Assessing NSAID Prescription Use as a Predisposing Factor for Gastroesophageal Reflux Disease in a Medicaid Population

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Purpose. The purpose of the study was to determine the incidence of GERD associated with prescription NSAID consumption.

Methods. All Georgia Medicaid patients > 25 years of age and continuously eligible for 1996, 1997, and 1998 were included in the study. Patients were excluded if they received a GERD diagnoses during 1996 and 1997. Patients were observed in 1998 and classified into GERD and control cohorts. Comorbidities, demographics, and NSAID prescription consumption were retained and modeled with logistic regression.

Results. The absolute risk of developing GERD without previous NSAID consumption was 0.38. The absolute risk of developing GERD for those patients who consumed one or more NSAID prescriptions during 1996 and 1997 was 0.80. Thus, the relative risk of GERD for NSAID patients was 2.11. GERD was significantly associated with one or more NSAID prescriptions (OR = 1.82), age (OR = 1.05 for 5 year range), gender (OR = 1.31 for females), asthma (OR = 3.24), obesity (OR = 2.77), hiatal hernia (OR = 4.17), tobacco use (OR = 2.56), and alcohol (OR = 1.83). The initial NSAID prescription was responsible for the greatest marginal increase in GERD.

Conclusions. Our study suggests that NSAIDs are associated with GERD especially for females, alcohol and tobacco users, and patients with asthma, hiatal hernia, or obesity.

KEY WORDS: NSAIDs; non-steroidal anti-inflammatory drugs; Medicaid; GERD; gastroesophageal reflux disease.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most common complaints for which patients seek medical care. The broad description of this disorder encompasses any symptom or tissue damage that results from the reflux of gastric contents into the esophagus. GERD is a chronic disease with little spontaneous resolution and frequent relapses. Symptoms caused by reflux are highly variable; among which, heartburn and acid regurgitation are hallmarks (1). Heartburn was cited as either the primary or secondary reason for 2.5 million physician office visits nationally over a one-year period (2). Among American adults, it is estimated that approximately 7%, 14%, and 40% experience daily, weekly, and monthly heartburn, respectively (3). Nearly 15% of adults afflicted consume antacids for symptomatic relief more frequently than once a week. It is also known that approximately 2% of adults have endoscopic evidence of erosive reflux esophagitis (4). GERD may progress to other complications such as esophageal stricture, esophageal ulceration, Barrett's esophagus and esophageal adenocarcinoma (4–6). In excess of one billion dollars are spent annually in the U.S. for esophageal disease (7).

Many risk factors have been cited for GERD; however, considerable controversy exits regarding the relationship between nonsteroidal anti-inflammatory drug (NSAIDs) consumption and the development of this condition (3,7–11). Experimental evidence suggests that prostaglandin E2 induces dysfunction of esophageal body contractions, increases mucosal inflammation, and decreases LES pressure (12). NSAIDs have been shown to reverse these negative effects. Other evidence suggests that prostaglandin E_2 is protective in terms of the function of the mucosal barrier and that NSAIDs might damage the esophagus by disrupting the esophageal mucosal barrier or by affecting the mechanisms of mucosal adaptation to acid (13,14). Given this disagreement, some health care providers suggest that patients with GERD avoid using NSAIDs, if possible (11), whereas others propose the use of NSAIDs as a treatment modality for esophagitis (15). Therefore, further studies are needed to more thoroughly investigate the relationship between NSAID consumption and GERD.

Studies have shown that certain morbidities such as asthma, obesity and hiatal hernia are associated with reflux events. According to Mansfield (16), there is a general agreement that reflux is more common in asthmatic patients than in the general population. Other studies describe the prevalence of GERD among patients with asthma at about 80% (17). Clinical and experimental reports have well documented the relationship between asthma and GERD regarding the mechanisms whereby GERD may trigger asthma (18,19). Obesity is known to predispose patients to gastroesophageal reflux. The mechanism by which this occurs is through an increased intra-abdominal pressure which may lead to stress reflux during transient episodes of lower esophageal sphincter relaxation (20). Hiatal hernias may contribute to prolonged acid exposure following reflux and result in GERD symptoms and esophageal damage. Most patients with severe esophagitis have hiatal hernias. Fein et al (21) concluded that structurally defective LES and hiatal hernia are important factors in the pathogenesis of reflux disease.

The purpose of this study was to determine the association between prescribed NSAID consumption and the presence of GERD, after controlling for demographics and related morbidity, in a Georgia Medicaid population over a three-year period. A secondary objective was to determine the quantity of NSAIDs prescribed and the influence of this on the presence of GERD.

