PASS information

Title	An Observational Study of Upper Gastrointestinal Tract (UGIT) Bleeding Events in Patients Taking Duloxetine and NSAIDs
Version identifier of the final study report	1.0
Date of last version of the final study report	26 June, 2013
EU PAS register number	N/A
Active substance	Duloxetine
Medicinal product	Cymbalta
Product reference	EU/1/04/296/001-009
Procedure number	EMEA/H/C/572
Marketing authorization holder(s)	Eli Lilly Nederland B.V. Grootslag 1-5 NL-3991 RA Houten The Netherlands
Joint PASS	No
Research question and objectives	• Primary objective: To examine whether concomitant use of duloxetine and prescription NSAIDs is associated with a synergistic effect on the risk of UGI bleeding • Secondary objective: To study the risk of UGI bleeding associated with duloxetine exposure without concomitant NSAIDs • Secondary objective: To characterize the severity of UGI bleeding cases across all study populations
Country(-ies) of study	USA
Author	Matthew F. Emons, MD MBA Senior Director, Physician Executive Cerner Research, Culver City, CA USA Phone: 310-598-4461 Hu Li, MBBS, PhD Global Patient Safety Epidemiologist

	Eli Lilly and Company 893 S Delaware Street Indianapolis, IN 46225 Telephone: +1 317 655 9951

Marketing authorization holder(s)

Marketing authorization holder(s)	Eli Lilly Nederland B.V. Grootslag 1-5 NL-3991 RA Houten The Netherlands
MAH contact person	Elizabeth Heaviside DPhil Global Regulatory Affairs, Europe Lilly UK Erl Wood Manor Windlesham, Surrey, GU20 6PH UNITED KINGDOM Phone: +44 (0)1276 483054 Fax: +44 (0)1276 483378

Table of Contents

1. Abstract

Title:
An Observational Study of UGIT Bleeding Events in Patients Taking Duloxetine and NSAIDs
Version Date: 27 June, 2013

Keywords:
Duloxetine, NSAIDs, UGI bleed, synergy

Rationale and background:
Several studies have examined the interaction of SSRI use with upper gastrointestinal (UGI) bleeding as well as the interaction between selective serotonin reuptake inhibitors (SSRIs) and non-steroidal anti-inflammatory drugs (NSAIDs) regarding the risk of UGI bleeding, with conflicting results. This study was designed to examine if there is a synergistic risk of UGI bleed associated with the concomitant use of the serotonin-norepinephrine reuptake inhibitor (SNRI) duloxetine and NSAIDs.

Research question and objectives:
1) To examine whether concomitant use of duloxetine and prescription (Rx) (NSAIDs) is associated with a synergistic effect on the risk of UGI bleeding
2) To study the risk of UGI bleeding associated with duloxetine exposure without concomitant NSAIDs
3) To characterize the severity of UGI bleeding cases across all study populations

Study design:
This study was a retrospective case-control analysis. The interaction between duloxetine and prescribed NSAIDs is described as the odds ratio (OR) for risk of UGI bleed where there is exposure to both duloxetine and prescription nonselective NSAIDs, COX-2 selective NSAIDs or prescription aspirin. Multivariable analysis using logistic regression provided adjusted OR and 95% confidence intervals (CIs). The primary endpoint of whether concomitant use of duloxetine and Rx NSAIDs is associated with a synergistic effect on the risk of UGI bleed was conducted with a relative excess risk due to interaction (RERI) calculation. The risk of UGI bleeding associated with duloxetine exposure was assessed via multivariable analysis, and the severity of UGI bleeding cases across all study populations was described. The interaction between duloxetine and prescription NSAIDs (nonselective NSAIDs, COX-2 selective NSAIDs, and prescription aspirin combined) as well as over the counter (OTC) NSAIDs was conducted as sensitivity analyses.

Setting:
Truven Health Analytics Marketscan data from 1 January, 2008 to 30 September, 2011 were used to define the index admissions of the study population. Encounters up to 12 months prior to each index admission were used identify exclusion criteria and comorbid conditions, and a 3-month window captured post-index events.

Subjects and study size:
The study consisted of adult patients with an inpatient admission with a length of stay > 24 hours during the intake period of 1 January, 2008 to 30 September, 2011, and ≥1 year of continuous eligibility pre- and 3 months post- their admission date. Patients were excluded based on esophageal varices, Mallory-Weiss syndrome, alcoholism, chronic liver disease, coagulopathies, pregnancy, malignant neoplasm and major organ transplant. Cases had hospitalization for either UGI hemorrhage or peptic ulcer disease, including perforation. After 1:10 case to control matching took place, 33,571 cases and 335,710 matched controls were divided into 8 mutually exclusive exposure subgroups.

Variables and data sources:
Baseline characteristics, comorbidities, prescription medication use, medication exposure characteristics, variables associated with the severity of upper GI bleed, and healthcare utilization were reported.

Results:
Patients had a mean age of 63 years and 55% were female. There was no evidence of a synergistic effect of concurrent duloxetine and prescription NSAID exposure on the risk of UGI bleed based on either logistic regression comparison of exposure groups (OR 1.18, 95% CI 0.34, 4.11) or RERI calculation (RERI 0.352, 95% CI 0.178, 0.724). None of the duloxetine exposure groups were associated with a statistically significant risk of UGI bleed event. The prescription NSAID exposure group was the only exposure group that was consistently demonstrated to have significantly higher risk of UGI bleed event in the model. The sensitivity analysis simulating OTC NSAID/aspirin exposure did not impact the results. Although these results are not consistent with some previously published studies, we conclude the findings support no impact on the benefit risk profile for duloxetine. Univariate analysis using multiple definitions showed no evidence that duloxetine exposure was associated with more severe UGI bleeds, including categorization by increasing duloxetine dose. This is consistent with our other analyses finding no evidence of significant UGI bleed risk associated with duloxetine. Some selection bias was evident based on the artificially lower OR for anticoagulation or antiplatelet exposure; on investigation, there was no evidence that this bias impacted the primary analysis.

Discussion:
The primary objective of the study was to assess the potential synergistic effect of duloxetine and NSAID exposure on UGI bleed risk. Our findings demonstrate no evidence of such an effect. A sensitivity analysis simulating exposure to OTC NSAIDs/ASA showed no impact on the risk of bleed for the exposure groups. Channeling bias was investigated and concluded to have no impact on the on the primary analysis. Exposure to increasing duloxetine doses was not associated with any measures consistent with severe UGI bleed. Our model also failed to confirm a statistically significant risk of UGI bleed with duloxetine exposure alone after adjusting for other factors. These results provide no evidence of the safety concerns that prompted this study.

2. List of Abbreviations

AD	Antidepressant
AE	Adverse event
APAP	Paracetamol
ASA	Acetylsalicylic acid (aspirin)
CCI	Charlson Comorbidity Index
CI	Confidence intervals
CKD	Chronic kidney disease
CL	Confidence limit
COPD	Chronic obstructive pulmonary disease
CPT	Current Procedural Terminology
CR	Controlled release
CV	Cardiovascular
DLX	Duloxetine
ER	Extended release
EU	European Union
GI	Gastrointestinal
HTN	Hypertension
ICD-9	International Classification of Diseases, Ninth Revision
ICD-9-CM Dx	International Classification of Diseases, Ninth Revision, Clinical Modification Diagnosis Codes
ICD-9 Px	International Classification of Diseases, Ninth Revision, Procedural Codes
IR	Immediate release
NSAID	Non-steroidal anti-inflammatory drug

OR	Odds ratio
OTC	Over-the-counter
RERI	Relative excess risk due to interaction
SD	Standard deviation
SNRI	Selective norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
THAM	Truven Health Analytics Marketscan
UGI	Upper gastrointestinal
US	United States
XR	Extended release

3. Investigator(s)

Sponsor	**Eli Lilly and Company**
Project Team	**Company Global Patient Safety Epidemiologist** Hu Li, MBBS, PhD Global Patient Safety Epidemiologist Eli Lilly and Company 893 S. Delaware Street Indianapolis, IN 46225 Telephone: +1 317 655 9951 **Company Global Medical Director:** Rodrigo Escobar, MD Senior Medical Director, Psychosis Team Eli Lilly and Company 893 S. Delaware Street Indianapolis, IN 46225 Phone: +1-317-655-9803 **Company Qualified Person for Pharmacovigilance:** Valerie Simmons, MB BS FFPM Eli Lilly and Company Erl Wood Manor Sunninghill Road Windlesham, Surrey GU20 6PH Phone: +44-1276-483320
Subcontractor:	Cerner Research, Culver City, CA USA
Principal Investigator/Study Site:	Matthew F. Emons, MD, MBA Senior Director, Physician Executive Cerner Research, Culver City, CA USA Phone: 310-598-4461

4. Other Responsible Parties

Other responsible parties	Not applicable. N/A

5. Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	01 March, 2013	3/21/2013	
End of data collection	01 March, 2013	3/21/2013	
Registration in the EU PAS register	N/A	N/A	
Final report of study results	15 June, 2013	11 June, 2013	

6. Rationale and Background

Several studies have been conducted to investigate the association of selective serotonin reuptake inhibitor (SSRI) use with upper gastrointestinal (UGI) bleeding as well as the interaction between SSRI and nonsteroidal anti-inflammatory drugs (NSAIDs) on the risk of UGI bleeding. Most of the epidemiologic evidence pointing to the risk of GI bleed with antidepressants (ADs) has demonstrated a higher risk associated with ADs according to their inhibitory action on the serotonin reuptake mechanism.[1-8] One possible mechanism of increased bleeding related to SSRI use is that therapeutic doses of SSRIs block the uptake of serotonin by platelets, which leads to depletion of serotonin from platelets, impaired platelet function, and inadequate hemostasis that may subsequently result in hemorrhage at the site of an injury of the UGI tract.

Duloxetine (Cymbalta, Arclaim, Xeristar, and Yentreve) is a serotonin-norepinephrine reuptake inhibitor (SNRI). It has been marketed in the United States and European Union since 2004. Currently, duloxetine is approved in the EU for major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathic pain and stress urinary incontinence (the latter under the trade name Yentreve). In the US, duloxetine has 5 indications: major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain. Consistent with a class effect also seen with SSRIs, bleeding events were reported more frequently by patients taking duloxetine versus placebo in clinical trials. The types of bleeding events observed were generally not serious (for example, epistaxis), and the risk of bleeding events did not appear to worsen when duloxetine was taken in combination with an NSAID.

The issue of a positive interaction between SSRIs and NSAIDs affecting the risk of UGI bleeding is a matter of controversy. Some studies have shown the existence of an interaction resulting in higher risk of UGI bleed in the presence of combined SSRI and NSAID use [9]. Differences in study design, data sources, study population, and study methods may account in part for the discrepancies in findings from different studies. Only a few studies collected information on over-the-counter (OTC) use of NSAIDs and investigated their impact on outcomes. This study was requested by the European Medical Agency and designed to examine if there is a synergistic risk of UGI bleed associated with the concomitant use of duloxetine and NSAIDs using claims data.

7. Study Objectives

- Primary objective: To examine whether concomitant use of duloxetine and prescription NSAIDs is associated with a synergistic effect on the risk of UGI bleeding
- Secondary objective: To study the risk of UGI bleeding associated with duloxetine exposure without concomitant NSAIDs
- Secondary objective: To characterize the severity of UGI bleeding cases across all study populations

8. Amendments and Updates

N/A

9. Research Methods

9.1 Study design

This study is a retrospective case-control analysis of the Truven Health Analytics Marketscan® (THAM) administrative claims databases including the Commercial Claims and Encounter and the Medicare Supplemental and Coordination of Benefits data. The interaction between duloxetine and prescribed NSAIDs is described as the OR for risk of upper GI bleed where there is exposure to both duloxetine and prescription nonselective NSAIDs, COX-2 selective NSAIDs or prescription aspirin. Multivariable analysis using logistic regression provided adjusted OR and 95% CIs. The primary endpoint of whether concomitant use of duloxetine and Rx NSAIDs is associated with a synergistic effect on the risk of UGI bleed was conducted with a relative excess risk due to interaction (RERI) calculation. The risk of UGI bleeding associated with duloxetine exposure was assessed via multivariable analysis, and the severity of UGI bleeding cases across all study populations was described. The interaction between duloxetine and prescription NSAIDs (nonselective NSAIDs, COX-2 selective NSAIDs, and prescription aspirin combined) as well as OTC NSAIDs was conducted as sensitivity analyses.

The case-control methodology was employed over a cohort analysis for several reasons. First, the study results are more easily comparable against a large number of existing case-control studies that have addressed a similar subject as this analysis. Further, the association of UGI bleed with medications based on current, rather than total, exposure lends itself to the case-control rather than a total exposure (cohort) methodology. Finally, estimating the probability of OTC NSAID utilization was more easily accomplished in the 30 days prior to the index event, rather than throughout the entire follow-up period.

9.2 Setting

This study is a retrospective analysis of the Truven Health Analytics Marketscan® (THAM) administrative claims databases. THAM is a unique and proprietary database that captures person-specific clinical utilization, expenditures, and enrollment across inpatients, outpatients and prescriptions from a selection of large employers, health plans, and government and public organizations in the US. The THAM databases link paid claims and encounter data to detailed patient information across sites and types of providers and over time. The annual medical databases include private sector health data from approximately 100 payers. Historically, more than 500 million claim records are available in the databases. These data represent the medical experience of insured employees and their dependents for active employees, early retirees, COBRA continuees and Medicare-eligible retirees with employer-provided Medicare Supplemental plans. The database complies with all aspects of the Health Insurance Portability and Accountability Act of 1996.

The Commercial Claims and Encounters Database include claims for active employees, early retirees, COBRA continuees, and their dependents insured by employer-sponsored plans (ie, non-Medicare eligibles). The Medicare Supplemental Database is a separate database created for Medicare-eligible retirees with employer-sponsored Medicare Supplemental plans. This database contains predominantly

fee-for-service plan data. The Medicare Database table structure is identical to the Commercial Claims and Encounters table structure. Both the Medicare-paid and the employer-paid supplemental insurance amounts are included in this database. The only plans selected for this database were those in which Medicare-paid amounts and employer-paid amounts were available and evident on the claims.

THAM data from 1 January, 2008-30 September, 2011 were used to define the index admissions of the study population. We included encounters up to 12 months prior to each index admission to identify exclusion criteria and comorbid conditions, and a 3-month window following the index date to capture inpatient length of stay and examine any acute post-index events.

9.3 Subjects

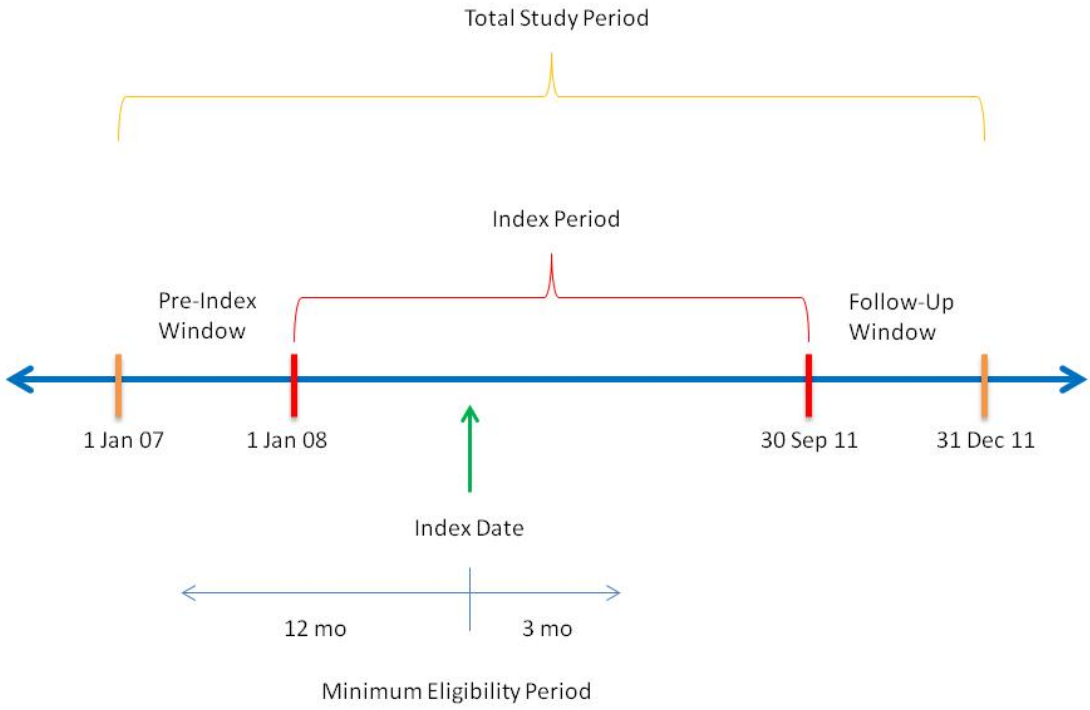
The initial study population consisted of all patients in THAM (Commercial Claims and Encounter and Medicare Supplemental) database from 1 January, 2007 to 31 December, 2011 with an inpatient admission with a length of stay >24 hours during the intake period of 1 January, 2008 to 30 September, 2011 who were ≥18 years of age at the time of admission, and who had at least 1 year of continuous eligibility prior to and 3 months after their admission date. The dataset was obtained from Truven Health Analytics with a number of exclusions already applied.

Patients were *excluded* from the dataset if they demonstrated any of the following during the study period (*note: see Appendix 2 for corresponding codes and definitions. Patients with these codes were excluded from the dataset by Truven prior to delivery)*:

- Esophageal varices
- Mallory-Weiss syndrome
- Alcoholism
- Chronic liver disease
- Coagulopathies
- Pregnancy
- Malignant neoplasm
- Major organ transplant

The date of the first inpatient encounter for UGI bleed within the index period was defined as the index date (Figure 1). For patients who had multiple occurrences of UGI bleed during the index period, only the first inpatient hospitalization for UGI bleed was included in the analysis.

Figure 1. Study time frame and minimum pre-index period requirement



9.3.1 Inclusion criteria for cases

Cases were identified through ICD-9 diagnosis and procedure codes as well as CPT codes as described in Wahl[10] and Abraham.[11] Patients were *included* as cases if there was evidence of hospitalization for UGI hemorrhage or peptic ulcer disease, including perforation (Appendix 3).

9.3.2 Selection of controls

Controls were randomly selected from the remaining study population based on age, gender and date of inpatient admission, allowing a +/- 30 day window when matching with cases. *Note, while the initial data analysis plan called for a +/- 90 day window to allow matching on date on inpatient admission, the large sample size enabled matching to take place within a smaller window.* Patients were *excluded* from being controls if they demonstrated blood in stool (ICD-9-CM Dx 578.1) or hemorrhage of gastrointestinal tract, unspecified (ICD-9-CM Dx 578.9).

Ten controls with an inpatient admission and an absence of ICD-9 diagnosis and procedure codes and CPT codes for UGI bleed (Appendix 3) during the intake period were selected for each case. The index date for controls was the date of the matched inpatient admission during the intake period.

9.3.3 Determination of study groups

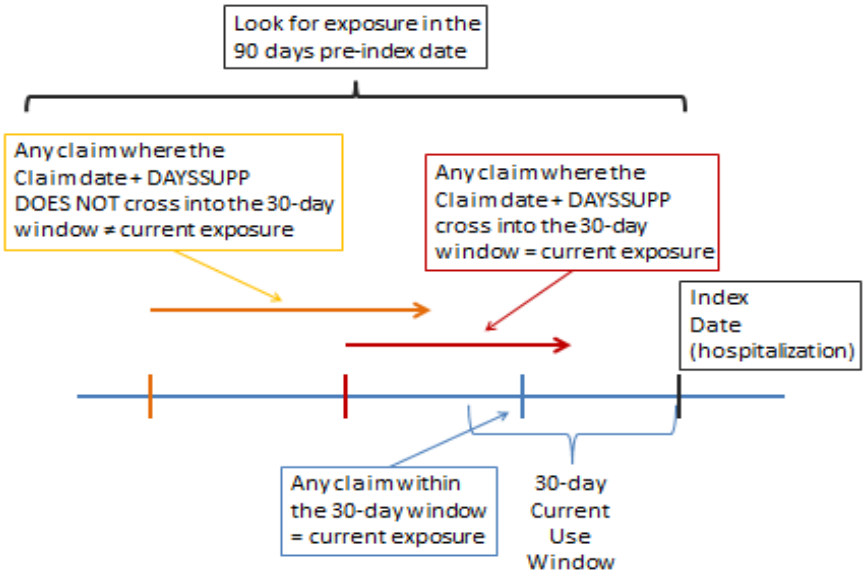
As non-selective NSAIDs, COX-2 inhibitors, and aspirin have different risk profiles for UGI bleeding events,[12,13] the study examined the interaction with duloxetine separately for prescription versions of each drug class in the analyses.

