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A Study of the Increased Risk of Bleeding Events in Patients with Blood Clotting Disorders, Associated with Antidepressant Medication Use

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A STUDY OF THE INCREASED RISK OF BLEEDING EVENTS IN PATIENTS WITH BLOOD CLOTTING DISORDERS, ASSOCIATED WITH ANTIDEPRESSANT MEDICATION USE

BY

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ABSTRACT

Background: Patients with blood clotting disorders have severely depleted levels of blood clotting factor (BCF) proteins in their blood, which results in a significantly higher risk of bleeding events than a typically healthy patient. Serotonin based antidepressant medications, such as selective serotonin reuptake inhibitors (SSRI) or serotonin norepinephrine reuptake inhibitors (SNRI) alter the levels of serotonin in the blood as a mechanism to treat depression.

Serotonin is used for many different chemical processes within the body including blood aggregation. We sought to quantify the potential risk associated with the use of these types of antidepressant medications to patients with blood clotting disorders.

Objective: To determine if patients with BCF disorders who are prescribed SSRI or SNRI medications are at an increased risk of having a major bleeding event.

Methods: A retrospective cohort study was conducted using data from the Optum Clinformatics Data Mart. An initial cohort of 16,124 patients with blood clotting disorders was formed; patients were excluded based upon enrollment eligibility, drug prescription date outside the study timeframe, and age under 12 years. A final study sample of 7,998 patients was formed. A follow up period of six months was selected to analyze major bleeding events; these events were identified using ICD-9 codes for hemorrhages. Patients were classified as to whether a bleeding event occurred during the period. The use of antidepressant medications was determined by prescription drug

dispensings three months prior to the follow up period. Both univariate and multivariate logistic regression models were built to enhance a final multivariate predictive model.

Results: The use of SSRI and SNRI antidepressant medications was not associated with an increased risk of bleeding events (p=0.93). Risk factors for having a major bleeding event included older age (P=<0.0001), male gender (P=<0.0001), diabetes (P=0.0001), nonsteroidal anti-inflammatory drug (NSAID) use (p=0.0040), anticoagulant use (P=<0.0001), and Hemophilia A (p=0.0001). Patients who were between 46-65 years old were 1.85 times more likely to have a major bleeding event than those between the ages of 26-45 (95% CI: 1.31-2.61). This risk increases to 3.47 times for those between the ages of 66-90 (95% CI: 2.36-5.11). Males were 1.84 times more likely to have a major bleeding event in comparison to females (95% CI: 1.42-2.38). Patients who had diabetes are at 1.84 times the risk of a major bleeding event than those with diabetes (95% CI: 1.35-2.52). Patients with Hemophilia A had approximately twice the risk of experiencing a bleeding event as compared with patients having other blood clotting disorders (OR 2.13; 95% CI: 1.54-2.93).

Conclusion: SSRI and SNRI antidepressant medications were not associated with an increased risk of bleeding events in this study. Factors associated with major bleeding events included male gender, older age, the use of NSAIDs or anticoagulants, and a diagnosis of Hemophilia A.

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CHAPTER 1

INTRODUCTION

Blood Clotting Factor disorders (BCF) are defined as inherited disorders that affect the body's ability to clot blood, thus increasing the frequency and duration of bleeding events. There are 12 different BCF proteins within the human body responsible for blood coagulation. (1) The most common types of BCF disorders are Hemophilia A, Hemophilia B, and Von Willebrand disorder. Hemophilia is an extremely rare disease; there are an estimated 20,000 cases in the U.S. (2) Hemophilia is a life-long disease that is typically diagnosed at an extremely young age either by blood test or by the occurrence of a bleeding event. Von Willebrand disease (VWD) is the most common BCF disorder that affects approximately 1% of the population. (3) VWD is a genetically inherited deficiency in the clotting protein which binds BCF VIII to the vessel walls. VWD occurs equally in both men and women; hemophilia occurs almost solely in the male population. (2, 3) This is due to hemophilia being an X-linked chromosome disease. The male chromosome consists of both an X and a Y chromosome while the female chromosome has two X. For a male to inherit hemophilia the trait only has to be present in the mother, while a female would need both the mother and father to have a hemophilia mutation. In most cases females who inherit the hemophilia trait will be a carrier, but they will not exhibit symptoms. (4)

Patients with hemophilia can be categorized based upon their severity of disease. Approximately 60% of patients with hemophilia are considered to be severe cases having less than 1% of normal BCF activity, approximately 15% are moderate cases ranging from 1-5%, and approximately 25% are mild cases ranging from 5-40%. (4) Patients with

severe hemophilia can experience a bleed (minor or major event) once or twice a week, while moderate cases experience a bleed approximately once a month, and mild cases bleed only after surgery or trauma.(4) If left untreated hemophilia can cause serious damage to joints, muscle tissue, and organ tissue as a result of continuous bleeding and swelling.

Antidepressant medications are prescribed for numerous reasons including but not limited to depression, attention-deficit hyperactivity disorder (ADHD), anxiety disorder, and bipolar disorder.(5) It is estimated that approximately one in ten adults in the U.S. are prescribed an antidepressant medication. (6) Due to the burden of disease, the prevalence of depression among patients with hemophilia is approximately 37%. (7) Selective Serotonin Reuptake Inhibitors (SSRI) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRI) are the most commonly prescribed classes of antidepressants prescribed in the U.S.; in a study using data from the National Ambulatory Medical Care Survey (NAMCS) it was found that 65% of all antidepressant drugs prescribed in 2000 were SSRI, while newer SNRI drugs accounted for 17% of the antidepressant utilization. (8) Serotonin based antidepressants can affect the body's ability to clot blood, this may have potential negative repercussions for patients with depleted BCF activity.

SSRI and SNRI drugs impair platelet aggregation by preventing serotonin reabsorption. (9, 10) Serotonin is an important neurotransmitter indirectly involved in platelet aggregation. Coated-platelets are rich in collagen, thrombin, and prothrombinase, a serine based protein that activates the proteins responsible for procoagulant activity. (11) Coated-platelets clot a bleed by adhering to the wall of the blood vessel (von Willebrand factor protein produced by the vessel walls), other platelets then crash into the adhered

platelets and begin to clump together due to the collagen and thrombin. This webbing created by the platelets coated with collagen and thrombin, traps red blood cells as well as other proteins in the blood to create a clot. Reducing the level of serotonin available will diminish the levels of coated-platelets in the blood.

We hypothesize that patients who are prescribed SSRI or SNRI medications will be more likely to experience a major bleeding event than those not using an SSRI or SNRI antidepressant medication. Furthermore, we hypothesize that patients with BCF disorders would be prescribed different classes of antidepressant medications as a result of this increased risk. The objective of this study is to determine if patients with BCF who are prescribed SSRI or SNRI antidepressants are at a higher risk of a major bleeding event occurring. A secondary objective of our study is to describe the prescribing frequency of antidepressant medication classes for patients with BCF disorders.

