Retrospective Case-Control Studies of Rare Adverse Events Associated with Intranasal Steroids

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1. Introduction

This research explored the putative associations between exposure to intranasal steroids and the subsequent development of glaucoma, cataract or adrenal insufficiency, using a retrospective nested case-control design. The goals of this study were to determine the odds ratios for developing glaucoma or cataract in relation to recent and length of exposure to intranasal steroid or intranasal fluticasone, and to determine the odds ratio for developing adrenal Insufficiency after discontinuation of intranasal steroids or intranasal fluticasone.

The medical literature includes several studies on the putative association between intranasal steroids and the development of open-angle glaucoma and/or ocular hypertension, as well as studies on the relationship between cataract and prior exposure to intranasal steroids or fluticasone.

For example, Garbe et al. (1) undertook a case-control study to determine whether the use of inhaled and nasal glucocorticoids is associated with an increased risk of ocular hypertension or open-angle glaucoma. The OR was adjusted for age, sex, diabetes mellitus, systemic hypertension, use of ophthalmic and oral glucocorticoids, and characteristics of health care system use in the year before the index date. The data source was Quebec universal health insurance program for all elderly registered in the Regie de l'assurance maladie du Quebec (RAMQ) database. Garbe et al. identified all prescriptions for inhaled and nasal glucocorticoids that had been filled by cases and controls in the year before the index date and studied the risk of current exposure for both routes of administration. To study the risk of prolonged exposure, Garbe et al. examined the risk in patients who had used inhaled or nasal steroids continuously for the last 3 or more months before the index date.

Garbe et al. concluded that current use of inhaled and nasal glucocorticoids was not associated with an increased risk of ocular hypertension or open-angle glaucoma, and that current users of high doses of inhaled steroids prescribed regularly for 3 or more months were at an increased risk with an OR of 1.44 (95% confidence interval, 1.01-2.06). The adjusted odds ratios and 95% confidence intervals (CIs) for ocular hypertension or open-angle glaucoma according to continuous use or any other use of intranasal steroids were: 1.09 (0.87-1.37) for any use, and 1.02 (0.59-1.77) for continuous use.

Ernst et al. (2) undertook a matched nested case–control analysis in a population-based cohort of elderly people who had been dispensed medications for airway disease, as identified through a universal drug benefit plan. Inhaled corticosteroid use was associated with a dose-related increase in both the risk of all cataracts and severe cataracts requiring extraction, and the increase in risk of severe cataracts was apparent even at daily doses of 500 mg. An excess risk with nasal corticosteroids was not apparent for severe cataracts. Ernst et al. concluded that among the elderly, even low doses of inhaled corticosteroids are associated with a small but significant excess risk of cataracts requiring extraction. Such an excess risk was not observed with nasal corticosteroids. The adjusted relative risk (RR) of severe cataracts for the mean daily dose of inhaled (ICS) and nasal corticosteroid (NCS) in the 4-yr period prior to the index date were 1.24 (1.18-1.31) and 1.03 (0.99-1.07), respectively.

No published studies on intranasal steroid exposure and adrenal insufficiency were found in the literature at the time of writing the protocol. However, Mortimer et al. (3) evaluated oral and inhaled steroid exposure and adrenal insufficiency using a case-control study designed based on computerized general practice data from The Health Improvement Network. From a cohort of 2.4 million people, 154 cases of adrenal insufficiency and 870 controls were identified. There was a dose related increased risk of adrenal insufficiency in people prescribed an oral corticosteroid with an odds ratio of 2.0 (95% CI 1.6

to 2.5) per course of treatment per year. Adrenal insufficiency was associated with a prescription for an inhaled corticosteroid during the 90 day period before the diagnosis with an odds ratio of 3.4 (95% CI 1.9 to 5.9), and this effect was dose related (p for trend 0.001). After adjusting for oral corticosteroid exposure, this odds ratio was reduced to 1.6 (95% CI 0.8 to 3.2) although the dose relation remained (p for trend 0.036). Mortimer et al. concluded that people prescribed an oral or inhaled corticosteroid are at a dose related increased risk of adrenal insufficiency although the absolute risk is small. This analysis suggests that the increased risk in people prescribed an inhaled corticosteroid is largely due to oral corticosteroid exposure, but inhaled corticosteroids may have an effect when they are taken at higher doses.

On this background, there was interest in assessing the safety of intranasal steroids and the three main outcome groups of glaucoma/ocular hypertension, cataract and adrenal Insufficiency in the context of a large medical and pharmacy claims database.

2.0 Methods

2.1 Population Sample

Population samples were drawn from the IMS LifeLink medical and pharmacy claims database for the time period, January 1, 2006 through December 31, 2011. (4) The disease event time period after a 12-month qualifying period was January 1, 2007 through December 31, 2011. The qualifying period was defined as a 12-month period prior January 1, 2007 in which there were no diagnoses for conditions comprising the specific Diagnosis Groups (e.g., no ICD-9 diagnosis codes that define cases in the Diagnosis Group of interest).

Using a random selection procedure for cases, IMS compiled three separate Diagnosis Groups of cases and controls from the IMS LifeLink database – i.e., 50,000 glaucoma (GLAU)/ocular hypertension (OHTN) cases matched to up to 6 controls (or a total control subgroup up to 300,000); 50,000 cataract (CAT) cases matched to up to 6 controls (or a total control subgroup up to 300,000); and 10,000 adrenal insufficiency (ADINSUF) cases with up to 6 controls (or a total control subgroup up to 60,000).

2.2 Case and Control Definitions

Glaucoma and/or Ocular Hypertension Diagnosis Group (GLAU/OHTN Group): Cases must have been enrolled continuously in the IMS database with both medical and pharmacy claims for at least 1 year without having a diagnosis of glaucoma and/or ocular hypertension or having received treatment for these conditions, in order to quality as a new or incident case of the GLAU/OHTN Group. Cases and controls were allowed to have an index date of the disease event in 2007, 2008, 2009, 2010, 2011, provided they were continuously enrolled for at least 12 months prior to the index data of the disease event. In addition, cases met the following criteria: (a) identification in the medical claims with any diagnoses, procedures, or medications for open-angle Glaucoma or unspecified glaucoma or ocular hypertension (as defined with ICD-9 code list) or Ocular Hypertension by an Ophthalmologist or Optometrist, including: 365.0: borderline glaucoma (including the diagnosis of ocular hypertension); 365.1: open-angle glaucoma; 365.3 glucocorticoid-induced glaucoma; 365.9 unspecified glaucoma; and 365.04, ocular hypertension; (b) not a case and a control for the same diagnosis group (i.e. Glaucoma/Ocular HTN); (c) >39 years of age; (d) enrollment for at least 1 year without having a diagnosis of OHT or OAG or having received treatment for these conditions, in order to quality as a new or incident case of glaucoma.

Controls for the GLAU/OHTN Group were selected from all non-cases in the database who visited an ophthalmologist or optometrist, and were seen by a relevant specialty of interest (ophthalmologist or optometrist) within +/- 1 year of case event date. Up to six controls were matched by IMS to cases on age (+/- 2years of case as of the case event date) and gender. A control was only assigned to one case within the GLAU/OHTN Group. A case or a control was not allowed to be a case and a control.

Cataract Diagnosis Group (CAT Group): Cases must have been enrolled continuously in the IMS database with both medical and pharmacy claims for at least 1 year in the IMS database without having a diagnosis of cataract or having received treatment for this conditions, in order to quality as a new or incident case of CAT Group. Cases and controls may have an index date of the disease event in 2007, 2008, 2009, 2010, 2011, provided they are continuously enrolled for at least 12 months prior to the index data of the disease event. In addition, cases met the following criteria: (a) identification in the medical claims with any diagnoses, procedures, or medications for Cataract by an Ophthalmologist or Optometrist, including 366.45 and drug-induced cataract, 336.9: unspecified cataract; (b) 13: surgery of

the lens for lens extraction or insertion of prosthetic lens; (c) not a case and a control for the same diagnosis group (i.e. Cataract); (d) >39 years of age.

Controls for the CAT Group were selected from all non-cases in the database who visited an ophthalmologist or optometrist and were seen by a relevant specialty of interest (ophthalmologist or optometrist) within +/- 1 year of case event date. Up to six controls were matched by IMS to cases on age (+/- 2years of case as of the case event date) and gender. A case or a control was not allowed to be a case and a control.

Adrenal Insufficiency Diagnosis Group (AI Group): Cases must have been enrolled continuously in the IMS database with both medical and pharmacy claims for at least 1 year in the IMS database without having a diagnosis. Cases and controls were allowed to have an index date of the disease event in 2007, 2008, 2009, 2010, 2011, provided they were continuously enrolled for at least 12 months prior to the index data of the disease event. In addition, cases met the following criteria: (a) consulted a physician and either had a diagnosis of adrenal insufficiency (i.e., adrenal suppression, insufficiency or crisis including Addison's disease) or received medical treatment for these conditions; (b) identification in the medical claims with any diagnoses having the following ICD-9 codes: 255.41 adrenal insufficiency/glucocorticoids deficiency (which includes adrenal crisis, adrenal insufficiency NOS, corticoadrenal insufficiency NOS, combined glucocorticoids and mineralcorticoid deficiency, Addison's crisis, Addison's disease NOS) or 255.9: unspecified disorder of adrenal glands; (c) not a case and a control for the same diagnosis group (i.e. Adrenal Insufficiency); (d) >12 years of age.

Controls for the AI Group were selected from all non-cases in the database who visited a physician within +/- 1 year of case event date. Up to six controls were matched by IMS to cases on age (+/- 2years of case as of the case event date) and gender. A case or a control was not allowed to be a case and a control.

