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ORIGINAL RESEARCH ARTICLE

Intranasal Fluticasone Propionate Observational Cohort Safety Studies: Reviewing Evidence from Databases on Two Continents

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Abstract

Purpose Our objective was to highlight the importance of database selection in observational research and to determine the incidence of corticosteroid-related events in patients exposed to fluticasone propionate intranasal spray (FPNS) compared with other intranasal steroids (INS).

Methods After a feasibility study using an electronic medical record database in the UK (1990–2002), a retrospective cohort study was conducted using a large administrative claims database in the USA from 1994 to 2002 comparing the incidence and rate ratios of steroid-related events among intermittent, sub-chronic, and chronic FPNS use and other INS use episodes.

Results Most patients used INS intermittently; power was low to evaluate risk associated with chronic use. Significantly elevated adjusted rate ratios were observed in the US study comparing FPNS with other INS for hypercorticism, sinusitis, abscess, and empyema, as well as a significantly decreased rate ratio for cataracts. The US claims database provided greater granularity on covariates and markers of severity to improve control of confounding for this study and time period, but neither database was able to assess the indication for prescription and the UK study could not address the use of INS without a prescription.

Conclusions The FPNS results were consistent with the risk profile for INS and did not raise any new safety signals at the time of study conduct, which is consistent with the current safety profile. We were not able to discern the extent of potential off-label use of FPNS or other INS. Differences in the available data and healthcare systems highlight important considerations for database selection in the feasibility phase to assess the precision and limitations prior to formal risk evaluation.

Key Points

The results of these studies, along with findings from other observational studies and randomized longer duration clinical studies, were consistent with the labeled risk profile for intranasal steroids and did not raise any new safety signals associated with the use of fluticasone propionate intranasal spray.

Database selection can benefit from a feasibility phase to assess the precision based on number of events of interest in the target population, prescribing patterns (e.g., extent of channeling), and availability of potential confounders of interest and detail/completeness of data prior to embarking upon a full comparative safety risk evaluation.

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1 Introduction

To illustrate the importance of database selection and highlight the differences between databases, we present lessons gleaned from conducting similar analyses with

nearly identical designs in different databases, evaluating the use and effects of intranasal corticosteroids (INS). In mid-2000, we conducted two parallel retrospective cohort studies of the safety of fluticasone propionate intranasal spray (FPNS) compared with other INS. We utilized the UK Clinical Practice Research Datalink (CPRD; formerly known as General Practice Research Database [GPRD]) and a large US managed care database to evaluate the utilization and safety of FPNS.

INS are common treatments for rhinitis (allergic and non-allergic), providing broad relief of symptoms, including nasal congestion, sneezing, nasal itching, and rhinorrhea [1]. INS are a mainstay of pharmacotherapy in adults and children; they have well-established efficacy and tolerability, yet concerns remain among patients and healthcare providers regarding systemic effects, particularly with concurrent exposure to oral and high-dose inhaled corticosteroids [2, 3]. Systemic concerns, particularly with chronic use, include growth inhibition via suppression of the hypothalamus–pituitary–adrenal axis, decreased bone mineral density (i.e., fractures and osteoporosis), ocular effects (i.e., cataracts, glaucoma, and myopathy), hypertension, hyperglycemia, and bruising [2, 4].

FPNS is an INS that was approved in the 1990s for use among adults and children aged 4 years and older. In the USA, FPNS is a prescription medication approved for the treatment of seasonal and chronic allergic and non-allergic rhinitis. In the UK, FPNS is a non-prescription medication approved for prophylaxis and treatment of seasonal allergic rhinitis and perennial rhinitis. FP nasal drops are additionally approved for the regular treatment of nasal polyps in the UK. FP is one of the more potent glucocorticosteroids available for prescription [5]. Clinical trials of FPNS compared with placebo [6–10], including year-long trials [11, 12], did not show evidence of growth changes, bone density effects, or ocular effects in children or adults.

