

GSK Medicine: Fluticasone propionate, beclomethasone dipropionate
Study No.: WWE113666/WE50001
Title: An Epidemiological Study of Overall Patterns of Use & Outcomes in Users of Fluticasone Propionate (Flonase) Nasal Spray
Rationale: The study was undertaken as part of a multifaceted epidemiological program to evaluate the utilization, safety and outcomes associated with prescription use of intranasal fluticasone propionate (FP).
Objectives: The primary objectives were to: 1) characterize intranasal FP and other intranasal steroid (INS) users with respect to demographics and patterns of use; 2) compare the demographic characteristics of fluticasone propionate users with other INS users; 3) to determine the rate of events of interest among patients with intermittent, sub-chronic and chronic FP use episodes compared to patients with intermittent, sub-chronic and chronic episodes of other INS use and 4) assess potential effect modifiers of the association between INS use and events by the use of stratified analysis and to create statistical models including covariates to control for potential confounding variables.
Indication: Management of the nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older
Study Investigators/Centers: Research conducted by The Degge Group; principal investigator, Dr. Judith Jones.
Research Methods:
Data Source: The study was conducted in a large US managed care database from i3 Magnifi (formerly Constella Health Strategies), which had claims for approximately six million lives (two million in any given year) in 22 states. Approximately 17 percent of this database's membership belonged to a Medicare Risk plan, which allowed analysis of some of the population over age 65. Roughly four percent of the population belonged to a Medicare Supplement plan; these patients were not included in the analysis due to the possibility of incomplete records. The database contained administrative data, including diagnoses, procedures, prescriptions (NDC, days supply) and hospitalizations.
Study Design: This was an inception cohort study that analysed data from an administrative medical claims database. The two inception cohorts were: 1) patients initiated on intranasal FP and 2) patients initiated on another INS (not FP). The candidates for the inception cohorts did not use any intranasal steroid in the year prior to initiation. The study period was January 1, 1995 through September 30, 2002. Patient records dated between January 1, 1994 and September 30, 2002 were used to develop the overall study cohort.
Study Population: Overall cohort eligibility was based on meeting criteria for continuous coverage in the medical claims database, such that it was reasonable to assume that patients' medical care was received from the health plan and that the occurrence of events was reliably captured in the database. Eligibility interruptions of 30 days or less were assumed to be simple administrative lags in data entry. In these cases, eligibility intervals on either side of the interruption were combined into one continuous interval. All patients were required to have at least 12 months of continuous eligibility before the index date. When patient history was divided into FP or other INS use episodes, there had to be at least 120 days of plan eligibility after the last prescription claim in the episode to be included in the outcome analysis. The index date was the first FP prescription claim or the first INS prescription claim (other than FP). The first prescription claim determined cohort placement. Additionally, the first episode (containing the index date) must have at least 120 days after the last prescription claim free from exposure to another intranasal steroid. If a patient received another intranasal steroid after the index date, he or she was censored at that point in time. (Of note, patients within the other INS cohort were allowed to switch between (non-fluticasone propionate) INS therapies without being censored) Patients under four years of age at index date were excluded from the cohort. Medical claims and patient eligibility data were linked with a unique encrypted patient identification number by the data vendor. The Degge Group had access to only the encrypted patient identification number and therefore, patient confidentiality was maintained at all times.
Study Exposures, Outcomes: This study evaluated outcomes in patients exposed to FP and other INS. A continuous interval of exposure to FP or other INS was defined as a the time period covered by a series of prescription claims having no more than 60 days between any two consecutive claims. FP and other INS exposure episodes were identified within all eligible patient histories as 1) intermittent exposure episode defined as a continuous interval of exposure to the same drug consisting of 1, 2, or 3 continuous prescription claims; 2) sub-chronic use episode defined as a continuous interval of exposure to the same drug consisting of 4, 5, 6, 7, or 8 continuous prescription claims or 3) chronic use episode defined as a continuous interval of exposure to the same drug consisting of 9 or more continuous prescription claims. A span of at least six months had to occur between the first and last prescription claim.

The following outcomes were investigated:

Cataracts
 Glaucoma
 Nasal septum perforation
 Hypercorticism (Cushings)
 Adrenal insufficiency
 Fractures (limited to hip, wrist and vertebral) as proxies for osteoporosis
 Osteoporosis
 Sinusitis (acute and chronic)
 Infectious complications of sinusitis to include:
 Cellulitis (periorbital)
 Empyema (maxillary)
 Abscess (brain)
 Meningitis
 Encephalitis

Data Analysis Methods: For the descriptive analyses, patients in the FP and other INS cohorts were compared on the basis of sex, age group (10 year age ranges), geographic region of residence, seasonality (by month) of use of first INS prescription, various risk factors for each outcome, the number of inhaled and oral corticosteroid prescriptions in the year prior to the index date, the number of INS prescriptions per year and average number of days between prescription refills (stratified by eligible time).