9.3.4 Current exposure

"Current exposure" was assessed for all medication classes of interest. If a patient had a claim for duloxetine, prescription non-selective NSAIDs, COX-2 selective NSAIDs, prescription aspirin, or SSRI and SNRI other than duloxetine (see definitions in **Appendix 4**) within 30 days before the index date, the patient was determined to have current exposure to that medication. If the claim occurred within 90 days prior to the index date and the days' supply associated with the claim extended into the 30-day period prior to the index date, "current exposure" was also assigned to that medication. No allowances for poor adherence to therapy were considered in determining current exposure (Figure 2).

Figure 2. Determination of "current exposure" to a medication

Note: DAYSSUPP indicates the supply of medication associated with the medication claim expressed in days.



Current exposure was determined separately for the 4 main drug classes of interest: duloxetine, non-selective NSAIDs, COX-2 selective NSAIDs, and prescription aspirin. **Error! Reference source not found.** shows the medications associated with each drug class.

Current exposure to SSRI and SNRI other than duloxetine was also identified, as these medications could act as potential drug exposure confounders to the primary study question (Appendix 4). Current exposure to these medications served as an exclusion for Groups 1-8; this exclusion criterion was applied to cases and controls after they had been assigned to Groups 1-8, pulling them out of those groups and reassigning them to Group 9.

Note: The National Drug Codes associated with each drug class listed in Appendix 4 were provided by Multum and Redbook and are listed in the embedded file in Annex 1.

9.3.5 Definition of study groups

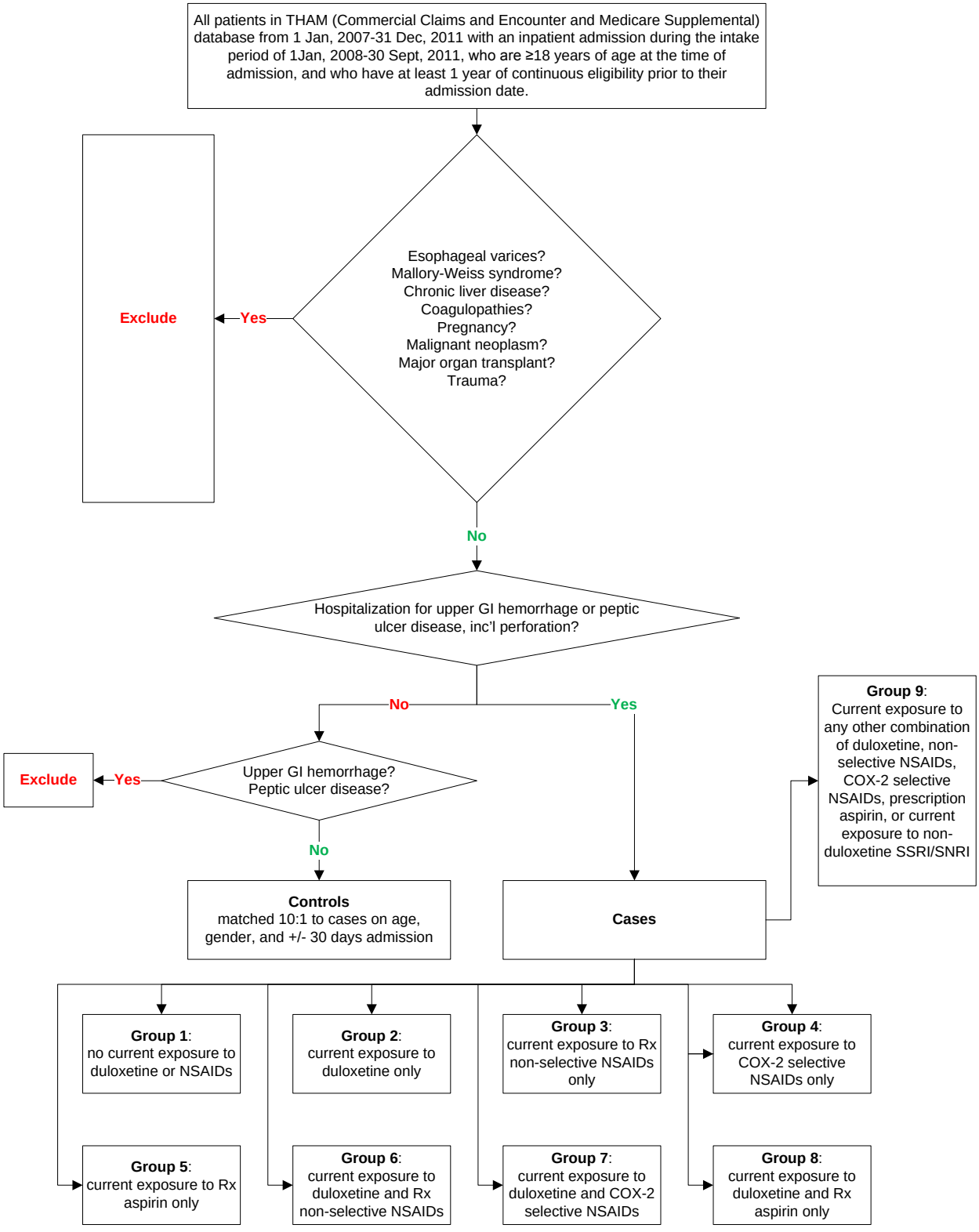
Following the identification of cases and matching of those cases to controls, patients were assigned to 1 of 9 study groups:

- **Group 1**: Patients with no current exposure to duloxetine, non-selective NSAIDs, COX-2 selective NSAIDs, prescription aspirin or SSRI and SNRI other than duloxetine
- **Group 2**: Patients with current exposure to duloxetine only
- **Group 3**: Patients with current exposure to prescription non-selective NSAIDs only

- **Group 4**: Patients with current exposure to COX-2 selective NSAIDs only
- **Group 5**: Patients with current exposure to prescription aspirin only
- **Group 6**: Patients with current exposure to duloxetine and prescription non-selective NSAIDs
- **Group 7**: Patients with current exposure to duloxetine and COX-2 selective NSAIDs only
- **Group 8**: Patients with current exposure to duloxetine and prescription aspirin only
- **Group 9**: Patients with current exposure to any other combination of duloxetine, non-selective NSAIDs, COX-2 selective NSAIDs, or prescription aspirin; or current exposure to SSRI and SNRI other than duloxetine. This group was included for purposes of classifying patient allocation in the attrition table, and was not carried forward for further analysis.

A flow diagram depicting the inclusion and exclusion criteria is presented in **Figure 3** below.

Figure 3. Study population and diagram of inclusion and exclusion criteria



9.4 Variables

Appendix 5 contains the codes and definitions used to derive the variables noted below.

A. Baseline characteristics

- Age (at index date)
- Gender
- Region
- Comorbidity burden (within 12 months pre-index): these include specific morbidities that are most relevant to the risk of UGI bleed as well as morbidities that may increase the severity of UGI bleed
- The Charlson Comorbidity Index (CCI) score
- Comorbidities
    - Hypertension (HTN)
    - Heart failure
    - Ischemic heart disease
    - Cerebrovascular disease
    - Dyslipidemia
    - Diabetes
    - Asthma
    - Chronic obstructive pulmonary disease (COPD)
    - Chronic kidney disease
    - Esophagitis
    - Peptic/UGI ulcer
    - Gastritis
    - Celiac disease
    - Major depressive disorder
    - Generalized anxiety disorder
    - Diabetic peripheral neuropathic pain
    - Fibromyalgia
    - Chronic musculoskeletal pain
    - Trauma
    - Heart disease indicator (used in the OTC NSAID model only)
- Prescription medications (current and use within 12 months pre-index, in non-mutually exclusive groups) including specific medications that are most relevant to the risk of UGI bleed
    - Anticoagulants
    - Antiplatelet agents
    - Glucocorticoids
    - Estrogens/progestin
    - H2 inhibitors
    - Proton pump inhibitors

B. Exposure characteristics

- Current exposure
- Duration of treatment (duloxetine only)
- Dose (duloxetine only)

C. Severity of UGI bleed (for cases only)

- Endoscopy procedure (yes/no, type)
- Upper GI surgical procedure (yes/no, type)
- Blood transfusion (yes/no)
- Length of inpatient stay
- Re-admission for UGI bleed within 30 days of initial discharge
- Death
- Other ancillary severity of bleed measures
    - Invasive procedure to control bleeding
    - Acute post-hemorrhagic anaemia
    - Other GI procedures suggestive of severity
    - Any ancillary severity of bleed indicator (any of the 3 ancillary severity measures listed above)

D. Healthcare utilization

- Number of inpatient visits
- Number of outpatient visits
- Number of emergency room visits
- Unique drug classes
- Total plan-paid cost

9.5 Data source and measurement

THAM is a data aggregation service that facilitates the collection of clinical and billing data to be used for research, analytic and comparative purposes. THAM does not require or extract any direct patient identifiers. Distribution of such patient identifiers is expressly prohibited by HIPAA de-identification requirements (US data anonymisation standards). The database complies with all aspects of the HIPAA 1996.

9.6 Bias

Following the assessment of our multivariable analysis results, we investigated the possibility that selection or channeling bias impacted the ORs seen in antiplatelet and anticoagulant exposure. Those investigations are described further in Section 10.4 below.

We concluded that the bias did not impact our primary endpoint.

9.7 Study size

9.7.1 Sample size considerations

Based on the following assumptions, we estimated the sample size required to detect the combined exposure duloxetine + prescription NSAID has a non-additive (synergistic) effect on UGI tract bleeding:

- Power = 80%
- Alpha = 0.05 (two-sided)
- 10 matched controls per case
- The probability of duloxetine exposure in the control group = 1.2%
- The correlation coefficient for exposure between matched cases and controls = 0.2
- An OR = 2.5 for GI Bleeding with duloxetine exposure only based on the table below

Reference	Bleed OR*, SSRI only
De Abajo 1999[2]	2.6
Dalton 2003[1]	3.6
Tata 2005*[6]	2.4
Lewis 2008[4]	2.0

**OR with no SSRI or NSAID as reference*

[¥]Observed to expected ratio

Estimating the sample size required to test an interaction term in a matched case control study is complex. The seminal work of Smith and Day[14] shows that the size of a study would have to be at least 4 times larger than the size determined to detect main effects of the same magnitude. Consequently, the sample size of main effects in a matched case-control study can be first determined and then quadrupled to ensure adequate power for inferences on the interaction term. In the table below, a sample size of at least 2,272 cases of UGI bleeding are required (under the original assumptions) to reject the null hypothesis. Estimated OR has a greater effect on the sample size estimate than the prevalence of duloxetine exposure in the control group or the correlation coefficient.

Probability of Duloxetine exposure in the Control Group	**Alpha**	**Power**	**Number of Controls per Case**	**Correlation Coefficient**	**Odds Ratio for GI Bleed in exposed subjects relative to unexposed subjects**	**Sample Size of Cases for the Main Effect**	**Estimated Minimum Sample Size (4x) for an Interaction**
.012	.05	0.8	10	0.2	2.0	**1,116**	**4,464**
.012	.05	0.8	10	0.2	2.5	**568**	**2,272**
.012	.05	0.8	10	0.2	3.0	**360**	**1,440**
.010	.05	0.8	10	0.2	2.0	**1,333**	**5,332**

Probability of Duloxetine exposure in the Control Group	Alpha	Power	Number of Controls per Case	Correlation Coefficient	Odds Ratio for GI Bleed in exposed subjects relative to unexposed subjects	Sample Size of Cases for the Main Effect	Estimated Minimum Sample Size (4x) for an Interaction
.010	.05	0.8	10	0.2	2.5	**678**	**2,712**
.010	.05	0.8	10	0.2	3.0	**429**	**1,716**
.012	.05	0.8	10	0.15	2.0	**1,064**	**4,256**
.012	.05	0.8	10	0.15	2.5	**537**	**2,148**
.012	.05	0.8	10	0.15	3.0	**337**	**1,348**
.010	.05	0.8	10	0.15	2.0	**1,272**	**5,088**
.010	.05	0.8	10	0.15	2.5	**641**	**2,564**
.010	.05	0.8	10	0.15	3.0	**402**	**1,608**

In the table above, the second row represents the original assumptions that were made. A sample size of at least 2,272 cases of UGI bleeding is required to reject the null hypothesis that the interaction effect is additive rather than synergistic. The other rows in the table show that the estimated OR has a greater effect on the sample size estimate than the prevalence of duloxetine exposure in the control group or the correlation coefficient.

9.7.2 Population size estimate

A preliminary evaluation of the THAM database demonstrated that there would be sufficient sample size to adequately power an estimate of the primary endpoint. A query of the THAM database for the period from 1 January, 2006 through 30 June, 2011 revealed that there were 67,396 patients with an inpatient encounter meeting the definition of UGI bleed utilizing the definition described in section 9.3.2. All eligible cases within the THAM database were employed in conducting the study.

9.8 Data transformations

Medication data were cleaned as follows:

Data cleaning rules for all categories of drugs

1) if DAYSSUPP <0 (negative number), switch to a positive number

Data cleaning for duloxetine

1) if DAYSSUPP and METQTY both = 0, set DAYSSUPP = 30

2) if METQTY >=1 and DAYSSUPP = 0, set DAYSSUPP = METQTY

3) if METQTY < 30 and DAYSSUP > METQTY, set METQTY = DAYSSUPP

4) if DAYSSUP < 30 and METQTY > DAYSSUP, set DAYSSUP = METQTY
5) if METQTY >=30 and <=100 and DAYSSUPP < METQTY/4, then set METQTY = DAYSSUP
6) if METQTY >270 and <2701, set METQTY to METQTY*0.1
7) if METQTY >2701, set METQTY to METQTY*0.01
Note: for duloxetine, "METQTY" must also be clean for the calculation of dose.

Data cleaning for Rx Aspirin
1) if DAYSSUPP and METQTY both = 0, set DAYSSUPP = 30
2) if METQTY >=1 and DAYSSUPP = 0, set DAYSSUPP = 0.5*METQTY
3) If MSTFMDS= balm, cream, crystal, elixir, emulsion, film, gel/jelly, granule, kit, liquid, lotion, oil, ointment, pad, patch, patient pack, powder, solution, spray, stick, suspension, remove
4) If GENNME= bismuth subsalicylate, meclocycline, physostigmine, thiosalicylate, remove

Data cleaning for non-selective NSAIDs
1) if DAYSSUPP and METQTY both = 0, set DAYSSUPP = 30
2) if METQTY >=1 and DAYSSUPP = 0, set DAYSSUPP = 0.5*METQTY
3) if METQTY >=120 and DAYSSUPP <30, then set DAYSSUPP = 30
4) if MSTFMDS= cream, crystal, gel/jelly/powder, kit, solution, remove

Data cleaning for COX-2 NSAID
1) if DAYSSUPP and METQTY both = 0, set DAYSSUPP = 30
2) if METQTY >=1 and DAYSSUPP = 0, set DAYSSUPP = METQTY

Data cleaning for SSRI and SNRI other than DLX
1) if DAYSSUPP and METQTY both = 0 or both = 1, set DAYSSUPP = 30
2) if METQTY >=1 and DAYSSUPP = 0, set DAYSSUPP = METQTY
3) if MSTFMDS=crystal or powder, remove

9.9 Statistical methods

9.9.1 Main summary measures

Continuous variables were summarized to report the mean, standard deviation, median, 25th percentile, and 75th percentiles for key values. Binary and categorical data were summarized with proportions or percentages.

For patient demographics and index encounter characteristics, cases and controls were compared separately for pre-match and post-match populations. For all descriptive results other than the severity of bleed assessment, post-match cases were compared to controls. For relevant continuous variables, we used Student's *t* test or Wilcoxon 2-sample test with the *P* value from the 2-sided *t* approximation. For comparisons of variables that were proportions, we used the Chi-square test. In the severity of bleed assessment, all cases were reported separately from 3 dosage tiers of duloxetine (<60 mg/day; 60 mg/day; and >60 mg/day). The 3 dose tiers were compared with a 3x2 Chi-square test, and a directional relationship test was conducted to assess the effects of dose escalation.

All comparisons were considered to be significant at alpha = 0.05.

9.9.2 Main statistical methods

First, we characterized the study population.

Based on current medication exposure, 8 mutually exclusive exposure groups, which consisted of 29,916 cases and 300,009 controls, were obtained from the preselected age/gender-matched cases (n=33,571) and controls (n=335,710).

Group Current Exposure

1. No current exposure to duloxetine, NSAIDs or prescription aspirin
2. Current exposure to duloxetine only
3. Current exposure to prescription non-selective NSAIDs only
4. Current exposure to COX-2 selective NSAIDs only
5. Current exposure to prescription aspirin only
6. Current exposure to duloxetine and prescription non-selective NSAIDs
7. Current exposure to duloxetine and COX-2 selective NSAIDs only
8. Current exposure to duloxetine and prescription aspirin only

<u>Primary analysis</u>

To fulfill the primary research objective, multivariable logistic regression (described below) was used to determine if there was a synergistic risk of UGI tract bleed associated with the concomitant use of duloxetine and prescription non-selective NSAIDs, COX-2 selective NSAIDs, or prescription aspirin. In addition, we calculated the relative risk for GI bleeding due to interaction (RERI) in a separate analysis.

Relative Excess Risk due to Interaction (RERI) calculation

We calculated the RERI of GI bleeding for patients who were concurrently taking duloxetine and NSAID with the approach proposed by Hosmer and Lemeshow.[15] However, the CI for RERI based on the Wald-type statistics using approximate variance estimators, as Hosmer and Lemeshow acknowledged, were not well studied and have some limitations.[16] We obtained the 95% CI through bootstrapping for a better coverage.[17]

Specifically, we took a subset of the analytical cohort consisting of patients taking Duloxetine only (medication exposure group 2), NSAID only (group 3), and Duloxetine plus NSAID (group 6). Then, we took a bootstrap sample of the same size with replacement, and obtained the adjusted OR estimates for the main effect by 1) exposure to Duloxetine, 2) exposure to NSAID, and 3) concurrent exposure to both Duloxetine and NSAID, also known as interaction effect. Covariates adjusted in these logistic regression models remained the same throughout the multivariable regression analysis.

For each bootstrapping sample, the RERI as proposed by Hosmer and Lemeshow is obtained from:

$$\text{RERI} = \exp(\beta_1 + \beta_2 + \beta_3) - \exp(\beta_1) - \exp(\beta_2) + 1$$

where β_1, β_2, β_3 represent the coefficients from the logistic regression model for the main effect of exposure to Duloxetine only (medication exposure group 2), NSAID only (group 3), and Duloxetine plus NASID (group 6), respectively. A total of 400 bootstrapping samples were used to obtain the 95% CI.

Secondary Endpoints

- We studied the risk of UGI bleeding associated with duloxetine exposure without concomitant NSAIDs via multivariable regression.

For the logistic regression, we assumed that the probability of a patient suffering UGI tract bleed from the 8 exposure groups follows a binomial (n, π) distribution. The logit of the probability (π), log $(\pi/(1-\pi))$, is a function of current medication exposure which can be modified by a number of significant covariates that may include sociodemographic, comorbid, previous drug therapeutics, and the availability and utilization of healthcare.

Based on descriptive and bivariate analysis, covariates considered in the multivariable logistic regression model included age, gender, region, baseline comorbidity, CCI, current and pre-index drug therapy, and healthcare unit utilization. Specific variables known to affect the risk of UGI bleed were retained, while model diagnostic and multicollinearity checks were applied in determining variables included in the final model.

Due to the relatively small number of cases for UGI tract bleed in some medication exposure groups and the large number of categorical predictors considered in the multivariable analysis, the Firth's penalized likelihood approach was used to construct the multivariable logistic regression model.[18]

Covariates to be adjusted in the final models were determined by the *P* value with Wald χ^2 tests to be less than 0.05 to remain in the models. Appropriate data transformation was applied on continuous covariate variables that severely deviated from a normal distribution. The final models report the adjusted OR and 95% confidence intervals (CI) for current medication exposure group with no current exposure to duloxetine or NSAIDs as the reference, along with those predictors that remain in the model.

With the exclusion of Group 9 (Patients with current exposure to any other combination of duloxetine, non-selective NSAID, COX-2 or prescription aspirin; or current exposure to SSRI and SNRI other than DLX), the balance in patient age and gender was altered in the analytic cohort from the original balance of the case-control match. One way to adjust for this imbalance was to include age and gender in the final model. This method was used in the primary analysis.

- We characterized the severity of upper GI bleeding cases across all study populations through descriptive and univariate analysis.

The variables used to define severity of UGI bleed are outlined under section 9.4.

