TIMOTHY EDWARD NIECKO
A Pharmacoepidemiologic Assessment of Nonsteroidal Anti-inflammatory Drug Exposure and the Association with Colorectal Cancer, Gastrointestinal and Renal Adverse Events
(Under the Direction of DR. BRADLEY C. MARTIN)

INTRODUCTION: Colorectal cancer (CRC) is the second leading cause of cancer-related deaths and is a growing health concern. Recently, epidemiological studies have associated NSAID use with a protective effect against CRC. METHODS: A retrospective, longitudinal, cohort design was used to assess the relationship of NSAID exposure and the incidence of CRC, gastrointestinal (GI), and renal adverse events in a Georgia Medicaid population. RESULTS: Over 700,000 person-years and 1.4 million drug claims were utilized. NSAID exposure reduced the risk of CRC by 25% and a dose/response relationship was confirmed with higher usage conferring more protection. Frequent users of NSAIDs did not experience an increased risk for GI and renal adverse events, though less frequent NSAID use trended toward an increase risk of GI events. CONCLUSION: This study confirms the NSAID/CRC protective relationship and found that long term NSAID use was not associated with an increase in GI and renal adverse events.

INDEX WORDS: Colon, Rectal, Colorectal, Cancer, Gastrointestinal, Renal, Nonsteroidal anti-inflammatory drug, Aspirin, Epidemiology, Medicaid

A PHARMACOEPIDEMIOLOGIC ASSESSMENT OF NONSTEROIDAL ANTI-INFLAMMATORY DRUG EXPOSURE AND THE ASSOCIATION WITH COLORECTAL CANCER, GASTROINTESTINAL AND RENAL ADVERSE EVENTS

by

TIMOTHY EDWARD NIECKO

B.A., The University of North Carolina at Chapel Hill, 1995

A Thesis Submitted to the Graduate Faculty of The University of Georgia in Partial Fulfillment of the Requirements for the Degree

MASTER OF SCIENCE

ATHENS, GEORGIA

2001

A PHARMACOEPIDEMIOLOGIC ASSESSMENT OF NONSTEROIDAL ANTI-INFLAMMATORY DRUG EXPOSURE AND THE ASSOCIATION WITH COLORECTAL CANCER, GASTROINTESTINAL AND RENAL ADVERSE EVENTS

by

TIMOTHY EDWARD NIECKO

Approved:

Major Professor Dr. Bradley C. Martin

Committee: Dr. Joseph DiPiro
Dr. Jeffrey Kotzan

Electronic Version Approved:

Gordhan L. Patel
Dean of the Graduate School
The University of Georgia
December 2001

TABLE OF CONTENTS

CHAPTER 1

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most popular and widely used drugs because of their many therapeutic applications, and are available in both prescription and over-the-counter (OTC) strengths. Over 35 million NSAID prescriptions and billions of OTC aspirin and other NSAIDs are sold annually in the United States.[1] Additionally, the usage of NSAIDs is projected to increase due to the aging population that is dependent upon these agents. Therapeutic benefits of NSAIDs are primarily two-fold, analgesic relief for acute and chronic pain, and the relief of inflammation in and around the joint. For over 30 years, NSAIDs have been a staple analgesic and anti-inflammatory therapy for those individuals suffering from osteoarthritis and other rheumatic musculoskeletal conditions.

Recently, studies have shown an association between NSAID exposure and a protective effect against the development of adenomatous polyps. It is generally agreed that adenomatous polyps are bio-markers and precursors for colon and rectal cancer (CRC). Colorectal cancer is the third most commonly diagnosed cancer for both men and women and is the second leading cause of cancer-related deaths behind lung cancer.[2]

In the past, CRC has not received the same level of public attention that other cancers, such as lung and breast cancer, have commanded. Recently, however, there has been a heightening in awareness of the prevalence of this disease and the devastation this

cancer poses. Surgery remains the most common form of curative treatment for CRC. Often by the time the disease is diagnosed, the cancer is generally in an advanced stage and prognoses and outcomes tend to be poor. This is largely a result of patients with CRC being asymptomatic of the disease in its earlier and more treatable stages and the failure of many patients and health care providers to adequately screen for CRC. This scenario gives emphasis to the necessity for implementing effective preventative measures, such as fecal occult blood tests and colonoscopy. The role of pharmacotherapy, in particular NSAIDs, and their apparent ability to slow, or arrest the carcinogenesis process is now being examined. The notion of a pharmacological agent, such as NSAIDs, as a prophylactic treatment has great appeal. Although the body of evidence of NSAIDs as a protective agent against CRC is gaining strength, it is not conclusive. Additionally, those on NSAID therapy must also reckon with well-documented side effects such as gastrointestinal and renal injury with extended exposure.

CHAPTER 2

NSAID EXPOSURE

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used drugs in many countries. Use of the majority of NSAIDs increases with age and is primarily used for symptoms associated with osteoarthritis and other chronic rheumatic conditions.[3] Population-based studies in the United States, Canada, England, and Australia have shown that non-aspirin NSAID use is common in those persons age 65 and greater and that 10 to 20 percent of these people have a current NSAID prescription.[3] Brooks states that 35 percent of all NSAIDs prescribed are for people age 60 and older.[1]

Many hypothesize that NSAID usage will increase as the population ages and arthritic and degenerative musculoskeletal conditions become more prevalent. However, it has been suggested that the prescribing of NSAIDs has plateaued in some countries and has actually declined over the last two years in others.[1] Australia has seen a reduction in NSAID prescriptions by about 25 percent since 1992, although nearly 70 percent of NSAID use is still for osteoarthritis, soft tissue, and back pain.[4]

CHAPTER 3

MECHANISM OF ACTION

It is generally agreed that the primary mechanism of action of NSAIDs is through the inhibition of the enzyme cyclo-oxygenase (COX) enzyme system which is responsible for the production of prostaglandins. Studies have shown that the COX enzyme can be divided into two isoforms; a constitutive isoform (COX-1), which is responsible for maintaining normal function in the GI and renal tract, and an inducible isoform (COX-2), which is found in areas of inflammation and in the brain.[1] It has been suggested that the anti-inflammatory, or therapeutic effects of NSAIDs are due to the inhibition of COX-2, whereas the adverse side-effects are due to the inhibition of COX-1.[5] Unfortunately, the vast majority of NSAIDs currently available are not selective for COX-2 and thus are responsible for the majority of the adverse reactions so commonly observed during NSAID therapy.

In the past decade, several studies have demonstrated that the continuous intake of NSAIDs decreases the risk of CRC. However, the mechanism of action that facilitates this protective effect is not clearly understood. It is hypothesized that NSAIDs may inhibit the evolution and formation of cancerous adenomas by their inhibition of cyclo-oxygenase and decreasing prostaglandin synthesis.[6] Experiments in human and animal models have shown that tumors produce large amounts of prostaglandins. NSAIDs reversibly interrupt the prostaglandin synthesis by

inhibiting cyclo-oxygenase. Aspirin works differently from NSAIDs in that it acetylates prostaglandin H synthase and thus irreversibly inactivates cyclo-oxengenase. Early studies in rodents demonstrated that administration of NSAIDs several weeks after a carcinogen prevented colorectal carcinoma. NSAIDs may prevent tumor formation by their actions on prostaglandins, which may have an immune-modulating effect. High levels of prostaglandin E_2 may suppress the immune system, which keeps malignant cells in check. NSAIDs reduce the production of prostaglandin E_2. An alternative prostaglandin-based theory suggests that inhibition of cyclo-oxengenase prevents the formation of free radicals, which could damage cells and lead to malignant transformation.[6]

Another mechanism that may explain the anti-proliferative and anti-tumor effects of NSAIDs include the interference of membrane – associated processes, such as G-protein signal transduction and transmembrane calcium influx. Other possible explanations include the inhibition of other enzymes, such as phosphodiesterase , folate-dependent enzymes, and cyclic adenosine 5'-monophosphatase –dependent protein kinase, as well as enhancement of immunologic responses and of cellular apoptosis.[6]

Shiff and Rigas reviewed the chemoproventive actions of NSAIDs and the association with CRC. They concluded that the bulk of most studies investigating the role of NSAIDs and the development of CRC generally fell under the four categories of: 1) cyclo-oxegenase (COX) mediated carcinogen activation, 2) cell proliferation, 3) apoptosis, and 4) immune surveillance.[7]

CHAPTER 4

NSAID ADVERSE EVENTS

The adverse side effects related to NSAID exposure are well known and documented and are a basis for serious health concerns. These side effects also constitute one of the most widely reported events to drug regulatory agencies such as the U.S. Food and Drug Administration (FDA).[1] The most commonly reported adverse events related to NSAID exposure are GI complications such as perforation, ulceration, and bleeding. Acute and chronic renal complications are also a major concern with NSAID use. A more comprehensive list of the major side effects associated with NSAID exposure is shown in Table 1.

Table 1. Side Effects Associated with Nonsteroidal Anti-inflammatory Drug Therapy[1]

System	**Side Effect**
Gastrointestinal	Peptic ulcer
	Esophagitis and strictures
	Small and large bowel erosive disease
Renal	Reversible acute renal failure
	Fluid and electrolyte disturbance

	Chronic renal failure and interstitial
	Interstitial nephritis
	Nephrotic syndrome
Cardiovascular	Exacerbation of hypertension
	Exacerbation of congestive cardiac failure
	Exacerbation of angina
Hepatic	Elevated transaminases
	Fulminant hepatic failure (rare)
Central nervous system	Headache
	Drowsiness
	Confusion and behavior disturbance
	Aseptic meningitis
Hematologic	Thrombocytompenia
	Hemolytic anemia
	Agranulocytosis and aplastic anemia
Other	Exacerbation of asthma and nasal polyposis
	Skin rash

Gastrointestinal tract complications associated with NSAID use are the most common serious adverse drug reactions in the United States.[8] Endoscopic studies have shown that 20 percent of long-term NSAID users will develop peptic ulcer disease. Also, a significant number of those patients whose ulcers bleed will die. Renal events are believed to be caused by inhibiting renal prostaglandins and capable of producing acute renal failure, exacerbation of renal insufficiency, hyperkalemia, and, occasionally, interstitial nephritis. However, acute renal failure is reversible by means of discontinuation of NSAID therapy. Cardiovascular events such as hypertension occur

relatively frequently resulting in an increase in arterial pressure. Interactions can occur with NSAID therapy and can interfere with patients taking antihypertensive therapy such as β blockers and angiotensin-converting enzyme (ACE) inhibitors by modifying the effect of renal prostaglandins. In addition, NSAIDs also cause fluid retention, which can exacerbate congestive heart failure.

In addition, many observational studies have suggested that the risk of adverse events associated with NSAID exposure may be higher in selected sub-groups of patients (e.g. elderly patients, women, and persons with an ulcer history).[9-11]

CHAPTER 5

GASTROINTESTINAL INJURY AND NSAID EXPOSURE

5.1 Epidemiology

Numerous epidemiological studies have documented the association between NSAID exposure and increased risk of GI adverse events.[8-21] The epidemiologic evidence affirms that the most clinically significant and prevalent side effects associated with NSAID exposure are adverse GI events. NSAID exposure has long been associated with GI toxicity and has been reported as the most prevalent, serious adverse drug event in the United States.[10;22] Hospitalization rates for peptic disorders have been reported to be as high as 6 per 1,000 persons. These upper GI complications include gastric bleeding and perforation, duodenal lesions and ulcers, and other peptic disorders.

5.1.1 Case-control studies

Griffin *et al* (1991) evaluated NSAID use and the relative risk of peptic ulcer disease in elderly persons in a retrospective nested case-control study using administrative claims.[18] Participants were Tennessee Medicaid enrollees 65 years of age or older. The 1,415 case patients had been hospitalized for confirmed peptic ulcer disease or upper GI hemorrhage at some point from 1984 through 1986. The 7,063 control subjects represented a stratified random sample of the other Medicaid enrollees. NSAID exposure was categorized according to recency of use, dose, duration, and the

specific drug prescribed. The distribution of NSAID exposure was categorized as follows; current use (64%), intermediate use (45%), former use (20%), and non-users (5%).

The estimated relative risk for the development of peptic ulcer disease among current users of NSAIDs, compared with that among non-users, was 4.1 (95% CI, 3.5 – 4.7). For current users, the risk increased with increasing dose, from a relative risk of 2.8 (95% CI, 1.8 – 4.3) for the lowest dose category to 5.5 (95% CI, 4.2 – 7.4) for the standard dose category. The risk was greatest in the first month of use with a relative risk of 7.2 (95% CI, 4.9 – 10.5). Twenty-nine percent of the peptic ulcers in the study sample were estimated to be a result of NSAIDs, and the excess risk associated with such use was 17.4 hospitalizations for ulcer disease per 1,000 person-years of exposure.[18]

In this sample of elderly Medicaid enrollees, current users of prescription NSAIDs were four times more likely than non-users to be hospitalized for confirmed peptic ulcer disease or upper GI hemorrhage. This association was consistent across demographic sub-groups and for both gastric and duodenal ulcers. These results support other findings indicating that a clinically significant risk for serious ulcer disease is associated with the use of NSAIDs. The data also shows that the risk increases with dose and recency of use.[18]

Garicia Rodriguez and Jick (1994) assessed the risk of upper GI bleeding and perforation and the association with individual NSAIDs in a retrospective case-control study.[14] The study sample consisted of 1,457 cases and 10,000 randomly selected control subjects identified from general practitioners' computerized records in the United

Kingdom from 1990 to 1993. Validation studies have shown that more than 90% of information from manual records are present in the computerized records.

The adjusted relative risk of upper GI bleeding associated with current NSAID use was 4.7 (95% CI, 3.8 – 5.7). Previous GI bleeding was the single most important predictor of GI bleeding. For all NSAIDs together, the risk was greater for high doses than for low doses, 7.0 (95% CI, 5.2 – 9.6) and 2.6 (95% CI, 1.8 – 3.8), respectively. The estimates for the individual NSAIDs varied widely. Users of azapropazone and piroxicam had the highest relative risks of 23.4 (95% CI, 6.9 – 79.5) and 18.0 (95% CI, 8.2 – 39.6), respectively. All the other NSAIDs with sufficient data for individual analysis (ibuprofen, naproxen, doclofenac, ketoprofen, and indomethacin) had relative risks similar to that of overall NSAID use.[14]

The relative risk was significantly higher for current multiple users than for current single users. The risk was substantially lower for recent past users and that for past users was similar to the risk in non-users. The relative risks associated with NSAID use were slightly greater for gastric than for duodenal bleeding and greater for perforation than for bleeding only.

5.1.2 Cohort studies

Singh *et al* (1996) investigated NSAID use in rheumatoid arthritis patients and the association with both minor and major GI tract complications in a prospective cohort study.[8] Study subjects consisted of 1,921 patients with rheumatoid arthritis from 8 ARAMIS (Arthritis, Rheumatism, and Aging Medical Information System) centers which collect detailed clinical and outcome information. Patients were included in the study if

treated with NSAIDs and had at least 2.5 years of observation available. Patient data was obtained from validated self-reports collected every 6 months and review of hospital records.

Approximately 15% of the 1,921 patients reported an NSAID-induced GI side effect during the 2.5 year observational period. Of these patients, 42 (2.2%) had a serious GI complication requiring hospitalization and 81% did not have a preceding GI adverse event. Patients taking antacids and H_2 receptor antagonists did not have a significantly lower risk for serious GI complications than did those not taking such medications.[8]

Smalley and colleagues (1995) investigated NSAID use and the association of the incidence of hospitalizations for peptic ulcer disease in elderly persons in a large retrospective cohort study.[23] Study subjects consisted of 103,954 elderly Tennessee Medicaid recipients age 65 or greater with 209,068 person-years of follow-up from 1984 to 1986. The study population was predominately female (74% of person time) and had a substantial proportion of African-Americans (28%), and very old (18% older than age 85 years, 44% aged 75 – 84, and 41% aged 65 – 74). There were 1,371 patients hospitalized with peptic ulcer disease or upper GI hemorrhage identified by Medicaid hospital claims and verified by medical record review.

The rates of ulcer hospitalizations among nonusers and current users of NSAIDs were 4.2 and 16.7 per 1,000 person-years, respectively, resulting in a significant difference of 12.5 (95% CI, 11.4 - 13.6). Among new users, the ulcer hospitalization rates were 26.3 per 1,000 person-years during the first 30 days of use (95% CI, 18.6 - 25.6), and 20.9 per 1,000 person-years over the next 31 to 180 days (95% CI, 13.1 - 20.1), both resulting in significant differences from the reference nonuse group. It was

concluded that NSAID use was associated with a substantial rate of hospitalization for peptic ulcer disease in the cohort of elderly.[23]

5.1.3 Meta-analyses

Gabriel *et al* (1991) conducted a meta-analysis to assess the association between non-aspirin NSAID exposure among NSAID users as well as selected sub-groups and relative risk for serious GI complications.[11] Critical appraisal of the study characteristics were done as well as consultation with internationally recognized experts in the field to identify studies to evaluate. The results of 16 primary studies were selected and combined. Summary estimates of 9 case-control and 7 cohort studies were weighted by sample size and quality scores. Studies were excluded from analysis if the primary objective was to assess effectiveness, if it involved the treatment of children under the age of 18 years, if the study population had fewer than ten patients, if the only NSAID studied was salicylate, if the outcome examined was the identification of ulcer rather than the presence of serious GI complications.[11]

Those exposed to NSAIDs are approximately three times more likely to develop serious adverse GI events than are non-users. The overall odds ratio of the risk of adverse GI events related to NSAID exposure was 2.74 (95% CI, 2.54 – 2.97).[11] The odds ratios by sub-groups were as follows: elderly patients age 60 and greater, 5.52 (95% CI, 4.63 – 6.60), patients under 65 years of age, 1.65 (95% CI, 1.08 – 2.53), women, 2.32 (95% CI, 1.91 – 2.82), and men 2.40 (95% CI, 1.85 – 3.11). The summary odds ratio for the first GI event was 2.39 (95% CI, 2.16 – 2.65) while the relative risk for a subsequent or unspecified GI event was 4.76 (95% CI, 4.05 – 5.59). The summary odds ratio for less

than 1 month of NSAID exposure was 8.00 (95% CI, 6.37 – 10.06); for more than 1 month but less than 3 months of exposure, the summary odds ratio was 3.31 (95% CI, 2.27 – 4.82); and for more than 3 months of exposure the summary odds ratio was 1.92 [11]

Additional risk factors include age greater than 60 years, previous history of GI events, and concomitant corticosteroid use. Another possible risk factor is the first three months of NSAID therapy. The risk for serious GI events appears to be equal among men and women. These results represent summary statistics from the 16 studies assessed and cannot be generalizable to all NSAID users or drugs.[11]

CHAPTER 6

RENAL INJURY AND NSAID EXPOSURE

6.1 Epidemiology

Numerous epidemiological studies have documented the association between NSAID exposure and increased risk of renal adverse events.[24-29] However, renal injury as a result of NSAID exposure is a far more uncommon event than GI injury caused by NSAIDs, affecting approximately 2 persons per 100,000. This is largely thought to be a result of NSAIDs inhibiting the ability of the kidney to produce adequate amounts of vasodilator prostaglandins.[29]

6.1.1 Case-control studies

Perez Gutthann *et al* (1996) assessed the association between the use of NSAIDs and the risk of hospitalization due to acute renal failure (ARF) in a population-based case-control study.[30] A total of 306 records were reviewed and 28 cases of ARF were identified by means of ICD-9-CM codes from the health department database from the province of Saskatchewan, Canada between 1982 and 1986. The incidence rate of hospitalization for ARF among the general population not exposed to NSAIDs was 2 per 100,000 person-years. Independent risk factors identified for ARF included exposure to NSAIDs, aspirin and other nephrotoxic drugs, male gender, and increasing age. The greatest risk factor for ARF was observed among persons with a recent history of

hospitalization for disorders other than renal (OR = 6.9). Current NSAID users had an adjusted odds ratio for ARF of 4.1 (95% CI, 1.5 – 10.8). The risk of ARF was especially high during the first month of use (OR = 8.5). High daily doses of prescribed NSAIDs had an odds ratio of 9.8 for ARF. The risk of ARF quickly reversed back to baseline after termination of NSAID therapy. A strong dose dependent relationship was also discovered as users of higher doses were more than twice the risk of ARF than lower dose users. It was noted that NSAID users who used nephrotoxic drugs concomitantly with NSAIDs experienced a substantially greater risk than the risk anticipated merely from combining the risks calculated separately, possibly suggesting a synergistic effect among the drugs.[30]

Perneger and colleagues (1994) assessed the risk of kidney failure associated with the use of acetaminophen, aspirin, and NSAIDs.[26] Exposure to analgesic drugs heightens the risk of end-stage renal disease (ESRD), but the extent of the risk remains unclear. The study subjects were between the age of 20 and 64 years of age and consisted of 716 patients treated for ESRD and 361 controls matched on age. Study participants were interviewed by telephone about their use of analgesics. Drug exposure was measured by average use and by cumulative intake.

