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USE AND UNINTENDED
CONSEQUENCES OF ANTIDEPRESSANT
MEDICATIONS BY DEPRESSED OLDER ADULTS
BY
EUN SUN NOH

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
IN
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UNIVERSITY OF RHODE ISLAND

2013

DOCTOR OF PHILOSOPHY DISSERTATION
OF
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APPROVED:

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ABSTRACT

Background

National guidelines suggest 12-18 months of antidepressant treatment for depressed patients to maximize the benefits of treatment; however, patterns of medication use according to the guidelines are less well understood, especially in older adults who are at higher risk of adverse drug events. In addition, selective serotonin reuptake inhibitors (SSRIs) are recommended as a first-line therapy for older adults because of their favorable adverse event profile; however, several observational studies have suggested an association between SSRI use and an increased risk of gastrointestinal (GI) bleeding. While this link remains controversial, it is important to evaluate the risk of GI bleeding in association with SSRI use, especially in older adults who take multiple medications that may increase the risk of GI bleeding.

Objectives

The purpose of this dissertation is to describe the patterns of antidepressant medication use by older adults and quantify the adverse events associated with antidepressant use. The third manuscript focuses on methodology to perform a systematic literature review of published articles reporting effect measure modification (EMM) and characterize the sample size considerations related to EMM.

Methods

In the first manuscript, we performed a cross-sectional study using the Medicare Current Beneficiary Survey (MCBS) data from 2004 to 2008. We estimated a 6-month discontinuation rate of antidepressant medications in older adults who initiated antidepressant treatment following diagnosis with depression. We further developed a multivariable logistic regression model to identify predictors of discontinuation of antidepressant medication.

For the second manuscript, we conducted a nested case-control study using the MCBS data from 2004-2008. We identified cases as all older adults diagnosed with upper GI bleeding. Using incidence density sampling, we randomly selected up to 6 controls who had no evidence of upper GI bleeding after matching on age ($\pm$ 5 years), gender, calendar year, and Charlson comorbidity score. We developed a conditional logistic regression model to estimate the risk of upper GI bleeding associated with SSRI use, simultaneously adjusting for potential confounders. Furthermore, we evaluated whether use of non-steroidal anti-inflammatory drugs (NSAIDs) modified the effect of SSRI use on upper GI bleeding.

In the third manuscript, we systematically reviewed the published EMM literature by searching the PubMed articles published between January 2008 and June 2013. The included studies evaluated EMM by medication use, employed an observational study design, and published in English. We characterized these publications and calculated frequencies to summarize the percentage of studies identified, including specific sample size calculations.

Results

We found that less than 5% of older adults in Medicare programs were diagnosed with major depression between 2006 and 2008. Nearly 1 in 2 depressed older adults were treated with antidepressant medications and 19.2% initiated medication after diagnosis. Of these new users of antidepressant medications, 30.3% discontinued medication treatment within 180 days of starting. Living in a metropolitan area was a significant predictor of antidepressant discontinuation. In addition, SSRI use did not significantly increase the risk of upper GI bleeding in older adults (Adjusted Odds Ratio [AOR]=1.3; 95% Confidence Interval [CI], 0.7-2.5). Furthermore, after adjusting for confounding factors, use of SSRIs along with NSAIDs was not significantly associated with an increased risk of upper GI bleeding (AOR=1.8; 95% CI, 0.5-6.7). Through a systematic literature review, we found that none of the studies performed sample size calculations specifically related to the EMM, although 14.3% of the identified studies mentioned sample size related issues in the study.

Conclusions

Older adults tend to persist in antidepressant medication use. Information obtained from this study can be used by both primary care physicians and policy administrators to improve care for older Medicare beneficiaries. Physicians and other healthcare providers can utilize the information obtained from this study to more fully evaluate the risk-benefit ratio of prescribing specific antidepressants to older adults. In addition, the descriptive information obtained in this study (e.g., treatment patterns, average

length of treatment) can provide points of discussion for physicians and other healthcare providers when they are working with older adults regarding barriers to persistence in antidepressant use and adverse events the beneficiary may be experiencing. The third methodologically focused manuscript provided important insights into the correct (or incorrect) reporting of sample size related issues in the medical literature by elucidating current practices.

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PREFACE

This dissertation uses the manuscript format. As the prevalence of depression among older adults continues to rise, antidepressant treatments have been investigated many times over the past decade; however, especially for older adults, many questions remain unanswered regarding the benefits and risks of drug therapies according to specific clinical and health-system characteristics. The purpose of this dissertation is to describe the patterns of antidepressant medication use by community dwelling older adults and quantify the adverse events associated with the use of antidepressants. This dissertation consists of three manuscripts, as follows:

- Manuscript I: Use of Antidepressant Medications in Depressed Older Adults
and Predictors of Discontinuation of Antidepressant Use
- Manuscript II: Use of Selective Serotonin Reuptake Inhibitors and the Risk of
Upper Gastrointestinal Bleeding in Older Adults
- Manuscript III: A Systematic Literature Review: Effect Measure Modification
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INTRODUCTION

Epidemiology of Major Depressive Disorder

Major depressive disorder (MDD) is highly prevalent in the United States. According to the National Health and Nutrition Examination Survey (NHANES), approximately 6.8% of US adults aged 18 years or older had moderate to severe MDD between 2005 and 2008.[1] The lifetime prevalence of MDD in the US is 18.3%,[2] exceeding the lifetime prevalence in Europe (approximately 13%)[3] and Australia (9.7%).[4]

In addition, for older adults MDD is a significant health problem. In 2005, an estimated 3.8 million Americans over the age of 65 (approximately 10.4% of that population) were diagnosed with depression.[5] In the primary care setting, where many elderly depressed patients are identified, 17-37% of elderly patients are diagnosed with depression.[6]

In addition to newly developed MDD, relapse and reoccurrence are common. Approximately 20% of all patients who recovered from an episode of MDD experienced a recurrence within the first 6 months,[7, 8] and more than 1 in 3 patients experienced a recurrence within 2-3 years after recovery.[9] A study of community-dwelling older adults aged 56 years or older in Rotterdam, the Netherlands estimated the incidence of depression recurrence at 27.5% (95% confidence interval, 23.7-32.1) per 1000 person-years between 1993 and 2005.[10]

Economic Burden and Health Service Use for MDD

A 2004 report from the World Health Organization (WHO) projected MDD as the leading cause of burden of disease worldwide by 2030.[11] MDD is a chronic and often recurrent disease, leading to impairment of physical and social activities and increasing use of health care services.[12] The economic burden of depression is also substantial. In 2000, the overall expenditure for MDD, including direct medical costs, suicide-related morbidity and mortality costs, and loss of work productivity exceeded \$83.1 billion in the US.[13] Direct medical costs, including physician's office visits, emergency room visits, hospitalization, antidepressant treatments and psychotherapy were estimated at \$26.1 billion. Suicide-related morbidity and mortality costs were estimated at \$5.4 billion, and the costs of unemployment and loss of work performance due to MDD were \$30.9 billion to \$51.5 billion.[13-15]

Depression in Older Adults

In older adults, depression is often not recognized by physicians and is treated inadequately, [16, 17] due to the presence of comorbidities (e.g., arthritis, dementia, diabetes, cardiovascular disease), which may mask the symptoms of depression.[18] Older adults are generally at higher risk of chronic disease and comorbid depression, which may have a substantial influence on their health. MDD is often associated with a range of chronic diseases,[19] including cardiovascular disease and hypertension;[20] diabetes;[21] cancer;[22] stroke;[23] and arthritis and pain-related disorders.[24] Moreover, depression is often linked to a poorer prognosis,[25, 26]

because depression may cause poor health behaviors,[27] low adherence to treatments,[28-30] or immunodeficiency.[31]

Underdiagnosed and undertreated depression in older adults may contribute to the high suicide rate in this population. Older adults account for 15.7% of all suicides in the US.[32] Studies revealed that presence of depression was a risk factor for completed suicide in older adults.[33, 34] In addition, the Prevention of Suicide in Primary Care Elderly: Collaborative Trial (PROSPECT) reported reduced rates of mortality in older people with appropriately managed MDD compared to individuals receiving usual care,[35] showing the importance of careful recognition and adequate treatment for MDD in older adults.

Clinical Guidelines for Treatment of Depression

As the prevalence of depression is increasing, much research has focused on treatment by medication. Based on this evidence, many renowned organizations, including the American Psychiatric Association (APA),[36] the National Institute for Health and Clinical Excellence (NICE),[37] the British Association for Psychopharmacology (BAP),[38] and the Canadian Network for Mood and Anxiety Treatments (CANMAT)[39, 40] have developed clinical guidelines for the treatment of depression. These guidelines provide similar principles for treating depression, including personalized treatment plans, potential long-term treatment, measurement-based care, and remission treatment.[41]

These guidelines note the importance of antidepressant medication treatment in managing MDD, regardless of the severity of the disease. The guidelines recommend use of antidepressant medications as a first-line therapy for moderate depression. In particular, the NICE guidelines emphasize that antidepressant therapy is more cost-effective than behavioral interventions for acute, moderate MDD.[37] Furthermore, the combination of antidepressants with electroconvulsive therapy is recommended for patients with severe depression. For patients with mild MDD, the guidelines recommend various treatments, including cognitive-behavioral therapy, interpersonal therapy, and pharmacotherapy; however, all of the guidelines indicate the need for antidepressant treatment for those who have shown partial response or failure of psychotherapy.[36-38, 40]

Antidepressant Treatment Duration

Antidepressant medication therapy can be classified into acute, continuation, and maintenance phases based on treatment duration and outcome.[42] The goal of treatment in the acute phase is remission of depressive symptoms. The APA guidelines require 6-12 weeks of use of the initial selected antidepressants,[36] while the BAP/NICE/CANMAT guidelines recommend 8-12 weeks in the acute phase. [37, 38, 40] The continuation phase follows successful acute phase therapy and aims to achieve recovery. The APA guidelines specify 4-9 months of continuous treatment[36]; the NICE, BAP and CANMAT recommend at least 6 months of continuous use of the antidepressant.[37, 38, 40] The maintenance phase follows the continuation phase and aims to prevent reoccurrence. The APA guidelines mention the

need for maintenance treatment, especially for patients with chronic and/or recurrent (i.e., 3+ histories of) MDD,[36] although the duration of treatment is not specified. Most guidelines agree on the need for long-term use of the antidepressant to prevent recurrence (e.g., more than 2 years for patients at risk of recurrence).[37, 38, 40]

Antidepressant Medications

Antidepressant medications commonly prescribed for MDD can be categorized into five classes: 1) selective serotonin reuptake inhibitors (SSRIs); 2) serotonin norepinephrine reuptake inhibitors (SNRIs); 3) tricyclic antidepressants (TCA); 4) monoamine oxidase inhibitors (MAOIs); and 5) other antidepressants, including bupropion, mirtazapine, trazodone (also known as second generation antidepressants).[43] As the effectiveness of these medications is generally comparable between classes, initial selection of antidepressants is based on the anticipated risk profiles.[36] For example, due to severe drug-drug interactions, MAOIs are restricted to patients who do not respond to other therapy.[44] Similarly, TCAs are carefully used in patients who have cardiac risk factors.[45] By contrast, serotonin reuptake inhibitors (e.g., SSRIs) are considered a lower risk choice than other classes of medications due to their favorable adverse event profiles.[46, 47]

Effect Measure Modification

Effect measure modification (EMM) is a phenomenon in which an association between an exposure and outcome varies by a third factor.[48] The key to detecting modified effects between groups is to have an adequate sample size for each group to

ensure sufficient power to detect and characterize EMM. Researchers should conduct and report sample size considerations related to EMM in the medical literature.

Nevertheless, no standardized guide to reporting sample size related issues has been provided, especially research related to EMM utilizing large quantities of administrative data.

Objectives

The purpose of this dissertation is to describe the patterns of antidepressant use by community-dwelling older adults and quantify the adverse events associated with use of antidepressant medications. According to the guidelines, initial selection of antidepressants is generally based on the risk profiles of these medications because the efficacy of the medications is relatively comparable.[36-38, 40] Furthermore, in order to achieve maximum benefits of antidepressant treatment, the guidelines suggest 12-18 months of medication use; however, patterns of antidepressant use according to the guidelines are less well understood, especially in older adults, who are at higher risk of adverse drug events.[49] In addition, SSRIs are recommended as the first-line treatment for depressed older adults because of their favorable adverse event profile[36]; however, a safety concern has recently been raised. Several studies reported a potential association between gastrointestinal (GI) bleeding and the use of antidepressants,[50-53] while other studies do not support such a relationship.[54-56] These conflicting findings may warrant further studies, and this association has not yet been examined with in older adults in the US.