To analyze events, episodes were created within each patient's claims history. Episodes of FP or other INS exposure are defined as any series of prescriptions filled within 60 days of one another. A break of more than 60 days constituted a separate episode. Observation periods to capture incident events began with the first prescription filled in the episode and terminated 120 days (30 days to complete dose plus a 90 day observance tail) after the last fill date. Episodes with exposures to another study medication during the 120 day assessment period were excluded. Of note, episodes containing a subsequent exposure(s) to the same INS after 60 days from the last fill date were not censored. Only one episode per person was evaluated; that episode was randomly selected from the eligible episodes. Person-time exposure accumulated from the episode index date to an event claim date or 120 days after the last fill date within that prescription series, which ever occurred first.

Additionally, a sensitivity analysis was conducted excluding patients with any corticosteroid use in the prior year.

Rates and rate ratios with 95% confidence intervals were calculated for events in the intermittent, sub-chronic and chronic FP and other INS episode groups. If an event was present, the investigator assessed exposure status in the months prior to the event, counting the number of prescriptions and amount of time that preceded the event. Depending on the number of prescriptions observed and duration of use, events were grouped into an exposure episode. Each event (or event group) was analyzed separately. Patients with an event of interest during the 12 months prior to their entry into the cohort or during the 12 months prior to an episode index date were automatically excluded from the analysis of that event. This exclusion criterion was applied to rule out prevalent conditions. For glaucoma, drug codes were used as a proxy measure for diagnosis codes that were recorded in the patient's medical history.

In order to assess potential effect modifiers of the association between INS use and events, the following variables were stratified: 1) the duration of use (intermittent, sub-chronic, chronic); 2) concurrent oral and/or inhaled corticosteroid use (intranasal only, intranasal and current inhaled, intranasal and current oral, intranasal and current inhaled + oral); 3) past steroid use (inhaled and/or oral, recent and/or remote past); 4) drug interactions (INS and concurrent ritonavir, ketoconazole or itraconazole use).

Additionally, covariates were added to the statistical model in order to control for potential confounders. The covariates used in each model were endpoint specific, such that they would be both associated with the endpoint and with the probability of receiving an intranasal FP prescription. To be included in the analysis, comorbid conditions must have been diagnosed prior to the episode index date.

A historical cohort study design was used to analyze the association between the selected outcomes and INS use. Poisson regression modeling was used to estimate the relative rate adjusting for the potential confounders and to

calculate the associated 95% confidence intervals (CIs). A manual stepwise regression procedure was used to identify those risk factors / modifiers that were independently associated with the endpoint event under evaluation. A threshold of $P < 0.1$ will be used for inclusion into the model. Covariates known to be major contributing factors were forced in the model, regardless of the results of their statistical significance. An alpha level of 0.05 was used to test for statistical significance. Analyses were performed using SAS (Version 8.02; SAS Institute, Cary, NC, USA).

Limitations: Medicare data claims are generally not captured in insurance claims databases, and therefore, patients 65 years of age and older were under-represented. Studies in i3 Magnifi (formerly Constella Health Strategies) database was mostly focused on patients 65 and under. i3 Magnifi's data prior to 2001 included some Medicare Risk plans and patients over 65 which were included (though underrepresented) in the sample.

Another limitation of this database studies is that laboratory data—used for disease diagnosis—were not available for study. Currently such databases are in developmental stages and do not cover a large number of patients.

Study Results: There were a total of 126,613 patients eligible to participate in the study. Of this total, 52,870 patients were in the FP cohort and 73,743 patients were in the INS cohort (cohorts mutually exclusive). The mean age of the FP cohort was 43 (SD \pm 20) years of age and the mean age of the INS cohort was 45 (SD \pm 21) years of age. Females comprised 59% of both cohorts and men comprised 41%. Regarding the regional distribution of patients, the largest concentration of patients were from the South (~ 67%), followed by the Midwest (~ 30%), West (~ 3%), and Northeast regions (~ 0.2). Concerning seasonal trends, a similar proportion of patients received their first FP/INS prescription throughout the seasons (winter, spring, summer, fall), ranging from 20% – 29% each season.

Nearly 86% of patients in the FP cohort and 84% of patients in the INS cohort received only one prescription during the selected episode/study. Of the 126,613 patients, roughly 97% of FP and INS patients were categorized as intermittent users, 2.5% as sub-chronic users, and 0.5% as chronic users. Factoring in the exposure time and 90 day observation period, the 52,870 FP patients accounted for 18,884 person-years and the 73,743 patients in the INS cohort accounted for 26,429 person-years of observation.

Thirteen outcomes associated with corticosteroid use were evaluated in FP patients as compared to INS patients. These outcomes included: adrenal insufficiency, cataracts, fracture, glaucoma, hypercorticism, nasal septum perforation, osteoporosis, sinusitis, abscess, cellulitis, empyema, encephalitis, and meningitis. For the various outcomes, several variables were assessed and incorporated into the multivariate statistical model to control for potential confounding. After adjusting for these factors, five outcomes were more likely to occur in FP patients than INS patients. These included hypercorticism, nasal septum perforation, sinusitis, abscess, and empyema. FP patients were 2.6 times (95% confidence interval (CI), 1.21-5.59; $p \leq 0.01$) more likely to have received a diagnosis for hypercorticism than INS patients. Nasal septum perforation was 1.10 times (95% CI, 1.00- 1.22; $p < 0.05$) more likely to occur in FP than INS patients. Sinusitis was 1.10 times (95% CI, 1.07- 1.14; $p \leq 0.01$) more likely to occur in FP than INS patients. Abscess was 1.13 times (95% CI, 1.07- 1.20; $p \leq 0.01$) more likely to occur in FP than INS patients. Finally, empyema was 2.20 times (95% CI, 1.27- 3.83; $p \leq 0.01$) more likely to occur in FP than INS patients. In contrast, FP patients were less likely to have received a diagnosis for cataracts than patients taking other INS (adjusted rate ratio (aRR), 0.80; 95% CI, 0.71-0.89; $p \leq 0.01$). All other outcomes assessed were not found to be statistically different between the FP and INS cohorts.