Heavier acetaminophen use was associated with an increased risk of ESRD in a dose-dependent fashion. Cumulative NSAID dosages between 1,000 and 4,999 pills taken during a lifetime did not increase the risk of renal failure, however, a cumulative dose of 5,000 or more pills was associated with a steep increased risk of ESRD (OR, 8.8). This raises concern about the safety of persons taking large quantities of NSAIDs.[26]

6.1.2 Cohort studies

Perez-Gutthann *et al* (1999) examined the effects of low-dose diclofenac, naproxen, and ibuprofen and their impact within 30 days on upper GI bleeding, acute liver and renal failure, and other disorders in a large cohort study in the United Kingdom.[25] The evaluation of the safety of diclofenac as a potential OTC analgesic with respect to the most widely marketed OTC NSAIDs, naproxen and ibuprofen was the primary objective of the study. The study was designed to reflect as closely as possible the OTC setting for those patients using a low-dose, short-term prescription NSAID. The only eligibility criteria were no diagnosis of cancer and no prescription for NSAIDs in the three months preceding the study entry date.

The study sample comprised 22,146 persons using diclofenac, 46,919 using naproxen, and 54,830 using ibuprofen. For the three cohorts, the prescribed daily dose could not exceed 75 mg (diclofenac), 750 mg (naproxen), and 1200 mg (ibuprofen). In the short follow-up period, only 17 cases of upper GI bleeding believed to be associated with NSAID were identified. There were no cases of acute renal failure, blood dyscrasia, skin disorder, or anaphylaxis. These study findings are in agreement with results of other studies examining similar end points within the same time frame.[25]

6.1.3 Case studies

Shankel *et al* (1992) investigated acute renal failure and glomerulopathy believed to be caused by NSAIDs.[28] Cases comprised of acute renal failure (27 patients) or glomerulopathy (7 patients) identified between 1972 and 1986 and all having previous NSAID exposure. The patients ranged in age from 17 to 81 years of age, with a mean of

56 years of age. The 27 patients who developed acute renal failure had been taking NSAIDs for a mean of 46 days (range, 30 to 270 days) before the conditions set in, while the seven patients who developed glomerulopathy had been taking NSAIDs for a mean of 95 days (range, 14 to 180 days). The 23 cases of acute renal failure and 7 cases of glomerulopathy cleared an average of 23 and 118 days, respectively, after treatment with NSAIDs were stopped. Indomethacin was the drug most commonly implicated with acute renal failure accounting for 10 cases, as well as 3 cases of glomerulopathy. Ibuprofen and naproxen accounted for five cases each of acute renal failure.

6.2 Randomized controlled trials

Whelton *et al* (1990) evaluated the renal effects of ibuprofen, piroxicam, and sulindac in patients with asymptomatic renal failure in a prospective, randomized, triple-crossover study.[29] Study subjects consisted of 12 women with mild, but stable chronic renal failure and with serum creatinine levels between 130 and 270 :mol/L (1.5 and 3.0 mg/dL). Patients were assigned to receive an 11-day course of each of the three NSAIDs in a triple-crossover fashion, with at least a 1-month washout period between regimens. The washout interval was selected to ensure an adequate period of drug elimination and prostaglandin recovery before starting the next NSAID therapy to minimize the risk of any carryover and treatment effects.

Two patients were withdrawn from ibuprofen therapy on day 8 because of an increase in serum creatinine levels. All patients on piroxicam and sulindac therapy completed their regimens as scheduled. Although there was substantial interpatient variability, the overall mean serum creatinine values increased significantly during the

sulindac therapy ($p<0.05$), but not during the piroxicam therapy. There was no statistically significant change in glomerular filtration rate during the ibuprofen and piroxicam therapies, however interpretation of ibuprofen results are confounded by the exclusion of day 12 values for the three patients in whom ibuprofen was stopped.[29]

It was concluded that ibuprofen may result in acute renal failure in patients with asymptomatic, mild chronic renal failure. More specifically, therapeutic doses of ibuprofen (2,400mg /day) caused detectable changes in serum creatinine levels. As a result, ibuprofen therapy was discontinued prematurely in 25% of the patients because of increased serum creatinine levels or hyperkalemia. In contrast, all patients tolerated the 11-day course of both piroxicam and sulindac without interruption. It is conceivable that the 11-day length of therapy was not long enough to induce acute renal deterioration.[29]

CHAPTER 7

CRC PROTECTION AND NSAID EXPOSURE

7.1 Epidemiology

Numerous epidemiological studies have documented the association between NSAID exposure and a protective effect against the development of CRC.[31-47] One recent epidemiologic study indicates up to a 40 to 50 percent reduction in mortality from CRC in individuals exposed to NSAIDs compared to those not exposed[44]

7.1.1 Case-control studies

Rosenberg *et al* (1991) assessed the association between NSAID use the incidence of large-bowel cancer in a hospital-based, case-control study.[43] Study subjects comprised 1,326 patients with CRC (colon, 802 patients; rectum 524 patients) and 4,891 control patients. The cancer control group of patients was made up of 1,011 patients with cancer of the pancreas (247 patients), prostate (179 patients), kidney (161 patients), stomach (151 patients), bone and connective tissue (136 patients), vulva (76 patients), and thyroid (61 patients). The non-cancer control group comprised 3,880 patients who had no history of cancer. Patients had been diagnosed within the last 6 months , had no other primary cancer, and no cancer history. NSAID use was defined as any drug in the following classes: salicylates (e.g., aspirin), indoles (e.g., indomethacin), propionic acids (e.g., ibuprofen), fenamates (e.g., mefenamic acid), pyrazolines (e.g., phenylbutazone),

and oxicams (e.g., piroxicam). Regular use was defined as therapy that had begun within the year prior to the baseline interview. NSAID use that did not meet the criterion for regular use was classified as nonregular use.

Relative risks were estimated for NSAID use relative to never use. Potential confounding variables controlled for in the analysis were age, gender, race, alcohol consumption, history of cholecystectomy, history of large-bowel cancer in a parent or sibling, years of education (as a proxy for socio-economic status), geographic area, year of interview, and number of previous hospitalizations. For regular NSAID use within one year prior to the study, the adjusted RR was 0.5 (95% CI, 0.2 – 0.9). For regular use initiated longer than one year prior to study inclusion, the adjusted RR was 0.5 (95% CI, 0.4 – 0.8). For regular use that ended at least a year before study inclusion, the adjusted RR was 1.0 (95% CI, 0.6 – 1.8). Approximately 75% of discontinued use had ended two years before the study, and approximately 50% had ended five years before the study start date.

Cancer of the colon and rectum were also analyzed separately. For recent regular use, the adjusted RR for colon cancer was 0.5 (95% CI, 0.3 – 0.8), for rectal cancer, the risk estimate was 0.6 (95% CI, 0.4 – 1.1). Colon cancer was further sub-divided into right-sided cancer (cecum to hepatic flexure) and left-sided cancer (transverse to sigmoid). The estimates for recent regular use for the right-side were 0.4 (95% CI, 0.2 – 0.8), and left side, 0.6 (95% CI, 0.4 – 1.0). Overall, the risk of large-bowel cancer appeared approximately halved among persons who recently used NSAIDs regularly, and longer duration of use appeared to have a greater protective effect. However, almost all NSAID use was aspirin.[43]

Martinez *et al* (1995) examined the relation between aspirin and other NSAID drugs and the risk of colorectal adenomatous polyps among endoscoped individuals in a case-control study.[40] Most epidemiological studies support the inverse relationship between NSAID exposure and CRC. However, few studies have investigated the relationship between the use of aspirin and other NSAIDs and adenomatous polyps, which are recognized as a precursor of CRC.[40] The study subjects were comprised of 157 cases and 480 controls, 35 to 79 years of age, and who underwent endoscopy at collaborating gastroenterology clinics in the Houston, TX. Cases were individuals who met eligibility criteria, had a lower GI endoscopy, and had a first-time diagnosis of villous, tubular, or tubulovillous adenomatous polyps. Individuals with both adenomatous and hyperplastic polyps were included in the case group. The control group consisted of individuals who met eligibility criteria but presented no colorectal polyps.

Patients were excluded from the study if they presented with a history of colorectal polyps, familial polyposis coli, Gardner's syndrome, hereditary nonpolyposis colorectal cancer, ulcerative colitis, inflammatory bowel disease, and chronic renal failure. Potential confounding variables controlled for were age, gender, race, cigarette smoking, family history of CRC, body mass index, dietary fiber intake, and alcohol consumption. Individuals who reported use of aspirin and other NSAIDs had a significantly lower risk of having adenomatous polyps with a crude odds ratio of 0.59 (95% CI, 0.38 – 0.92). The association became stronger after controlling for potential confounding variables and resulted in an adjusted OR of 0.46 (95% CI, 0.29 – 0.75). Although not significant, a decrease in risk was observed for individuals who used aspirin and other NSAIDs on a weekly basis with an adjusted OR of 0.77 (95% CI, 0.39 – 1.55).

The risk was further decreased and became significant for individuals who used these once per day or more compared to nonusers, adjusted OR = 0.36 (95% CI, 0.20 – 0.63). Individuals who had used aspirin and other NSAIDs for less than five years had and OR = 0.39 (95% CI, 0.21 – 0.71), while those who had more than 5 years of exposure, the adjusted risk was 0.60 (95% CI, 0.32 – 1.14), although non-significant.[40]

The results of this study suggest that the use of aspirin and other NSAIDs is inversely associated with the risk of colorectal adenomatous polyps. Individuals who took aspirin and other NSAIDs once per day or more had over a 60% reduction in the risk of exhibiting adenomatous polyps than nonusers. Increased duration of use was not significantly associated with a decreased risk, although a trend was present. However, the non-significant findings may have been influenced by a small sample size.[40]

Muscat *et al* (1994) investigated the association between NSAID exposure and CRC in a hospital-based, case-control study.[48] Study subjects consisted of 511 patients with histologically confirmed colorectal cancer (346 colon patients, 165 rectum patients) and 500 controls that were matched on age (+/- 5 years), gender, race, hospital, and month of interview. Information from a standardized questionnaire was used to collect sociodemographic variables, medical history, family history of cancer, pregnancy history, lifetime physical activity, smoking, and alcohol use. A food frequency section was used to obtain information on the major sources of total dietary fat and fiber. Information on NSAID exposure was collected regarding ever taken NSAIDs, frequency and duration of therapy, age of patient at first exposure, and specific medical reasons for taking NSAIDs. Regular use of NSAIDs and acetaminophen was defined as at least 3 times per week for at least 1 year before the baseline interview.

Case and control patients had similar ages, levels of education, and religious affiliations. Thirty-eight percent of the case subjects and 47% of the control subjects took NSAIDs for at least one year. The odds ratios for men who regularly took NSAIDs were: 0.77 (95% CI, 0.34 – 1.75) for 1 to 4 years of use, 0.93 (95% CI, 0.45 – 1.97), for 5 to 9 years of use, and 0.47 (95% CI, 0.21 – 0.94) for more than 9 years of use. Among women who took NSAIDs regularly, there was a significant decrease in risk for 1 to 4 years of use, 0.17 (95% CI, 0.06 – 0.49). For 5 to 9 years of use the odds ratio was 0.13 (95% CI, 0.02 – 1.39), but for women with more than 9 years of use there was a decreasing trend in the risk, 0.60 (95% CI, 0.26 – 1.36). Overall, regular NSAID use was associated with a significant reduction of CRC in both men and women. There were little differences in risk when comparing the effects of NSAIDs between the left-sided colon and right-sided colon, or between cancers of the colon and rectum.

The association of CRC with other suspected risk factors was evaluated to determine possible confounding in the analysis. No association was observed with body mass index and dietary intake of red meat, cheese, fruits, and vegetables. There was no association with levels of physical activity, cigarette smoking, alcohol consumption, and coffee consumption. However, family history of CRC was significantly related to the risk of CRC, OR 2.8 (95% CI, 1.8 – 4.2), but unrelated to pain reliever use.

While these results support the hypothesis that regular NSAID exposure reduces the risk of large bowel cancer, the evidence that the protective effect increases with duration of use was not established. Studies conducted by Rosenberg *et al*[43] and Thun *et al*[49] found non-significant trends with increasing duration of NSAID use. Their studies demonstrated that risk reduction among men increased with long-term NSAID use

greater than 9 years. However, a greater protective effect was exhibited among women who took NSAID for 1 to 9 years compared to women who used them for more than 9 years. These results demonstrate that, at least in men, the reduction in risk increases with the duration of NSAID exposure.[48]

7.1.2 Cohort studies

Smalley *et al* (1999) investigated the use of NSAIDs and incidence of CRC in a population-based retrospective cohort study.[44] Tennessee Medicaid enrollees (n = 104,217) aged 65 years or older with at least 5 years of continuous eligibility were studied to determine how the dose, duration, and specific non-aspirin NSAIDs affect the incidence of histologically confirmed CRC. Five years of continuous enrollment was required to ensure that 5 years of medication history was available. Subjects left the cohort on the first of the following events; diagnosis of an incident colorectal cancer, death, loss of eligibility, or the end of the study (December 31, 1992).

The study cohort consisted of 104,217 individuals who contributed 447,065 person-years of follow-up. NSAID users comprised of 280,296 person years of observation while non-users consisted of 166,769 person years. There were 662 subjects identified with colon cancer and 146 with rectal cancer. Potential confounding variables age, gender, and race were controlled for in the analysis. For tumors of the colon, increased cumulative use of NSAIDs was associated with decreased rates of cancer.

Users of at least 48 months had a relative risk of 0.49 (95% CI, 0.24 - 1.00) for colon cancer when compare to those with no exposure to NSAIDs. Subjects with more than 12 months of cumulative NSAID use in the past year, the RR was 0.61 (95% CI,

0.48 – 0.77), whereas those with no recent use in the past 12 months had an RR of 0.76 (95% CI, 0.50 – 1.15) when compared to those with no use of NSAIDs. Protection was more pronounced for right-sided lesions, where the RR was 0.48 (95% CI, 0.34 – 0.68), while the RR for left-sided lesions had a RR of 0.77 (95% CI, 0.55 – 1.08). No specific NSAID offered a unique protective effect against CRC and low doses appeared to be at least as effective protectively as higher doses. In this study cohort, continuous and long-term use of nonaspririn NSAIDs reduced the risk of colon cancer by as much as 50%.[44]

Giovannucci *et al* (1991) examined aspirin use and the risk of CRC and adenomas in male health professionals throughout the United States in a prospective cohort study.[34] The study objective was to determine whether regular use of aspirin decreases the risk of CRC. Subjects were male health professionals (n = 47,900) between 40 and 70 years of age. The cohort was initiated in 1986 to study various potential causes of cardiovascular disease and cancer and, particularly, the impact of diet. Data was collected by mailed questionnaire at years 1986, 1988, and 1990 on the history of cancer and clinically diagnosed conditions, as well as aspirin and other NSAID usage. Current use of aspirin and other NSAIDs was defined as two or more dosages of aspirin, acetaminophen, or other NSAIDs per week.

Two-hundred fifty-one subjects were diagnosed with CRC during the study period. Regular users of aspirin, i.e., two or more times per week, in 1986 had a lower relative risk of total CRC, 0.68 (95% CI, 0.52 – 0.92) and advanced (metastatic and fatal) CRC, 0.51 (95% CI, 0.32 – 0.84). Potential confounding variables controlled for in the study were age, history of polyp, pervious endoscopy, parental history of CRC, smoking, body mass, physical activity, and intake of red meat, vitamin E, and alcohol. The

association was greater among men who reported regular use of aspirin consistently on subsequent questionnaires. Also, earlier diagnosis and treatment of adenomas among those screened with fecal occult blood tests did not account for the inverse association between aspirin and CRC. It was concluded that long-term use of aspirin may substantially decrease the incidence of CRC.[34]

Schreinemachers and Everson (1994) investigated the association between aspirin use and lung, colon, and breast cancer in a large prospective cohort study.[50] The study was sponsored by the National Center for Health Statistics which conducted the National Health and Examination Survey I (NHANES I) and the NHANES I Epidemiologic Follow-up Studies (NHEFS). Study subjects were drawn from a probability sample of civilian, noninstitutionalizied U.S. citizens from 1 and 74 years of age for NHANES I, while data for subjects who had undergone a medical examination and were 25 to 74 years of age were collected for NHEFS.

