

GSK Medicine: Fluticasone propionate, beclomethasone, salmeterol, fluticasone propionate/salmeterol
Study No: WWE112876/WEUKBRE1156/EPI40468
Title: Pneumonia and upper respiratory tract infections among COPD patients using fluticasone propionate/salmeterol in combination (ADVAIR®) versus other inhaled corticosteroids and bronchodilators alone
Rationale: In the recently published TORCH study, patients randomized to fluticasone propionate and salmeterol/fluticasone propionate/ in combination were found to have a small but significantly increased risk of pneumonia. This finding has raised several questions about the possible association between inhaled corticosteroid (ICS) use and the risk for pneumonia in COPD.
Objectives: The objective is to evaluate the risk of pneumonia associated with ICS, used with and without a long-acting beta-agonist (LABA) in a population-based COPD cohort.
Indication:
Study Investigators/Centers: Lovelace Clinic Foundation and GlaxoSmithKline
Research Methods:
Study Design: The first phase of this project was a cohort analysis. The second phase was a case-control approach with closely matched pneumonia cases and at-risk controls "nested" within the cohort of individuals diagnosed with COPD in the administrative claims dataset. The final phase of this project explored associations between pneumonia rates and the major COPD inhaler therapies.
Data Source: COPD patients were identified from three administrative healthcare claims databases in the US.
Study Population: Cohort Definition: COPD patients were identified using ICD-9 diagnosis codes, and were continuously enrolled in their health plan from September 1, 2000 until August 31, 2001. All study subjects were required to have one inpatient visit or two outpatient visits on separate days for COPD during the baseline year. Participants were also required to have been dispensed at least one of the respiratory drugs used to treat COPD at any time during the study period, including inhaled corticosteroids, long-acting beta agonists and short-acting bronchodilators based on the NDC for all drugs within these classes. COPD patients with other chronic lung diseases (ie: coal workers pneumoconiosis or idiopathic pulmonary fibrosis) not typically included in the classification of COPD were excluded. A total of 5245 individuals were included in the study cohort.
Pneumonia Definition: Pneumonia cases were defined as a pneumonia diagnosis with evidence of a confirming chest x-ray or a diagnosis made in an inpatient setting. We identified 2154 individuals with at least one pneumonia event during the study period (9/01/00 through 8/31/03). Case and Control Definition Cases were defined as persons who had a pneumonia event after September 1, 2001 (the end of the baseline year). Pneumonia events in the baseline year (9/01/00 -8 /31/01) were included as covariates in the analysis. Controls were randomly selected from the matched risk set for each case. The matching criteria were: 1) date of COPD diagnosis for the case + 30 days (same entry point); 2) age + 1 year; and 3) gender. Controls were matched with a 1:4 ratio, matching up to four controls per case. Study Exposures, Cohort Analysis: Patients were classified into the following drug treatment categories based on all pharmacy dispensings in the treatment period: 1) ADVAIR only users, 2) ICS only users, 3) LABA only users, 4) ICS / LABA users, 5) ADVAIR & ICS users (typically ICS initial use then switched to ADVAIR but not for all cases), 6) ADVAIR & LABA, 7) ADVAIR & ICS & LABA, and) short-acting bronchodilators (SABD) only. We conducted a subanalysis where an initial 60-day period with no

respiratory drug dispensings was imposed as the exposure-free period to eliminate those patients who may have been on a particular drug prior to 9/01/00. We defined the treatment index date as the date of the first respiratory treatment. The time period between the index date and the first pneumonia event is referred to as the treatment period.

Case-Control Analysis: In the case-control analysis focusing on any exposure (dispensings) in the 90 day period prior to the event, the following categories were identified: ADVAIR, ADVAIR and ICS, ADVAIR and LABA, ICS with LABA, ICS without LABA, LABA without ICS, no treatment, and SABD. The categories were mutually exclusive.

Confounders: Covariates measured in the baseline (period prior to cohort entry for cohort analyses and period prior to pneumonia date for case control analyses) were age, gender, asthma diagnosis, Charlson-Deyo co-morbidity score, COPD hospitalizations, the number of emergency department visits for COPD, the number of outpatient encounters for COPD, prior pneumonia, and oral corticosteroid use.