This dissertation has three specific aims related to antidepressant use in older adults, namely:

1. To describe patterns of persistence with antidepressant medication use and identify factors associated with non-persistence in older adults.
2. To examine the association between the use of SSRIs and the risk of GI bleeding in older adults.
3. To perform a systematic review of published articles reporting EMM and characterize the sample size considerations related to EMM reported in these studies.

The corresponding hypotheses for each of the aforementioned studies are:

1. The duration of treatment with antidepressants will be suboptimal according to national guidelines, and subgroups of the population may be more likely to demonstrate low persistence in antidepressant therapy.
2. The use of SSRIs increases the risk of GI bleeding in older adults. Further, this risk will be modified by concomitant medications.
3. Few published pharmacoepidemiologic studies assessing EMM utilize and present formal sample size calculations in the published manuscript.

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Manuscript I. Use of Antidepressant Medications in Depressed Older Adults and Predictors of Discontinuation of Antidepressant Use

BACKGROUND

Clinical trials suggest that discontinuation of antidepressant medications is associated with a high risk of relapse and reoccurrence in patients diagnosed with depression,[1-3] indicating that continuous use of antidepressants is key to achieving remission of depressive symptoms and preventing recurrence of the disease. To maximize the benefits of medication therapy, guidelines recommend that the initial treatment last 12-18 months.[4, 5]

Despite the well-known benefit of continuous use of antidepressants, the rate of persistence in antidepressant use in the real world remains suboptimal. A study based on data from the Medical Expenditure Panel Survey (MEPS) reported that 42.4% of US adults diagnosed with depression discontinued their antidepressant medication therapy within the first 30 days; 72.4% stopped taking antidepressants during the next 90 days.[6] In addition, 6-month discontinuation rates ranged from 53.0 to 87.6%.[7-9] Similarly, European studies showed low persistence rates for antidepressant use: more than 50% of antidepressant users discontinued their medication within 6 months.[10, 11]

Factors Associated with Medication Discontinuation

There is a wide range of reasons for medication treatment discontinuation, including the patient's individual characteristics (e.g., socioeconomic status, side effects), the patient-physician relationship, and the accessibility and quality of health care.[12, 13]

A systematic literature review by Rivero-Santana et al. summarized predictors of non-adherence to antidepressant therapy in depressed patients.[14] The authors evaluated various socioeconomic and clinical characteristics and noted that the most consistent predictors were age, race/ethnicity, cognitive impairment and substance use.

Furthermore, Linden et al. reported that drug-induced adverse events limited continuous use of antidepressant medications.[15]

Several qualitative studies addressed barriers to continuation of medication treatments, including: 1) limited confidence in the physicians; 2) limited involvement in making decisions regarding antidepressant treatments; 3) poor knowledge of antidepressant use; 4) self-reported changes in depression; 5) pessimism about the curability of depression; and 6) negative expectations regarding aging.[16-18] In addition, health care systems affecting access to and quality of care are associated with medication adherence.[13]

Unique Clinical Challenges in Older Adults

Compared to younger adults, older adults are more likely to have several comorbid diseases and to take multiple medications simultaneously. Moreover, older people may show slower improvement in symptoms than younger adults in response to

medication.[19] Guidelines recommend appropriate antidepressant dose adjustments in the geriatric population because older adults may present an altered profile of drug absorption and metabolism, which could modify the efficacy of treatments or contribute to the development of unintended adverse events.[5, 20]

In this study, we described patterns of antidepressant use in older adults. We hypothesized that antidepressant medication treatment would be suboptimal (according to national guidelines) and further, subgroups of the population would be more prone to suboptimal persistence in antidepressant use. To evaluate these hypotheses, we calculated how long older adults persisted in antidepressant use and compared our findings to the recommendations for treatment by the national guidelines (e.g., how many respondents take antidepressants through the recommended acute, continuous, and maintenance phases of treatment). We further identified independent predictors of discontinuation of antidepressant treatment in older adults.

METHOD

To achieve our aims, we employed a retrospective, cross-sectional study design to characterize the use of antidepressant medications in older adults with depression as well as quantify the rates of persistence to their antidepressant treatments.

Data Source

We used the Medicare Current Beneficiary Survey (MCBS) from 2004 to 2008. The MCBS is a nationally representative survey of a sample of older adults and persons with disabilities.[21] The MCBS survey questionnaire was originally designed by the Center for Medicare and Medicaid Services (CMS) to facilitate administration, monitoring and assessment of the Medicare programs.[22] The MCBS consists of two sections, including the Cost and Use file (use of health care services, costs, and event level information) and the Access to Care file (information regarding accessibility, usual source of care, and satisfaction with the services). We utilized the Cost and Use files for this dissertation. The survey instruments used to collect data in the MCBS are publicly available on the CMS website (<https://www.cms.gov/MCBS/Ques/list.asp#TopOfPage>).

The MCBS includes approximately 12,000 beneficiaries annually who completed the survey. The survey is a 4-year rotating panel, with each panel interviewing $\approx 4,000$ persons. Each year, the oldest panel retires in May through August, with the new panel starting in September through December. Each panel is interviewed three times (rounds) per year, for 12 consecutive rounds. Survey responses are collected through

computer assisted in-person interview (CAPI). Community interviews are performed face-to-face with respondents, while facility interviews are administered to nurses and/or other primary caregivers who can answer questions regarding physical functioning and medical treatment for the sample. The MCBS generally has a high response rate of 84.3-97.3%, high data completeness, and limited loss to follow-up (approximately 8-10%).[23-25]

The MCBS Cost and Use file provides comprehensive information, including beneficiaries' demographic and socioeconomic characteristics, health status and behaviors (e.g., smoking status, alcohol consumption), health insurance coverage, medical histories, prescription drug use, and deaths. In addition, the MCBS is linked to the Medicare Part A and B claim files, which supplement the survey data with diagnoses, utilization and payment information.

Since the implementation of the Medicare Part D prescription drug program in January 2006, the MCBS has been linked to Medicare Part D claims data.[26] Before 2006, 'Prescription Medicine Event' files were collected every four months by interview. While the MCBS interviewer was visiting the survey respondents, the interviewer inspected the bottle of medicines that the respondents were taking and verified the date when the corresponding medications were prescribed. However, date of prescription and day's supply were not provided in the prescription medicine event files. After 2006, approximately 60% of the Medicare beneficiaries were enrolled in Part D programs,[27] and comprehensive prescription information, including date of

prescription, day's supply, and quantity have been available for the Part D enrollees in the MCBS data. Therefore, it became possible to reliably measure utilization patterns of medications for individual beneficiaries using the MCBS data.

All data being used for this research is de-identified and previously collected for research or administrative purposes. This study was reviewed by the Institutional Review Board at the University of Rhode Island and granted exempt status.

Study Population Identification

Because we were interested in the patterns of antidepressant use by depressed older adults, we restricted a sample of this study to community-dwelling older adults with diagnosed depression. We assembled a subsample of all 2006-2008 MCBS respondents due to the limited availability of the prescription drug event claims data collected for Medicare Part D.

We first identified beneficiaries who were at least 65 years of age using Medicare Administrative Identification files. We then identified community-dwelling beneficiaries. Based on resident records, we included persons who lived in the community for the entire year and those who lived in the community most of the time but spend part of the year in a facility. Next, we utilized outpatient and inpatient claims data to identify patients diagnosed with depression. Diagnosis codes for major depression include the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 296.2, 296.3, 300.4, 309.1 309.2, 298.0, and

311.[28, 29] During the study period, we observed the first date of diagnosis with depression and defined it as the index date. We followed patients for 1 year from the index date to characterize the patterns of antidepressant medication use.

Within the eligible sample, we evaluated prescription drug event files to identify older adults who were newly treated with antidepressant medications. We first excluded patients who were not prescribed any antidepressant medications during the follow-up period. We then excluded patients who were exposed to antidepressants within the 90 days prior to the index date. We set this exclusion criterion in order to identify new users of antidepressant medications. Further, we excluded individuals who were lost to follow-up within 180 days from the index date to ensure a minimal period in which to characterize persistence patterns.

Identification of Antidepressant Medication Use

Using therapeutic class codes in prescription drug event files, we first identified the generic/brand names of possible antidepressant medications under the subclass of '80' (Psychotherapeutic drugs) or '97' (Psychotherapeutic drugs). Next, we reviewed text strings of the generic/brand names of antidepressants and then manually reviewed identified drugs for accidental inclusions and omissions.

We categorized antidepressant medications into five groups, including: 1) SSRIs (i.e., citalopram, escitalopram, fluoxetine, paroxetine, sertraline); 2) SNRIs (i.e., desvenlafaxine, duloxetine, venlafaxine); 3) TCAs (i.e., amitriptyline, amoxapine,

clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline); 4) MAOIs (i.e., phenelzine); and 5) other antidepressants (i.e., bupropion, mirtazapine, trazodone, nefazodone).[30] Patients treated with combination antidepressant therapy (N=18, 18.2%) or those who switched therapy (N=7, 7.1%) were classified based on the antidepressant medication taken for the longest period.

Definition and Measurement of Persistence

We defined persistence as the number of days from the start of medication therapy to discontinuation of that therapy.[31] To define discontinuation of the treatment, we identified gaps in treatment longer than 60 days.

To quantify rates of non-persistence in antidepressant use, we used the Health Effectiveness Data and Information Set (HEDIS®) measurement. HEDIS is a set of standardized measurement in health care performance. It defines measures addressing the incomplete prescribing and use of antidepressants among adult patients who are newly diagnosed with depression.[32] According to HEDIS, effective acute phase treatment is defined as the percentage of patients continuing their antidepressant medication treatment for at least 84 days (12 weeks).[33] Similarly, effective continuation phase treatment is defined as the percentage of patients who use antidepressant medications for at least 180 days (6 months). We further examined the 84-day and 180-day discontinuation rates by each pharmacological class of antidepressants.

Independent Predictors

We examined demographic and clinical characteristics that potentially predict antidepressant discontinuation. Demographic characteristics included age (65-74 years old, 75-84 years old, 85 years or older), gender, race/ethnicity (non-Hispanic White [NHW], non-Hispanic Black [NHB], Hispanic, Other), US region of residence (Northeast, South, Midwest, West), residence type (metropolitan area vs. non-metropolitan area), marital status (married, widow, divorced/separated/never married), education (college degree or more, high school graduate, no high school diploma), the number of children living (0, 1-2, ≥ 3), and income (less than \$25,000 vs. more than \$25,000). Further, we utilized self-reported general health status. We dichotomized the responses on the overall health status compared to other people of the same age as excellent/very good/good versus fair/poor. Responses for health status compared to one year ago were categorized as 1) much better/somewhat better, 2) about the same, and 3) somewhat worse/much worse.

Amongst clinical characteristics, we assessed comorbid conditions and use of concurrent medications. We used inpatient/outpatient claims data to identify comorbidities of interest. During a visit to a physician's office, up to nine ICD-9-CM diagnosis codes are captured. Using the Elixhauser comorbidity index algorithm,[34] we first identified 31 individual comorbid diseases. Similar to the Charlson comorbidity index score, the Elixhauser comorbidity index score condensed into one number can reliably summarize the burden of disease and adequately discriminate hospital mortality.[35] Therefore, we created a composite variable summing each

Elixhauser comorbidity score except depression and considered this composite variable as a continuous variable ranging from 0 to 30. We further identified certain conditions related to MDD, including pain-related disorders (e.g., headaches, lower back pain, fibromyalgia, neuropathic pain, and other pain), sleep disorders, and other mental disorders other than depression (e.g., bipolar disorder, anxiety disorders, obsessive compulsive disorder, fatigue, and eating disorders).

For overall medication use, we calculated the total number of medications taken by the beneficiaries during the study period, excluding antidepressant medications. We restricted this count to oral, buccal, sublingual, and inhalation agents and excluded non-oral administration route agents (e.g., injections, topical agents). We then calculated the number of medications prescribed per month and then divided the number of monthly medications by the eligible follow-up period of the individual. Moreover, we identified each class of medications using the same approach to identify antidepressants. Concurrent medication groups identified in this study included antihypertensive agents, oral antidiabetic agents, cholesterol-lowering medications, pain management medications (e.g., NSAIDs), hypnotics/sedatives, and anticonvulsants.

Statistical Analyses

We generated descriptive statistics including proportions, means, and medians to describe the overall prevalence of depression in older adults and common comorbidities associated with depression in this population. In addition, we described

the prevalence and incidence of overall and specific use of antidepressant medications in older adults diagnosed with MDD. We further characterized the overall sample characteristics, including age, gender, race/ethnicity, health status (as measured by the Elixhauser comorbidity index), and concurrent medication use.

Bivariate Analyses

We conducted bivariate analyses to assess differences in characteristics between the 6-month non-persistent group and the persistent group. We evaluated demographic characteristics, clinical comorbidities, and concurrent medications between the two groups. We used chi-squared analyses to compare differences in categorical variables and t-tests for continuous variables.