Of the 14,407 subjects age 25 to 74 who underwent a medical examination and were followed up after NHANES I, a total of 1,888 were reported to have either lung, colon, or breast cancer. After various exclusion criteria, 12,668 subjects were available for analyses in which 1,257 subjects presented with cancer. Aspirin use among subjects with cancer was 51%, while those without cancer was 60%. Potential confounding variables controlled for in the study were age, gender, race, education, socioeconomic status, body mass index, alcohol consumption, and arthritis. Men aged 65 years or younger exhibited a reduced risk of CRC, RR = 0.35 (95% CI, 0.17 – 0.73). Also, all men taken together exhibited a decreasing trend in the risk of CRC for aspirin users, RR = 0.74 (95% CI, 0.49 – 1.13). Surprisingly, all women showed a slight increasing trend

in the risk of CRC for aspirin use, but was non-significant, IRR = 1.06 (95% CI, 0.69 – 1.64).[50] Overall, aspirin use in this cohort was associated with a reduced incidence of cancer.

7.1.3 Randomized controlled trials

Randomized controlled trials (RCTs) have the ability to control for confounding factors that may bias results and are recognized as the preferred study design to assess interventions and to infer causality of outcomes. Six randomized controlled trials were identified and reviewed. Two of the RCTs evaluated the effect of sulindac on familial adenomatous polyps,[33;51] two RCTs assessed the effect of aspirin on colorectal tumors,[35;52] and two RCTs evaluated the effect of NSAIDs on sporadic colonic polyps.[53;54] These studies and their results are summarized below.

Giardiello *et al* (1993) evaluated the treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis in a randomized, double-blind, placebo-controlled study.[33] Familial adenomatous polyposis (FAP) is a rare genetic disorder characterized by the formation of hundreds of colorectal adenomas. Virtually all patients with FAP will have colorectal cancer by the fifth decade of life if prophylactic colectomy is not performed.

Study subjects consisted of 22 patients recruited from the Johns Hopkins Polyposis Registry. Patients with FAP who had not undergone colectomy or ileorectal anastomosis and had at least five or more adenomatous polyps at the time of the study were eligible. Reasons patients were excluded from the study included; if NSAIDs were used more than one week during the three months before the study began, had a history

of peptic ulcer disease or GI hemorrhage, or history of cancer. Patients received sulindac at a dose of 300mg per day (150mg twice daily) for nine months or placebo. The number and size of polyps were evaluated every three months for one year.[33]

A statistically significant decrease in the mean number of polyps and their diameter occurred in patients treated with sulindac, as compared to those given placebo. When treatement was stopped at nine months, the number of polyps had decreased to 44% of baseline values ($p = 0.014$), and the diameter of polyps to 35% of baseline values ($p<0.001$), compared with the changes in the placebo group. No patient had complete resolution of polyps. However, three months after sulindac was stopped, both the number and size of the polyps increased in sulindac treated patients, but remained significantly lower than the values at baseline. Also, no side-effects from sulindac were reported. Although this RCT had a relatively small sample size ($n = 22$) and short follow-up period (9 months), it was found that sulindac reduces the number and size of colorectal adenomas in patients with FAP.[33]

Labayle *et al* (1991) evaluated rectal polyps in FAP patients and the effect that sulindac therapy had in a randomized, placebo-controlled, double-blind crossover study.[51] Study patients consisted of 10 patients with rectal polyps that had previously been treated by coloctomy and ileorectal anastomosis. Patients received sulindac at a dose of 300mg per day (100mg three times daily) or placebo during 4-month periods of treatment separated by a 1-month wash-out phase. Each patient served as his or her own control.

All patients completed the study except for one (non-compliance with treatment). In spite of the small sample size, the difference between sulindac and placebo was statistically significant. Patients while on sulindac therapy exhibited either a complete (6

patients) or almost complete (3 patients) regression of rectal polyps. Patients with placebo exhibited an increase (5 patients), no change (2 patients), and a relative decrease (2 patients) in the number of polyps. After switching to placebo, polyps reappeared in less than four months in four of five patients. As expected, the number of polyps either increased or stayed the same in most of the patients receiving placebo. The difference between sulindac and placebo was statistically significant ($p<0.01$) despite the small sample size ($n = 10$). Digestive and renal tolerance was excellent, and no adverse events were observed with the dosage chosen. The first RCT of sulindac in a FAP population demonstrated significant and often complete regression of rectal polyps.[51]

Gann *et al* (1993) investigated the relationship between low-dose aspirin and the incidence of invasive and non-invasive colorectal tumors in a RCT.[52] Data was collected from the Physician's Health Study, a randomized, double-blind, placebo controlled trial of aspirin and beta-carotene. The Physicians Health Study was originally intended to assess the hypothesis that aspirin exposure reduces the risk for cardiovascular disease and beta-carotene reduces cancer risk. The study subjects included 22,071 U.S. male physicians who were between 40 and 84 years of age and reduces the . The aspirin intervention was terminated after a mean follow-up of 5 years. Cox proportional hazards models were used to assess the association between aspirin intake and rectal bleeding – an indicator for the presence of colorectal tumor(s).

The relative risk for developing CRC for aspirin compared to placebo was 1.15 (95% CI, 0.80 – 1.65). For in situ cancers and polyps, the RR was 0.86 (95% CI, 0.68 – 1.10). There was no significant trend for decreasing RR by year of follow-up for

invasive cancers or non-invasive tumors. Also, aspirin and placebo groups did not differ in stage or prevalence of rectal bleeding at diagnosis.[52]

Regular aspirin use, at a dose adequate for preventing myocardial infarction, was not associated with a substantial reduction in the incidence of CRC during the 5 years of randomized treatment and follow-up. A small decrease in polyps in the aspirin group could not be reliably distinguished from occurring by chance alone. The results of this study is not consistent with almost all the observational studies with similar endpoints. It is possible that the aspirin dose (325 mg every other day) or duration (5 years and less) was insufficient to provide a protective effect.[55]

Greenberg *et al* (1993) assessed the relationship of aspirin exposure and the risk of large-bowel neoplasm in a multi-center, RCT from the Polyp Prevention Study.[35] Study subjects consisted of 793 patients enrolled in a clinical trial of nutrient supplements to prevent large-bowel adenomas. Unlike invasive cancers, adenomas usually do not cause symptoms or detectable GI bleeding, thus, adenomas are unlikely to influence aspirin use. Each patient had at least one large-bowel adenoma diagnosed and removed shortly before study entry and had been determined by colonoscopy to be free of further tumors. Complete colonoscopies were performed on all patients one year after study entry.[35]

Patients who reported taking aspirin had a lower risk of new adenomas at their 1-year follow-up colonoscopy with an odds ratio of 0.52 (95% CI, 0.31 – 0.89) compared with patients who did not report using aspirin. In subgroup analyses, consistent aspirin use was associated with lower risk of adenomas in both men and women and for those patients who had prior adenomas.

This study was able to avoid many of the potential difficulties found in previous studies in that colonoscopies were performed regularly so to minimize the possibility that aspirin related symptoms did not affect the discovery of large-bowel polyps. Also, because large-bowel adenomas are almost all asymptomatic, it is unlikely that subjects would avoid aspirin use because of the presence of an adenoma.[35]

Hixson and colleagues (1993) examined the effect of 6-months of open-label therapy of sulindac or piroxicam exposure on sporadic colon polyps in a 6 month, open-label RCT.[53] Patients were included if they presented with left-sided colonic polyps (size 3 - 12 mm) and randomized to drug therapy where compliance was determined by pill count. Polyps were measured during sigmoidoscopy after 3 and 6 months of treatment with polyps being removed at the 6-month examination. Study medication was initiated with either open-label sulindac 200mg twice daily or piroxicam 20mg once daily.

Seven patients completed 6 months of therapy (five sulindac and two piroxicam) and two additional patients on piroxicam had to be withdrawn because of adverse events (bleeding gastric ulcer and rash). Compliance with the study medication ranged from 83% to 100%. Polyp size remained unaltered except in two patients. In one patient, a 6-mm polyp disappeared after 3months of therapy with sulindac, and two additional polyps appeared to regress. In another patient, a polyp partially regressed after 6 months of piroxicam treatment. There did not appear to be a dramatic regression of sporadic colon adenomatous polyps in this short, small sample sized pilot study.[53]

Ladenheim *et al* (1995) investigated the effect of sulindac and the regression on sporadic colonic polyps in a double blind, placebo controlled RCT.[54] The impetus of this study is the profound regressive effect that sulindac has on familial adenomatous polyps

(FAP).[33] Asypmtomatic patients undergoing routine screening for using flexible sigmoidoscopy were enrolled if they had polyps 1cm or greater in size. Twenty-two patients were randomized to take 150mg of sulindac twice daily and 22 patients were randomized to placebo. Treatment duration was 4 months and was followed by colonoscopy with the removal of all polyps.

No significant difference was noted in age, mean initial polyps size, or compliance with the treatment protocol between the sulindac and placebo group. Logistic regression found that none of the covariates were significant at the 5% level and that sulindac does not significantly reduce the size or number of sporadic colonic polyps compared to placebo. The lack of a significant effect of sulindac on sporadic polyps as compared to FAP polyps suggests that the two polyp types may have a different biological response to sulindac. Also, the small sample size of this study may have rendered it with insufficient power to detect clinical differences.[54]

Overall, results of previous RCTs appear to support the association of aspirin and NSAID exposure and the reduction in risk colorectal cancer. However, some studies did not confirm this hypothesis, due possibly to small sample sizes and short follow-up periods.

7.1.4 COX-2 studies

New COX-2 inhibitors are beginning to be studied as chemopreventive agents against CRC. These agents have a very high specificity for the COX-2 enzyme and virtually no activity against COX-1, therefore making these agents attractive as a chemoprevention strategy due to a reduced side effect profile. Most studies to date have

been performed in laboratory animal models, although a few have been conducted in human subjects and many are ongoing. As such, there have been several animal studies suggesting that the COX-2 NSAIDS reduce the incidence of colon tumor burden / formation.[56-58] These animal studies provided the impetus to investigate these drugs in humans.

Steinbach *et al* (2000) investigated the effects of celecoxib, a selective COX-2 inhibitor, in patients with familial adenomatous polyposis in a double-blind, randomized, placebo-controlled study using human subjects.[59] Study subjects consisted of 77 patients on celecoxib treatment (100 or 400mg twice daily) or placebo for six months. Patients underwent endoscopy at the beginning and end of the study to determine the number and size of polyps. Twice daily treatment with 400mg celecoxib brought a 28% reduction in the number of polyps and the 100mg dose led to a 12% reduction. Polyps in the placebo group were reduced by only 4.5%. At least a 25% reduction in polyps was experienced by 53% of patients in the 400mg treatment group, compared with 31% in the 100mg group, and 7% of the placebo group. The average polyp burden improved by 31% for the 400mg group and by 15% for the 100mg group while the placebo group only experienced a 5% reduction in polyp burden. There were no significant differences in the number of adverse events for the three groups. These study findings are consistent with other evidence that COX-2 plays a role in colonic tumorigenesis and that COX-2 inhibitors may help control this process. Also, celecoxib is approved by the Food and Drug Administration (FDA) for familial adenomatous polyposis as an adjunct to polypectomy.[59]

CHAPTER 8

RATIONALE

Epidemiological evidence has suggested that aspirin and other NSAIDs may reduce the risk of CRC and adenomatous polyps believed to be a precursor to CRC. Additionally, screening for CRC continues to be low in comparison to what screening guidelines suggest. The possibility of primary prevention by means of pharmaceutical intervention has great appeal. Recently, efforts to establish pharmacotherapy as a preventive measure for protection against CRC are gaining in strength, partly due to the new line of COX-II agents that have shown promising preliminary results. However, there is a lack of evidence confirming this relationship as few randomized, controlled clinical trials have been conducted.

The literature suggests a strong relationship between NSAID exposure and its protective effect on CRC. In addition, it is widely accepted that NSAID exposure elevates the risk of adverse GI events and renal complications. However, few have attempted to evaluate both the protective benefits of CRC and the adverse events commonly associated with NSAID exposure in the same study. Since most studies of this nature are epidemiological based, this makes the comparison of clinical benefits and risks difficult because study populations and methodologies frequently differ.

In addition, the results of this study will be of interest in comparison to the results of studies that utilize the new COX II agents as study medications. Additionally, results

from long term studies that utilize COX II agents will not have outcomes that are evaluable for many years.

CHAPTER 9

OBJECTIVES

The objectives of this research are to describe the utilization patterns of non-OTC NSAID use in a Medicaid population and to relate NSAID use to three primary outcome measures; incident CRC, GI adverse events, and renal adverse events. It is hoped that this study will provide meaningful insights for patients, physicians, pharmacists, and health system payers as to the risk benefit profiles of NSAID use. This study will attempt to calculate the absolute risk, relative risk, and adjusted relative risk of developing CRC, GI events, and renal events stratified by NSAID users and non-users. Additionally, the dose/response relationship of NSAIDs with the outcome variables will also be investigated.

9.1 Aim I

The first aim of this research is to determine the absolute risk, relative risk, and adjusted relative risk for the development of incident CRC for prescription NSAID users/non-users. Additionally, a dose/response relationship of NSAIDs and their impact on the incidence of CRC will also be assessed.

9.2 Aim II

The second aim of this research is to determine the absolute risk, relative risk, and adjusted relative risk for the development of GI adverse events for prescription NSAID users/non-users. Additionally, the dose/response relationship of NSAIDs and their impact on GI events will also be assessed.

9.3 Aim III

The third aim of this research is to determine the absolute risk, relative risk, and adjusted relative risk for the development of acute renal failure and other nephritic syndrome adverse events for prescription NSAID users/non-users. Additionally, the dose/response relationship of NSAIDs and their impact on renal events will also be assessed.

CHAPTER 10

METHODS

The literature review, study design, data source, criteria for cohort inclusion, operational definitions of prescription NSAID exposure, and outcomes of interest are described in the following sections.

10.1 Literature review

Literature collected for review was conducted using the National Library of Medicine's Internet Grateful Med (version 2.6.3) retrieval engine to search Medline®. Criteria used for searches were publications of English language, human subjects, and published since 1988. Only those publications that were recent and from deemed reputable journals were reviewed.

10.2 Study design

The study was a 7.75-year, retrospective, longitudinal, cohort design. Subjects were followed for 7.75 years from January 1, 1990 to September 30, 1997. Subjects were included if they had attained a minimum of 50 years of age by January 1, 1990 and demonstrated a minimum of 5 years of continuous eligibility for Medicaid benefits up to a maximum of 7.75 years. Subjects eligible for benefits between the dates of January 1,

1990 to September 30, 1992 (2.75 years) were recruited. Subjects were excluded from the cohort if they were unable to attain 5 years of continuous eligibility either due to death or loss of Medicaid benefits. Study follow-up was terminated after the minimum of 5 years in the occurrence of three events; 1) death, 2) loss of benefits, and 3) end of study (i.e., September 30, 1997).

NSAID exposure was dichotomously defined as never exposed/any exposure as indicated from the prescription drug file during the study period. NSAID exposure information was collected up until the time an outcome of interest was diagnosed and a claim for reimbursement submitted. Also, NSAID exposure was independently measured for each outcome such that three different cumulative exposure amounts for NSAIDs were calculated should a subject incur all three outcomes. This was performed so to maximize the data collected on the study endpoints. Also, outcomes were measured independently such that the occurrence of one endpoint did not affect, nor contingent upon, the measurement another endpoint. Outcomes of interest were identified by an algorithm of literature based ICD-9-CM codes found in the medical history file. In the event that multiple outcomes occurred, drug exposure was calculated up until the incidence of each corresponding event. Subjects were required to be free of study outcomes for one year following study inclusion. Subjects who experienced an outcome event (i.e., CRC, GI, and renal events) during the 'washout' period were excluded from the study. The washout period was intended as a means to identify incident outcome events.

10.3 Data source

A large administrative claims database maintained by the Georgia Department of Medical Assistance (GDMA) was used to supply data for Georgia Medicaid recipients. The Medicaid database contains demographic, medical, and drug utilization information for the state of Georgia's qualifying indigent population.

The data used for this study are housed at the University of Georgia. Analyses were conducted on a mainframe system in a TSO environment using the Statistical Analysis System (SAS® version 8.0) of SAS Institute, Inc. The data consisted of three separate files, with each file containing a unique recipient identifier variable (BASE_ID):

1) **Eligibility file**. The recipient eligibility file contains the demographic profile and eligibility history for each Medicaid enrollee.

2) **Prescription file**. The prescription file contains all outpatient prescription transactions reimbursed by the GDMA drug program.

3) **Medical history file**. The medical history file contains information for all reimbursed non-drug medical claims. For example, the records contain fields that identify ICD-9-CM diagnosis codes, Current Procedural Terminology codes (CPT), category of service rendered, date of service, type of provider, place of service provided, and Medicaid reimbursement amount.

10.4 Study cohort

The study cohort consists of enrollees in the Georgia Medicaid program aged 50 years and older and who have had 5 years or more of continuous eligibility within the 7.75 year study period. The continuous eligibility criteria are required as to assure that at least 5 years of medication history is available. Criteria for study cohort inclusion, exclusion, and termination are defined below.

Criteria for inclusion:

- attainment of 5 years of continuous Medicaid eligibility
- attainment of 50 years of age by the study start date (January 1, 1990)

Criteria for exclusion:

- Incidence of one or more of the study endpoints before completion of the first 12 months of study eligibility
- Subjects who were 100 years of age or older as of January 1, 1990 were excluded (*post hoc* decision)
- Subjects whose gender could not be determined were excluded (*post hoc* decision)

Criteria for termination of follow-up:

- Loss of eligibility for Medicaid benefits *after* completion of at least 5 years continuous eligibility
- Death *after* completion of at least 5 years continuous eligibility
- End of study (September 30, 1997).

- Date of study outcome attained*

10.5 Prescription NSAID exposure

The Medicaid prescription file contains all outpatient prescription transactions reimbursed by the GDMA drug program. This file was used to identify and quantify the exposure of prescription NSAIDs used by the study cohort and includes data on the date of service a specific drug was dispensed (D_O_S), the dosage form (DOSAGE), the quantity or units dispensed per prescription (QUANTITY), and the strength of the prescription product (STRENGTH). Since most aspirin and salicylates are nonprescription, and thus not included in the prescription files, these drugs are often analyzed as a separate class of study drugs. However, since the mechanism of action of aspirin closely resembles that of NSAIDs and thus has similar effects on the endpoints studied, aspirin exposure was addressed in most analyses.