METHODOLOGY

A retrospective longitudinal review of Georgia Medicaid claims data was used to evaluate the association between prescribed NSAID consumption and the presence of GERD. The target cohort was the beneficiaries in the Georgia Medicaid population who were older than 25 years of age on January 1, 1996 and continuously eligible for Medicaid benefits in 1996, 1997, and 1998. These individuals were divided into two cohorts: those who received NSAID prescriptions

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during 1996 and 1997 and those who did not. All prescribed NSAID products in the Medicaid prescription file were captured using the therapeutic categories supplied by Multum Information Services at www.multum.com.

Phase I, the washout period, was limited to 1996 and 1997. Patients with one or more GERD diagnoses during these washout years were excluded. Individuals were also excluded if they had one or more physician office visits or inpatient claims filed for GERD, cancer of the esophagus, antireflux surgery; or were confined to a nursing facility. The information obtained in Phase I included prescribed NSAID consumption, demographic, morbidities related to GERD and treatment for alcohol and tobacco use.

Phase II of the study was limited to the year 1998. Patients were classified into a GERD group or control group (non-GERD) based on whether or not they had received an ICD-9 diagnostic code for this disease. Descriptive statistics (frequency and percentage) were calculated for the potential risk factors defined in this study, including age, race, gender, NSAID prescription use, observed tobacco use, observed alcohol treatment, asthma, obesity, and presence of hiatal hernia. Logistic regression models were applied to identify which of the risk factors were associated with the incidence of GERD.

Multiple logistic regression models were employed to quantify the relationship between predisposing prescribed NSAID consumption and the presence of GERD, accounting for other risk factors. Gender, race, tobacco use, alcohol use, status of asthma, obesity and hiatal hernia were dichotomized into binary values. Race was dichotomized into white vs. non-white. Prescribed NSAID consumption was defined as a binary or a continuous counted variable. Age was stratified into 11 intervals. The stepwise option was chosen to select those variables associated with GERD. SAS/STAT version 6.12 (SAS Institute, Cary, NC) was used in all phases of data analysis. Significance was established at an a priori level of $P < 0.05$.

RESULTS

Continuously eligible recipients who met the washout criteria for Phase I totaled 163,085. An NSAID cohort was created from the continuously eligible patients totaling 63,902 (39%) patients, and the control cohort totaled of 99,183 (61%) patients. Table I summarizes the characteristics for both NSAID and Control cohorts, including age, sex, race, use of tobacco, use of alcohol, and the presence of hiatal hernia, obesity and/or asthma. The NSAID cohort was slightly older, more feminine, more non-white, more alcohol and tobacco dependent, and more likely to have associated comorbidities including obesity, asthma, and hiatal hernias.

To assess prescribed NSAID use as a predisposing factor to GERD, absolute and relative risk ratios were calculated. The absolute risk for those patients who did not have GERD in 1996 or 1997 and developed GERD in 1998 for the NSAID cohort was calculated as

$$R_{NSAID} = \text{1998 GERD patients within NSAID cohort / NSAID patients} = 512/63{,}902 = 0.80.$$

The absolute risk for the control cohort was calculated as:

$$R_{Control} = \text{1998 GERD patients in Control cohort/ Control patients} = 374/99{,}183 = 0.38.$$

Table I. Characteristics of Individuals with/without NSAID Use[a]

	NSAID cohort(n = 63,902)		Control cohort(99,183)	
Characteristic	N	%	N	%
Age	Mean = 61.0		Mean = 60.1	
25–35	7722	12.1	14578	14.7
35–45	8178	12.8	13931	14.1
45–55	6994	10.9	10187	10.3
55–65	8124	12.7	10364	10.5
65–75	14876	23.3	21457	21.6
75≤	18008	28.2	22665	28.9
Sex				
Male	14934	23.4	30866	31.1
Female	48968	76.6	68317	68.9
Race				
White	22910	35.9	44175	44.5
Black	32477	50.8	45213	45.6
Other	8515	13.3	9795	9.9
Asthma	1606	2.51	1253	1.26
Obesity	1019	1.59	630	0.64
Hiatal Hernia	258	0.4	167	0.17
Tobacco	581	0.91	566	0.57
Alcohol	1296	2.03	1472	1.48

[a] Percentages may not equal 100% due to rounding.

The relative risk is 0.80/0.38 or 2.11. The computed relative risk does not account for differences in the demographics and comorbidities between the NSAID and control cohorts.