Exclusion criteria for the GLAU/OHTN Group: Cases and controls were excluded if they were on oral steroid replacement therapy in the 12 months prior to the index date, were diagnosed with Cushing's disease at any time over the study period; had no available age; were identified in the medical claims as having any one of the following ICD-9 codes: 365.02 borderline glaucoma with anatomical narrow angle, 365.06 primary angle closure without glaucoma damage, 365.13 pigmentary open-angle glaucoma, 365.14 open-angle glaucoma of childhood, 365.20 unspecified primary angle-closure glaucoma, 365.21 intermittent angle-closure glaucoma, 365.22 acute angle-closure glaucoma, 365.23 chronic angle closure glaucoma, 365.24 residual state angle-closure glaucoma, 365.41 glaucoma associated with chamber angle anomalies; 365.42 glaucoma associated with abnormalities of the iris, 365.43 glaucoma associated with other anterior segment anomalies, 365.44 glaucoma associated with systemic syndromes, 365.51 phagolytic glaucoma, 365.52 pseudoexfoliation glaucoma, 365.59 glaucoma associated with other lens disorders, 365.60 glaucoma associated with unspecified ocular disorders, 365.61 glaucoma associated with pupillary block, 365.62 glaucoma associated with ocular inflammations, 365.63, glaucoma associated with vascular disease of the eye, 365.64, glaucoma associated with ocular trauma, 365.81 hypersecretion glaucoma, 365.82 glaucoma with increased episcleral venous pressure, 365.83 aqueous misdirection, 365.89 other specified glaucoma, 92020 special eye evaluation, 92081 visual field examination(s), 92082 visual field examination(s), 92083 visual field examination(s), 92100 serial tonometry

exam(s), 92120 tonography and eye examination, 92130 water provocation tonography, 92132 computerized ophthalmic imaging of the anterior segment, 92133 computerized ophthalmic imaging of the optic nerve, 92135 ophthalmic diagnostic imaging post segmentation, 92140 glaucoma provocative tests, 66500 incision of iris, 66625 removal or iris, 66761 revision of iris, or 66762 revision of iris.

Exclusion criteria for the Cataract Group: Cases and controls were excluded if they were on oral steroid replacement therapy in the 12 months prior to the index date, were diagnosed with Cushing's disease at any time over the study period; had no available age; cataract ICD 9 diagnostic codes of 366.11 pseudoexfoliation of lens capsule, 366.20 unspecified traumatic cataract, 366.21 LOC traumatic opacities cataract, 366.22 total traumatic cataract, 366.23 partly resolved traumatic cataract, 366.32 cataract inflammatory ocular D/O, 366.33 cataract with ocular neovascularization, 366.34 cataract degenerative ocular D/O, 366.41 diabetic cataract, 366.42 tetanic cataract, 366.43 myotonic cataract, 366.46 cataract with radiation and other physical influences, 366.50 unspecified after-cataract, 366.51 Soemmerings ring, 366.52 other after-cataract no obscuring vision, 366.53 after cataract obscuring vision, 366.8 other cataract.

Exclusion criteria for the Adrenal Insufficiency Group: Cases and controls were excluded if they were on oral steroid replacement therapy in the 12 months prior to the index date, were diagnosed with Cushing's disease at any time over the study period, or had no available age.

2.3 Approaches for Determining Exposures Related to Disease Outcomes

2.3.1 Glaucoma and Cataract

The following lists shows the main parameters used in analyses to assess current exposure to intranasal steroids prior to the disease index date in the Glaucoma/Ocular Hypertension Disease Group and the Cataract Disease Group.

- **Intranasal Steroids:** Beclomethasone, Budesonoide, Flunisolide, Fluticasone, Mometasone, Triamcinolone Both the fluticasone propionate and fluticasone furoate were combined under "Fluticasone" in the main analysis and assessed separately as the fluticasone propionate and fluticasone furoate.
- **Exposure to Intranasal Steroids:** Prescriptions for intranasal steroids that had been filled in the year before the index date
- **Continuous Use of Intranasal Steroids:** Use of intranasal steroids at least 3 months before the index date
- **Current Exposure:** A drug supply for intranasal steroids that continued into the 14-day period before the index date.
- **Covariates:** age, sex, systemic hypertension, diabetes mellitus, current exposure to ophthalmic, oral and inhaled glucocorticoids, characteristics of health care system use in the year before the index date, exposure to CYP-inhibitors, and exposure to certain HIV medications. These covariates are known from the literature to be related to increased risk of GLAU/OHTN and/or CAT.
    - **Definition of systemic hypertension:** filling a prescription for the following antihypertensive medications before the index date: thiazide diuretics, centrally

acting antiadrenergic agents, peripherally acting antiadrenergic agents, ß-adrenergic blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, and vasodilators.

- **Definition of diabetes mellitus:** any use of oral hypoglycemic therapy or insulin before the index date.
- **Definition of health care system use characteristics in the year before the index date (as markers for general ill health):** number of drugs filled, number of office visits, and number of inpatient stays.
- **Use of CYP-inhibitors and HIV medications:** identified from the pharmacy claims data in the IMS LifeLink database.

GLAU/OHTN Group and CAT Group – Strategy 1: Intranasal steroid exposure was assessed in relation to one or more prescriptions for an intranasal steroid within 5 days of the first diagnosis of allergic rhinitis (AR) and/or chronic rhinitis (CR) with or without a concurrent acute or chronic sinusitis (ASIN, CSIN) diagnosis in patients with no history in the 12 months prior to the AR or CR diagnosis of: AR, CR, ASIN, or CSIN; or exposure to corticosteroids. Cases were followed forward to a diagnosis of GLAU and/or OHTN, or a diagnosis of CAT (depending on the diagnosis group being assessed). Current and continuous use of intranasal steroids (INS) and of intranasal fluticasone (INS-FLUT) were assessed as a drug supply for INS or INS-FLUT that continued into the 14-day period before the disease index date, and use of INS or INS-FLUT at least 3 months before the index date.

GLAU/OHTN Group and CAT Group – Strategy 2: A second strategy was used in which subjects were be required to have been enrolled in the database for at least 1 year without having had a diagnosis of a condition in the diagnosis group of interest (i.e., either GLAU/OHTN, or CAT) or having received treatment for these conditions, who consulted an ophthalmologist and who either had a diagnosis of ocular hypertension or open-angle glaucoma or received medical or surgical treatment for these conditions. The index date for the case was the first of these new or incident case-defining events. INS or INS-FLUT exposure was assessed by looking back for 12 months prior to the index date, using the same definitions for current and continuous use as noted above.

2.3.2 Adrenal Insufficiency

For assessing the possible relationship between adrenal insufficiency and INS or INS-FLUT exposure, cessation of INS or INS-FLUT was used as the key event marker in relation to the time period prior to a diagnostic event of adrenal insufficiency. Cases by definition had a 12-month qualifying lead-in period with no diagnosis of adrenal Insufficiency. A 28-day cut-off period for exposure to INS or INS-FLUT was used, in terms of a comparison of continuous INS use over the period of adrenal insufficiency diagnosis, $\leq$ 28 days pre-adrenal insufficiency diagnosis, and > 28 days pre-adrenal insufficiency diagnosis. The main group of interest was the group that used INS for $\geq$ 90 days and discontinued INS 1-28 days prior to a diagnosis of adrenal insufficiency.

2.4 Data Sources

IMS LifeLink Health Plan Claims Database: The IMS LifeLink Health Plan Claims Database has more than 100 data contributors, 88 million enrollees and 72 million patients. The data set provides a

complete picture of patient interactions within the healthcare system. The data is representative of the national, commercially insured population on a variety of demographic measures, including age and gender. Enrollees represented within the data set include employer sponsored plans, and individuals purchasing coverage in the marketplace and government sponsored but commercially administered Medicaid and Medicare plans.

IMS LifeLink Pharmacy Claims Database: The IMS LifeLink Pharmacy claims database (NCPDP) contains history back to 2001. It represents patients receiving prescriptions via retail pharmacy. The NCPDP prescription claims represent dispensed prescriptions for approximately 55% of all pharmacies making up more than 2 billion prescriptions per year. The prescription data samples nearly 59,000 pharmacies in the US and includes cash, Medicaid and third party transactions. The data is nationally representative and is available in near real-time.

The IMS pharmacy claims also provide standard fields for patient demographics for age and gender, zip codes, GP_2, GP_3 and label name, NDC number, generic code, data filled, new refill, Dec quantity (declared quantity), days supply, daily average consumption (DACON, calculated by dividing the total days supply of a product by the total units – i.e., tablets, capsules, milliliters, etc.) dispensed, provider. Length of exposure will be estimated based on days supply of any intranasal steroids or intranasal fluticasone.

IMS provided a list of medications in the IMS LifeLink pharmacy claims database by NDC number. From this list, NDC number groupings were defined for intranasal corticosteroids, ophthalmic corticosteroids, inhaled corticosteroids, oral corticosteroids, dermal corticosteroids, drug exclusions relating to treatments for glaucoma and cataract in the 12 month period prior to first index disease diagnosis for each Diagnosis Group. (Available on request)

HIPAA Compliance: All IMS LifeLink claims data are certified HIPAA-compliant with all de-identified patients being assigned a longitudinally stable identifier.

IMS Data Dictionary: (Available on request)

2.5 Sample Size and Power

Based on the size of the dataset, and the work on power tables for nested case control studies by Pang (5) -- i.e., 500 matched case-control sets using four controls per case were predicted to give a power of .81 for a relative risk of 1.5, and a power of .91 using eight controls per case. It was anticipated that the total number of cases derived from the sample of 50,000 individuals in the IMS data base would be in excess of 1%.

2.6 Methods for Assembling Study Data

IMS provided matched cases and controls: 50,000 cases and 300,000 controls for the GLAU/OHTN Group; 50,000 cases and 300,000 controls for the CAT Group; and 10,000 cases and 60,000 controls for the AI Group.

IMS linked the records from the medical and pharmacy claims. IMS generated unique patient identification codes for the extracted databases containing medical and pharmacy claims for the specified years. The unique patient number was derived from the patient ID numbers found in the medical and pharmacy claims. IMS documented this procedure as well its related quality control process and provide this information to UCSF for review and for the data archive.

The data from IMS comprised the above stated datasets, the IMS documentation of the datasets and the data dictionary for reference.

2.7 Analysis

2.7.1 Glaucoma/Ocular Hypertension Diagnosis Group

Garbe Approach

The main analysis had features that mainly followed those of Garbe et al. (Ref 1), modified for differences in data sources and study design. Garbe et al. derived data from a single public insurer that covered the elderly. On the other hand, the data for this study came from a data base for multiple insurance companies that included younger adults as well as elderly. Garbe used a case-control study design that included date of index diagnosis or physician visit as a matching variable to control for seasonal variation and secular trend. This study was a nested case control study that used all cases and selected controls from a cohort of individuals from a large extract of the IMS data base. In this nested case control study, cases were used only once.

This study estimated the odds ratio of the dependent variable of an observation being a case (disease outcome present, event = 1) versus control (disease outcome absent, event = 0) using conditional (fixed effects) logistic regression. The statistic of interest was the odds ratio of exposure to an intranasal steroid compared to no history of exposure.

The analysis utilized the 'clogit' procedure in STATA, which uses fixed effects to model the data conditional on the matches between cases and controls. The clogit procedure uses a maximum likelihood method for estimation, specifically, the exact conditional likelihood.