9.9.3 Missing values

Only patients for whom complete data were available were included in the final analysis. Data cleaning methods used to address missing medication days' supply are described in Section 9.8. Prescription aspirin use was anticipated to under-capture actual ASA exposure since most ASA use is OTC. The same applies to NSAIDs. This was addressed through the sensitivity analysis that simulated OTC ASA/NSAID use. No imputation of missing data was required in the analysis. Ancillary UGI severity measures were added to address potential missing transfusion procedure codes due to the finite number of fields on most hospital billing forms (UB-04).

9.9.4 Sensitivity analyses

Given the anticipated low capture of prescription aspirin and an unknown volume of COX-2 selective NSAID use, we also conducted sensitivity analyses of combined exposure groups. Specifically, the 8 groups proposed in the primary analysis were condensed to 4, and all multivariable tests described above were also run on the following exposure groupings:

1. No current medication exposure
2. Duloxetine only
3. Prescription nonselective NSAIDs, COX-2 selective NSAIDs, aspirin
4. Duloxetine + prescription nonselective NSAIDs, COX-2 selective NSAIDs, aspirin

Once the results of the primary multivariable analysis were reviewed, we proposed an approach for the multivariable analysis wherein the estimated prevalence of OTC NSAID use by gender, age and cardiovascular (CV) disease status was considered in generating the ORs for the exposure categories.

The OTC NSAID regression was completed for both the original, 8-exposure group model as well as the collapsed, 4-group model described above.

Using information from published population surveys, point estimates for OTC aspirin and NSAID utilization were estimated using a) gender, b) age group, and c) CV disease status (Appendix 8).

To assign probabilistic OTC use, we first stratified all cases and controls into 12 gender × age group × CV disease status (2×3×2=12) strata. Within each stratum, OTC NSAID utilization (yes vs no) was assigned using a random number generator for each patient based on the prevalence rate of OTC utilization for the particular patient group (stratum). A logistic regression analysis was then conducted to generate the ORs of GI bleeding for the different exposure categories.

To reduce the potential bias in parameter estimates due to the randomness of assigning OTC NSAID utilization within each stratum, we replicated the process 400 times, each with a different random number generator such that, over all the replicates, each patient would have equal probability to be assigned as an OTC NSAID user or nonuser, and each have a different set of parameter estimates from the logistic regression model using the same set of predictor variables.

Adjusted OR estimates of GI bleeding for the different exposure categories, along with their descriptive statistics such as the mean, median, standard deviation, 25th and 75th percentiles, were summarized over all 400 replicates.

Note: as described above, with the exclusion of Group 9 (patients with current exposure to any other combination of duloxetine, non-selective NSAID, COX-2 or prescription aspirin; or current exposure to SSRI and SNRI other than duloxetine), the balance in patient age and gender was altered in the analytic cohort from the original balance of the case-control match. In the primary analysis, we adjusted for this by including age and gender in the final model. Another approach we considered was to reweight each subject in the control while excluding those controls whose matched cases were moved to group 9. Re-weighting the controls with the ratio of 10 / (number of matches) would balance the analytic cohort in age and gender, in which each case is seemingly matched with the same 1:10 ratio. This method was considered as a sensitivity analysis for the primary analysis described above, but was not conducted.

Number of Matches	Frequency	Percent	Cumulative Frequency	Cumulative Percent	Weight
	1	0.00	1	0.00	3.33
4	14	0.05	15	0.05	2.50
5	98	0.33	113	0.38	2.00
6	527	1.76	640	2.14	1.67
7	2,024	6.77	2,664	8.90	1.43
8	5,932	19.83	8,596	28.73	1.25
9	10,829	36.20	19,425	64.93	1.11
10	10,491	35.07	29,916	100.00	1.00

Finally, outside the a priori analysis plan, we conducted a post hoc sensitivity analysis to observe the effects of removing Group 9 (patients with current exposure to any other combination of duloxetine, non-selective NSAIDs, COX-2 selective NSAIDs, or prescription aspirin; or current exposure to SSRI and SNRI other than duloxetine) from the study population and planned analyses.

9.9.5 Amendments to the statistical analysis plan

Ancillary UGI bleed severity measures were added. Further statistical investigations were performed to assess bias, as referenced above in Section 9.6.

9.10 Quality Control

The Principal Investigator reviewed data for accuracy and completeness.

Data for this study were entered and stored in a validated database.

Cerner constructed an analytical data file for the study population meeting the study criteria. This analytical file included all variables in the data specifications contained in the Data Analysis Plan. The analytic files were quality checked independently by two Cerner scientists.

The electronic data were stored at Cerner on a networked computer that is password protected and is protected from access outside of the network by a firewall. Access to this computer and the data through the network requires a login account and a password for the network and also a separate login account and password to gain access to the computer containing the data. Access to the data was limited to Cerner Research project team members who need to work with those data for purposes outlined in this proposal. All Cerner research associates completed HIPAA and security training.

10. Results

In this section, we will provide an overview of the matched study population for the multivariable analysis including the univariate analysis, presenting clinical characteristics and outcomes, followed by the primary and secondary analyses results, sensitivity analysis and exploration of bias.

10.1 Participants

Out of 1,929,028 relevant encounters, we were able to match 99.9% of patients. The final study population consisted of 33,571 cases, which were matched to 335,710 controls (Table 1). Group 1, the reference group, encompassed the bulk of the study population, with more than 75% of both cases and controls having no current exposure to any medication of interest. The next most populous subgroup was patients with current exposure to prescription non-selective NSAIDs only, which was populated by 9.2% of cases and 7.5% of controls (Table 2).

Approximately 10% of cases and controls were found to show current exposure to a combination of duloxetine, non-selective NSAIDs, COX-2s, prescription or aspirin, or SSRI and SNRI other than DLX; these

patients were not included in further analysis. As previously discussed, cases and controls were assigned to the 8 classes of interest before the 'exclusion' for current exposure to SSRI and SNRI other than DLX was applied; any bias this might have produced in the study groups was controlled for in the multivariable analysis.

Table 1. Attrition table used to derive the unmatched cases and controls

	Relevant Patients	Excluded Patients
All patients in THAM (Commercial Claims and Encounter and Medicare Supplemental) database from 1/1/2007-12/31/2011 with an inpatient admission with a length of stay >24 hours during the intake period of 1/1/2008-9/30/2011 who are ≥18 years of age at the time of admission, and who have at least 1 year of continuous eligibility prior to and 3 months after their admission date.	1,929,028	
1. Exclusions applied as part of the data extract		
A. Esophageal varices		
B. Mallory-Weiss syndrome		
C. Alcoholism		
D. Chronic liver disease		
E. Coagulopathies		
F. Pregnancy		
G. Malignant neoplasm		
H. Major organ transplant		
2. Hospitalization for either UGI hemorrhage or peptic ulcer disease, including perforation.	33,620	1,895,408
A. Exclusions for blood in stool, hemorrhage of GI unspec (ICD-9 codes 578.1, 578.9) - controls only		1,847,834
3. Unmatched Cases and Controls	44	1,512,124
4. Matched Cases	33,571	
5. Matched Controls	335,710	

Table 2. Matched cases and controls exposure groups

Qualifying patients	Cases		Controls	
Group 1. Patients with no current exposure to duloxetine or non-specific NSAIDs or COX-2 or prescription aspirin or non-duloxetine SSRI/SNRI*	25,688	**76.52%**	262,627	**78.23%**
Group 2. Patients with current exposure to duloxetine only	320	**0.95%**	3,604	**1.07%**
Group 3. Patients with current exposure to prescription non-selective NSAIDs only	3,078	**9.17%**	25,224	**7.51%**
Group 4. Patients with current exposure to COX-2 selective NSAIDs only	508	**1.51%**	5,807	**1.73%**
Group 5. Patients with current exposure to prescription aspirin only	166	**0.49%**	1,475	**0.44%**
Group 6. Patients with current exposure to duloxetine and prescription non-selective NSAIDs only	119	**0.35%**	925	**0.28%**
Group 7. Patients with current exposure to duloxetine and COX-2 selective NSAIDs only	29	**0.09%**	280	**0.08%**
Group 8. Patients with current exposure to duloxetine and prescription aspirin only	8	**0.02%**	67	**0.02%**
Group 9. Patients with current exposure to any other combination of duloxetine, non-selective NSAID, COX-2 or prescription aspirin; or current exposure toSSRI and SNRI other than DLX. (Note: this group was included for attrition table purposes only and was not included in further analyses.)	3,655	**10.89%**	35,701	**10.63%**

*SSRI and SNRI other than DLX was also be an exclusion for Groups 2-8

10.2 Descriptive data

The univariate analysis of the age and gender matched study population reveals that the cases carried consistently more burden of comorbid illnesses compared to controls. However, this higher prevalence of comorbid diseases was not consistently associated with higher prior healthcare utilization or prescription drug use.

10.2.1 Demographics

Comparison of the pre-matched population (33,630 cases and 1,847,834 controls) to the post-match population (33,571 cases and 335,710 controls) show the strength of the match: the mean age for matched cases and controls was 63.1, with 42.1% of each group being ≥65 years of age (Table 3). Both pre-matched and matched populations were older and more likely (>50%) to be female (Table 3). This trend is likely indicative of the group that was hospitalized, rather than a bias in the dataset itself:

younger people tend not to be hospitalized, while older people do and are more likely to be hospitalized for UGI bleeds.

Patients were predominantly (<60% for both cases and cases and controls) from the North Central and South regions. No particular clinical significance is associated with this dispersal.

Table 3. Patient demographics and index encounter characteristics

	Pre-Match					*Post-Match*				
	Cases		**Controls**		**P-value**	**Cases**		**Controls**		**P-value**
	n = 33,620		**n = 1,847,834**			**33,571**		**335,710**		
Continuous Variables										
Age at index date (continuous), years										
N	33,620		1,847,834			33,571		335,710		
Mean	63.09		57.29		<0.0001	63.06		63.06		1.0000
SD	17.25		17.28			17.23		17.23		
25th percentile	52.00		46.00			52.00		52.00		
Median	62.00		57.00			62.00		62.00		
75th percentile	78.00		69.00			78.00		78.00		
Categorical Variables										
	#	**%**	**#**	**%**		**#**	**%**	**#**	**%**	
Age at index admission (categorical), years										
18-34	1,864	5.5%	171,429	9.3%		1,862	5.6%	18,620	5.6%	1.0000
35-44	2,867	8.5%	243,354	13.2%		2,865	8.5%	28,650	8.5%	
45-54	5,623	16.7%	395,541	21.4%	<0.0001	5,621	16.7%	56,210	16.7%	
55-64	9,087	27.0%	502,801	27.2%		9,083	27.1%	90,830	27.1%	
≥65	14,179	42.2%	534,709	28.9%		14,140	42.1%	141,400	42.1%	
Unknown/missing										
Gender										
Male	15,183	45.2%	771,212	41.7%	<0.0001	15,153	45.1%	151,530	45.1%	1.0000
Female	18,437	54.8%	1,076,562	58.3%		18,418	54.9%	184,180	54.9%	
Unknown										
Region										
Northeast	4,855	14.4%	278,229	15.1%		4,849	14.4%	47,397	14.1%	<0.0001
North Central	10,856	32.3%	543,289	29.4%		10,846	32.3%	107,613	32.1%	
South	12,176	36.2%	705,397	38.2%	<0.0001	12,163	36.2%	125,057	37.3%	
West	5,198	15.5%	291,236	15.8%		5,189	15.5%	51,728	15.4%	
Unknown/not mapped	535	1.6%	29,683	1.6%		524	1.6%	3,915	1.2%	

10.2.2 Comorbidities

Comorbidities were assessed for the 12-month pre-index period, including the index date (Table 4). The difference in CCI between cases and controls was clinically significant, with mean CCI higher in cases (1.8 vs 0.9, P<0.0001). Differences were seen when looking at the distribution of CCI by category: 22.9% of cases had a CCI of 2 vs 12.3% of the control group. These differences were significant: P<0.0001.

All comorbid conditions were found to be significantly more common (P<0.0001) in the case population. Most clinically significant were hypertension (43.1% vs 23.5%), ischemic heart disease (19.8% vs 10.4%), dyslipidemia (21.2% vs 12.8%), and diabetes (18.4% vs 11.0%). Unsurprisingly, comorbidities related to the GI conditions were also much higher in cases vs controls, including esophagitis (9.3% vs 1.1%), peptic/UGI ulcer (61.3% vs 0.3%), gastritis (27.5% vs 2.2%), and celiac disease (0.2% vs 0.1%).

Table 4. Comorbidities

	Cases		Controls		P-value
	N	%	N	%	
Continuous variables					
Comorbidity indices					
Charlson Comorbidity Index (CCI) (continuous), score*					
N	33,571		335,710		
Mean	1.81		0.91		<0.0001
SD	1.44		1.3		
25th percentile	1		0		
Median	1		0		
75th percentile	2		1		
Categorical variables					
CCI (categorical), score*					
0	4,196	12.50%	175,941	52.41%	<0.0001
1	13,501	40.22%	81,508	24.28%	
2	7,676	22.86%	41,313	12.31%	
3	4,215	12.56%	19,100	5.69%	
4-6	3,651	10.88%	16,465	4.90%	
7-9	325	0.97%	1,337	0.40%	
≥10	7	0.02%	46	0.01%	
Unknown/missing					
Comorbidities					
Hypertension	14,479	43.13%	78,911	23.51%	<0.0001
Heart failure	2,942	8.76%	16,637	4.96%	<0.0001

Ischemic heart disease	6,651	19.81%	35,061	10.44%	<0.0001
Cerebrovascular disease	3,569	10.63%	23,753	7.08%	<0.0001
Dyslipidemia	7,100	21.15%	42,933	12.79%	<0.0001
Diabetes	6,170	18.38%	36,783	10.96%	<0.0001
Asthma	1,625	4.84%	8,979	2.67%	<0.0001
COPD	2,308	6.87%	14,936	4.45%	<0.0001
Chronic kidney disease	2,137	6.37%	10,206	3.04%	<0.0001
Esophagitis	3,108	9.26%	3,688	1.10%	<0.0001
Peptic/UGI ulcer	20,581	61.31%	1,071	0.32%	<0.0001
Gastritis	9,235	27.51%	7,533	2.24%	<0.0001
Celiac disease	61	0.18%	169	0.05%	<0.0001
Major depressive disorder	2,101	6.26%	9,595	2.86%	<0.0001
Generalized anxiety disorder	1,534	4.57%	7,391	2.20%	<0.0001
Diabetic peripheral neuropathic pain	591	1.76%	2,850	0.85%	<0.0001
Fibromyalgia	498	1.48%	2,973	0.89%	<0.0001
Chronic musculoskeletal pain	8,098	24.12%	73,350	21.85%	<0.0001
Trauma	960	2.86%	6,367	1.90%	<0.0001
Heart disease indicator					
CV disease	10,081	30.03%	57,909	17.25%	<0.0001

10.2.3 Treatment history

The current rate of anticoagulants was twice as high in controls as in cases (5.3% in cases vs 10.6% in controls, P<0.0001). Current uses of antiplatelet agents and glucocorticoids were also higher in the control population, though the difference between cases and controls was <2% in each case. Far more cases than controls showed current use of proton pump inhibitors (42.4% vs 13.5%, P<0.0001); this could perhaps be explained by the elevated rate of GI comorbidities seen in the case population.

Non-current, 12-month pre-index drug therapy was calculated in terms of total days' supply dispensed in the 12-month period for patients without current drug therapy. Mean days' supply was higher in cases for coagulants (224.5 vs 205.2, P = 0.0041), antiplatelet agents (265.6 vs 247.3, P = 0.0018), glucocorticoids (65.5 vs 56.4, P = 0.0028), and H2 inhibitors (163.0 vs 136.6, P = 0.0034). Non-current use of proton pump inhibitors was higher in the control population, but not clinically significantly so. The numbers of patients using H2 and proton pump inhibitors in the 12-month pre-index period was approximately 1/3 of the numbers of patients showing current use of those medication classes, indicating a steep rise in their use before inpatient hospitalization.

Table 5. Treatment history

	Cases		Controls		P-value
	N	%	N	%	
Current Drug Therapy (claim within 30 days of index date, not incl index date)					
Anticoagulants	1,779	5.30%	35,487	10.57%	<0.0001
Antiplatelet agents	2,558	7.62%	28,612	8.52%	<0.0001
Glucocorticoids	2,920	8.70%	33,887	10.09%	<0.0001
Estrogens/progestin	978	2.91%	12,600	3.75%	<0.0001
H2 inhibitors	876	2.61%	6,662	1.98%	<0.0001
Proton pump inhibitors	14,228	42.38%	45,388	13.52%	<0.0001
12-month Pre-index Drug Therapy (calculated only for those patients without Current Drug Therapy)					
Anticoagulants					
N	269		4519		
Mean	224.52		205.2		0.0041
SD	160.93		152.4		
25th percentile	90		60		
Median	210		180		
75th percentile	348		300		
Antiplatelet agents					
N	517		6048		
Mean	265.63		247.26		0.0018
SD	120.71		129.04		
25th percentile	180		120		
Median	270		270		
75th percentile	360		360		
Glucocorticoids					
N	1097		19390		
Mean	65.46		56.44		0.0028
SD	99.13		97.15		
25th percentile	6		6		
Median	18		12		
75th percentile	90		54		
Estrogens/progestin					
N	285		5538		
Mean	179.85		171.84		0.3581
SD	135.88		143.93		
25th percentile	60		38		
Median	150		120		
75th percentile	270		270		
H2 inhibitors					
N	199		2473		
Mean	162.96		136.56		0.0034
SD	127.2		121.73		

25th percentile	30	30	
Median	120	90	
75th percentile	270	210	
Proton pump inhibitors			
N	1489	16378	
Mean	186.5	193.75	0.0498
SD	137.19	136.45	
25th percentile	60	60	
Median	180	180	
75th percentile	284	330	

10.2.4 Exposure characteristics

More than 75% of both cases and controls had no current exposure to any medication. A total of 320 (0.95%) of cases and 3,604 (1.07%) of controls used duloxetine only. Within this population, approximately 27% of both cases and controls utilized a <60 mg/d dose, just under 60% (58.8% of cases and 56.6% of controls) utilized a 60 mg/d dose, and approximately 15% of each population received a dose of >60 mg/d. The differences seen in cases and controls were not statistically significant (P = 0.7559).

In those patients without current exposure to medication, the numbers of patients with exposure to the 4 main classes of interest were approximately the same as those with current exposure, though the exposure period was by definition much longer.

Table 6a. Exposure characteristics—current exposure

Patient count	**Cases**		**Controls**		**P-value**
	N	**%**	**N**	**%**	
Current Exposure					
No current exposure	25,688	76.52%	262,627	78.23%	<0.001
Duloxetine only	320	0.95%	3,604	1.07%	0.0403
Non-selective NSAIDs only	3,078	9.17%	25,224	7.51%	<0.001
COX-2 selective NSAIDs only	508	1.51%	5,807	1.73%	0.0035
Rx aspirin only	166	0.49%	1,475	0.44%	0.1478
Duloxetine + Non-selective NSAIDs	119	0.35%	925	0.28%	0.0094
Duloxetine + COX-2 selective NSAIDs	29	0.09%	280	0.08%	0.8572
Duloxetine + Rx aspirin	8	0.02%	67	0.02%	0.635
Any other exposure combination*	3,655	10.89%	35,701	10.63%	0.1522
Current Exposure					
Duloxetine <60 mg/d	86	26.88%	1008	27.97%	0.7559
Duloxetine 60 mg/d	188	58.75%	2041	56.63%	
Duloxetine >60 mg/d	46	14.38%	555	15.40%	

*These patients were used to populate Group 9 and excluded from further analysis

Table 6b. Exposure characteristics—non-current exposure

Days' supply per patient with exposure	Cases	Controls	P-value
Exposure History, 12 months Pre-index (calculated only for those patients without Current Exposure)			
Duloxetine			
N	455	4104	
Mean	171.96	167.49	0.4403
SD	116.13	117.23	
25th percentile	60	60	
Median	174	150	
75th percentile	270	270	
Non-selective NSAIDs			
N	3736	39654	
Mean	81.28	70.89	<0.0001
SD	95.57	85.76	
25th percentile	16	15	
Median	30	30	
75th percentile	109.5	90	
COX-2 selective NSAIDs			
N	723	7727	
Mean	151.04	138.3	0.0034
SD	112.64	111.56	
25th percentile	40	30	
Median	120	90	
75th percentile	263	240	
Prescription aspirin			
N	256	2362	
Mean	123.26	116.24	0.3632
SD	125.29	116.36	
25th percentile	14	20	
Median	65.5	65	
75th percentile	240	200	

10.3 Outcome data

10.3.1 Healthcare utilization

Controls had slightly more inpatient and outpatient visits in the 12-month pre-index period (0.78 vs 0.42 mean inpatient visits in controls vs cases, P<0.0001; and 14.4 vs 13.7 mean outpatient visits, P<0.0001). Controls also demonstrated a higher number of unique drug classes (11.5 vs 11.3 classes in controls vs cases, P<0.0001) and total plan-paid cost (mean $10,666.77 vs $9,090.76, P<0.0001). There is no clear clinical explanation as to why one group would have slightly higher utilization.