Multivariable Logistic Regression Model

We developed a multivariable logistic regression model to identify independent predictors of non-persistence in the antidepressant use suggested by national guidelines. The dependent variable was non-persistence in antidepressant use within 6 months (coded as 1=discontinuation of the treatment within 180 days; 0=otherwise). We considered demographic characteristics, clinical diagnoses, and concurrent use of medications as potential predictors. We developed a preliminary model by first including all variables identified as potential predictors during the bivariate analyses. Any factors with a p-value less than 0.25 between the non-persistence group and the persistence group were included in the preliminary model. We then refined this model by sequentially removing variables from the model if the variables did not predict

discontinuation of therapy ($P > 0.10$). We confirmed variable removal through likelihood ratio testing. After a final model resulted, we checked for multicollinearity (using Variance Inflation Factor [VIF]) and two-way interactions (through likelihood ratio testing) between all covariates in the final model. We also performed the Hosmer and Lemeshow Goodness-of-Fit test for the final model. All statistical tests were conducted with a two-tailed alpha, and all analyses were performed using SAS software (SAS Institute Inc., Cary, NC, version 9.3).

RESULTS

Overall, the prevalence of major depression in older Medicare beneficiaries living in the community was 4.5% (=739/16601). Of these depressed individuals, 50.3% took antidepressant medications and 19.2% were newly treated with an antidepressant medication following the diagnosis of depression.

Sample Characteristics

We identified 99 community-dwelling older Medicare beneficiaries who were diagnosed with depression and who initiated antidepressant treatment within one year of the index date. As presented in Table 1.2, mean of age in this eligible sample was 77.4 years. Most of the patients were female (n=73, 73.7%) and non-Hispanic White (n=85, 85.9). The average number of comorbid conditions except depression (mean $\pm$ Standard Deviation [SD]) was 4.9 ± 3.1 , and the median number of comorbidities was 4.0. In addition, the average number of medications taken by these patients other than antidepressants was 6.0 ± 2.7 , and the median number of medications was 5.4.

Community-dwelling older beneficiaries diagnosed with depression had high rates of comorbidity, including hypertension (83.8%), pain-related disease (73.7%), dyslipidemia (61.6%), cardiovascular disease (56.6%), mental disorders other than major depression (54.6%), arthritis (52.5%), fluid and electrolyte disorders (48.5%), chronic obstructive pulmonary disease (COPD, 39.4%), and diabetes mellitus (32.3%).

Antidepressant Treatment Discontinuation Rates

Within the eligible sample, the mean number of days of antidepressant treatment one year from the index date was 293 ± 93 days, and the median was 339 days (range 7-365 days). We observed a gap between the date of diagnosis of depression and the date of initiation of antidepressant therapy. The mean lag time was 72 ± 93 days, and the median was 26 days (range 0-358 days).

Approximately 8.1% of the patients who initiated antidepressant medication therapy for diagnosed depression discontinued their treatment during the first 30 days following initiation. The discontinuation rate within 84 days (12 weeks) from the antidepressant treatment initiation was 13.1%. Nearly 1 in 3 patients (30.3%) discontinued their antidepressants by 6 months (180 days), and the discontinuation rate increased to 75.8% at 1 year (Table 1.1).

Within subgroup analyses, the pattern of medication discontinuation by antidepressant classes (SSRI/SNRI vs. TCA/Other) was similar to that of overall use. Patients using SSRIs or SNRIs showed higher rates of discontinuation than TCA or Other antidepressant users. In the acute phase, 13.6% of SSRI/SNRI users discontinued the medications, whereas 12.1% of TCA/Other users discontinued their medications. Similarly, the 6-month discontinuation rate was 34.9% in the SSRI/SNRI group and 21.2% in the TCA/Other group. The difference in discontinuation rates reached 27.3% at the 1-year follow-up (84.9% for SSRI/SNRI users vs. 57.6% for TCA/Other users; $p=0.003$).

Bivariate Analyses by Persistence Status

In Table 1.2, we present the demographic characteristics of the 99 patients stratified by persistence. Of the 99, 69.7% continued antidepressant therapy for 180 days, whereas 30.3% discontinued treatment within 180 days. First, we found that patients in the non-persistence group tended to be older than those in the persistence group.

Approximately 39.1% of people in the persistence group were between 75-84 years of age, while 23.3% of non-persistent patients were in the same age group. On the contrary, 17.4% of the persistent group were 85 years of age or older, whereas 33.3% of the non-persistent group were over 85 years of age. The percentage of female beneficiaries was higher in the non-persistent group (80.0%) compared to the persistent group (71.0%). The proportion of non-Hispanic White patients in the non-persistent group (83.3%) was slightly less than the proportion in the persistent group (87.0%). Older Medicare beneficiaries who discontinued their antidepressant treatment were more likely living in metropolitan areas (70.0%) compared to those who persisted in therapy (52.2%). There was approximately a 20% difference in the proportion of widows in the non-persistent group versus the persistence group: 66.7% of patients in the non-persistent group were widowed, while 46.4% of patients in the persistent group were widowed. Lastly, persons whose annual income was less than \$25,000 were slightly better represented in the non-persistence group (86.7%) compared to the persistence group (82.6%). No differences in demographic characteristics between the non-persistent group and the persistent group were statistically significant at alpha equals 0.05.

Clinical characteristics of community-dwelling depressed older Medicare beneficiaries stratified by the status of antidepressant treatment persistence are presented in Table

1.3. Analyzing self-reported overall health suggested better overall health in the non-persistent group. For people with good health status: 53.3% in the non-persistent group vs. 39.1% in the persistent group; for individual with fair/poor health status: 46.7% in the non-persistent group vs. 60.9% in the persistent group. In addition, older depressed Medicare beneficiaries in the non-persistence group had fewer comorbid conditions (mean $\pm$ SD, 4.4 ± 3.1) than those in the persistent group (5.1 ± 3.0).

Compared to people in the persistent group, those who discontinued their antidepressant treatments within 180 days were less likely to have chronic diseases, including hypertension (80.0% for those in the non-persistent group vs. 85.5% for those in the persistent group), cardiovascular disease (46.7% vs. 60.9%), COPD (33.3% vs. 42.0%), diabetes (23.3% vs. 36.2%), and cancer (3.3% vs. 13.0%). On the contrary, the non-persistent group had a higher prevalence of fluid and electrolyte disorders than the persistent group (56.7% vs. 44.9%). The prevalence of arthritis and pain-related disorders was similar between the groups.

The average number of medications (excluding antidepressants) taken by older adults was 4.7 ± 2.4 in the non-persistent group and 5.6 ± 2.7 in the persistent group. As for comorbidities, the non-persistent group showed lower rates of use of antihypertensive medications (86.7% in the non-persistent group vs. 97.1% in the persistent group, $p=0.05$), antidiabetic medications (13.3% vs. 24.6%), anticoagulants (16.7% vs. 37.7%, $p=0.04$), and acid suppressive medications (46.7% vs. 63.8%). The proportion

of SSRI or SNRI users in the non-persistent group was slightly higher than in the persistent group, while the proportion of TCA or other antidepressant users was slightly lower in the non-persistent group.

Independent Predictors for Non-persistence

In Table 1.4, we described independent predictors of antidepressant discontinuation within 180 days as adjusted odds ratios and corresponding 95% confidence intervals from multivariable analyses. The significant predictors of discontinuation included residence type (metropolitan area vs. non-metropolitan area). Older adults living in metropolitan areas were 3.5 times more likely to discontinue their antidepressant treatments compared to those who lived in non-metropolitan areas (Adjusted Odds Ratio [AOR]=3.5; 95% Confidence Interval [CI], 1.2-10.2). No other potential predictors significantly predicted non-persistence of antidepressant medication use.

DISCUSSION

We described patterns of antidepressant use in community-dwelling older adults who were Medicare beneficiaries. We found that less than 5% of older adults were diagnosed with major depression. Approximately 1 in 2 depressed patients were treated with antidepressant medications and 19.2% of depressed older adults initiated antidepressant treatment following the diagnosis for depression. Of these new users of antidepressant medications, one-third discontinued their medication within 180 days. We found that older adults living in metropolitan areas were significantly more likely to discontinue treatment. Our findings suggest that new users of antidepressants in depressed older adults tend to persist in treatment; however, physicians should pay careful attention when prescribing antidepressants to older adults living in metropolitan areas to encourage persistence in treatment.

Discontinuation Rates

Rates of discontinuation of antidepressant medication treatments at 6 months varied from 12.2% to 87.6% in published studies,[7-9, 36-40] with our estimate of 30.3% falling towards the lower end of this range. One possible explanation for the diverse rates of discontinuation in the published literature might be the various definitions for discontinuation used in each of the studies. Discontinuation in the analysis of administrative claims data was defined as no evidence of a fill/refill[37] or gaps between prescriptions of 15 days,[8] 30 days,[39] 45 days,[40] or 1.5 times the supply.[38]

The relatively lower rate of discontinuation in our study may be explained by methodological differences in the definition of persistence and the impact of new health care service implementation. We identified non-persistence by 60-day gaps between prescriptions. This gap is larger than that used in published articles,[8, 39, 40] and therefore may indicate a higher rate of persistence. In addition, our focus was on the continuity of any antidepressant medication rather than on continuation of a specific treatment. Thus, we classified patients who switched therapies as persistent if they continued on any antidepressant medication, not just the one initially prescribed. We also considered a patient with combination therapy a persistent user if the individual continued on one of any antidepressant medications without a significant gap. The fact that some other authors defined switching as discontinuation or excluded patients with combination therapy could explain the lower rate of discontinuation in our study. We believe that this is a strength of our study, as early discontinuation due to costs,[41] side effects,[15, 36] or low efficacy of treatments[42] may necessitate changes to other medications. Therefore, our study better reflects the realities of treatment over the initial 6-month period.

Secondly, the introduction of Medicare Part D prescription drug plans may influence medication persistence. One of the most prevalent reasons that patients stopped taking their medications was the cost of the drugs[43] and inadequate insurance coverage.[44] Therefore, implementation of Medicare Part D could increase older Medicare beneficiaries' ability to continue the medication therapy by relieving the burden of immediate medication costs.[45] We used the MCBS 2006-2008 data, and

our study sample of Medicare beneficiaries was eligible for the new coverage. As a result, we think that the new medication coverage may reduce cost-related non-persistence and that the lower discontinuation rate in our study may be a reflection of positive effects of the new medication coverage policy among older adults.

The 6-month rate of discontinuation of antidepressant treatments stratified by antidepressant class (SSRI/SNRI vs. TCA/Other) revealed that older beneficiaries taking SSRIs or SNRIs had a higher discontinuation rate than those using TCAs or other antidepressants. Clinical guidelines recommend SSRIs as an initial choice when patients require antidepressant treatments.[4] In other words, patients taking SSRIs are relatively healthier and less likely to have severe depression. By contrast, patients put on a TCA or a second generation antidepressant may have a higher chance of failure with SSRIs/SNRIs or may suffer from adverse events related to SSRIs/SNRIs. A study suggested that healthier patients were more likely to discontinue their medication therapy.[46] Similarly, SSRI/SNRI users are relatively healthier than TCA/Other antidepressant users, which may explain the higher rate of discontinuation in SSRI/SNRI users.

According to the 2012 published HEDIS report, 66.3% of adults who were newly diagnosed with depression and treated with antidepressants in Medicare Health Maintenance Organizations (HMO) persisted with their medication therapy for at least 12 weeks in 2011.[47] Similarly, 70.8% of persons enrolled in a Medicare Preferred Provider Organization (PPO) continued the treatment for at least 12 weeks. Regarding

the national average of effective continuation phase treatment, 53.3% in Medicare HMO and 58.4% in Medicare PPO continuously used the antidepressants for at least 6 months. While the HEDIS data provide important benchmarking information for our study, several key differences exist. Notably, our study included only older adults, while the HEDIS report is approaching whole Medicare beneficiaries, including aged and disabled individuals. Furthermore, the HEDIS measure is applicable to adults aged 18 years or older who are diagnosed with a new episode of MDD and treated with antidepressants. Our study attempted to identify a new episode of antidepressant use among older adults diagnosed with depression during the study period; however, a new episode of antidepressant treatment was not necessarily a new diagnosis of depression or incident antidepressant utilization. Therefore, the rate of persistence in our study may be estimated higher than the national HEDIS average of persistence in Medicare beneficiaries.