Several stratification analyses were conducted to further assess the effect of various factors on the outcome. These factors included: episode type (intermittent, sub-chronic, and chronic use), concurrent oral corticosteroid use, and interacting drugs.

As stated previously, roughly 97% of FP and INS patients were categorized as intermittent users, 2.5% as sub-chronic users, and 0.5% as chronic users. After stratification, intermittent users were found to have roughly the same adjusted and unadjusted rate ratios as the overall analyses. All outcomes that were statistically significant in the overall analyses were significant in the intermittent user subgroup, with the exception of nasal septum perforation (aRR, 1.10; 95% CI, 1.00-1.21; $p = 0.06$). All sub-chronic and chronic exposure subcategories were not found to be statistically different for any of the outcomes, with the exception cataracts (sub-chronic: aRR 0.55; 95% CI, 0.32-0.94; $p < 0.05$). Several of the adjusted and unadjusted results for sub-chronic and chronic users were not able to be calculated due to the limited number of patients and outcomes in these categories.

Roughly, 85% of FP and INS patients did not have an inhaled corticosteroid (ICS) or oral corticosteroid (OCS) dispensing during a FP or INS episode. Approximately 8% of FP and INS patients were dispensed concomitant OCS, 4% had concomitant ICS, and 2% had concomitant ICS/OCS dispensings during the episode. For the subgroup of

INS patients without a concomitant steroid, the adjusted rate ratios slightly increased for three of the outcomes found to be statistically significant in the overall analyses: nasal septum perforation, sinusitis, and abscess. Similarly, when comparing FP to INS patients, the adjusted ratio for cataracts was found to have decreased slightly (aRR, 0.76; 95% CI, 0.67-0.85; $p \leq 0.01$). In contrast, when excluding patients taking concomitant steroids, the adjusted rate ratios for hypercorticism and empyema decreased and were not statistically significant (aRR, 2.12; 95% CI, 0.75-5.97; $p = 0.16$ and aRR, 1.60; 95% CI, 0.87-2.94; $p = 0.18$, respectively). All other outcomes by corresponding sub-groupings (INS only, ICS, OCS, and ICS/OCS) were different between FP and INS users.

To further explore the effect of episode type and concurrent corticosteroid (ICS or OCS) use, patients were divided in categories by episode type and steroid use. Due to the limited number of patients and events in sub-chronic, chronic, and concurrent steroid subcategories, the results from the adjusted analyses and several of the unadjusted analyses are not available. Thus, the adjusted rate ratios are provided for only intermittent non-concomitant corticosteroid users. The unadjusted rate ratios are provided for all subgroups with at least one event in the FP and INS cohorts. With regards to intermittent non-concomitant steroid users, virtually the same rate-ratios as non-concomitant steroid users were found. FP users in the intermittent non-concomitant steroid subgroup were more likely to have nasal perforation, sinusitis, and abscess than INS users. Additionally, FP users in the intermittent non-concomitant steroid subgroup were less likely to have cataracts than INS users. Empyema and hypercorticism, two outcomes in the overall analysis found to be statistically more likely to occur in the FP group as compared to the INS group, were no longer significant in this subgroup. All other rate ratios for each of the outcomes were not found to be statistically different between FP and INS users.

Less than 1% of FP and INS patients took concomitant itraconazole, ketoconazole, and/or ritonavir (interacting drugs) during the study. Thus, due to the small number of patients taking these medications and the small number of associated events, many of the unadjusted and all of the adjusted rate ratios are not available for these patients. When patients taking interacting drugs were removed from the outcome analyses (INS only), virtually the same rate ratios are produced as those found in the analyses including these patients. Additionally, due to the limited numbers in the subgroups the analyses stratified by episode type and interacting drugs did not provide any pertinent results. The unadjusted and adjusted rate ratios for intermittent, sub-chronic, and chronic patients not taking an interacting drug (INS only) yielded virtually identical results as all intermittent, sub-chronic, and chronic patients.