Both univariate and multivariate regressions were run. The univariate analysis was used to model the dependent variable as a function of the exposure variable only. The multivariate regression analysis modeled the dependent variable as a function of the exposure variable(s), and explanatory variables to account for effect modifiers and confounders.

There were four groups of explanatory variables. The first group of explanatory variables consisted of demographic information (age and sex) and calendar time period of the index date. The cases and controls were matched on these variables with a ratio of an average of six controls to one case. The match on gender was exact. The match on age was approximate (i.e., each control will be at most two years older or younger than the corresponding case at the time of the index date). The match on calendar time was approximate with the index date of control within one year before or after that of the matched case. These variables defined the basic risk set for the nested case-control study design, and the final analysis matched on these three variables. The second group of variables consisted of indicator variables for exposure to other forms of steroid drugs (e.g., exposure to oral or dermal steroids in the same timeframe as the exposure, such as current use into the 14-day period prior to the index date). The third group of variables consisted of indicator variables for exposure to conditions and treatments (i.e., 12 months prior to the index date in general unless otherwise noted) that might alter susceptibility to the outcome as a function of exposure to intranasal steroids (e.g., use of anti-diabetics, anti-hypertensives, CYP inhibitors, anti-retrovirals (HIV medications) 90-days prior to the index date, and pituitary disease/surgery (for adrenal insufficiency). The fourth group of variables consisted of descriptors of prior utilization of healthcare services 12 months prior to the index date in order to control of detection bias due to differential exposure to diagnostic opportunities. Three categories of utilization were assessed: physician visits, hospitalizations, and prescription drug use.

The utilization variables were classified using several approaches – i.e., (a) as indicator variables for any versus no utilization; (b) as indicator variables for tertiles of the common distribution of utilization across cases and controls; (c) as indicator variables for no utilization (the reference group), and tertiles of the common distribution of utilization across cases and controls for subjects that had any

history of utilization; (d) as count variables (i.e., the count of the utilization measure: claims for the claim measure of utilization; physician visit, hospital admissions, and number of prescription drugs used, as appropriate for the each approach to the measurement of utilization), with the count measure being treated as a continuous variable. Approach (d), which was used in the published Garbe et al analysis produced substantial evidence of model misspecification, and therefore was not used in the final analysis. Approach (c) performed best in terms of specification diagnostics, and was therefore favored for use in final results.

Cases and controls were matched on the first group of variables constituting the risk set (sex, age, and index date).

Two versions of the Garbe approach were estimated: (a) the Univariate Model that used only matching for adjustment for confounders (i.e., named 'univariate' since only the exposure variable appears as an explanatory variable in the regression); and (b) the Full Model that included the other explanatory variables in the logistic regression along with the matched analysis. The Garbe analysis that included only the matching variables used all intranasal steroids as the exposure. The Full Model included two models that used different definitions of exposure: one model used exposure to all intranasal steroids, and the other used fluticasone only.

The Univariate Model used three time frames to define exposure: any history of use, current use (defined as use into 14 days before disease index date), and non-current use (defined as exposure prior to twelve months but not 14 days before the disease index date).

The use of different measures of utilization (count variables treated as continuous covariates, tertiles, and indicator variable) permitted an exploration of functional form of the effect of utilization variables on the results. Garbe used only counts of utilization episodes treated as continuous covariates, which assumed a linear effect of utilization on the outcome.

Several diagnostics, sensitivity and robustness analyses were explored to evaluate the performance of the regression specification and estimates, The influence statistics delta-Beta (for sensitivity of the regression coefficients to groups of observations) and delta-Chi-square (for sensitivity of fit to groups of observations) for the logistic regression predictions were used to identify unusual influential observations The predictive performance of logistic regression was evaluated using in-sample classification statistics. Sensitivity to the matching technique was evaluated by comparing different case to control ratios, including one-to-one matching using several measures of the closest control match from the control set for each case. The univariate common spans for support and imbalances of explanatory variables used for statistical adjustment were examined.

Stratified Model

Examination of the distribution of utilization of covariates in the Full Analysis following Garbe (described above) revealed substantial lack of common support and imbalance between the cases and controls. Exploratory analysis indicated that for the utilization variables, the results were only potentially sensitive to the physician visit measure. Therefore the analysis was repeated, stratified by physician visit, measured as a 0-1 indicator variable and as indicator variables for tertiles. In the main analysis, the other utilization variables (drug and inpatient stay) were omitted. As with the Garbe model, the Stratified Model used two definitions of exposure: one used exposure to all intranasal steroids, and another used exposure only to fluticasone. The remainder of the statistical analysis remained the same as for the Full Model for each stratum, except that the stratification variable was omitted from the regression.

Coarsened Exact Matching (CEM) Model

Examination of the results of the Stratified Model revealed continued lack of common support and imbalance, particularly for the highest tertile of utilization. Therefore we matched on the utilization variables as well as age, gender and index date, using the technique of coarsened exact matching (STAT command 'cem'). Coarsened exact matching allowed adjustment of the maximum univariate distance for inclusion in the same group of candidates for potential matches, and is a 'far-sighted' matching technique which considers the impact of a particular match on the availability of a control for alternative matches. The CEM estimate was designed to force the same matches for age, gender and index date as in the preceding full and stratified analyses. The cut-points for physician visits were 0, one to less than 3, 3 to less than 5, and 5 or more physician visits. The cut-points for inpatient admissions were 0, 1, and 2 or more impatient visits. The cut-points for distinct drugs prescriptions were 0, 1 to less than 3, 3 to less than 6, and 6 or more). The CEM analysis searched for matches that minimized a multivariate distance function, and groups of potential matches could be finer than the specified cut-points. The STATA CEM algorithm found at least several dozen groups for matches on utilization. Use of the CEM algorithm substantially reduced the problem of lack of common support and imbalance of cases and controls, at the cost of omitting observations in both groups.

The CEM analysis also included two models that used different definitions of exposure: one model used exposure to all intranasal steroids, and the other used fluticasone only.

Sensitivity analysis for the CEM algorithm included alternative specification of cut-points, and different case to control ratios including one-to-one and k-to-k matching to explore the potential sensitivity to the matching scheme. The results were approximately the same, in terms of practical significance for all the sensitivity analyses.

2.7.2 Cataract Diagnosis Group

The analysis for the Cataract Diagnosis Group followed that of glaucoma except that only the Full Model, the Stratified Model, and the CEM Model were estimated. The Univariate Model was not estimated. As with glaucoma, two analyses were done for each model one that defined exposure as use of all intranasal steroids and one that defined exposure as use of fluticasone only. The time frame for exposure was any exposure (including both current and non-current use, as defined in the analysis of glaucoma described above

2.7.3 Adrenal Suppression Diagnosis Group

The analysis of adrenal suppression involved estimated the OR of exposure to two different time profiles of INS withdrawal compared to continuous use (the reference group) prior to the index disease date. The two time profiles of exposure were used: (a) exposure 1-28 days before the index date with no record of exposure afterwards ('Discontinued 1-28 days pre AI diagnosis); and (b) exposure up to 29 days before the index date with no record of exposure afterwards ('Discontinued ≥28 days pre AI diagnosis). Only the Full Model was estimated for AI, which was analogous to the Garbe type Full Model, with other explanatory variables entered into the regression for statistical adjustment. The potential confounder of pituitary diagnosis and/or surgery in the 12 months before the disease index date was included, as well as indicator variables for the tertiles of the measures of drug, physician visit, and hospital utilization, using zero utilization as the reference group.

2.8 IRB Approval

This research was conducted under an approved IRB application by the UCSF Committee on Human Research.

3.0 Results

3.1 Glaucoma/Ocular Hypertension Diagnosis Group

3.1.1 Overview of Study Population Characteristics

Table 1 shows the distribution of gender and explanatory variable descriptors in cases and controls for INS in the GLAU/OHTN Group. Cases and controls were comparable in gender distribution. A review of the table shows that certain explanatory variable descriptors used in the regression analyses were significantly different despite the small absolute difference, as a result of the large data sets for cases and controls. A similar pattern was observed for Fluticasone.

Table 2 shows the distribution of cases and controls by different definitions of exposure for all INS and for Fluticasone., with a general picture emerging that more cases were exposed to INS than controls.

Of interest, was whether arbitrary cut-offs in exposure of less than or equal to 90 days, or more than or equal to 90 days (Garbe approach), affected the number of cases included as continuous users. Table 2 shows that the distributions by these two versions of exposure time did resulted in minimum change in the absolute numbers of cases and controls.

An assessment was also made of INS exposure by number of days supply of INS for those cases and controls who were diagnosed with new AR or CR as the first diagnosis after a 12 month period of no AR or CR diagnosis. (Table 3) Significantly more cases were exposure to INS for 90 or more days, based on days supply in this subset of the study population.

Table 1
Distribution of Gender and Explanatory Variable Descriptors in Cases and Controls

Gender	**Cases**		**Controls**		**p**
Male	17,908	42%	104,643	42%	ns
Female	24,518	58%	142,733	58%	ns
Explanatory Variable Descriptors	**Cases (yes)~**		**Controls (yes)~**		
Current use of INS	1,602	4%	6,936	3%	<0.001
Current use of FLU-PRO	965	2.3%	3,431	1.4%	<0.001
Current use of FLU-FUR	22	0.5%	154	0.6%	ns
Current use, oral steroids	953	0.3%	4,315	1%	<0.001
Current use, inhaled steroids	1,115	2.6%	5,027	2%	<0.001
Current use, dermal steroids	614	1.4%	2,930	1%	<0.001
Anti-HTN meds,12m pre index date	16,387	38.6%	76,386	31%	<0.001
DM meds, 12m pre index date	5,612	13.2%	27,800	11%	<0.001
Antiretrovirals, 90d pre index date	40	0.1%	195	0%	ns
Current use of strong CYP inhibitors	196	0.5%	1,084	0%	ns
	Cases		**Controls**		
No use, any Rx, 12m pre index date	10,214	24.1%	70,108	28%	<0.001
Low use, any Rx, 12m pre index date	12,276	28.9%	64,428	26%	<0.001
Mid use, any Rx, 12m pre index date	11,402	26.9%	58,541	24%	<0.001
High use, any Rx, 12m pre index date	8,534	20.1%	54,299	22%	<0.001
No MD visits, 12m pre index date	2,668	6.3%	31,201	13%	<0.001
Low use, MD visits, 12m pre index date	15,648	36.9%	95,914	39%	<0.001
Mid use, MD visits, 12m pre index date	11,966	28.2%	63,035	25%	<0.001
High use, MD visits, 12m pre index date	12,144	28.6%	57,226	23%	<0.001
No inpt hosp, 12m pre index date	35,171	82.9%	182,823	74%	<0.001
Low use, inpt hosp, 12m pre index date	6,227	14.7%	55,793	23%	<0.001
High use, inpt hosp, 12m pre index date	1,028	2.4%	8,760	4%	<0.001

inpt hosp = inpatient hospitalization; FLU-PRO, fluticasone propionate; FLU-FUR, fluticasone furoate