Data Analysis Methods:

Cohort Analysis: The first cohort analysis, focused on a traditional Cox proportional hazards model (CPH). Seven separate models were generated each using the SABD alone group as the reference cohort based on the drug or combination of drugs taken prior to the first hazard event (pneumonia or censored): 1) ADVAIR only vs. SABD, 2) ADVAIR/ ICS vs. SABD, 3) ADVAIR/LABA vs. SABD, 4) ADVAIR / ICS / LABA vs. SABD, 5) ICS alone vs. SABD, 6) ICS/LABA vs. SABD, and 7) LABA alone vs. SABD. The final cohort consisted of 3091 individuals with no pneumonia diagnoses during the study period (9/01/00 through 8/31/03) and 2154 individuals with at least one pneumonia event (including before or after onset of initial treatment for COPD). We also repeated the analysis with a imposed 60-day exposure-free period to increase the odds that exposures were truly incident.

The second cohort analysis used the propensity score method to match patients in the treatment group with similar individuals in the reference group in order to minimize potential selection bias.

Treatment groups were matched to SABD on site, sex, age, # of COPD outpatient visits, # of COPD in-patient admissions, # of COPD emergency room visits and Charlson-Deyo comorbidity. Seven proportional hazards models were generated using the propensity score matched cohort data, adjusting for the same covariates used in the traditional proportional hazards models.

Case Control Analysis: Counts and frequency distributions of demographic and severity measures were presented for cases and controls. The nested case-control data were analyzed using conditional logistic regression for 1:4 matched case-control using the SAS PHREG procedure with the ties=discrete option and each risk set defined as a unique strata.

Rate Analysis: A historical cohort design was used to calculate pneumonia rates by 60-day intervals. Considering low compliance rates in this population, this approach can illustrate what proportion of pneumonias occur soon after initiation of therapy. Because patients can be on several different medications at the same time, switch from medication to medication, or start and stop the same medication, the population was divided into several exposure (treatment) categories.

Limitations: The classification scheme for the cohort analysis has some important limitations. For the combination treatment groups, it does not take into account dose frequency ratios over the treatment period (one individual might have one dispensing fill for ICS and ten for ADVAIR while another may have ten ICS fills and one ADVAIR), nor does it take into account the order of treatments (e.g. ICS first then ADVAIR or ADVAIR then ICS). For all groups, it does not account for different dosages or compliance during the treatment period. Furthermore the rate analysis is not adjusted for the many factors associated with pneumonia susceptibility.

Study Results:

Cohort Analysis: The following are the major findings from both the unmatched cohort with a 60 day exposure-free period and the propensity score matched cohorts.

ADVAIR users had a consistently lower risk of pneumonia as compared to patients in the SABD group. Older age was a risk factor for pneumonia. Patients aged 73 years and older had approximately twice the risk of those in the 40 to 56 age group (Tables 3-4). Men had a slightly higher risk of pneumonia yet this was not significant in all models. An increased numbers of outpatient visits during the baseline year were associated with increased risk of subsequent pneumonia. A history of oral corticosteroid use in the baseline year was consistently associated with an increased pneumonia risk. Asthma was associated with a non-statistically significant increased risk of pneumonia. Emergency department visits and hospitalizations for COPD during the baseline year were associated with a higher risk of subsequent pneumonia in some models. Use of ICS alone was not associated with pneumonia in any model. The combination of ICS and LABA was also associated with a reduced risk of pneumonia with risk estimates that were similar to those of ADVAIR (not statistically significant in the propensity score models).

Nested Case Control Analysis: ADVAIR was not significantly associated with either an increased or decreased risk of pneumonia. A reduced risk of pneumonia was associated with the ICS and LABA combination group for the prior 180 day (OR=0.566, p<0.05) and 365 day exposure windows (OR= 0.651, p<0.05), but not for the 90 day exposure window (OR=0.580, p = 0.1). The ICS without LABA treatment group was associated with a non-statistically significant elevation in odds of pneumonia (OR=1.29; 95% CI: 0.96, 1.73; p=0.088).(Table 7)

Pneumonia Rate Analysis: Patients treated with short acting bronchodilators alone had the highest initial (pneumonia occurring in the 0-60 days after exposure) pneumonia rate (6.1%). Those who used inhaled corticosteroids without long-acting bronchodilators had a similar initial pneumonia rate (5.7%). Patients who used long-acting bronchodilators (over 90% salmeterol), either alone or in some combination with ICS, had the lowest initial pneumonia rate (2.8%). Those who used ADVAIR had an initial rate of 4.0%, but in time periods after 60 days they had among the lowest rates of pneumonia of any cohort. ADVAIR had the best compliance at 180 and 360 days treatment of any therapy (Table 8-9).