CHAPTER 2

REVIEW OF THE LITERATURE

Although a literature review of studies comparing bleeding rates for patients with BCF disorders and the potential impact of antidepressant medication yielded no direct results, there was still enough relevant literature available to help provide a basis for this study.

Von Willebrand's Disease is the most common genetic BCF disorder, found in 0.1-1% of the population. Within this patient population it is estimated that 10% of patients display symptoms of the disease. (12) Von Willebrand factor (vWF) is an adhesive glycoprotein responsible for gluing platelets to the vessel wall to form a clot. James et al. (13) identifies some of the major areas of bleeding associated with VWD: mucocutaneous (mucosa/skin transition) and epistaxis (nasal) bleeding, as well as easy and frequent tissue bruising. (13-15) Female patients frequently experience abnormally heavy bleeding during menstruation (menorrhagia). (16) Fressinaud et al. (17) also notes that gastrointestinal (GI) bleeding is reported in approximately 10% of VWD patients.

Hemophilia is a genetically transmitted disease on the X-chromosome. Both males and females can inherit the disease, but typically only males exhibit symptoms. Females who inherit the mutation for hemophilia are considered carriers and are not symptomatic. Plug et al (18) conducted an analysis of bleeding in carriers of hemophilia compared to those who are non-carriers. The researchers conducted this analysis using self-reported information collected from a survey of 546 women within the Netherlands; of these women, 274 were carriers of either hemophilia A or B. The researchers found that there was a significant increase in bleeding events for patients who were carriers of hemophilia

when compared to non-carriers. They also reported a statistically significant increase in the duration of bleeding for carriers after a tooth extraction, tonsillectomy, or operation. Carriers were twice as likely (Relative Risk (RR), 2.3: 95 % Confidence Interval (CI), 1.5 to 3.4) to have a bleed lasting longer than three hours after one of these procedures when compared to non-carriers. Hemophilia has an estimated incidence of 1 in 5,000 male births. (2) Soucie et al. (2) conducted a study for the Center for Disease Control and Prevention (CDC) in 1994, estimated that there were approximately 17,000 cases of hemophilia (A and B) in the U.S. Using birth and death rates since that time the CDC estimates that number has risen to approximately 20,000. (2) Males who inherit the hemophilia trait will be symptomatic due to only inheriting the X chromosome from his carrier mother and the Y from his father. Males who have hemophilia typically have frequent minor bleeds. Major bleeding events are usually the result of surgery or trauma. For male patients the majority of bleeding events occur internally and can result in serious damage caused to joints, muscle tissue, and organ tissue due to continuous bleeding and swelling. (2, 19)

A study conducted by Dawson et al (20) using commercial claims data from 2008-2013 was used to obtain a baseline measure for the utilization of each antidepressant drug class among privately insured patients, irrespective of comorbidity. The study population consisted solely of privately insured women age 15-44. The population ranged from 4.6 million to 6.8 million (per year) during the 5 year duration. They found that 15.4% of women had a prescription for an antidepressant filled at least once a year. Antidepressant drug claims were categorized by class: SSRI, SNRI, Tricyclic antidepressants (TCA), Monoamine oxidase inhibitors (MAOI) and other. It was found that 10.7% of the study

population were prescribed a SSRI, 2.8% were prescribed an SNRI, 1.4% were prescribed a TCA, 0% were prescribed a MAOI, and 3.9% were prescribed other types. They also found that 11.7% of the population filled a prescription for only one class of antidepressant, while 3.7% filled prescriptions for multiple classes of antidepressants.

A study by Turner et al. (9, 21, 22) details how SSRI drugs impact the likelihood of a bleeding event. The authors explain how SSRIs impact platelet aggregation by preventing serotonin from being reabsorbed at a normal rate. The authors concluded that the effect on platelets by SSRI drugs may have a clinical importance when considering a patient's risk of bleeding.

Prodan et al. (11) detailed the clinical background of SSRIs and their impact on coated-platelets. The authors explain that coated-platelets are rich in prothrombinase, a serine based protein that activates proteins responsible for procoagulant activity. This study found that patients prescribed SSRIs had a statistically significantly lower level of coated-platelets in the blood, with an analysis of variance test which yielded a p-value of 0.046. The study also identified smoking and aspirin use as having a significant impact on coated-platelet levels.

It is estimated that approximately one in ten adults in the United States (US) is prescribed an antidepressant medication, for a range of indications. (6) It is important to note, due to the burden of disease, the prevalence of depression among hemophilia patients is estimated at 37%. Iannone et al. (7) identified three covariates that could have a significant effect on the rate of depression for patients with hemophilia: unemployment

(P=0.01), lack of social support (p=0.04), and occurrences of bleeds per year (P=0.06). This study determined that the increase in number of bleeding events per year was slightly above the threshold for statistical significance; the study reported a 22% increase in the odds of depression for every five bleeding episodes (per year). Barlow et al (23) also reported that many hemophilia patients struggle with the physical burden of hemophilia, with symptoms including joint bleeds and co-morbidities due to blood transfusions. The authors discussed how these comorbidities diminish the patient's quality of life by affecting their education, work, and social activities.

This study will provide patients and physicians more knowledge about the effects of SSRI and SNRI antidepressants use for patients with BCF disorders. The aim of this study was to determine if patients who are prescribed a SSRI or SNRI medication are more likely to experience a major bleeding event then those not using an antidepressant medication. The study also determined prescribing frequencies for particular antidepressant medications used in patients with BCF disorders.

CHAPTER 3

METHODOLOGY

Study Population and Design

This study was conducted as a retrospective cohort study of privately insured U.S. citizens who were continuously enrolled throughout 2012. The study population was selected from the Optum Clinformatics Data Mart. Patients were deemed eligible if they had continuous enrollment during the entire year of 2012. The population included patients with Hemophilia A and B, Von Willebrand's Disease, and other non-specified blood clotting disorders. BCF disorders are typically diagnosed at an extremely young age and persists throughout a patient's lifetime. We formed our cohort to include all patients having any of the International Classification of Diseases (ICD-9) diagnosis codes designating a BCF disorder (286.0 - 286.5) available from 2010 to 2012. Most antidepressant medications are not FDA approved for children under the age of 12. (6) Based upon this information the inclusion criterion for age ranged from 12-100 years old. A sample of 621 patients would be required for a cohort study based upon the following characteristics: alpha=0.05, power=0.8, incidence=0.3, and a relative risk= 1.25. (24) By expanding our study from hemophilia A to all BCF disorders we were able surpass the required sample size and yield a study population of 7,998.