Initial analysis detected a negative relationship between GERD and age (Fig. 1). As age increases, the incidence of GERD increases before age 55 and decreases dramatically after age 65. Hence, the logistic regression analysis was limited to individuals between 25 and 65 years of age. The results of this analysis are summarized in Table II. The use of one or more NSAID prescriptions increased the odds of GERD by 83%. Comorbidities of asthma, obesity, hiatal hernia, tobacco, and alcohol use all increased the odds of GERD by significant amounts. Each additional 5 years of age between 25 and 65 increased the odds of GERD by 5.5%.

To calculate the impact of the amount of prescribed NSAID consumed in relationship to GERD, NSAID use was defined as a count variable. The number of prescribed NSAID during the two-year study period, truncated at 16, served as the criterion variable. Again, logistic regression was applied and the outcomes are reported in Table III. Each additional NSAID prescription is associated with a 5.3% increase in the odds of GERD. However, the incidence of GERD does not ascend as the number of NSAID prescrip-

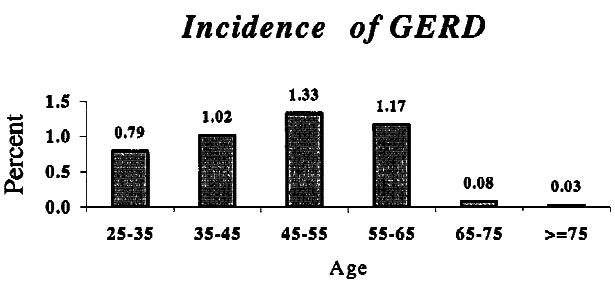

Fig. 1. Incidence of GERD for different age cohorts.

Table II. Binary Multiple Logistic Regression Model for Age between 25 and 65 Years Old with NSAID Use as a Binary Variable

Variable	Variable coding	Coefficient	*P*-value	Odds ratio	95% C.I.
NSAID	Non-user			1.000[a]	
	User	0.6030	0.0001	1.828	1.588–2.103
Age	1–8 (5 y age range)	0.0534	0.0004	1.055	1.024–1.087
Gender	Male	–0.3647	0.0001	0.694	0.592–1.228
	Female			1.000[a]	
Asthma	With	1.1758	0.0001	3.241	2.629–3.995
	Without			1.000[a]	
Obesity	With	1.0205	0.0001	2.774	2.136–3.604
	Without			1.000[a]	
Hiatal Hernia	With	1.4299	0.0001	4.178	2.782–6.276
	Without			1.000[a]	
Tobacco	With	0.9418	0.0001	2.564	1.873–3.504
	Without			1.000[a]	
Alcohol	With	0.6049	0.0001	1.831	1.380–2.429
	Without			1.000[a]	

[a] Reference cohort

tions increases (Fig. 2). The largest increase in GERD is observed between 0 (no NSAIDs) and 1 (a single NSAID) prescription. Therefore, the impact of each additional NSAID prescription beyond the initial prescription does very little to increase the odds of GERD. Other demographic and comorbidity variables display odds ratios similar to those presented in the previous model. However, the age variable changed from a positive to a negative coefficient.

DISCUSSION

In 1994, statistics from the U.S. Department of Health and Human Services indicate that about seven million people in this country suffer from GERD (22). Although GERD has associated morbidity, the mortality due to this disorder is rare (approximately 1 death per 100,000 patients) (11). Patients with GERD may experience severe and possibly lifelong symptoms that can lead to a significant reduction in their overall quality of life (23). Dimenas reported that GERD has a greater impact on quality of life than untreated hypertension, mild congestive heart failure, angina, and even duodenal ulcers (24).

Reflux signals an increased risk of esophageal adenocarcinomas by promoting cellular proliferation, and by exposing the esophageal epithelium to potentially noxious gastric contents (25). The mortality rate from gastroesophageal adenocarcinomas is high and the probability of developing esophageal cancer secondary to gastroesophageal reflux is 20 times higher than in individuals without reflux (26).