Table 1. Distribution of patients by demographic characteristics and Cohort Grouping

Characteristics	FP Cohort		INS Cohort		All Patients	
	# Patients	% Patients	# Patients	% Patients	# Patients	% Patients
All Patients	52,870	100.0	73,743	100.0	126,613	100.0
Female	30,993	58.6	43,498	59.0	74,491	58.8
4-14	2,701	5.1	4,020	5.5	6,721	5.3
15-24	2,427	4.6	3,147	4.3	5,574	4.4
25-34	4,300	8.1	5,017	6.8	9,317	7.4
35-44	6,527	12.3	8,730	11.8	15,257	12.1
45-54	6,561	12.4	8,805	11.9	15,366	12.1
55-64	3,680	7.0	4,857	6.6	8,537	6.7
65-74	2,865	5.4	5,003	6.8	7,868	6.2
75-84	1,522	2.9	3,092	4.2	4,614	3.6
85+	410	0.8	827	1.1	1,237	1.0
Male	21,877	41.4	30,245	41.0	52,122	41.2
4-14	3,054	5.8	4,731	6.4	7,785	6.1
15-24	1,842	3.5	2,185	3.0	4,027	3.2
25-34	2,542	4.8	3,101	4.2	5,643	4.5
35-44	4,300	8.1	5,336	7.2	9,636	7.6
45-54	4,123	7.8	5,111	6.9	9,234	7.3
55-64	2,572	4.9	3,366	4.6	5,938	4.7
65-74	2,106	4.0	3,669	5.0	5,775	4.6
75-84	1,094	2.1	2,172	2.9	3,266	2.6
85+	244	0.5	574	0.8	818	0.6

Region						
Northeast	105	0.2	203	0.3	308	0.2
Midwest	15,903	30.1	21,525	29.2	37,428	29.6
South	35,671	67.5	49,529	67.2	85,200	67.3
West	1,191	2.3	2,486	3.4	3,677	2.9
Season*						
Winter	14,280		20,934	28.4	35,214	27.8
Spring	15,455	29.2	20,656	28.0	36,111	28.5
Summer	11,447	21.7	15,408	20.9	26,855	21.2
Fall	11,688	22.1	16,745	22.7	28,433	22.5

* Date of first FP/INS prescription.

Table 2a. Patients and person-time of plan eligibility by selection group (FP/INS cohorts) by eligibility time during the randomly selected episode (person-months).

Eligibility time person-months*	FP Cohort		INS Cohort	
	Number of randomly selected episodes	Patient-years accrued during the episodes	Number of randomly selected episodes	Patient-years accrued during the window
4 to < 6	50,401	17,041	70,309	23,807
6 to < 12	2,134	1,367	2,913	1,863
12 to < 24	298	375	455	587
24 to < 36	22	50	53	121
36 to < 48	13	43	8	27
48 to < 60	2	9	2	9
>= 60	0	0	3	16
Totals	52,870	18,884	73,743	26,429

* Eligibility time refers to the time observed within the randomly selected episode, regardless of outcomes prior to end of episode.

Table 2b. Average number of FP/INS prescriptions per year and average number of days between prescription refills -stratified by eligibility time during the randomly selected episode (person-months).

Eligibility time person-months	FP Cohort		INS Cohort	
	Avg. number of prescriptions per Year	Avg. number of days between refills**	Avg. number of prescriptions per Year	Avg. number of days between refills***
4 to < 6	3	34	3	30
6 to < 12	6	38	6	37
12 to < 24	8	37	9	35
24 to < 36	9	37	10	34
36 to < 48	10	35	11	30
48 to < 60	11	32	12	29
>= 60	0	0	13	27
Totals	3	35	3	32

** Only 7,503 FP patients are included in the calculation of average time in between refills. 45,377 patients only had 1 prescription.

*** Only 11,643 INS patients are included in the calculation of average time in between refills. 62,100 patients only had 1 prescription.

Table 2c. Number of FP/INS prescriptions during the randomly selected episodes.

Number of Prescriptions	FP Cohort		INS Cohort	
	# Patients	% Patients	# Patients	% Patients
1	45,369	85.8	62,100	84.2
2	4,660	8.8	7,333	9.9
3	1,311	2.5	2,009	2.7
4	568	1.1	832	1.1
5	312	0.6	437	0.6
6+	650	1.2	1,032	1.4
Totals	52,870	100.0	73,743	100.0

Table 3. Event Rates and Rate Ratios (Random Episodes)

Events	FP Cohort (n= 52,870)*			INS Cohort (n=73,743)			Rate Ratios	
	# of Events	PY	Rate / 10,000 PY	# of Events	PY	Rate / 10,000 PY	Rate Ratio (95% CI)	Adjusted Rate Ratio (95% CI)
Adrenal Insufficiency	14	18,701	7	13	26,224	5	1.51 (0.71 - 3.21)	1.57 (0.74 - 3.35)
Cataract	483	18,088	267	992	24,785	400	0.67 (0.60 - 0.74)†	0.80 (0.71 - 0.89)†
Fracture	134	18,714	72	180	26,184	69	1.04 (0.83 - 1.30)	1.10 (0.88 - 1.38)
Glaucoma	241	18,294	132	378	25,400	149	0.89 (0.75 - 1.04)	0.97 (0.83 - 1.15)
Hypercorticism	19	18,845	10	10	26,387	4	2.66 (1.24 - 5.72)†	2.59 (1.21 - 5.59)†
Nasal Septum Perforation	745	17,998	414	939	25,382	370	1.12 (1.02 - 1.23)‡	1.10 (1.00 - 1.22)‡
Osteoporosis	59	18,775	31	79	26,315	30	1.05 (0.75 - 1.47)	1.08 (0.77 - 1.52)
Sinusitis	5,870	12,719	4,615	7,710	18,556	4,155	1.11 (1.07 - 1.15)†	1.10 (1.07 - 1.14)†
Abscess	2,076	15,503	1,339	2,562	21,977	1,166	1.15 (1.08 - 1.21)†	1.13 (1.07 - 1.20)†
Cellulitis	36	18,837	19	60	26,371	23	0.84 (0.56 - 1.27)	0.84 (0.56 - 1.27)
Empyema	30	18,859	16	22	26,401	8	1.91 (1.10 - 3.31)	2.20 (1.27 - 3.83)†
Encephalitis	5	18,879	3	3	26,426	1	2.33 (0.56 - 9.76)	2.19 (0.52 - 9.26)
Meningitis	8	18,869	4	18	26,412	7	0.62 (0.27 - 1.43)	0.63 (0.27 - 1.45)