Discussion of Independent Predictors of Non-Persistence

We found that older adults living in metropolitan areas were at significantly increased risk of antidepressant treatment discontinuation. Consistent with our finding, other studies have reported higher proportion of adherence/persistence among patients in rural areas compared to urban areas.[48, 49] A study by Ohl et al. suggested that HIV-positive veterans living in rural areas were 24% more likely to be adherent to antiretroviral therapy compared to urban veterans (OR=1.24; 95% CI,1.1-1.6)[49] Another study conducted by Egede et al. also documented slightly higher adherence to diabetic medication therapy in rural patients than in urban patients.[48] Studies found

that people living in rural areas were older, more likely to be Non-Hispanic White, relatively lower levels of education, exhibited less use of substances, and were more likely to have a chronic medical condition.[49-51] In the published literature, older age and white race/ethnicity are consistently identified as predictors of better persistence in use of antidepressant medication.[6, 14, 18, 52, 53] Therefore, differences in demographic characteristics and comorbid conditions between rural residents and urban residents could explain the association between metropolitan areas and higher rates of medication discontinuation.

Other studies, however, found no disparity in medication adherence between rural and urban residents[54, 55] or reported better adherence by urban patients compared to rural patients.[56] These studies showed that rural patients with a history of stroke were not significantly different in medication adherence compared to urban patients.[55] Similarly, adherence to cardiovascular medications was not significantly associated with a residence type,[54] with the exception of angiotensin-converting enzyme (ACE) inhibitors (for which rural people showed a higher discontinuation rate).[56] One explanation for a higher adherence in urban areas is that patients in metropolitan areas have more health care resources and better access to health care services,[57] and can therefore visit physicians or healthcare providers more often.[58] Urban patients can be diagnosed adequately and can manage their disease properly,[57] leading to a higher adherence to treatments.

The reasons for differences in treatment compliance between metropolitan and non-metropolitan areas remain unclear. As patients with depression have shown different patterns of health service utilizations,[59] our finding on older adults with diagnosed depression may imply unique characteristics. Future research may be necessary to evaluate the reasons for a higher rate of antidepressant discontinuation among older adults living in metropolitan areas.

Although our study focused on demographic and clinical characteristics to identify factors associated with medication persistence, it is important to note that there are many other factors affecting medication adherence beyond demographics and clinical characteristics, which may be difficult to measure using the claims data. For example, Bajcar's conceptual model demonstrates patient's perspective when taking medications.[60] According to Bajcar's theory, patients' need for medication information related to 4 concepts, including 1) making sense of medication taking, 2) medication-taking acts, 3) medication-taking self-assessment, and 4) context of medication taking. Further, Bajcar suggests that the decision to self-adjust medications or to not take the medication at all is related to patient's significant information-seeking activities. According to Bajcar, the decision to take (or not take) a medication is a cognitive process for individuals. Our study focused on non-cognitive factors and therefore was unable to quantify the effect of cognitive factors as suggested by Bajcar's model.

Limitations

This study has several limitations. First, the sample size is relatively small. The lack of significance of potential predictors of antidepressant discontinuation may be a result of small sample size. Secondly, this study may introduce misclassification bias by identifying patients diagnosed with depression using claims data; therefore, the prevalence of depression in Medicare beneficiaries may be underestimated in this study. Similarly, our study identified new episodes of antidepressant use among older adults diagnosed with depression during the study period. Since a new episode of antidepressant treatment is not necessarily indicative of newly diagnosed depression or incident use of antidepressants, our findings may apply to initiation and re-initiation of antidepressant therapy.

Third, this study may introduce selection bias as participation in the MCBS is voluntary. Although the MCBS obtains high response rates across the four-year interviews (ranging from 82.6% at the first year of the interview to 67.3% at the fourth year),[61, 62] non-response may detract from the generalizability of our study's findings. One study suggests that Medicare beneficiaries with older age or poor health condition were more likely to refuse participation in the MCBS survey or less likely to respond the survey.[62] Thus, the rate of non-persistence in our study might be underestimated.

Fourth, we categorized patients with combination or switching therapy into either SSRI/SNRI or TCA/Other antidepressant subgroup based on the longest duration of therapy. This method of categorization may result in misclassification of subgroups if

patients took both classes of antidepressants for the similar/same duration of time. We observed 7 cases out of 18 combination therapy users and 1 case out of 7 switching therapy users that might influence estimates of discontinuation rate by the subgroups. Appendix B and C present persistence status and subgroup categorized among patients with combination therapy and switching therapy.

Despite the noted limitations, our study has several strengths. First, the MCBS data is a nationally representative sample of Medicare beneficiaries, which allows our findings to be generalized to the entire population of older Medicare population. Second, following the implementation of Medicare Part D prescription drug plans in 2006, self-reported medication event files were augmented with prescription related claims data. The potential recall bias might thus be minimized.

CONCLUSIONS

Our study suggests that approximately 5% of older adults enrolled in Medicare programs are diagnosed with depression and half of these depressed older adults are treated with antidepressant medications. Nearly 1 in 5 of depressed older adults initiate antidepressant treatments following the diagnosis of depression, and those new users tend to persist in antidepressant therapy for at least 6 months. Older adults living in metropolitan areas are less likely to continue antidepressant use.

Information obtained from this study can be used by both primary care physicians and policy administrators to improve care for older Medicare beneficiaries. Physicians and other healthcare providers can use the information obtained from this study to more fully evaluate the benefit-to-risk ratio of prescribing specific antidepressant medications to older adults they see. In addition, the descriptive information obtained in this study (e.g., treatment patterns, average length of treatment) provides points of discussion for physicians and others providing health care to older adults regarding barriers to persistence in use of antidepressant treatment and potential adverse event.

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Table 1.1 Discontinuation rates of antidepressant medication treatments, overall and by antidepressant medication class

Percentage of discontinuation rate	Overall	Antidepressant Medication Class		Chi-sq (p-value)
		SSRI/SNRI	TCA/Other	
Phase	(N=99, %)	(N=66, %)	(N=33, %)	
Acute phase (84 days)	13.1	13.6	12.1	0.83
Continuation phase (180 days)	30.3	34.9	21.2	0.16
At 1 year (365 days)	75.8	84.9	57.6	0.003**

*p<0.05, **p<0.01, ***p<0.001

Table 1.2 Demographic characteristics of the study sample by persistent status

Demographic Characteristics	Overall (N=99)	Persistence status		p-value
		Nonpersistence within 6 month (N=30)	Persistence within 6 month (N=69)	
Age (years)				0.14
65-74	43.4	43.3	43.5	
75-84	34.3	23.3	39.1	
85+	22.2	33.3	17.4	
Gender (%)				0.35
Male	26.3	20.0	29.0	
Female	73.7	80.0	71.0	
Race/ethnicity (%)				0.45
NHW	85.9	83.3	87.0	
Other	14.1	16.7	13.0	
NHB	8.1	6.7	8.7	
Hispanic	1.0	0.0	1.5	
Other	5.1	10.0	2.9	
US Region (%)				0.57
Northeast	17.2	13.3	18.8	
South	39.4	40.0	39.1	
Midwest	27.3	23.3	29.0	
West	16.2	23.3	13.0	
Residence type (%)				0.10
Metropolitan area	57.6	70.0	52.2	
Non-metropolitan	42.4	30.0	47.8	
Marital status (%)				0.18
Married	33.3	23.3	37.7	
Widowed	52.5	66.7	46.4	
Divorced ¹⁾	14.1	10.0	15.9	
# of children living (%)				0.21
0	8.1	3.3	10.1	
1-2	29.3	40.0	24.6	
3+	62.6	56.7	65.2	
Education (%)				0.80
No highschool diploma	51.5	46.7	53.6	
High school graduate	32.3	36.7	30.4	
≥ College degree	16.2	16.7	15.9	
Income (%)				0.61
<\$25,000	83.8	86.7	82.6	
≥ \$25,000	16.2	13.3	17.4	

Abbreviation: NHW=non-Hispanic White; NHB=non-Hispanic Black

¹⁾ Divorced includes Divorced/Separated/Never Married.

Table 1.3 Clinical characteristics of the eligible sample by persistent status

Clinical Characteristics	Overall (N=99)	Persistence status		p-value
		Nonpersistence within 6 month (N=30)	Persistence within 6 month (N=69)	
Overall health	%	%	%	0.19
Excellent/Good	43.4	53.3	39.1	
Fair/Poor	56.6	46.7	60.9	
Health compared to 1 yr ago				0.96
Better	11.1	10.0	11.6	
About the same	38.4	40.0	37.7	
Worse	50.5	50.0	50.7	
# Comorbidities				
Mean $\pm$ SD	4.9 $\pm$ 3.1	4.4 $\pm$ 3.1	5.1 $\pm$ 3.0	0.75 ¹⁾
Median	4	4	4	-
Hypertension (Yes, %)	83.8	80.0	85.5	0.49
Diabetes Mellitus	32.3	23.3	36.2	0.21
Dyslipidemia	61.6	56.7	63.8	0.50
Cardiovascular disease	56.6	46.7	60.9	0.19
Cerebrovascular disease	17.2	13.3	18.8	0.50
COPD	39.4	33.3	42.0	0.42
Cancer	10.1	3.3	13.0	0.14
Arthritis	52.5	53.3	52.2	0.92
Pain-related disease	73.7	73.3	73.9	0.95
Other mental disorder	54.6	50.0	56.5	0.55
Sleep disorder	17.2	16.7	17.4	0.93
Alcohol/drug abuse	8.1	3.3	10.1	0.25
Hypothyroidism	29.3	26.7	30.4	0.71
Fluid/electrolyte disorders	48.5	56.7	44.9	0.28
# Medication use				
Mean $\pm$ SD	5.3 $\pm$ 2.6	4.7 $\pm$ 2.4	5.6 $\pm$ 2.7	0.44 ¹⁾
Median	4.8	4.2	5.3	-
SSRI	64.7	70.0	62.3	0.46
SNRI	9.1	10.0	8.7	0.84
TCA	8.1	6.7	8.7	0.73
Other	18.2	13.3	20.3	0.41
Antihypertensive medications	93.9	86.7	97.1	0.05
Antidiabetic medications	21.2	13.3	24.6	0.21
Cholesterol lowering meds	52.5	50.0	53.6	0.74
Anticoagulants/warfarin	31.3	16.7	37.7	0.04
PPI/H2RA	58.6	46.7	63.8	0.11
NSAID	71.7	66.7	73.9	0.46

Abbreviations: COPD=chronic obstructive pulmonary disease; NSAID=non-steroidal anti-inflammatory drugs

¹⁾ t-test was performed.

Table 1.4 Independent predictors of non-persistence with antidepressant medication treatments

Independent predictors	Adjusted Odds Ratio	95% Confidence Interval
Age (years)		
65-74 (Reference)	1.0	NA
75-84	0.4	0.1 - 1.3
85+	1.2	0.3 - 4.0
Gender		
Male (Reference)	1.0	NA
Female	2.1	0.7 - 6.9
Race/ethnicity		
non-Hispanic White (Reference)	1.0	NA
OTHER ¹⁾	0.8	0.2 - 3.1
Residence type		
Non-metropolitan area (Reference)	1.0	NA
Metropolitan area	3.5	1.2 – 10.2
Clinical characteristics		
Fluid and electronic disorder (1=yes)	2.2	0.8 - 5.9
Antihypertensive medications (1=yes)	0.2	0.04 - 1.6
Warfarin (1=yes)	0.3	0.1 - 1.1

Hosmer and Lemeshow Goodness-of-fit Test ($P [\chi^2_{df=7} > 2.59]=0.92$).

Abbreviation: NA = not applicable

¹⁾ OTHER includes non-Hispanic Black, Hispanic, and other race/ethnicity.