Table 1: Baseline Characteristics of COPD Subjects by Treatment Criteria For example., non-exposed, controls, other comparator group(s)/ subgroup(s) as per design and analysis.

Cohort characteristics (Unmatched N=5245)	ANY ADVAIR N=1239	ICS/LAB A N=253	ICS alone N=1236	LABA alone N=466	SABD alone N=2051
HMO member (%)					

Health System 1 N=843	218 (17.6)	23 (9.1)	307 (24.8)	8 (1.7)	287 (14.0)
Health System 2 N=1806	455 (36.7)	81 (32.0)	611 (49.4)	33 (7.1)	626 (30.5)
Health System 3 N=2596	566 (45.7)	149 (58.9)	318 (25.7)	425 (91.2)	1138 (55.5)
Mean age, yr [SD] (95% CI)	64.8 [10.6] (64.2, 65.4)	67.1 [9.5] (65.9, 68.3)	67.8 [10.8] (67.2, 68.4)	65.4 [9.9] (64.5, 66.3)	68.0 [10.7] (67.5, 68.4)
Age group (%)					
40 – 56 (N=940)	299 (24.1)	32 (12.6)	204 (16.5)	79 (17.0)	326 (15.9)
57 – 65 (N=1247)	322 (26.0)	77 (30.4)	249 (20.1)	156 (33.5)	443 (21.6)
66 – 72 (N=1265)	282 (22.8)	65 (25.7)	314 (25.4)	106 (22.7)	498 (24.3)
73 + (N=1793)	336 (27.1)	79 (31.2)	469 (37.9)	125 (26.8)	784 (38.2)
Male, N=2428 (%)	566 (45.7)	96 (37.9)	538 (43.5)	206 (44.2)	1022 (49.8)
COPD outpatient visits in baseline year (%)					
0 – 2	336 (27.1)	54 (21.3)	407 (32.9)	142 (30.5)	892 (43.5)
3 – 4	337 (27.2)	69 (27.3)	328 (26.5)	105 (22.5)	513 (25.0)

5 – 12	362 (29.2)	75 (29.6)	296 (24.0)	152 (32.6)	412 (20.1)
13 +	204 (16.5)	55 (21.7)	205 (16.6)	67 (14.4)	234 (11.4)
At least one COPD ED visit in baseline year (%)	154 (12.4)	35 (13.8)	126 (10.2)	68 (14.6)	249 (12.1)
At least one COPD Inpatient admit in baseline year (%)	215 (17.4)	44 (17.4)	219 (17.7)	60 (12.9)	285 (13.9)
Charlson-Deyo Outpatient Index >= 1 in baseline year (%)	420 (33.9)	85 (33.6)	464 (37.5)	186 (39.9)	754 (36.8)

Table 2: Baseline Characteristics of Cohort Subjects According to Treatment Group Status at 1st Event. (Pneumonia/Censored) for Propensity Score Matched Cohorts. (Index date = 1st treatment after 60 day exposure free period after 9/01/00)

Cohort characteristics (Unmatched N=2847)	ADVAI R Only N=309	ADVAI R & ICS N=162	ADVAI R & LABA N=127 4	ADVAI R & ICS & LABA N=116	ICS/ LAB A N=14 2	ICS alon e N=69 6	LABA alone N=296	SABD alone N=999
# of COPD outpatient visits in baseline year (%)								
0 – 2	114 (36.9)	56 (34.6)	39 (30.7)	27 (23.3)	39 (27.5)	277 (39.8)	104 (35.1)	407 (40.7)
3 – 4	95 (30.7)	53 (32.7)	28 (22.1)	37 (31.9)	40 (28.2)	197 (28.3)	71 (24.0)	270 (27.0)
5 – 12	65 (21.0)	34 (21.0)	50 (39.4)	40 (34.5)	39 (27.5)	151 (21.7)	91 (30.7)	209 (20.9)

