# Morbidities Associated With Chronic Oral Glucocorticoid Exposure in Children With Asthma: A Real-world Analysis of Medical and Pharmacy Claims



David P. Skoner,[1] Evgeniya N. Antonova,[2,*] Amanda M. Kong,[3] Gregory M. Lenhart,[3] Ahmar Iqbal,[2] W. Gerald Teague[4]

[1]West Virginia University School of Medicine, Morgantown, WV, USA; [2]Genentech, Inc., South San Francisco, CA, USA; [3]Truven Health Analytics, an IBM Company, Cambridge, MA, USA; [4]Child Health Research Center, University of Virginia School of Medicine, Charlottesville, VA, USA

*Former employee

## Introduction

- More than 6 million children under 18 years of age in the United States suffer from asthma.[1]
- Oral glucocorticoids (OGC) are recommended in short courses for severely uncontrolled asthma and acute exacerbations.[2]
- Although a mainstay of asthma therapy, chronic use of OGC may increase risk of morbidities, specifically potential glucocorticoid-related adverse events (AEs), in children.
- There is a lack of contemporary research evaluating the impact of chronic OGC (C-OGC) exposure in children with asthma in the United States.

## Objective

- To assess the potential AEs of C-OGC exposure among children with asthma compared with those who did not have C-OGC exposure.

## Methods

### Data Source

- This retrospective, observational cohort study used the Truven Health MarketScan® Commercial Research Database (private insurance).
- This nationally representative, de-identified US administrative database contains inpatient and outpatient medical claims and outpatient prescription drug claims for individuals with private insurance.

### Patient Selection

- Patients 6–17 years of age with evidence of asthma (≥2 non-diagnostic claims with a diagnosis of asthma in any position [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), 493.xx] and ≥2 claims for asthma medications) from 2009–2014 were selected (**Figure**).
- Patients were stratified into cohorts of C-OGC initiators and C-OGC non-initiators.
  - C-OGC was defined as at least 15 consecutive days with OGC "on hand" based on the service dates and days' supply fields on outpatient pharmacy claims for OGC.
- For initiators, the date of initiation of C-OGC was known as the index date. For C-OGC non-initiators, an index date was randomly assigned.
- Selection criteria are shown in the **Figure**.

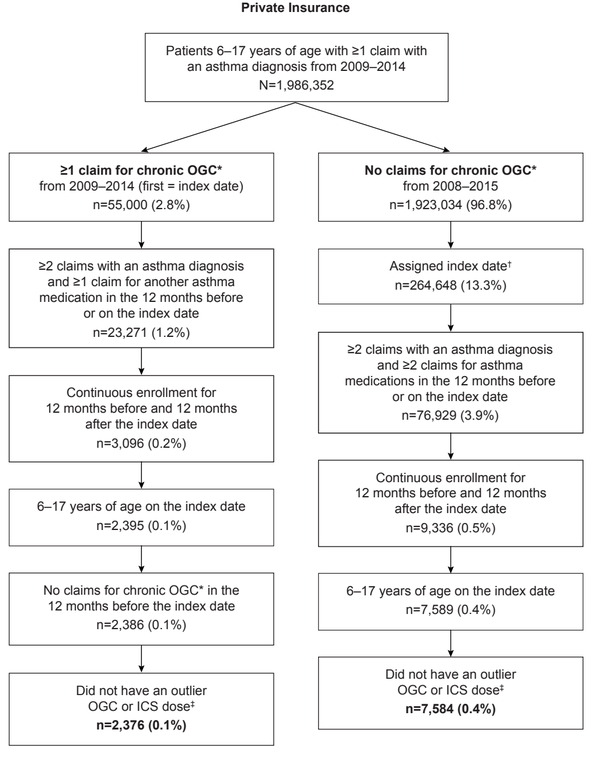
### Outcomes and Covariates

- The following AEs were evaluated based on at least 1 non-diagnostic claim during the 12-month follow-up period: adrenal insufficiency, behavioral problems, gastrointestinal disorders, hypertension, obesity, oropharyngitis, persistent cough, recurrent pneumonia, short stature, sinusitis, sleep disorders, and bone-related conditions (fracture, osteoporosis, osteopenia).
- Patient demographic characteristics were measured on the index date from enrollment records.
- Clinical characteristics were measured in the baseline period using medical claims and outpatient pharmacy claims, including measures of overall health and asthma-specific measures.

### Statistical Analysis

- Demographic and clinical characteristics were described for each cohort.
- A Cox proportional hazard model was used to estimate hazard ratios for the potential AEs, adjusted for the following: time-varying monthly cumulative dose of OGC and cumulative inhaled corticosteroids (ICS), use of other prescription corticosteroids (topical, injection, intravenous), number of ICD-9-CM diagnoses, number of National Drug Codes, demographics, and index year.
- A threshold of $P \leq 0.05$ was considered statistically significant.