Table2
Distribution of Cases and Controls by Different Definitions of Exposure

Exposure	Case		Control		p* value
	n	%	n	%	
INS Exposure in 12m pre Diagnosis Date					
INS non-exposure	38,105	90%	229,413	93%	
Exposure	4,321	10%	17,963	7%	<0.001
Subsets of Exposure	(n=4,321)		(n=17,963)		
INS current	1,602	37%	6,936	39%	
INS non-current	2,719	63%	11,027	61%	<0.001
INS >=90d	4,291	99%	7,751	43%	
INS <90d	30	1%	10,212	57%	<0.001
INS >90d	4,260	99%	5,880	33%	
INS <=90d	61	1%	12,083	67%	<0.001
FLUT Exposure in 12m pre Diagnosis Date					
FLUT non-exposure	39,760	94%	236,899	96%	
Exposure	2,666	6%	10,477	4%	ns
Subsets of Exposure	(n=2,666)		(n=10,477)		
FLUT current	982	37%	4,082	39%	
FLUT non-current	1684	63%	6,395	61%	<0.001)
FLUT >=90d	2649	99%	4,295	41%	
FLUT <90d	17	1%	6,182	59%	<0.001
FLUT >90d	2635	99%	3,216	31%	
FLUT <=90d	31	1%	7,261	69%	<0.001

* Pearson Chi-squared test

Table 3
INS Exposure by Number of Days Supply

Days Supply	Non Case		Case	
	n	%	n	%
No INS Use	1,856	34%	373	18%
>=90d	1,581	29%	1,723	81%
<90d	1,985	37%	24	1%
Total	5,422	100%	2,120	100%

Pearson chi2(2): p<0.001
*sample further limited to individuals classified as new allergic rhinitis (AR) or chronic rhinitis (CR)" cases, e.g., no AR or CR in 12-month prior to the first diagnosis of AR/CR.

3.1.2 Overview of Regression Analyses

Table 4 shows the distribution of cases in the GLAU/OHTN Group by exposure. Of the total IMS sample, 2.95% of the sample qualified as having current exposure to INS.

Table 4
GLAUCOMA/OCULAR HYPERTENSION
INS Exposure (Non-exposure, Current and Non-current) to Intranasal Steroids 12 Months Prior to Disease (Glaucoma/Ocular Hypertension) Diagnosis

Exposure	Frequency	Percent
INS non-exposure	267,518	92.31
INS use/current	8,538	2.95
INS use/non-current	13,746	4.74
Total	289,802	100

Various approaches were taken to assess the odds ratios associated with intranasal steroid use and fluticasone use and the subsequent development of glaucoma/ocular hypertension. These models are shown in the following sets of tables (Tables 5-14), in sequence as:

- Summary of regression models (Table 5)
- The Garbe type Full Model, with use of three utilization (high, medium, low) tertiles as variables based on 'tertile among positive use > zero=reference group';
- The Stratified Model (i.e., stratified by tertile rates of physician visit)
- The CEM Model (i.e., exacting matching technique).

In all cases, the odds ratios associated with intranasal steroids (or fluticasone) and the subsequent diagnosis of glaucoma/ocular hypertension was significantly elevated (i.e., 1.12 to 1.37), depending on the model, the strata within the model, and/or whether intranasal steroids or only fluticasone was being considered. (Table 5) The complete regression analyses are shown in subsequent tables. The fluticasone results followed the results for any INS, which are the main results shown in this report.

Table 5
GLAUCOMA/OCULAR HYPERTENSION
Summary of Regression Models
(Total Sample = 289,802; see Table 1)

Model	Exposure	OR	n	p
Garbe Type Approach	**(1) INS any exposure vs. non-exposure**	1.36	267,518 (non-exposure)	<0.001
	(2a)INS Use/ Current (vs. non exposure)	1.30	287,996 (regression estimation sample)	<0.001
	(2b)INS Use/Non-current (vs. non exposure)	1.40	287,996 (regression estimation sample}	<0.001
		OR	**n**	**p**
Full	INS	1.23	349,556	<0.001
	INFLUT	1.26	349,546	<0.001
Stratified	**INS** Top 3rd rate of MD visits	1.34	31,310	<0.001
	INS Mid 3rd rate of MD Visits	1.16	33,670	=0.025
	INS Bottom 3rd MD Visits	1.12	65,106	=0.06
	INS No MD Visits	0.94	4,176	=0.77
	INFLUT Top 3rd rate of MD visits	1.30	31,310	<0.001
	INFLUT Mid 3rd rate of MD Visits	1.37	33,670	<0.001
	INFLUT Bottom 3rd rate of MD Visits	1.14	65,106	=0.08
	INFLUT No MD Visits	0.71	4,176	=0.71
CEM Matched	INS	1.28	19,238	<0.001
	INFLUT	1.27	19,214	<0.001

INS: Intranasal Steroids (Any)
INFLUT: Intranasal Fluticasone
Garbe Model: removed negative days supply,
Full Model: three utilization variables included as covariates (bottom tertile of MD visits, middle tertile of MD visits, top tertile of MD visits (vs. reference group as no MD visits); bottom tertile of prescription drug use, middle tertile of prescription drug use, top tertile of prescription drug use (vs. reference group as no drug use); bottom tertile of inpatient hospitalizations, middle tertile of inpatient hospitalizations, top tertile of inpatient hospitalizations (vs. reference group=no hospitalizations)
Stratified Model: stratified by zero/tertiles of physician visit. Prescription drug use and inpatient hospitalizations omitted as covariates.
CEM Model: matched on age, gender, index date, and three utilization variables.

3.1.3 Analysis Using Garbe Type Approach

Garbe et al. (Ref 1) focused on long term use within 12 months pre-disease onset, and reported no significant elevation of odds ratios in terms of glaucoma and intranasal steroids. In following this approach we defined drug exposure variables based on computed days supply in the year before the glaucoma index date. **"Current exposure"** was defined as 14-days into disease index date, and subdivided into: (a) current use; (b) any use in 12 months prior to disease index date but not current use; (c) non-exposure (no use in 12 month prior to disease index date). **"Long-term exposure"** in the year before disease index date was defined in two ways: Version 1, (a) >=90d, (b) <90d, (c) non-exposure (reference group); Version 2, (a) >90d, (b) <=90d, (c) non-exposure (reference group). **"Any exposure"** was defined as any use in the year before disease index date versus no use in 12 month prior to disease index date. (Table 6)

Of note in using the Garbe type approach (Table 6), there is little difference in absolute numbers and percentages of cases and controls between Version 1 and Version 2. Further, very few patients with glaucoma appear in the <90 day exposure window, in comparison to controls. Correspondingly, relatively more cases than controls have exposure to any intranasal steroid or fluticasone than controls. (Table 6)

The Univariate Model with an OR of 1.45 is shown in Table 7.

Table 6
GLAUCOMA/OCULAR HYPERTENSION
Version 1 and 2 Comparison of Long Term INS Exposure Definitions

Garbe Approach	**N**		**%**		50,000 cases and 300,000 controls
Cases and Controls	**289,802 (total sample; see Table 1)**		**83%**		60,198, excluded for not meeting criteria re: age >=45, not current user of oral hydrocortisone, or having negative INS days supply
Current vs. Non-current use in 12 months before disease index date					
INS non-exposure^	229,413		93%		^ No INS in 12m pre disease index date
INS current ^	6,936		3%		^ INS use in 12m pre disease index date
INS/non-current^	11,027		5%		^ INS use in 12m pre disease index date
Total	247,376		85%		
	Controls		**Cases**		
	n	**%**	**n**	**%**	
Version 1 of Duration of Exposure in 12 months before disease index date					
INS non-exposure	229,413	93%	38,105	90%	^ No INS in 12 m pre disease index date
INS >=90 days	7,751	3%	4,291	10%	
INS <90 days	10,212	4%	30	<1%	
Total	247,376	100%	42,426	15%	
Version 2 of Duration of Exposure in 12 months before disease index date					
INS non-exposure	229,413	93%	38,105	90%	^ No INS in 12 m pre disease index date
INS >90 days	5,880	2%	4,260	10%	
INS <=90 days	12,083	5%	61	<1%	
Total	247,376	100%	42,426	15%	

#	289,802 = 42,426 cases and 247,376 controls
*	For all models, there was no use of oral hydrocortisone (i.e., exclusion criterion
^	Current use is days supply that extends in to 14 day period pre disease index date
	No exposure – no INS in 12 months pre index date
	Any use in 12 months prior to disease index date but not current use

Table 7
GLAUCOMA/OCULAR HYPERTENSION
Intranasal Steroids
Garbe Approach:
Univariate Analysis

case_yes	**Odds Ratio**	**Std. Err.**	**z**	**P>|z|**	**[95% Conf.**	**Interval]**
Use of INS	1.45521	0.0262204	20.82	<0.001	1.404716	1.507519

Table 8
GLAUCOMA/OCULAR HYPERTENSION
Intranasal Steroids
Garbe Approach
Full Model – Any INS Exposure

Conditional (fixed-effects) logistic regression

Number of obs	287996
LR chi2(16)	321.3
Prob>chi2	<0.001
Pseudo R2	0.002
Log Likelihood	-80252.543

Explanatory Variable Description	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Current use of INS	1.3594	0.0259367	16.09	<0.001	1.309504	1.411198
Current use, oral steroids	1.319444	0.0496745	7.36	<0.001	1.225589	1.420487
Current use, inhaled steroids	1.199595	0.0420877	5.19	<0.001	1.119877	1.284987
Current use, dermal steroids	1.189814	0.0546287	3.79	<0.001	1.08742	1.30185
Anti-HTN meds,12m pre Ind date	1.516366	0.0198152	31.86	<0.001	1.478022	1.555704
DM meds, 12m pre Ind date	1.114035	0.0194587	6.18	<0.001	1.076542	1.152834
Antiretrovirals, 90d pre Ind date	1.045789	0.1931137	0.24	0.808	0.7282195	1.501846
Current use of CYP inhibitors	0.9855369	0.07969	-0.18	0.857	0.8410953	1.154784
Low use, any Rx, 12m pre Ind date	1.1052	0.0168844	6.55	<0.001	1.072598	1.138793
Mid use, any Rx, 12m pre Ind date	0.9590854	0.015895	-2.52	0.012	0.9284324	0.9907505
High use, any Rx, 12m pre Ind date	0.6594868	0.0128971	-21.29	<0.001	0.6346872	0.6852554
Low use, MD visits, 12m pre Ind date	2.151444	0.0485497	33.95	<0.001	2.058362	2.248735
Mid use, MD visits, 12m pre Ind date	2.72683	0.0644006	42.47	<0.001	2.603484	2.85602
High use, MD visits, 12m pre Ind date	3.387151	0.0825384	50.07	<0.001	3.229181	3.552849
Low use, inpt hosp, 12m pre Ind date	0.5143051	0.0081145	-42.14	<0.001	0.4986443	0.5304578
High use, inpt hosp, 12m pre Ind date	0.5390341	0.0188317	-17.69	<0.001	0.50336	0.5772366

Ind date = index date
NOTE: 1125 groups (1806 obs) dropped because of all positive or all negative outcomes
Current INS use: use of drug into 14 days before the disease diagnosis.