Cumulative drug exposure was used to determine prescription NSAID exposure in the study population and was defined as the number of units of drug dispensed multiplied by the dose of the drug (i.e., QUANTITY * STRENGTH). Use was considered current for the duration of the prescribed days' supply of the drug. All study NSAID dosages were standardized and converted to ibuprofen dosage equivalents. Standardization was predicated on the assumption that the high daily doses of NSAID therapy for arthritis were equivalent in safety and efficacy. Therefore, standardization of other NSAID

---

* Persons follow-up was specific for each outcome. For persons experiencing only one outcome, their follow-up was terminated at the date of the outcome. For persons experiencing multiple outcomes, their follow-up was terminated on the date in which the first outcome occurs for each study endpoint.

therapies was determined as a factor of 2,400mg of ibuprofen (highest recommended daily dose for the treatment of arthritis).[44] It has been a trend in recent years to use a higher dose of ibuprofen than was originally recommended.[18] Drug exposure was only calculated up until the first incidence of each of the three outcomes of interest, i.e. CRC, GI and renal events. The list of NSAIDs included in the study was adapted from Smalley *et al* (1999).[44] See Table 2.

Individual NSAIDs that were used exclusively were analyzed separately for their impact on the study outcomes.[44] However, the analysis of separate NSAID products was contingent upon collecting adequate data for analysis, therefore individual NSAID products could not be identified *a priori*. Only those NSAIDs that were utilized by a minimum of 1,000 persons and used exclusively were analyzed separately after converting to ibuprofen equivalents as collected from the study cohort.

Table 2. Individual NSAIDs Included in Study[44]

Generic	**Brand**	**NSAID class**	**Low daily dose (mg)**	**High daily dose (mg)**	**Standard-ization to ibuprofen**
diclofenac	Arthrotec	heteroaryl acetic acid	100	150	16.00
etodolac	Lodine	indole/indene acetic acid	800	1,200	2.00
fenoprofen	Nalfon	arylropionic acid	900	2,400	1.00
flurbiprofen	Ansaid	arylropionic acid	200	300	8.00
ibuprofen	Motrin, Advil, etc.	arylropionic acid	1,200	2,400	1.00

indomethacin	Indocin	indole/indene acetic acid	50	150	16.00
ketoprofen	Orudis	arylropionic acid	200	300	8.00
ketorolac	Toradol	acetic acid	10	40	60.00
meclofenamate	Meclofenamate	anthranilic acid (fenamates)	100	400	6.00
mefenamic acid	Ponstel	fenamates	500	1,000	2.40
nabumetone	Relafen	acetic acid	1,000	2,000	1.20
naproxen	Anaprox	arylropionic acid	550	1,100	2.18
oxaprozin	Daypro	propionic acids	1,200	1,800	1.33
phenylbutazone	Butazolidin	enolic acid	300	400	6.00
piroxicam	Feldene	enolic acid	Less than 20	20	120.00
sulindac	Clinoril	indole/indene acetic acid	300	400	6.00
tolmetin	Tolectin	heteroaryl acetic acid	1,200	1,800	1.33

10.6 Outcomes of interest

The first incidence of diagnosed CRC, GI, and renal events associated with NSAID use were the major outcomes of interest. These endpoints were identified in the Georgia Medicaid population from the medical history file by an algorithm that incorporated the use of International Classification of Diseases 9th revision Clinical Modification (ICD-9-CM) codes.[60] The ICD-9-CM algorithms were derived from epidemiological-based studies published in recent peer reviewed professional journals and are described in detail below. Only original investigations that utilized ICD-9 codes

to identify similar outcomes measures for endpoints were used. These algorithms were then modified if, after clinical consultation, it was determined that some events would not be relevant or be missed.

10.6.1 Incident CRC

The CRC events of interest are diagnosed cancer of the colon and rectum, but excluding the anus. The ICD-9-CM algorithm to identify cases of CRC was derived from Smalley *et al* in which they investigated the association between NSAID usage and incidence of CRC.[44] The study population used were participants in the Tennessee Medicaid Program from 1985 to 1992 aged 65 years or older and with at least five years of continuous eligibility. The outcome measures identified by ICD-9-CM codes were incidence of histologically confirmed cancer of the colon (153.x) and rectum (154.x). Modifications to the algorithm were conducted after additional clinical consulting. See Appendix A.

10.6.2 Gastrointestinal injury

The GI events of interest are diagnosed cases ulceration, perforation, and hemorrhage of the upper GI tract commonly associated with NSAID exposure. The ICD-9-CM algorithm to identify cases of GI events was derived from Cattaruzzi *et al* in which they examined the positive predictive value of the ICD-9 codes for upper GI bleeding and perforation in an Italian medical database.[61] The outcome measures identified by ICD-9-CM codes were gastric ulcer (531.x), duodenal ulcer (532.x), gastrojejunal ulcer (534.x), and peptic ulcer (533.x). Nonspecific codes in the algorithm were used to identify

hematemesis (578.0), melena (578.1), and unspecified hemorrhage of the intestinal tract (578.9). See Appendix B.<ibid>

10.6.3 Renal injury

The renal events of interest are diagnosed cases acute renal failure and other impairment of renal function that is associated with NSAID exposure. The ICD-9-CM algorithm to identify cases of renal events was derived from Perez *et al* in which they examined the association between NSAID exposure and the risk of hospitalization for acute renal failure in the general public.[30] The study used a population-based case-control design among the persons in the Canadian province of Saskatchewan between 1982 and 1986. Data was derived from patient records maintained in a health department database. The outcome measures identified by ICD-9-CM codes were acute nephritis (580.9), nephrotic syndrome (581.x), non-specified nephritis and nephropathy (583.x), acute renal failure (584.x), renal failure (586.x), and disorder of the kidney (593.9). See Appendix C.<ibid>

10.7 Statistical Analyses

The statistical analyses of the data consisted of calculating absolute, crude, and adjusted relative risks for CRC, GI, and renal events for exposure and non-exposure study groups. Absolute risk was calculated by dividing the number of incident cases by persons years observed in the study for each cohort resulting in the number of cases per 100,000 person years. Crude Relative Risks was calculated by dividing the standardized

absolute rates (i.e., cases per 100,00 person years) for NSAID users by non-users and confidence intervals were estimated by Poisson regression. Adjusted relative risk was approximated from the calculated odds ratios from the Poisson regression models. Statistical significance was determined at $p<0.05$.

NSAID non-users were operationally defined as those subjects without any NSAID prescription records, while NSAID users will be defined as those with any use and further categorized as low/moderate/high use. Stratification thresholds for low, moderate, and high exposure were identified after exposure data was collected upon clinician input and consultation. Adjusted relative risks were calculated by Poisson regression (SAS® procedure GENMOD) and included terms for age, gender, race, length of eligibility, cumulative exposure of NSAIDs, obesity, and alcoholism. Age, gender, race, and length of follow-up are commonly controlled for in studies using administrative claims.[18;44] Obesity and alcoholism were controlled for as studies have shown that obesity, often a proxy variable for lifestyle and diet, and alcohol have been associated with an increased risk of CRC.[62;63]

Poisson regression was substituted for logistic regression because all three measured outcomes occurred in 5% or less of the study cohort. Poisson regression is appropriate when the dependent variable is non-negative, integer values, and often represent counts such as the incidence of a disease.[64] The Poisson model is considered better suited to handle rare events and produces more stable estimates than the logistic procedure in such situations.[65] Poisson models are suitable to modeling situations where the dependent variable is restricted to be positive, sample sizes are large, and the mean rate of events are relatively rare.[64;66]

Most analyses in this study were stratified by NSAID exposure/non-exposure, and further by level of NSAID exposure, and specific NSAID drugs. The homogeneity, or similarities, between study groups were assessed by Chi-square and Student's t-test methods.

10.7.1 Model specification

Three models were specified to determine the adjusted odds ratio of the covariates for the three primary outcome measures. Poisson regression was used to estimate the effects of the independent variables on the response variable. The covariates in the models; age, gender, race, alcoholism, obesity, and length of eligibility, were specified identically for all three models except for the NSAID exposure variable, which took differing forms depending on the analysis. The first set of models measured NSAID exposure dichotomously by means of exposure vs. no exposure. The second set of models measured the amount of NSAID exposure as a class variable of 4 levels; 1) no exposure, 2) "low" exposure, 3) "moderate" exposure, and 4) "high" exposure. The third set of models measured NSAID exposure by type of drug used as a class variable of 4 levels; 1) no exposure, 2) aspirin products only, 3) NSAID products only, and 4) both NSAID and aspirin products used. The fourth set of models measured NSAID exposure for those subjects who used only a single NSAID agent exclusively and that had a minimum of 1,000 persons (ibuprofen, naproxen, indomethacin, and fenoprofen qualified). The term for length of eligibility was used as an "OFFSET" variable in the Poisson regression to control for varying lengths of follow-up time for each subject.

1) $Y(CRC) = b_0 + b_1(\text{NSAID exposure}) + b_2(AGE) + b_3(GENDER) + b_4(RACE) + b_5(ALCOHOLISM) + b_6(OBESITY) + b_7(ELIGIBILITY) + Error$

2) $Y(GI) = b_0 + b_1(\text{NSAID exposure}) + b_2(AGE) + b_3(GENDER) + b_4(RACE) + b_5(ALCOHOLISM) + b_6(OBESITY) + b_7(ELIGIBILITY) + Error$

3) $Y(RENAL) = b_0 + b_1(\text{NSAID exposure}) + b_2(AGE) + b_3(GENDER) + b_4(RACE) + b_5(ALCOHOLISM) + b_6(OBESITY) + b_7(ELIGIBILITY) + Error$

Y = outcome event, i.e., CRC, GI, or renal (0 = absence, 1 = presence)

- 1st set of models: NSAID exposure (0 = absence, 1 = presence)
- 2nd set of models; NSAID exposure (0 = absence, 1 = "low", 2 = "moderate", 3 =

- 3rd set of models: NSAID exposure (0 = no exposure, 1 = aspirin only, 2 = NSAID only, 4 = both aspirin and NSAID)
- 4th set of models: exclusive NSAID use (0 = no exposure, 1 = single NSAID use only, i.e., ibuprofen, naproxen, indomethacin, and fenoprofen)

Model performance was evaluated by examining the parameter estimates for overdispersion. Overdispersion occurs when the observed variance is larger than the nominal variance for a particular distribution.[66] Although overdispersion doesn't bias the coefficients, it can lead to underestimates of the standard errors and overestimates of chi-square statistics.[64] The criterion for assessing goodness of fit is to expect the Pearson chi-

squares to have values close to their degrees of freedom with the distribution used (Poisson); an indication of overdispersion is when their ratio is greater than 1.00.[66] Overdispersion appeared to be present as the Pearson chi-squares/DF criterion were as follows; CRC = 2.05, GI = 2.26, and renal = 2.00. The overdispersion was corrected for by using a scaling factor (the square root of the Pearson chi-square divided by the degrees of freedom). In SAS, overdispersion is corrected for by invoking the "PSCALE" option in the PROC GENMOD procedure.

10.7.2 Independent variables

The independent variables included in the analyses were operationalized as follows:

1) **Age.** Data for the covariate 'AGE' was found in the eligibility file and is a continuous variable coded in number of years since birth from the study start date of January 1, 1990.

2) **Gender.** Data for the covariate 'GENDER' was found in the eligibility file and is a dichotomous, dummy variable coded '0' for female and '1' for male.

3) **Race.** Data for the covariate 'RACE' was found in the eligibility file and is a dichotomous, dummy variable coded '0' for non-caucasian and '1' for caucasian. Those races included in the 'non-caucasian' category consist of; African-American, Native American, Asian and Pacific Islander, and Hispanic.

4) **Obesity.** Data for the covariate 'OBESE' was found in the medical history file and is a dichotomous, dummy variable coded '0' for no obesity and '1' for obesity. The ICD-9-CM algorithm used to identify cases of obesity is located in Appendix D.

5) **Alcoholism.** Data for the covariate 'ALCOHOL' was found in the medical history file and is a dichotomous, dummy variable coded '0' for no alcoholism and '1' for alcoholism. The ICD-9-CM algorithm used to identify cases of alcoholism is located in Appendix E.

6) **Eligibility.** The length of continuous eligibility is a covariate that was created and calculated from the eligibility file. Eligibility is a continuous ratio level variable coded in the number of months of continuous eligibility for Medicaid benefits.

7) **NSAID exposure.** NSAID exposure is a covariate that was created and calculated from the prescription medication file. NSAID exposure is coded as a dichotomous, or dummy, variable coded '0' for non-exposure and '1' for exposure. Exposure is defined as one or more prescription claims of study drugs.

8) **NSAID cumulative dosing**. NSAID cumulative dosing is a covariate that was created and calculated from the prescription medication file. Cumulative dosing is a continuous ratio level variable coded as the cumulative dosage of drug taken in ibuprofen equivalents. Stratification thresholds for low, moderate, and high exposure

were identified after exposure data was collected upon clinician input and consultation.

9) **NSAID medications.** Particular NSAID medication is a separate covariate that was calculated from the prescription medication file. Each drug was analyzed as a continuous ratio level variable coded in the cumulative dosage of drug taken and standardized to ibuprofen equivalent dosing. Only those NSAIDs that were utilized by a minimum of 1,000 persons and used exclusively were analyzed separately.

10.7.3 Dependent variables

The first incidence of diagnosed CRC and adverse gastrointestinal and renal events were the major outcomes of interest. These endpoints were identified from the medical history file by an algorithm of ICD-9-CM codes derived from scientific literature.

1) **CRC**. Incident CRC cases were analyzed as dichotomous, or dummy, dependent variables, coded '0' for absence of CRC and '1' for presence of CRC. The ICD-9-CM algorithm used to identify cases of CRC is located in Appendix A.

2) **GI adverse events**. Adverse GI events were analyzed as dichotomous, or dummy, dependent variables, coded '0' for absence of GI events and '1' for presence of GI events. The ICD-9-CM algorithm used to identify cases of GI events is located in Appendix B.

3) **Renal adverse events**. Adverse renal events were analyzed as dichotomous, or dummy, dependent variables, coded ‘0’ for absence of renal events and ‘1’ for presence of GI events. The ICD-9-CM algorithm used to identify cases of renal events is located in Appendix C.

CHAPTER 11

RESULTS

11.1 Eligibility cohort descriptive statistics

The data set used to determine study eligibility contained 2,740,982 subjects, of whom 355,265 met the minimum age requirement and 103,078 met the following; 50 years of age and at least 5 years continuous eligibility between January 1, 1990 to September 30, 1997. Subjects who experienced an outcome within the first 12 months of eligibility, or 'washout' period, were excluded from the analysis. This resulted in 2,435 subjects excluded as a result of incurring outcomes during the washout period. One subject was excluded due to the inability to determine gender. The final study cohort contained 100,642 subjects.

Overall, the average length of follow-up was 7.05 years (Std = 0.94 years) per subject resulting in a total of 709,366 person years. The minimum length of follow-up was 1.00 year while the maximum was 7.75 years. Each study outcome required independent measurement of study drug exposure, thus the average number of subjects, follow-up years, and other summary variables per exposure group vary slightly by outcome. Overall, 29% of subjects had no exposure to NSAIDs leaving 71% in the exposure group. Because persons that experienced one event but not other study events which may have consumed NSAID after experiencing an event were retained in all analyses, the number of persons not exposed to NSAIDs varied slightly and ranged from

29,185 for CRC outcomes to 29,606 for GI outcomes and NSAID exposure ranged from 71,036 for GI to 71,457 for CRC outcomes. See Table 3 through Table 8.

Table 3. Person Years of Study Follow-up by Drug Exposure Type for CRC Outcomes

Exposure to study drugs	N (%)	Total person years	Mean (Std)
No exposure	29,185 (29.00)	200,807	6.88 (0.99)
Exposure	71,457 (71.00)	514,945	7.21 (0.86)
Only ASA	4,325 (4.30)	30,178	6.98 (0.96)
Only NSAIDs	48,115 (47.81)	346,083	7.19 (0.87)
Both NSAIDs and ASA	19,017 (18.90)	138,684	7.29 (0.79)
Total	100,642 (100.00)	715,752	7.11 (0.91)

Table 4. Person Years of Study Follow-up by Drug Exposure Length for CRC Outcomes

Exposure to study drugs	N (%)	Total person years	Mean (Std)
No exposure	29,185 (29.00)	200,807	6.88 (0.99)
Exposure	71,457 (71.00)	514,945	7.21 (0.86)
0 to 1 year	49,377 (49.06)	353,083	7.15 (0.89)
1 to 3 years	16,291 (16.19)	118,729	7.29 (0.80)
3 years and greater	5,789 (5.75)	43,134	7.45 (0.64)
Total	100,642 (100.00)	715,752	7.11 (0.91)

Table 5. Person Years of Study Follow-up by Drug Exposure Type for GI Outcomes

Exposure to study drugs	N (%)	Total person years	Mean (Std)
No exposure	29,606 (29.42)	200,141	6.76 (1.21)
Exposure	71,036 (70.58)	502,741	7.08 (1.12)
Only ASA	4,347 (4.32)	29,834	6.86 (1.17)
Only NSAIDs	48,006 (47.70)	338,676	7.05 (1.14)
Both NSAIDs and ASA	18,683 (18.56)	134,232	7.18 (1.03)
Total	100,642 (100.00)	702,882	6.98 (1.16)

Table 6. Person Years of Study Follow-up by Drug Exposure Length for GI Outcomes

Exposure to study drugs	N (%)	Total person years	Mean (Std)
No exposure	29,606 (29.42)	200,141	6.76 (1.21)
Exposure	71,036 (70.58)	502,741	7.08 (1.12)
0 to 1 year	49,360 (49.05)	345,371	7.00 (1.19)
1 to 3 years	16,068 (15.97)	115,739	7.20 (0.97)
3 years and greater	5,608 (5.57)	41,631	7.42 (0.69)
Total	100,642 (100.00)	702,882	6.98 (1.16)

Table 7. Person Years of Study Follow-up by Drug Exposure Type for Renal Outcomes

Exposure to study drugs	N (%)	Total person years	Mean (Std)
No exposure	29,387 (29.20)	200,326	6.82 (1.11)
Exposure	71,255 (70.80)	509,137	7.15 (0.98)
Only ASA	4,314 (4.29)	29,819	6.91 (1.08)
Only NSAIDs	48,116 (47.81)	342,906	7.13 (1.00)
Both NSAIDs and ASA	18,825 (18.70)	136,412	7.25 (0.90)
Total	100,642 (100.00)	709,463	7.05 (1.03)

Table 8. Person Years of Study Follow-up by Drug Exposure Length for Renal Outcomes

Exposure to study drugs	N (%)	Total person years	Mean (Std)
No exposure	29,387 (29.20)	200,326	6.82 (1.11)
Exposure	71,255 (70.80)	509,137	7.15 (0.98)
0 to 1 year	49,333 (49.02)	349,185	7.08 (1.04)
1 to 3 years	16,212 (16.11)	117,478	7.25 (0.88)
3 years and greater	5,710 (5.67)	42,474	7.44 (0.66)
Total	100,642 (100.00)	709,463	7.05 (1.03)

Table 9 contains the year subjects were enrolled in the study.