The primary objectives of the studies, when conducted, were to characterize and compare users of FPNS and users of other non-FP INS in terms of demographics and patterns of use; to determine the rates of events of interest among FPNS compared with INS users with intermittent, subchronic, and chronic steroid use; and to assess potential effect modifiers of the association between INS use and events of interest. The study in the UK CPRD database was conducted only through the feasibility stage because of limitations experienced in obtaining the occurrence of and details from specialist physician encounters (e.g., procedures) within the database; however, this work informed the US study. Therefore, we briefly describe the general design in the methods and main results of the UK analysis to illustrate the primary objective of this paper: highlighting the differences between the two databases and lessons learned from conducting similar analyses with nearly identical designs in different databases. A more detailed description of the methodological nuances and results from the UK feasibility study are provided in Resource 2 of the Electronic Supplementary Material (ESM).

2 Methods

2.1 Data Sources

The GPRD, now CPRD, contains computerized healthcare information entered by general practitioners (GPs) in the UK [13, 14], including demographics, prescriptions, clinical events, preventive care, specialist referrals, and hospital admissions (though not all procedures, laboratory tests, or diagnoses recorded during a hospitalization). All members of the population are registered with a single practice, which centralizes the medical information from GPs, specialist referrals, and hospital attendance. An approximate 6 % sample of the UK population, with patient records in CPRD from 1 January 1990 to 31 January 2002 was used to develop the overall UK study cohort. The protocol for the UK study was submitted to the CPRD Scientific and Ethical Group for review and comments.

A large US managed care database ('i3 Magnifi'), with claims for approximately 6 million lives (2 million in any given year) in 22 states during the study timeframe, was used for the primary US study. The database contained linked administrative claims data from ambulatory and inpatient sources, including diagnoses, procedures, pharmacy, and hospitalizations. Patient records from 1 January 1994 to 30 September 2002 were used to develop the overall US study cohort. Approximately 17 % of the database membership belonged to a Medicare Risk plan, including claims for adults aged ≥65 years. Roughly 4 % of the population belonged to a Medicare Supplement Plan and were excluded due to the possibility of incomplete records.

2.2 Study Design and Population

Parallel study designs were used for the UK feasibility and US studies, which generally only differed on the detail of data provided by the individual databases, e.g., GP-recorded information versus healthcare insurance claims, including information from specialist physicians. The UK study was conducted through the feasibility stage and informed the US study regarding the ability to control confounding factors. Analyses included two inception cohorts: patients initiated on FPNS and patients initiated on another INS (not FPNS) with no use of any INS in the year prior to study initiation. Patients initiating FPNS or another INS during the analysis period (UK: 1 January 1990 to 1

January 2002; USA: 1 January 1995 through 30 September 2002) were identified, and the first FPNS or other INS prescription claim was assigned as the index date and determined cohort placement.

Patients without continuous coverage in the database (USA: 12 months prior) before the index date were excluded, as were patients aged <4 years at index (see Online Resource 2 in the ESM for specifics of the UK study).

2.3 Exposure

Patient histories were divided into FPNS or other INS use episodes (intermittent, sub-chronic, or chronic use) of consecutive prescriptions, with no more than 60 days between prescriptions (between fill dates or repeat prescriptions) to be considered in the same episode. A break of more than 60 days constituted a separate episode. Intermittent exposure was defined as exposure to the same drug (FPNS or other INS) consisting of one to three consecutive prescriptions, sub-chronic four to eight consecutive prescriptions, and chronic nine or more consecutive prescriptions. A span of at least 6 months had to elapse between the first and last prescription claim of a chronic episode. The first exposure episode (i.e., episode including the index date) was required to have at least 120 days free from exposure to another INS after the last claim in the episode. If a patient in the FPNS cohort received another INS during the study period, he or she was censored at the date of other INS dispensing.

2.4 Outcomes

The same outcomes were assessed in both studies: cataracts, glaucoma, nasal septum perforation, hypercorticism (Cushing's syndrome), adrenal insufficiency, fractures (hip, wrist, or vertebral) as proxies for osteoporosis, sinusitis (acute and chronic), and infectious complications of sinusitis (cellulitis [periorbital], empyema [maxillary], abscess [brain], meningitis, encephalitis). Otitis media, asthma, and diabetes were also assessed in the UK feasibility study. Outcomes were identified by International Classification of Diseases, ninth edition (ICD-9) codes in the US database, along with drug codes as a proxy measure for glaucoma diagnosis.