Cases did show significantly higher visits to the emergency department, with a mean number of visits per patient of 0.45, versus 0.38 mean visits per patient in controls (P<0.0001).

Table 7. Healthcare utilization. *Note: all results are presented for the 12-month pre-index period.*

	Cases		Controls		P-value
	N	%	N	%	
	33,571		335,710		
Number of inpatient visits					
N (pts with visit; total visits)	33,571(1,963; 14,202)		335,710(40,665; 261,837)		
Mean	0.42		0.78		<0.0001
SD	3.28		3.93		
25th percentile	0		0		
Median	0		0		
75th percentile	0		0		
Number of outpatient visits					
N (pts with visit; total visits)	33,571(31,662; 45,913)		335,710(318,635; 4,844,859)		
Mean	13.68		14.43		<0.0001
SD	15.1		14.86		
25th percentile	4		5		
Median	10		11		
75th percentile	18		19		
Number of emergency room visits					
N (pts with visit, total visits)	33,571(8,718; 15140)		335,710(76,812; 126,198)		
Mean	0.45		0.38		<0.0001
SD	1.13		1		
25th percentile	0		0		
Median	0		0		
75th percentile	1		0		

Unique drug classes			
N	33,571	335,710	
Mean	11.33	11.47	<0.0001
SD	11.74	11.27	
25th percentile	0	1	
Median	9	9	
75th percentile	18	18	
Total Plan-Paid Cost ($)			
N	33,571	335,710	
Mean	9,090.76	10,666.77	<0.0001
SD	18,552.63	23,674.32	
25th percentile	1,778.25	2,000.45	
Median	4,744.62	5,178.52	
75th percentile	10,047.7	11,234.72	

10.4 Main results

Primary objective: to examine whether concomitant use of duloxetine and prescription NSAIDs is associated with a synergistic effect on the risk of UGI bleeding.

Logistic regression analysis was used to examine the potential synergistic effect of duloxetine with NSAIDs. This comparison analysis was not supportive of synergy, as the effect for the combined exposure group was not significantly different than the effect of the singular exposure groups combined.

Contrast	Odds Ratio	Lower 95% CI	Upper 95% CI
8 exposure groups adjusted			
GRP6 vs GRP2+GRP3*	1.1844	0.3409	4.1148
4 exposure groups adjusted			
GRP4 vs GRP2¥	1.0283	0.9409	1.1239

*GRP6 vs GRP2+GRP3 = [duloxetine + Rx NSAIDs] vs [(duloxetine only) + (Rx NSAIDs only)]
¥GRP 4 vs GRP2 = [duloxetine + Rx NSAIDs, COX-2, ASA] vs [duloxetine only]

We also did a relative excess risk due to interaction (RERI) calculation.

In the RERI calculation, we focused on 3 groups: duloxetine only, prescription NSAIDs only, and duloxetine + prescription NSAIDs. These 3 groups were utilized to determine the synergistic effect of the 2 medications. Bootstrapping, with a random sample run 400 times, was used to determine the variation around the RERI estimate.

The RERI calculation is consistent with the logistic regression analysis in demonstrating no evidence of an excess risk due to concurrent drug exposure to duloxetine and prescription NSAIDs.

The Relative Excess Risk due to Interaction and confidence intervals with 400 bootstrapping samples:

RERI	RERI	SD	95% lower CI	95% upper CI
Adjusted	0.352	0.259	-0.178	0.724
Unadjusted	0.347	0.139	0.073	0.620

Secondary objective: To study the risk of UGI bleeding associated with duloxetine exposure without concomitant NSAIDs

Logistic regression was used to investigate the impact of the study exposure groups on the risk of UGI bleeding. The outputs of the unadjusted and adjusted models follow.

Notes: Age and gender were included in all models to adjust for any residual confounding, but should not be used in interpreting risk of bleed. See Appendix 9 for non-medication exposure inputs into the adjusted models and sensitivity analyses. All exposure groups in the following tables are compared to Group 1, the reference group containing no current exposure.

Table 8 shows the point estimates for the 8 groups, unadjusted by covariate.

8 exposure groups, unadjusted	Cases		Controls		Unadjusted OR	Lower 95% CI	Upper 95% CI
	N	%	N	%			
1. No current exposure	25,688	76.52%	262,627	78.23%	1.0	n/a	n/a
2. Duloxetine only	320	0.95%	3,604	1.07%	0.909	0.81	1.02
3. Rx non-selective NSAIDs	3,078	9.17%	25,224	7.51%	1.248	1.199	1.298
4. COX-2 selective NSAIDs only	508	1.51%	5,807	1.73%	0.895	0.817	0.981
5. Rx aspirin only	166	0.49%	1,475	0.44%	1.154	0.982	1.355
6. Duloxetine + Rx non-selective NSAIDs	119	0.35%	925	0.28%	1.320	1.091	1.598
7. Duloxetine + COX-2 selective NSAIDs	29	0.09%	280	0.08%	1.075	0.735	1.573
8. Duloxetine + Rx aspirin	8	0.02%	67	0.02%	1.287	0.628	2.64

Table 9 shows the model output for the original 8 exposure groups, adjusted.

- As expected, prescription NSAID exposure (group 3) was significantly associated with a higher risk of UGI bleed.

- Group 4 (COX-2 exposure) and Group 5 (prescription aspirin) had marginally elevated ORs but failed to reach significance at the 5% level.
- Similarly, duloxetine + prescription NSAIDs exposure, despite a mildly elevated OR, failed to reach statistical significance.
- The wide confidence intervals for Groups 5, 7 and 8 are a reflection of the smaller sample sizes and were the rationale behind collapsing the original 8 groups into 4 groups.

See Table A in Appendix 9 for values associated with the following summary

- CCI and all comorbidities listed showed a significant association with UGI bleed risk.
    - The GI comorbidities, in general, would be expected to carry a high risk as some can themselves be associated with UGI bleed.
    - The extreme OR for peptic ulcer disease can be attributed in part as an artifact of the UGI event data specifications.
- The decreased risk seen with anticoagulants or antiplatelet exposure is felt to be an artifact due to selection bias and is discussed in Section 9.6.
- A minimal decreased risk was observed with higher prior utilization, but not felt to be clinically meaningful.

8 exposure groups, adjusted	Cases		Controls		Adjusted OR	Lower 95% CI	Upper 95% CI
	N	%	N	%			
1. No current exposure	25,688	76.52%	262,627	78.23%	1.000	n/a	n/a
2. Duloxetine only	320	0.95%	3,604	1.07%	1.056	0.891	1.252
3. Rx non-selective NSAIDs	3,078	9.17%	25,224	7.51%	1.15	1.075	1.231
4. COX-2 selective NSAIDs only	508	1.51%	5,807	1.73%	1.053	0.918	1.208
5. Rx aspirin only	166	0.49%	1,475	0.44%	1.021	0.794	1.313
6. Duloxetine + Rx non-selective NSAIDs	119	0.35%	925	0.28%	1.26	0.928	1.711
7. Duloxetine + COX-2 selective NSAIDs	29	0.09%	280	0.08%	1.011	0.544	1.879
8. Duloxetine + Rx aspirin	8	0.02%	67	0.02%	1.568	0.544	4.518

Note: Adjusted for gender, age, CCI, COPD, asthma, HTN, ischemic heart disease, heart failure, diabetes, CKD, gastritis, celiac disease, depression, peptic/UGI ulcer, esophagitis, diabetic peripheral neuropathic pain, chronic musculoskeletal pain, trauma, H2+ proton pump inhibitors, #inpatient visits, #outpatient visits, #unique prescriptions

Secondary Objective: To characterize the severity of UGI bleeding cases across all study populations

Among the original severity of UGI bleed variables in the descriptive analysis, lower percentages of duloxetine patients met the definitions for endoscopy procedure, UGI surgical procedure or blood transfusion compared to cases, though this did not reach statistical significance. No dose effect was noted based on the defined duloxetine dose threshold of 60 mg and there is no evidence that increasing doses of duloxetine are associated with any of the severity of UGI bleed measures tested. Mean length of stay for survivors, which was 4.4 days for cases, was not significantly different in the duloxetine dose groups. Unadjusted in-hospital mortality for index admission was <1% for cases and was ≤0.5% in the duloxetine dose groups. Unadjusted "30-day readmission rates for UGI bleed" were higher in the duloxetine dose groups than all cases (49.5% in the 60-mg group), though totals were low and statistical significance was not reached across the dose groups. These readmissions cannot be accurately attributed to bleeds, however, since the definition includes UGI bleed and peptic ulcer disease with or without perforation.

Ancillary severity measures were calculated for additional insight. It was suspected that transfusions were incompletely captured in the claims data. Similar patterns were seen with lower portions of duloxetine patients meeting criteria for invasive procedures to control UGI hemorrhage, post hemorrhagic anemia, or other GI procedures suggestive of severity.

The severity measures demonstrated among all cases did not significantly differ by dose of duloxetine prescribed.

Table 10. Severity of UGI bleed. *Note: The dosage results are presented for all cases, followed by dosages in Group 2: current exposure to duloxetine only*

	All Cases		Duloxetine <60 mg/day		Duloxetine 60 mg/day		Duloxetine >60 mg/day		P-value (3x2 chi2)	Directional relationship test
	N	%	N	%	N	%	N	%		
	33,571		86		188		46			
Endoscopy procedure (y)	3,343	9.96%	6	6.98%	13	6.91%	1	2.17%	0.4668	0.3594
Upper GI surgical procedure (y)	18,257	54.38%	36	41.68%	93	49.47%	25	54.35%	0.3327	0.1429
Blood transfusion (y)	4,962	14.78%	6	6.98%	23	12.23%	6	13.04	0.3831	0.2136
Length of stay, days--total population										
N	33,571		86		188		46			
Mean	4.46		4.38		3.95		3.26		0.3145	0.4525
SD	5.59		5.73		3.41		2.14			
25th percentile	2		2		2		2			
Median	3		3		3		3			
75th percentile	5		5		5		5			
Length of stay, days--survivors										
N	33,246		86		188		46			
Mean	4.4		4.38		3.95		3.26		0.3145	0.4525
SD	5.4		5.73		3.41		2.14			
25th percentile	2		2		2		2			
Median	3		3		3		3			
75th percentile	5		5		5		5			
Readmission for UGI bleed within 30 days of discharge (y) *Note: calculated for survivors only*	1,295	3.90%	36	41.86%	93	49.47%	25	54.35%	0.3327	0.2136
Death - index admission only	325	0.97%	0	0.00%	0	0.00%	0	0.00%	n/a	n/a
Other ancillary severity of bleed measures										
Invasive procedure to control bleeding:	3,239	9.65%	6	6.98%	10	5.32%	1	2.17%	0.503	0.2553
Acute post-hemorrhagic anemia	6,915	20.60%	9	10.47%	21	11.17%	9	19.75%	0.2516	0.1861
Other GI procedures suggestive of severity	144	0.43%	0	0.00%	0	0.00%	0	0.00%		
Any ancillary severity of bleed indicator	8,637	25.73%	13	15.12%	25	13.30%	9	19.57%	0.5555	0.6383

Sensitivity Analyses

Table 11 shows the sensitivity analysis of 4 collapsed exposure groups, unadjusted by covariate:

4 exposure groups, unadjusted	Cases		Controls		Unadjusted OR	Lower 95% CI	Upper 95% CI
	N	%	N	%			
Group 1. No current exposure	25,688	76.52%	262,627	78.23%	1.000	n/a	n/a
Group 2. Duloxetine only	320	0.95%	3,604	1.07%	0.909	0.810	1.020
Group 3. Rx non-selective NSAIDs, COX-2 and Aspirin	3,752	11.18%	32,506	9.68%	1.180	1.138	1.224
Group 4. Duloxetine and Rx non-selective NSAIDs, COX-2 and Aspirin	156	0.46%	1,272	0.38%	1.258	1.065	1.485

Table 12 shows the output for the 8 original groups collapsed into 4, adjusted by covariates:

- In the collapsed exposure groups, the statistically significant association with Group 3 persisted, but neither the duloxetine nor the duloxetine + NSAID/ASA groups had a statistically significant association at the 5% level.
- There were no meaningful changes in the other risk factors (seen in Table B, in Appendix 9).

4 exposure groups, adjusted	Cases		Controls		Adjusted OR	Lower 95% CI	Upper 95% CI
	N	%	N	%			
Group 1. No current exposure	25,688	76.52%	262,627	78.23%	1.000	n/a	n/a
Group 2. Duloxetine only	320	0.95%	3,604	1.07%	1.056	0.891	1.252
Group 3. Rx non-selective NSAIDs, COX-2 and Aspirin	3,752	11.18%	32,506	9.68%	1.126	1.059	1.197
Group 4. Duloxetine and Rx non-selective NSAIDs, COX-2 and Aspirin	156	0.46%	1,272	0.38%	1.208	0.924	1.578

Note: Adjusted for gender, age, CCI, COPD, asthma, HTN, ischemic heart disease, heart failure, diabetes, CKD, gastritis, celiac disease, depression, peptic/UGI ulcer, esophagitis, diabetic peripheral neuropathic pain, chronic musculoskeletal pain, trauma, H2+ proton pump inhibitors, #inpatient visits, #outpatient visits, #unique prescriptions

- **Table 13** displays the sensitivity analysis of the original 8 exposure groups, adjusted by covariate, and **including OTC exposure estimates.** With OTC exposure estimates added to the model and run over 400 observations of patients regrouped based on their OTC exposure assignment, no changes were seen in the exposure groups with respect to UGI bleed risk. The prescription NSAID group remained as the only exposure group with a statistically significant risk of an UGI bleed event.

8 exposure groups, adjusted, with OTC NSAID estimate	Cases		Controls		Adjusted OR	5th percentile	95th percentile
	N	%	N	%			
Group 1. No current exposure	11,450	0.341	125,040	0.372	1.000	n/a	n/a
Group 2. Duloxetine only	143	0.004	1,700	0.005	1.141	0.966	1.323
Group 3. Rx non-selective NSAIDs	17,730	0.528	166,904	0.497	1.046	1.013	1.078
Group 4. COX-2 selective NSAIDs only	201	0.006	2,618	0.008	0.988	0.863	1.134
Group 5. Rx aspirin only	59	0.002	571	0.002	0.993	0.709	1.289
Group 6. Duloxetine + Rx non-selective NSAIDs	319	0.010	3,025	0.009	1.085	0.993	1.171
Group 7. Duloxetine + COX-2 selective NSAIDs	12	0.000	128	0.000	0.914	0.385	1.546
Group 8. Duloxetine + Rx aspirin	2	0.000	23	0.000	1.732	0.101	3.987

Based on a bootstrap model of 400 iterations. Adjusted for gender, age, CCI, COPD, asthma, HTN, ischemic heart disease, heart failure, diabetes, CKD, gastritis, celiac disease, depression, peptic/UGI ulcer, esophagitis, diabetic peripheral neuropathic pain, chronic musculoskeletal pain, trauma, H2+ proton pump inhibitors, #inpatient visits, #outpatient visits, #unique prescriptions

- **Table 14** displays the sensitivity analysis of the 4 collapsed exposure groups, adjusted by covariate, and **including OTC exposure estimates.**

4 exposure groups, adjusted, with OTC NSAID estimate	Cases		Controls		Adjusted OR	5th percentile	95th percentile
	N	%	N	%			
Group 1. No current exposure	11,450	0.341	125,040	0.372	1.000	n/a	n/a
Group 2. Duloxetine only	143	0.004	1,700	0.005	1.153	0.973	1.340
Group 3. Rx non-selective NSAIDs, COX-2 and Aspirin	3,752	0.112	32,506	0.097	1.140	1.118	1.161
Group 4. Duloxetine and Rx non-selective NSAIDs, COX-2 and Aspirin	14,571	0.434	140,763	0.419	1.027	0.993	1.060

Based on a bootstrap model of 400 iterations. Adjusted for gender, age, CCI, COPD, asthma, HTN, ischemic heart disease, heart failure, diabetes, CKD, gastritis, celiac disease, depression, peptic/UGI ulcer, esophagitis, diabetic peripheral neuropathic pain, chronic musculoskeletal pain, trauma, H2+ proton pump inhibitors, #inpatient visits, #outpatient visits, #unique prescriptions

10.5 Other analyses

As discussed in Section 9.6 above, further analysis was conducted to investigate potential sources of bias.

The observed decreased OR for antiplatelet or anticoagulant exposure should not be construed as a true protective effect, which is counterintuitive from a clinical perspective. The unadjusted ORs for both anticoagulants and antiplatelet exposure were consistent with significantly lower UGI event rates for matched patients compared to those without exposure before adjusting for other variables:

Odds Ratio Estimates

Effect	Point Estimate	95% Wald Confidence Limits
Anticoagulant (1 vs 0)	0.453	0.429-0.477
Antiplatelet (1 vs 0)	0.844	0.806-0.883

These results are consistent with selection bias or channeling. Such bias may occur when controls have systematically different exposures not because of an effect on the disease of interest, but because of other circumstances (eg, comorbidities). Clinicians can be expected to be very cautious in the use of anticoagulants and antiplatelet agents in patients that may represent a higher risk of bleed, including peptic ulcer disease, which was highly prevalent among cases. Anticoagulation guidelines such as those for antithrombotic therapy in atrial fibrillation emphasize the need for patient-level decisions based on risk/benefit assessment and the value of thrombotic event reduction vs the value of avoiding bleeding.[19] Decision support tools for anticoagulation in atrial fibrillation have been piloted that incorporate stroke risk (CHA2DS2-VASc) and bleeding risk (HAS-BLED) scores.[20] Cases in the duloxetine and various NSAID exposure groups may have also been affected by published drug interaction precautions related to the potential increased risk of UGI bleed. Some prescription NSAIDs carry an absolute contraindication regarding concurrent warfarin use.

An additional factor likely contributing to the selection bias was that in addition to controls being excluded based on a history of peptic ulcer disease or UGI bleed, they were also excluded if they had melena or unspecified GI hemorrhage during the 12 months prior to index. The exclusion of these patients with even traces of GI blood loss (often the first sign of GI pathology) removes those patients with the highest risk of GI bleed on an anticoagulant or even patients who may have experienced GI blood loss as a complication of anticoagulant or antiplatelet use.

The effects of the selection bias is also seen below where, despite the higher prevalence of comorbid conditions such as heart disease and cerebrovascular disease, cases had lower rates of pre-index exposure to anticoagulants and antiplatelet agents compared to controls.

	Cases		Controls		P-value
	N	%	N	%	
Current Drug Therapy (claim within 30 days of index date, not incl index date)					
Anticoagulants	1,779	5.30%	35,487	10.57%	<0.0001
Antiplatelet agents	2,558	7.62%	28,612	8.52%	<0.0001

The model adjusted for the drug exposure and comorbid conditions, but could not account for other aspects of selection bias. We then investigated the potential effect of this finding in the context of duloxetine exposure by referencing the full model comparing the 3 exposure groups (duloxetine only; prescription NSAID, COX-2, aspirin; duloxetine and prescription NSAID, COX-2 and aspirin) to the reference group (no current exposure to medication). We ran the model separately for each exposure group comparison to assess the impact on the OR for anticoagulation and antiplatelet exposure. This was initially run with the two drug exposure variables combined and then repeated with each as an individual variable.

Each of the following models feature exposure classes being compared to Group 1, the reference group containing no current medication.