Most of the subjects, 84,885 (84%), entered the study in first year (1990). Over half, (58,093) were eligible for the entire 7.75 years. Right censoring of the subjects were as follows: 2,901 (2.9%) were censored due to loss of Medicaid eligibility and 19,854 (19.7%) subjects were censored due to death.

Table 9. Subjects Included into Study by Year

Year included in study	**N (%)**
1990	84,885 (84.34)
1991	9,573 (9.51)
1992	6,184 (6.14)
Total	100,642 (100.00)

11.1.1 Demographics

The cohort average age at January 1, 1990 was 69.90 years of age (Std = 10.18), 21,416 (21.3%) were males and the racial frequency distribution was 43,629 (43.4%) Caucasian, 43,423 (43.2%) African-American, 100 (0.10%) Hispanic, 56 (0.06%) Asian/Pacific Islander, and 29 (0.03%) Native American, while 13,405 (13.3%) subject's race could not be determined. Subject's demographic profile by exposure status for each outcome is displayed in Table 10. Younger persons, non-caucasians, and females were more likely to have and NSAID prescription filled (exposed) than their respective counterparts

Table 10. Study Cohort Demographics by Drug Exposure Status by Outcome Event

	CRC cases		GI cases		renal cases		Total
Exposure to study drugs	**No exposure**	**Exposure**	**No exposure**	**Exposure**	**No exposure**	**Exposure**	
***Age (mean, (Std))**	70.8 (10.1)	69.5 (10.2)	70.6 (10.1)	69.6 (10.2)	70.7 (10.1)	69.6 (10.2)	69.9 (10.2)
†Gender (n, (%))							
Male	7,318 (7.3)	14,098 (14.0)	7,450 (7.4)	13,966 (13.9)	7,379 (7.3)	14,037 (14.0)	21,672 (21.3)
Female	21,867 (21.7)	57,359 (57.0)	22,156 (22.0)	57,070 (56.7)	22,008 (21.9)	57,218 (56.9)	79,882 (78.6)
†Race (n, (%))							
Caucasian	14,994 (14.9)	28,635 (28.5)	15,157 (15.1)	28,472 (28.3)	15,043 (15.0)	28,586 (28.4)	44,041 (43.3)
Non-Caucasian	14,191 (14.1)	42,822 (42.6)	14,449 (14.4)	42,564 (42.3)	14,344 (14.3)	42,669 (42.4)	43,965 (43.2)

Between group comparisons of *age (t-test), †gender, and †race (chi-square) were performed for each study outcome and all were significant at $p<0.05$.

11.2 NSAID Exposure Descriptive Statistics

Study drug exposure was measured until the occurrence of each study outcome a subject may incur. Study drug exposure was measured such that it was possible for a subject to have three differing amounts of cumulative exposure if all three outcomes were experienced by a single subject. For those subjects who had fewer than two study outcomes, only one amount of study drug exposure was measured.

Cumulative NSAID exposure was measured and standardized to the maximum daily dose (2,400 mgs) of ibuprofen. A complete list of study drugs by their trade name, generic name grouping, and ibuprofen equivalent factor can be found in Appendix F (Table 39). Cumulative doses were then converted to kilograms (kgs) to facilitate interpretation (i.e., 1 kg. of NSAID exposure translates to 1.14 years of continuous daily exposure at the highest daily dose). The average cumulative exposure to study NSAIDs across all three outcomes was 0.58 Kgs (Std = 0.99), or 241.50 days worth (7.93 months) of continuous exposure. The maximum exposure was 11.54 Kgs (only 3 subjects had greater than 10 Kgs of cumulative exposure) and exposure at the 99^{th} was 4.51 Kgs and the 95^{th} percentile was 2.78 Kgs. The median exposure was 0.12 Kgs., or 49.97 days, while cumulative exposure at the 25^{th} and 75^{th} percentile was 0.00 and 0.71 Kgs, respectively.

NSAID exposure was categorized into four classes: 1) “No exposure” was defined as not having a claim for a study drug, 2) “Low exposure” was defined as having up to one year of continuous exposure, 3) “Moderate” exposure was defined as one to three years of exposure, and 4) “High” exposure was defined as greater than three years of exposure. Cut-points for the categorization of NSAID exposure was determined by

evaluating the distribution of cumulative exposure and establishing classes qualitatively by years of exposure. In other words, quantitative means for establishing cut-points such as receiver operating characteristic (ROC) curves were not used. Approximately, 29% of the cohort had no exposure to study drugs and 49% had one year or less of continuous exposure, 16% had between one and three years, and 6% had three years or greater of exposure.

Overall, 71% of subjects had any study drug exposure and accounted for 1,418,400 NSAID prescription claims. Of those subjects who had exposure, 68% had non-ASA NSAID exposure, 6% had only aspirin exposure, and 26% had exposure to both NSAIDs and aspirin. For all study drug claims, ibuprofen consisted of 36% of the prescriptions, aspirin 19%, indomethacin 9%, both fenoprofen and naproxen 8%, and sulindac 6%. See Table 11. Of single NSAID users, ibuprofen was used by 11,666 (11.6%) subjects, aspirin products had 4,324 (4.3%) exclusive users, naproxen 1,951 (1.9%), indomethacin 1,689 (1.7%), and fenoprofen 1,343 (1.3%).

Table 11 Frequency of Study Drug Claims by Generic Class

Generic Drug	N (%)
aspirin	269,300 (18.99)
diclofenac	20,993 (1.48)
etodolac	15,272 (1.08)
fenoprofen	116,726 (8.23)
flurbiprofen	7,700 (0.54)
ibuprofen	506,956 (35.74)
indomethacin	126,854 (8.94)
ketoprofen	12,867 (0.91)
ketorolac	12,138 (0.86)
meclofenamate	49,773 (3.51)
mefenamic acid	305 (0.02)
nabumetone	16,780 (1.18)
naproxen	114,618 (8.08)
oxaprozin	11,293 (0.80)
phenylbutazone	1,774 (0.13)
piroxicam	46,519 (3.28)
sulindac	84,119 (5.93)
tolmetin	4,413 (0.31)
Total	1,418,400 (100)

11.3 Medical History Descriptive Statistics

Of the 100,642 study subjects, 372 (0.37%) were diagnosed with CRC, 3,829 (3.80%) were diagnosed with any GI event, and 2,453 (2.44%) were diagnosed with any renal event. A majority of the subjects, 94,747 (94.14%) did not incur a study outcome,

5,163 (5.13%) who incurred only one outcome, while 732 (0.73%) subjects experienced multiple outcomes. See Table 12.

Table 12. Frequency of Single and Multiple Study Outcomes

Study outcome	N (%)
No outcome	94,747 (94.14)
CRC only	245 (0.24)
GI only	3,115 (3.10)
Renal only	1,803 (1.79)
CRC and GI	82 (0.08)
CRC and renal	18 (0.02)
GI and renal	605 (0.60)
CRC and GI and renal	27 (0.03)
Total	100,642 (100)

The frequency distributions of study outcomes and those subjects who presented with identified risk factors are presented in Table 13 and Table 14, respectively. There were 5,895 (5.86%) subjects identified as having any of the three outcomes (CRC, GI, or renal), 1,925 (1.91%) identified as having any claim for alcohol abuse, and 1,902 (1.89) having any claim for obesity.

Table 13. Frequency Distribution of Study Outcomes by ICD-9 Heading

CRC	N (%)	GI	N (%)	Renal	N (%)
colon (153.x)	201 (0.20%)	gastric ulcer (531.x)	703 (0.70%)	acute glomerulonephritis (580.x)	35 (0.03%)
rectum (154.x)	226 (0.22%)	duodenal ulcer (532.x)	463 (0.46%)	nephrotic syndrome (581.x)	115 (0.11%)
secondary neoplasm (197.x)	19 (0.02%)	peptic ulcer (533.x)	1,767 (1.76%)	nephritis and nephropathy (583.x)	204 (0.20%)
digestive organ cancer (230.x)	47 (0.05%)	gastrojejunal ulcer (534.x)	64 (0.06%)	acute renal failure (584.x)	512 (0.51%)
		gastrointestinal hemorrhage (578.x)	2,011 (2.00%)	renal failure (586.x)	1,004 (1.00%)
				other disorders of kidney (593.x)	1444 (1.43%)
Any CRC event*	372 (0.37%)	Any GI event*	3,829 (3.80%)	Any renal event*	2,453 (2.44%)

*Individual codes do not sum to event total since some subjects had multiple diagnoses

Table 14. Frequency Distribution of Risk Factors by ICD-9 Heading

Alcoholism	**N (%)**	**Obesity**	**N (%)**
alcoholic psychoses (291.x)	667 (0.66%)	obesity (278.x)	1,902 (1.89%)
alcohol dependence (303.x)	1,684 (1.67%)		
nondependent drug abuse (305.x)	1,946 (1.93%)		
alcoholism (v113)	41 (0.04%)		
Any alcohol abuse event*	1,925 (1.91%)	Any obesity event	1,902 (1.89%)

*Individual codes do not sum to event total since some subjects had multiple diagnoses

Study outcomes were first assessed by a dichotomous exposure status of no exposure and any exposure defined as one or more claims for study NSAIDs. Persons with exposure to NSAIDs after the first occurrence of an endpoint was considered as non-exposed in that particular analysis. The number of person years of observation was used to define the denominator of the outcome rate instead of number of subjects to account for varying follow-up lengths per subject.

For CRC events, NSAID users trended to have fewer cases of CRC than non-users. The rate per 100,000 person years was 47.58 for the exposure group and 63.24 for the non-exposure group with an unadjusted relative risk (RR) of 0.75 (0.55 – 1.04) using the non-exposure group as a reference. However, after multivariate adjustment, the adjusted RR was significant and was 0.69 (0.50 – 0.94). See Table 15.

For GI events, a small non-significant increase in risk for GI adverse events was observed by NSAID users who had any exposure, however this estimate was non-significant. The rate per 100,000 person years was 558.14 for the exposure group and 511.14 for the non-exposure group with an unadjusted RR of 1.09 (0.97 – 1.23). After multivariate adjustment, the non-significant adjusted RR was 0.92 (0.83 – 1.03). See Table 16.

For renal events, a small non-significant increase in risk for renal adverse events was observed by NSAID users who had any exposure. The rate per 100,000 person years was 347.84 for the exposure group and 340.45 for the non-exposure group with an unadjusted RR of 1.02 (0.90 – 1.17). After multivariate adjustment, the adjusted RR of 0.84 (0.74 – 0.95) indicated that there might be a small protective effect. See Table 17.

Table 15. Effect of NSAID Exposure/non-exposure on the Incidence of Any CRC Event

Exposure to study drugs*	**Person years**	**CRC cases**	**Rate per 100,000 person years**	**RR**	**RR adjusted (95% CI)**
Exposure	514,945	245	47.58	0.75	0.69 (0.50 – 0.94)
No exposure	200,807	127	63.24	--	--

*Exposure defined as ever used NSAID(s) prior to incurring study outcome.

Table 16. Effect of NSAID Exposure/non-exposure on the Incidence of Any GI Event

Exposure to study drugs*	Person years	GI cases	Rate per 100,000 person years	RR	RR adjusted (95% CI)
Exposure	502,741	2,806	558.14	1.09	0.92 (0.83 – 1.03)
No exposure	200,141	1,023	511.14	--	--

*Exposure defined as ever used NSAID(s) prior to incurring study outcome.

Table 17. Effect of NSAID Exposure/non-exposure on the Incidence of Any Renal Event

Exposure to study drugs*	Person years	Renal cases	Rate per 100,000 person years	RR	RR adjusted (95% CI)
Exposure	509,137	1,771	347.84	1.02	0.84 (0.74 – 0.95)
No exposure	200,326	682	340.45	--	--

*Exposure defined as ever used NSAID(s) prior to incurring study outcome.

The covariates controlled for demonstrated that, overall, alcohol abuse significantly elevated the risk of all three outcomes and obesity significantly elevated the risk for GI and renal events. Gender did not significantly alter the risk for all three outcomes. Caucasian race was significantly associated with a reduced risk of renal events when compared to non-Caucasians, while the estimates for CRC and GI events

were not significant. Older age classes, both (65 - 75) and (>75), appeared to be protective of the three study outcomes relative to the 50 to 65 age class.

Table 18 Relative Risks for Covariates in CRC, GI and Renal Poisson Regression Analyses

Covariate	CRC RR (95% CI)	GI RR (95% CI)	Renal RR (95% CI)
Gender (male)	0.89 (0.62 – 1.27)	0.90 (0.80 – 1.00)	0.99 (0.87 – 1.13)
Race (white)	0.92 (0.67 – 1.27)	1.03 (0.93 – 1.15)	0.55 (0.48 – 0.63)
Age (>75)	0.42 (0.29 – 0.61)	0.09 (0.07 – 0.11)	0.13 (0.10 – 0.16)
Age (65 – 75)	0.30 (0.20 – 0.45)	0.08 (0.06 – 0.09)	0.17 (0.14 – 0.20)
Age (50 – 65)	(reference)	(reference)	(reference)
Obesity	0.91 (0.38 – 2.18)	1.59 (1.31 – 1.93)	2.02 (1.63 – 2.49)
Alcoholism	2.00 (1.18 – 3.39)	2.26 (1.96 – 2.61)	1.65 (1.36 – 1.99)

NSAID use was stratified into four categories to determine the effect of cumulative exposure on study endpoints. 'Low' exposure was defined as continuous NSAID use at the high daily dose for one year or less (0.876 Kgs of ibuprofen equivalent), 'moderate' use was one to three years of continuous use (0.876 to 2.628 Kgs of ibuprofen equivalent), and 'high' use was greater than 3 years of continuous use (2.628 Kgs or greater of ibuprofen equivalent).

Greater cumulative NSAID exposure monotonically increased the protective effect against CRC. The rate per 100,000 person years for none, low, moderate, and high NSAID exposure was 63.24, 56.36, 35.37, and 9.27, respectively. The unadjusted RR

was 0.89 (0.64 – 1.24) for 'low' users, 0.56 (0.33 – 0.93) for 'moderate' users, and 0.15 (0.03 – 0.63) for 'high' users. The adjusted RR was 0.81 (0.59 – 1.10) for 'low' users, 0.52 (0.32 – 0.85) for 'moderate' users, and 0.13 (0.03 – 0.53) for 'high' users. See Table 19.

'Low' NSAID users had a crude increased risk of GI events relative to non-users, however, moderate and high users had relatively fewer GI events than non-users. The unadjusted RR was 1.26 (1.12 – 1.41) for 'low' users, 0.84 (0.71 – 1.00) for 'moderate' users, and 0.41 (0.29 – 0.58) for 'high' users. The adjusted RR for stratified NSAID users was 1.05 (0.94 – 1.17) for 'low' users, 0.74 (0.63 – 0.86) for 'moderate' users, and 0.33 (0.24 – 0.45) for 'high' users. The low NSAID users class had the largest number of person years (345,371) and was the only one which exhibited an unadjusted significant increase in risk for adverse GI events. However, an unexpected protective effect was exhibited in the 'moderate' and 'high' use class. See Table 20.

For renal events, a trend similar to GI events was found with the 'low' users experiencing a greater risk for renal events, and 'moderate' or 'high' users of NSAIDs experiencing relatively fewer events than non-users. The rate per 100,000 person years for none, low, moderate, and high NSAID exposure was 340.45, 397.78, 270.69, and 150.68, respectively. The unadjusted RR was 1.17 (1.02 – 1.34) for 'low' users, 0.80 (0.65 – 0.97) for 'moderate' users, and 0.44 (0.30 – 0.65) for 'high' users. The adjusted RR was 0.96 (0.84 – 1.09) for 'low' users, 0.65 (0.54 – 0.78) for 'moderate' users, and 0.34 (0.24 – 0.48) for 'high' users. Again, the low NSAID users class had the largest number of person years (349,185) and was the only one which exhibited an unadjusted

significant increase in risk for adverse renal events. However, an unexpected protective effect was exhibited in the 'moderate' and 'high' use class. See Table 21

Table 19. Effect of cumulative NSAID exposure on the incidence of any CRC event

Cumulative NSAID exposure*	Person years	CRC cases	Rate per 100,000 person years	RR	RR adjusted (95% CI)
High	43,134	4	9.27	0.15	0.13 (0.03 – 0.53)
Moderate	118,729	42	35.37	0.56	0.52 (0.32 – 0.85)
Low	353,083	199	56.36	0.89	0.81 (0.59 – 1.10)
None	200,807	127	63.24	--	--

*Low = 0 – 1 year of use, Moderate = 1 – 3 years, and High = 3<.

Table 20. Effect of cumulative NSAID exposure on the incidence of any GI event

Cumulative NSAID exposure*	Person years	GI Cases	Rate per 100,000 person years	RR	RR adjusted (95% CI)
High	41,631	88	211.38	0.41	0.33 (0.24 – 0.45)
Moderate	115,739	498	430.28	0.84	0.74 (0.63 – 0.86)
Low	345,371	2,220	642.79	1.26	1.05 (0.94 – 1.17)
None	200,141	1,023	511.14	--	--

*Low = 0 – 1 year of use, Moderate = 1 – 3 years, and High = 3<.

Table 21. Effect of cumulative NSAID exposure on the incidence of any renal event

Cumulative NSAID exposure*	Person years	Renal cases	Rate per 100,000 person years	RR	RR adjusted (95% CI)
High	42,474	64	150.68	0.44	0.34 (0.24 – 0.48)
Moderate	117,478	318	270.69	0.80	0.65 (0.54 – 0.78)
Low	349,185	1,389	397.78	1.17	0.96 (0.84 – 1.09)
None	200,326	682	340.45	--	--

*Low = 0 – 1 year of use, Moderate = 1 – 3 years, and High = 3<.

Analyses of outcomes were then analyzed by type of NSAID exposure. Study drugs were separated into exposure categories of only aspirin products used, only NSAIDs used, and both aspirin and NSAIDs used. The 2000 Drug Facts and Comparisons were used as a reference to categorize study drugs.[67] Aspirin and NSAIDs were separated for analysis because of the different therapeutic properties and side effect profiles than compared to NSAIDs.