2.5 Analysis

Patients in the FPNS and other INS cohorts were compared on sex, age, comorbid diseases (diagnosed prior to episode index date), oral corticosteroid (OCS) and inhaled corticosteroid (ICS) use, use of other medications, and prior healthcare utilization, as well as region, seasonality (month) of first INS prescription, number of INS prescriptions per year, and average number of days between prescription refills (stratified by eligible time). Risk factors for each outcome were identified utilizing an historical cohort (Online Resource 1 in the ESM). Patients with key variables missing (e.g., demographics) were not eligible for the analysis. Poisson regression modeling estimated the relative rate adjusting for the potential confounders with 95 % confidence intervals (CIs) specific to each outcome (for details see Online Resource 1 in the ESM). Manual stepwise regression identified risk factors/modifiers that were independently associated with the endpoint under evaluation (threshold of $p < 0.1$ for inclusion in modeling). Covariates known to be major contributing factors were forced into the model. An alpha level of 0.05 was used to test for statistical significance.

Outcomes were analyzed based on exposure episodes, with one episode per person randomly selected from all eligible episodes. One episode per person was randomly selected to provide a more representative sample of the INS user population and avoid correlated multiple episodes, as the vast majority of INS utilization is intermittent based on exposure to triggers. Capture of incident events began with the first prescription in the episode and terminated 120 days (30 days of medication use plus a 90-day observance tail) after the last prescription. Episodes with fewer than 120 days of eligibility after the last prescription were excluded from the outcome analyses, as were episodes with exposures to another study medication during the 120-day assessment period. Person-time accumulated from the episode index date to the first of an outcome event date or a set time (USA: 120 days) after the last prescription when the observations were censored.

Incidence rates and rate ratios (RRs) were calculated for events during the randomly selected episodes overall as well as stratified by episodes that were intermittent, sub-chronic, and chronic use episodes. Each outcome was analyzed separately. Patients with the outcome of interest prior to the cohort index date (USA: 12 months prior) or prior to an episode start date (USA: 12 months prior) were excluded from the analysis of that specific outcome to rule out prevalent conditions.

3 Results

The UK feasibility study included 333,182 (FPNS: 62,380; other INS 270,802) intranasal corticosteroid users. The US study contained 126,613 INS users (FPNS 52,870; other INS 73,743), who were predominantly female, distributed throughout the study age range (≥4 years), and evenly distributed by season of INS initiation (Table 1).

Table 1 US study population (US analysis)

	FPNS cohort 52,870	INS cohort 73,743	Total 126,613
Male	21,877 (41.4)	30,245 (41.0)	52,122 (41.2)
Age (years)			
4–14	5755 (10.9)	8751 (11.9)	14,506 (11.5)
15–24	4269 (8.1)	5332 (7.2)	9601 (7.6)
25–34	6842 (12.9)	8118 (11.0)	14,960 (11.8)
35–44	10,827 (20.5)	14,066 (19.1)	24,893 (19.7)
45–54	10,684 (20.2)	13,916 (18.9)	24,600 (19.4)
55–64	6252 (11.8)	8223 (11.2)	14,475 (11.4)
65–74	4971 (9.4)	8672 (11.8)	13,643 (10.8)
75–84	2616 (4.9)	5264 (7.1)	7880 (6.2)
≥85	654 (1.2)	1401 (1.9)	2055 (1.6)
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	1191 (2.3)	2486 (3.4)	3677 (2.9)
Season[a]			
Winter	14,280 (27.0)	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)

Data are presented as *n* (%)