**Figure 1. Attrition for Chronic OGC Initiators and Non-initiators**




ICS, inhaled corticosteroid; OGC, oral glucocorticoid. The cumulative dose of OGC and ICS were measured during the follow-up period on a monthly basis. For OGC claims, daily dose was calculated by multiplying the strength of the prescription and the number of pills and then dividing by the days' supply. For ICS claims, daily dose was calculated as described above, but used an estimated days' supply based on timing of refills. For both OGC and ICS, daily dose was summed to arrive at cumulative dose. *Chronic OGC use was defined as at least 15 consecutive days with an OGC "on hand." †Index date was assigned as the date of an asthma-related medical or pharmacy claim within 30 days of a randomly assigned date based on index date distribution among the chronic OGC initiators. ‡An outlier dose was defined as a 12-month cumulative OGC dose of >19,000 mg or a 12-month cumulative ICS dose of >400,000 µg.

## Results

### Patient Sample

- A total of 2,376 children were selected who initiated C-OGC and 7,584 children who did not initiate C-OGC (**Figure**).
- Mean age was approximately 10.5 years and 62% of children were male (**Table 1**).
- The mean cumulative prednisone-equivalent exposure totaled 1,125.5 mg/year for the C-OGC initiators and 178.6 mg/year for the C-OGC non-initiators.
- High-dose ICS (based on National Heart, Lung, and Blood Institute dosing guidelines) were used by 21.8% of children in the C-OGC cohort compared with 12.2% of patients without C-OGC.

**Table 1. Patient Demographic Characteristics for Chronic OGC Initiators and Non-initiators**

| | Private Insurance | |
|---|---|---|
| Characteristic | C-OGC Initiators n=2,376 | C-OGC Non-initiators n=7,584 |
| Mean (SD) age, y | 10.5 (3.4) | 9.2 (1.7) |
| Age group, y, n (%) | | |
| 6–11 | 1,496 (63.0) | 4,786 (63.1) |
| 12–17 | 880 (37.0) | 2,798 (36.9) |
| Sex, n (%) | | |
| Male | 1,473 (62.0) | 4,674 (61.6) |
| Female | 903 (38.0) | 2,910 (38.4) |
| Geographic region, n (%) | | |
| Northeast | 527 (22.2) | 2,126 (28.0) |
| North Central | 532 (22.4) | 1,538 (20.3) |
| South | 881 (37.1) | 2,694 (35.5) |
| West | 369 (15.5) | 981 (12.9) |
| Unknown | 67 (2.8) | 245 (3.2) |
| Index year, n (%) | | |
| 2009 | 589 (24.8) | 2,363 (31.2) |
| 2010 | 390 (16.4) | 1,189 (15.7) |
| 2011 | 547 (23.0) | 2,272 (30.0) |
| 2012 | 268 (11.3) | 566 (7.5) |
| 2013 | 354 (14.9) | 845 (11.1) |
| 2014 | 228 (9.6) | 349 (4.6) |
| Mean (SD) no. of unique 3-digit ICD-9-CM diagnoses | 7.9 (5.6) | 7.4 (4.8) |
| Mean (SD) no. of unique NDCs | 7.1 (5.0) | 6.3 (4.0) |
| Use of asthma medications, n (%) | | |
| ICS | 929 (39.1) | 3,507 (46.2) |
| Combined ICS/LABA | 644 (27.1) | 1,897 (25.0) |
| LTRA | 932 (39.2) | 3,413 (45.0) |
| OGC | 1,294 (54.5) | 3,357 (44.3) |
| SABA | 1,769 (74.5) | 5,922 (78.1) |
| Presence of asthma exacerbation, n (%)* | 1,430 (60.2) | 3,525 (46.5) |
| Persistent asthma, n (%)† | 1,357 (57.1) | 4,414 (58.2) |
| Poor asthma control, n (%)‡ | 858 (36.1) | 1,756 (23.2) |

C-OGC, chronic oral glucocorticoid; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LTRA, leukotriene receptor antagonist; NDC, National Drug Code; OGC, oral glucocorticoid; SABA, short-acting beta agonist. *Defined as an inpatient admission with a primary diagnosis of asthma, an emergency department visit with an asthma diagnosis in the principal diagnosis position, or a prescription claim for OGC with a days' supply <15 days. †Defined as having ≥4 asthma medication prescription fills, ≥1 emergency department visit or inpatient admission with a principal diagnosis of asthma, or ≥4 asthma outpatient visits with ≥2 asthma medication prescription fills. ‡Defined as having an inpatient admission with a primary diagnosis of asthma, or an emergency department visit with an asthma diagnosis in the principal diagnosis position, or ≥2 OGC claims with <15 days' supply or ≥6 claims for a SABA.

### Outcomes

- C-OGC initiation was associated with increased risk for experiencing any potential AEs among children and adolescents with asthma (hazard ratio, 1.22; 95% CI, 1.12–1.33; $P<0.0001$).
- The following potential individual AEs were significantly associated with C-OGC initiation: adrenal insufficiency, recurrent pneumonia, gastrointestinal disorders, persistent cough, behavioral problems, sleep disorders, sinusitis (**Table 2**).
- Other potential AEs that were studied, but did not demonstrate statistical significance, were as follows: bone-related events (fracture, osteoporosis, osteopenia), hypertension, short stature, obesity, and oropharyngitis.
- Among C-OGC initiators, higher doses of OGC were associated with increased risk for adrenal insufficiency, gastrointestinal disorders, oropharyngitis, and recurrent pneumonia.