† p ≤ 0.01 (INS control)

‡ p < 0.05 (INS control)

Table 4. Event Rates and Rate Ratios by Event and Episode Type (Random Episode)

Event	Episode Type	FP Cohort (n=52,870)	INS Cohort (n=73,743)	Rate Ratios	
		Rate / 10,000 PY	Rate / 10,000 PY	Rate Ratio (95% CI)	Adjusted Rate Ratio (95% CI)
Adrenal Insufficiency	intermittent	8	5	1.63(0.75-3.52)	1.68(0.77-3.64)
	sub-chronic	0	8	N/A	N/A

	chronic	0	0	N/A	N/A
Cataract	intermittent	272	401	0.68(0.61-0.76)†	0.81(0.72-0.91)†
	sub-chronic	225	439	0.51(0.30-0.87)‡	0.55(0.32-0.94)‡
	chronic	132	293	0.45(0.17-1.22)	N/A
Fracture	intermittent	73	67	1.08(0.86-1.37)	1.14(0.90-1.44)
	sub-chronic	55	78	0.71(0.24-2.07)	N/A
	chronic	51	104	0.49(0.10-2.34)	N/A
Glaucoma	intermittent	133	150	0.89(0.75-1.05)	0.98(0.83-1.15)
	sub-chronic	127	147	0.86(0.41-1.83)	N/A
	chronic	77	94	0.82(0.20-3.28)	N/A
Hypercorticism	intermittent	10	4	2.51(1.16-5.43)‡	2.43(1.12-5.27)‡
	sub-chronic	11	0	N/A	N/A
	chronic	0	0	N/A	N/A
Nasal Septum Perforation	intermittent	431	388	1.11(1.01-1.22)‡	1.10(1.00-1.21)
	sub-chronic	200	189	1.06(0.57-1.98)	N/A
	chronic	132	46	2.86(0.68-12.0)	N/A
Osteoporosis	intermittent	33	30	1.12(0.79-1.59)	1.16(0.82-1.64)
	sub-chronic	11	39	0.29(0.03-2.44)	N/A
	chronic	0	29	N/A	N/A
Sinusitis	intermittent	4,855	4,399	1.10(1.07-1.14)†	1.10(1.06-1.14)†
	sub-chronic	1,198	1,264	0.95(0.70-1.28)	N/A
	chronic	777	542	1.43(0.78-2.63)	N/A
Abscess	intermittent	1,311	1,147	1.14(1.08-1.21)†	1.13(1.07-1.20)†
	sub-chronic	500	564	0.89(0.60-1.31)	N/A
	chronic	407	200	2.03(0.94-4.40)	N/A
Cellulitis	intermittent	21	24	0.85(0.56-1.29)	0.85(0.56-1.29)
	sub-chronic	0	8	N/A	N/A
	chronic	0	0	N/A	N/A
Empyema	intermittent	17	9	1.92(1.10-3.37)‡	2.19(1.25-3.86)†

	sub-chronic	0	8	N/A	N/A
	chronic	25	0	N/A	N/A
Encephalitis	intermittent	3	1	2.32(0.55-9.71)	2.20(0.52-9.29)
	sub-chronic	0	0	N/A	N/A
	chronic	0	0	N/A	N/A
Meningitis	intermittent	5	7	0.70(0.30-1.63)	0.72(0.31-1.69)
	sub-chronic	0	15	N/A	N/A
	chronic	0	0	N/A	N/A

N/A: Rate Ratios with insufficient number of events to provide meaningful results.

† $p \leq 0.01$ (INS control)

‡ $p < 0.05$ (INS control)

Table 5. Event Rates and Rate Ratios by Event and Concurrent Steroid Use (Random Episode)