Dependent Variable:

Major bleeding events (hemorrhages) was the dependent variable used for this study. Major bleeding events were identified using a series of ICD-9 codes for hemorrhages validated in a study by Arnason et al (appendix 4). (25) A patient who had one or more documented bleeding event, requiring an inpatient or outpatient visit during a 6 month

follow-up period (July 1, 2012 – December 31, 2016) were assigned a designation of 1, whereas if no events occurred a designation of 0 was specified. The data source used in our study captured only bleeding events that were serious enough to require medical attention.

Independent Variables

SSRI or SNRI antidepressant use was the independent variable of interest. Patients were classified as exposed to these medications if they received at least 1 drug claim for either an SSRI or SNRI antidepressant during the 3 month period (April 1, 2016 – June 30, 2016) preceding the 6 month follow-up period for identifying bleeding events. Patients without an SSRI or SNRI antidepressant drug claim during this 3 month period were categorized as unexposed to these medications. Patients who initiated antidepressant drug therapy after this 3 month period were excluded from the analysis. As antidepressant polytherapy is common, we excluded users of non-SSRI/SNRI medications from our multivariate analyses. To describe antidepressant medication utilization overall, we determined the frequency of use of other antidepressant types including tricyclics, MAOIs, serotonin modulators, and miscellaneous antidepressant drugs (Appendix 3). We also created an independent variable describing the type of BCF disorder documented. BCF types were categorized into four groups: Hemophilia A, Hemophilia B or C, VWD, and other clotting factor/ intrinsic anticoagulants. Approximately 6% of the sample population had ICD-9 codes for multiple blood clotting disorders; these patients were included in the other clotting factor/ intrinsic anticoagulants group.

Independent Variables:

This study also investigated age, gender, geographic region, HIV, HEPC, and diabetes as other variables that may impact the risk of a major bleeding event occurring. Values for age, gender, and geographic region were determined during the three month baseline period. HIV, HEPC, and diabetes status were determined using the available eligibility period preceding the follow-up period. Age was tested as a continuous variable and as a categorical variable for the predictive model; the categorical version of age was used to display the distribution for descriptive statistics. The variable "U.S. state" was used to form geographic regions, i.e. Northeast, Midwest, Southeast, Southwest, and West. (26) There are numerous indications for which antidepressant drugs can be used.

Statistical analysis:

The analysis was conducted using the occurrence of at least one major bleeding episode as the dependent variable. Descriptive statistics were applied to present the frequency and percent of all variables, stratified by exposure and outcome status. Exposure to an SSRI or SNRI antidepressant was the primary independent variable of analysis in this study. A final logistic regression model was constructed using all variables deemed statistically significant. We excluded patients from the multivariate model who were identified as users of only other classes of antidepressant drugs (i.e. TCA, MAOI, serotonin modulator, or miscellaneous antidepressant). We first created univariate logistic regression models for each independent variable, testing each for a statistically significant relationship with the study outcome of bleeding events. Univariate models with a P-value < 0.20 were considered eligible for inclusion in the initial multivariate model. This saturated logistic regression model included the variables age (continuous), gender,

region, HIV, HEPC, diabetes, NSAID or anticoagulants, SSRI/ SNRI use, and BCF disorder type (hemophilia A, Hemophilia B/C, VWD, and other/ multiple BCF disorders). Variables within the model having a P-value<0.05 were considered statistically significant for this preliminary model.

To construct a final model we used backwards selection to eliminate variables which were included in model selection due to their statistically significant univariate p-values (<0.20). Several models were tested against the saturated model for their goodness-of-fit; with the intent to simplify a final model, creating the best predictive model possible. The likelihood ratio test (LRT) statistic was used to evaluate the different models created. Using the LRT statistic we concluded which variables should be included in the final model, using the following equation:

-2(LRT initial model – LRT Complex model)= X -> Zscore -> Chi Sq P-value

Based upon the Chi-Sq distribution and p-value (corresponding to degrees of freedom), we decided whether a variable should be included or excluded in the final model. The Akaike information criterion (AIC) and Hosmer-Lemeshow test were also applied. A smaller AIC value indicated a stronger model fit, while the Hosmer-Lemeshow uses the Pearson Chi-Sq statistic to assess model fit. A correlation procedure was performed for the 17 variables included in the saturated model. The objective of this correlation analysis was to analyze the variables for collinearity effects. A correlation coefficient of 0 would represent no correlation between the variables, thus they do not vary together. Variance inflation factor (VIF) and tolerance values (TOL) were also analyzed to identify

multicollinearity among variables. VIF values greater than 10 would identify variables with possible collinearity, while a minimum value for TOL of 0.20 would identify variables with multicollinearity effects.(27) Statistically significant variables were tested by creating new variable interaction terms, and testing models both with and without the new variable. These models were tested against each-other using the -2logL equation:

-2(LRT initial model – LRT Complex model)= X -> Zscore -> Chi Sq P-value

If the Chi-Sq value was statistically significant a variable interaction would be identified.

A relative risk (RR) was calculated to evaluate the effect of the variables included in the multivariate logistic regression model with risk of bleeding event, including a 95% confidence interval of the point estimate. The RR reflects the increase in risk of bleeding associated with a particular variable, and was calculated as the probability of an event occurring in the exposed group (event=1) divided by the probability of an event occurring in the unexposed group.

To analyze the prescribing frequency of all types of antidepressants, dispersions of the six antidepressant classifications available were identified. Based upon the antidepressant classes of interest and univariate analyses we further segmented three of the antidepressant classes down to the drug level, SSRI (6 drugs), SNRI (3 drugs), and serotonin modulators (3 drugs). (Appendix 2)

CHAPTER 4

Results

Study population characteristics

There were 16,124 patients identified as having a blood clotting factor disorder during the timeframe. Patients who did not have continuous enrollment through 2012 were excluded (N=6855). We then excluded patients under the age of 12 (N=304), and next excluded patients having a new a prescription for antidepressant medication occurring after the 3 month baseline exposure period (N=667). After all exclusions were applied the study cohort was reduced to 7,998 patients. We identified 1,531 (19.1%) patients as being prescribed an antidepressant medication during the 3 month baseline period. Of these 1,531 patients, we identified 876 as having an SSRI dispensing, and 377 who had an SNRI dispensing. Using the ICD9 codes for hemorrhage listed in appendix 4, we identified major bleeding events that occurred between 6/1/12 to 12/31/12. A total of 238 patients had at least one major bleeding event, among the 7,998 patients in the study population (3.476%). Of these 238 patients who had a major bleeding event, 42 (3.4%) were prescribed either an SSRI or SNRI antidepressant medication, while 196 (2.9%) were not.