For CRC events, exclusive use of aspirin, NSAIDs, and combinations of both exhibited a protective effect. The rate per 100,000 person years for none, ASA only, NSAID only, and both were 63.24, 39.76, 51.43, and 39.66, respectively. The unadjusted RR was 0.63 (0.26 – 1.52) for exclusive ASA users, 0.81 (0.58 – 1.14) for exclusive NSAID users, and 0.63 (0.39 – 1.00) for those who used both therapies. The adjusted RR was 0.66 (0.28 – 1.54) for exclusive ASA users, 0.73 (0.52 – 1.01) for exclusive NSAID users, and 0.58 (0.37 – 0.92) for those who used both therapies. See Table 22.

For GI events, exclusive NSAID use increased the risk of adverse events, while for the two smallest classes of 'ASA' and 'both' appeared to have a protective effect. The rate per 100,000 person years for none, aspirin only, NSAID only, and both were 511.14, 475.97, 598.51, and 474.55, respectively. Exclusive NSAID users had an unadjusted significant increased risk of GI events of 1.17 (1.04 – 1.32) compared to those without exposure, while the non-significant unadjusted risk for exclusive ASA users and users of both were 0.93 (0.70 – 1.24) and 0.93 (0.39 – 1.00), respectively. The adjusted RR was 1.12 (0.86 – 1.46) for exclusive ASA users, 0.94 (0.84 – 1.06) for exclusive NSAID users, and 0.82 (0.71 – 0.95) for those who used both therapies. See Table 23.

Exclusive aspirin use and NSAID use did not alter the risk of renal adverse events. The rate per 100,000 person years for none, ASA only, NSAID only, and both were 340.45, 355.48, 377.07, and 272.70, respectively. Exclusive aspirin use and NSAID use trended to increase the risk of GI events 1.04 (0.77 – 1.42) and 1.11 (0.96 – 1.27), respectively, compared to those without exposure, while users of 'both' had a protective effect against renal adverse events with an unadjusted RR of 0.80 (0.66 – 0.97). The adjusted RR was 1.24 (0.93 – 1.65) for exclusive ASA users, 0.87 (0.77 – 1.00) for exclusive NSAID users, and 0.67 (0.56 – 0.80) for those who used both therapies. See Table 24.

Table 22. Effect of NSAID type exposure on the incidence of any CRC event

Type of NSAID exposure	Person years	CRC cases	Rate per 100,000 person years	RR	RR adjusted (95% CI)
Both	138,684	55	39.66	0.63	0.58 (0.37 – 0.92)
NSAID only	346,083	178	51.43	0.81	0.73 (0.52 – 1.01)
ASA only	30,178	12	39.76	0.63	0.66 (0.28 – 1.54)
None	200,807	127	63.24	--	--

Table 23. Effect of NSAID type exposure on the incidence of any GI event

Type of NSAID exposure	Person years	GI cases	Rate per 100,000 person years	RR	RR adjusted (95% CI)
Both	134,232	637	474.55	0.93	0.82 (0.71 – 0.95)
NSAID only	338,676	2027	598.51	1.17	0.94 (0.84 – 1.06)
ASA only	29,834	142	475.97	0.93	1.12 (0.86 – 1.46)
None	200,141	1,023	511.14	--	--

Table 24. Effect of NSAID type exposure on the incidence of any renal event

Type of NSAID exposure	Person years	Renal cases	Rate per 100,000 person years	RR	RR adjusted (95% CI)
Both	136,412	372	272.70	0.80	0.67 (0.56 – 0.80)
NSAID only	342,906	1293	377.07	1.11	0.87 (0.77 – 1.00)
ASA only	29,819	106	355.48	1.04	1.24 (0.93 – 1.65)
None	200,326	682	340.45	--	--

Study drug exposure and non-exposure and its impact on outcomes that were subdivided into ICD-9 diagnosis codes were examined next . ICD-9 codes used to identify CRC outcomes were 153.x (colon), 154.x (rectum), 197.x (secondary malignant neoplasm), and 230.x (cancer of the digestive organs). Overall, exposure to NSAIDs trended to demonstrate a protective effect against CRC for each of the diagnosis codes, however, for only colon cancer did NSAIDs demonstrate a significant protective effect. The unadjusted RR for colon, rectal, secondary malignant neoplasms, and cancers of the digestive organs were 0.64 (0.42 – 0.99), 0.74 (0.49 – 1.12), 0.84 (0.22 – 3.23), and 0.63 (0.25 – 1.61) for the exposure group, respectively. The adjusted RR was 0.54 (0.35 – 0.81) for colon cancer, 0.73 (0.49 – 1.08) for rectal cancer, 0.76 (0.20 – 2.90) for secondary malignant neoplasms, and 0.56 (0.22 – 1.40) for cancers of the digestive organs. See Table 25.

ICD-9 codes used to identify GI outcomes were 531.x (gastric ulcer), 532.x (duodenal ulcer), 533.x (peptic ulcer), 534.x (gastojejunal ulcer), and 578.x

(gastrointestinal hemorrhage). The unadjusted overall risk trended non-significantly higher for GI adverse events for each of the diagnosis codes. The unadjusted RR for gastric ulcer, duodenal ulcer, peptic ulcer, gastojejunal ulcer, and gastrointestinal hemorrhage, were 1.11 (0.84 – 1.48), 1.05 (0.74 – 1.49), 1.13 (0.94 – 1.35), 1.30 (0.48 – 3.51), and 1.01 (0.87 – 1.18) for the exposure group, respectively. The adjusted RR for was 0.94 (0.70 – 1.22) for gastric ulcer , 0.90 (0.65 – 1.24) for duodenal ulcer, 0.95 (0.80 – 1.12) for peptic ulcer, 1.12 (0.38 – 3.23) for gastojejunal ulcer, and 0.85 (0.73 – 0.98) for gastrointestinal hemorrhage. Gastrojejunal ulcer was the only diagnosis that demonstrated an increasing trend for both the unadjusted and adjusted RR. See Table 26.

ICD9 codes used to identify renal outcomes were 580.x (acute glomerulonephritis), 581.x (nephrotic syndrome), 583.x (nephritis and nephropathy), 584.x (acute renal failure), 586.x (renal failure), and 593.x (other disorders of the kidney). The unadjusted RR for codes acute glomerulonephritis, nephrotic syndrome, nephritis and nephropathy, acute renal failure, renal failure, and other disorders of the kidney, were 0.59 (0.19 – 1.81), 0.98 (0.51 – 1.88), 1.04 (0.63 – 1.70), 0.77 (0.59 – 1.01), 1.00 (0.81 – 1.23), and 1.06 (0.88 – 1.26) for the exposure group, respectively. The adjusted RR was 0.45[*] for acute glomerulonephritis, 0.73 (0.41 – 1.31) for nephrotic syndrome, 0.76 (0.49 – 1.19) for nephritis and nephropathy, 0.59 (0.46 – 0.77) for acute renal failure, 0.82 (0.67 – 1.00) for renal failure, and 0.86 (0.72 – 1.02) for other disorders of the kidney. See Table 27.

---

[*] CI's are not available because the algorithm did not converge (due to small 'n=35')

Table 25. Occurrence of CRC events stratified by ICD-9-CM series heading for NSAID exposure/non-exposure

ICD-9-CM series heading	No exposure to study drugs (200,807 person years) n=29,185		Exposure to study drugs (514,945 person years) n=71,457		RR*	RR adjusted (95% CI)
	Cases	Rate per 100,000 person years	Cases	Rate per 100,000 person years		
153.x (colon)	76	37.85	125	24.27	0.64	0.54 (0.35 – 0.81)
154.x (rectum)	78	38.84	148	28.74	0.74	0.73 (0.49 – 1.08)
197.x (secondary neoplasm)	6	2.99	13	2.52	0.84	0.76 (0.20 – 2.90)
230.x (cancer of digestive organs)	18	8.96	29	5.63	0.63	0.56 (0.22 – 1.40)

*Non-exposure group used as reference.

Table 26. Occurrence of GI events stratified by ICD-9-CM series heading for NSAID exposure/non-exposure

ICD-9-CM series heading	No exposure to study drugs (200,141 person years) n=29,606		Exposure to study drugs (502,741 person years) n=71,036		RR*	RR adjusted (95% CI)
	Cases	Rate per 100,000 person years	Cases	Rate per 100,000 person years		
531.x (gastric ulcer)	185	92.43	518	103.04	1.11	0.94 (0.70 – 1.22)
532.x (duodenal ulcer)	127	63.46	336	66.83	1.05	0.90 (0.65 – 1.24)
533.x (peptic ulcer)	460	229.84	1,307	259.97	1.13	0.95 (0.80 – 1.12)
534.x (gastrojejunal ulcer)	15	7.49	49	9.75	1.30	1.12 (0.38 – 3.23)
578.x (gastrointestinal hemorrhage)	569	284.30	1,442	286.83	1.01	0.85 (0.73 – 0.98)

*Non-exposure group used as reference.

Table 27. Occurrence of renal events stratified by ICD-9-CM series heading for NSAID exposure/non-exposure

ICD-9-CM series heading	No exposure to study drugs (200,326 person years) n=29,387		Exposure to study drugs (509,137 person years) n=71,255		RR*	RR adjusted (95% CI)
	Cases	Rate per 100,000 person years	Cases	Rate per 100,000 person years		
580.x (acute glomerulonephritis)	14	6.99	21	4.12	0.59	0.45 (algorithm did not converge)
581.x (nephrotic syndrome)	33	16.47	82	16.11	0.98	0.73 (0.41 – 1.31)
583.x (nephritis and nephropathy NOS)	56	27.95	148	29.07	1.04	0.76 (0.49 – 1.19)
584.x (acute renal failure)	173	86.36	339	66.58	0.77	0.59 (0.46 – 0.77)
586.x (renal failure)	283	141.27	721	141.61	1.00	0.82 (0.67 – 1.00)
593.x (other disorders of kidney)	392	195.68	1,052	206.62	1.06	0.86 (0.72 – 1.02)

*Non-exposure group used as reference.

The next set of analyses examined the effect that exclusive use of one NSAID had on the study outcomes. Study drugs included for analysis were required be used exclusively by a minimum of 1,000 subjects, of which four met the criteria; ibuprofen , naproxen, indomethacin, and fenoprofen. These four agents, with the possible exception of indomethacin, are generally regarded as having a relatively lower specificity towards the COX-1 enzyme responsible for many side effects than other NSAIDs. NSAIDs with higher specificity towards COX-1 include NSAIDs such as sulindac, tolmetin, and piroxicam and are generally considered to have more toxic profiles than other NSAIDs.

On average for all three outcomes, those who used only ibuprofen, 82% were in the "low" usage category, 14% were "moderate", and 4% were "high". Of those who used only naproxen, 94% were in the "low" category, 5% were "moderate", and 1% were "high". For indomethacin, 86% were in the "low" usage category, 10% were "moderate", and 4% were "high". For fenoprofen, 82% were in the "low" usage category, 14% were "moderate", and 4% were "high".

The exclusive use of all four drugs trended non-significantly to lower the risk of CRC events. The unadjusted risk for ibuprofen, naproxen, indomethacin, and fenoprofen were 0.67, 0.11, 0.26, and 0.49, respectively. The adjusted RR was 0.61 (0.35 – 1.07) for ibuprofen, 0.10 (0.00 – 2.34) for naproxen, 0.25 (0.03 – 2.11) for indomethacin, and 0.48 (0.08 – 2.73) for fenoprofen. Ibuprofen was the most commonly used exclusive agent with nearly a 5-fold increase in use over naproxen. See Table 28.

For GI events, the exclusive use of ibuprofen, naproxen, and indomethacin demonstrated an unexpected significant protective effect, although the estimate for fenoprofen was non-significant. The unadjusted risk was 0.70, 0.68, 0.71, and 0.66,

respectively. The adjusted RR was 0.58 (0.47 – 0.70) for ibuprofen, 0.54 (0.34 – 0.85) for naproxen, 0.62 (0.38 – 0.99) for indomethacin, and 0.60 (0.35 – 1.05) for fenoprofen. See Table 29.

Similar to the GI events, the exclusive use of ibuprofen, naproxen, and indomethacin demonstrated an unexpected significant protective effect, while the estimate for fenoprofen was non-significant. The unadjusted risk was 0.85, 0.49, 0.91, and 0.64, respectively. The adjusted RR was 0.68 (0.55 – 0.84) for ibuprofen, 0.40 (0.21 – 0.76) for naproxen, 0.76 (0.46 – 1.26) for indomethacin, and 0.60 (0.31 – 1.16) for fenoprofen. See Table 30.

Table 28. Effect of exclusive NSAID exposure on the incidence of any CRC event

Exclusive NSAID exposure	**Person years**	**CRC cases**	**Rate per 100,000 person years**	**RR**	**RR adjusted (95% CI)**
ibuprofen (n = 11,656)	82,799	35	42.27	0.67	0.61 (0.35 – 1.07)
naproxen (n = 1,946)	13,808	1	7.24	0.11	0.10 (0.00 – 2.34)
indomethacin (n = 1,688)	12,044	2	16.61	0.26	0.25 (0.03 – 2.11)
fenoprofen (n = 1,342)	9,652	3	31.08	0.49	0.48 (0.08 – 2.73)
None (n = 29,185)	200,807	127	63.24	--	--

Table 29. Effect of exclusive NSAID exposure on the incidence of any GI event

Exclusive NSAID exposure	Person years	GI cases	Rate per 100,000 person years	RR	RR adjusted (95% CI)
ibuprofen (n = 11,576)	81,403	291	357.48	0.70	0.58 (0.47 – 0.70)
naproxen (n = 1,912)	13,440	47	349.70	0.68	0.54 (0.34 – 0.85)
indomethacin (n = 1,670)	11,792	43	364.65	0.71	0.62 (0.38 – 0.99)
fenoprofen (n = 1,335)	9,496	32	336.98	0.66	0.60 (0.35 – 1.05)
None (n = 29,606)	200,141	1,023	511.14	--	--

Table 30. Effect of exclusive NSAID exposure on the incidence of any renal event

Cumulative NSAID exposure	Person years	Renal cases	Rate per 100,000 person years	RR	RR adjusted (95% CI)
ibuprofen (n = 11,622)	82,043	237	288.87	0.85	0.68 (0.55 – 0.84)
naproxen (n = 1,933)	13,671	23	168.24	0.49	0.40 (0.21 – 0.76)
indomethacin (n = 1,676)	11,881	37	311.42	0.91	0.76 (0.46 – 1.26)
fenoprofen (n = 1,339)	9,569	21	219.46	0.64	0.60 (0.31 – 1.16)
None (n = 29,387)	200,326	682	340.45	--	--

11.4 Sub-analyses using Smalley's criteria for NSAIDs

Analyses then examined the impact that a sub-set of study drugs had on the outcomes. For comparative purposes, the sub-set of NSAIDs used in Smalley's 1999 study were used.[44] NSAIDs kept for analyses were diclofenac, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, nabumetone, naproxen, phenylbutazone, piroxicam, sulindac, and tolmetin. NSAIDs excluded from analyses were aspirin products, ketorolac, mefenamic acid, and oxaprozin.

For CRC events, an overall protective trend was observed for NSAID users. The rate per 100,000 person years was 48.73 for the exposure group and 58.58 for the non-exposure group with an unadjusted RR of 0.83 (0.61 – 1.14) using the non-exposure group as a reference. The adjusted RR was 0.75 (0.55 – 1.02). See Table 31.

For GI events, the unadjusted RR demonstrated a significant increase in risk for those exposed to NSAIDs, although after multivariate adjustment the estimate was non-significant. NSAIDs users had an increased risk of about 100 more cases per 100,000 person years than that of non-users. The rate per 100,000 person years was 578.37 for the exposure group and 477.54 for the non-exposure group. Users of NSAIDs had a significantly higher unadjusted RR of 1.21 (1.08 – 1.36). The adjusted RR was 0.99

Table 32.

For renal events, the unadjusted RR trended to increase the risk for renal adverse events for users of NSAIDs. However, after multivariate adjustment, the adjusted RR demonstrated a significant protective effect of NSAID use. The rate per 100,000 person years was 357.35 for the exposure group and 322.29 for the non-exposure group with an

unadjusted RR of 1.11 (0.97 – 1.26). The adjusted RR was 0.87 (0.77 – 0.99). See Table 33.

Table 31. Effect of NSAID Exposure/non-exposure on the Incidence of Any CRC Event Using Smalley's NSAID Criteria

Exposure to study drugs*	Person years	CRC cases	Rate per 100,000 person years	RR	RR adjusted (95% CI)
Exposure	480,196	234	48.73	0.83	0.75 (0.55 – 1.02)
No exposure	235,556	138	58.58	--	--

*Exposure defined as ever used NSAID(s) prior to incurring study outcome.

Table 32. Effect of NSAID Exposure/non-exposure on the Incidence of Any GI Event Using Smalley's NSAID Criteria

Exposure to study drugs*	Person years	GI cases	Rate per 100,000 person years	RR	RR adjusted (95% CI)
Exposure	468,557	2,710	578.37	1.21	0.99 (0.89 – 1.10)
No exposure	234,325	1,119	477.54	--	--

*Exposure defined as ever used NSAID(s) prior to incurring study outcome.

Table 33. Effect of NSAID Exposure/non-exposure on the Incidence of Any Renal Event Using Smalley's NSAID Criteria

Exposure to study drugs*	Person years	Renal cases	Rate per 100,000 person years	RR	RR adjusted (95% CI)
Exposure	474,891	1697	357.35	1.11	0.87 (0.77 – 0.99)
No exposure	234,572	756	322.29	--	--

*Exposure defined as ever used NSAID(s) prior to incurring study outcome.

CHAPTER 12

DISCUSSION

This is the first study to assess the risks of GI and renal events with the potential benefits of CRC protection association with NSAIDs in a single study. By exploring the GDMA claims, over 700k persons years were utilized. To our knowledge, this study utilizes more person years of data to assess the association of NSAID exposure with these outcomes than other studies measuring similar endpoints. Overall, our study found that NSAID exposure exhibited a protective effect against CRC, with a reduction in risk of about 25% for any exposure to NSAIDs and greater reductions in relative risks at higher levels of NSAID consumption. This study found little evidence to an association between NSAID exposure and GI and renal adverse events commonly associated with NSAID exposure. This study did demonstrate a significantly elevated risk of GI events for low (less than 1 year of exposure) volume NSAID users and exclusive non-ASA NSAID users in the crude analyses, however after multivariate adjustment these associations were no longer significant. Similarly this study did not demonstrate an increased risk for renal adverse events by taking NSAIDs.

To gain a sense of the benefit risk ratio of taking NSAIDs, the attributable risk (protection) was calculated for any NSAID use using the point estimates of the crude unadjusted rates for any NSAID use (tables 15-17). The attributable risk of those exposed to NSAIDs resulted in 16 cases of CRC avoided per 100,000 person years.