**Table 2. Risk of Potential Glucocorticoid-Related AEs During 12-Month Follow-up, Chronic OGC Initiators Versus Non-initiators**

| | Observed AE Rate per 1,000 PY at Risk | | C-OGC Initiation vs No C-OGC Initiation | | Additional 1,000 mg* of OGC for C-OGC Initiators | |
|---|---|---|---|---|---|---|
| Measure* | C-OGC Initiators | C-OGC Non-initiators | HR† (95% CI) | *P* Value | HR† (95% CI) | *P* Value |
| Adrenal insufficiency | 7.2 | 0.5 | 12.13 (3.35–44.01) | **0.0001** | 1.27 (1.02–1.58) | **0.0305** |
| Behavioral problems | 122.3 | 85.6 | 1.37 (1.16–1.61) | **0.0002** | 1.06 (0.97–1.004) | 0.2116 |
| Gastrointestinal disorders | 105.3 | 49.8 | 1.68 (1.39–2.02) | **<0.0001** | 1.12 (1.04–1.21) | **0.0042** |
| **Hypertension** | **7.7** | **3.5** | **1.61 (0.83–3.15)** | **0.1598** | **1.10 (0.85–1.43)** | 0.4661 |
| Obesity | 32.0 | 34.1 | 0.88 (0.66–1.17) | 0.3781 | 1.13 (1.00–1.28) | **0.0478** |
| Oropharyngitis | 338.4 | 329.7 | 1.04 (0.95–1.15) | 0.3665 | 0.95 (0.89–1.03) | 0.2067 |
| Persistent cough | 93.6 | 44.6 | 1.67 (1.38–2.03) | **<0.0001** | 1.10 (1.00–1.21) | 0.0590 |
| Recurrent pneumonia | 43.0 | 18.0 | 1.97 (1.48–2.61) | **<0.0001** | 1.21 (1.09–1.34) | **0.0005** |
| Short stature | 8.1 | 6.5 | 0.94 (0.52–1.70) | 0.8393 | 1.09 (0.86–1.38) | 0.5002 |
| Sinusitis | 338.2 | 243.9 | 1.17 (1.04–1.30) | **0.0068** | 1.05 (0.98–1.13) | 0.1447 |
| Sleep disorders | 32.4 | 20.1 | 1.45 (1.07–1.97) | **0.0156** | 1.01 (0.85–1.20) | 0.8962 |
| Bone-related conditions | 62.7 | 54.6 | 1.12 (0.91–1.37) | 0.2894 | 0.95 (0.82–1.10) | 0.4600 |

AE, adverse event; C-OGC, chronic oral glucocorticoid; HR, hazard ratio; OGC, oral glucocorticoid; PY, person-year. Bone-related conditions include osteoporosis, osteopenia, and fracture. *Prednisone-equivalent milligrams. †Adjusted for age, sex, region, index year, and number of unique 3-digit International Classification of Diseases, Ninth Revision, Clinical Modification diagnoses, and number of unique National Drug Codes.

### Limitations

- Administrative claims are not intended for research purposes; instead, they support reimbursement. These data were subject to data coding limitations and may contain data entry error.
- There may be systematic differences between the study cohorts that account for differences found in outcomes that could not be controlled for through modeling.
- Certain AEs may be underreported in claims.
- OGC may be used to treat some of the AEs analyzed here.
- Only patients with private insurance were analyzed; the results may not be generalizable to other populations.

## Conclusions

- Children with asthma who initiate C-OGC are at potentially greater risk for experiencing AEs, including adrenal suppression, recurrent pneumonia, and behavioral problems, compared with children with asthma who do not initiate C-OGC.
- In appropriate patients with uncontrolled asthma, clinicians should consider effective alternative treatments to avoid these potential complications.

**References** 1. Centers for Disease Control and Prevention; National Center for Health Statistics. 2015 National Health Interview Survey (NHIS) data. https://www.cdc.gov/asthma/most_recent_data.htm. Accessed February 23, 2018. 2. Global Initiative for Asthma. 2017 Pocket Guide for Asthma Management and Prevention. http://ginasthma.org/2017-pocket-guide-for-asthma-management-and-prevention/. Accessed February 19, 2018.

**Disclosures** **DPS:** consultant, advisory board, and speaker/honoraria for ALK, Genentech, Inc., and Novartis; speaker/honoraria for Greer and Mylan. **ENA:** employee of Genentech, Inc. at the time of the study. **AMK, GML:** employees of Truven Health Analytics, an IBM Company. **AI:** employee of Genentech, Inc.; owns stock in GlaxoSmithKline and Pfizer. **WGT:** consultant, advisory board, and speaker/honoraria for Genentech, Inc., Novartis, and Teva; consultant and advisory board for Aviragen, Boehringer Ingelheim, and GlaxoSmithKline; research grant from the National Heart, Lung, and Blood Institute, National Institutes of Health, and Teva; and endowed Chair from the Ivy Foundation.

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