FPNS fluticasone propionate intranasal spray, *INS* intranasal corticosteroids

[a] Date of first FPNS/INS prescription

3.1 UK Feasibility Analysis

Comparing FPNS with other INS users, elevated incidence rates for the following events were observed: abscess, diabetes, nasal septum perforation, osteoporosis, and chronic sinusitis. Cox models for randomly selected intermittent episodes compared the time to the outcome of interest adjusting for prevalence of all other events of interest, age, sex, OCS use, ICS use, prescription antihistamine use, nasal polyps, and number of visits to a GP in the prior 12 months. Crude hazard ratios (HRs) comparing FPNS with other INS suggested that use of FPNS was associated with an increased risk of nasal septum perforation (FPNS n = 198, INS n = 643 INS; HR 1.39, 95 % CI 1.18–1.63), osteoporosis (FPNS n = 60, INS n = 161; HR 1.66, 95 % CI 1.23–2.23), chronic sinusitis (FPNS n = 280, INS n = 704; HR 1.80, 95 % CI 1.57–2.07), diabetes (FPNS n = 76, INS n = 281; HR 1.19, 95 % CI 0.92–1.53), and abscess (FPNS n = 9, INS n = 26; HR 1.55, 95 % CI 0.73–3.31). The final adjusted HRs for these outcomes were all less than 1.50, suggesting weak associations with FPNS exposure. Additional results and discussion of the UK feasibility study are posted on the GlaxoSmithKline Clinical Study Register (http://download.gsk-clinicalstudyregister.com/files/ed97c9c9-9928-4ee0-8f5f-72bbb212a638) and described in Online Resource 2 (ESM).

The reduction from crude to adjusted HRs suggested that some confounding was removed; however, concern remained about residual confounding by indication/severity given the limited detailed information from CPRD available at the time (discussed below) for modeling. Based on the prevalent conditions in year prior to the index date, including evidence of prevalent asthma, acute and chronic sinusitis, nasal septum perforation, and chronic and acute otitis, allergic rhinitis appeared to be more severe among patients prescribed FPNS than another INS.

3.2 US Analysis

While age, sex, acute sinusitis, OCS, ICS, antihistamine prescriptions, nasal polyps, prevalent conditions, and GP visits were included in the UK models, the US database allowed a more granular characterization of patients' risk profiles, including dispensed medications and additional comorbid diagnoses (Online Resource 1 [ESM]), along with utilization and procedure data from both primary and specialist care, which consequently allowed for better control and clearer understanding of potential confounding factors. The covariates used in each model were outcome specific (Online Resource 1 [ESM]), such that they were associated with both the outcome and the probability of receiving a FPNS prescription.

After adjusting for risk factors identified in the historical cohort, five outcomes (hypercorticism, nasal septum perforation, sinusitis, abscess, and empyema) were statistically significantly more likely to occur in FPNS than INS patients, though absolute risks were lower than in the UK feasibility study (Table 2). The relative risk of nasal septum perforation was 1.10, 95 % CI 1.00–1.22, as compared with the UK study (HR 1.41, 95 % CI 1.21–1.67). Similar reductions in the adjusted risk were also observed for sinusitis, osteoporosis, and abscess when comparing the US and UK studies (Fig. 1). Adrenal insufficiency and encephalitis occurred more frequently among FPNS patients, though 95 % CIs included the null value. In contrast, FPNS patients were significantly less likely to have received a diagnosis for cataracts than patients taking other INS.

Nearly 86 % of FPNS patients and 84 % of INS patients received only one prescription during the selected episode for the overall analysis. Of the 126,613 total patients in the study, roughly 97 % of FPNS and INS patients were categorized as intermittent users, 2.5 % as sub-chronic users, and 0.5 % as chronic users. After stratification by usage, intermittent users were found to have roughly the same

Table 2 Event rates from randomly selected intranasal corticosteroids exposure episodes (US analysis)

Events	FPNS cohort (n = 52,870)			INS cohort (n = 73,743)			Crude rate ratio
	# of Events	PY	Rate/10,000 PY	# of Events	PY	Rate/10,000 PY	FPNS vs INS RR (95 % CI)
Adrenal insufficiency	14	18,701	7	13	26,224	5	1.51 (0.71–3.21)
Cataract	483	18,088	267	992	24,785	400	0.67 (0.60–0.74)
Fracture	134	18,714	72	180	26,184	69	1.04 (0.83–1.30)
Glaucoma	241	18,294	132	378	25,400	149	0.89 (0.75–1.04)
Hypercorticism	19	18,845	10	10	26,387	4	2.66 (1.24–5.72)
Nasal septum perforation	745	17,998	414	939	25,382	370	1.12 (1.02–1.23)
Osteoporosis	59	18,775	31	79	26,315	30	1.05 (0.75–1.47)
Sinusitis	5870	12,719	4615	7710	18,556	4155	1.11 (1.07–1.15)
Abscess	2076	15,503	1339	2562	21,977	1166	1.15 (1.08–1.21)
Cellulitis	36	18,837	19	60	26,371	23	0.84 (0.56–1.27)
Empyema	30	18,859	16	22	26,401	8	1.91 (1.10–3.31)
Encephalitis	5	18,879	3	3	26,426	1	2.33 (0.56–9.76)
Meningitis	8	18,869	4	18	26,412	7	0.62 (0.27–1.43)