Event	Concurrent Steroid Use	FP Cohort (n=52,870)	INS Cohort (n=73,743)	Rate Ratios	
		Rate / 10,000 PY	Rate / 10,000 PY	Rate Ratio (95% CI)	Adjusted Rate Ratio (95% CI)
Adrenal Insufficiency	INS only	7	4	1.54(0.66-3.63)	1.61(0.68-3.79)
	ICS	13	17	0.77(0.07-8.48)	N/A
	OCS	12	5	2.64(0.24-29.1)	N/A
	ICS & OCS	0	0	N/A	N/A
Cataract	INS only	262	418	0.63(0.56-0.70)†	0.76(0.67-0.85)†
	ICS	346	355	0.97(0.59-1.61)	N/A
	OCS	294	252	1.17(0.79-1.73)	N/A
	ICS & OCS	212	358	0.59(0.26-1.36)	N/A
Fracture	INS only	66	67	0.98(0.76-1.26)	1.04(0.81-1.34)
	ICS	106	52	2.05(0.71-5.91)	N/A
	OCS	108	82	1.31(0.68-2.52)	N/A
	ICS & OCS	75	102	0.74(0.18-2.95)	N/A
Glaucoma	INS only	133	153	0.87(0.73-1.04)	0.97(0.81-1.15)
	ICS	108	143	0.76(0.32-1.77)	N/A
	OCS	123	99	1.24(0.67-2.29)	N/A
	ICS & OCS	154	196	0.79(0.29-2.13)	N/A
Hypercorticism	INS only	6	3	2.10(0.75-5.91)	2.12(0.75-5.97)
	ICS	13	0	N/A	N/A
	OCS	42	9	4.60(0.96-22.1)	N/A
	ICS & OCS	49	34	1.46(0.21-10.4)	N/A
Nasal Septum Perforation	INS only	409	347	1.18(1.06-1.31)†	1.17(1.05-1.30)†
	ICS	192	223	0.86(0.45-1.66)	N/A

	OCS	597	724	0.82(0.64-1.07)	N/A
	ICS & OCS	294	254	1.16(0.53-2.55)	N/A
Osteoporosis	INS only	30	28	1.09(0.74-1.58)	1.13(0.77-1.65)
	ICS	66	43	1.54(0.45-5.33)	N/A
	OCS	24	50	0.48(0.15-1.50)	N/A
	ICS & OCS	50	17	2.93(0.27-32.3)	N/A
Sinusitis	INS only	4,913	4,384	1.12(1.08-1.16) [†]	1.11(1.07-1.15) [†]
	ICS	1,820	2,049	0.89(0.69-1.14)	N/A
	OCS	3,596	3,435	1.05(0.91-1.20)	N/A
	ICS & OCS	1,801	1,753	1.03(0.71-1.50)	N/A
Abscess	INS only	1,283	1,098	1.17(1.10-1.24) [†]	1.15(1.08-1.23) [†]
	ICS	878	716	1.23(0.87-1.72)	N/A
	OCS	1,296	1,348	0.96(0.79-1.16)	N/A
	ICS & OCS	628	772	0.81(0.48-1.37)	N/A
Cellulitis	INS only	19	21	0.92(0.59-1.45)	0.93(0.59-1.46)
	ICS	26	34	0.77(0.14-4.19)	N/A
	OCS	18	32	0.56(0.15-2.18)	N/A
	ICS & OCS	0	34	N/A	N/A
Empyema	INS only	13	9	1.40(0.76-2.56)	1.60(0.87-2.94)
	ICS	65	0	N/A	N/A
	OCS	24	5	5.26(0.59-47.0)	N/A
	ICS & OCS	0	0	N/A	N/A
Encephalitis	INS only	3	1	2.33(0.56-9.77)	2.28(0.54-9.63)
	ICS	0	0	N/A	N/A
	OCS	0	0	N/A	N/A
	ICS & OCS	0	0	N/A	N/A
Meningitis	INS only	4	7	0.53(0.21-1.34)	0.53(0.20-1.36)
	ICS	0	9	N/A	N/A
	OCS	12	5	2.63(0.24-29.0)	N/A
	ICS & OCS	0	0	N/A	N/A

N/A: Rate Ratios with insufficient number of events to provide meaningful results.

[†] p ≤ 0.01 (INS control)

[‡] p < 0.05 (INS control)

Table 6. Event Rates and Rate Ratios by Episode Type and Concurrent Steroid Use (Random Episode)

			FP Cohort (n=52,870)	INS Cohort (n=73,743)	Rate Ratios	
Event	Episode Type	Current Steroid Use	Rate / 10,000 PY	Rate / 10,000 PY	Rate Ratio (95% CI)	Adjusted Rate Ratio (95% CI)*

Adrenal Insufficiency	intermittent	INS only	7	5	1.54(0.65-3.62)	1.60(0.68-3.79)
		ICS	15	10	1.50(0.09-23.9)	N/A
		OCS	14	5	2.61(0.24-28.7)	N/A
		ICS & OCS	0	0	N/A	N/A
	sub-chronic	INS only	0	0	N/A	N/A
		ICS	0	85	N/A	N/A
		OCS	0	0	N/A	N/A
		ICS & OCS	0	0	N/A	N/A
	chronic	INS only	0	0	N/A	N/A
		ICS	0	0	N/A	N/A
		OCS	0	0	N/A	N/A
		ICS & OCS	0	0	N/A	N/A
Cataract	intermittent	INS only	267	417	0.64(0.57-0.72) [†]	0.77(0.68-0.87) [†]
		ICS	364	386	0.94(0.56-1.59)	N/A
		OCS	300	258	1.16(0.77-1.76)	N/A
		ICS & OCS	210	271	0.77(0.29-2.09)	N/A
	sub-chronic	INS only	212	477	0.44(0.24-0.83)	N/A
		ICS	0	180	N/A	N/A
		OCS	369	203	1.82(0.41-8.14)	N/A
		ICS & OCS	372	908	0.41(0.08-2.03)	N/A
	chronic	INS only	115	320	0.36(0.10-1.27)	N/A
		ICS	857	182	4.72(0.43-52.0)	N/A
		OCS	0	221	N/A	N/A
		ICS & OCS	0	340	N/A	N/A
Fracture	intermittent	INS only	67	65	1.03(0.79-1.33)	1.09(0.84-1.41)
		ICS	91	51	1.79(0.55-5.88)	N/A
		OCS	121	83	1.46(0.75-2.87)	N/A
		ICS & OCS	100	135	0.74(0.19-2.96)	N/A
	sub-chronic	INS only	62	76	0.81(0.24-2.78)	N/A
		ICS	134	83	1.61(0.10-25.7)	N/A
		OCS	0	125	N/A	N/A
		ICS & OCS	0	0	N/A	N/A
	chronic	INS only	37	159	0.23(0.03-1.90)	N/A
		ICS	390	0	N/A	N/A
		OCS	0	0	N/A	N/A