13 +	35 (11.3)	19 (11.7)	10 (7.9)	12 (10.3)	24 (16.9)	71 (10.2)	30 (10.1)	113 (11.3)
At least one COPD ED visit in baseline year (%)	27 (8.7)	16 (9.9)	15 (11.8)	13 (11.2)	19 (13.4)	62 (8.9)	38 (12.8)	115 (11.5)
At least one COPD Inpatient admit in baseline year (%)	35 (11.3)	24 (14.8)	10 (7.9)	11 (9.5)	18 (12.7)	118 (17.0)	29 (9.8)	165 (16.5)
Charlson-Deyo Outpatient Index >= 1 in baseline year (%)	92 (29.8)	64 (39.5)	34 (26.8)	39 (33.6)	40 (28.2)	246 (35.3)	112 (37.8)	377 (37.7)

Table 3: Cox Proportional Hazards Models for the Unmatched Cohorts versus the SABD Cohort. Single Pneumonia Event Model. (Index date is 1st treatment after 60 day exposure free period after 9/01/00)

	Advair Only			Advair & ICS			Advair & LABA			Advair & ICS & LABA		
Variable	Odd s Ratio	95% Confidence Limits		Odd s Rati o	95% Confidenc e Limits		Odd s Rati o	95% Confiden ce Limits		Odd s Rati o	95% Confiden ce Limits	
SABD (reference)	1.0	---		1.0	---		1.0	---		1.0	---	
Treatment	0.62 4*	0.46 2	0.844	0.40 1*	0.27 3	0.5 89	0.62 1*	0.3 94	0.9 80	0.27 4*	0.1 66	0.4 55
40-56 years old	1.0	---		1.0	---		1.0	---		1.0	---	
57-65 years old	1.51 3*	1.06 3	2.153	1.31 5	0.92 9	1.8 61	1.43 4*	1.0 02	2.0 50	1.26 3	0.8 84	1.8 03
66-72 years old	1.72 6*	1.22 3	2.436	1.50 0*	1.07 0	2.1 03	1.58 9*	1.1 16	2.2 62	1.45 9*	1.0 35	2.0 57
73+ years old	2.11 9*	1.53 1	2.932	1.81 4*	1.32 4	2.4 84	2.06 4*	1.4 82	2.8 73	1.81 3*	1.3 14	2.5 02

Female	1.0	---	---	1.0	---	---	1.0	---	---	1.0	---	---
Male	1.181	0.982	1.420	1.249*	1.035	1.508	1.224*	1.012	1.482	1.225*	1.011	1.484
<3 COPD outpatient encounters	1.0	---	---	1.0	---	---	1.0	---	---	1.0	---	---
3-4 COPD outpatient encounters	1.029	0.807	1.212	0.991	0.773	1.271	1.025	0.798	1.316	0.988	0.767	1.272
5-12 COPD outpatient encounters	1.418*	1.107	1.816	1.334*	1.034	1.722	1.293*	1.001	1.671	1.317*	1.017	1.706
13+ COPD outpatient encounters	1.598	1.177	2.170	1.728*	1.273	2.346	1.622*	1.181	2.227	1.630*	1.187	2.237
No COPD emergency dept. encounter	1.0	---	---	1.0	---	---	1.0	---	---	1.0	---	---
≥ 1 COPD emergency dept. encounter	1.314*	1.017	1.697	1.282	0.988	1.664	1.305*	1.004	1.696	1.306*	1.004	1.698
No COPDD hospitalization	1.0	---	---	1.0	---	---	1.0	---	---	1.0	---	---
≥ 1 COPD hospitalization	1.276	0.996	1.636	1.233	0.960	1.584	1.295*	1.003	1.673	1.261	0.976	1.630
Charlson score = 0	1.0	---	---	1.0	---	---	1.0	---	---	1.0	---	---

Charlson score ≥ 1 based on outpatient encounters	1.102	0.906	1.341	1.136	0.930	1.387	1.134	0.925	1.390	1.135	0.925	1.392
No Asthma	1.0	---	---	1.0	---	---	1.0	---	---	1.0	---	---
Asthma	1.313	0.995	1.732	1.248	0.940	1.656	1.204	0.896	1.619	1.326	0.994	1.771
No Oral Steroid Use	1.0	---	---	1.0	---	---	1.0	---	---	1.0	---	---
Oral steroid use	1.316*	1.076	1.610	1.385*	1.127	1.702	1.344*	1.090	1.657	1.374*	1.113	1.696
No Pneumonia before treatment	1.0	---	---	1.0	---	---	1.0	---	---	1.0	---	---
Pneumonia before treatment	1.306*	1.047	1.627	1.329*	1.063	1.662	1.270*	1.001	1.594	1.294*	1.030	1.625