FPNS fluticasone propionate intranasal spray, *INS* intranasal corticosteroids (non-FP), *RR* rate ratio, *PY* patient years

adjusted and unadjusted RRs as in the overall analysis. Outcomes that were statistically significant in the overall analyses were significant in the intermittent user subgroup (data not shown). A robust assessment of study outcomes within these usage categories was not possible because of the limited number of patients and outcomes in the sub-chronic and chronic subgroups.

Roughly 85 % of FPNS and INS patients were dispensed only an INS with no concurrent ICS or OCS dispensing during a FPNS or INS episode. Approximately 8 % of FPNS and INS patients were dispensed concurrent OCS, 4 % received concurrent ICS, and 2 % received concurrent ICS and OCS during the randomly selected analysis episode. For patients without concurrent steroid exposure (i.e., only FPNS or INS exposure), the adjusted RRs were similar to the overall analysis, with the exception of hypercorticism and empyema, which were decreased and not statistically significant (RR 2.12, 95 % CI 0.75–5.97 for hypercorticism and RR 1.60, 95 % CI 0.87–2.94). We were unable to calculate adjusted RRs by concurrent corticosteroid stratum (ICS, OCS, and ICS and OCS) because the numbers of events were insufficient to provide meaningful results, including many strata with zero events. Crude RRs by concurrent corticosteroid stratum were not statistically different between FPNS and INS users, and they were generally based on small numbers of events (data not shown).

We explored the effect of both episode type and concurrent corticosteroid (ICS and/or OCS) use, and patients were divided into categories by episode type and steroid use. Only the category of intermittent non-concurrent corticosteroid users could be reliably assessed as the other sub-categories had only small numbers. Virtually the same RRs were found, and the same trend of significantly different outcomes was observed for intermittent non-concurrent steroid users as all non-concurrent steroid users (data not shown). Data not presented here on episode type, concurrent corticosteroid use, and the combined effect, are described in the ESM.

4 Discussion

Despite the established safety of INS, concerns remain regarding systemic effects reported with concurrent corticosteroids use [2]. We present two parallel retrospective cohort studies of the safety of FPNS versus other INS in the UK and USA, emphasizing the importance of database selection and adding to the existing literature on INS safety. The conclusion drawn from these complementary sources was a reassuring safety profile for FPNS and that the vast majority of patients used the medicine in intermittent episodes. Although these data are from the 1990s and early 2000s, and patterns of use and healthcare may have evolved somewhat, the conclusion drawn from these analyses is consistent with the current safety profile of INS.

The databases utilized in the UK feasibility and US primary analysis recorded different details regarding exposures, outcomes, and confounders during the study period, as well as different healthcare delivery systems with varying incentives for prescribing choices that influenced the interpretability of study results. For example, the UK database contained data input by GPs, including medications prescribed and referrals to specialists, while the US database contained pharmacy and specialist