3.1.3 Full Model: Current INS Use

The Full Model included the following explanatory variables: (1) indicator variables for exposure to intranasal steroids and other forms of steroid drugs, (2) indicator variables for exposure to conditions and treatments (hypertension, diabetes, CYP inhibitors, and HIV medications), and (3) health care utilization variables (prescription drugs, physician visits, and inpatient hospitalizations). Utilization variables were included in the Full Model as covariates to control for individuals' interactions with the health care system. (Table 9)

Table 9
GLAUCOMA/OCULAR HYPERTENSION
Intranasal Steroids
Garbe Approach
Full Model – Current INS Use

Conditional (fixed-effects) logistic regression

Number of obs	349556
LR chi2(16)	7213.35
Prob > chi2	<0.001
Pseudo R2	0.0371
Log likelihood	-93581.379

Explanatory Variable Description	Odds Ratio	Stnd Error	z	P>|z|	[95% Conf.	Interval]
Current use of INS	1.226654	0.0336861	7.44	<0.001	1.162376	1.294487
Current use, oral steroids	1.28623	0.0454381	7.13	<0.001	1.200186	1.378443
Current use, inhaled steroids	1.195385	0.0399203	5.34	<0.001	1.119648	1.276245
Current use, dermal steroids	1.152182	0.0500334	3.26	0.001	1.058176	1.25454
Anti-HTN meds,12m pre Ind date	1.546738	0.0192804	34.99	<0.001	1.509407	1.584992
DM meds, 12m pre Ind date	1.127848	0.0187749	7.23	<0.001	1.091644	1.165253
Antiretrovirals, 90d pre Ind date	1.334677	0.2010548	1.92	0.055	0.993463	1.793084
Current use of CYP inhibitors	0.9524175	0.0720898	-0.64	0.52	0.8211051	1.104729
Low use, any Rx, 12m pre Ind date	1.0515	0.0143834	3.67	<0.001	1.023683	1.080072
Mid use, any Rx, 12m pre Ind date	0.9347956	0.0138946	-4.54	<0.001	0.9079555	0.9624291
High use, any Rx, 12m pre Ind date	0.6805637	0.0119359	-21.94	<0.001	0.6575672	0.7043643
Low use, MD visits, 12m pre Ind date	2.138559	0.0442545	36.73	<0.001	2.053558	2.227079
Mid use, MD visits, 12m pre Ind date	2.634161	0.0571064	44.68	<0.001	2.524579	2.7485
High use, MD visits, 12m pre Ind date	3.259601	0.073149	52.65	<0.001	3.119339	3.40617
Low use, inpt hosp, 12m pre Ind date	0.5232527	0.0074057	-45.76	<0.001	0.5089373	0.5379707
High use, inpt hosp, 12m pre Ind date	0.5441491	0.0179761	-18.42	<0.001	0.5100329	0.5805474

Ind date = Index Date (abbreviated re space constraints)
Current INS use: use of drug into 14 days before the disease diagnosis.

Table 9 A
GLAUCOMA/OCULAR HYPERTENSION
Fluticasone Propionate (FLUT-PRO)
Garbe Approach
Full Model – Current FLUT-PRO Use

Conditional (fixed-effects) logistic regression

Number of obs	349556
LR chi2(16)	7270.69
Prob > chi2	<0.001
Pseudo R2	0.0374
Log likelihood	-93552.71

Explanatory Variable Description	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval	
Current use of FLU-PRO	1.474848	0.0526437	10.89	<0.001	1.375194	1.581722
Current use, oral steroids	1.286704	0.0454683	7.13	<0.001	1.200604	1.378979
Current use, inhaled steroids	1.195199	0.0397749	5.36	<0.001	1.11973	1.275755
Current use, dermal steroids	1.149417	0.0499325	3.21	0.001	1.055602	1.25157
Anti-HTN meds,12m pre Ind date	1.546369	0.0192786	34.97	<0.001	1.509042	1.58462
DM meds, 12m pre Ind date	1.127993	0.0187755	7.24	<0.001	1.091788	1.1654
Antiretrovirals, 90d pre Ind date	1.331147	0.200531	1.9	0.058	0.990824	1.788362
Current use of CYP inhibitors	0.952824	0.0721338	-0.64	0.523	0.8214333	1.105231
Low use, any Rx, 12m pre Ind date	1.050927	0.0143749	3.63	<0.001	1.023126	1.079482
Mid use, any Rx, 12m pre Ind date	0.9344368	0.0138796	-4.57	<0.001	0.9076255	0.9620402
High use, any Rx, 12m pre Ind date	0.6808483	0.0119129	-21.97	<0.001	0.6578954	0.7046021
Low use, MD visits, 12m pre Ind date	2.138622	0.0442602	36.73	<0.001	2.053609	2.227153
Mid use, MD visits, 12m pre Ind date	2.634081	0.0571101	44.67	<0.001	2.524493	2.748427
High use, MD visits, 12m pre Ind date	3.260584	0.0731769	52.66	<0.001	3.120268	3.407209
Low use, inpt hosp, 12m pre Ind date	0.5232218	0.0074044	-45.77	<0.001	0.5089089	0.5379373
High use, inpt hosp, 12m pre Ind date	0.5436907	0.0179595	-18.45	<0.001	0.509606	0.5800552

TABLE 9 B
GLAUCOMA/OCULAR HYPERTENSION
Fluticasone Furoate (FLUT-FUR)
Garbe Approach
Full Model – Current FLUT-PRO Use

Conditional (fixed-effects) logistic regression

Number of obs	349556
LR chi2(16)	7160.7
Prob > chi2	<0.001
Pseudo R2	0.0368
Log likelihood	-93607.71

Explanatory Variable Description	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval	
Current use of FLUT-FUR	0.8438586	0.1733152	-0.83	0.408	0.5642173	1.262098
Current use, oral steroids	1.289972	0.0455505	7.21	<0.001	1.203714	1.382411
Current use, inhaled steroids	1.23377	0.0408261	6.35	<0.001	1.156292	1.31644
Current use, dermal steroids	1.154657	0.0501297	3.31	0.001	1.060469	1.257211
Anti-HTN meds,12m pre Ind date	1.547951	0.0192929	35.06	<0.001	1.510596	1.58623
DM meds, 12m pre Ind date	1.123485	0.0186905	7		1.087443	1.160721
Antiretrovirals, 90d pre Ind date	1.325968	0.1997248	1.87	0.061	0.9870068	1.781336
Current use of CYP inhibitors	0.9604669	0.0726714	-0.53	0.594	0.8280915	1.114003
Low use, any Rx, 12m pre Ind date	1.0546	0.0144182	3.89	<0.001	1.026716	1.083241
Mid use, any Rx, 12m pre Ind date	0.9409019	0.0139583	-4.11	<0.001	0.9139381	0.9686613
High use, any Rx, 12m pre Ind date	0.6889644	0.0120247	-21.35	<0.001	0.6657949	0.7129402
Low use, MD visits, 12m pre Ind date	2.139168	0.0442638	36.75	<0.001	2.054148	2.227707
Mid use, MD visits, 12m pre Ind date	2.63509	0.0571223	44.7	<0.001	2.525478	2.74946
High use, MD visits, 12m pre Ind date	3.264393	0.0732466	52.73	<0.001	3.123944	3.411158
Low use, inpt hosp, 12m pre Ind date	0.522034	0.0073855	-45.95	<0.001	0.5077575	0.5367118
High use, inpt hosp, 12m pre Ind date	0.5410362	0.0178678	-18.6	<0.001	0.5071252	0.5772148

3.1.4 Stratified Models

Since individuals may be more likely to be diagnosed with glaucoma or ocular hypertension if they are engaging the health care system more frequently, even if just by chance alone, the frequency of physician visits during the 12 months prior to the date of diagnosis of glaucoma or ocular hypertension was used to stratify cases and controls into four frequency subgroups – upper tertile, mid-tertile and lowest tertile of frequency of physician visits, and a subgroup with no physician visits. (Tables 7-10)

A trend exists in the OR from highest frequency of physician visits to no physician visits (OR 1.33, 1.16, 1.11, and 0.93 for top, middle and bottom tertiles, and no visit group). Given the variance of the regression coefficient estimates, the null hypothesis of that the logarithm of the OR across the tertiles of utilization follows a positive linear trend cannot be rejected (P=0.93), however the estimated slope using weighted regression for the linear trend (0.094 increase in OR per tertile, SE 0.022) is only marginally statistically significant at the conventional 5% significance level (P = 0.051).

A sensitivity analysis indicated that the coefficient for intra-nasal steroid exposure was only sensitive to prior utilization as measured by physician visits. Even though the drug and hospital admission prior utilization measures often produce statistically significant regression coefficients in the logistic regressions, their omission from the regression as explanatory variables, and use as stratification variables did not change the estimated coefficient for intranasal steroid exposure substantially. This result strongly suggests that while these variables have a significant effect on the diagnosis, that effect is independent of exposure to intra-nasal steroids, and that there is some correlation between the physician visit measure of health services utilization, exposure to intra-nasal steroids, and the diagnosis.