		ICS & OCS	0	0	N/A	N/A
Glaucoma	intermittent	INS only	136	154	0.88(0.74-1.05)	0.98(0.82-1.17)
		ICS	109	137	0.80(0.32-2.00)	N/A
		OCS	110	102	1.08(0.56-2.10)	N/A
		ICS & OCS	171	212	0.81(0.27-2.41)	N/A
	sub-chronic	INS only	96	147	0.65(0.25-1.71)	N/A
		ICS	144	265	0.54(0.06-5.22)	N/A
		OCS	265	64	4.18(0.43-40.2)	N/A
		ICS & OCS	170	141	1.20(0.08-19.2)	N/A
	chronic	INS only	76	96	0.79(0.15-4.33)	N/A
		ICS	0	0	N/A	N/A
		OCS	165	104	1.58(0.10-25.3)	N/A
		ICS & OCS	0	151	N/A	N/A
Hypertorticism	intermittent	INS only	6	3	2.09(0.75-5.88)	2.12(0.75-5.98)
		ICS	15	0	N/A	N/A
		OCS	47	10	4.55(0.94-21.9)	N/A
		ICS & OCS	33	45	0.74(0.07-8.11)	N/A
	sub-chronic	INS only	0	0	N/A	N/A
		ICS	0	0	N/A	N/A
		OCS	0	0	N/A	N/A
		ICS & OCS	167	0	N/A	N/A
	chronic	INS only	0	0	N/A	N/A
		ICS	0	0	N/A	N/A
		OCS	0	0	N/A	N/A
		ICS & OCS	0	0	N/A	N/A
Nasal Perforation	intermittent	INS only	424	360	1.18(1.06-1.31) [†]	1.17(1.05-1.30) [†]
		ICS	206	242	0.85(0.43-1.68)	N/A
		OCS	625	792	0.79(0.61-1.03)	N/A
		ICS & OCS	352	333	1.06(0.47-2.38)	N/A
	sub-chronic	INS only	180	190	0.95(0.44-2.02)	N/A
		ICS	0	180	N/A	N/A
		OCS	544	275	1.98(0.56-7.02)	N/A
		ICS & OCS	0	0	N/A	N/A
	chronic	INS only	114	46	2.45(0.41-14.6)	N/A
		ICS	396	0	N/A	N/A

		OCS	0	106	N/A	N/A
		ICS & OCS	298	0	N/A	N/A
Osteoporosis	intermittent	INS only	31	27	1.17(0.80-1.73)	1.21(0.82-1.80)
		ICS	76	40	1.87(0.50-6.97)	N/A
		OCS	27	57	0.47(0.15-1.48)	N/A
		ICS & OCS	66	22	2.94(0.27-32.4)	N/A
	sub-chronic	INS only	15	43	0.36(0.04-3.21)	N/A
		ICS	0	83	N/A	N/A
		OCS	0	0	N/A	N/A
		ICS & OCS	0	0	N/A	N/A
	chronic	INS only	0	45	N/A	N/A
		ICS	0	0	N/A	N/A
		OCS	0	0	N/A	N/A
		ICS & OCS	0	0	N/A	N/A
Sinusitis	intermittent	INS only	5,123	4,606	1.11(1.07-1.15) [†]	1.11(1.07-1.15) [†]
		ICS	1,985	2,188	0.91(0.70-1.17)	N/A
		OCS	3,925	3,771	1.04(0.91-1.20)	N/A
		ICS & OCS	1,886	1,913	0.99(0.65-1.49)	N/A
	sub-chronic	INS only	1,262	1,246	1.01(0.72-1.43)	N/A
		ICS	565	1,616	0.35(0.10-1.23)	N/A
		OCS	924	698	1.33(0.43-4.11)	N/A
		ICS & OCS	1,847	2,147	0.86(0.31-2.37)	N/A
	chronic	INS only	834	594	1.41(0.69-2.84)	N/A
		ICS	1,191	477	2.50(0.35-17.7)	N/A
		OCS	266	524	0.51(0.05-4.87)	N/A
		ICS & OCS	939	239	3.93(0.36-43.4)	N/A
Abscess	intermittent	INS only	1,333	1,142	1.17(1.10-1.24) [†]	1.16(1.08-1.23) [†]
		ICS	968	803	1.21(0.85-1.71)	N/A
		OCS	1,362	1,447	0.94(0.77-1.15)	N/A
		ICS & OCS	745	869	0.86(0.49-1.49)	N/A
	sub-chronic	INS only	518	557	0.93(0.59-1.47)	N/A
		ICS	289	370	0.78(0.14-4.27)	N/A
		OCS	806	722	1.12(0.44-2.83)	N/A
		ICS & OCS	0	634	N/A	N/A
	chronic	INS only	334	152	2.20(0.76-6.33)	N/A