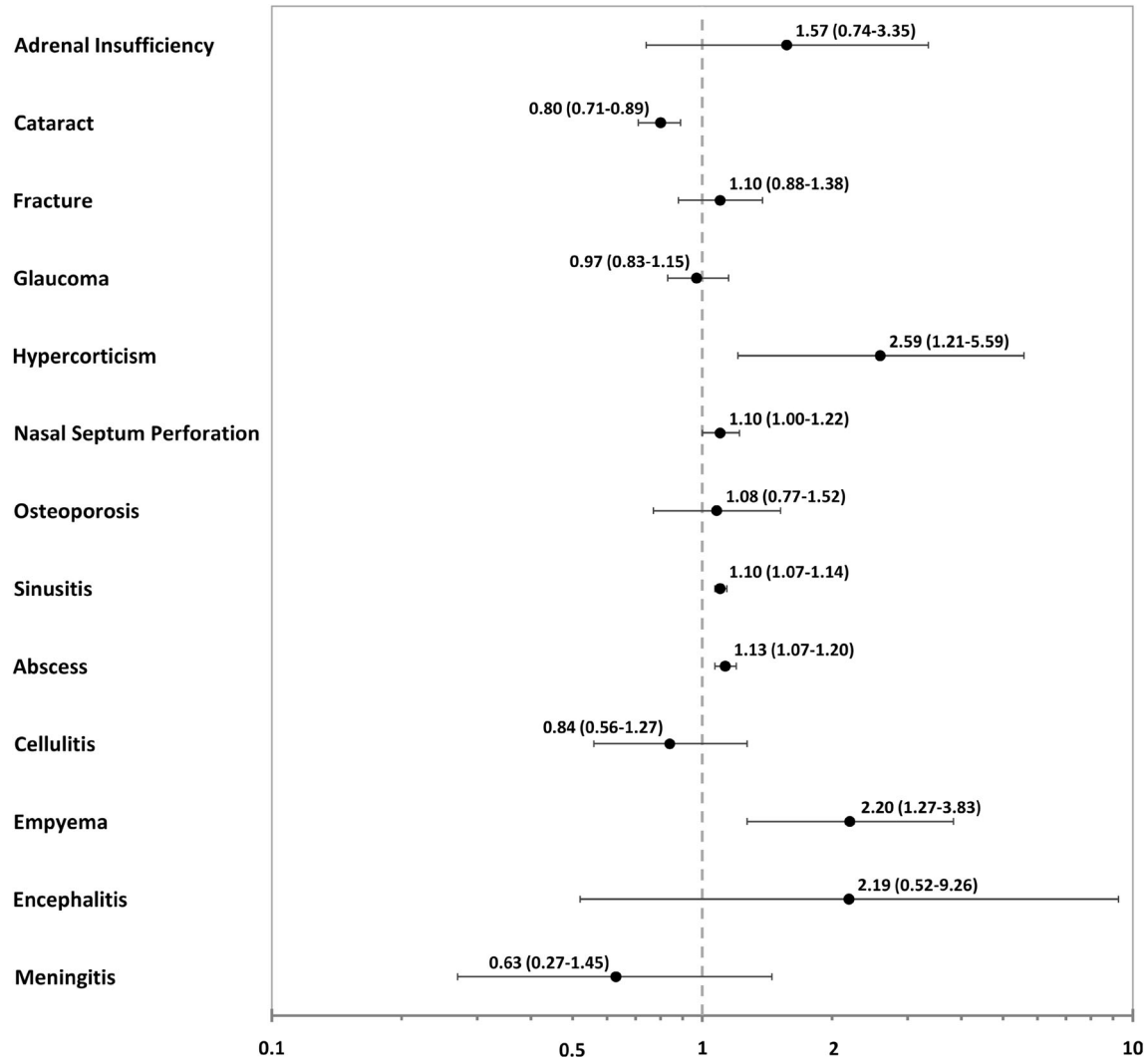

Fig. 1 Adjusted rate ratios and 95 % confidence intervals associated with fluticasone propionate intranasal spray exposure for selected outcomes compared with other intranasal corticosteroid exposure (US analysis). US study results adjusted for outcome specific covariates (supplemental Table 1)

physician claims, including diagnoses, procedures, medications dispensed, and specialist healthcare utilization. Neither database provided the indication for the specific FPNS or INS prescription, and we could not examine use without a prescription in the UK. After adjustment in the UK study, concern remained about residual confounding given the limited detail about the indication and clinical severity in the electronic medical records. It is possible that restriction of newer or more expensive therapies, such as FPNS, in the UK health system to patients who remain symptomatic while receiving cheaper medicines incentivized GP prescribing of FPNS to more severe patients and caused channeling or confounding by severity. Higher baseline prevalence of conditions was observed comparing FPNS with other INS in the UK study: acute sinusitis (31.6 vs. 28.9 %), asthma (21.6 vs. 16.0 %), chronic sinusitis (2.7 vs. 1.1 %), nasal septum perforation (1.5 vs. 0.7 %), and chronic (2.0 vs. 1.3 %), and acute otitis (15.4 vs. 11.0 %). The US managed care database provided additional information on confounding variables during the study period, with detailed information from specialist claims, including procedure codes (e.g., nasal polyp or sinus surgery), providing unique detail not captured in the CPRD.