Table 10
GLAUCOMA/OCULAR HYPERTENSION
Intranasal Steroids
Stratified Analysis - Physician Visits - Top Tertile

Conditional (fixed-effects) logistic regression	
Number of obs	31310
LR chi2(16)	397.9
Prob > chi2	<0.001
Pseudo R2	0.0183
Log likelihood	-10676.243

Explanatory Variable Description	Odds Ratio	Stnd Error	Z	P>|z|	[95% Conf.	Interval]
Current use of INS	1.335915	0.0793029	4.88	<0.001	1.189185	1.500749
Current use, oral steroids	1.232501	0.0865454	2.98	0.003	1.074031	1.414354
Current use, inhaled steroids	1.215688	0.0843277	2.82	0.005	1.061152	1.392729
Current use, dermal steroids	1.104627	0.1048255	1.05	0.294	0.9171483	1.33043
Anti-HTN meds,12m pre index date	1.605518	0.0460718	16.5	<0.001	1.517711	1.698404
DM meds, 12m pre index date	1.066022	0.0427541	1.59	0.111	0.9854339	1.1532
Antiretrovirals, 90d pre index date	1.496356	0.6510532	0.93	0.354	0.6377983	3.51064
Current use of CYP inhibitors	1.03405	0.1605196	0.22	0.829	0.7627922	1.40177

Current INS use: use of drug into 14 days before the disease diagnosis.

Table 11
GLAUCOMA/OCULAR HYPERTENSION
Intranasal Steroids
Stratified Analysis - Physician Visits - Mid Tertile

Conditional (fixed-effects) logistic regression
Number of obs 21310
LR chi2(16) 397.9
Prob > chi2 <0.001
Pseudo R2 0.0183
Log likelihood -10676.243

Explanatory Variable Description	Odds Ratio	Stnd Error	Z	P>|z|	[95% Conf.	Interval]
Current use of INS	1.162373	0.0778846	2.25	0.025	1.019321	1.325501
Current use, oral steroids	1.22034	0.1074317	2.26	0.024	1.026942	1.450159
Current use, inhaled steroids	1.008656	0.0850844	0.1	0.919	0.8549495	1.189996
Current use, dermal steroids	1.202582	0.1232537	1.8	0.072	0.9837259	1.470128
Anti-HTN meds,12m pre index date	1.469497	0.0418863	13.5	<0.001	1.389652	1.553929
DM meds, 12m pre index date	1.060713	0.0421789	1.48	0.138	0.9811837	1.146689
Antiretrovirals, 90d pre index date	1.908949	0.7038565	1.75	0.08	0.9267111	3.93228
Current use of CYP inhibitors	0.8083183	0.1494923	-1.15	0.25	0.5625475	1.161464

Current INS use: use of drug into 14 days before the disease diagnosis.

Table 12
GLAUCOMA/OCULAR HYPERTENSION
Intranasal Steroids
Stratified Analysis - Physician Visits -Bottom Tertile

Conditional (fixed-effects) logistic regression

Number of obs	65106
LR chi2(16)	272.6
Prob > chi2	<0.001
Pseudo R2	0.0062
Log likelihood	-21992.158

Explanatory Variable Description	Odds Ratio	Stnd Error	z	P>|z|	[95% Conf.	Interval]
Current use of INS	1.1185	0.0668121	1.87	0.061	0.9949254	1.257423
Current use, oral steroids	0.8994171	0.0785714	-1.21	0.225	0.7578822	1.067384
Current use, inhaled steroids	1.030642	0.0762008	0.41	0.683	0.8916079	1.191356
Current use, dermal steroids	1.021954	0.0967172	0.23	0.819	0.8489339	1.230236
Anti-HTN meds,12m pre index date	1.42158	0.0328231	15.24	<0.001	1.358681	1.487389
DM meds, 12m pre index date	1.007441	0.0330209	0.23	0.821	0.9447561	1.074285
Antiretrovirals, 90d pre index date	0.8409452	0.2695603	-0.54	0.589	0.4486625	1.576216
Current use of CYP inhibitors	1.005343	0.167111	0.03	0.974	0.7258135	1.392526

Current INS use: use of drug into 14 days before the disease diagnosis.

Table 13
GLAUCOMA/OCULAR HYPERTENSION
Intranasal Steroids
Stratified Analysis - Physician Visits – No Visits

Conditional (fixed-effects) logistic regression

Number of obs	4176
LR chi2(16)	28.38
Prob > chi2	0.0004
Pseudo R2	0.0097
Log likelihood	-21992.158

Explanatory Variable Description	Odds Ratio	Stnd Error	z	P>|z|	[95% Conf.	Interval]
Current use of INS	0.9395166	0.2040323	-0.29	0.774	0.6138345	1.437996
Current use, oral steroids	0.8153419	0.2260672	-0.74	0.462	0.4735108	1.403944
Current use, inhaled steroids	1.399911	0.3638316	1.29	0.196	0.8411555	2.329831
Current use, dermal steroids	1.067436	0.3781852	0.18	0.854	0.5330491	2.137552
Anti-HTN meds,12m pre Index date	1.315064	0.1050194	3.43	0.001	1.12453	1.537882
DM meds, 12m pre Index date	1.23681	0.1317811	1.99	0.046	1.00371	1.524045
Antiretrovirals, 90d pre Index date	9.72E-06	0.0038865	-0.03	0.977	0	.
Current use of CYP inhibitors	0.8463269	0.4538823	-0.31	0.756	0.2958296	2.421223

Current INS use: use of drug into 14 days before the disease diagnosis.

3.1.4 CEM Model [matched by age, sex, index date, and three utilization variables]

OR for the CEM analysis with an exact match on age, sex, index date (+/- 6 months????) and three utilizations shows an elevated OR in the range of the other models. (Table 11)

Table 14
GLAUCOMA/OCULAR HYPERTENSION
Intranasal Steroids
CEM Model

Conditional (fixed-effects) logistic regression	
Number of obs	19238
LR chi2(16)	88.22
Prob > chi2	<0.001
Pseudo R2	0.0057
Log likelihood	-21992.16

Explanatory Variable Description	Odds Ratio	Stnd Error	z	P>|z|	[95% Conf. Interval]	
Current use of INS	1.279003	0.0511522	6.15	<0.001	1.182575	1.383294
Current use, oral steroids	1.314719	0.1337174	2.69	0.007	1.077107	1.604748
Current use, inhaled steroids	1.094759	0.078686	1.26	0.208	0.9509076	1.260372
Current use, dermal steroids	1.250853	0.1591256	1.76	0.079	0.974814	1.605058
Anti-HTN meds,12m pre index date	1.240132	0.0552777	4.83	<0.001	1.136387	1.353348
DM meds, 12m pre index date	1.038781	0.0633046	0.62	0.532	0.9218293	1.170569
Antiretrovirals, 90d pre index date	2.933432	1.273122	2.48	0.013	1.253	6.867539
Current use of CYP inhibitors	0.7422769	0.1625817	-1.36	0.174	0.4831994	1.140264

Current INS use: use of drug into 14 days before the disease diagnosis.

3.2 Cataract

3.2.1 Overview

The same approach used for the Glaucoma/Ocular Hypertension Diagnosis Group was used to assess the Cataract Diagnosis Group. For the most part, the analysis of the Cataract Diagnosis Group tracked approximately what was observed in the Glaucoma/Ocular Hypertension Diagnosis Group. (Table 15)

Table 15
CATARACT
INTRANASAL STEROIDS
Summary of Regression Models

Model	Exposure	OR	n	p
Full	INS	1.28	349,496	<0.001
	INFLUT	1.36	349,496	<0.001
	INS FLUT-PRO	1.61	349,496	<0.001
	INS FLUT-FUR	0.92	349,496	=0.62
Stratified	INS High Use MD visits	1.21	32,984	<0.001
	INS Mid Use MD Visits	1.33	32,091	<0.001
	INS Low Use MD Visits	1.09	63,751	=0.15
	INS No MD Visits	1.23	4,738	=0.31
	INFLUT High Use MD visits	1.33	32,984	<0.001
	INFLUT Mid Use MD Visits	1.45	32,091	<0.001
	INFLUT Low Use MD Visits	1.09	63,751	=0.24
	INFLUT No MD Visits	0.71	4,176	=0.71
CEM Matched	INS	1.28	19,912	<0.001
	INFLUT	1.37	19,974	<0.001

INS: Intranasal Steroids (Any)
INFLUT: Intranasal Fluticasone
Full Model: three utilization variables included as covariates (bottom tertile of MD visits, middle tertile of MD visits, top tertile of MD visits (vs. reference group as no MD visits); bottom tertile of prescription drug use, middle tertile of prescription drug use, top tertile of prescription drug use (vs. reference group as no drug use); bottom tertile of inpatient hospitalizations, middle tertile of inpatient hospitalizations, top tertile of inpatient hospitalizations (vs. reference group=no hospitalizations)
Stratified Model: stratified by zero/tertiles of physician visit. Prescription drug use and inpatient hospitalizations omitted as covariates.
CEM Model: matched on age, gender, index date, and three utilization variables.

3.2.2 Full Model - Cataract

Table 16
CATARACT
INTRANASAL STEROIDS
Full Model. Current Use

Conditional (Fixed Effects) Logistic Regression

Number of obs	349496
LR chi2(16)	8691.20
Prob > chi2	0.0001
Pseudo R2	0.0447
Log likelihood	-92827.137

Explanatory Variable Description	Odds Ratio	Std. Err.	z	P>|z |	[95% Conf.	Interval]
Current use of INS	1.280074	0.0336882	9.38	<0.001	1.21572	1.347834
Current use, oral steroids	1.336236	0.0452953	8.55	<0.001	1.250344	1.428029
Current use, inhaled steroids	1.219643	0.0393974	6.15	<0.001	1.144819	1.299357
Current use, dermal steroids	1.144305	0.048432	3.18	0.001	1.053211	1.243278
Anti-HTN meds,12m pre Ind date	1.597971	0.0197758	37.88	<0.001	1.559678	1.637205
DM meds, 12m pre Ind date	1.425167	0.0224809	22.46	<0.001	1.381779	1.469917
Antiretrovirals, 90d pre Ind date	1.879418	0.2187331	5.42	<0.001	1.49609	2.360963
Current use of CYP inhibitors	1.128402	0.0764644	1.78	0.075	0.9880608	1.288678
Low use, any Rx, 12m pre Ind date	1.144826	0.0161529	9.59	<0.001	1.113601	1.176927
Mid use, any Rx, 12m pre Ind date	1.073312	0.0161338	4.71	<0.001	1.042152	1.105404
High use, any Rx, 12m pre Ind date	0.826783	0.0143564	-10.95	<0.001	0.7991184	0.8554053
Low use, MD visits, 12m pre Ind date	2.19823	0.0456698	37.91	<0.001	2.110516	2.289588
Mid use, MD visits, 12m pre Ind date	2.820604	0.0613843	47.65	<0.001	2.702823	2.943518
High use, MD visits, 12m pre Ind date	3.802245	0.0852794	59.55	<0.001	3.638721	3.973118
Low use, inpt hosp, 12m pre Ind date	0.6537741	0.0091091	-30.5	<0.001	0.6361621	0.6718737
High use, inpt hosp, 12m pre Ind date	0.6792467	0.0211385	-12.43	<0.001	0.6390543	0.721967