Figure 1.1 Overview of study design to identify older adults with depression and newly initiative antidepressant medication therapy

Abbreviations: LBDT= look-back date, FUPDT=follow-up date

Definition of Index date: the first date of diagnosis with depression

Figure 1.2 Summary of study inclusion and exclusion criteria applied for the identification of the final study population

Manuscript II. Use of Selective Serotonin Reuptake Inhibitors and the Risk of Upper Gastrointestinal Bleeding in Older Adults

BACKGROUND

Antidepressant medications are the third most frequently prescribed medicine in the US.[1] Approximately 11% of Americans over 12 years of age received antidepressant treatments, and 14.5% of older adults took antidepressant medications between 2005 and 2008.[2]

Due to a more favorable adverse event profile compared to other classes of antidepressants,[3, 4] selective serotonin reuptake inhibitors (SSRIs) have been widely used. In a large claims data analysis from 2002-2008 in the US, SSRIs were prescribed to 69.6% of new antidepressant users, followed by second generation antidepressants (mostly bupropion, 17.3%), and serotonin norepinephrine reuptake inhibitors (SNRIs, $\approx 9.6\%$).[5]

Association between SSRIs and Gastrointestinal Bleeding

Recently, however, SSRIs have been the target of an important debate concerning safety, particularly in terms of an increased risk of gastrointestinal (GI) bleeding. In 1999, de Abajo and colleagues conducted a population based case-control study using the United Kingdom general practice research database and reported a three-fold increased risk of upper GI bleeding among patients who taking SSRIs.[6] Since the

initial study, eight studies have found a positive association[7-14] and four have found a negative association.[15-18]

Biological Plausibility of the Effect of SSRIs on GI Bleeding

It has been postulated that SSRIs may impair platelet function during the thrombotic process.[19-21] Platelet aggregation is stimulated by the release of serotonin stored in platelets. As platelets themselves are not able to synthesize serotonin, they are dependent on the reuptake of serotonin from plasma. Therefore, serotonin reuptake inhibitors (e.g., SSRIs) may decrease the concentration of stored serotonin in platelets by blocking the reuptake of serotonin into platelets, resulting in impairment of platelet aggregation.[21]

Another hypothesis posited that SSRIs directly increase acid secretion in the stomach [22] triggering ulcers and resulting in upper GI bleeding.[23] Animal testing further supports this hypothesis by confirming enhanced gastric acid secretion when low-dose aspirin was used concurrently with an SSRI.[24] As several observational studies found no significant associations between SSRI use and bleeding other than in the upper GI region (e.g., lower GI or intracranial hemorrhage),[25, 26] it has been suggested that the mechanism of GI bleeding may differ from the mechanism leading to other bleeding. This hypothesis may clarify why, in many observational studies, the bleeding risks of SSRIs were restricted to upper GI bleeding.

Effect Modification by Concurrent Medications

While the association between SSRI use and GI bleeding is unclear, modified effects of SSRIs on upper GI bleeding with concomitant medication use have received considerable research attention. A meta-analysis pooling four observational studies found that the risk of upper GI bleeding increased 2.4 times with SSRI use; however, the risk increased 6.3 times with concomitant use of SSRIs and non-steroidal anti-inflammatory drugs (NSAIDs).[27] Dall et al. tested the risk of upper GI bleeding when SSRIs were used with NSAIDs and/or low-dose aspirin. In this study, the odds ratio was 1.7 (95% Confidence Interval [CI], 1.0-2.8) for SSRIs associated with upper GI bleeding. The odds ratio increased to 8.0 (95% CI, 4.8-13.0) with use of both SSRIs and NSAIDs, and the risk was 28 times (95% CI, 7.6-103.0) higher in patients using SSRIs, NSAIDs, and aspirin together compared to patients using none of these medicines.[7] Furthermore, the increased risk of upper GI bleeding associated with SSRIs and/or NSAIDs was attenuated by using acid suppressing medication (OR=0.3; 95% CI, 0.1-0.8).[9]

Research in Older Adults

National guidelines published by the American Psychiatric Association (APA) recommend review of concurrent medication use when patients suffer from GI bleeding after initiating SSRI therapy.[28] The possible link between SSRI use and GI bleeding or effect modification by concurrent medications may have substantial importance, especially in older adults who are already at higher risk of GI bleeding. As older adults generally have multiple comorbid conditions and take multiple medications, older adults are more likely to have additional risk factors for upper GI

bleeding, including higher use of NSAIDs, anticoagulants, and corticosteroids, and respiratory disease.[29-33]

In this study, we examined the association between the use of SSRIs and the risks of upper GI bleeding in a community-dwelling population of older adults. We hypothesized that the use of SSRIs would increase the risk of upper GI bleeding in older adults and further, this risk would be modified by certain medications.

METHOD

We performed a nested case-control study among older Medicare beneficiaries to quantify the effect of SSRI use on the increased risk of upper GI bleeding in older adults.

Data Source

We used the Medicare Current Beneficiary Survey (MCBS) Cost and Use files from 2004 to 2008. The MCBS is a multipurpose survey of a nationally representative sample of aged and disabled individuals, which allows study results to be generalized to the whole population of Medicare beneficiaries in the US.[34] The MCBS survey questionnaire was originally designed by the Center for Medicare and Medicaid Services (CMS) to facilitate administration, monitoring, and assessment of the Medicare programs.[35]

The MCBS has a unique feature, augmenting survey with Medicare Parts A, B and D. The MCBS Cost and Use files provide comprehensive information, including beneficiaries' demographic and socioeconomic characteristics, health status and behaviors (e.g., smoking status, alcohol consumption), health insurance coverage, medical histories, prescription drugs, and dates of death.

Cohort Identification

We assembled a cohort of older adults over the age of 65 who were living in the community. We then restricted this cohort to include only beneficiaries whose claims

data was available from 2006 to 2008 and those with at least 1 year of continuous eligibility from the date of cohort entry.

From this eligible population, we excluded community-dwelling older beneficiaries if they were diagnosed with certain diseases, including 1) Mallory-Weiss syndrome, 2) esophageal varices, 3) alcohol abuse, 4) liver cirrhosis, 5) cancer, 6) blood loss anemia, or 7) *Helicobacter pylori* infection. These conditions predispose patients to GI bleeding.[36, 37] We then followed eligible beneficiaries from the date of study entry until one of the following events: 1) diagnosed with upper GI bleeding; 2) death; or 3) end of the study period. The final sample size in the cohort was 13,240. Figure 2.1 presents the conceptual design of this nested case-control study and Figure 2.2 describes the inclusion and exclusion criteria of this study and the corresponding sample sizes.

Case Identifications

Within the larger cohort, we first identified all patients who had an episode of upper GI bleeding using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes using inpatient and outpatient medical claims. We then marked cases as those who were diagnosed with upper GI bleeding following 90 days after cohort entry. We set a 90-day window to ensure at least 90 days to evaluate patient's comorbid conditions and medication use before the events. We assigned an index date for each identified case based on the first observed date of

upper GI bleeding. During the follow-up period, we identified 152 cases of upper GI bleeding.

The ICD-9-CM codes for upper GI bleeding that we utilized are presented in Table 2.1. Based on the published literature, we comprehensively assessed ICD-9-CM codes for GI bleeding. While validity of the ICD-9-CM codes for upper GI bleeding/hemorrhage varied across databases,[38-40] a study using databases from a large number of health plans in the US documented positive predictive values of approximately 60-65% for ICD-9-CM codes 531, 532, or 534, and less than 10% for ICD-9-CM codes 533 or 578.[38]

Control Selection

We used incidence density sampling to identify controls representative of the exposure distribution that gave rise to the case. We randomly selected controls from the large cohort of Medicare beneficiaries who had not been diagnosed with upper GI bleeding. Utilizing an incidence density sampling (also known as a risk-set sampling) method, we identified eligible controls by matching on age (± 5 years), sex, calendar year of cohort entry, and the Charlson comorbidity index scores (0, 1-2, ≥ 3).[41] We individually matched cases to controls using a 6:1 control-to-case ratio. While a 4:1 control-to-case ratio is reported as the most efficient matching ratio,[42] a 6:1 matching ratio as obtaining additional controls beyond 4 would not result in additional costs and could increase statistical power, particularly in large samples with high correlation between cases and matched controls or with low prevalence of exposure or,

alternatively, when assessing multiple potential exposures simultaneously.[35, 36] Controls were assigned an index date based on the date of their matched cases. The final sample eligible for study inclusion was 152 cases and 820 matched controls.

Exposure Definition

We looked back 90 days prior to the index date to identify patients with exposure to SSRIs. We used prescription drug event files linked to Medicare Part D claims data. Using the therapeutic class codes in prescription drug event files, we first identified the generic/brand names of possible antidepressants in subclass of '80' (psychotherapeutic drugs) or '97' (psychotherapeutic drugs). Next, we pulled the generic/brand names of antidepressants and then manually reviewed identified drugs to make sure all SSRIs were properly identified. The SSRIs that we identified included citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline.

Potential Confounders

We assessed additional demographic and clinical characteristics that might influence the relationship between SSRIs and GI bleeding. Demographic characteristics included race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Other), US geographic region (Northeast, South, Midwest, West), residence type (metropolitan versus non-metropolitan area), marital status (married, widow, divorced/separated/never married), education (college degree or more, high school graduate, no high school diploma), and income (less than \$25,000 vs. more than \$25,000). We further identified self-reported overall health status (excellent/very

good/good versus fair/poor) and health status compared to one year ago (much better/somewhat better/about the same vs. somewhat worse/much worse) as potential confounders.

Based on the published literature, we considered the following clinical conditions as potential risk factors for upper GI bleeding: a respiratory disease and psychiatric disorder;[33] a history of GI bleeding;[43] and concurrent medications, including NSAIDs,[29] anticoagulants (i.e., antiplatelet agents, low-dose aspirin, warfarin),[30, 31] corticosteroids,[32] antihypertensive medications (i.e., angiotensin-converting enzyme inhibitors [ACEI], angiotensin-receptor blockers [ARB], calcium channel blockers [CCB], beta blockers, diuretics), cholesterol-lowering medications, antidiabetic medications, acid suppressing medications (i.e., proton pump inhibitor [PPI], histamine 2 receptor antagonist [H2RA]), anticonvulsants, and sedative/hypnotic medications.[44-46]

We assessed the presence of the above risk factors within 90 days prior to the index date using inpatient/outpatient medical claims data and prescription drug files. We utilized the Elixhauser comorbidity index algorithm[41] to identify the comorbid conditions. We quantified patients who had diagnosis codes for upper GI bleeding in the first 90 days of cohort entry to control for a history of GI bleeding. The confounding medications were identified using the same approach used to identify SSRIs from prescription drug event files. We further identified use of antidepressants other than SSRIs as a potential confounder.

Evaluation of Effect Measure Modification by NSAID use

We tested whether NSAID use is effect modifier in the association between SSRI use and upper GI bleeding. We classified medication exposure as four exclusive groups, including 1) SSRI user; 2) NSAID user; 3) Both SSRI and NSAID user; and 4) non-user. We then estimated crude odds ratio and adjusted odds ratio for each exposure group compared to patients who did not use any of these two medications.

Sample Size Estimation

We performed sample size calculations to evaluate EMM of the association between SSRI and upper GI bleeding from NSAID use. In our sample size calculations, we held the two-tailed test at alpha level of 0.05 and the beta level at 0.20 (i.e. Power of 80%) and used 6:1 ratio of the control group to the case group. We further needed proportion of SSRI and/or NSAID use in the control group as well as expected odds ratio due to exposure of SSRI and/or NSAID. We found these estimates based on a meta-analysis by Loke et al.[27] According to the meta-analysis, proportion of both SSRI and NSAID use in the control group would be 0.4% and expected odds ratio due to exposure of both medications would be 6.33 (95% CI, 3.40-11.82). Based on these assumptions, we estimated a sample size of 148 individuals for cases and 888 for controls.

Descriptive Analyses and Conditional Logistic Regression Models

We first conducted bivariate analyses to summarize differences in baseline characteristics between cases and matched controls. As the controls were matched with the cases, we performed univariate conditional logistic regression for categorical variables and paired t-tests for continuous variables to confirm statistical significance.

We then developed a conditional logistic regression model to estimate the effect of SSRI use on the risk of upper GI bleeding. We employed a conditional logistic regression model because of the matched design in selecting cases and controls.[47] Our dependent variable was an episode of upper GI bleeding (coded as 1=diagnosed with upper GI bleeding [case], 0=no evidence of GI bleeding [control]). The independent variable was use of SSRIs (coded as 1=SSRI users vs. 0=non-users within 90 days prior to the index date).

Based on the descriptive statistics obtained from bivariate analyses, we considered variables that had 5% or more difference in proportion between the cases and controls as potential confounders. Next, we manually added these variables sequentially into the model with assessment of the β -coefficient of the risk estimates of SSRIs. Any factors that changed the estimated β -coefficient by at least 10% were considered confounding and retained in the model. We also retained a basic demographic characteristic (i.e., race/ethnicity) in the model because of its clinical and social importance. After a final model resulted, we checked for multicollinearity by assessing variance inflation factor (VIF) values. We considered VIF values greater than 8 as indicative of potential correlations between independent variables.[48]

We estimated crude (unadjusted) and multivariable (adjusted) odds ratios and corresponding 95% confidence intervals. Adjusted odds ratios were estimated by simultaneously adjusting for potentially confounding covariates. As we utilized incidence density sampling to select controls, the odds ratio from our conditional logistic regression model approximates the incidence rate ratio.[49]

All statistical tests were conducted with a two-tailed alpha of 0.05. All statistical analyses were performed using SAS software (SAS Institute Inc., Cary, NC, version 9.3).