However, the attributable risk of GI and renal events resulted in 47 and 7 additional cases per 100,000 person years for those exposed to NSAIDs, respectively. Based on the non-significant point estimates, the risk/benefit profile of NSAID exposure demonstrated that for every one case of CRC avoided, 3.00 GI cases and 0.47 renal cases were created. It should be noted that none of these point estimates for the relative risks were statistically different than 1.00, however after multivariate adjustment, NSAID use was associated with a statistically significant reduction in CRC incidence and renal adverse events and a non-significant reduction in the risk of GI adverse events. The multivariate adjusted results portray a picture where there is only benefit and no increased risk of renal or GI events.

These results must be interpreted with caution as the washout period required subjects to be free of all outcomes for one year. Subsequently, many of the NSAID users able to meet the inclusion criteria and remain in the study might tolerate NSAID therapy better than most typical users. Therefore, these subjects are less likely to be considered naïve to NSAIDs and may demonstrate a lower risk for GI and renal events relative to those persons with NSAID exposure and who don't tolerate therapy as well. Studies have shown that the initial doses of NSAIDs and not long term NSAID use are most likely to result in GI adverse related events.[11;13;18;23] In order to be reasonably certain that we could temporally relate NSAID use that precedes the development of our outcome events, it was necessary to exclude persons who experienced events in the first year of the study. This criteria was necessary because it would be unclear if claims occurring in year one represent new diagnoses or ongoing treatment of outcomes that occurred in the periods prior to when we had data available (left censoring). As a result of this exclusion

criteria, persons whom may have had events shortly after an initial exposure to NSAIDs may have been omitted and consequently the GI risks reported in this study may be understated, particularly for low volume NSAID users.

The drugs assessed in this study were more inclusive than most other pharmacoepidemiolgic studies of this nature as both NSAIDs and aspirin products were examined. Studies measuring similar endpoints have typically only included either aspirin products or non-aspirin NSAIDs and ordinarily have not measured exposure of both in the same study. The NSAIDs included in this study reflect real life usage patterns more so than other studies that limit exposure to a narrow selection of NSAIDs.

The age span of the population studied (age 50 to 99) varies more years than other studies of this nature. Many other studies that examine the NSAID/CRC relationship often limit study inclusion criteria to persons age 65 years and greater. Studies have shown that the risk for CRC begins to escalate at age 50, which often leaves a large number of persons at risk unstudied. A breakpoint for age class was conducted at age 65 because of the potential of Medicare to pick up reimbursement for study outcomes procedures. Older age classes, both (65 - 75) and (>75), appeared to be at less risk for the three study outcomes than the 50 to 64 age group, possibly as a result of Medicare picking up claims for those aged 65 and greater, although Medicaid frequently covers the billing of procedures not paid for entirely by Medicare. Gender did not appear to be an overwhelming risk factor as only females in the GI model had a significant increase in risk. Race was only significant in the renal model where Caucasian race had a protective effect for renal events. Obesity significantly increased the risk in the GI and renal models, while alcoholism significantly doubled the risk in all three outcomes. Excess

alcohol consumption can lead to gastric irritation and ulcers and often requires invasive diagnostic procedures, which can lead to the detection of GI and CRC events.

12.1 CRC outcomes

This study confirms previous observational studies that NSAID usage has a protective effect against CRC, that there is a dose dependent relationship with the degree of protection, and that the most commonly prescribed NSAIDs offer a protective effect. The protective effect of NSAIDs against CRC appears to be dependent upon long-term, continuous use. Persons who had 1 to 3 years of continuous NSAID usage experienced half the risk for a CRC diagnosis than did persons who had no exposure. However, the estimates for NSAID users in the "High" category should be interpreted with caution as sample sizes were relatively small for these categories and estimates can become unstable.

This study was similar in study design, sample size, and demographic make-up to that of Smalley's 1999 retrospective, cohort study of Tennessee Medicaid recipients to measure the association of NSAIDs and CRC.[44] As a result, it would be expected that risk estimates would be similar in comparison. A greater protective effect was observed against colon cancer than rectum cancer as these results concur with Smalley's 1999 study.[44] The diagnosis of "cancer of the digestive organs" (230.x) had approximately the same point estimate as that for colon cancer. Also, both studies demonstrated that higher cumulative doses of NSAIDs offered a more protective effect against CRC. Both studies examined the effect of individual NSAIDs use although ibuprofen was the only agent with a large enough sample size to provide reliable estimates for comparison. For

exclusive ibuprofen users the adjusted RR was 0.61 (95% CI, 0.35 – 1.07) compared with Smalley's 1999 study estimate of 0.63 (95% CI, 0.31 – 1.27).

For validation purposes, the adjusted RR estimates stratified by cumulative NSAID use were compared to Smalley's estimates and found to be very similar. For up to one year of cumulative use, the adjusted RR was 0.81 (95% CI, 0.59 – 1.10) compared to Smalley's adjusted RR of 0.83 (95% CI, 0.67 – 1.03) for 3 months to one year of cumulative NSAID use. For up to three years of use, the adjusted RR was 0.52 (95% CI, 0.32 – 0.85) compared to Smalley's estimate of 0.59 (95% CI, 0.39 – 0.92) for up to four years continuous use. There did not appear to be a large difference in the protective effect for persons using either NSAIDs or aspirin products exclusively. This concurs with the literature as neither class of drug has been shown to posses a greater margin of protective effect than the other. However, as aspirin products are generally considered more toxic to the GI tract than non-aspirin NSAIDs, it might be recommended that high risk persons seeking pharmacologic protection against CRC use an NSAID regimen. Also, risk profiles vary widely between agents and compatible regimens regarding side effects are difficult to predetermine.

The potential confounding effect of those subjects who experienced GI outcomes was not assessed for persons who also experienced CRC outcomes. It would be reasonable to assume that those subjects experiencing a GI diagnostic procedure would have a higher likelihood of CRC detection than those who did not experience a GI diagnostic procedure. Smalley's 1999 study assessed the effect of NSAID associated diagnostic testing of cohort members with no lower GI tract test in the previous 5 years and the adjusted RR of colon cancer among recent users with more than 12 months of

cumulative use was 0.63 (95% CI, 0.49 – 0.81). However, this estimate did not vary greatly from the cohort members who were not controlled for GI diagnostic screening, i.e., persons who may have had a GI diagnostic screening procedure, with an adjusted RR of 0.61 (95% CI, 0.48 – 0.77).[44]

12.2 Gastrointestinal outcomes

This study found little evidence that long term exposure to NSAIDS was associated with higher rates of GI events. The study did find that low NSAID use trended to have higher rates of GI events than did non-users which may indicate that NSAID naïve patients may be at a slightly higher risk of GI events. However, these results must be interpreted with caution. As stated above, numerous subjects who experienced GI outcomes were not included for analysis because of the one year 'washout' criteria. Subsequently, many of the NSAID users able to meet the inclusion criteria and remain in the study might tolerate NSAID therapy better than most typical users. As a result, this may have biased the results by underestimating the risk of NSAID related GI events by only considering events that occurred one year after the index date. A selection bias for NSAID users may have occurred in the sense that 'moderate' and 'high' users may be predisposed to tolerate NSAIDs better than other users in general. For those subjects who had exposure during the first year in the study, the risk is highest early in an NSAID regimen and then tapers over time.

The unadjusted relative risks of NSAID exposure and GI outcomes demonstrated a significant increase in risk for those with "low" cumulative doses of NSAIDs and those who only took NSAIDs, i.e., no ASA consumption. Multivariate adjustment of risk often lowered the risk to insignificant estimates and indicated that "moderate" and "high" users

of NSAIDs as having a protective effect. However, the unadjusted relative risk for categories of NSAID exposure, e.g., 'low' exposure in Table 20 and 'NSAID only' exposure in Table 23 with larger sample sizes demonstrated a significantly higher risk for GI events relative to other categories of exposure with smaller sample sizes, e.g, 'high' exposure and 'ASA only' exposure, Table 20 and Table 23, respectively. The estimates in the exposure categories with smaller sample sizes are susceptible to being unstable and should be interpreted with caution.

Often, subjects intolerant to NSAID therapy will experience adverse events quickly and discontinue usage. For those subjects who tolerate the first couple of weeks (or months) of therapy, these patients might be considered "tolerant" of NSAIDs. The risk estimates experienced in this study may differ from estimates in the literature as typically study designs do not employ a 'washout' criteria for the endpoints and are short term in nature, i.e., usually not more than three years of follow-up with the highest risk for events occurring in the first few months of exposure. The inability to capture short term events due to the 'washout' criteria necessary to capture incident outcome events may account for the lower relative risk for GI events relative to what the literature might suggest.

Several studies have shown evidence that the risk for NSAID associated GI events are highest at the initiation of a regimen and then the risk tapers over time.[11;13;18;23] For example, this initial increased risk was confirmed by Griffin *et al* who evaluated the association of NSAID exposure and peptic ulcer disease in an elderly Medicaid population and concluded that the risk for peptic disease was greatest in the first month of NSAID use.[18]

> "The increased risk that we noted for short-term users is consistent with the development of mucosal adaptation; that is, an increased capacity to withstand injury, seen in the gastric mucosa with long-term administration of aspirin, but could also result from early discontinuation of these drugs among patients who are intolerant of their effect."[18]

Mucosal adaptation, or gastric adaptation, is described as the phenomenon in which visible gastric mucosal injury lessens or resolves completely despite continued administration of an injurious substance such as aspirin.[68-71] Although the mechanism remains unclear, it is suggested that increased cell proliferation and correction of NSAID drug induced reduction in gastric blood flow as possibly being a factor.[68] The required washout period may have facilitated a selection bias of NSAID users who are predisposed to demonstrate gastric adaptation to NSAID usage. Gastric adaptation may account in part for the lower than anticipated risk estimates of NSAID related GI events in this study population.

12.3 Renal outcomes

This study found no evidence that long term exposure to NSAIDS was associated with higher rates of renal events. Similar to the GI results, the results of the renal outcomes were inconclusive, due possibly to the same study design issues that affected the GI endpoints. Like NSAID related GI events, the risk for renal events is often highest

shortly after initiating an NSAID regimen.[30] Therefore, in accordance with the GI outcome results, the renal results should be interpreted with caution.

The unadjusted relative risks of NSAID exposure and GI outcomes demonstrated a significant increase in risk for those with "low" cumulative doses of NSAIDs. After multivariate adjustment, the risk was often lowered to insignificant estimates and sometimes demonstrated NSAIDs as having a protective effect. However, similar to the GI results, relative risk estimates for categories of NSAID exposure with larger sample sizes usually demonstrated a significantly higher risk for renal events relative to other categories of exposure with smaller sample sizes. Again, estimates in the exposure categories with smaller sample sizes are susceptible to being unstable and should be interpreted with caution.

In the general population, adverse renal events associated with NSAID exposure is a rare event. The association of renal impairment and NSAID exposure is
The crude incidence rate of hospitalization for acute renal failure has been shown to be as low as less than 2 per 100,000 person years.[30] In addition, there are also many underlying factors that contribute to renal impairment with NSAID exposure accounting for less than 16% of cases that are drug induced.[72] Therefore, the strength of the NSAID/renal impairment relationship appears to be not as strong as the NSAID/GI relationship.

12.4 Limitations

Numerous limitations are inherent in non-experimental, epidemiological type study methodologies. Common limitations of observational studies include; non-randomization to treatment, no control of intervention, and sample biases. These

limitations have the potential to hinder the accurate estimate that the impact of NSAID exposure would have on the study outcomes. For example, non-randomization to treatment does not control for between-group differences in characteristics of subjects. For instance, subjects taking NSAIDs for the protective effect against cardiovascular adverse events may also be prone to exhibit health promoting behaviors that are not detected in the data.

The use of Medicaid data presents limitations that are not unique to this variety of data. For example, information on some risk factors of cancer such as weight, diet, and family history was not available and thus these factors could not be controlled for in the analysis.[44] In other studies, covariates such as body mass index, fat intake, or history of family cancer had only a minor impact on the risk estimates of the effect of NSAIDs on colon cancer.[44] Also, any NSAIDs or aspirins that were bought over-the-counter could not be captured by the database and thus could not be taken into account. Potentially, this could lead to overstating the effect that NSAID exposure has on study endpoints. The protective effect that NSAIDs exhibit against CRC could be exaggerated, while the adverse effects on GI and renal function might also be distorted. The issue of whether subjects were actually compliant with the usage of their NSAIDs (i.e., scheduling and proper dosages taken) also poses a limitation.

Other limitations include the bias of left censored data: i.e., do not know if and to what extent persons starting taking NSAIDs prior to study start date or eligibility. In addition, the reliance on ICD-9 codes as markers for illness without patient, medical chart, or provider confirmation.

The study design implemented in this study after reviewing the results may have facilitated the underestimation of the GI and renal events as only those subjects who were free of all outcomes for one year were included for analysis. The one year washout period may have influenced the estimates of GI and possibly renal risk by eliminating persons who experience one of these adverse events shortly after an initial NSAID exposure. As a result of the one year exclusion criteria of outcomes, over 2,000 GI outcomes were eliminated. It is not uncommon for those subject starting a regimen of NSAID therapy to experience adverse GI and renal events relatively quickly after starting therapy. Studies have shown that the risk of GI events as a result of NSAID therapy is higher early in therapy and that the risk of adverse events decreases over time.[11;23] Therefore, it is not unreasonable to presume that the GI and renal results may have been underestimated relative to rates found in the literature as a consequence of eliminating potentially NSAID naïve patients whom experience an adverse event in the initial periods of the study.

12.5 Conclusion

The results of this study confirm the association of NSAIDs having a protective effect against the development of CRC with a risk reduction of approximately 25% with any NSAID exposure. There was a dose dependent relationship observed between increasing NSAID exposure and decreasing CRC risk with the greatest reduction in CRC risk associated with the highest doses of NSAIDs. This study did not find any evidence that long term NSAID exposure was associated with increased risk of GI events such as gastric bleeding or duodenal ulcer or renal events such as acute renal failure. The lack of association between NSAID use and GI and renal events should be interpreted with

caution for reasons already cited. These results are important to the Medicaid population of the state of Georgia because, to our knowledge, the NSAID/CRC relationship has never been assessed in this population. This study establishes baseline prevalence rates for CRC diagnoses and could serve as a measure of effectiveness for future intervention programs in this population. Intervention programs could include early screening or a chemopreventive regimen of NSAIDs for individuals at high risk. The fact that some COX-2s have shown to exhibit fewer side effects and have already received FDA approval for familial adenomatous polyposis adjunct therapy is a promising indication that chemoprotection may be used more widespread in the future against CRC.

APPENDIX A

Table 34. ICD-9-CM Codes Used to Identify Cases of CRC[44]

Code	Condition/Location
153.0	Malignant neoplasm of hepatic flexure
153.1	Malignant neoplasm of transverse colon
153.2	Malignant neoplasm of descending colon (left colon)
153.3	Malignant neoplasm of sigmoid colon (sigmoid flexure)
153.4	Malignant neoplasm of cecum (ileocecal valve)
153.6	Malignant neoplasm of ascending colon (right colon)
153.7	Malignant neoplasm of splenic flexure
153.8	Other specified, or overlapping, sites of large intestine
153.9	Malignant neoplasm of colon (unspecified)
154.0	Malignant neoplasm of rectum – rectosigmoid junction
154.1	Malignant neoplasm of rectum – rectum
154.8	Malignant neoplasm of rectum - other specified, or overlapping, sites of rectum
197.5	Secondary malignant neoplasm - large intestine and rectum
230.3	Carcinoma of digestive organs – colon
230.4	Carcinoma of digestive organs - rectum

APPENDIX B

Table 35. ICD-9-CM Codes Used to Identify Gastrointestinal Related Adverse Events[61]

Code	Condition/Location
531.0	Gastric ulcer with hemorrhage
531.1	Gastric ulcer acute with perforation
531.2	Gastric ulcer acute with hemorrhage or perforation
531.3	Gastric ulcer acute without hemorrhage or perforation
531.4	Gastric ulcer chronic/unspecified with hemorrhage
531.5	Gastric ulcer chronic/unspecified with perforation
531.6	Gastric ulcer chronic/unspecified with hemorrhage or perforation
531.7	Gastric ulcer chronic without hemorrhage or perforation
531.9	Gastric ulcer/unspecified
532.0	Duodenal ulcer acute with hemorrhage
532.1	Duodenal ulcer acute with perforation
532.2	Duodenal ulcer acute with hemorrhage or perforation
532.3	Duodenal ulcer acute without hemorrhage or perforation
532.4	Duodenal ulcer chronic/unspecified with hemorrhage
532.5	Duodenal ulcer chronic/unspecified with perforation

532.6	Duodenal ulcer chronic/unspecified with hemorrhage or perforation
532.7	Duodenal ulcer chronic without hemorrhage or perforation
532.9	Duodenal ulcer/unspecified
533.0	Peptic ulcer acute with hemorrhage
533.1	Peptic ulcer acute with perforation
533.2	Peptic ulcer acute with hemorrhage or perforation
533.3	Peptic ulcer acute without hemorrhage and perforation
533.4	Peptic ulcer chronic/unspecified with hemorrhage
533.5	Peptic ulcer chronic/unspecified with perforation
533.6	Peptic ulcer chronic/unspecified with hemorrhage or perforation
533.7	Peptic ulcer chronic without hemorrhage or perforation
533.9	Peptic ulcer/unspecified
534.0	Gastrojejunal ulcer acute with hemorrhage
534.1	Gastrojejunal ulcer acute with perforation
534.2	Gastrojejunal ulcer acute with hemorrhage or perforation
534.3	Gastrojejunal ulcer acute without hemorrhage or perforation
534.4	Gastrojejunal ulcer chronic/unspecified with hemorrhage
534.5	Gastrojejunal ulcer chronic/unspecified with perforation
534.6	Gastrojejunal ulcer chronic/unspecified with hemorrhage or perforation
534.7	Gastrojejunal ulcer chronic without hemorrhage or perforation
534.9	Gastrojejunal ulcer/unspecified
578.0	Gastrointestinal hemorrhage – hematemesis
578.1	Gastrointestinal hemorrhage – blood in stool
578.9	Gastrointestinal hemorrhage of the intestinal tract/unspecified

APPENDIX C

Table 36. ICD-9-CM Codes Used to Identify Renal Related Adverse Events[30]