Ind date = Index date

Table 16 A
CATARACT
Fluticasone Propionate (FLUT-PRO)
Full Model – Current FLUT-PRO Use

Conditional (fixed-effects) logistic regression

Number of obs	349496
LR chi2(16)	8789.94
Prob > chi2	0.001
Pseudo R2	0.0452
Log likelihood	-92777.8

Explanatory Variable Description	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval
Current use of FLU-PRO	1.605792	0.054117	14.05	<0.001	1.503151	1.715441
Current use, oral steroids	1.338908	0.045404	8.61	<0.001	1.252811	1.430923
Current use, inhaled steroids	1.216098	0.039191	6.07	<0.001	1.14166	1.29539
Current use, dermal steroids	1.144824	0.048468	3.19	0.001	1.053664	1.243872
Anti-HTN meds,12m pre Ind date	1.597078	0.01977	37.82	<0.001	1.558797	1.6363
DM meds, 12m pre Ind date	1.425739	0.022492	22.48	<0.001	1.382331	1.47051
Antiretrovirals, 90d pre Ind date	1.886645	0.219605	5.45	<0.001	1.501794	2.370118
Current use of CYP inhibitors	1.128509	0.076511	1.78	0.075	0.988087	1.288887
Low use, any Rx, 12m pre Ind date	1.14413	0.016143	9.54	<0.001	1.112925	1.17621
Mid use, any Rx, 12m pre Ind date	1.072413	0.016113	4.65	<0.001	1.041293	1.104462
High use, any Rx, 12m pre Ind date	0.826762	0.014326	-10.98	<0.001	0.799155	0.855322
Low use, MD visits, 12m pre Ind date	2.198491	0.045681	37.91	<0.001	2.110756	2.289873
Mid use, MD visits, 12m pre Ind date	2.820802	0.061398	47.64	<0.001	2.702995	2.943742
High use, MD visits, 12m pre Ind date	3.802433	0.085293	59.54	<0.001	3.638884	3.973334
Low use, inpt hosp, 12m pre Ind date	0.653624	0.009106	-30.52	<0.001	0.636018	0.671716
High use, inpt hosp, 12m pre Ind date	0.678664	0.021121	-12.46	<0.001	0.638506	0.721349

Table 16 B
CATARACT
Fluticasone Furoate (FLUT-FUR)
Full Model – Current FLUT-FUR Use

Conditional (fixed-effects)logistic regression	
Number of Obs	349496
LRChi2(16)	86-6.99
Prob > chi2	< 0.001
Pseudo R2	0.0443
Log likelihood	-92869.2

Current use of FLUT-FUR	0.9204855	0.155469	-0.49	0.624	0.661074	1.281693
Current use, oral steroids	1.34058	0.045416	8.65	<0.001	1.254456	1.432616
Current use, inhaled steroids	1.264651	0.040509	7.33	<0.001	1.187697	1.346592
Current use, dermal steroids	1.149357	0.048624	3.29	0.001	1.0579	1.24872
Anti-HTN meds,12m pre Ind date	1.600327	0.019801	38	<0.001	1.561984	1.639611
DM meds, 12m pre Ind date	1.418223	0.022353	22.17	<0.001	1.375082	1.462718
Antiretrovirals, 90d pre Ind date	1.869028	0.217496	5.37	<0.001	1.487862	2.347842
Current use of CYP inhibitors	1.139743	0.077178	1.93	0.053	0.998085	1.301506
Low use, any Rx, 12m pre Ind date	1.148905	0.016202	9.84	<0.001	1.117584	1.181103
Mid use, any Rx, 12m pre Ind date	1.081869	0.016231	5.24	<0.001	1.05052	1.114154
High use, any Rx, 12m pre Ind date	0.8388559	0.014501	-10.17	<0.001	0.810911	0.867764
Low use, MD visits, 12m pre Ind date	2.197975	0.045659	37.91	<0.001	2.110282	2.289313
Mid use, MD visits, 12m pre Ind date	2.822397	0.061415	47.68	<0.001	2.704556	2.945373
High use, MD visits, 12m pre Ind date	3.809227	0.085421	59.64	<0.001	3.645431	3.980384
Low use, inpt hosp, 12m pre Ind date	0.6512927	0.00907	-30.79	<0.001	0.633757	0.669313
High use, inpt hosp, 12m pre Ind date	0.6747306	0.020991	-12.65	<0.001	0.634819	0.717152

3.2.3 Stratified Model - Cataract

Table 17
CATARACT
INTRANASAL STEROIDS
Stratified Analysis – Physician Visits Top Tertile

Conditional (fixed-effects) logistic regression

Number of obs	32984
LR chi2(8)	520.12
Prob > chi2	0.0001
Pseudo R2	0.0227
Log likelihood	-11184.389

Explanatory Variable Description	Odds Ratio	Std. Err.	z	P>|z |	[95% Conf.	Interval]
Current use of INS	1.212617	0.0693212	3.37	0.001	1.084084	1.356388
Current use, oral steroids	1.298171	0.0879746	3.85	<0.001	1.136705	1.482574
Current use, inhaled steroids	1.168675	0.0815938	2.23	0.026	1.019213	1.340054
Current use, dermal steroids	1.314233	0.1188798	3.02	0.003	1.100719	1.569164
Anti-HTN meds,12m pre index date	1.200634	0.0453223	4.84	<0.001	1.115011	1.292833
DM meds, 12m pre index date	1.852178	0.6560407	1.74	0.082	0.9250979	3.708327
Antiretrovirals, 90d pre index date	1.071393	0.1573354	0.47	0.639	0.8034313	1.428725

Table 18
CATARACT
INTRANASAL STEROIDS
Stratified analysis - Physician Visits Mid Tertile

Conditional (fixed-effects) logistic regression

Number of obs	32091
LR chi2(8)	447.48
Prob > chi2	0.0001
Pseudo R2	0.0199
Log likelihood	-11027.304

Explanatory Variable Description	Odds Ratio	Std. Err.	z	P>|z |	[95% Conf.	Interval]
Current use of INS	1.325502	0.0874972	4.27	<0.001	1.164641	1.508581
Current use, oral steroids	1.1616	0.101663	1.71	0.087	0.9784973	1.378966
Current use, inhaled steroids	1.08763	0.0934089	0.98	0.328	0.9191316	1.287019
Current use, dermal steroids	1.158413	0.1299237	1.31	0.19	0.9298124	1.443216
Anti-HTN meds,12m pre index date	1.578971	0.045944	15.7	<0.001	1.491442	1.671637
DM meds, 12m pre index date	1.252085	0.0497403	5.66	<0.001	1.158295	1.35347
Antiretrovirals, 90d pre index date	2.166626	0.6817751	2.46	0.014	1.169325	4.014511
Current use of CYP inhibitors	1.529378	0.2716107	2.39	0.017	1.079805	2.16613
Current use of INS	1.529378	0.2716107	2.39	0.017	1.079805	2.16613

Table 19
CATARACT
INTRANASAL STEROIDS
Stratified analysis - Physician Visits Low Tertile

Conditional (fixed-effects) logistic regression

Number of obs	4738
LR chi2(8)	46.63
Prob > chi2	<0.0001
Pseudo R2	0.0140
Log likelihood	-1638.7119

Explanatory Variable Description	Odds Ratio	Std. Err.	z	P>|z |	[95% Conf. Interval]	
Current use of INS	1.088227	0.063565	1.45	0.148	0.97051	1.220224
Current use, oral steroids	1.041192	0.084872	0.5	0.62	0.887453	1.221564
Current use, inhaled steroids	1.277963	0.090638	3.46	0.001	1.112109	1.468551
Current use, dermal steroids	1.135507	0.102987	1.4	0.161	0.950579	1.356411
Anti-HTN meds,12m pre index date	1.490765	0.034771	17.12	<0.001	1.424149	1.560496
DM meds, 12m pre index date	1.503098	0.047097	13.01	<0.001	1.413567	1.5983
Antiretrovirals, 90d pre index date	1.889561	0.446871	2.69	0.007	1.188657	3.003761
Current use of CYP inhibitors	0.987335	0.15195	-0.08	0.934	0.73024	1.334945

Table 20
CATARACT
INTRANASAL STEROIDS
Stratified analysis - Physician Visits No Visits

Conditional (fixed-effects) logistic regression

Number of obs	4738
LR chi2(8)	46.63
Prob > chi2	<0.0001
Pseudo R2	0.0140
Log likelihood	-1638.7119

Explanatory Variable Description	Odds Ratio	Std. Err.	z	P>|z |	[95% Conf. Interval]	
Current use of INS	1.23133	0.254551	1.01	0.314	0.82112	1.846469
Current use, oral steroids	1.490687	0.424637	1.4	0.161	0.85293	2.605311
Current use, inhaled steroids	0.770001	0.20634	-0.98	0.329	0.455399	1.30194
Current use, dermal steroids	1.048159	0.339617	0.15	0.885	0.555427	1.978005
Anti-HTN meds,12m pre index date	1.278184	0.098295	3.19	0.001	1.099346	1.486115
DM meds, 12m pre index date	1.492965	0.145275	4.12	<0.001	1.233737	1.806662
Antiretrovirals, 90d pre index date	0.7693861	0.584669	-0.34	0.73	0.173501	3.411822
Current use of CYP inhibitors	1.00061	0.481967	0	0.999	0.389282	2.571968

3.2.4 CEM Model

Table 21
CATARACT
INTRANASAL STEROIDS
CEM Model

Conditional (fixed-effects) logistic regression

Number of obs	19912
LR chi2(8)	180.57
Prob > chi2	0.0001
Pseudo R2	0.0109
Log likelihood	-8209.8282

Explanatory Variable Description	Odds Ratio	Std. Err.	z	P>|z |	[95% Conf. Interval]	
Current use of INS	1.28142	0.049425	6.43	<0.001	1.188119	1.382047
Current use, oral steroids	1.029479	0.106031	0.28	0.778	0.841295	1.87774
Current use, inhaled steroids	1.120533	0.079531	1.6	0.109	0.975011	1.287774
Current use, dermal steroids	1.21235	0.14999	1.56	0.12	0.951303	1.545031
Anti-HTN meds,12m pre index date	1.384364	0.059126	7.62	<0.001	1.273197	1.505238
DM meds, 12m pre index date	1.402597	0.078099	6.08	<0.001	1.257583	1.564333
Antiretrovirals, 90d pre index date	1.85745	0.726998	1.58	0.114	0.862503	4.000129
Current use of CYP inhibitors	1.201055	0.219266	1	0.316	0.839782	1.717748

3.3 Adrenal Insufficiency

For analyzing cases and controls with adrenal insufficiency (AI), we examined the appearance of AI after discontinuation of INS, as defined by pharmacy claims. The ORs for the time period of 28 days or less and for more than 28 days were not statistically significant, whether for all intranasal steroids (Table 28) or FLUT-PRO (Table 28 A). Because of the small number of cases for FLUT-FF a regression analysis could not be done. The ORs for FLUT-FUR were (a) for INS discontinuation at 1-28 days pre index date, OR 1.0267 (SE 0.2549, z 0.11, P= 0.91, and 95% CI 0.631-1.670); and (b) for INS discontinuation >= 29 days pre index date, OR 0.9929 (SE 0.1521, z -0.05, P=0.96, and 95% CI 0.7353-1.3408).