The adjusted HR for chronic sinusitis in the UK study was 1.40 (95 % CI 1.23–1.63) and suggested FPNS was prescribed more often than other INS after multiple acute events (confounding by severity). In the US study, the adjusted RR for sinusitis, 1.10 (95 % CI 1.07–1.14), was lower than that observed in the UK analysis, with the list of covariates evaluated for inclusion in the US multivariate model extended to include age, sex, past and concurrent steroid use, interacting

drugs, asthma, cystic fibrosis, Kartagener's, immune system disorders, chemotherapy, upper respiratory infections, immunosuppressants, HIV/AIDS, region, and season. Age, sex, region, season, asthma, upper respiratory infections, recent past ICS use, concurrent corticosteroid use (all categories), itraconazole, and ketoconazole were all found to be independent risk factors in the multivariate model. Similar attenuation with the more extensive US list of covariates was observed for nasal septum perforation and abscess.

Approximately 97 % of subjects in the US study were categorized as intermittent users and presented challenges for study outcomes, for example, fracture, which depend upon a longer exposure window to examine a biologically plausible mechanism associated with chronic use of INS. A minority of patients were also observed with concomitant exposure to ICS and/or OCS ($\sim$14 %), which limited the conclusions that could be drawn regarding total steroid exposure from the concurrent steroid analysis. Further, in these observational analyses, new users of FPNS may have been exposed to another INS earlier due to the prescribing patterns in clinical practice. In such situations, pragmatic randomized study designs would be the optimal way to overcome limitations of retrospective database design and obtain a less biased assessment of comparative safety.

Despite the limitations, these studies analyzed large patient populations and allowed a 'real world' comparison of the effects of FPNS to other INS. Although the data utilized in these analyses are older, the potential safety issues with INS and ability to identify the safety outcomes in both the UK and US database have not changed, and these data confirmed the safety profile of INS.

In the overall assessment of the US study, rates of diagnosed hypercorticism, sinusitis, abscess, and empyema were statistically elevated among the group dispensed FPNS compared with the group dispensed INS. However, associations with hypercorticism and empyema were not statistically significant after the concomitant ICS- or OCS-exposed patients were excluded, suggesting confounding due to additional corticosteroid burden, though this is potentially related to statistical power. Although sinusitis and the associated nasal discharge is not a labeled indication, INS may have been prescribed to manage the condition. Therefore, we could not rule out the potential for off-label use, challenging the temporal association between exposure and outcome in a retrospective claim-based observational study.

5 Conclusion

The results of both studies were consistent with both the labeled risk profile for INS during the observational study timeframes and the current risk profile [2, 14–16], and did not raise any new safety signals associated with FPNS use. The parallel designs in two unique databases and somewhat differing results highlight that variability in prescribing practices, healthcare systems, and availability/extent of detail in linked data are all important considerations for choice of observational databases in the feasibility phase of study design. A feasibility phase allows assessment of precision and limitations based on number of events of interest and extent of exposure (e.g., intermittent vs. chronic use), profile of prescribing patterns based on disease severity (e.g., extent of channeling) over time, and availability/details of potential confounders of interest before the more appropriate database(s) is selected for a full risk-evaluation study. These observational study data presented for FPNS versus INS, considered in the context of the healthcare systems, add to the evidence base of randomized and observational studies informing decision making for regulatory authorities, physicians, and patients.

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Compliance with Ethical Standards

Ethical standards The analyses were conducted in de-identified electronic medical record/insurance claims databases. The manuscript does not contain clinical studies or patient data.

Conflict of interest KJD and DH are full-time employees of GlaxoSmithKline (GSK) R&D; KJD is a GSK shareholder. These studies were funded by GSK. The decision to submit for publication is in accordance with GSK's data disclosure and dissemination policy for transparent conduct of research activities. The authors had full control of all primary data and agree to allow the journal to review their data if requested. Stephen Motsko was formerly employed by The Degge Group, Ltd., and is currently employed by Eli Lilly.

Prior postings and presentations The study reports and results of the two studies summarized appear on the GSK Clinical Study Register (http://download.gsk-clinicalstudyregister.com/files/ed97c9c9-9928-4ee0-8f5f-72bbb212a638).

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