Table 15a. As above, the full model containing all 3 exposure comparisons and a combined anticoagulant and antiplatelet variable. *Complete model outputs are listed in Table E, Appendix 10.*

Effect	OR	LowerCL	UpperCL
Duloxetine	1.056	0.891	1.252
Rx NSAIDs,COX-2, ASA	1.126	1.059	1.197
Duloxetine + Rx NSAIDs, COX-2, ASA	1.208	0.924	1.578
Anticoagulants + Antiplatelets	0.829	0.787	0.874

Note: Adjusted for gender, age, CCI, COPD, asthma, HTN, ischemic heart disease, heart failure, diabetes, CKD, gastritis, celiac disease, depression, peptic/UGI ulcer, esophagitis, diabetic peripheral neuropathic pain, chronic musculoskeletal pain, trauma, H2+ proton pump inhibitors, #inpatient visits, #outpatient visits, #unique prescriptions

Table 15b displays model results for duloxetine exposure only, with the combined anticoagulant and antiplatelet variable. *Complete model outputs are listed in Table F, Appendix 10.*

Effect	OR	LowerCL	UpperCL
Duloxetine	1.068	0.901	1.267
Anticoagulants + Antiplatelets	0.843	0.796	0.892

Note: Adjusted for gender, age, CCI, COPD, asthma, HTN, ischemic heart disease, heart failure, diabetes, CKD, gastritis, celiac disease, depression, peptic/UGI ulcer, esophagitis, diabetic peripheral neuropathic pain, chronic musculoskeletal pain, trauma, H2+ proton pump inhibitors, #inpatient visits, #outpatient visits, #unique prescriptions

Table 15c displays model results for prescription NSAIDs, COX-2 NSAIDs, and aspirin exposure only, with the combined anticoagulant and antiplatelet variable. *Complete model outputs are listed in Table G, Appendix 10.*

Effect	OR	LowerCL	UpperCL
Rx NSAIDs,COX-2, ASA	1.129	1.062	1.201
Anticoagulants + Antiplatelets	0.83	0.787	0.875

Note: Adjusted for gender, age, CCI, COPD, asthma, HTN, ischemic heart disease, heart failure, diabetes, CKD, gastritis, celiac disease, depression, peptic/UGI ulcer, esophagitis, diabetic peripheral neuropathic pain, chronic musculoskeletal pain, trauma, H2+ proton pump inhibitors, #inpatient visits, #outpatient visits, #unique prescriptions

Table 15d displays model results for prescription NSAIDS, COX-2 NSAIDs, and aspirin exposure only, with the combined anticoagulant and antiplatelet variable. *Complete model outputs are listed in Table H, Appendix 10.*

Effect	OR	LowerCL	UpperCL
Duloxetine + Rx NSAIDs, COX-2, ASA	1.226	0.937	1.603
Anticoagulants + Antiplatelets	0.84	0.794	0.89

Note: Adjusted for gender, age, CCI, COPD, asthma, HTN, ischemic heart disease, heart failure, diabetes, CKD, gastritis, celiac disease, depression, peptic/UGI ulcer, esophagitis, diabetic peripheral neuropathic pain, chronic musculoskeletal pain, trauma, H2+ proton pump inhibitors, #inpatient visits, #outpatient visits, #unique prescriptions

Table 16a. Here, we display the full model containing all 3 exposure comparisons and separated anticoagulant and antiplatelet variables. *Complete model outputs are listed in Table I, Appendix 10.*

Effect	OR	LowerCL	UpperCL
Duloxetine	1.056	0.891	1.251
Rx NSAIDs,COX-2, ASA	1.13	1.063	1.202
Duloxetine + Rx NSAIDs, COX-2, ASA	1.209	0.925	1.58
Anticoagulants	0.746	0.694	0.801
Antiplatelets	0.946	0.886	1.01

Note: Adjusted for gender, age, CCI, COPD, asthma, HTN, ischemic heart disease, heart failure, diabetes, CKD, gastritis, celiac disease, depression, peptic/UGI ulcer, esophagitis, diabetic peripheral neuropathic pain, chronic musculoskeletal pain, trauma, H2+ proton pump inhibitors, #inpatient visits, #outpatient visits, #unique prescriptions

Table 16b displays model results for duloxetine exposure only, with separated anticoagulant and antiplatelet variables. *Complete model outputs are listed in Table J, Appendix 10.*

Effect	OR	LowerCL	UpperCL
Duloxetine	1.067	0.9	1.266
Anticoagulants	0.772	0.714	0.836
Antiplatelets	0.935	0.871	1.004

Note: Adjusted for gender, age, CCI, COPD, asthma, HTN, ischemic heart disease, heart failure, diabetes, CKD, gastritis, celiac disease, depression, peptic/UGI ulcer, esophagitis, diabetic peripheral neuropathic pain, chronic musculoskeletal pain, trauma, H2+ proton pump inhibitors, #inpatient visits, #outpatient visits, #unique prescriptions

Table 16c displays model results for prescription NSAIDs, COX-2 NSAIDs, and aspirin exposure only, with separated anticoagulant and antiplatelet variables. *Complete model outputs are listed in Table K, Appendix 10.*

Effect	OR	LowerCL	UpperCL
Rx NSAIDs,COX-2, ASA	1.133	1.066	1.205
Anticoagulants	0.75	0.697	0.806
Antiplatelets	0.943	0.882	1.008

Note: Adjusted for gender, age, CCI, COPD, asthma, HTN, ischemic heart disease, heart failure, diabetes, CKD, gastritis, celiac disease, depression, peptic/UGI ulcer, esophagitis, diabetic peripheral neuropathic pain, chronic musculoskeletal pain, trauma, H2+ proton pump inhibitors, #inpatient visits, #outpatient visits, #unique prescriptions

Table 16d displays model results for prescription NSAIDS, COX-2 NSAIDs, and aspirin exposure only, with separated anticoagulant and antiplatelet variables. *Complete model outputs are listed in Table L, Appendix 10.*

Effect	OR	LowerCL	UpperCL
Duloxetine + Rx NSAIDs, COX-2, ASA	1.227	0.938	1.604
Anticoagulants	0.767	0.709	0.831
Antiplatelets	0.935	0.87	1.005

Note: Adjusted for gender, age, CCI, COPD, asthma, HTN, ischemic heart disease, heart failure, diabetes, CKD, gastritis, celiac disease, depression, peptic/UGI ulcer, esophagitis, diabetic peripheral neuropathic pain, chronic musculoskeletal pain, trauma, H2+ proton pump inhibitors, #inpatient visits, #outpatient visits, #unique prescriptions

As seen in the full model (Table 15a), combined anticoagulant or antiplatelet exposure is associated with the artificially decreased risk (OR 0.829 95%CI 0.787, 0.874). Note that when the full model was run with the anticoagulant and antiplatelet separately (table16a), the OR for antiplatelet exposure failed to reach statistical significance at the 5% level (OR 0.946 95%CI 0.886, 1.01). Thus, anticoagulation exposure is driving the effect, but we found that there was ultimately no difference whether the variables are combined or separate.

In viewing the OR estimates when run separately by exposure group comparison, we saw no difference in directionality or effect size in the combined medication exposure variable (see Tables 15a-d, 16a-d). As above, there are also no significant differences when the medication exposure variables are entered separately in the models across exposure group comparisons.

We conclude from these investigations that regardless of how these variables go into the model, they do not impact our primary endpoint. The apparent decreased risk observed with exposure to anticoagulants or antiplatelet agents is consistent with selection bias or channeling. Our investigation supports that the model's assessment of the potential synergistic effect of duloxetine and NSAIDs on UGI bleed is unaffected by this bias.

Separate from the a priori analysis plan, we investigated the effects of excluding the patients in e (those patients who could not be assigned to a mutually exclusive drug category) on our findings via a sensitivity analysis. Including this group in our analyses did not affect parameter estimates for the covariates included in the final model, or the main effect by different drug exposures. No directional changes or changes in significance level were found.

10.6 Adverse events/adverse reactions

Studies using de-identified or anonymised individual-level administrative claims databases are aggregate analyses of population outcomes, and individual patient data cannot be retrieved and validated, making it impossible to assess causality of adverse events (AEs). Consequently, AEs are not reportable as individual AE reports. Further, individual AE reports are not applicable since this study included no chart reviews to supplement the administrative claims data and there are no narrative/verbatim fields in the study dataset that could confirm a direct link between an AE and a Lilly drug in an individual patient.

The study identified no aggregate risk other than the known association of NSAIDs with UGI bleed.

11. Discussion

11.1 Key results

- Primary objective: To examine whether concomitant use of duloxetine and prescription NSAIDs is associated with a synergistic effect on the risk of UGI bleeding.

There was no evidence of a synergistic effect of concurrent duloxetine and prescription NSAID exposure, based on either logistic regression comparison of exposure groups or RERI calculation. This was found with the original 8 exposure groups and a sensitivity analysis using collapsed groups combining prescription NSAID classes. Similarly, the RERI calculation provided no evidence of an excessive risk due to interaction between duloxetine and prescription NSAIDs. A sensitivity analysis simulating OTC NSAID/ASA exposure did not demonstrate any change in the adjusted ORs for the duloxetine + prescription NSAID exposure group or the collapsed duloxetine + prescription NSAID, COX-2 or ASA exposure groups, both showing no statistically significant risk of UGI bleed event.

Some selection or channeling bias was observed and investigated further. This was primarily evidenced by an artificially decreased risk of bleed associated with anticoagulation or antiplatelet exposure. The directionality was noted before adjusting for the covariates and remained when the model was run separately for each exposure group comparison of interest. Since the directionality did not change, there was no evidence that this bias affected the primary study objective related to the potential synergistic effect of duloxetine and NSAID exposure.

A number of prior studies of SSRIs and UGI bleeding risk limited the number of covariates in their model (eg, selecting those that impacted the OR >10%) and either did not address anticoagulant or antiplatelet exposure[4,6] or describe adjusting for it without reporting an OR[21] for the covariate. Van Walraven et al[7] reported in their study of UGI bleeding in elderly patients on SSRIs that anticoagulant use was associated with an increased relative risk of UGI bleed: RR 2.2 (95% CI 1.7, 2.8), but concurrent drug exposure did not have a significant impact on UGI bleed risk based on increasing serotonin inhibition. In an analysis of SSRI and UGI bleed risk using the General Practice Research Database, Opatrny et al did not find any evidence of an interaction effect between the concurrent use of SSRI and warfarin or SSRI and clopidogrel.[22] This emphasizes that the main objective of this study is to assess the synergistic effect of duloxetine and NSAID exposure on UGI bleeding risk rather than the individual risk ORs. To our knowledge, no study has demonstrated a synergistic effect between anticoagulant or antiplatelet use SSRI or SNRI use (with or without NSAIDs) and the risk of UGI bleed.

Regarding our unexpected finding related to anticoagulant/antiplatelet exposure, similar counterintuitive findings have been reported in previous studies. Tata et al reported that the risk of UGI bleed in individuals exposed to both SSRIs and NSAIDs decreased considerably with increasing CCI.[6] This decreased relative risk was not explained by increased use of PPIs and H2 blockers among those with higher CCI. The investigators concluded that the effect was an interaction and reported results without adjusting for CCI. For our study, we concluded in our investigation of the channeling bias that it had no impact on the primary analysis.

We interpret these findings as evidence of no impact on the benefit risk profile for duloxetine.

- Secondary objective: To study the risk of UGI bleeding associated with duloxetine exposure without concomitant NSAIDs.

None of the duloxetine exposure groups were associated with a statistically significant risk of UGI bleed event. The prescription NSAID exposure group was the only exposure group that was consistently demonstrated to have significantly higher risk of UGI bleed event in the model. The sensitivity analysis simulating OTC NSAID/ASA exposure did not impact the results. Although these results are not consistent with some previously published studies, we conclude the findings support no impact on the benefit risk profile for duloxetine.

- Secondary objective: To characterize the severity of UGI bleeding cases across all study populations.

Univariate analysis using multiple definitions showed no evidence that duloxetine exposure was associated with more severe UGI bleeds, including categorization by increasing duloxetine dose. This is consistent with our other analyses finding no evidence of significant UGI bleed risk associated with duloxetine.

11.2 Limitations

Some of the limitations that should be considered include the following:

- Most retrospective data sets were not designed for the primary purpose of conducting research. The internal validity is typically not sufficient to make positive inferences of cause and effect.
- Selection or channeling bias. The populations of patients selected for one particular treatment over another may have very different characteristics. Some of these differences can often be measured (such as age) but some may be unknown or not measurable. Selection bias or channeling was noted in our study and further data exploration supported no evidence of impact on the primary analysis related to duloxetine and NSAID use.
- Missing data. Treatments may not be captured within the data set and there may be incomplete encounter histories for patients selected for the study. For this study, relevant missing data include OTC medication exposure and non-covered treatment (eg, alternative medicine). The sensitivity analysis simulating OTC NSAID/ASA use addressed the former with some inherent caveats.
- Medical billing codes used to indicate diagnoses and procedures are subject to non-clinical influences and can result in some misclassification bias.

Despite these limitations, large retrospective databases have been widely used to answer study questions such as those addressed in this analysis.

11.3 Interpretation

The primary objective of the study was to assess the potential synergistic effect of duloxetine and NSAID exposure on UGI bleed risk. Our findings demonstrate no evidence of such an effect. A sensitivity analysis simulating exposure to OTC NSAIDs/ASA showed no impact on the risk of bleed for the exposure groups. Channeling bias was investigated and concluded to have no impact on the primary analysis. Exposure to increasing duloxetine doses was not associated with any measures consistent with severe UGI bleed. Our model also failed to confirm a statistically significant risk of UGI bleed with duloxetine exposure alone after adjusting for other factors. These results provide no evidence of the safety concerns that prompted this study.

11.4 Generalisability

The generalisability of this study is supported on several levels. We used one of the largest administrative claims databases available for the US population in which there is extensive experience conducting a wide range of studies including case-control safety studies. Because of the insurance benefit design inherent in the population represented in the database, we can be quite confident in the capture of most if not all events of interest, including hospitalization for UGI bleed and exposure to duloxetine and prescription NSAIDs. We utilized a validated method for defining our case population. The longitudinality of the THAM database allowed us to define the patient-specific confounders to be used in our regression equations to calculate adjusted ORs for our study groups.

Other published studies related to SSRIs and UGI bleed risk and with or without concurrent NSAID exposure do not suggest any inherent differences between the US and EU populations.[6,22] This study was designed to identify the most serious AEs (UGI bleed events) that might be associated with duloxetine with or without concurrent NSAID use. Based on comparable prescribing indications in the US and EU and with no known racial, ethnic or genetic risk factors, there is no reason to suspect that these study findings would not be generalisable to the EU.

12. Other information

The protocol for this study was submitted to the New England Institutional Review Board for review and received a waiver of informed consent on 14 January, 2013.

13. Conclusion

The objectives of this study were met. There was no evidence of a synergistic effect between duloxetine and prescription NSAIDs, nor did analysis show that higher doses of duloxetine are associated with severe GI bleeds. Estimations of OTC NSAIDs use did not demonstrate any increased risk to the duloxetine and NSAID exposure groups when added in a sensitivity analysis. We found no evidence of a safety concern warranting further investigation.

14. References

1. Dalton SO, Johansen C, Mellemkjaer L, Norgard B, Sorensen HT, Olsen JH. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding: a population-based cohort study. *Arch Intern Med* 2003; 163(1):59-64.

2. de Abajo FJ, Rodriguez LA, Montero D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. *BMJ* 1999; 319(7217):1106-1109.

3. Helin-Salmivaara A, Huttunen T, Gronroos JM, Klaukka T, Huupponen R. Risk of serious upper gastrointestinal events with concurrent use of NSAIDs and SSRIs: a case-control study in the general population. *Eur J Clin Pharmacol* 2007; 63(4):403-408.

4. Lewis JD, Strom BL, Localio AR, Metz DC, Farrar JT, Weinrieb RM et al. Moderate and high affinity serotonin reuptake inhibitors increase the risk of upper gastrointestinal toxicity. *Pharmacoepidemiol Drug Saf* 2008; 17(4):328-335.

5. Targownik LE, Bolton JM, Metge CJ, Leung S, Sareen J. Selective serotonin reuptake inhibitors are associated with a modest increase in the risk of upper gastrointestinal bleeding. *Am J Gastroenterol* 2009; 104(6):1475-1482.

6. Tata LJ, Fortun PJ, Hubbard RB, Smeeth L, Hawkey CJ, Smith CJ et al. Does concurrent prescription of selective serotonin reuptake inhibitors and non-steroidal anti-inflammatory drugs substantially increase the risk of upper gastrointestinal bleeding? *Aliment Pharmacol Ther* 2005; 22(3):175-181.

7. van Walraven C, Mamdani MM, Wells PS, Williams JI. Inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding in elderly patients: retrospective cohort study. *BMJ* 2001; 323(7314):655-658.

8. Wessinger S, Kaplan M, Choi L, Williams M, Lau C, Sharp L et al. Increased use of selective serotonin reuptake inhibitors in patients admitted with gastrointestinal haemorrhage: a multicentre retrospective analysis. *Aliment Pharmacol Ther* 2006; 23(7):937-944.

9. Vidal X, Ibanez L, Vendrell L, Conforti A, Laporte JR. Risk of upper gastrointestinal bleeding and the degree of serotonin reuptake inhibition by antidepressants: a case-control study. *Drug Saf* 2008; 31(2):159-168.

10. Wahl PM, Rodgers K, Schneeweiss S, Gage BF, Butler J, Wilmer C et al. Validation of claims-based diagnostic and procedure codes for cardiovascular and gastrointestinal serious adverse events in a commercially-insured population. *Pharmacoepidemiol Drug Saf* 2010; 19(6):596-603.

11. Abraham NS, Cohen DC, Rivers B, Richardson P. Validation of administrative data used for the diagnosis of upper gastrointestinal events following nonsteroidal anti-inflammatory drug prescription. *Aliment Pharmacol Ther* 2006; 24(2):299-306.

12. Taha AS, Angerson WJ, Prasad R, McCloskey C, Blatchford O. Upper gastrointestinal bleeding and the changing use of COX-2 non-steroidal anti-inflammatory drugs and low-dose aspirin. *Aliment Pharmacol Ther* 2007; 26(8):1171-1178.

13. Moore RA, Derry S, McQuay HJ. Cyclo-oxygenase-2 selective inhibitors and nonsteroidal anti-inflammatory drugs: balancing gastrointestinal and cardiovascular risk. *BMC Musculoskelet Disord* 2007; 8:73.

14. Smith PG, Day NE. The design of case-control studies: the influence of confounding and interaction effects. *Int J Epidemiol* 1984; 13(3):356-365.

15. Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. *Epidemiology* 1992; 3(5):452-456.

16. Assmann SF, Hosmer DW, Lemeshow S, Mundt KA. Confidence intervals for measures of interaction. *Epidemiology* 1996; 7(3):286-290.

17. Richardson DB, Kaufman JS. Estimation of the relative excess risk due to interaction and associated confidence bounds. *Am J Epidemiol* 2009; 169(6):756-760.

18. Firth D. Bias reduction of maximum likelihood estimates. *Biometrika* 1993; 80:27-38.

19. You JJ, Singer DE, Howard PA, Lane DA, Eckman MH, Fang MC et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(2 Suppl):e531S-e575S.

20. LaHaye SA, Gibbens SL, Ball DG, Day AG, Olesen JB, Skanes AC. A clinical decision aid for the selection of antithrombotic therapy for the prevention of stroke due to atrial fibrillation. *Eur Heart J* 2012; 33(17):2163-2171.

21. Meijer WE, Heerdink ER, Nolen WA, Herings RM, Leufkens HG, Egberts AC. Association of risk of abnormal bleeding with degree of serotonin reuptake inhibition by antidepressants. *Arch Intern Med* 2004; 164(21):2367-2370.

22. Opatrny L, Delaney JA, Suissa S. Gastro-intestinal haemorrhage risks of selective serotonin receptor antagonist therapy: a new look. *Br J Clin Pharmacol* 2008; 66(1):76-81.

23. Soni A. Aspirin use among the Adult US Noninstitutionalized Population, with and without Indicators of Heart Disease, 2005. Statistical Brief 179. Agency for Healthcare Research and Quality, Rockville, MD. MEPS. Available at: http://meps.ahrq.gov/mepsweb/data_files/publications/st179/stat179.pdf. Last updated July, 2007. Accessed June 11, 2013.

24. Wilcox CM, Cryer B, Triadafilopoulos G. Patterns of use and public perception of over-the-counter pain relievers: focus on nonsteroidal anti-inflammatory drugs. *J Rheumatol* 2005; 32(11):2218-24.

25. Patterns of medication use in the United States. A report from the Slone Survey, Slone Epidemiology Center, Boston University. Slone. Available at: http://www.bu.edu/slone/research/studies/slone-survey/. Last updated 2006. Accessed June 11, 2013.

26. Paulose-Ram R, Hirsch R, Dillon C, Gu Q. Frequent monthly use of selected non-prescription and prescription non-narcotic analgesics among U.S. adults. *Pharmacoepidemiol Drug Saf* 2005; 14(4):257-266.

Appendices

Appendix 1. Contact details

Matthew F. Emons, MD, MBA
Senior Director, Physician Executive
Cerner Research, Culver City, CA USA
+1 310-598-4461
memons@cerner.com

Hu Li, MBBS, PhD
Global Patient Safety Epidemiologist
Eli Lilly and Company
893 S. Delaware Street
Indianapolis, IN 46225
Telephone: +1 317 655 9951

Appendix 2. Exclusion criteria

Note: these criteria were applied by Truven prior to receipt of the dataset.