RESULTS

We identified 152 cases and randomly selected 820 matched controls from the MCBS data from 2006 through 2008. As presented in Table 2.2, the cases and matched controls were comparable in matching factors, including age, gender, the year of cohort entry, and Charlson comorbidity index scores. The mean age of the cases was 80.3 years old (± 7.8 years) compared to 79.7 years (± 7.3 years) in the controls. Approximately 40% of the cases were male and 60% of them were female. The selected controls had the same gender proportion as the cases. Most identified cases were eligible for the MCBS sample from 2006 ($\approx 90\%$) and controls had the same year of cohort entry as the cases. Approximately 50% of the cases and controls have Charlson comorbidity index scores of 1 or 2.

Table 2.3 presents demographic characteristics stratified by case and control status. Overall, the selected controls showed demographic characteristics similar to those of the cases. Most parents were non-Hispanic White (89.5% for cases versus 86.3% for controls), living in metropolitan areas (67.1% of cases vs. 70.2% of controls), and reported at least good health (60.5% in cases vs. 68.9% in controls). In addition, their income level was low (those whose income was less than \$25,000 was 63.8% in cases and 57.6% in control). Cases were more likely to be widowed than controls (54.0% for cases vs. 43.1% for controls).

In Table 2.4, we present clinical characteristics of cases and controls. Although we matched on an overall marker of comorbidity, the prevalence of chronic diseases was

higher in the cases than in the controls. The cases were more likely than the controls to have hypertension (52.6% of the cases compared to 17.7% of controls), cardiovascular diseases (42% in the cases versus 14.3% in the controls), dyslipidemia (31.6% in the cases vs. 10.1% in the controls), diabetes mellitus (21.1% vs. 10.7%), and chronic obstructive pulmonary disease (COPD, 15.8% vs. 7.0%). Similarly, pain-related disorders occurred more frequently in the cases (32.9%) than in the controls (11.6%). Fatigue was also more prevalent in the cases (15.1%) than in the controls (3.3%).

The prevalence of concurrent medication use in the cases and controls within 90 days prior to the index date is presented in Table 2.5. The cases showed a higher prevalence of use of NSAIDs (20.4% for cases versus 12.4% for controls), anticoagulant agents (15.8% vs. 10.6%), and acid-suppressing medications (18.4% vs. 12.9%). In addition, the cases were more likely to use ACE inhibitors (21.1%) and diuretics (26.3%) compared to the controls (15.0%, 19.6%, respectively). There was no significant difference in the use of antidiabetics or cholesterol-lowering medications between the cases and controls.

The results of the conditional logistic regression model designed to determine the risk of upper GI bleeding associated with SSRI use are presented in Table 2.6. Before adjusting for potential confounders, patients exposed to SSRIs were approximately 30% more likely to be diagnosed with upper GI bleeding, although this association was not statistically significant (Odds Ratio [OR]=1.3; 95% Confidence Interval [CI] 0.7-2.5). When controlling for race/ethnicity, certain medications (i.e., anticoagulants,

NSAIDs, systematic corticosteroids, acid suppressing medication, ACE inhibitors) and certain comorbid conditions (i.e., hypertension, cardiovascular diseases, dyslipidemia, COPD, fatigue, fluid/electrolyte disorder), the association became negative, although it was still not statistically significant (Adjusted OR [AOR]=0.7; 95% CI, 0.3-1.7).

Table 2.7 presents the modified effects of SSRIs on upper GI bleeding by NSAIDs. Compared to patients who were exposed neither SSRIs and NSAIDs, patients who took SSRIs had almost same odds of developing upper GI bleeding as non-users, while patients who used NSAIDs were at 70% increased risk of upper GI bleeding relative to non-users (OR=1.7; 95% CI, 1.1-2.8). Older adults who took both SSRIs and NSAIDs were 2.9 times more likely to have upper GI bleeding than non-users (OR=2.9; 95% CI, 1.0-8.1); however, after we controlled for potentially confounding factors, the associations were no longer statistically significant.

DISCUSSION

We tested the hypothesis that SSRI use was associated with an increased risk of upper GI bleeding among older adults. Our findings did not confirm the association. Further, after adjusting for confounding factors, we did not find a significant association that concurrent medications (i.e., NSAID) increased the risk of upper GI bleeding associated with SSRI use.

While the results surrounding the link between SSRI use and upper GI bleeding are conflicting, our study supports the finding of no significant association.[15-17] A prescription event monitoring cohort study performed by Dunn et al. in England did not support a significant association between SSRI use and GI bleeding (RR=1.2; 95% CI, 0.9-1.7).[15] In addition, a multicenter case-control study using American medical records did not find that SSRI users were more likely to be hospitalized with upper GI bleeding (OR=1.3; 95% CI, 0.8-1.9).[17] Another population-based multicenter case-control study failed to find any association between admission to a hospital for upper GI bleeding and highly selective SSRI use (OR=1.24; 95% CI, 0.88-1.76).[16]

Several observational studies, however, identified a positive association between SSRI use and upper GI bleeding.[8, 9, 12] Dalton et al. found that SSRIs yields a 3.6 times increased risk of GI bleeding in a population in Denmark (RR=3.6; 95% CI, 2.7-4.7).[8] Similarly, Vertel et al. reported that SSRI users in the Netherlands were 40% more likely to be hospitalized due to GI bleeding (OR=1.4; 95% CI, 1.2-1.6).[12] A Canadian study also duplicated this positive association (OR=1.4; 95% CI, 1.1-1.9)[9]

One of the possible reasons why our study did not find an association while others did is potential residual confounding. A recent study demonstrated that the number of comorbidities (excluding GI related disorders) was a significant predictor of upper GI bleeding.[37] It found an approximately 40% increased risk of GI bleeding over patients with a single comorbidity, as identified by the Charlson comorbidity algorithm (OR=1.4; 95% CI, 1.3-1.5). This association became stronger if patients had comorbidity index scores greater than or equal to 2 (OR=2.3; 95% CI, 2.1-2.4).

In our study, we matched cases and controls on overall Charlson comorbidity index scores. As we minimized potential confounding by indication, our estimates might more accurately control for confounding related to comorbidity compared to other studies. In the published literature suggesting an increased risk of upper GI bleeding associated with SSRI, the risk estimates varied depending on how well the study could control for potential confounders (especially comorbid conditions). A cohort study using prescription and hospital discharge records found a 3.6 times increased risk of upper GI bleeding associated with SSRIs, adjusted for age, gender, and calendar year.[8] A population-based case-control study adjusted for age, gender, year, smoking status and use of anticoagulant and steroids found a 3-fold increased risk of upper GI bleeding in patients using SSRIs.[6] Another cohort study adjusted for comprehensive risk factors (i.e., age; gender; year; diabetes; history of GI bleeding; use of NSAIDs, aspirin, corticosteroids, anticoagulants, and acid-suppressing medications) suggested a hazard ratio of 1.1 for upper GI bleeding associated with

serotonin reuptake inhibitors. In studies controlling for more comorbid conditions, estimates of the association between SSRIs and upper GI bleeding were closer to 1. Therefore, the established association between SSRI use and GI bleeding may be overestimated when potential confounders are not adequately controlled for.

A study by van Walraven et al. examined this association in older adults in Canada.[11] They observed an approximately 10% increased risk of upper GI bleeding with a 1 unit increase in affinity for serotonin transporters. Although their study population was also older adults, direct comparison of the findings may be problematic because of some notable differences between the two studies. First, they classified antidepressant medications based on the level of affinity for the serotonin transporters and defined exposure as low, intermediate, and high based on serotonin reuptake inhibition. Thus, SSRIs were categorized into different groups if a degree of affinity was different. We used any SSRI exposure versus no exposure in the previous 90 days, ignoring receptor affinity. Furthermore, their risk ratio was estimated compared to low-affinity medication users; however, we restricted exposure group to SSRI users and estimated the risk ratio compared to non-users. Second, they identified cases by hospitalization for acute upper GI bleeding, while we identified as cases all patients who had the diagnosis code for upper GI bleeding. When cases were defined by admission to a hospital for GI bleeding, it may be possible to miss patients who have less severe GI bleeding.

Our study examined whether NSAID use modified the effect of SSRIs on upper GI

bleeding. Due to the small sample size, we could not obtain significant estimates. However, available evidence suggested that the concurrent medications that were additional risk factors for upper GI bleeding amplified the association between SSRI use and upper GI bleeding.[7, 9, 27, 50]

Limitations

We believe that our study can provide additional information about the association between SSRI use and upper GI bleeding, especially among older adults who are at higher risk. However, our study has several potential limitations. First, although we controlled for important confounders, we did not control for such factors (e.g., smoking). Second, misclassification bias may be introduced by using administrative claims data. We identified cases of upper GI bleeding using the ICD-9-CM diagnosis code. We may thus have missed patients who had GI bleeding if there was no diagnosis code for the bleeding. Therefore, the risk may be underestimated. Third, the study sample size was small, including 152 cases and 820 matched controls. Although the direction of the association was less influenced by a small sample size, the estimates may be less accurate in terms of lack of significance).

CONCLUSIONS

In our study, we did not find an increased risk of upper GI bleeding associated with SSRI use in older adults. Further, after adjusting for confounding factors, we found that the effect of SSRIs on upper GI bleeding modified by NSAIDs was not significant. While the results of our study do not confirm other studies that reported an increased risk of upper GI bleeding resulting from NSAID use, our results highlight the importance of physicians weighing the risk to benefits when prescribing NSAIDs and SSRI's simultaneously for older adults. As this study does not provide conclusive data to guide clinicians, clinicians must weigh the potential risks, including upper GI bleeding, when prescribing these medications. Patient counseling is an important component of risk management strategies when prescribing medications. Pending more definitive information on the risk of upper GI bleeding from SSRIs and NSAIDS, patients should be cautioned about this possible adverse event.

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Table 2.1 ICD-9-CM codes for upper GI bleeding identification [38-40]

Upper Gastrointestinal Bleeding	ICD-9-CM code
Gastrointestinal hemorrhage	
Gastrointestinal hemorrhage	578.0, 578.1, 578.9
Upper gastrointestinal hemorrhage	
Bleeding gastric ulcer	531.0, 531.2, 531.4, 531.6
Bleeding duodenal ulcer	532.0, 532.2, 532.4, 532.5, 532.6, 532.9
Bleeding peptic ulcer	533.0, 533.2, 533.4, 533.6
Bleeding gastrojejunal ulcer	534.0, 534.2, 534.4, 534.6
Gastritis or duodenitis with hemorrhage	535.01, 535.11, 535.41, 535.51, 525.61
Angiodysplasia or dieulafoy lesion of the stomach and duodenum with hemorrhage	537.83, 537.84

Table 2.2 Confirmation of on matching factors between cases and controls

Matching factors	Case (N=152)	Control (N=820)
Age (years)		
Mean $\pm$ SD	80.3 $\pm$ 7.8	79.7 $\pm$ 7.3
Median	81	80
Range	66-100	65-100
Gender, N (%)		
Male	60 (39.5)	330 (40.2)
Female	92 (60.5)	490 (59.8)
Calendar year of cohort entry, N (%)		
2006	137 (90.1)	736 (89.8)
2007	15 (9.9)	84 (10.2)
Charlson comorbidity score, N (%)		
0	51 (33.6)	292 (35.6)
1-2	77 (50.7)	405 (49.4)
≥ 3	24 (15.8)	123 (15.0)

Table 2.3 Prevalence of baseline demographic characteristics between cases and controls

Characteristic	Cases (N=152)	Control (N=820)	Crude Odds Ratio	95% CI
Race/ethnicity	%	%		
non-Hispanic White	89.5	86.3	1.0	NA
non-Hispanic Black	5.3	8.1	0.6	0.3 - 1.3
Hispanic	2.0	2.7	0.7	0.2 - 2.4
Other	3.3	2.9	1.1	0.4 - 2.9
Geographic region				
Northeast	13.8	19.6	1.0	NA
South	39.5	37.7	1.5	0.9 - 2.5
Midwest	29.0	24.0	1.7	1.0 - 2.9
West	17.1	17.6	1.4	0.7 - 2.6
Unknown	0.7	1.1	0.9	0.1 - 7.4
Residence type				
Metropolitan area	67.1	70.2	1.0	NA
Non-metropolitan area	32.9	29.8	1.1	0.7 - 1.7
Marital status				
Married	34.9	47.6	1.0	NA
Widowed	54.0	43.1	2.0	1.3 - 3.2
Divorced/Separated/Other	11.2	9.4	1.7	0.9 - 3.1
Education				
No high school diploma	39.5	33.9	1.0	NA
High school graduate	32.2	28.3	1.0	0.6 - 1.5
College degree or more	27.6	37.0	0.7	0.4 - 1.0
Unknown	0.7	0.9	0.7	0.1 - 5.8
Income				
≥ \$25,000	63.8	57.6	1.0	NA
< \$25,000	36.2	42.4	1.3	0.9 - 1.9
Overall health status				
Excellent/Very good/Good	60.5	68.9	1.0	NA
Fair/Poor	38.2	30.6	1.4	1.0 - 2.0
Unknown	1.3	0.5	3.3	0.5 - 20.3
General health compare to 1 year				
Much better/better/same	63.2	67.8	1.0	NA
Much worse/Worse	36.2	32.0	1.2	0.8 - 1.7
Unknown	0.7	0.2	2.4	0.2 - 27.6