*Significant at the 0.05 level

Table 4: Cox Proportional Hazards Models for the Unmatched Cohorts versus the SABD Cohort Continued. Single Pneumonia Event Model. (Index date is 1st treatment after 60 day exposure free period after 9/01/00)

Variable	ICS Only		ICS & LABA			LABA Only			
	Odds Ratio	95% Confidence Limits		Odds Ratio	95% Confidence Limits		Odds Ratio	95% Confidence Limits	
SABD (reference)	1.0	-----	-----	1.0	-----	-----	1.0	-----	-----
Treatment	1.017	0.862	1.199	0.622*	0.437	0.888	0.843	0.650	1.094
40-56 years old	1.0	---	---	1.0	---	---	1.0	---	---
57-65 years old	1.248	0.947	1.644	1.308	0.922	1.855	1.091	0.794	1.500

66-72 years old	1.427*	1.090	1.869	1.479*	1.052	2.081	1.304	0.95 5	1.779
73+ years old	1.715*	1.337	2.199	1.850*	1.344	2.547	1.627*	1.21 9	2.172
Female	1.0	---	---	1.0	---	---	1.0	---	---
Male	1.282*	1.102	1.490	1.205	0.999	1.454	1.297*	1.08 3	1.553
<3 COPD outpatient encounters	1.0	---	---	1.0	---	---	1.0	---	---
3-4 COPD outpatient encounters	0.991	0.812	1.208	1.028	0.803	1.317	1.048	0.82 6	1.329
5-12 COPD outpatient encounters	1.298*	1.061	1.589	1.281	0.990	1.658	1.317*	1.03 5	1.675
13+ COPD outpatient encounters	1.528*	1.197	1.952	1.727*	1.277	2.334	1.742*	1.29 9	2.336
No COPD emergency dept. encounter	1.0	---	---	1.0	---	---	1.0	---	---
≥ 1 COPD emergency dept. encounter	1.423*	1.148	1.764	1.337*	1.036	1.725	1.197	0.93 4	1.533
No COPD hospitalization	1.0	---	---	1.0	---	---	1.0	---	---
≥ 1 COPD hospitalization	1.482*	1.226	1.792	1.262	0.983	1.620	1.326*	1.04 4	1.683
Charlson Score = 0	1.0	---	---	1.0	---	---	1.0	---	---
Charlson score ≥ 1 based on outpatient encounters	1.211*	1.034	1.418	1.143	0.937	1.395	1.191	0.98 6	1.440
No Asthma	1.0	---	---	1.0	---	---	1.0	---	---
Asthma	1.274*	1.037	1.563	1.236	0.931	1.640	1.327*	1.02 2	1.724

No Oral steroid use	1.0	---	---	1.0	---	---	1.0	---	---
Oral steroid use	1.280*	1.089	1.506	1.366*	1.112	1.678	1.359*	1.116	1.654
No Pneumonia before treatment	1.0	---	---	1.0	---	---	1.0	---	---
Pneumonia before treatment	1.316*	1.088	1.592	1.337*	1.070	1.671	1.289*	1.036	1.604

*Significant at the 0.05 level.

Table 5: Baseline Characteristics of Pneumonia Cases According to Treatment Group. Status 90 Days Prior to Pneumonia Case Date