Code	Condition/Location
580.0	Acute nephritis
580.4	Acute nephritis – rapid progression
580.8	Acute nephritis with other lesions
580.9	Acute nephritis nos
581.0	Nephrotic syndrome
581.1	Nephrotic syndrome epimembranous
581.2	Nephrotic syndrome membranoproliferation
581.3	Nephrotic syndrome minimal change
581.8	Nephrotic syndrome with other lesions
581.9	Nephrotic syndrome nos
583.0	Nephritis and nephropathy
583.1	Nephritis membranous
583.2	Nephritis membrane proliferative
583.6	Nephritis cortical necrosis
583.7	Nephritis with medullary necrosis
583.8	Nephritis with other lesions
583.9	Nephritis
584.0	Acute renal failure
584.5	Acute renal failure with tubular necrosis
584.6	Acute renal failure – cortical necrosis
584.7	Acute renal failure – medullary necrosis
584.8	Acute renal failure with other lesion
584.9	Acute renal failure nos

586	Renal failure nos
593.0	Nephroptosis
593.9	Renal and ureteral disease nos

APPENDIX D

Table 37. ICD-9-CM Codes Used to Identify Cases of Obesity

Code	**Condition/Location**
278.0	Obesity
278.00	Obesity nos
278.01	Morbid obesity
278.1	Localized adiposity
278.2	Hypervitaminosis A
278.3	Hypercarotinemia
278.4	Hypervitaminosis D
278.8	Other hyperalimentation

APPENDIX E

Table 38. ICD-9-CM Codes Used to Identify Cases of Alcoholism

Code	Condition/Location
291.1	Alcohol amnestic syndrome
291.2	Alcoholic dementia
291.5	Alcoholic jealousy
291.8	Alcoholic psychosis
291.81	Alcohol withdrawal
291.89	Alcoholic psychosis
291.9	Alcoholic psychosis
303.9	Alcohol dependence
303.90	Alcohol dependence – unspecified
303.91	Alcohol dependence – continuous
303.92	Alcohol dependence – episodic
303.93	Alcohol dependence - in remission
305.0	Alcohol abuse
305.00	Alcohol abuse – unspecified
305.01	Alcohol abuse – continuous
305.02	Alcohol abuse – episodic
305.03	Alcohol abuse - in remission
V11.3	Alcoholism

APPENDIX F

Table 39. NSAIDs Included in Study

Trade name	Generic class	Ibuprofen equivalent factor
a.s.a.	aspirin	0.40
aspirin	aspirin	0.40
aspirin e.c.	aspirin	0.40
aspir-low	aspirin	0.40
diflunisal	aspirin	2.40
disalcid	aspirin	0.80
dolobid	aspirin	2.40
easprin	aspirin	0.62
ecotrin	aspirin	0.80
genacote	aspirin	0.80
salflex	aspirin	0.80
salgesic	aspirin	0.80
salsalate	aspirin	0.80

salsitab	aspirin	0.80
sloprin	aspirin	0.80
tricosal	aspirin	0.80
trilisate	aspirin	0.80
diclofenac sodium	diclofenac	16.00
voltaren	diclofenac	16.00
voltaren-xr	diclofenac	16.00
etodolac	etodolac	2.00
lodine	etodolac	2.00
lodine xl	etodolac	2.00
fenoprofen calcium	fenoprofen calcium	1.00
fenprofen calcium	fenoprofen calcium	1.00
nalfon	fenoprofen calcium	1.00
ansaid	flurbiprofen	8.00
flurbiprofen	flurbiprofen	8.00
advil	ibuprofen	1.00
children's advil	ibuprofen	1.00
children's motrin	ibuprofen	1.00
ibu	ibuprofen	1.00
ibuprofen	ibuprofen	1.00
ibu-tab	ibuprofen	1.00
motrin	ibuprofen	1.00
pedia-profen	ibuprofen	1.00
rufen	ibuprofen	1.00
indameth	indomethacin	16.00
indochron	indomethacin	16.00
indocin	indomethacin	16.00
indocin sr	indomethacin	16.00
indo-lemmon	indomethacin	16.00
indomethacin	indomethacin	16.00

ketoprofen	ketoprofen	8.00
orudis	ketoprofen	8.00
oruvail	ketoprofen	8.00
ketorolac tromethamine	ketorolac	60.00
toradol	ketorolac	60.00
meclofenamate sodium	meclofenamate	6.00
meclomen	meclofenamate	6.00
mefenamic acid	mefenamic acid	2.40
ponstel	mefenamic acid	2.40
relafen	nabumetone	1.20
anaprox	naproxen	2.18
anaprox ds	naproxen	2.18
ec-naprosyn	naproxen	2.18
naprelan	naproxen	2.18
naprosyn	naproxen	2.18
naproxen	naproxen	2.18
naproxen sodium	naproxen	2.18
daypro	oxaprozin	1.33
butazolidin	phenylbutazone	6.00
phenylbutazone	phenylbutazone	6.00
feldene	piroxicam	120.00
piroxicam	piroxicam	120.00
clinoril	sulindac	6.00
sulindac	sulindac	6.00
tolectin	tolmetin	1.33
tolectin 200	tolmetin	1.33
tolectin 600	tolmetin	1.33
tolectin ds	tolmetin	1.33
tolmetin sodium	tolmetin	1.33

REFERENCES

1. Brooks P: Use and benefits of nonsteroidal anti-inflammatory drugs. *Am.J.Med.* 1998;104:9S-13S.

2. American Cancer Society. American Cancer Society: Cancer facts & figures - 1998. 4-5. 1998.

3. Griffin MR: Epidemiology of nonsteroidal anti-inflammatory drug-associated gastrointestinal injury. *Am.J.Med.* 1998;104:23S-29S.

4. McManus P, Primrose JG, Henry DA, Birkett DJ, Lindner J, Day RO: Pattern of non-steroidal anti-inflammatory drug use in Australia 1990- 1994. A report from the Drug Utilization Sub-Committee of the Pharmaceutical Benefits Advisory Committee. *Med.J.Aust.* 1996;164:589-592.

5. Vane JR, Botting RM: Mechanism of action of nonsteroidal anti-inflammatory drugs. *Am.J.Med.* 1998;104:2S-8S.

6. Garay CA, Engstrom PF: Chemoprevention of colorectal cancer: dietary and pharmacologic approaches. *Oncology (Huntingt.)* 1999;13:89-97.

7. Shiff SJ, Rigas B: Nonsteroidal anti-inflammatory drugs and colorectal cancer: evolving concepts of their chemopreventive actions. *Gastroenterology* 1997;113:1992-1998.

8. Singh G, Ramey DR, Morfeld D, Shi H, Hatoum HT, Fries JF: Gastrointestinal tract complications of nonsteroidal anti-inflammatory drug treatment in rheumatoid arthritis. A prospective observational cohort study. *Arch.Intern.Med.* 1996;156:1530-1536.

9. Bollini P, Garcia RL, Perez GS, Walker AM: The impact of research quality and study design on epidemiologic estimates of the effect of nonsteroidal anti-inflammatory drugs on upper gastrointestinal tract disease. *Arch.Intern.Med.* 1992;152:1289-1295.

10. Fries JF, Williams CA, Bloch DA, Michel BA: Nonsteroidal anti-inflammatory drug-associated gastropathy: incidence and risk factor models. *Am.J.Med.* 1991;91:213-222.

11. Gabriel SE, Jaakkimainen L, Bombardier C: Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. *Ann.Intern.Med.* 1991;115:787-796.

12. Fries JF, Miller SR, Spitz PW, Williams CA, Hubert HB, Bloch DA: Toward an epidemiology of gastropathy associated with nonsteroidal antiinflammatory drug use. *Gastroenterology* 1989;96:647-655.

13. Garcia RL, Walker AM, Perez GS: Nonsteroidal antiinflammatory drugs and gastrointestinal hospitalizations in Saskatchewan: a cohort study. *Epidemiology.* 1992;3:337-342.

14. Garcia RL, Jick H: Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994;343:769-772.

15. Garcia RL: Nonsteroidal antiinflammatory drugs, ulcers and risk: a collaborative meta-analysis. *Semin.Arthritis Rheum.* 1997;26:16-20.

16. Garcia RL: Variability in risk of gastrointestinal complications with different nonsteroidal anti-inflammatory drugs. *Am.J.Med.* 1998;104:30S-34S.

17. Griffin MR, Ray WA, Schaffner W: Nonsteroidal anti-inflammatory drug use and death from peptic ulcer in elderly persons. *Ann.Intern.Med.* 1988;109:359-363.

18. Griffin MR, Piper JM, Daugherty JR, Snowden M, Ray WA: Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. *Ann.Intern.Med.* 1991;114:257-263.

19. Langman MJ: Epidemiology of non-steroidal anti- inflammatory drug damage to stomach and duodenum. *Ital.J.Gastroenterol.Hepatol.* 1999;31 Suppl 1:S2-S5

20. Singh G, Triadafilopoulos G: Epidemiology of NSAID induced gastrointestinal complications. *J.Rheumatol.* 1999;26 Suppl 56:18-24.

21. Smalley WE, Griffin MR, Fought RL, Ray WA: Excess costs from gastrointestinal disease associated with nonsteroidal anti-inflammatory drugs. *J.Gen.Intern.Med.* 1996;11:461-469.

22. Klein WA, Krevsky B, Klepper L, et al: Nonsteroidal antiinflammatory drugs and upper gastrointestinal hemorrhage in an urban hospital. *Dig.Dis.Sci.* 1993;38:2049-2055.

23. Smalley WE, Ray WA, Daugherty JR, Griffin MR: Nonsteroidal anti-inflammatory drugs and the incidence of hospitalizations for peptic ulcer disease in elderly persons. *Am.J.Epidemiol.* 1995;141:539-545.

24. Bennett WM, Henrich WL, Stoff JS: The renal effects of nonsteroidal anti-inflammatory drugs: summary and recommendations. *Am.J.Kidney Dis.* 1996;28:S56-S62

25. Perez-Gutthann S, Garcia-Rodriguez LA, Duque-Oliart A, Varas-Lorenzo C: Low-dose diclofenac, naproxen, and ibuprofen cohort study. *Pharmacotherapy.* 1999;19:854-859.

26. Perneger TV, Whelton PK, Klag MJ: Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. *N.Engl.J.Med.* 1994;331:1675-1679.

27. Sandler DP, Burr FR, Weinberg CR: Nonsteroidal anti-inflammatory drugs and the risk for chronic renal disease. *Ann.Intern.Med.* 1991;115:165-172.

28. Shankel SW, Johnson DC, Clark PS, Shankel TL, O'Neil WMJ: Acute renal failure and glomerulopathy caused by nonsteroidal anti- inflammatory drugs. *Arch.Intern.Med.* 1992;152:986-990.

29. Whelton A, Stout RL, Spilman PS, Klassen DK: Renal effects of ibuprofen, piroxicam, and sulindac in patients with asymptomatic renal failure. A prospective, randomized, crossover comparison. *Ann.Intern.Med.* 1990;112:568-576.

30. Perez GS, Garcia RL, Raiford DS, Duque OA, Ris RJ: Nonsteroidal anti-inflammatory drugs and the risk of hospitalization for acute renal failure. *Arch.Intern.Med.* 1996;156:2433-2439.

31. DuBois RN, Giardiello FM, Smalley WE: Nonsteroidal anti-inflammatory drugs, eicosanoids, and colorectal cancer prevention. *Gastroenterol.Clin North Am.* 1996;25:773-791.

32. Friend WG: Sulindac suppression of colorectal polyps in Gardner's syndrome. *Am.Fam.Physician.* 1990;41:891-894.

33. Giardiello FM, Hamilton SR, Krush AJ, et al: Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. *N.Engl.J Med* 1993;328:1313-1316.

34. Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC: Aspirin use and the risk for colorectal cancer and adenoma in male health professionals. *Ann.Intern.Med.* 1994;121:241-246.

35. Greenberg ER, Baron JA, Freeman DHJ, Mandel JS, Haile R: Reduced risk of large-bowel adenomas among aspirin users. The Polyp Prevention Study Group. *J.Natl.Cancer Inst.* 1993;85:912-916.

36. Greenberg ER, Baron JA: Aspirin and other nonsteroid anti-inflammatory drugs as cancer-preventive agents. *IARC.Sci.Publ.* 1996;91-98.

37. Heath CWJ, Thun MJ, Greenberg ER, Levin B, Marnett LJ: Nonsteroidal antiinflammatory drugs and human cancer. Report of an interdisciplinary research workshop. *Cancer* 1994;74:2885-2888.

38. Kune GA, Kune S, Watson LF: Colorectal cancer risk, chronic illnesses, operations, and medications: case control results from the Melbourne Colorectal Cancer Study. *Cancer Res.* 1988;48:4399-4404.

39. Luk GD: Prevention of gastrointestinal cancer--the potential role of NSAIDs in colorectal cancer. *Schweiz.Med.Wochenschr.* 1996;126:801-812.

40. Martinez ME, McPherson RS, Levin B, Annegers JF: Aspirin and other nonsteroidal anti-inflammatory drugs and risk of colorectal adenomatous polyps among endoscoped individuals. *Cancer Epidemiol.Biomarkers.Prev.* 1995;4:703-707.

41. Paganini-Hill A: Aspirin and the prevention of colorectal cancer: a review of the evidence. *Semin.Surg.Oncol.* 1994;10:158-164.

42. Peleg II, Lubin MF, Cotsonis GA, Clark WS, Wilcox CM: Long-term use of nonsteroidal antiinflammatory drugs and other chemopreventors and risk of subsequent colorectal neoplasia. *Dig.Dis.Sci.* 1996;41:1319-1326.

43. Rosenberg L, Palmer JR, Zauber AG, Warshauer ME, Stolley PD, Shapiro S: A hypothesis: nonsteroidal anti-inflammatory drugs reduce the incidence of large-bowel cancer. *J Natl Cancer Inst* 1991;83:355-358.

44. Smalley W, Ray WA, Daugherty J, Griffin MR: Use of nonsteroidal anti-inflammatory drugs and incidence of colorectal cancer: a population-based study. *Arch.Intern.Med.* 1999;159:161-166.

45. Suh O, Mettlin C, Petrelli NJ: Aspirin use, cancer, and polyps of the large bowel. *Cancer* 1993;72:1171-1177.

46. Thun MJ, Namboodiri MM, Heath CWJ: Aspirin use and reduced risk of fatal colon cancer. *N.Engl.J.Med.* 1991;325:1593-1596.

47. Thun MJ: Aspirin and gastrointestinal cancer. *Adv.Exp.Med Biol.* 1997;400A:395-402.

48. Muscat JE, Stellman SD, Wynder EL: Nonsteroidal antiinflammatory drugs and colorectal cancer. *Cancer* 1994;74:1847-1854.

49. Thun MJ, Namboodiri MM, Calle EE, Flanders WD, Heath CWJ: Aspirin use and risk of fatal cancer. *Cancer Res.* 1993;53:1322-1327.

50. Schreinemachers DM, Everson RB: Aspirin use and lung, colon, and breast cancer incidence in a prospective study. *Epidemiology.* 1994;5:138-146.

51. Labayle D, Fischer D, Vielh P, et al: Sulindac causes regression of rectal polyps in familial adenomatous polyposis. *Gastroenterology* 1991;101:635-639.

52. Gann PH, Manson JE, Glynn RJ, Buring JE, Hennekens CH: Low-dose aspirin and incidence of colorectal tumors in a randomized trial. *J.Natl.Cancer Inst.* 1993;85:1220-1224.

53. Hixson LJ, Earnest DL, Fennerty MB, Sampliner RE: NSAID effect on sporadic colon polyps. *Am.J Gastroenterol.* 1993;88:1652-1656.

54. Ladenheim J, Garcia G, Titzer D, et al: Effect of sulindac on sporadic colonic polyps. *Gastroenterology* 1995;108:1083-1087.

55. Smalley WE, DuBois RN: Colorectal cancer and nonsteroidal anti-inflammatory drugs. *Adv.Pharmacol.* 1997;39:1-20.

56. Kawamori T, Rao CV, Seibert K, Reddy BS: Chemopreventive activity of celecoxib, a specific cyclooxygenase-2 inhibitor, against colon carcinogenesis. *Cancer Res.* 1998;58:409-412.

57. Tomozawa S, Nagawa H, Tsuno N, et al: Inhibition of haematogenous metastasis of colon cancer in mice by a selective COX-2 inhibitor, JTE-522. *Br.J.Cancer* 1999;81:1274-1279.

58. Reddy BS, Hirose Y, Lubet R, et al: Chemoprevention of colon cancer by specific cyclooxygenase-2 inhibitor, celecoxib, administered during different stages of carcinogenesis. *Cancer Res.2000.Jan 15;60(2):293.-7.* 60:293-297.

59. Steinbach G, Lynch PM, Phillips RK, et al: The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N.Engl.J.Med.2000.Jun 29;342(26):1946.-52.* 342:1946-1952.

60. World Health Organization. The International Classification of Diseases, 9th Revision, Clinical Modification. Washington, D. C., U.S. Department of Health and Human Services.

61. Cattaruzzi C, Troncon MG, Agostinis L, Garcia RL: Positive predictive value of ICD-9th codes for upper gastrointestinal bleeding and perforation in the

Sistema Informativo Sanitario Regionale database. *J.Clin.Epidemiol.* 1999;52:499-502.

62. Singh PN, Fraser GE: Dietary risk factors for colon cancer in a low-risk population. *Am J Epidemiol* 1998;148:761-774.

63. Kearney J, Giovannucci E, Rimm EB, et al: Diet, alcohol, and smoking and the occurrence of hyperplastic polyps of the colon and rectum. *Cancer Causes.Control.* 1995;6:45-56.

64. Allison PD: *Logistic Regression Using the SAS System: Theory and Application*. SAS Institute Inc.; 1999:217-231.

65. Flynn, M. J. Modeling Event Count Data with PROC GENMOD and the SAS System. 2001.

66. Stokes ME, Davis CS, Koch GG: *Categorical Data Analysis using The SAS System*. SAS Institute Inc.; 2001:349-361.

67. Drug Facts and Comparisons. Facts and Comparisons, July 2000. 2000.

68. Olivero JJ, Graham DY: Gastric adaptation to nonsteroidal anti-inflammatory drugs in man. *Scand.J.Gastroenterol.Suppl* 1992;193:53-58.

69. Graham DY, Smith JL, Spjut HJ, Torres E: Gastric adaptation. Studies in humans during continuous aspirin administration. *Gastroenterology* 1988;95:327-333.

70. Graham DY, Smith JL: Aspirin and the stomach. *Ann.Intern.Med.* 1986;104:390-398.

71. Graham DY, Smith JL, Dobbs SM: Gastric adaptation occurs with aspirin administration in man. *Dig.Dis.Sci.* 1983;28:1-6.

72. Delmas PD: Non-steroidal anti-inflammatory drugs and renal function. *Br.J.Rheumatol.* 1995;34 Suppl 1:25-28.