- Age <18 on the index date

TRM Variable	Definition
THAM [AGEGRP] = 1	Patient is <18 (0-17)

- Lack of continuous eligibility in the 12-month pre-index period

TRM Variable	Definition
THAM [DTSTART]	Start date of continuous enrollment period
THAM [DTEND]	End date of continuous enrollment period

- Esophageal varices (any of the below codes apply)

ICD-9 Dx	Description
Esophageal varices	
456.0	Esophageal varices with bleeding
456.1	Esophageal varices without mention of bleeding
456.2x	Esophageal varices in disease classified elsewhere

- Mallory-Weiss syndrome

ICD-9 Dx	Description
Mallory-Weiss syndrome	
530.7	Gastroesophageal laceration-hemorrhage syndrome

- Alcoholism (any of the below codes apply)

ICD-9 Dx/V code	Description
Alcoholism	
303.xx	Alcohol dependence syndrome
291.x	Alcohol induced mental disorders
305.0	Alcohol abuse, continuous
V11.3	Alcoholism

- Chronic liver disease (any of the below codes apply)

ICD-9 Dx	Description
Chronic liver disease and cirrhosis	
567.23	Spontaneous bacterial peritonitis
571.xx	Chronic liver disease and cirrhosis
572.x	Liver abscess and sequelae of chronic liver disease
573.0	Chronic passive congestion of liver
573.1	Hepatitis in viral diseases classified elsewhere
573.2	Hepatitis in other infectious diseases classified elsewhere
573.3	Hepatitis unspecified

- Coagulopathies (any of the below codes apply)

ICD-9 Dx	Description
Coagulopathies	
286.x	Coagulation defects
790.92	Abnormal coagulation profile

- Pregnancy (any of the below codes apply)

Pregnancy	
ICD-9 Dx	**Description**
640.X1-649.X1	Complications mainly related to pregnancy, delivered, without or without mention of antepartum condition
640.X2-649.X2	Complications mainly related to pregnancy, with mention of postpartum complication
640.X3-649.X3	Complications mainly related to pregnancy, with antepartum condition or complication
650.X	Normal delivery
651.X1-659.X1	Normal delivery, and other indications for care in pregnancy, labor, and delivery: delivered, with or without mention of antepartum condition
651.X2-659.X2	Normal delivery, and other indications for care in pregnancy, labor, and delivery: delivered, with mention of antepartum condition
651.X3-659.X3	Normal delivery, and other indications for care in pregnancy, labor, and delivery: antepartum condition or complication

660.X1-669.X1	Complications occurring mainly in the course of labor and delivery: delivered, with or without mention of antepartum condition
660.X2-669.X2	Complications occurring mainly in the course of labor and delivery: delivered, with mention of antepartum condition
660.X3-669.X3	Complications occurring mainly in the course of labor and delivery: antepartum condition
670.X1-677.X1	Complications of the puerperium: delivered, with or without mention of antepartum condition
670.X2-677.X2	Complications of the puerperium: delivered, with mention of antepartum condition
670.X3-677.X3	Complications of the puerperium: with mention of antepartum condition
V22.x	Normal pregnancy
V23.xx	Supervision of high-risk pregnancy
V27.x	Outcome of delivery
V28.xx	Encounter for antenatal screening of mother
V61.6	Illegitimacy or illegitimate pregnancy
V61.7	Other unwanted pregnancy

- Malignant neoplasm (any of the below codes apply)

Cancer (solid tumor and skin)	
ICD-9 Dx	**Description**
140.x	Malignant neoplasm of lip
141.x	Malignant neoplasm tongue
142.x	Malignant neoplasm of major salivary glands
143.x	Malignant neoplasm of gum
144.x	Malignant neoplasm of floor of mouth
145.x	Malignant neoplasm of other and unspecified parts of mouth
146.x	Malignant neoplasm of oropharynx
147.x	Malignant neoplasm of nasopharynx
148.x	Malignant neoplasm of hypopharynx
149.x	Malignant neoplasm of other and ill-defined sites within the lip oral cavity and pharynx
150.x	Malignant neoplasm of esophagus
151.x	Malignant neoplasm of stomach
152.x	Malignant neoplasm of small intestine including duodenum
153.x	Malignant neoplasm of colon
154.x	Malignant neoplasm of rectum rectosigmoid junction and anus

155.x	Malignant neoplasm of liver and intrahepatic bile ducts
156.x	Malignant neoplasm of gallbladder and extrahepatic bile ducts
157.x	Malignant neoplasm of pancreas
158.x	Malignant neoplasm of retroperitoneum and peritoneum
159.x	Malignant neoplasm of other and ill-defined sites within the digestive organs and peritoneum
160.x	Malignant neoplasm of nasal cavities middle ear and accessory sinuses
161.x	Malignant neoplasm of larynx
162.x	Malignant neoplasm of trachea bronchus and lung
163.x	Malignant neoplasm of pleura
164.x	Malignant neoplasm of thymus heart and mediastinum
165.x	Malignant neoplasm of other and ill-defined sites within the respiratory system and intrathoracic organs
170.x	Malignant neoplasm of bone and articular cartilage
171.x	Malignant neoplasm of connective and other soft tissue
172.x	Malignant melanoma of skin
173.x	Other and unspecified malignant neoplasm of skin
174.x	Malignant neoplasm of female breast
175.x	Malignant neoplasm of male breast
179.x	Malignant neoplasm of uterus-part unspecified
180.x	Malignant neoplasm of cervix uteri
181.x	Malignant neoplasm of placenta
182.x	Malignant neoplasm of body of uterus
183.x	Malignant neoplasm of ovary and other uterine adnexa
184.x	Malignant neoplasm of other and unspecified female genital organs
185.x	Malignant neoplasm of prostate
186.x	Malignant neoplasm of testis
187.x	Malignant neoplasm of penis and other male genital organs
188.x	Malignant neoplasm of bladder
189.x	Malignant neoplasm of kidney and other and unspecified urinary organs
190.x	Malignant neoplasm of eye
191.x	Malignant neoplasm of brain
192.x	Malignant neoplasm of other and unspecified parts of nervous system
193.x	Malignant neoplasm of thyroid gland
194.x	Malignant neoplasm of other endocrine glands and related structures
195.x	Malignant neoplasm of other and ill-defined sites
196.x	Secondary and unspecified malignant neoplasm of lymph nodes
197.x	Secondary malignant neoplasm of respiratory and digestive systems
198.x	Secondary malignant neoplasm of other specified sites
199.x	Malignant neoplasm without specification of site

209.0x	Malignant carcinoid tumors of the small intestine
209.1x	Malignant carcinoid tumors of the appendix, large intestine, and rectum
209.2x	Malignant carcinoid tumors of other and unspecified sites
209.3x	Malignant poorly differentiated neuroendocrine tumors
Hematologic malignancy	
200.xx	Lymphosarcoma and reticulosarcoma
201.xx	Hodgkin's disease
202.xx	Other malignant neoplasms of lymphoid and histiocytic tissue
203.xx	Multiple myeloma and immunoproliferative neoplasms
204.x	Lymphoid leukemia
205.xx	Myeloid leukemia
206.xx	Monocytic leukemia
207.xx	Other specified leukemia
208.xx	Leukemia of unspecified cell type

- Major organ transplant (any of the below codes apply)

Major organ transplant	
ICD-9 Px	**Description**
0.18	Infusion of immunosuppressive antibody therapy during induction phase of solid organ transplantation
0.91	Transplant from live related donor
0.92	Transplant from live non-related donor
0.93	Transplant from cadaver
33.5	Lung Transplant
33.5	Lung Transplantation, Not Otherwise Specified
33.51	Unilateral Lung Transplantation
33.52	Bilateral Lung Transplantation
33.6	Combined Heart-Lung Transplantation
37.51	Heart transplantation
41.94	Transplantation Of Spleen
50.5	Liver Transplant
50.51	Auxiliary Liver Transplant
50.59	Other Transplant Of Liver
52.8	Pancreatic Transplant, Not Otherwise Specified
52.83	Heterotransplant Of Pancreas
52.85	Allotransplantation Of Cells Of Islets Of Langerhans

52.86	Transplantation Of Cells Of Islets Of Langerhans, Not Otherwise Specified
55.53	Removal Of Transplanted Or Rejected Kidney
55.69	Other Kidney Transplantation
V Code	**Description**
V42.0	Kidney
V42.1	Heart
V42.4	Bone
V42.6	Lung
V42.7	Liver
V42.81	Bone marrow
V42.83	Pancreas

Appendix 3. ICD-9-CM diagnosis and procedure codes and CPT codes indicative of UGI hemorrhage or peptic ulcer disease, including perforation

ICD-9 Dx	Description
531.x	Gastric ulcer
532.x	Duodenal ulcer
533.x	Peptic ulcer site unspecified
534.x	Gastrojejunal ulcer
578.0	Hematemesis
ICD-9 Px	**Description**
44.4x	UGI endoscopy including esophagus, stomach and either duodenum and/or jejunum as appropriate; diagnostic, with control of bleeding by any method
CPT code	**Description**
43255	Upper GI endoscopy including esophagus, stomach and either duodenum and/or jejunum as appropriate; diagnostic, with control of bleeding by any method

Appendix 4 Medications associated with each drug class

Drug Class	Associated Medications
Duloxetine	Duloxetine
Non-selective NSAIDs	Sulindac Oxaprozin Piroxicam Indomethacin Etodolac Meclofenamate Meloxicam Ibuprofen Naproxen sodium Naproxen Ketoprofen Nabumetone Tolmetin sodium Diclofenac Fenoprofen calcium Flurbiprofen Ketorolac tromethamine Mefenamic acid Phenylbutazone
COX-2 selective NSAIDs	Celecoxib Rofecoxib Valdecoxib
Prescription aspirin	Aspirin Diflunisal Choline salicylate Salsalate Sodium salicylate Sodium thiosalicylate Magnesium salicylate Phenyl salicylate Choline salicylate-magnesium salicylate ASA/citric acid/Na bicarb Al hydroxide/ASA/Ca carbonate/Mg hydroxide Salicylamide
SSRI and SNRI other than duloxetine	Fluoxetine Sertraline Paroxetine IR

	Paroxetine ER Fluvoxamine Citalopram Escitalopram Venlafaxine IR Venlafaxine ER Desvenlafaxine

Appendix 5. Variable definitions

Demographic Characteristic Variables

Characteristic	Description/Derivation	Type	Notes
Age at index date (continuous), years	Patient's age in years at Index Date	Continuous	xx
Age at index admission (categorical), years	THAM [AGEGRP]	Categorical	18-34 35-44 45-54 55-65 ≥65 Unknown/Missing
Gender	THAM [SEX]	Categorical	Male Female Unknown
Region	THAM [REGION]	Categorical	Northeast North Central South West Unknown/Not Mapped

Patient Disease Profile and Comorbidities

Comorbidity	ICD-9 Dx	Description	Type	Value/category
Charlson Comorbidity Index (CCI)	n/a	Compute using data during the index inpatient admission as well as data 12 months prior to the index inpatient admission. See computation algorithm in **Appendix 6. *Charlson Comorbidity Index (CCI) Algorithm***	Continuous	xx (range 0-29)
			Categorical	0 1 2 3 4-7 7-9 ≥10 Unknown/missing
Hypertension	401.x	Essential hypertension	Binary	Yes/No
	402.x	Hypertensive heart disease		
	403.x	Hypertensive kidney disease		
	404.x	Hypertensive heart and kidney disease		
	405.x	Secondary hypertension		
	437.2	Hypertensive encephalopathy		
Ischemic heart disease	410.x	Acute myocardial infarction	Binary	Yes/No
	411.x	Other acute and subacute forms of		

		ischemic heart disease		
	412.x	Old myocardial infarction		
	413.x	Angina pectoris		
	414.x	Other forms of chronic ischemic heart disease		
Heart failure	428.x	Heart failure	Binary	Yes/No
Cerebrovascular disease	***Acute/subacute***		Binary	Yes/No
	430	Subarachnoid hemorrhage		
	431	Intracerebral hemorrhage		
	432.x	Other and unspecified intracranial hemorrhage		
	433.xx	Occlusion and stenosis of precerebral arteries		
	434.xx	Occlusion of cerebral arteries		
	435.x	Transient cerebral ischemia		
	436	Acute but ill-defined cerebrovascular disease		
	997.02	Iatrogenic cerebrovascular infarction or hemorrhage		
	Chronic/unspecified			
	437.0	Cerebral atherosclerosis		
	437.1	Other generalized ischemic cerebrovascular disease		
	438.xx	Late effects of cerebrovascular disease		
	V12.54	History of transient ischemic attack, and cerebral infarction without residual deficits		
Dyslipidemia	272.x	Disorders of lipoid metabolism	Binary	Yes/No
Diabetes	***Type 1 diabetes mellitus***		Binary	Yes/No
	250.x1	Diabetes mellitus [type I [juvenile type], not stated as uncontrolled]		
	250.x3	Diabetes mellitus [type I [juvenile type], uncontrolled]		
	Type 2/unspecified diabetes mellitus			
	250.x0	Diabetes mellitus [type II or unspecified type, not stated as uncontrolled]		
	250.x2	Diabetes mellitus [type II or unspecified type, uncontrolled]		
	Secondary diabetes mellitus			
	249.xx	Secondary diabetes mellitus		
Asthma	493.xx	Asthma	Binary	Yes/No
Chronic	491.xx	Chronic bronchitis	Binary	Yes/No

obstructive pulmonary disease (COPD)	492.x	Emphysema		
	496	Chronic airway obstruction not elsewhere classified		
Chronic kidney disease (CKD)	250.4x	Diabetes with renal manifestations	Binary	Yes/No
	403.xx	Hypertensive kidney disease		
	404.xx	Hypertensive heart and kidney disease		
	581.xx	Nephrotic syndrome		
	582.xx	Chronic glomerulonephritis		
	583.xx	Nephritis and nephropathy, not specified as acute or chronic		
	585.x	Chronic kidney disease		
	587	Renal sclerosis, unspecified		
	588.0	Renal osteodystrophy		
Esophagitis	530.1x	Esophagitis	Binary	Yes/No
Peptic/upper gastrointestinal ulcer	531.xx	Gastric ulcer	Binary	Yes/No
	532.x	Duodenal ulcer		
	533.x	Peptic ulcer site unspecified		
	543.xx	Gastrojejunal ulcer		
Gastritis	535.x	Gastritis and duodenitis	Binary	Yes/No
Celiac disease	579.0	Celiac disease	Binary	Yes/No
Major depressive disorder	296.2x	Major depressive disorder single episode	Binary	Yes/No
	296.3x	Major depressive disorder recurrent episode		
	300.4	Dysthymic disorder		
	309.1	Adjustment reaction with prolonged depressive reaction		
	311	Depressive disorder not elsewhere classified		
Generalized anxiety disorder	300.0x	Anxiety states	Binary	Yes/No
	300.1x	Dissociative, conversion and factitious disorders		
	300.2x	Phobic disorders		
	300.3x	Obsessive-compulsive disorders		
	300.5	Neurasthenia		
	300.6	Depersonalization disorder		
	300.7	Hypochondriasis		
	300.8x	Somatoform disorders		
	300.9x	Unspecified nonpsychotic mental disorder		
	308.x	Acute reaction to stress		
Diabetic peripheral	250.6x	Diabetes with neurological manifestations	Binary	Yes/No

neuropathy	337.1x	Peripheral autonomic neuropathy in disorders classified elsewhere		
	355.7x	Other mononeuritis of lower limb		
	357.2x	Polyneuropathy in diabetes		
Fibromyalgia	729.1	Myalgia and myositis, unspecified	Binary	Yes/No
Chronic musculoskeletal pain	715.x	Osteoarthritis	Binary	Yes/No
	780.96	Generalized pain		
	720.x	Ankylosing spondylitis and other inflammatory spondylopathies		
	721.x	Spondylosis and allied disorders		
	722.x	Intervertebral disc disorders		
	723.x	Other disorders of cervical region		
	724.x	Other and unspecified disorders of back		
	338.2x	Chronic pain		
	338.4	Chronic pain syndrome		
Trauma	***Head trauma***		Binary	Yes/No
	ICD-9 Dx	**Description**		
	800.xx	Fracture of vault of skull		
	801.xx	Fracture of base of skull		
	802.3x	Mandible, open		
	802.7	Orbital floor, open		
	803.xx	Other and unqualified skull fractures		
	804.xx	Multiple fractures involving face and skull		
	851.xx	Cerebral laceration and contusion		
	852.xx	Subarachnoid, subdural, and extradural hemorrhage, following injury		
	853.xx	Other and unspecified intracranial hemorrhage following injury		
	854.xx	Intracranial injury of other and unspecified nature		
	900.xx	Injury to blood vessels of head and neck		
	Other major trauma			
	805.xx	Fracture of vertebral column		
	806.xx	Fracture of vertebral column with spinal cord injury		
	807.1x	Fracture of rib, open		
	807.3	Open fracture of sternum		
	807.4	Flail chest		

	807.6	Fracture of larynx and trachea, open		
	807.x6	Fracture or ribs, six ribs		
	807.x7	Fracture or ribs, seven ribs		
	807.x8	Fracture or ribs, eight or more ribs		
	808.1	Open fracture of acetabulum		
	808.3	Open fracture of pubis		
	808.43	Multiple closed pelvic fractures with disruption of pelvic circle		
	808.5	Open fracture of other specified part of pelvis		
	809.1	Fracture of bones of trunk, open		
	812.5x	Fracture of lower end of humerus, open		
	820.1x	Transcervical fracture, open		
	820.3x	Pertrochanteric fracture of femur, open		
	820.9	Fracture of unspecified part of neck of femur, open		
	823.3x	Fracture of shaft of tibia and fibula, open		
	827.1	Other, multiple, and ill-defined fractures of lower limb, open		
	860.1	Pneumothorax with open wound into thorax		
	860.3	Hemothorax with open wound into thorax		
	860.5	Pneumohemothorax with open wound into thorax		
	861.xx-869.x	Injury to internal organs		
	874.1x	Open wound, larynx and trachea, complicated		
	875.1	Open wound of chest wall, complicated		
	884.x	Multiple and unspecified wounds, upper limb		
	887.x	Traumatic amputation of arm and hand		
	894.x	Multiple and unspecified wounds, lower limb		
	896.x	Traumatic amputation of foot		
	897.x	Traumatic amputation of leg		
	901.xx	Injury to blood vessels of thorax		
	902.xx	Injury to blood vessels of abdomen		

		and pelvis		
	903.xx	Injury to blood vessels of upper extremity		
	904.xx	Injury to blood vessels of lower extremity and unspecified sites		
	926.xx	Crushing injury of trunk		
	929.x	Crushing injury of multiple and unspecified sites		
	952.xx	Spinal cord injury without evidence of spinal bone injury		
	959.8	Injury, other specified sites, including multiple		

Heart Disease Indicator

Note: These codes were only applicable for the heart disease indicator for the OTC algorithm.