Case Cohort*	ADVAIR	ICS	LABA	ICS/LAB A	SABD	None
HMO (%)						
Health System 1	52 (40.3)	150 (62.2)	7 (7.3)	8 (44.4)	191 (40.2)	186 (37.9)
Health System 2	33 (25.6)	64 (26.6)	0 (0)	0 (0)	49 (10.3)	97 (19.8)
Health System 3	44 (34.1)	27 (11.2)	89 (92.7)	10 (55.6)	235 (49.5)	208 (42.4)
Mean age, yr	66.8	69.7	66.4	65.1	70.3	69.8
[Median]	[67.0]	[71.0]	[67.0]	[64.5]	[71.0]	[72.0]
(95% CI)	(65.0, 68.6)	(68.4, 71.0)	(64.4, 68.3)	(61.2, 69.0)	(69.4, 71.1)	(68.9, 70.8)
Age group (%)						
40 -5 6	23 (17.8)	30 (12.5)	17 (17.7)	2 (11.1)	47 (9.9)	56 (11.4)
57 -6 5	35 (27.7)	39 (16.2)	25 (26.0)	7 (38.9)	85 (17.9)	95 (19.4)

66 - 72	28 (21.7)	62 (25.7)	25 (26.0)	6 (33.3)	127 (26.7)	105 (21.4)
73 +	43 (33.3)	110 (45.6)	29 (30.2)	3 (16.7)	216 (45.5)	235 (47.9)
Male (%)	63 (48.8)	117 (48.6)	38 (39.6)	8 (44.4)	219 (46.1)	256 (52.1)
COPD outpatient visits (%)						
0 - 2	24 (18.6)	59 (24.5)	8 (8.3)	3 (16.7)	123 (25.9)	226 (46.0)
3 - 4	17 (13.2)	38 (15.8)	16 (16.7)	4 (22.2)	75 (15.8)	73 (14.9)
5 - 12	48 (37.2)	71 (29.5)	39 (40.6)	5 (27.8)	134 (28.2)	105 (21.4)
13 +	40 (31.0)	73 (30.3)	33 (34.4)	6 (33.3)	143 (30.1)	87 (17.7)
At least one COPD ED visit (%)	32 (24.8)	38 (15.8)	35 (36.5)	6 (33.3)	115 (24.2)	79 (16.1)
At least one COPD inpatient admit (%)	61 (47.3)	104 (43.2)	47 (49.0)	9 (50.0)	195 (41.1)	110 (22.4)
Charlson-Deyo Outpatient Index >= 1 in prior year (%)	54 (41.9)	93 (38.6)	46 (47.9)	7 (38.9)	204 (43.0)	236 (48.1)

Cases: 1474 out of 1478 possible. Matched on age, gender, COPD diagnosis date.

* Excludes 4 cases not matched, 19 in ADVAIR/ICS group, 5 in ADVAIR/LABA group

Table 6: Baseline Characteristics of Matched Controls According to Treatment Group. Status 90 Days Prior to Pneumonia Case Date

Control Cohort*	ADVAIR	ICS	LABA	ICS/LAB A	SABD	None
HMO (%)						
Health System 1	34 (9.4)	73 (21.0)	8 (1.3)	7 (6.5)	120 (6.2)	401 (6.9)
Health System 1	3 (0.8)	14 (4.0)	0 (0)	0 (0)	11 (0.6)	50 (0.9)
Health System 1	324 (89.8)	260 (74.9)	613 (98.7)	101 (93.5)	1821 (93.3)	5345 (92.2)
Mean age, yr	67.3	68.7	66.8	66.6	70.1	69.9
[Median]	[67.0]	[70.0]	[67.0]	[66.0]	[71.0]	[72.0]
(95% CI)	(66.3, 68.4)	(67.5, 69.9)	(66.1, 67.6)	(64.9, 68.2)	(69.7, 70.5)	(69.5, 70.3)
Age group (%)						
40 – 56	62 (17.2)	60 (17.3)	70 (11.3)	10 (9.3)	177 (9.1)	287 (11.9)
57 – 65	70 (19.4)	76 (21.9)	210 (33.8)	33 (30.6)	358 (18.3)	416 (17.3)
66 – 72	99 (27.4)	57 (16.4)	149 (24.0)	43 (39.8)	526 (27.0)	618 (25.7)
73 +	130 (36.0)	154 (44.4)	192 (30.9)	22 (20.4)	891 (45.7)	1086 (45.1)
Male (%)	168 (46.5)	158 (45.5)	261 (42.0)	49 (45.4)	945 (48.4)	1219 (50.6)
COPD outpatient visits (%)						