The study population's predominant characteristics were 65.15% female, 40.67% of patients were between 46-65 years old, 30% lived in the southeast, 0.79% of patients had a diagnosis for HIV, 1.68% of patients had a diagnosis of HEPC, 13.43% of patients had a diagnosis of diabetes, 20.63% were prescribed a NSAID, 12.59% were prescribed an anticoagulant, 16.90% were prescribed an SSRI or SNRI, while 22.73% were prescribed an antidepressant of any kind. The prevalence of major bleeding events within the study population was 2.98%.

The bivariate analyses identified several variables that were associated with major bleeding events: older age (p=0.0001), male gender (p=0.0001), diabetes (p=0.0001), NSAID use (p=0.0004), anticoagulant use (p=0.0004), Hemophilia A (p=0.0004), and VWD (p=0.0006).

Antidepressant drug utilization in this patient population was similar to that of the general population. We found that 876 (57.2%) patients were prescribed an SSRI, 377 (24.6%) patients were prescribed an SNRI, 150 (9.8%) patients were prescribed a TCA, less than 10 were prescribed an MAOI antidepressant, 171 (11.2%) received a serotonin modulator, and 254 (16.6%) patients were prescribed an antidepressant classified as miscellaneous. During the 3 month baseline period 1,265 patients received only one class of antidepressant, 236 patients received 2 different classes of antidepressants, and 31 patients received 3 classes of antidepressant drugs.

The use of SSRI or SNRI antidepressants was more frequent among older patients, females, and patients with diabetes ($p < 0.0001$ for all comparisons). Users of NSAIDs and oral anticoagulants were also more likely to be prescribed SSRI or SNRI antidepressants as compared with patients not receiving NSAIDs or oral anticoagulants ($p < 0.0001$). Further detail is presented in Table 1c.

Univariate Logistic Regression Models

In univariate logistic regression analyses we identified variables having a statistically significant association with the occurrence of a major bleeding event (Table 3). In the univariate analysis, there was no significant increase in the occurrence of a bleeding event among patients prescribed an SSRI or SNRI medication (P=0.68, RR=1.09, 95% CI= 0.74 – 1.60). Univariate analyses were also conducted for age, gender, region, HIV,

HEPC, diabetes, and drugs known to affect bleeding. Age was tested as both a continuous variable and a categorical variable, and both versions had a statistically significant effect on the risk of bleeding (p=<0.0001). When analyzing age in categories there was a noticeable increase in risk with advancing age. Using 26 to 45 years old as the reference group, there was no difference in risk when compared to the age group 12 to 25 years old. When comparing patients between the ages of 46-65 years to patients age 26-45 years of age, the RR was 1.75 (CI: 1.23-2.51). For patients between 66 and 91 years of age (reference 26-45 years), the risk of major bleeding was more than 3 times higher (RR 3.40; 95% CI: 2.27-5.08). A univariate model for patient gender was also tested using female gender as the reference category. This model had a p=value of <0.0001 and a RR of 1.83 (95% CI: 1.40-2.40). Based upon this information we can conclude that male patients were at a significantly higher risk of having a major bleeding event as compared with female patients. U.S. regions were also evaluated, but no statistically significant effect was found between different geographic areas. Comorbidities of interest at the beginning of this study were identified as HIV, HEPC, and diabetes. Due to contaminated blood in the 1970's and 1980's many patients who required numerous blood transfusions over time contracted HIV and HEPC. (28, 29) This study found no significant increase in the risk of major bleeding events for patients with either disease. The RR for HIV was 1.80 (95% CI: 0.56-5.80) with a p-value=0.3245, and the relative risk for HEPC was 2.05 (95% CI: 0.94-4.45; p=0.0695). (Table 3) A univariate analysis assessing the influence of diabetes revealed that patients with this disease were at an increased risk of a major bleeding event occurring (RR 1.78; 95% CI: 1.27-2.49; p=0.0007). Lastly, a univariate analysis was conducted analyzing drug classes that are known to increase the risk of bleeding. Users of NSAIDs were 54% more likely to experience a bleeding event (RR

1.54; 95% CI: 1.14-2.08), while users of anticoagulants were twice as likely to experience a bleeding event (RR 2.00; 95% CI: 1.43-2.78).

Univariate analyses were also conducted to assess bleeding risk according to type of BCF disorder. We found that patients with Hemophilia A had a RR of 2.03 (95% CI: 1.52-2.72, p=0.0001); patients with Hemophilia B/C had a non-significant RR of 0.93 (95% CI: 0.59-1.47, p= 0.7661), patients with VWD had a non-significant RR of 0.75 (95% CI: CI: 0.54-1.03, p=0.0737), and those with other/multiple clotting factors had a RR of 1.12 (95% CI: 0.86-1.03, p= 0.4088). Based upon these findings we conclude that older age, male gender, diabetes, NSAID use, anticoagulant use, and the presence of HEP-C, Hemophilia A, and VWD met the selection criteria for advancing to the multivariate model analysis.

Multivariate Logistic Regression Modeling

Two multivariate logistic regression models were constructed, a saturated model and a reduced model which includes statistically significant variables or strata. The saturated model (Table 4) included the variables age, gender, region, HIV, HEPC, diabetes, SSRI or SNRI use, NSAID use, anticoagulant use, Hemophilia A, Hemophilia B/C, VWD, and other/ multiple BCF disorders. Several variables were statistically significant in this model: age, gender, NSAID use, anticoagulant use, and Hemophilia A ($p < 0.05$ for all). Within this model VWD was just above significance (p – 0.074). Next, a reduced model was constructed using the variables determined to be statistically significant from the univariate analyses. This reduced model included nine variables: age, gender, diabetes, Hemophilia A, VWD, NSAID use, HEP-C, SSRI or SNRI use, and anticoagulant use.

Based upon this model a final model was constructed eliminating non-significant variables using backwards elimination. The final model included age, gender, NSAID use, anticoagulant use, hemophilia A, VWD, and SSRI or SNRI use, as risk factors for the occurrence of a major bleeding event. Based upon this final model we can conclude that the risk of a major bleeding event was higher for males, the older population, those patients prescribed NSAID or anticoagulant medications, and patients who had Hemophilia A or VWD.

Discussion

BCF disorders are complex diseases to live with; patients must deal with sporadic bleeding under normal conditions. Serotonin-based antidepressant medications lower levels of serotonin in the blood, a necessary component in blood coagulation. Any association between serotonin-based antidepressants and bleeding events would be a relevant concern for BCF disorder patients and their physicians.