		ICS	396	0	N/A	N/A
		OCS	598	468	1.28(0.29-5.71)	N/A
		ICS & OCS	685	314	2.18(0.31-15.5)	N/A
Cellulitis	intermittent	INS only	21	22	0.94(0.60-1.48)	0.94(0.60-1.49)
		ICS	30	40	0.75(0.14-4.08)	N/A
		OCS	20	36	0.56(0.14-2.15)	N/A
		ICS & OCS	0	45	N/A	N/A
	sub-chronic	INS only	0	11	N/A	N/A
		ICS	0	0	N/A	N/A
		OCS	0	0	N/A	N/A
		ICS & OCS	0	0	N/A	N/A
	chronic	INS only	0	0	N/A	N/A
		ICS	0	0	N/A	N/A
		OCS	0	0	N/A	N/A
		ICS & OCS	0	0	N/A	N/A
Empyema	intermittent	INS only	14	10	1.47(0.79-2.70)	1.67(0.90-3.09)
		ICS	60	0	N/A	N/A
		OCS	27	5	5.19(0.58-46.5)	N/A
		ICS & OCS	0	0	N/A	N/A
	sub-chronic	INS only	0	11	N/A	N/A
		ICS	0	0	N/A	N/A
		OCS	0	0	N/A	N/A
		ICS & OCS	0	0	N/A	N/A
	chronic	INS only	0	0	N/A	N/A
		ICS	373	0	N/A	N/A
		OCS	0	0	N/A	N/A
		ICS & OCS	0	0	N/A	N/A
Encephalitis	intermittent	INS only	3	1	2.33(0.56-9.73)	2.30(0.55-9.71)
		ICS	0	0	N/A	N/A
		OCS	0	0	N/A	N/A
		ICS & OCS	0	0	N/A	N/A
	sub-chronic	INS only	0	0	N/A	N/A
		ICS	0	0	N/A	N/A
		OCS	0	0	N/A	N/A
		ICS & OCS	0	0	N/A	N/A

Meningitis	chronic	INS only	0	0	N/A	N/A
		ICS	0	0	N/A	N/A
		OCS	0	0	N/A	N/A
		ICS & OCS	0	0	N/A	N/A
	intermittent	INS only	4	7	0.60(0.23-1.56)	0.62(0.24-1.63)
		ICS	0	10	N/A	N/A
		OCS	13	5	2.60(0.24-28.7)	N/A
		ICS & OCS	0	0	N/A	N/A
	sub-chronic	INS only	0	21	N/A	N/A
		ICS	0	0	N/A	N/A
		OCS	0	0	N/A	N/A
		ICS & OCS	0	0	N/A	N/A
	chronic	INS only	0	0	N/A	N/A
		ICS	0	0	N/A	N/A
		OCS	0	0	N/A	N/A
		ICS & OCS	0	0	N/A	N/A

N/A: Rate Ratios with insufficient number of events to provide meaningful results.

† $p \leq 0.01$ (INS control)

‡ $p < 0.05$ (INS control)

Conclusion: This extensive analysis of very large patient cohorts of FP and other INS has allowed a “real-world” evaluation of events historically associated with corticosteroid exposure. Although the vast majority of patients had intermittent exposure as one dispensing of FP or other INS, results suggested a somewhat higher rate of a few outcomes in the FP-exposed group. Rates of five of the thirteen outcomes assessed were statistically elevated in the intermittent user FP versus other INS cohorts; three were found to have rate ratios between 1.1 and 1.2 (nasal septum perforation, sinusitis, and abscess), indicating marginal clinical impact. Hypercorticism and empyema occurred twice as often in FP patients as compared to other INS patients. Of note, when patients taking concomitant corticosteroids were removed from the analyses of hypercorticism and empyema, the statistical difference between FP and other INS groups dissipated suggesting potential confounding by concomitant corticosteroid use. In contrast to these findings, FP patients were less likely to have a cataract diagnosis than other INS patients. Rates of the seven other incident outcomes evaluated (adrenal insufficiency, fracture, glaucoma, osteoporosis, cellulitis, encephalitis, and meningitis) were not found to be statistically different between the FP and INS cohorts.

Publications:

Motsko SP, Corrao MA, Vendiola RM, Davis KJ, Goehring EL, Jones, JK. 2006. Risk of adverse effects with fluticasone propionate as compared to other intranasal steroids [abstract]. In: 22nd International Conference on Pharmacoepidemiology & Therapeutic Risk Management; 2006 Aug 24-27; Lisbon, Portugal. Bethesda (MD): International Society for Pharmacoepidemiology. 429.

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