0 – 2	107 (29.6)	152 (43.8)	158 (25.4)	24 (22.2)	672 (34.4)	1420 (59.0)
3 – 4	65 (18.0)	64 (18.4)	149 (24.0)	25 (23.2)	408 (20.9)	490 (20.4)
5 – 12	119 (33.0)	91 (26.2)	203 (32.7)	52 (48.2)	620 (31.8)	335 (13.9)
13 +	70 (19.4)	40 (11.5)	111 (17.9)	7 (6.5)	252 (12.9)	162 (6.7)
At least one COPD ED visit (%)	44 (12.2)	31 (8.9)	70 (11.3)	15 (13.9)	292 (15.0)	207 (8.6)
At least one COPD inpatient admit (%)	35 (9.7)	20 (5.8)	50 (8.0)	16 (14.8)	193 (9.9)	131 (5.4)
Charlson-Deyo Outpatient Index >= 1 in prior year (%)	102 (28.2)	104 (30.0)	246 (39.6)	28 (25.9)	781 (40.0)	1015 (42.2)

Controls: 5796 out of 5836 possible. Matched 1:4 on age, gender, COPD diagnosis date.

* Excludes 22 in ADVAIR/ICS group, 18 in ADVAIR/LABA group.

Table 7: Nested Case-Control Analysis of Pneumonia Associated with COPD Treatments, by Varying Treatment Exposure Time Windows

Variable	0-3 Months Prior to Case Date			0-6 Months Prior to Case Date			0-12 Months Prior to Case Date		
	Odds Ratio	95% LCL	95% UCL	Odds Ratio	95% LCL	95% UCL	Odds Ratio	95% LCL	95% UCL
SABD (reference)	1.0	--	--	1.0	--	--	1.0	--	--
ADVAIR & ICS	1.805	0.742	4.393	1.255	0.603	2.611	1.745	0.978	3.113

ADVAIR & LABA	1.920	0.623	5.914	1.406	0.649	3.044	0.803	0.438	1.471
ADVAIR	1.025	0.741	1.417	0.974	0.706	1.344	0.817	0.581	1.148
ICS with LABA	0.580	0.302	1.116	0.566*	0.339	0.947	0.651*	0.433	0.980
ICS without LABA	1.289	0.963	1.726	1.282	0.983	1.672	1.259	0.996	1.592
LABA without ICS	0.915	0.686	1.220	0.965	0.734	1.268	0.888	0.682	1.156
None	1.066	0.877	1.296	1.018	0.827	1.252	1.009	0.786	1.296
<3 COPD outpatient encounters	1.0	---	---	1.0	---	---	1.0	---	---
3-4 COPD outpatient encounters	1.067	0.849	1.341	1.064	0.846	1.337	1.052	0.837	1.323
5-12 COPD outpatient encounters	1.513*	1.214	1.885	1.496*	1.200	1.864	1.508*	1.211	1.878
13+ COPD outpatient encounters	1.588*	1.223	2.061	1.565*	1.205	2.033	1.587*	1.220	2.064
No COPD emergency dept. encounter	1.0	---	---	1.0	---	---	1.0	---	---
≥ 1 COPD emergency dept. encounter	1.919*	1.562	2.356	1.941*	1.580	2.385	1.929*	1.570	2.371

No COPD hospitalization	1.0	---	---	1.0	---	---	1.0	---	---
≥ 1 COPD hospitalization	2.833*	2.304	3.484	2.837*	2.306	3.489	2.875*	2.336	3.539
Charlson Score = 0	1.0	---	---	1.0	---	---	1.0	---	---
Charlson score ≥ 1 based on outpatient encounters	1.034	0.881	1.215	1.037	0.883	1.218	1.030	0.877	1.210
No Asthma in baseline year	1.0	---	---	1.0	---	---	1.0	---	---
Asthma in baseline year	0.950	0.774	1.167	0.969	0.789	1.191	0.967	0.787	1.189
No Oral steroid use	1.0	---	---	1.0	---	---	1.0	---	---
Oral steroid use	1.408*	1.184	1.676	1.394*	1.170	1.659	1.410*	1.183	1.679
No pneumonia in baseline year	1.0	---	---	1.0	---	---	1.0	---	---
Pneumonia in baseline year	1.083	0.887	1.321	1.083	0.888	1.322	1.083	0.887	1.322

*Significant at the $p < 0.05$ level; Controls matched to cases 1:4 on age, gender, COPD diagnosis date