Table 2.4 Baseline clinical characteristics between cases and controls

Clinical Characteristic (%)	Cases (N=152)	Control (N=820)	Crude Odds Ratio	95% CI
Cardiovascular disease	42.1	14.3	5.8	3.7-9.0
Congestive heart failure	19.1	6.3	4.3	2.4-7.6
Cardiac arrhythmia	24.3	8.7	3.7	2.3-6.0
Valvular Disease	7.9	2.9	2.9	1.4-6.1
Peripheral vascular disease	9.9	3.1	3.7	1.9-7.4
Cerebrovascular disease	9.2	2.0	6.0	2.6-13.7
Hypertension (Uncomplicated)	52.6	17.7	5.5	3.7-8.2
Diabetes Mellitus (Uncomplicated)	21.1	10.7	2.3	1.4-3.6
Dyslipidemia	31.6	10.1	4.4	2.9-6.8
COPD	15.8	7.0	2.7	1.6-4.6
Hypothyroidism	11.8	4.4	2.9	1.6-5.4
Renal failure	11.8	4.6	2.8	1.5-5.2
Major depression	5.9	1.0	6.0	2.3-15.6
Fatigue	15.1	3.3	5.6	3.1-10.2
Pain	32.9	11.6	3.7	2.5-5.7
Rheumatoid arthritis/Osteoporosis	13.2	4.0	3.6	2.0-6.6
Fluid/Electrolyte disorder	20.4	4.4	5.5	3.2-9.5
Coagulopathy	4.6	1.0	5.0	1.7-14.4
History of GI bleeding	0.7	0.2	2.8	0.3-31.2

Abbreviation: COPD=chronic obstructive pulmonary disease.

Table 2.5 Concurrent medication use between cases and controls

Concurrent Medication Use (%)	Cases (N=152)	Control (N=820)	Crude Odds Ratio	95% CI
Other antidepressant medications ¹⁾	7.2	3.1	2.5	1.2-5.2
NSAIDs	20.4	12.4	1.9	1.2-2.9
Anticoagulants	15.8	10.6	1.6	0.9-2.6
Corticosteroids	7.2	6.5	1.2	0.6-2.4
Acid suppressing medication	18.4	12.9	1.5	1.0-2.5
Hypertension agents	45.4	38.1	1.4	1.0-2.0
ACEI	21.1	15.0	1.5	1.0-2.4
ARB	10.5	8.3	1.3	0.7-2.3
Calcium channel blocker	17.1	12.7	1.4	0.9-2.3
Beta blockers	22.4	17.8	1.3	0.9-2.0
Diuretics	26.3	19.6	1.4	1.0-2.2
Diabetic medications	9.2	11.1	0.8	0.4-1.4
Cholesterol-lowering medications	23.0	19.3	1.3	0.8-2.0
Statins	18.4	18.2	1.0	0.7-1.6
Antiparkinsonian agents	1.3	2.1	0.6	0.1-2.7
Anticonvulsants	4.0	4.4	0.9	0.4-2.2
Sedative hypnotics	5.9	2.2	3.1	1.3-7.3

Abbreviation: NSAIDs=non-steroidal anti-inflammatory drugs; ACEI=angiotensin-converting enzyme inhibitors; ARB=angiotensin-receptor antagonists

¹⁾ Other antidepressant medication included serotonin norepinephrine reuptake inhibitor (SNRI), tricyclic agents, and other class of antidepressant (i.e. bupropion, mirtazapine, reboxetine, trazodone).

Table 2.6 Association between use of SSRI and upper GI bleeding

	Cases (N=152) %	Control (N=820) %	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio ¹⁾ (95% CI)
	N (%)	N (%)		
SSRI use	12 (7.9%)	50 (6.1%)	1.3 (0.7 – 2.5)	0.7 (0.3 – 1.7)

¹⁾Adjusted odds ratio was found after controlling for race/ethnicity, use of NSAIDs, anticoagulant agents, oral corticosteroids, acid suppressing medications, other antidepressant medication; comorbid conditions including uncomplicated hypertension, cardiovascular disease, dyslipidemia, COPD, fluid/electrolyte disorder, and fatigue.

Table 2.7 Evaluation of the interaction between SSRI and NSAID use on Risk of upper GI bleeding compared with non use of NSAIDs and SSRIs

Category	Cases (N=152)	Control (N=820)	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio ¹⁾ (95% CI)
	N (%)	N (%)		
Non-users	115 (75.6%)	681 (83.1%)	1.0 (reference)	1.0 (reference)
SSRI only	6 (4.0%)	37 (4.5%)	1.0 (0.4-2.4)	0.5 (0.2-1.6)
NSAID only	25 (16.4%)	89 (10.8%)	1.7 (1.1-2.8)	1.5 (0.8-2.8)
Both	6 (4.0%)	13 (1.6%)	2.9 (1.0-8.1)	1.8 (0.5-6.7)

¹⁾ Adjusted odds ratio was found after controlling for race/ethnicity, anticoagulant agents, oral corticosteroids, acid suppressing medications, other antidepressant medication; comorbid conditions including uncomplicated hypertension, cardiovascular disease, dyslipidemia, COPD, fluid/electrolyte disorder, and fatigue.

Figure 2.1 Conceptual study design: a nested case-control study to evaluate the effect of SSRIs on rate of upper GI bleeding

Figure 2.2 Sample selection inclusion and exclusion criteria

Manuscript III. A Systematic Literature Review: Effect Measure Modification and Sample Size Considerations in Observational Studies

BACKGROUND

Effect Measure Modification (EMM) is a phenomenon in which an association between an exposure and outcome varies by a third factor.[1] When EMM occurs, estimates of the association differ at different levels of the effect modifier, therefore the overall estimate of the association may be misleading.[2, 3] Unlike confounding in observational studies, EMM should be described and reported separately.[2, 3] Therefore, evaluating and characterizing EMM may be crucial when examining a potential association in data analysis.

Common statistical methods to identify EMM include stratification and regression analysis.[4] Stratification is the assembly of subgroups by strata of the potential effect modifier followed by the evaluation of stratum-specific associations of exposure with the outcome of interest if heterogeneity is present.[2] Another method to test EMM is by testing the interaction terms in a regression model (e.g., effect modifier x independent variable [exposure of interest]).

An important consideration for formal evaluation of EMM is to have adequate statistical power to quantify the association across categories or levels of the effect modifying factor. A stratified analysis dividing the sample into subgroups generally requires a large sample size. Smith and Day suggested that an at least four times larger

sample size was required to evaluate EMM compared with the sample size required to assess a main association under optimal conditions (e.g., 50% of the study population classified as an exposure and 50% being exposed to the potential effect modifier).[5] If the prevalence of the exposure or effect modifier is lower or higher than 50%, then the sample size to detect EMM is typically larger.[5]

When seeking to evaluate EMM, researchers should conduct an analysis and report the sample size considerations related to the EMM in the medical literature.

However, how the sample size considerations are determined in a study is less well understood, especially in research related to EMM utilizing large sets of administrative data.

In this study, we performed a systematic literature review of published articles reporting EMM and characterized sample size considerations related to EMM reported in these studies. We hypothesized that few published pharmacoepidemiologic studies formally assessing EMM would utilize and present formal sample size calculations in the published manuscript.

METHODS

We performed a systematic literature review. To identify recently published articles of interest, we searched the PubMed electronic database from January 1, 2008 to June 30, 2013. As the focus of this manuscript is the incorporation and presentation of sample size calculations or estimates related to effect measure modification in pharmacoepidemiological studies, we searched using the following terms: effect measure modification; effect modification; statistical interaction; biological interaction; epidemiology; epidemiological study; observational study; case-control; cohort study; cross-sectional; and medication. We further limited the search to English language articles and human subject studies.

We first used a computerized literature search to identify relevant articles by reading the titles and abstracts. Articles identified as potentially relevant through this preliminary search were retrieved and reviewed systematically to eliminate articles whose study base did not include medication use or an observational study. We further excluded studies if the effect measure modification being evaluated in the study was not related to medication use (e.g. age, race/ethnicity, socioeconomic characteristics). From these articles, we identified new articles by reviewing the reference lists and retrieving the articles.

After completion of the literature review, the literature was summarized by first describing the ways in which effect measure modification was used in the identified studies, including whether its assessment was a primary or secondary objective of the

study, and the major findings related to EMM. Second, we characterized the incorporation and presentation of sample size calculations in the identified studies. We developed a table that denotes whether sample size calculations related to EMM were performed and, if they were performed, what power resulted. For this study, analyses were largely descriptive and included frequencies to summarize the percentage of studies including specific sample size calculations.

RESULTS

Using the provided search keywords, we initially found 685 publications. By reviewing the titles and abstracts of the potential literature, we selected 21 studies and eliminated 664 articles. The most frequent reasons for exclusion included the following: 1) the research topic was not related to EMM/association/statistical interactions (e.g., treatment effect, regimen/dose modification, prevalence of drug-drug interaction; n=311); 2) the study design was not observational (e.g., an experimental design; n=148); and 3) the effect modifier was not related to medication use (e.g., age, race/ethnicity, certain disease/health condition, or genetic type; n=205).

In Table 3.1, we present the characteristics of the included studies and state whether sample size considerations were presented in the study. In the included studies, the research questions were mostly related to risk assessments, varying from predictors of the increased risk of mortality associated with a psychotic disorder to associations between glycemia and lipid levels among patients with diabetes mellitus. The most popular effect modifier in the review was the use of cholesterol-lowering medications, including statins.

While wide variation in methods to evaluate EMM existed, the two most common methods to evaluate the EMM were likelihood ratio testing after stratification or 2-way interactions using the Wald test. The EMM was mostly tested as a secondary objective of the study (N=20), not as a primary objective (N=1). None of the studies in the review presented sample size considerations to detect the EMM; however, 3

publications mentioned the sample size considerations but did not present enough information to fully assess the required sample size to adequately assess EMM.

A study performed by Dratva et al. provided the most detailed information regarding the sample size consideration among the reviewed literature.[6] They employed a prospective cohort study to examine the association between the menstruation cycle and bronchial hyper-reactivity. Using the population-based Swiss cohort study on air pollution and lung disease in adults (SAPALDIA II), they found 571 eligible individuals to examine the primary hypothesis (association between the menstruation cycle and bronchial hyper-reactivity). As a second step, they assessed the impact of oral contraceptive use on the hypothesized association. To achieve this objective, they enlarged the main study sample by including women currently using oral contraceptive, and found 130 more eligible women during this consideration. The authors preliminarily evaluated the EMM using interaction terms in the logistic regression model and then stratified the sample by oral contraceptive use status. They confirmed a significant interaction between the menstruation cycle and oral contraceptive use. When performing the stratified analyses, the authors observed insignificant effects of the menstruation cycle on the reduced risk of bronchial hyper-reactivity modified by oral contraceptive use due to a lack of power.

Mordukhovich et al. evaluated whether calcium channel blockers modified the effects of low-level environmental arsenic exposure on the prolonged QT interval as a secondary objective.[7] They initially utilized 2,280 individuals in their cohort. After

applying the inclusion and exclusion criteria, they found 226 eligible individuals to test the primary objective in a cross-sectional design. Using 2-way interaction terms in a regression model, they tested the interaction between arsenic exposure and calcium channel blocker use. However, they did not further report the results as the interaction was not significant. The authors also noted in the discussion that the effect modification by calcium channel blockers was not significant, potentially due to a small sample size.

Henz et al. reviewed the comorbid conditions and concurrent medications to identify predictors affecting the serum potassium concentration in patients admitted to the hospital.[8] They employed a retrospective cross-sectional study and utilized 10,320 patient records. As the primary finding, they reported that certain medications and comorbidities influenced the serum potassium concentrations. Using 2-way interactions in a regression model, they further found significant drug-drug interactions between angiotensin converting enzyme inhibitors and K-sparing diuretics and between beta blockers and non-steroidal anti-inflammatory drugs, which both affected the serum potassium concentration. However, they did not confirm the interaction between loop diuretics and angiotensin receptor blockers. With respect to the insignificant interactions, the authors suggested that the power might be limited even though the study sample size was relatively large.

The other studies did not mention the sample size for assessing the EMM or interactions. Among these 18 studies, 10[9-18] confirmed significant

interactions/EMM, whereas 6[19-24] did not find significant interactions/EMM and 2[25, 26] found statistical significance in one group (with significant estimates not presenting in all subgroups).