For the Adrenal Suppression Diagnosis Group, the main exposure variable was the defined by days between the last INS use prior to the AI diagnosis date and the AI diagnosis date. Individuals without INS use prior to AI diagnosis were classified as have missing values and were therefore excluded in the subsequent descriptive and regression analyses (i.e., n=2,300 of 60,000 in the IMS data set).

Table 22
ADRENAL INSUFFICIENCY
INTRANASAL STEROIDS
Summary of Regression Model

Exposure	OR	n (Cases)	p
INS Continuous Use		3,047	
INS Discontinued 1-28 days pre AI Diagnosis	1.026	1,448	=0.915
INS Discontinued ≥29 days pre AI Diagnosis	0.992	7,805	=0.963
Total		57,700	

Table 23
ADRENAL INSUFFICIENCY
INTRANASAL STEROIDS
Full Model

Number of obs	1,117
LR chi2(11)	131.64
Prob > chi2	<0.0001
Pseudo R2	0.1680
Log likelihood	-325.9587

Explanatory Variable Description	Odds Ratio	Std. Err.	z	P>|z |	[95% Conf. Interval]	
GC discontin.1-28d pre index date	**1.026717**	0.254981	0.11	**0.915**	0.631042	1.670488
GC DC >=29d pre index date	**0.9929626**	0.152183	-0.05	**0.963**	0.73532	1.340878
Pit Dx/surg, 12 m pre index date	10.82544	8.445799	3.05	0.002	2.346146	49.95011
Low Rx use, 12 m pre index date	1.920052	0.847686	1.48	0.14	0.808193	4.561536
Mid Rx use, 12 m pre index date	1.458613	0.644433	0.85	0.393	0.613577	3.467456
High Rx use, 12 m pre index date	2.067454	0.888091	1.69	0.091	0.890832	4.798176
Low Rx use, 12 m pre index date	1.705326	0.665551	1.37	0.171	0.793601	3.664482
Mid Rx use, 12 m pre index date	2.988456	1.125031	2.91	0.004	1.428909	6.250132
High Rx use, 12 m pre index date	6.762516	2.532767	5.1	0	3.245694	14.08994
Low inpt hosp, 12 m pre index dt	0.7194322	0.148535	-1.59	0.111	0.480009	1.078277
High inpt hosp, 12 m pre index dt	1.358546	0.558184	0.75	0.456	0.607215	3.039529

Full titles for abbreviated listing above.
pituitary diagnosed disease/surgery in 12-month prior to AI index date
low use, prescription drugs in 12-month prior to AI index date
medium use, prescription drugs in 12-month prior to AI index date
high use, prescription drugs in 12-month prior to AI index date
low use, physician visits in 12-month prior to AI index date
medium use, physician visits in 12-month prior to AI index date
high use, physician visits in 12-month prior to AI index date
low use, inpatient hospitalizations in 12-month prior to AI index date
high use, inpatient hospitalizations in 12-month prior to AI index date

TABLE 23A
ADRENAL SUPPRESSION
Fluticasone Propionate (FLUT PRO)
Full Model – Current FLU PRO Use

Conditional (fixed-effects) logistic regression

Number of obs	466
LR chi2 (11)	41.48
Prob > chi2	< 0.001
Pseudo R2	0.1302
Log likelihood	-141.91

Explanatory Variable Description	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval	
fpdcdxtime_catv1						
GC discontin.1-28d pre index date	**1.214975**	0.415417	0.57	**0.569**	0.621627	2.37468
GC DC >=29d pre index date	**1.212289**	0.279587	0.83	**0.404**	0.771429	1.905095
Pit Dx/surg, 12 m pre index date	1.701194	1.537764	0.59	0.557	0.289285	10.0042
Low Rx use, 12 m pre index date	4.650262	3.479458	2.05	0.04	1.072962	20.15443
Mid Rx use, 12 m pre index date	2.529401	1.819817	1.29	0.197	0.617458	10.36163
High Rx use, 12 m pre index date	3.265747	2.304689	1.68	0.094	0.818986	13.02234
Low Rx use, 12 m pre index date	1.115949	0.613142	0.2	0.842	0.380158	3.275855
Mid Rx use, 12 m pre index date	1.364273	0.721729	0.59	0.557	0.483724	3.847729
High Rx use, 12 m pre index date	3.879772	1.980238	2.66	0.008	1.426765	10.55018
Low inpt hosp, 12 m pre index dt	0.976764	0.294338	-0.08	0.938	0.541115	1.763154
High inpt hosp, 12 m pre index dt	0.576318	0.345308	-0.92	0.358	0.178096	1.864964

Full titles for abbreviated listing above.
pituitary diagnosed disease/surgery in 12-month prior to AI index date
low use, prescription drugs in 12-month prior to AI index date
medium use, prescription drugs in 12-month prior to AI index date
high use, prescription drugs in 12-month prior to AI index date
low use, physician visits in 12-month prior to AI index date
medium use, physician visits in 12-month prior to AI index date
high use, physician visits in 12-month prior to AI index date
low use, inpatient hospitalizations in 12-month prior to AI index date
high use, inpatient hospitalizations in 12-month prior to AI index date

4.0 Conclusions and Discussion

Summary of Findings:

This report provides the analysis of IMS dataset pertaining to the potential risk of INS use, including intranasal fluticasone use, and the subsequent development of glaucoma/ocular hypertension and cataract, as well as the potential risk of developing adrenal suppression after discontinuation of INS, including intranasal fluticasone, therapy.

In all cases, the odds ratios associated with intranasal steroids and the subsequent diagnosis of glaucoma/ocular hypertension was significantly elevated (i.e., 1.12 to 1.6), depending on the model, the strata within the model, and/or whether intranasal steroid, all fluticasone, FLUT-PRO or FLUT-FUR were considered. This was also true for the CAT Group. Discontinuation of intranasal steroids does not appear to be a risk factor for adrenal suppression in the individuals represented in the IMS data set used in this study.

Examination of the distribution of utilization of covariates in the Full Analysis following Garbe revealed substantial lack of common support and imbalance between the cases and controls. Exploratory analysis indicated that for utilization variables the results were only potentially sensitive to the physician visit measure. A stratified analysis by frequency of physician visit showed similar results to the full model. However, the stratified model revealed continued lack of common support and imbalance, particularly for the highest tertile of MD visit utilization. A further matching analysis (CEM, coarsened exact matching) adjusted for the maximum univariate distance for inclusion in the same group of candidates for potential matches. Use of the CEM algorithm substantially reduced the problem of lack of common support and imbalance of cases and controls, though at the cost of omitting observations in both groups. Nonetheless, elevated odds ratios were observed for both the GLAU/OHTN Group and the CAT Group.

Investigation of the actual reported days supply comparison between cases and controls in the GLAU/OHTN Group showed that most cases had supply of medicines for more than 90 days.

The odds ratio associated with discontinuation of intranasal steroids and the subsequent development of adrenal suppression was not statistically significant in the full model for all intranasal steroids, all fluticasone, and FLUT-PRO (i.e., ORs ranging from 0.9 to 1.2), irrespective of the cut-off dates for steroid discontinuation.

Discussion

Medical literature supports elevated risk of glaucoma and cataract from oral and high dose inhaled glucocorticoids. The study by Garbe et al. showed the potential for open-angle glaucoma or ocular hypertension from high (but not low or medium) dose inhaled glucocorticoids, and not from intranasal steroid use. Hence the findings of this study appear to contradict the findings of Garbe et al.

Possible reasons for the differences in findings between the Garbe study and this study may be different utilization patterns between the US and Canada, particularly in relation to the fact that these is

a 20 year time frame difference between the two studies. Over this period, there may be changes in medication utilization (e.g., prescribing and reimbursement practices) that could affect exposure (although we have no evidence for this). While Garbe et al. assessed total physician claims, we examined frequency of physician visits, from the standpoint that persons being seen more often by physicians may have a greater opportunity even by chance of having a disease diagnosed. For both the Garbe et al. study and this study, one of the inclusion criteria was a visit to an ophthalmologist. There would have been no reason for Garbe et al. to assess tertile frequencies of MD visits as a marker of health services utilization, as we did, since they observed no elevated ORs associated with INS use. Garbe et al. did observe elevated ORs for high dose inhaled steroids, but did not explore the analysis on physician visit that we undertook. Our analysis for glaucoma showed a trend of higher ORs by increasing frequency of physician visits. Prior utilization as measured by physician visits seems to be correlated with both exposure and diagnosis, and there is a borderline statistically significant trend in the estimated coefficients for INS exposure. Increasing prior utilization of physician visits may be an indicator of some unmeasured chronic or sub-acute condition, or general frailty, which renders someone more susceptible to glaucoma and ocular hypertension as a result of exposure to INS, and that whatever the cause of this increased susceptibility, it is independent of the increasing consumption of more drug classes, or hospital admissions.

The Garbe et al. study showed a dose effect of inhaled steroids but not intranasal steroids on increased risk of glaucoma or ocular hypertension. However, there is some uncertainty in their actual ability to assess exposure. Our study suffered the same limitation, since for example days supply only means days of possession of the medicine by the patient, not the actual use of the medication. Hence it is possible that a segment of the Garbe study population that was prescribed higher doses of intranasal steroids did not actually use them as frequently as might be presumed, thus yielding a non-significant OR. Recent studies show that intranasal steroids can have an effect on ocular symptoms of allergy. Hence, it seems biologically plausible that intranasal steroids could have an effect on elevating risk for glaucoma and cataract, by a systemic affect based on high or inappropriate usage, and/or a direct effect on lacrimal glands resulting in direct exposure of INS to the eye. (6,7)

6.0 References

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