monthly number of canisters filled for individuals using 2-in-1 therapy is 0.92, for a difference of 0.49.

[†]Reference group is nonusers of the particular drug (ie, albuterol, oral steroids, or antibiotics) during the baseline period.

[‡]Reference group is individuals without a history of the particular diagnosis.

[§]Reference group is males.

^{||}Reference group is individuals under age 55 years.

Alternative explanations for these findings include unequal surveillance for study outcomes or selection bias. These possibilities are discussed below.

Information bias from unequal surveillance for study outcomes is a potential limitation in retrospective studies. We protected against this possibility by choosing a measure of severe respiratory exacerbation (ie, requiring an ED visit or hospitalization). It is unlikely that exacerbation severe enough to require urgent care would be underdetected in either study group.

Another potential limitation of retrospective studies of treatment effects is selection bias. Two-in-One therapy users were older (associated with a nonsignificant but slightly increased risk of ED and hospital use) and also had lower baseline healthcare utilization (associated with decreased risk) than separate inhaler therapy users. However, after controlling for age, diagnoses, other drug therapy, baseline healthcare utilization, and baseline charges, use of 2-in-1 therapy remained significantly associated with a decreased risk of ED and

hospital use. With respect to the compliance analyses, several factors associated with increased compliance occurred more frequently in the separate inhaler therapy group, which would bias against finding a difference between treatment groups. This discrepancy was partially balanced by one factor associated with decreased compliance (baseline ED visit/hospitalization) that was more common in the separate inhaler therapy group. Again, after controlling for these covariates, 2-in-1 therapy remained significantly associated with increased compliance. Similarly, after adjusting for baseline differences, the difference in the number of albuterol and ipratropium canisters filled was less than what would be expected if compliance with therapy using separate canisters were as high as compliance with 2-in-1 therapy.

We included subjects with a broad range of respiratory diagnoses because the diagnoses of chronic bronchitis, emphysema, and COPD often overlap with asthma.⁶ We assumed that patients treated with ipratropium who only had an asthma diagnosis

probably also were being treated for COPD because of the known ambiguities of diagnosis coding in this age group. In a review of the epidemiologic literature, we found 11 papers that used ICD-9 codes as a case definition for COPD.⁷⁻¹⁷ Of these, 2 included only ICD-9 code 496 (COPD),^{12,13} The remaining 9 papers all included codes 491-492 and 496, and 7 papers additionally included code 490.^{8-11,14-16} Two studies also included asthma (ICD-9 code 493). Including a broad range of diagnoses, while compatible with what was done in other studies, resulted in an imbalance between treatment groups in baseline prevalence of asthma diagnoses. However, when we conducted sensitivity analyses restricted to subjects with only a COPD diagnosis, the parameter estimates were comparable with those of the full sample. Hence, the difference between treatment groups in baseline asthma diagnosis is not an explanation for our findings.

Control for disease severity has been a dilemma in previous studies of respiratory medications among current users^{18,19} because disease severity may be an intervening variable in the causal pathway between level of medication use and outcome. Controlling for this intervening variable "controls away" the basic mechanism through which enhanced compliance exerts its effect. To avoid this bias, we adjusted for measures of disease severity that preceded treatment by using an inception cohort design.

The inception cohort design also prevented a prevalence-incidence bias that can occur in studies where current (prevalent) users of particular treatments are compared rather than new (incident) users. This is because individuals who are dissatisfied with treatment are most likely to quickly discontinue therapy and be underrepresented among current users. This can lead to biased estimation of relative effectiveness because mainly satisfied patients are compared.

CONCLUSION

A posthoc pharmacoeconomic analysis of exacerbations and healthcare use in 2 randomized, controlled trials found that ipratropium improves lung function and reduces COPD exacerbations and hospital days when added to β_2 -agonist therapy.³ Whether this benefit continues to be realized in uncontrolled, real-world use has not been previously studied. Further, the impact of a 2-in-1 inhaler on compliance and treatment effectiveness has not been previously studied. Our findings indicate that

in the circumstances of real-world use, ipratropium (either as 2-in-1 inhaler or separate inhaler therapy) decreases the incidence of severe exacerbations and healthcare use and that 2-in-1 therapy is associated with a further decrease in risk.