This project was conducted on 163,085 Georgia adult Medicaid recipients from 1996 to1998. Multiple logistic regression analyses were performed on NSAID prescription

Table III. Binary Multiple Logistic Regression Model for Age Older than 25 Years Old with NSAID Use as a Continuous Variable

Variable	Variable coding	Coefficient	*P*-value	Odds ratio	95% C.I.
NSAID	0–16	0.0518	0.0001	1.053	1.037–1.069
Age	1–11 (5 y age range)	–0.1956	0.0001	0.805	0.805–0.840
Gender	Male	–0.2744	0.0006	0.650	0.412–0.888
	Female			1.000[a]	
Asthma	With	1.3921	0.0001	4.023	3.255–4.973
	Without			1.000[a]	
Obesity	With	1.1740	0.0001	3.235	2.479–4.222
	Without			1.000[a]	
Hiatal Hernia	With	1.8875	0.0001	6.603	4.410–9.857
	Without			1.000[a]	
Tobacco	With	1.0648	0.0001	2.900	1.705–3.017
	Without			1.000[a]	
Alcohol	With	0.8190	0.0001	2.268	2.106–3.994
	Without			1.000[a]	

[a] Reference cohort

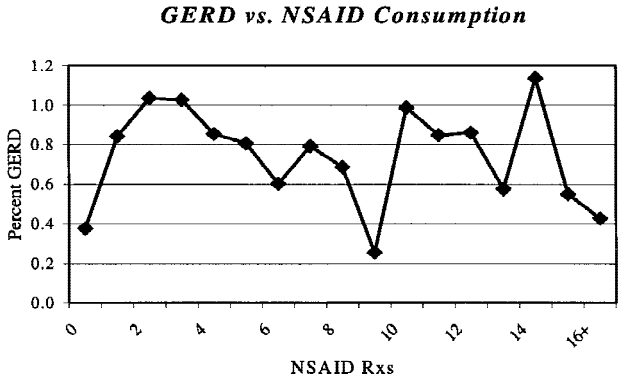

Fig. 2. Incidence of GERD and NSAID prescription consumption.

use, race, gender, age, tobacco use, alcohol use, and selected morbidities including asthma, obesity, and hiatal hernia. We discovered that under the modified incidence (which is more conservative than original incidence), the occurrence of new GERD cases is 8 out of every 1,000 individuals who used prescribed NSAIDs and 3.8 out of every 1,000 individuals who did not use these agents ($P < 0.001$). Consuming one or more NSAID prescriptions increased the odds of developing GERD by 83%. Each additional NSAID prescription did not contribute to an increase in this probability. Therefore, it can be concluded that prescribed NSAID consumption had a substantial impact on the incidence of GERD, after controlling for age, gender, and comorbidities in this adult Georgia Medicaid population.

Previous studies on smaller population samples indicated no sex-related differences in the frequency of symptoms suggestive of reflux disease (3,28). However, we discovered that females have a higher probability of experiencing GERD than males. It is conceivable that the sex specific variations may reflect inborn difference in anti-reflux barriers. As for racial factors, this study did not show any statistical difference between white and non-white with respect to the incidence of GERD even though esophageal disease is more prevalent in whites (28,29). The non-significance between whites and non-white may be due to the control of other confounding variables such as hiatal hernia. It is known that hiatal hernia has different distributions among races, with a greater prevalence in Western countries such as Europe and North America than in African or Asian countries (30).

Age usually causes a decrease in the pressure and contractile strength of the lower esophageal sphincter (31). Salivary secretion, which helps neutralize regurgitated acid covering the esophageal lining, is also reduced as people age (32). In addition, many diseases such as GERD, develop over extended time intervals. However, this study did not establish a positive correlation between age and the incidence of GERD when elderly individuals (age >65) were included. One possible explanation for this observation is that physicians may not routinely assign GERD ICD-9 diagnosis codes for these individuals as they often present with other, more serious comorbidities. This phenomenon requires further study.

We also observed a negative relationship between age and presence of GERD in the model that employed the number of NSAID prescriptions consumed as the criterion variable. We suspect that the elderly consume the greatest quantities of NSAIDs but there is no additive association with GERD and NSAID consumption beyond the initial NSAID prescription. Thus, the impact of age is confounded with the criterion variable, the number of NSAID prescriptions, producing spurious odds ratios.

The proportion of overweight individuals in the general population has increased and subsequently, obesity has emerged as a major risk factor for many diseases. Either an increase in intra-abdominal pressure or inappropriate relaxation of the lower esophageal sphincter may cause reflux in the presence of a normal resting lower esophageal sphincter pressure. Since obesity may increase intra-abdominal pressure, it has been assumed to predispose patients to GERD. A prevalence study conducted by Locke *et al.* (7) found that individuals with the greatest body mass index (>30 kg/m^2) demonstrated an odds ratio of 3.4 for reporting frequent reflux symptoms. This finding was supported by one of the conclusions in this study that severely obese patients were 2 times more likely to experience GERD. A recent report also linked excessive weight with the risk of esophageal adenocarcinomas, presumably because of the increased reflux resulting from obesity (33). Therefore, it may be a common practice to remind obese patients that weight loss is important to prevent GERD and possible esophageal adenocarcinomas.