The results of our analyses revealed that age, gender, NSAID use, anticoagulant use, and Hemophilia A were risk factors in major bleeding. This information coincides with the results of other research available. Studies have revealed that as patients get older they are at a significantly higher risk of bleeding events. (30-32) The risk of major bleeding events due to NSAID use likely varies by patient as well as the duration of on NSAID therapy. A 16 week study found that there was no increased risk of bleeding events for a hemophilic taking 1600 mg of ibuprofen daily. (30) A study assessing upper gastrointestinal bleeding in hemophiliacs found that patients taking an NSAID (naproxen,

ibuprofen, or diclofenac) for less than one month were at a statistically significant increased risk of GI bleeding. They also reported that patients with prolonged NSAID use (>1 month) were not at an increased risk of bleeding. The researchers further reported that Cox-2-inhibitors (Rofecoxib and Celecoxib) are a safer alternative to NSAIDs for hemophiliac patients. (31) There is little information known about the risk of bleeding in BCF patients taking anticoagulants. Our study results correspond to the known risks of anticoagulants in the general population. (33) Additionally, we tested two-way variable interactions but did not identify any interaction effects between the variables included in our study.

We did not identify an association between SSRI or SNRI use and major bleeding events in our study; although other studies have shown that there is a moderate increase in particular types of bleeding among patients using these drugs. Castro et al. (34) found that patients who used antidepressant medications that have a high affinity for serotonin transporters had an increase in the likelihood of gastrointestinal bleeding. A meta-analysis conducted by Hackam et al. (35) found an association between SSRI use and intracranial hemorrhages (adjusted RR: 1.51; 95% CI: 1.26-1.81). Their analysis also found an association between SSRI use and intracerebral hemorrhages (adjusted RR: 1.68; 95% CI: 1.46-1.91), and an increase in risk in patients who were taking both SSRIs and anticoagulants (RR 1.61; 95% CI: 1.04-2.51).

Strengths and Limitations:

Due in part to the rarity of hemophilia and other bleeding disorders, there exists little information published about antidepressant use in the hemophilia population. This study

provides only a preliminary investigation of the risk associated with antidepressant use among patients with BCF disorders using a retrospective cohort design. Further study examining particular SSRI and SNRI medication products and hemorrhage types may reveal increases in bleeding risk that were not evident in our aggregate analyses. Our analysis highlighted age, gender, and NSAID/ anticoagulant use as key risk factors for the occurrence of bleeding events. This study also provides descriptive statistics detailing the antidepressant medication classes used among this sample of patients having a BCF disorder, finding that SSRI and SNRI medications were commonly prescribed.

There were limitations of this study to be noted. The primary limitation of this study relates to data source, which was collected by a national health insurance company, and is based upon individual patient healthcare claims. We were only able to capture episodes of bleeding that that were serious enough to require medical care. Other limitations of claims data include a lack of detail about the event (intensity and outcomes), lack of patient history and demographics, and pharmacy claims do not indicate if the patient actually ingested the drug. Claims data also lack information about the patient's severity of disease and bleeding treatment course (prophylactic or acute treatment).

The sample sizes for users of the antidepressant medications fluvoxamine, olanzapine/ fluoxetine, venlafaxine, and nefazodone were all less than or equal to 10 total patients. In these instances it was possible that no bleeding events occurred because the sample size was so small. Another limitation to this study is the inability to identify major bleeding events as being related to antidepressant use, and not as a result of some other factor. We

may have also failed to identify patients having diseases such as diabetes, HIV and HEPC if no recent claim associated with these conditions was submitted.

Bleeding events were recorded as either the patient had at least one bleeding event requiring medical attention, or they did not. We did not ascertain the frequency of bleeding events per patient. We were also unable to identify bleeding events due to trauma or illness. Lastly, the generalizability of this study population may not extend to all patients with BCF disorders beyond the commercially insured. These results should not be generalized to programs such as Medicaid or Medicare.

Further research using data collected at hemophilia treatment centers or questionnaires from patients may be able to capture less severe bleeding events. It would also be worth investigating the association between antidepressant use and the duration of bleeding events. Being able to expand the type and number of bleeding events that occur may add further insight into a potential association between antidepressant use and bleeding events in the BCF disorder population.

CHAPTER 5

CONCLUSION

Serotonin based antidepressant medications are known to alter the serotonin levels within the blood. Altering serotonin levels reduce the concentration of coated-platelets within the blood responsible for blood clotting. There is little known information on the association between antidepressant use and episodes of major bleeding in patients with blood clotting factor disorders.

This study did not identify an association between the use SSRI or SNRI antidepressant medications and an increase in the occurrence of major bleeding events. Other important risk factors for major bleeding that were identified in our study included advancing patient age, male gender, and the use of NSAIDs and oral anticoagulants.

APPENDIX 1: TABLES

Table 1a: Demographic and Clinical Characteristics of Patients with Blood Clotting Factor Disorders and Association with the Occurrence of a Bleeding Event (N=7,998)

	No Bleeding Event	At least 1 Bleeding Event	Chi-Sq P-Value
Cohort Population	7760 (97%)	238 (3%)	
Age			<0.0001
12-25 Years old	1,116 (98.20%)	20 (1.80%)	
26-45 Years old	2,563 (98.16%)	48 (1.84%)	
46-65 Years old	3,144 (96.64%)	109 (3.35%)	
66-91 Years old	937 (93.89%)	61 (6.11%)	
Gender			<0.0001
Female	5090 (97.68%)	121 (2.32%)	
Male	2670 (95.80%)	117 (4.20%)	
Region			0.9390
Northeast	1,288 (97.21%)	37 (2.79%)	
Southeast	2,322 (96.79%)	77 (3.21%)	
Midwest	2,039 (97.10%)	61 (2.90%)	
West	1,083 (97.22%)	31 (2.78%)	
Southwest	1,027 (96.98%)	32 (3.02%)	
HIV			0.4367
Yes	60	< 5	
HEPC			0.1225
Yes	127 (94.78%)	7 (5.22%)	
Diabetes			0.0001
Yes	1,022 (95.16%)	52 (4.84%)	
NSAID Use			0.0004
Yes	1,579 (95.70%)	71 (4.30%)	
Anticoagulant Use			0.0004
Yes	959 (95.23%)	48 (4.77%)	
SSRI			0.8440
Yes	849 (96.92%)	27 (3.08%)	
SNRI			0.0726
Yes	360 (95.49%)	17 (4.51%)	

Table 1b: Occurrence of a Bleeding Event by Type of Blood Clotting Factor Disorder (N=7,998)

	No Event	Bleeding Event	P-value
Hemophilia A			0.0004
Yes	966 (95.64%)	44 (4.36%)	
Hemophilia B/ C			0.7668
Yes	587 (97.02%)	18 (2.98%)	
VWD			0.0006
Yes	1,786 (98.13%)	34 (1.87%)	
Other Clotting Factors/ Intrinsic Anticoagulants			0.4088
Yes	4,421 (96.89%)	142 (3.11%)	