Table 8: Pneumonia rates among COPD patients who were highly compliant with therapy (45 day maximum gap and a prescription fill within 30 days of the beginning of each interval)

	Short-Acting Beta-Agonists +/- Anticholinergics			Any ADVAIR		
Interval (days)	# on treatment at beginning of interval	Pneumonia cases N=553	Pneumonia rate during interval (%)	# on treatment at beginning of interval	Pneumonia cases N=89	Pneumonia rate during interval (%)
0-60	3824	234	6.1	897	36	4.0
61-120	1674	84	5.0	490	14	2.9
121-180	1117	52	4.7	339	8	2.4
181 -240	861	23	2.7	267	7	2.6
241-300	710	19	2.7	224	3	1.3
301-365	611	20	3.3	176	2	1.1
> 365	427	121	28.3	138	19	13.8
	Any Inhaled ICS (Including ADVAIR) +/- LABA			Long-Acting Bronchodilators +/- ICS (No ADVAIR)		
Interval (days)	# on treatment at beginning of interval	Pneumonia cases N=201	Pneumonia rate during interval (%)	# on treatment at beginning of interval	Pneumonia cases N=84	Pneumonia rate during interval (%)
0-60	2116	110	5.2	955	27	2.8
61-120	921	44	4.8	414	10	2.4
121-180	650	21	3.2	292	8	2.7
181 -240	424	8	1.9	237	7	3.0
241-300	321	8	2.5	177	7	4.0
301-365	271	8	3.0	152	3	2.0
> 365	152	2	1.3	97	22	22.7

Table 9: Pneumonia rates among COPD patients who were highly compliant with therapy (45 day maximum gap and a prescription fill within 30 days of the beginning of each interval)						
Anticholinergics +/- SABA				Inhaled Corticosteroids Only (No ADVAIR or LABA)		
Interval (days)	# on treatment at beginning of interval	Pneumonia cases N=545	Pneumonia rate during interval (%)	# on treatment at beginning of interval	Pneumonia cases N=141	Pneumonia rate during interval (%)
0-60	3497	166	4.7	1219	70	5.7
61-120	1778	84	4.7	485	23	4.7
121-180	1248	51	4.1	269	11	4.1
181-240	998	33	3.3	212	2	0.9
241-300	860	34	4.0	166	4	2.4
301-365	725	21	2.9	141	3	2.1
> 365	486	156	32.1	79	28	35.4
Inhaled Corticosteroids Only (No ADVAIR or LABA)				Long-Acting Bronchodilators Only (No ADVAIR or ICS)		
Interval (days)	# on treatment at beginning of interval	Pneumonia cases	Pneumonia rate during interval (%)	# on treatment at beginning of interval	Pneumonia cases	Pneumonia rate during interval (%)
0-60	1219	70	5.7	432	12	2.8
61-120	485	23	4.7	163	2	1.2
121-180	269	11	4.1	117	4	3.4

181 -240	212	2	0.9	92	3	3.3
241-300	166	4	2.4	67	2	3.0
301-365	141	3	2.1	63	2	3.2
> 365	79	28	35.4	40	8	20.0
		141			33	
	Short-Acting Bronchodilators Only			Anticholinergics Only		
Interval (days)	# on treatment at beginning of interval	Pneumonia cases N=169	Pneumonia rate during interval (%)	# on treatment at beginning of interval	Pneumonia cases N=154	Pneumonia rate during interval (%)
0-60	1751	100	5.7	1658	73	4.4
61-120	488	28	5.7	520	18	3.5
121-180	298	13	4.4	326	15	4.6
181 -240	225	5	2.2	247	11	4.5
241-300	183	5	2.7	212	9	4.2
301-365	165	6	3.6	164	2	1.2
> 365	114	18	15.8	119	26	21.8
<p>Conclusion: In the cohort analyses of COPD patients from three large US administrative healthcare databases, ADVAIR treatment (dispensing) was associated with a significantly lower risk of pneumonia relative to short acting bronchodilator only treatment. The risk of pneumonia was not associated with ICS only or LABA only compared to SABD. In the nested case control analysis, neither ADVAIR or ICS was associated with an increased risk for pneumonia. Patients dispensed separate ICS and LABA products used concurrently had a lower risk of pneumonia relative to patients treated with only SABD.</p>						
<p>Publications: No publication</p>						

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