In the current study, it was demonstrated that predisposition to hiatal hernia has the strongest positive association with GERD than other risk factors. Although the results of this study do not definitively establish a cause-effect relationship between hiatal hernia and GERD, they raise the question of the need for future studies evaluating this association.

It is believed that both GERD and asthma are common medical conditions that often exist simultaneously (34). The prevalence of GERD among asthmatic patients is estimated to range from 30% to 89% (35). The results of our study demonstrates that asthmatic patients are almost three times more likely to experience GERD. This finding supports previous studies (27). It is known that asthma exacerbation and the action of some of the medications used to treat asthma will promote reflux. Consequently, many asthmatic patients are diagnosed with GERD after a long duration of asthma therapy. At the same time, some asthma patients with GERD may not manifest reflux symptoms until after the esophagus is severely damaged (36). This study concluded that there exists an important causal relationship between asthma and GERD. Also, smoking and alcohol intake can promote reflux (37,38). We also confirmed the strong relationship between tobacco and alcohol consumption and the development of GERD.

The strength of this study was the size of the population and the study design. The population of this study is the largest among similar studies. Every year, more than one million Georgia residents are eligible for the Medicaid program. Hence, it can be assumed that this study considered a variety of health status, comorbidities, and even different health beliefs (39). Secondly, most population-based studies focus on point-prevalence and generally control only one risk factor in addition to demographic characteristics. The current project was a longitudinal study that controlled for many major risk factors in addition to demographics. Since the data source of this study was computerized, including demographic information, medical history and prescription claims information, the bias in data management is minimized. Therefore, the results of this study should be valid.

There are limitations when a study uses claims data as the principal data source. The limitations of this study include (1) accuracy of measurement of NSAID consumption, (2) data censoring, and (3) inclusion of potential risk factors. First, we defined NSAID consumption only based on prescription records, which means that actual consumption of these agents by the study population could not be accounted for. Additionally, patients may have taken over-the-counter NSAIDs in addition to their NSAID prescriptions. However, this behavior may be less than that observed in the fee-for-service market since Medicaid NSAID prescriptions were dispensed for only a $0.50 copayment fee. Nevertheless, the lack of verification may have biased the measurement of NSAID consumption.

Secondly, the window of observation was a maximum of 3 years, and consequently, subjects were both left and right censored. A censored variable can be observed for only a finite period of time. Because we did not observe NSAID consumption before the 2-year washout period, and could not determine if GERD developed following completion of the study, our data were both left and right censored.

Finally, diet and the use of certain medications by study subjects, such as calcium channel blockers, asthma medications containing theophylline, alpha-adrenergic agonists, nitroglycerin, disopyramide, and drugs with anticholonergic effects, might have had an impact on gastroesophageal reflux (25). Therefore, the association between the incidence of GERD and the differences in diet consumed, or the impact of certain pharmaceutical agents on gastroesophageal reflux disease in this population is unknown.

CONCLUSION

Our study results demonstrate that gastroesophageal reflux disease is associated with NSAID consumption, especially for females, for alcohol or tobacco abusers, and for patients with asthma, obesity, or hiatal hernia in a large Medicaid population. Since GERD is a common disease in the United States, its prevention is important. This study suggests that physicians may need to pay attention to the relationship between NSAID consumption and GERD, especially in the most vulnerable population, the elderly suffering associated comorbidities. Further, our study suggests that NSAIDs should not be prescribed to treat esophagitis given our verified association between NSAIDs and GERD.

The findings of this study raise the question of how patients requiring chronic NSAID therapy should be managed in regard to the risk of developing GERD. Clearly, monitoring of symptoms by physicians and pharmacists in patients receiving these medications is in order. This is especially true for those patients with additional risk factors for GERD and those who require medications that promote reflux. Chronic NSAID therapy may necessitate concomitant long-term acid suppression therapy such as the H-2 receptor antagonists or proton pump inhibitors. COX-2 therapy for those patients requiring long term NSAID therapy may offer an alternative for GERD patients. COX-2 NSAIDS are associated with fewer upper GI disturbances (40,41) and posses fewer long term adverse events (42) than other NSAIDS. However, their impact on GERD has not been evaluated. Additional work is required to assess the outcomes of concomitant therapy including studies of the relationship between the COX-2 inhibitors and GERD.

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