Table 1c: Exposure to SSRI or SNRI Antidepressants by Patient Characteristic (N=7,998)

	No Exposure to SSRI or SNRI	Exposure to SSRI or SNRI	P-Value
Cohort Population			
Age			<0.0001
12-25 Years old	1,050 (92.40%)	86 (7.60%)	
26-45 Years old	2,239 (85.75%)	372 (14.25%)	
46-65 Years old	2,658 (81.71%)	595 (18.29%)	
66-91 Years old	813 (82.87%)	168 (17.13%)	
Gender			<0.0001
Female	4,246 (81.48%)	965 (18.52%)	
Male	2,527 (90.67%)	260 (9.33%)	
Region			0.4986
Northeast	1,161 (87.62%)	164 (12.38%)	
Southeast	2,002 (83.41%)	398 (16.59%)	
Midwest	1,755 (83.57%)	345 (16.43%)	
West	953 (85.55%)	161 (14.45%)	
Southwest	902 (85.17%)	157 (14.83%)	
HIV			0.0567
Yes	59	>5	
HEP-C			0.9002
Yes	114 (85.07%)	20 (14.93%)	
Diabetes			<0.0001
Yes	852 (79.33%)	222 (20.67%)	
NSAID Use			<0.0001
Yes	1,333 (80.79%)	317 (19.21%)	
Anticoagulant Use			<0.0001
Yes	782 (77.66%)	225(22.34%)	

Table 2a: Frequency of Antidepressant Use by Drug Class (n=1,531)

Antidepressant Class	Number of Patients (%)
SSRI	876 (57.2%)
SNRI	377 (24.6%)
TCA	150 (9.8%)
MAOI	< 5
Serotonin Modulator	171 (11.2%)
Miscellaneous	254 (16.6%)

* Patients can be represented in multiple classes due to combination therapy

Table 2b: Frequency of a Bleeding Event by Antidepressant Medication Type (N=1,531)

Drug	Patients experiencing a bleeding event n (%)
SSRI	
Citalopram	
Yes	253 (16.5%)
Escitalopram	
Yes	166 (10.8%)
fluoxetine	
Yes	154 (10.0%)
Fluvoxamine	
Yes	6 (0.4%)
Paroxetine	
Yes	63 (4.1%)
Sertraline	
Yes	261 (17.0%)
SNRI	
Duloxetine	
Yes	176 (11.5%)
Desvenlafaxine	
Yes	48 (3.1%)
Venlafaxine	
Yes	156 (10.2%)
Modulators	
Nefazodone	
Yes	< 5
Trazodone	
Yes	156 (10.2%)
Vilazodone	
Yes	15 (1.0%)

Table 3: Univariate Logistic Regression Analyses: Risk of Bleeding Events in Patients with Blood Factor Clotting Disorders; Risk According to Demographics, Clinical Characteristics and Antidepressant Use

Univariate models	OR (95% CI)	P-Value
age (continuous)	1.02 (1.01-1.03)	<0.0001
Age (categorical)		<0.0001
12-25 years old	0.88 (0.50-1.53))	
26-45 years old (ref)	1.00	
46-65 years old	1.75 (1.23-2.51)	
66-91 years old	3.40 (2.27-5.08)	
Gender		<0.0001
Female (ref)	1.00	
Male	1.83 (1.40-2.40)	
Region		0.86
Northeast	1.00	
Midwest	0.95 (0.62-1.46)	
Southeast	1.14 (0.76-1.71)	
Southwest	1.05 (0.64-1.73)	
West	0.95 (0.58-1.56)	

Table 3 continued: Univariate Logistic Regression Analyses: Risk of Bleeding Events in Patients with Blood Factor Clotting Disorders; Risk According to Demographics, Clinical Characteristics and Antidepressant Use

Comorbidities	OR (95% CI)	P-Value
HIV		0.3245
no (ref)	1.00	
yes	1.80 (0.56-5.80)	
HEPC		0.0695
no (ref)	1.00	
yes	2.05 (0.94-4.45)	
Diabetes		0.0007
no (ref)	1.00	
yes	1.78 (1.27-2.49)	
NSAID Use		0.0051
no (ref)	1.00	
Yes	1.54 (1.14-2.08)	
Anticoagulant Use		<0.0001
no (ref)	1.00	
yes	2.00 (1.43-2.78)	
Antidepressant Class	OR (95% CI)	P-Value
SSRI or SNRI		0.6795
no (ref)	1.00	
yes	1.09 (0.74-1.60)	
Hemophilia A		<0.0001
Yes	2.03 (1.52-2.72)	
Hemophilia B/ C		0.7661
Yes	0.93 (0.59-1.47)	
VWD		0.0737
Yes	0.75 (0.54-1.03)	
Other Clotting Factors/ Intrinsic Anticoagulants		0.4088
Yes	1.12 (0.86-1.45)	

Table 4: Risk of Bleeding Events According to Demographic, Clinical Characteristics, and Antidepressant Medication Use: Saturated Logistic Regression Model