Initiation of combined ipratropium and albuterol therapy in a single inhaler (2-in-1 therapy) was associated with a reduced risk of respiratory-related ED or hospital use and with reduction in hospital length of stay and healthcare charges compared with initiation of separate ipratropium and albuterol prescriptions (separate inhaler therapy). Improved compliance with the simpler delivery system was supported by (1) a higher probability of therapy interruption or discontinuation with separate inhaler therapy and (2) a lower ratio of albuterol and/or ipratropium canisters filled (1.41 canisters for separate therapy vs 0.92 canister for 2-in-1 therapy) than would be expected if compliance were equal between the groups (2 canisters of separate therapy to every 1 canister of 2-in-1 therapy). Collectively, these analyses suggest that a combined delivery system of ipratropium and albuterol in a single inhaler can significantly decrease the morbidity and financial burden associated with chronic airway disease over and above the effect observed from therapy with separate single ingredient inhalers of these two agents.

REFERENCES

1. Bone R, Boyars M, Braun SR, et al, for the Combivent Inhalation Aerosol Study Group. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. An 85-day multicenter trial. *Chest*. 1994;105:1411-1419.
2. Dorinsky PM, Reisner C, Ferguson GT, Menjoge SS, Serby CW, Witek TJ Jr. The combination of ipratropium and albuterol optimizes pulmonary function reversibility testing in patients with chronic obstructive pulmonary disease. *Chest*. 1999;115:966-971.
3. Friedman M, Serby CW, Menjoge SS, Wilson JD, Hilleman DE, Witek TJ Jr. Pharmacoeconomic evaluation of a combination of ipratropium plus albuterol compared with ipratropium alone in COPD. *Chest*. 1999;115:635-641.
4. Gross N, Tashkin D, Miller R, Oren J, Coleman W, Linberg S. Inhalation by nebulization of albuterol-ipratropium combination (Dey combination) is superior to either agent alone in the treatment of COPD. Dey Combination Solution Study Group. *Respiration*. 1998;65(5):354-362.
5. Tashkin DP. Multiple dose regimens: Impact on compliance. *Chest*. 1995;107:176S-182S.
6. Osborne ML, Vollmer WM, Buist AS. Periodicity of asthma, emphysema, and chronic bronchitis in a northwest health maintenance organization. *Chest*. 1996;110:1458-1462.
7. Kraut A, Wald R, Mustard C. Prevalence of physician-diagnosed asthma by occupational groupings in Manitoba, Canada. *Am J Ind Med*. 1997;32:275-282.
8. Tager IB, Segal MR. Temporal trends in chronic obstructive lung

disease case fatality in hospitalized US veterans: 1970-1987. *Chest*. 1991;99:1126-1133.

9. Vilkman Sirkku, Keistinen T, Tuuponen T, Kivela S. Age distribution of patients treated in hospital for chronic obstructive pulmonary disease. *Age Aging*. 1996;25:109-112.

10. Vestbo J, Prescott E, Lange P, Schnohr P, Jensen G. Vital prognosis after hospitalization for COPD: A study of a random population sample. *Respir Med*. 1998;92:772-776.

11. Cooreman J, Thom TJ, Higgins MW. Mortality from chronic obstructive pulmonary diseases and asthma in France, 1969-1983: Comparisons with the United States and Canada. *Chest*. 1990;97:213-219.

12. Meijers JM, Swaen GMH, Slangen JJM. Mortality of Dutch coal miners in relation to pneumoconiosis, chronic obstructive pulmonary disease, and lung function. *Occup Environ Med*. 1997;54:708-713.

13. Rawson NSB, Malcolm E. Validity of the recording of ischaemic heart disease and chronic obstructive pulmonary disease in the Saskatchewan Healthcare data files. *Stat Med*. 1995;14:2627-2643.

14. Anderson HR, Spix C, Medina S, et al. Air pollution and daily admissions for chronic obstructive pulmonary disease in 6 European cities: Results from the APHEA project. *Eur Respir J*. 1997;10:1064-1071.

15. Wever-Hess J, Wever AMJ, Yntema JL. Mortality and morbidity from respiratory diseases in childhood in the Netherlands, 1980-7. *Eur Respir J*. 1991;4:429-433.

16. Cydulka RK, McFadden ER, Emerman CL, Sivinski LD, Pisanelli W, Rimm AA. Patterns of hospitalization in elderly patients with asthma and chronic obstructive pulmonary disease. *Am J Respir Care Med*. 1997;156:1807-1812.

17. Wever-Hess J, Wever AMJ. Asthma statistics in the Netherlands 1980-94. *Respir Med*. 1997;91:417-422.

18. Spitzer WO, Suissa S, Ernst P, et al. The use of b-agonists and the risk of death and near death from asthma. *N Engl J Med*. 1992;326:501-506.

19. Van Ganse E, Hubloue I, Vincken W, et al. Actual use of inhaled corticosteroids and risk of hospitalisation: A case-control study. *Eur J Clin Pharmacol*. 1997;51:449-454.