Comorbidity	**ICD-9 Dx**	**Description**	**Type**	**Value/category**
Cardiovascular (CV) Disease	410.x	Acute myocardial infarction	Binary	Yes/No
	411.x	Other acute and subacute forms of ischemic heart disease		
	412.x	Old myocardial infarction		
	430	Subarachnoid hemorrhage		
	431	Intracerebral hemorrhage		
	432.x	Other and unspecified intracranial hemorrhage		
	433.xx	Occlusion and stenosis of precerebral arteries		
	434.xx	Occlusion of cerebral arteries		
	435.x	Transient cerebral ischemia		
	436	Acute but ill-defined cerebrovascular disease		
	997.02	Iatrogenic cerebrovascular infarction or hemorrhage		
	437.0	Cerebral atherosclerosis		
	437.1	Other generalized ischemic cerebrovascular disease		
	438.xx	Late effects of cerebrovascular disease		
	V12.54	History of transient ischemic attack, and cerebral infarction without residual deficits		

	413.x	Angina pectoris		
	414.x	Other forms of chronic ischemic heart disease		
	428.x	Heart failure		

Drug Classes

Note: these classes are in addition to the study-specific variables of duloxetine, non-specific NSAIDs, COX-2 specific NSAIDs, prescription aspirin, and SSRI and SNRI other than duloxetine*, which are defined in Appendix 4.*

Flag 1. Anticoagulants	**[THERCLS]** 39
Flag 2. Antiplatelet agents	**[THERCLS]** 45
Flag 3. Glucocorticoids	**[THERCLS]** 166 *Note: listed as Adrenals & Combs*
Flag 4. Estrogens/progestin	**[THERCLS]** 170, 177
Flag 5. H2 inhibitors	**[THERCLS]** 161
Flag 6. Proton pump inhibitors	**[THERCLS]** 162 *Note: listed as Gastrointestinal Drugs, Misc*

Exposure and Dose Definitions

Term	Definition	Type	Value
Current exposure (primary exposure definition)	Exposure to duloxetine: any claim for these agents within a window of 90 days prior to the index date was considered. If the days' supply of the claim extended into the 30-day period prior to the index date, "current use" was assigned. Appropriate data cleaning on the days' supply field was performed where necessary. No allowances for poor adherence to therapy were considered in determining current exposure. Current exposure was determined in a similar manner for all drugs.	Binary	Yes/No
Exposure history	The calculation was the total days' supply dispensed in the 12 months prior to the index event, and was only calculated for those patients without current exposure, so that the two exposure groups were mutually exclusive.	Continuous	xx
Dose	This variable was calculated for duloxetine only. For patients meeting the definition of current use, a categorical dose was determined for duloxetine (<60 mg/day, 60 mg/day, >60 mg/day). The impact of duloxetine dose was explored in conjunction with the descriptive analysis of the severity of GI bleed. Dose was calculated for only the "current exposure" duloxetine claim, as (quantity	Categorical	<60 mg/day 60 mg/day >60 mg/day

	dispensed * capsule strength / days' supply).		
Days' supply	Based on THAM variable [DAYSUPP]. Describes the number of days of drug therapy covered by the prescriptions of interest (duloxetine, prescription NSAIDs, COX-2 NSAIDs, and prescription aspirin) in the 12-month pre-index period.	Continuous for each drug class	xx

Severity Measures

<table>
<tr><th>Term</th><th>Definition</th><th>Type</th><th>Value</th></tr>
<tr><td>Endoscopy procedure</td><td>
<table>
<tr><th>CPT Codes</th><th>Description</th></tr>
<tr><td>43250</td><td>Upper GI endoscopy including esophagus, stomach and either duodenum and/or jejunum; with removal of tumors, polyps, or other lesions by hot biopsy forceps or bipolar cautery</td></tr>
<tr><td>43251</td><td>Upper GI endoscopy including esophagus, stomach and either duodenum and/or jejunum; as appropriate; with removal of tumors, polyps, or other lesions by snare technique</td></tr>
<tr><td>43255</td><td>Upper GI endoscopy including esophagus, stomach and either duodenum and/or jejunum; diagnostic, with control of bleeding by any method</td></tr>
<tr><td>43256</td><td>Upper GI endoscopy including esophagus, stomach and either duodenum and/or jejunum as appropriate; diagnostic, with transendoscopic stent placement (includes predilation)</td></tr>
<tr><td>43258</td><td>Upper GI endoscopy including esophagus, stomach and either duodenum and/or jejunum as appropriate; with ablation of tumors, polyps, or other lesions not amenable by hot biopsy forceps, bipolar cautery or snare technique</td></tr>
<tr><td>43259</td><td>Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum; with endoscopic ultrasound examination, including the esophagus, stomach, and either the duodenum and/or jejunum as appropriate</td></tr>
</table>
</td><td>Binary</td><td>Yes/No</td></tr>
<tr><td>Upper GI surgical procedure</td><td>
<table>
<tr><th>ICD-9 Px</th><th>Description</th></tr>
<tr><td>42.x</td><td>Operations on esophagus</td></tr>
<tr><td>43.x</td><td>Incision and excision of stomach</td></tr>
<tr><td>44.x</td><td>Other operations on stomach</td></tr>
</table>
</td><td>Binary</td><td>Yes/No</td></tr>
<tr><td>Blood transfusion</td><td>
<table>
<tr><th>ICD-9 V/ Px/CPT codes</th><th>Description</th></tr>
<tr><td>V 58.2</td><td>Blood transfusion, without reported diagnosis</td></tr>
</table>
</td><td>Binary</td><td>Yes/No</td></tr>
</table>

<table>
<tr><td></td><td><table>
<tr><td>V 99.0x</td><td>Transfusion of blood and blood components</td></tr>
<tr><td>99.03</td><td>Whole blood transfus NEC</td></tr>
<tr><td>99.04</td><td>Packed cell transfusion</td></tr>
<tr><td>36430
(CPT code)</td><td>Blood Transfusion Service</td></tr>
</table></td><td></td><td></td></tr>
<tr><td>Invasive procedure to control bleeding</td><td><table>
<tr><th>ICD-9 Px/
CPT codes</th><th>Description</th></tr>
<tr><td>44.4x</td><td>Control of hemorrhage and suture of ulcer of stomach or duodenum</td></tr>
<tr><td>CPT 43227</td><td>Esophagoscopy, rigid or flexible; with control of bleeding, any method</td></tr>
<tr><td>CPT 43255</td><td>Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with control of bleeding, any method</td></tr>
</table></td><td>Binary</td><td>Yes/No</td></tr>
<tr><td>Acute post-hemorrhagic anemia (anemia due to acute blood loss)</td><td><table>
<tr><th>ICD-9 Dx</th><th>Description</th></tr>
<tr><td>285.1</td><td>Acute posthemorrhagic anemia</td></tr>
</table></td><td>Binary</td><td>Yes/No</td></tr>
<tr><td>Other GI procedures suggesting severity</td><td><table>
<tr><th>CPT</th><th>Description</th></tr>
<tr><td>43237</td><td>Endoscopic ultrasound exam
(limited to the esophagus)</td></tr>
<tr><td>43243</td><td>Directed injection sclerosis
of varices</td></tr>
<tr><td>43247</td><td>Upper GI endoscopy with removal of foreign body</td></tr>
<tr><td>43257</td><td>Upper GI endoscopy including esophagus, stomach and either the duodenum and/or jejunum as appropriate; with delivery of thermal energy to the muscle of lower esophageal sphincter and/or gastric cardia, for treatment of gastroesophageal reflux disease</td></tr>
</table></td><td>Binary</td><td>Yes/No</td></tr>
</table>

Any ancillary severity of bleed indicator	*Any codes associated with the severity classes listed above*	Binary	Yes/No
	Invasive procedure to control bleeding		
	Acute post-hemorrhagic anemia (anemia due to acute blood loss)		
	Other GI procedures suggesting severity		

Non-Coded Definitions of Severity

Variable	Definition and notes	Type	Value
Length of stay - total population	Duration of inpatient admission in days for UGI bleed. Calculated using **[DAYS]** for the entire patient population.	Continuous	xx
Length of stay - survivors	Duration of inpatient admission in days for UGI bleed for survivors only. Calculated using **[DAYS].** Calculated only for cases whose [DSTATUS] did not equal 20-29 or 40-42 (as seen below, in the definition of "death").	Continuous	xx
Readmission	Defines whether a patient had at least 1 readmission for UGI bleed during the 30 days following discharge from the index encounter. **Only patients whose [DSTATUS] did not equal 20-29 or 40-42 were considered.**	Binary	Yes/No
Death	Indicates the patient diedduring their inpatient stay for UGI bleed. Status was ascertained via THAM variable [**DSTATUS**] = 20-29 or 40-42.	Binary	Yes/No

Non-Code Definitions for Pre-Index Healthcare Utilization

Variable	Definition and notes	Type	Value
Inpatient visits	The number of inpatient visits in the 12-month pre-index window, not including the index date/event. Inpatient place of service codes associated are located in Appendix 7.	Continuous	xx
Outpatient visits	The number of outpatient visits in the 12-month pre-index window, not including the index date/event. Outpatient place of service codes associated are located in Appendix 7.	Continuous	xx
Emergency department visits	The number of emergency department visits in the 12-month pre-index window, not including the index date/event. Emergency department place of service codes associated are located in Appendix 7.	Continuous	xx

Unique drug classes	The count of unique therapeutic classes per patient in the 12 months pre-index period, not including the index date/event. Derived from the 3-digit [THERCLS] Marketscan variable, using the range of 1-251.	Continuous	1-251
Total plan paid cost ($)	The summation of all costs associated with each patient in the 12-month pre-index period, not including the index date/event. Reported in dollars as the plan paid amount.	Continuous	xx

Appendix 6. Charlson Comorbidity Index (CCI) algorithm

COMORBIDITY	SCORE	ICD-9 Dartmouth-Manitoba (Romano *et al*, 1993)
Myocardial Infarction	1	410.xx, 412*
Congestive Heart Failure	1	402.01, 402.11, 402.91, 425.x, 428.x, 429.3, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93†
Peripheral Vascular Disease	1	440.x*, 441.x*, 442.x*, 443.1-443.9*, 447.1*, 785.4*, **38.13-38.14(P)*, 38.16(P)*, 38.18(P)*, 38.33-38.34(P)*, 38.36(P)*, 38.38(P)*, 38.43-38.44(P)*, 38.46(P)*, 38.48(P)*, 39.22-39.26(P)*, 39.29(P)***
Cerebrovascular Disease	1	362.34, 430-436, 437-437.1, 437.9, 438, 781.4, 784.3, 997.0, **38.12(P), 38.42(P)**
Dementia	1	290.x*, 331-331.2*
Chronic Pulmonary Disease	1	415.0*, 416.8-416.9*, 491.x-494*, 496*
Connective Tissue (Rheumatologic) Disease	1	710.x*, 714.x*‡
Peptic Ulcer Disease	1	531.xx-534.xx
Mild Liver Disease	1	571.2*, 571.5-571.6*, 571.8-571.9*
Diabetes	1	250.0x-250.3x*
Diabetes with Chronic Complications	2	250.4x-250.9x*§
Hemiplegia or Paraplegia	2	342.x, 344.x
Renal Disease	2	585-586*, V42.0*, V45.1*, V56.x*, **39.27(P)*, 39.42(P)*, 39.93-39.95(P)*, 54.98(P)***
Malignancy Including Leukemia Lymphoma	2	140.x-171.x*, 174.x-195.x*, 200.xx-208.x*, 273.0*, 273.3*, V10.46*, **60.5(P)*, 62.4-62.41(P)***
Moderate or Severe Liver Disease	3	572.2-572.4*, 456.0-456.2x*, **39.1(P)*, 42.91(P)***§
Metastatic Solid Tumor	6	196.x-199.x*§
AIDS	6	042.x-044.x*‡

Notes from Romano *et al* (Table 1)

* Codes with asterisks were included if index or prior admission. Other codes were included only if recorded prior to index admission. Each asterisk applies to all codes within the indicated range.
† Blue CHF codes were introduced in October 1989. These codes were not part of the original Romano study but were incorporated in a later algorithm as noted in a footnote to Table 1.
‡ Rheumatologic diseases and AIDS were too rare to be part of the original Romano study. Romano notes, however, that these codes were part of their revisions for another project.
§ These comorbidities take precedence over less severe comorbidities involving the same organ system. For example, a patient with metastatic solid tumor would have that comorbidity coded as present and any associated primary malignancy diagnoses would be ignored. Moderate-to-severe liver disease and complicated diabetes are treated in the same way to avoid inadvertently double-counting one chronic condition that may be characterized using multiple diagnosis codes in administrative data.
Bold indicates procedure codes.

Appendix 7. Admission source categories

Note: These admission categories were used in the determination of prior GI events in the Comorbidities assessment.

Inpatient	
THAM value [STDPLAC]	Label
9	Prison-Correctional Facility
21	Inpatient Hospital
26	Military Treatment Facility
27	Inpatient Long-Term Care (NEC)
28	Other Inpatient Care (NEC)
31	Skilled Nursing Facility
32	Nursing Facility
51	Inpatient Psychiatric Facility
52	Psych Facility Partial Hospital
55	Residential Substance Abuse Facility
56	Psych Residential Treatment Center
61	Comprehensive Inpatient Rehabilitation Facility

Outpatient	
THAM value [STDPLAC]	Label
5	Indian Hlth Svc Free-standing Facility
6	Indian Hlth Svc Provider-based Facility
7	Tribal 638 Free-standing Facility
8	Tribal 638 Provider-based Facility
11	Office
17	Walk-in Retail Health Clinic
22	Outpatient hospital
24	Ambulatory Surgical Center
33	Custodial Care Facility
34	Hospice
49	Independent Clinic
50	Federally Qualified Health Center
53	Community Mental Health Center
54	Intermed Care/Mental Retarded
57	Non-resident Substance Abuse Facility
62	Comprehensive Outpatient Rehabilitation Facility

65	End-Stage Renal Disease Facility
71	State/Local Public Health Clinic
72	Rural Health Clinic
95	Outpatient (NEC)

Emergency Department (outpatient place of service for purposes of clinical location for diagnostic codes)	
THAM value [STDPLAC]	Label
20	Urgent Care Facility
23	Emergency Department-Hospital

Other (not to be included in this project)	
THAM value [STDPLAC]	Label
1	Pharmacy
3	School
4	Homeless Shelter
12	Patient Home
13	Assisted Living Facility
14	Group Home
15	Mobile Unit
16	Temporary Lodging
25	Birthing Center
35	Adult Living Care Facility
41	Ambulance (land)
42	Ambulance (air or water)
60	Mass Immunization Center
81	Independent Laboratory
98	Pharmacy
99	Other Unlisted Facility

Appendix 8. Predictive algorithm to estimate over-the-counter NSAIDs exposure

A predictive algorithm was developed using information on OTC NSAID use that considered the demographic and health characteristics identified in the national surveys. Rather than make a random assignment of possible OTC NSAID use in the 30 days prior to the GI bleed event, we used known covariates to derive a risk estimate (ie, a probability) of probable OTC NSAID use for each of the cases and controls in the study. This was possible because each case and control had a large number of observed covariates such as patient demographics, comorbidities, and previous prescription drug use. These covariates were compared to known factors to estimate the probability of current exposure to OTC NSAID prior to the GI bleed event. The algorithm assigned a binary probability of OTC NSAID use (yes, no) in the 30 days prior to admission to each case and control in the study based on patient characteristics available in the THAM database. As all OTC NSAIDs available in the US are non-selective NSAIDs, patients with a probability of "yes" were assigned to the non-selective NSAID exposure group for purposes of modeling the interaction with duloxetine.

Aspirin

The 2005 Medical Expenditure Panel Survey was used to derive estimates for OTC aspirin use.[23]

First, an exposure adjustment was calculated for males and females:

Male		Female		
CV	No CV	CV	No CV	Covariate
61.3	15.3	47.4	14.4	% with/out CV
1.13729128	1.033783784	0.87940631	0.972973	Exposure adjustment
Note: Exposure adjustment for whole population 53.9% with CV, 14.8% without CV.				

CV=presence of cardiovascular disease indicators

Second, the exposure adjustment calculated above was applied to the point estimates for males and females across the age categories reported in the MEPS data.

	18-44		45-64		65+		
	CV	no CV	CV	no CV	CV	no CV	Covariate
	16.6	4.2	55.5	22.7	63.7	41.4	Unadjusted % with/out CV
Male	18.9	4.3	63.1	23.5	72.4	42.8	With adjustment
Female	14.6	4.1	48.8	22.1	56.0	40.3	With adjustment
Note N > 12,000 for Medical Expenditure Panel Survey [23]							

The result highlighted in yellow populates columns A and B in the final table below.

NSAIDs

Data from the 2002 National Consumers League (NCL) survey as published by Wilcox,[24] as well as the 2006 Slone Survey,[25] were used to derive estimates for OTC NSAID use.

The NCL survey reports that 56% of participants use OTC pain medications on a monthly basis, and that 42.1% of that use is OTC NSAIDs (ibuprofen and naproxen), resulting in an estimate of 23.6% monthly use for OTC NSAIDs (excluding aspirin)[24].

The Slone survey reports weekly use for both prescription and OTC agents, with aspirin, ibuprofen and naproxen all in the top 10 products used. Per the Slone data, the past week utilization of ibuprofen and ibuprofen is 19.3% across all age and gender groups[25], which is slightly less than the NCL (monthly) data of 23.6%. The OTC NSAID data between these 2 surveys thus appear to be in general agreement.

To obtain the final point estimates, we applied an NCL/Slone ratio of 23.6/19.3 across the age and gender categories described in the Slone survey to arrive at the final point estimates.

Male				Female			
18-44	45-64	65+	All	18-44	45-64	65+	All
%	%	%	%	%	%	%	%
25.8	23.2	12	20.8	32	28.9	16.6	25.6

These results populate column C below.

Aspirin + OTC NSAID

The point estimates for aspirin + OTC NSAID are summed in columns D and E below, distinguishing between those with heart disease and without heart disease.

Finally, the point estimates were adjusted for the estimated prevalence of OTC aspirin and OTC NSAID use as reported by Paulrose-Ram using NHANES III data, using a formula of (use of ≥2 OTC-Rx analgesics per month) - (use of ≥2 analgesics where Rx NSAID or OTC APAP is one of them) = (use where ≥2 analgesics is OTC ASA and NSAID).[26]

Point estimate adjustment for prevalence of combined OTC ASA and OTC NSAID use			
	Use of ≥2 Rx or OTC analgesics per month	Use of ≥2 analgesics where Rx NSAID or OTC APAP is one of those used	Use where ≥2 analgesics are OTC ASA and NSAID
Males			
18-44	27	37	17.01
45-64	22	28	15.84
65+	21	26	15.54
Females			0
18-44	39	50	19.5
45-64	33	34	21.78
65+	25	26	18.5

These final results populate columns F and G in the final algorithm. Cells highlighted in yellow are used in our multivariable analysis.

Predictive algorithm point estimates - Use in last 30 days								
	A	B	C		D	E	F	G
	Aspirin use with heart disease indicator	Aspirin use without heart disease indicator	OTC NSAID use		Total use with heart diseaase indicator	Total use without heart disease indicator	Total use with heart disease indicator	Total use without heart disease indicator
Males					simple sum		adjusted for combined use	
18-44	18.9	4.3	25.8		44.7	30.1	41.5	29.4
45-64	63.1	23.5	23.2		86.3	46.7	82.6	43.0
65+	72.4	42.8	12.0		84.4	54.8	82.5	52.9
Females								
18-44	14.6	4.1	32.0		46.6	36.1	43.8	35.3
45-64	48.8	22.1	28.9		77.7	51.0	71.4	44.7
65+	56.0	40.3	25.6		81.6	65.9	76.9	61.2

Appendix 9. Comorbidities and covariates associated with multivariable analyses

Table A shows the covariates included in the model for the 8 exposure groups, adjusted (*Note: corresponds with the model summarized in Table 12*)

8 exposure groups, adjusted		95% Wald Confidence Limits	
Effect	**Odds Ratio**	**Lower 95% CL**	**Upper 95% CL**
Gender	0.944	0.908	0.981
Age	0.998	0.991	0.999
CCI	1.202	1.181	1.224
COPD	1.330	1.235	1.433
Asthma	1.357	1.239	1.488
HTN	1.912	1.832	1.992
Ischemic Heart Disease	1.916	1.821	2.016
Heart Failure	1.637	1.527	1.757
Diabetes	1.236	1.168	1.307
CKD	1.376	1.266	1.495
Gastritis	4.255	3.968	4.545
Celiac Disease	1.980	1.147	3.425
Depression	1.916	1.745	2.105
Peptic/UGI Ulcer	333.333	250.000	333.333
Esophagitis	3.021	2.762	3.311
Diabetic Peripheral Neuropathic Pain	1.445	1.261	1.656
Chronic Musculoskeletal Pain	1.101	1.052	1.152
Trauma	2.315	2.092	2.564
Anticoagulants + Antiplatelets	0.831	0.789	0.875
H2 + Proton Pump Inhibitors	2.242	2.146	2.347
Inpatient Visits (#)	0.883	0.875	0.891
Outpatient Visits (#)	0.985	0.984	0.987
Unique Prescriptions (#)	0.987	0.985	0.989

CCI=Charlson Comorbidity Index; COPD=chronic obstructive pulmonary disease; HTN=hypertension; CKD=chronic kidney disease

Table B shows the covariates included in the sensitivity analysis for the 4 exposure groups, adjusted (*Note: corresponds with the model summarized in Table 14*)

4 exposure groups, adjusted		95% Wald Confidence Limits	
Effect	Odds Ratio	Lower 95% CL	Upper 95% CL
Gender	0.944	0.908	0.981
Age	0.998	0.997	0.999
CCI	1.202	1.181	1.224
COPD	1.33	1.235	1.433
Asthma	1.359	1.239	1.488
HTN	1.912	1.832	1.992
Ischemic Heart Disease	1.916	1.821	2.016
Heart Failure	1.639	1.527	1.757
Diabetes	1.236	1.168	1.307
CKD	1.376	1.266	1.495
Gastritis	4.255	3.968	4.545
Celiac Disease	1.976	1.145	3.413
Depression	1.916	1.745	2.105
Peptic/UGI Ulcer	333.333	250	333.333
Esophagitis	3.021	2.762	3.311
Diabetic Peripheral Neuropathic Pain	1.445	1.261	1.656
Chronic Musculoskeletal Pain	1.101	1.052	1.153
Trauma	2.315	2.092	2.564
Anticoagulants + Antiplatelets	0.829	0.787	0.874
H2 + Proton Pump Inhibitors	2.242	2.146	2.347
Inpatient Visits (#)	0.883	0.875	0.891
Outpatient Visits (#)	0.985	0.984	0.987
Unique Prescriptions (#)	0.987	0.985	0.989

CCI=Charlson Comorbidity Index; COPD=chronic obstructive pulmonary disease; HTN=hypertension; CKD=chronic kidney disease

Table C shows the covariates included in the sensitivity analysis for the 8 exposure groups, adjusted **and including the OTC NSAID exposure estimate** (*Note: corresponds with the model summarized in Table 15*)

8 exposure groups, adjusted, with OTC NSAID estimate		95% Wald Confidence Limits	
Effect	Odds Ratio	Lower 95% CL	Upper 95% CL
Gender	1.059	1.059	1.060
Age	0.998	0.998	0.998
CCI	1.200	1.199	1.200
COPD	1.328	1.326	1.328
Asthma	1.359	1.357	1.359
HTN	1.912	1.908	1.912
Ischemic Heart Disease	1.898	1.887	1.905
Heart Failure	1.629	1.626	1.631
Diabetes	1.235	1.233	1.235
CKD	1.372	1.372	1.374
Gastritis	4.237	4.237	4.237
Celiac Disease	1.972	1.961	1.980
Depression	1.912	1.908	1.912
Peptic/UGI Ulcer	333.333	333.333	333.333
Esophagitis	3.021	3.021	3.021
Diabetic Peripheral Neuropathic Pain	1.443	1.441	1.443
Chronic Musculoskeletal Pain	1.111	1.110	1.112
Trauma	2.309	2.309	2.309
Anticoagulants + Antiplatelets	0.831	0.831	0.832
H2 + Proton Pump Inhibitors	2.247	2.247	2.252
Inpatient Visits (#)	0.883	0.883	0.883
Outpatient Visits (#)	0.985	0.985	0.985
Unique Prescriptions (#)	0.987	0.987	0.987

CCI=Charlson Comorbidity Index; COPD=chronic obstructive pulmonary disease; HTN=hypertension; CKD=chronic kidney disease. Based on a bootstrap model of 400 iterations.