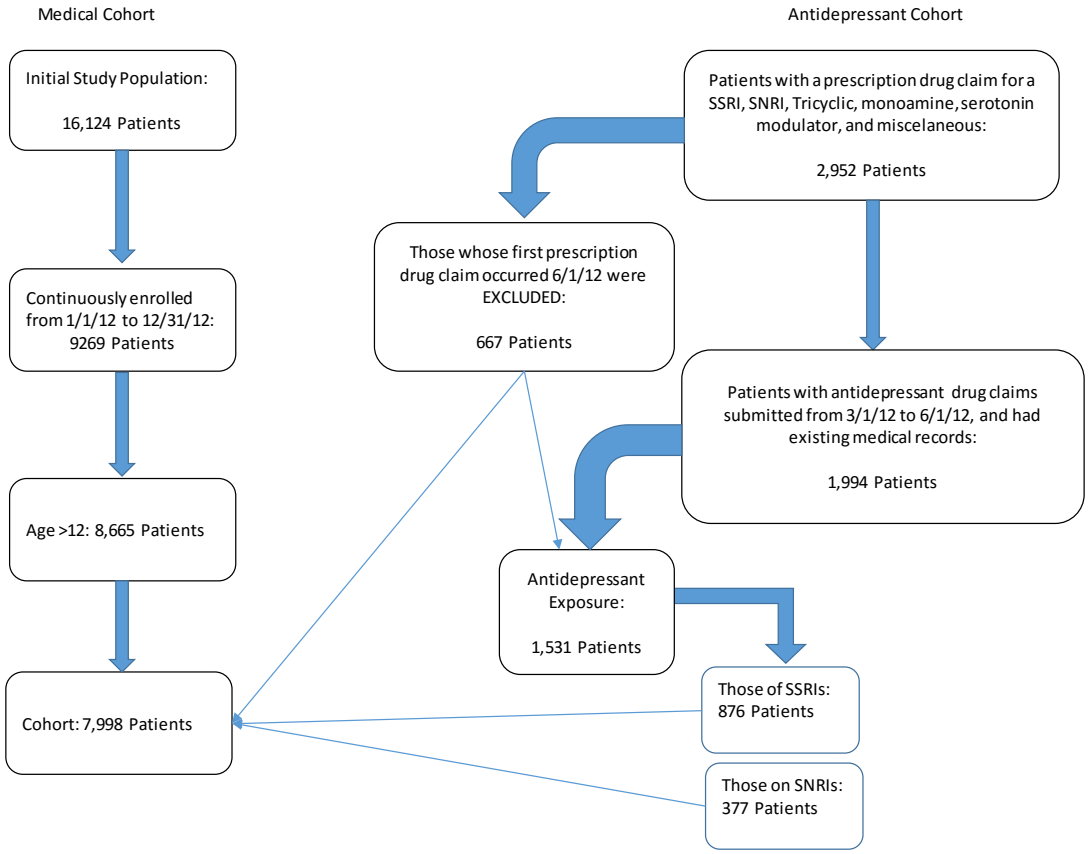
Variable		
	OR (95% CI)	P-Value
Age	1.02 (1.01-1.03)	<0.0001
Gender		0.0052
Female	1.00	Ref
Male	1.51 (1.13-2.00)	0.0052
Region		0.9178
Northeast	1.00	Ref
Midwest	0.93 (0.61-1.42)	0.5867
Southeast	1.03 (0.69-1.54)	0.9146
Southwest	0.99 (0.61-1.62)	0.9881
West	0.90 (0.55-1.47)	0.5981
HIV	1.19 (0.36-3.93)	0.9534
Diabetes	1.32 (0.95-1.84)	0.2599
Hepatitis C	1.63 (0.73-3.61)	0.6878
NSAID Use	1.56 (1.14-2.13)	0.0065
Anticoagulant Use	1.98 (1.40-2.80)	<0.0001
SSRI or SNRI	1.00 (0.67-1.50)	0.9898
Hemophilia A	2.37 (1.64-3.42)	<0.0001
Hemophilia B/ C	1.15 (0.70-1.92)	0.5770
VWD	1.49 (0.98-2.26)	0.0625
Other Clotting Factors/ Intrinsic Anticoagulants	1.29 (0.90-1.85)	0.1610

Table 5: Risk of Bleeding Events According to Demographic, Clinical Characteristics, and Antidepressant Medication Use: Fitted Multivariate Logistic Regression Model

Multivariate models	OR (95% CI)	P-Value
Age	1.02 (1.02-1.03)	<0.0001
Male gender	1.53 (1.15-2.02)	0.0031
NSAID Use	1.66 (1.18-2.35)	0.0039
Anticoagulant Use	2.22 (1.55-3.17)	<0.0001
Hemophilia A	2.12 (1.54-2.93)	<0.0001
VWD	1.27 (0.88-1.84)	0.2010
SSRI or SNRI Use	1.02 (0.68-1.1)	0.9325

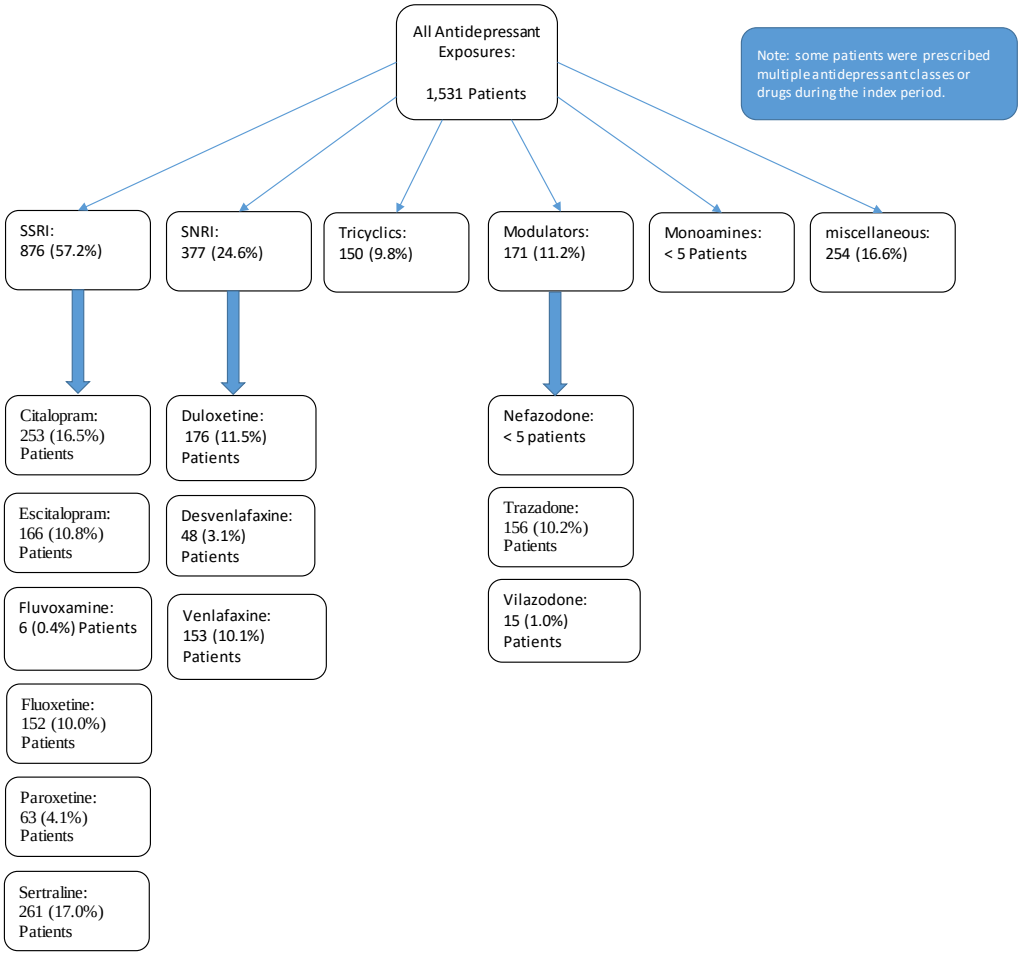
APPENDIX 2: Flow Charts

Figure 1: Study Sample Selection Flow Chart



SSRI: Selective Serotonin Reuptake Inhibitor
SNRI: Serotonin Norepinephrine Reuptake Inhibitor

Figure 2: Frequency of Utilization of Antidepressant Medications



APPENDIX 3: Diagnosis codes for blood clotting disorders, hemorrhages, and drug class codes

Blood Clotting Factor Disorders	ICD-9 Code
Congenital factor VIII disorder (hemophilia A)	286.0
Congenital factor IX disorder (Hemophilia B)	286.1
Congenital factor XI deficiency (Hemophilia C)	286.2
Congenital deficiency of other clotting factors	286.3
Von Willebrand's disease	286.4
Hemorrhagic disorder due to intrinsic circulating anticoagulants	286.5

Antidepressant drug classifications	Optum code
Selective Serotonin Reuptake Inhibitor	28160420
Serotonin Norepinephrine Reuptake Inhibitor	28160416
Tricyclics	28160428
Monoamine Oxidase Inhibitors	28160412
Antidepressants, Miscellaneous	28160492
Serotonin Modulators	28160424

Other drugs	Code
Anticoagulants, Miscellaneous	20120492
Heparins	20120416
Direct Factor Xa Inhibitors	20120414
Direct Thrombin inhibitors	20120412
Coumarin Derivatives	20120408
Cyclooxygenase=2 (COx-2) Inhibitors	28080408
Salicylates	28080424
Other NSAIDs Agents	28080492

Comorbidities	ICD-9 Codes
HIV	V08
AIDS	042
HIV-2	07953
Human T-cell lymphotrophic virus, type 1 (HTLV-I)	07951
HIV counseling	v6544
Acute Hepatitis C with Hepatic Coma	07041
Chronic Hepatitis C With Hepatic Coma	07044
Chronic Hepatitis C without Hepatic Coma	07054
Unspecified Viral Hepatitis C without Hepatic Coma	07070
Unspecified Viral Hepatitis C with Hepatic Coma	07071
Diabetes Mellitus w/o mention of complications, Type II, controlled	25000
Diabetes Mellitus w/o mention of complications, Type I, controlled	25001
Diabetes Mellitus w/o mention of complications, Type II, uncontrolled	25002
Diabetes Mellitus w/o mention of complications, Type I, uncontrolled	25003

APPENDIX 4: Identifying bleeding events using ICD-9 codes for Hemorrhages (25)

description	Code
hemopericardium	423
subarachnoid hemorrhage	430
intracerebral hemorrhage	431
Nontraum extradural hem	432
Subdural hemorrhage	432.1
Intracranial hemorr NOS	432.9
int hemrrhoid w comp nec	455.2
ext hemrrhoid w comp nec	455.5
hemrrhoid NOS w comp nec	455.8
hemorrhage NOS	459
esophag varices w bleed	456
esoph varices in oth dis	456.2
mallory–weiss syndrome	530.7
esophageal disorder nec	530.8
ac stomach ulcer w hem	531
ac stomach ulcer w hem-obst	531.01
ac stomach ulc w hem/perf	531.2
ac stomach ulc w hem/perf-obst	531.21
chr stomach ulc w hem	531.4
chr stomach ulc w hem-obst	531.41
chr stomach ulc hem/perf	531.6
chr stomach ulc hem/perf-obst	531.61
ac duodenal ulcer w hem	532
ac duodenal ulcer w hem-obst	532.01
ac duodenal ulc w hem/perf	532.2
ac duodenal ulc w hem/perf-obst	532.21
chr duoden ulcer w hem	532.4
chr duoden ulcer w hem-obst	532.41
chr duoden ulc w hem/perf	532.6
chr duoden ulc w hem/perf-obst	532.61
ac peptic ulc w hemorr	533
ac peptic ulc w hemorr-obst	533.01
ac peptic ulc w hem/perf	533.2
ac peptic ulc w hem/perf-obst	533.21
chr peptic ulcer w hem	533.4
chr peptic ulcer w hem-obst	533.41
chr peptic lc w hem/perf	533.6
chr peptic lc w hem/perf-obst	533.61
ac marginal ulcer w hem	534
ac marginal ulcer w hem-obst	534.01

ac margin ulc w hem/perf	534.2
ac margin ulc w hem/perf-obst	534.21
chr marginal ulcer w hem	534.4
chr marginal ulcer w hem-obst	534.41
chr marg ulc w hem/perf	534.6
chr marg ulc w hem/perf-obst	534.61
acute gastritis with hemorrhage	535.01
Atrophic gastritis with hemorrhage	535.11
gastr mucosoal hypertroph with hemorrhage	535.21
alcoholic gastritis with hemorrhage	535.31
gastritis nec with hemorrhage	535.41
gastritis/duodenitis NOS with hemorrhage	535.51
duodenitis with hemorrhage	535.61
gastroduodenal dis nec	537.8
diverticula sm intestine w hemorrhage	562.02
diverticulitis sm intestine w hemorrhage	562.03
diverticula of colon w hemorrhage	562.12
diverticulitis of colon w hemorrhage	562.13
hemoperitoneum	568.81
rectal and anal hemorrhage	569.3
angiodysplasia with hem nec	569.85
hematemesis	578
blood in stool	578.1
Gastrointest hemorr NOS	578.9
renalvascular disorder	593.81
hematuria	599.7
noninflam dis vagina nec	623.8
excessive menstruation	626.2
metrorrhagia	626.6
hemarthrosis (nonspecific)	719.1
hemarthrosis (shoulder)	719.11
hemarthrosis (upper arm)	719.12
hemarthrosis (forearm)	719.13
hemarthrosis (hand)	719.14
hemarthrosis (pelvis)	719.15
hemarthrosis (leg)	719.16
hemarthrosis (ankle)	719.17
hemarthrosis (joint, neck)	719.18
epistaxis	784.7
Hemorrhage from throat	784.8
hemoptysis	786.3

APPENDIX 5: IRB exempt approval

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FWA:	00003132
IRB:	00000599
DATE:	December 19, 2015
TO:	Stephen Kogut, PhD
FROM:	University of Rhode Island IRB
STUDY TITLE:	A Study of the Increased Risk of Bleeding Events in Hemophilia A, Associated With Antidepressant Use
IRB REFERENCE #:	840047-1
LOCAL REFERENCE #:	HU1516-099
SUBMISSION TYPE:	New Project
ACTION:	DETERMINATION OF NOT HUMAN SUBJECT RESEARCH
EFFECTIVE DATE:	December 19, 2015

Thank you for your submission of New Project materials for this research study. The University of Rhode Island IRB has determined this project does not meet the definition of human subject research under the purview of federal regulation 45 CFR 46 regarding human subject research at this time. Therefore, your project does not require Institutional Review Board (IRB) oversight. Any changes in focus of this project will require further review of the IRB.

If you have any questions, please contact us by email at researchintegrity@etal.uri.edu. Please include your study title and reference number in all correspondence with this office.

Matthew Delmonico, Ph.D., MPH
IRB Chair

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