Table D shows the covariates included in the sensitivity analysis for the 4 exposure groups, adjusted **and including the OTC NSAID exposure estimate** (*Note: corresponds with the model summarized in Table 16*)

4 exposure groups, adjusted, with OTC NSAID estimate		95% Wald Confidence Limits	
Effect	Odds Ratio	Lower 95% CL	Upper 95% CL
Gender	1.059	1.059	1.060
Age	0.998	0.998	0.998
CCI	1.202	1.201	1.202
COPD	1.330	1.330	1.330
Asthma	1.359	1.357	1.359
HTN	1.908	1.908	1.912
Ischemic Heart Disease	1.908	1.898	1.919
Heart Failure	1.634	1.631	1.639
Diabetes	1.236	1.235	1.236
CKD	1.376	1.374	1.376
Gastritis	4.255	4.255	4.255
Celiac Disease	1.976	1.969	1.980
Depression	1.919	1.912	1.923
Peptic/UGI Ulcer	333.333	333.333	333.333
Esophagitis	3.021	3.021	3.030
Diabetic Peripheral Neuropathic Pain	1.445	1.445	1.447
Chronic Musculoskeletal Pain	1.103	1.101	1.103
Trauma	2.315	2.315	2.315
Anticoagulants + Antiplatelets	1.206	1.206	1.207
H2 + Proton Pump Inhibitors	2.242	2.242	2.242
Inpatient Visits (#)	0.883	0.883	0.883
Outpatient Visits (#)	0.985	0.985	0.985
Unique Prescriptions (#)	0.987	0.987	0.987

CCI=Charlson Comorbidity Index; COPD=chronic obstructive pulmonary disease; HTN=hypertension; CKD=chronic kidney disease. Based on a bootstrap model of 400 iterations.

Appendix 10. Complete model outputs derived from the investigation into bias

All medication exposures are here compared to Group 1: no current medication.

Table E. The full model containing all 3 exposure comparisons and a combined anticoagulant and antiplatelet variable. *Note: corresponds with the model summarized in Table 17a.*

Effect	Reference	OR	LowerCL	UpperCL
Gender	M vs F	0.944	0.908	0.981
Age	n/a	0.998	0.997	0.999
Duloxetine	2 vs 1	1.056	0.891	1.252
Rx NSAIDs,COX-2, ASA	3 vs 1	1.126	1.059	1.197
Duloxetine + Rx NSAIDs, COX-2, ASA	4 vs 1	1.208	0.924	1.578
CCI	n/a	1.202	1.181	1.224
COPD	1 vs 0	1.33	1.234	1.433
Asthma	1 vs 0	1.358	1.239	1.488
HTN	1 vs 0	1.911	1.833	1.993
Ischemic Heart Disease	1 vs 0	1.916	1.821	2.017
Heart Failure	1 vs 0	1.638	1.528	1.757
Diabetes	1 vs 0	1.236	1.168	1.307
CKD	1 vs 0	1.375	1.266	1.494
Gastritis	1 vs 0	4.249	3.975	4.543
Celiac Disease	1 vs 0	1.978	1.145	3.416
Depression	1 vs 0	1.917	1.744	2.106
Peptic/UGI Ulcer	1 vs 0	301.781	280.354	324.846
Esophagitis	1 vs 0	3.023	2.76	3.311
Diabetic Peripheral Neuropathic Pain	1 vs 0	1.445	1.261	1.656
Chronic Musculoskeletal Pain	1 vs 0	1.101	1.051	1.153
Trauma	1 vs 0	2.317	2.093	2.565
Anticoagulants + Antiplatelets	1 vs 0	0.829	0.787	0.874
H2 + Proton Pump Inhibitors	1 vs 0	2.244	2.146	2.346
Inpatient Visits (#)	n/a	0.883	0.875	0.891
Outpatient Visits (#)	n/a	0.985	0.984	0.987
Unique Prescriptions (#)	n/a	0.987	0.985	0.989

CCI=Charlson Comorbidity Index; COPD=chronic obstructive pulmonary disease; HTN=hypertension; CKD=chronic kidney disease.

Table F displays complete model results for duloxetine exposure only, with the combined anticoagulant and antiplatelet variable. *Note: corresponds with the model summarized in Table 17b.*

Effect	Reference	OR	LowerCL	UpperCL
Gender	M vs F	0.946	0.908	0.985
Age	n/a	0.997	0.996	0.999
Duloxetine	2 vs 1	1.068	0.901	1.267
CCI	n/a	1.202	1.18	1.225
COPD	1 vs 0	1.355	1.252	1.466
Asthma	1 vs 0	1.374	1.246	1.515
HTN	1 vs 0	1.918	1.834	2.007
Ischemic Heart Disease	1 vs 0	1.901	1.8	2.007
Heart Failure	1 vs 0	1.609	1.494	1.732
Diabetes	1 vs 0	1.254	1.181	1.331
CKD	1 vs 0	1.409	1.292	1.537
Gastritis	1 vs 0	4.334	4.038	4.651
Celiac Disease	1 vs 0	1.97	1.112	3.491
Depression	1 vs 0	1.927	1.745	2.129
Peptic/UGI Ulcer	1 vs 0	292.987	270.87	316.91
Esophagitis	1 vs 0	3.221	2.928	3.544
Diabetic Peripheral Neuropathic Pain	1 vs 0	1.437	1.246	1.658
Chronic Musculoskeletal Pain	1 vs 0	1.097	1.043	1.154
Trauma	1 vs 0	2.375	2.133	2.644
Anticoagulants + Antiplatelets	1 vs 0	0.843	0.796	0.892
H2 + Proton Pump Inhibitors	1 vs 0	2.354	2.243	2.47
Inpatient Visits (#)	n/a	0.886	0.877	0.894
Outpatient Visits (#)	n/a	0.985	0.983	0.987
Unique Prescriptions (#)	n/a	0.985	0.983	0.987

CCI=Charlson Comorbidity Index; COPD=chronic obstructive pulmonary disease; HTN=hypertension; CKD=chronic kidney disease.

Table G displays model results for prescription NSAIDs, COX-2 NSAIDs, and aspirin exposure only, with the combined anticoagulant and antiplatelet variable. *Note: corresponds with the model summarized in Table 17c.*

Effect	Reference	OR	LowerCL	UpperCL
Gender	M vs F	0.937	0.902	0.975
Age	n/a	0.998	0.997	0.999
Rx NSAIDs,COX-2, ASA	3 vs 1	1.129	1.062	1.201
CCI	n/a	1.206	1.185	1.228
COPD	1 vs 0	1.335	1.238	1.439
Asthma	1 vs 0	1.343	1.224	1.474
HTN	1 vs 0	1.927	1.847	2.011
Ischemic Heart Disease	1 vs 0	1.912	1.816	2.013
Heart Failure	1 vs 0	1.645	1.534	1.765
Diabetes	1 vs 0	1.235	1.167	1.307
CKD	1 vs 0	1.375	1.265	1.495
Gastritis	1 vs 0	4.238	3.961	4.535
Celiac Disease	1 vs 0	2.005	1.158	3.472
Depression	1 vs 0	1.919	1.741	2.115
Peptic/UGI Ulcer	1 vs 0	306.421	284.389	330.159
Esophagitis	1 vs 0	3.093	2.821	3.391
Diabetic Peripheral Neuropathic Pain	1 vs 0	1.454	1.266	1.67
Chronic Musculoskeletal Pain	1 vs 0	1.098	1.048	1.15
Trauma	1 vs 0	2.36	2.131	2.615
Anticoagulants + Antiplatelets	1 vs 0	0.83	0.787	0.875
H2 + Proton Pump Inhibitors	1 vs 0	2.264	2.164	2.368
Inpatient Visits (#)	n/a	0.882	0.874	0.891
Outpatient Visits (#)	n/a	0.985	0.983	0.987
Unique Prescriptions (#)	n/a	0.986	0.984	0.988

CCI=Charlson Comorbidity Index; COPD=chronic obstructive pulmonary disease; HTN=hypertension; CKD=chronic kidney disease.

Table H displays model results for prescription NSAIDs, COX-2 NSAIDs, and aspirin exposure only, with the combined anticoagulant and antiplatelet variable. *Note: corresponds with the model summarized in Table 17d.*

Effect	Reference	OR	LowerCL	UpperCL
Gender	M vs F	0.941	0.903	0.98
Age	n/a	0.997	0.996	0.999
Duloxetine + Rx NSAIDs, COX-2, ASA	4 vs 1	1.226	0.937	1.603
CCI	n/a	1.204	1.182	1.227
COPD	1 vs 0	1.364	1.26	1.477
Asthma	1 vs 0	1.371	1.243	1.512
HTN	1 vs 0	1.91	1.825	1.998
Ischemic Heart Disease	1 vs 0	1.903	1.802	2.01
Heart Failure	1 vs 0	1.61	1.495	1.734
Diabetes	1 vs 0	1.259	1.186	1.337
CKD	1 vs 0	1.404	1.286	1.532
Gastritis	1 vs 0	4.349	4.051	4.669
Celiac Disease	1 vs 0	1.995	1.124	3.541
Depression	1 vs 0	1.907	1.723	2.11
Peptic/UGI Ulcer	1 vs 0	294.428	272.132	318.551
Esophagitis	1 vs 0	3.238	2.942	3.565
Diabetic Peripheral Neuropathic Pain	1 vs 0	1.469	1.273	1.696
Chronic Musculoskeletal Pain	1 vs 0	1.096	1.042	1.153
Trauma	1 vs 0	2.398	2.153	2.671
Anticoagulants + Antiplatelets	1 vs 0	0.84	0.794	0.89
H2 + Proton Pump Inhibitors	1 vs 0	2.366	2.254	2.483
Inpatient Visits (#)	n/a	0.886	0.877	0.894
Outpatient Visits (#)	n/a	0.985	0.983	0.987
Unique Prescriptions (#)	n/a	0.985	0.982	0.987

CCI=Charlson Comorbidity Index; COPD=chronic obstructive pulmonary disease; HTN=hypertension; CKD=chronic kidney disease.

Table I. Here, we display the full model containing all 3 exposure comparisons and separated anticoagulant and antiplatelet variables. *Note: corresponds with the model summarized in Table 18a.*

Effect	Reference	OR	LowerCL	UpperCL
Gender	M vs F	0.942	0.906	0.979
Age	n/a	0.998	0.997	0.999
Duloxetine	2 vs 1	1.056	0.891	1.251
Rx NSAIDs,COX-2, ASA	3 vs 1	1.13	1.063	1.202
Duloxetine + Rx NSAIDs, COX-2, ASA	4 vs 1	1.209	0.925	1.58
CCI	n/a	1.199	1.178	1.221
COPD	1 vs 0	1.333	1.237	1.437
Asthma	1 vs 0	1.362	1.243	1.492
HTN	1 vs 0	1.912	1.833	1.994
Ischemic Heart Disease	1 vs 0	1.88	1.785	1.98
Heart Failure	1 vs 0	1.657	1.545	1.777
Diabetes	1 vs 0	1.237	1.169	1.308
CKD	1 vs 0	1.379	1.27	1.499
Gastritis	1 vs 0	4.246	3.972	4.539
Celiac Disease	1 vs 0	1.991	1.153	3.438
Depression	1 vs 0	1.916	1.743	2.105
Peptic/UGI Ulcer	1 vs 0	302.529	281.047	325.653
Esophagitis	1 vs 0	3.024	2.761	3.313
Diabetic Peripheral Neuropathic Pain	1 vs 0	1.446	1.262	1.657
Chronic Musculoskeletal Pain	1 vs 0	1.111	1.06	1.163
Trauma	1 vs 0	2.317	2.093	2.564
Anticoagulants	1 vs 0	0.746	0.694	0.801
Antiplatelets	1 vs 0	0.946	0.886	1.01
H2 + Proton Pump Inhibitors	1 vs 0	2.236	2.139	2.337
Inpatient Visits (#)	n/a	0.883	0.875	0.891
Outpatient Visits (#)	n/a	0.985	0.984	0.987
Unique Prescriptions (#)	n/a	0.986	0.984	0.989

CCI=Charlson Comorbidity Index; COPD=chronic obstructive pulmonary disease; HTN=hypertension; CKD=chronic kidney disease.

Table J displays model results for duloxetine exposure only, with separated anticoagulant and antiplatelet variables. *Note: corresponds with the model summarized in Table 18b.*

Effect	Reference	OR	LowerCL	UpperCL
Gender	M vs F	0.944	0.906	0.984
Age	n/a	0.997	0.996	0.999
Duloxetine	2 vs 1	1.067	0.9	1.266
CCI	n/a	1.2	1.178	1.223
COPD	1 vs 0	1.357	1.254	1.469
Asthma	1 vs 0	1.377	1.249	1.518
HTN	1 vs 0	1.919	1.835	2.007
Ischemic Heart Disease	1 vs 0	1.873	1.772	1.978
Heart Failure	1 vs 0	1.624	1.508	1.749
Diabetes	1 vs 0	1.254	1.182	1.331
CKD	1 vs 0	1.412	1.295	1.541
Gastritis	1 vs 0	4.332	4.037	4.65
Celiac Disease	1 vs 0	1.98	1.118	3.506
Depression	1 vs 0	1.927	1.744	2.128
Peptic/UGI Ulcer	1 vs 0	293.601	271.436	317.576
Esophagitis	1 vs 0	3.222	2.929	3.546
Diabetic Peripheral Neuropathic Pain	1 vs 0	1.438	1.247	1.659
Chronic Musculoskeletal Pain	1 vs 0	1.104	1.05	1.161
Trauma	1 vs 0	2.376	2.134	2.645
Anticoagulants	1 vs 0	0.772	0.714	0.836
Antiplatelets	1 vs 0	0.935	0.871	1.004
H2 + Proton Pump Inhibitors	1 vs 0	2.347	2.237	2.463
Inpatient Visits (#)	n/a	0.886	0.877	0.894
Outpatient Visits (#)	n/a	0.985	0.983	0.987
Unique Prescriptions (#)	n/a	0.985	0.983	0.987

CCI=Charlson Comorbidity Index; COPD=chronic obstructive pulmonary disease; HTN=hypertension; CKD=chronic kidney disease.

Table K displays model results for prescription NSAIDs, COX-2 NSAIDs, and aspirin exposure only, with separated anticoagulant and antiplatelet variables. *Note: corresponds with the model summarized in Table 18c.*

Effect	Reference	OddsRatioEst	LowerCL	UpperCL
Gender	M vs F	0.935	0.9	0.972
Age	n/a	0.998	0.997	0.999
Rx NSAIDs,COX-2, ASA	3 vs 1	1.133	1.066	1.205
CCI	n/a	1.204	1.182	1.225
COPD	1 vs 0	1.338	1.24	1.443
Asthma	1 vs 0	1.347	1.227	1.478
HTN	1 vs 0	1.928	1.848	2.012
Ischemic Heart Disease	1 vs 0	1.877	1.781	1.977
Heart Failure	1 vs 0	1.664	1.551	1.786
Diabetes	1 vs 0	1.235	1.167	1.308
CKD	1 vs 0	1.379	1.269	1.5
Gastritis	1 vs 0	4.235	3.958	4.531
Celiac Disease	1 vs 0	2.019	1.166	3.494
Depression	1 vs 0	1.918	1.741	2.115
Peptic/UGI Ulcer	1 vs 0	307.167	285.08	330.965
Esophagitis	1 vs 0	3.095	2.823	3.393
Diabetic Peripheral Neuropathic Pain	1 vs 0	1.455	1.267	1.671
Chronic Musculoskeletal Pain	1 vs 0	1.107	1.056	1.16
Trauma	1 vs 0	2.36	2.13	2.614
Anticoagulants	1 vs 0	0.75	0.697	0.806
Antiplatelets	1 vs 0	0.943	0.882	1.008
H2 + Proton Pump Inhibitors	1 vs 0	2.256	2.157	2.36
Inpatient Visits (#)	n/a	0.882	0.874	0.891
Outpatient Visits (#)	n/a	0.985	0.984	0.987
Unique Prescriptions (#)	n/a	0.986	0.984	0.988

CCI=Charlson Comorbidity Index; COPD=chronic obstructive pulmonary disease; HTN=hypertension; CKD=chronic kidney disease.

Table L displays model results for prescription NSAIDs, COX-2 NSAIDs, and aspirin exposure only, with separated anticoagulant and antiplatelet variables. *Note: corresponds with the model summarized in Table 18d.*

Effect	Reference	OR	LowerCL	UpperCL
Gender	M vs F	0.939	0.901	0.979
Age	n/a	0.997	0.996	0.999
Duloxetine + Rx NSAIDs, COX-2, ASA	4 vs 1	1.227	0.938	1.604
CCI	n/a	1.202	1.179	1.225
COPD	1 vs 0	1.367	1.262	1.479
Asthma	1 vs 0	1.373	1.245	1.514
HTN	1 vs 0	1.91	1.826	1.999
Ischemic Heart Disease	1 vs 0	1.874	1.773	1.98
Heart Failure	1 vs 0	1.626	1.509	1.751
Diabetes	1 vs 0	1.259	1.186	1.337
CKD	1 vs 0	1.407	1.289	1.535
Gastritis	1 vs 0	4.346	4.048	4.666
Celiac Disease	1 vs 0	2.005	1.13	3.558
Depression	1 vs 0	1.906	1.722	2.11
Peptic/UGI Ulcer	1 vs 0	295.085	272.738	319.264
Esophagitis	1 vs 0	3.24	2.944	3.567
Diabetic Peripheral Neuropathic Pain	1 vs 0	1.47	1.273	1.697
Chronic Musculoskeletal Pain	1 vs 0	1.103	1.048	1.16
Trauma	1 vs 0	2.399	2.153	2.671
Anticoagulants	1 vs 0	0.767	0.709	0.831
Antiplatelets	1 vs 0	0.935	0.87	1.005
H2 + Proton Pump Inhibitors	1 vs 0	2.359	2.247	2.476
Inpatient Visits (#)	n/a	0.886	0.877	0.894
Outpatient Visits (#)	n/a	0.985	0.983	0.987
Unique Prescriptions (#)	n/a	0.985	0.982	0.987

CCI=Charlson Comorbidity Index; COPD=chronic obstructive pulmonary disease; HTN=hypertension; CKD=chronic kidney disease.

15. Annex 1. List of stand-alone documents

The National Drug Codes derived from Multum and Redbook that are associated with the medications used in this report are embedded here.

Final Medication NDC Codes.xls