DISCUSSION

We found that none of the studies performed sample size calculations specifically related to the EMM, although 14.3% of the identified studies mentioned sample size-related issues in the study. Only one study described the process of expanding the sample size to achieve the study objectives related to EMM; two other studies mentioned a problematic small sample size to explain insignificant interactions in the study findings.

One potential reason for the lack of sample size consideration in the reviewed articles would be the nature of an observational study. In contrast to clinical trials, which should be conducted as specified in the planned protocol, observational studies utilize data already collected or manipulate a closed cohort to examine associations.

Therefore, the authors often described an eligible population for the study but did not provide *a priori* consideration of the minimum number of samples required to obtain accurate estimates of the association. Furthermore, based on our review, we found that most of the studies sought to assess the EMM as a secondary objective. Considering that published articles usually perform sample size calculations to test the main association,[27] expecting the presentation of additional sample size calculations for the secondary objective might be unreasonable.

The substantial importance of adequate power in a study emphasizes the need to conduct sample size calculations in epidemiological studies (e.g., case-control studies and cohort studies).[27] A small sample size or more importantly, lack of statistical

power may not change the direction of the association between the exposure and the outcome of interest.[3] However, the estimates of the association may lack precision as evidenced by wide confidence intervals.[3] Even in the case utilizing a large sample of administrative data, a large study population does not necessarily mean a higher prevalence of the exposure of interest or effect modifier. Therefore, considering the sample size for a specific study aim in the method sections can ensure the acquisition of accurate estimates with adequate power to detect the association.

There are some suggestions to present observational studies in more informative ways. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) proposed 21 check points that authors should address in reporting the results of an observational study.[28] In particular, the STROBE guidelines recommend that interaction/EMM analyses should be preferably presented as separate effects of the two exposures and as their joint effect using one reference category. By providing this sufficient information, readers can calculate the interactions/EMM on additive and multiplicative scales. Another study performed by Knol et al. further suggested a four-step presentation of the EMM or interactions in observational studies.[29] The crucial point that the study provided was reporting the estimates with a 95% confidence interval for each stratified cell. Again, the reason for presenting this information is to provide the full findings to the readers to increase the transparency of the study.

Our study adds one more point to improve the reporting of the EMM or interactions. Authors should provide consideration of the sample size calculation to evaluate the EMM/interactions in addition to describing the actual eligible sample size from the data. While EMM or interaction is widely assessed in epidemiological studies, ensuring adequate power for the research is a practical issue to obtain accurate estimates. While it is well known that sample size and power are important considerations for primary endpoints, other researchers suggest that similar considerations should be made when evaluating EMM.[4] Practically however, manuscript limitations may not provide adequate space to discuss all methodological considerations, including sample size related to EMM. With increased research on gene-gene interaction,[30] more studies will investigate and publish EMM. Presentation of sample size considerations is important to the reader, particularly when no association (or no effect measure modification) is reported. As evaluation of EMM is typically performed as secondary analyses, consensus on publication of sample size considerations in the pharmacoepidemiologic scientific community is warranted. By including the sample size considerations, the research can clearly demonstrate that the estimates are reliable and accurate and have adequate power. Therefore, the authors can perform better quality research, and the readers can easily analyze the results presented in the study.

CONCLUSIONS

Our study evaluated the degree of reporting the sample size considerations related to EMM in the published medical literature. Studies examining the EMM largely failed to report sample size calculations to assess the associations of interest. This methodologically focused paper provided important insight for researchers on the correct (or incorrect) reporting of sample size related issues in the published medical literature by demonstrating what is currently being done and providing recommendations for future publications.

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Tables 3.1 Characteristics and sample size considerations of the studies included

Study No	Author	Research question	EMM evaluated	Method used	Result (primary/secondary)	Sample size presented/discussed
1	Aikens et al. (2009)[9]	Glycemic control associated with depressive symptom severity	Antidiabetic medication regimen (oral vs. insulin)	2-way interaction	Secondary	No
2	Allen et al. (2009)[10]	Aortic atherosclerosis associated with air pollution	Statin use modified the effect of pollution on aortic calcification	2-way interaction	Secondary	No
3	Almeida et al. (2012)[11]	Total plasma homocysteine (tHcy) associated with depression	Aspirin modifier on tHcy	2-way interaction	Secondary	No
4	Bruneau et al. (2012)[26]	Hepatitis C virus (HCV) infection associated with prescription opioid injection	Heroin use modified HCV infection rates.	2 way interaction	Secondary	No
5	Chen et al. (2011)[12]	Risks of cataracts associated with age	Diabetic mellitus, folate level, antihypertensive medication use	Stratified by risk factors of cataracts and evaluated EMM using likelihood ratio testing	Secondary	No
6	Dieset et al. (2012)[13]	high sensitivity CRP (hsCRP) cytokine associated with CVD risk factors	second generation antipsychotics modifies effects of CVD risk factors	2-way interaction	Secondary	No
7	Dratva et al. (2010)[6]	Bronchial hyperreactivity associated with time of menstrual cycle	Effect modifier of oral contraceptives	Preliminarily evaluated EMM using likelihood ratio test; further assessed EMM stratified by oral contraceptive use status	Secondary	Yes

Tables 3.1 Characteristics and sample size considerations of the studies included (Continued)

Study No	Author	Research question	EMM evaluated	Method used	Result (primary/secondary)	Sample size presented/discussed
8	Farzaneh-Far et al. (2009)[19]	Inflammatory biomarkers associated with n-3 fatty acid levels	Modified by Statin use	2-way interaction	Secondary	No
9	Hayashino et al. (2012)[20]	Diabetes distress (measured by the PAID scale) associated with poor glycemic control	Effects of the PAID scores modified by diabetic therapy (diet control vs. use of antidiabetic medications) on HbA1c level	Evaluated interactions using likelihood ratio tests	Secondary	No
10	Henz et al. (2008)[8]	Comorbidities and comedications predicting blood potassium concentration	ACEI, cyclosporine, and loop/potassium-sparing diuretics modified the association between GFR and serum potassium level	2-way interaction using the Wald test	Secondary	Yes
11	Hermann et al. (2009)[14]	Risk of colorectal adenomas associated with lifestyle factors and obesity	Folate intake modified the association between alcohol consumption and risk of adenoma	2-way interaction using the Wald test	Secondary	No
12	Maahs et al. (2010)[15]	Association between glycemia and lipid level in patients with type I diabetes mellitus	Dyslipidaemia medication use	Stratified by dyslipidaemia medication usage status; likelihood ratio testing	Secondary	No
13	Mordukhovich et al. (2009) [7]	QT interval duration associated with environmental arsenic exposure	Effect modification by use of calcium channel blockers; or antioxidant intake	2-way interaction	Secondary	Yes

Tables 3.1 Characteristics and sample size considerations of the studies included (Continued)

Study No	Author	Research question	EMM evaluated	Method used	Result (primary/secondary)	Sample size presented/discussed
14	Moyers et al. (2010)[21]	Exercise parameters (i.e., heart rate recovery, exercise capacity and time) associated with serum n-3 fatty acid levels	Modified association by statin or beta blocker use	2-way interaction	Secondary	No
15	Neuhouser et al. (2010)[16]	Sex hormone concentrations associated with dietary fat intake in postmenopausal breast cancer survivors	Tamoxifen modifier; effect modification between tamoxifen use and fat intake	2-way interaction	Secondary	No
16	Rajanna et al. (2012)[17]	HbA1c level associated with Fasting morning glucose	Cholesterol controlling medication (i.e. statins, niacin, and fibrates) modifiers	2-way interaction	Primary	No
17	Ross et al. (2011)[18]	Weight change associated with Insomnia	Sleep medications modified the association	2-way interaction	Secondary	No
18	Samadder et al. (2011)[22]	Colorectal cancer associated with inflammatory bowel disease	Modification of risk by statin and NSAID use	Stratified by medication use; evaluating EMM using likelihood ratio testing	Secondary	No
19	Shadman et al. (2009)[23]	Risk of colorectal cancer associated with NSAIDs/statins use	Effects of NSAIDs use on colorectal cancer modified by statin use	2-way interaction	Secondary	No
20	Suvisaari et al. (2013)[25]	Predictors of mortality in patients with psychotic disorder	Antipsychotic medication use modified the link between primary psychotic disorder and mortality	Stratification; evaluation using likelihood ratio testing	Secondary	No

Tables 3.1 Characteristics and sample size considerations of the studies included (Continued)

Study No	Author	Research question	EMM evaluated	Method used	Result (primary/secondary)	Sample size presented/discussed
21	Wu et al. (2010)[24]	All cause of mortality/CVD death associated with genetic variations in the RAS genes	Effect of RAS-gene-genotypes modified by use of ACE inhibitors	2-way interaction	Secondary	No

CVD=Cardiovascular disease; PAID= Problem Areas in Diabetes; RAS=Rennin-angiotensin system; ACEI=Angiotensin converting enzyme inhibitor; NSAID = Non-steroidal anti-inflammatory drugs; GFR= Glomerular filtration rate

APPENDICES

Appendix A. Prevalence of antidepressant medication use

Category	Antidepressants	Antidepressant prescription records in MCBS 2006-2008		755 prescription records (by the 99 eligible sample)		Eligible sample (N=99, multiple counted by using multiple meds)		Eligible sample (N=99, single count, subgroup classified)	
		N	%	N	%	N	%	N	%
SSRIs	Citalopram	4679	9.3	80	10.6	13	10.4	9	9.1
	Escitalopram	5658	11.3	172	22.8	26	20.8	23	23.2
	Fluoxetine	4077	8.1	36	4.8	6	4.8	5	5.1
	Paroxetine	4872	9.7	24	3.2	4	3.2	3	3.0
	Sertraline	6782	13.5	126	16.7	19	15.2	17	17.2
SNRIs	Desvenlafaxine	10	0.0	-	-	-	-	-	-
	Duloxetine	2374	4.7	61	8.1	9	7.2	6	6.1
	Venlafaxine	3288	6.6	22	2.9	3	2.4	3	3.0
TCA	Amitriptyline	3458	6.9	30	4.0	7	5.6	5	5.1
	Amoxapine	1	0.0	-	-	-	-	-	-
	Clomipramine	142	0.3	-	-	-	-	-	-
	Desipramine	76	0.2	-	-	-	-	-	-
	Doxepine	733	1.5	-	-	-	-	-	-
	Imipramine	387	0.8	-	-	-	-	-	-
	Maprotiline	10	0.0	-	-	-	-	-	-
	Nortriptyline	681	1.4	14	1.9	3	2.4	2	2.0
	Protriptyline	13	0.0	-	-	-	-	-	-
MAOIs	Phenelzine	89	0.2	-	-	-	-	-	-
Other	Bupropion	2539	5.1	45	6.0	8	6.4	5	5.1
	Mirtazapine	3692	7.4	70	9.3	14	11.2	13	13.1
	Trazodone	4673	9.3	75	9.9	13	10.4	8	8.1
	Nefazodone	65	0.1	-	-	-	-	-	-
Total		50122	100.0	755	100.0	125	100.0	99	100.0

Appendix B. Persistence status and classified subgroup in patients with combination therapy

No	Duration of Therapy					Persistence Status	Subgroup Category	Comments (medications in combination)
	SSRI	SNRI	TCA	Other	Therapy Days			
Combo1	355	.	.	244	355	persist	SSRI	Escitalopram/Trazodone
Combo2	323	.	.	136	323	persist	Other	Sertraline/Trazodone
Combo3	5	.	.	7	7	non-persist	Other [*]	Sertraline /Trazodone
Combo4	365	.	.	365	365	persist	SSRI [*]	Sertraline /Bupropion
Combo5	.	30	.	365	365	persist	Other	Duloxetine/Mirtazapine
Combo6	335	.	.	365	365	persist	Other [*]	Fluoxetine /Trazodone/Bupropion
Combo7	177	191	365	.	365	persist	Other [*]	Sertraline, Duloxetine /Amitriptyline
Combo8	357	.	.	365	365	persist	Other [*]	Escitalopram/Trazodone
Combo9	116	.	.	117	117	non-persist	Other [*]	Citalopram/Mirtazapine
Combo10	.	265	67	133	265	persist	SSRI	Duloxetine/Amitriptyline, Bupropion
Combo11	224	.	47	.	224	persist	SSRI	Escitalopram/Nortriptyline
Combo12	.	365	.	335	365	persist	SSRI [*]	Duloxetine/Trazodone
Combo13	60	.	.	30	60	non-persist	SSRI	Paroxetine/Mirtazapine
Combo14	108	.	.	90	108	non-persist	SSRI	Citalopram/Trazodone
Combo15	128	.	.	2	128	non-persist	SSRI	Escitalopram/Trazodone
Combo16	30	144	.	330	330	persist	Other	Escitalo,Citalopram, Duloxetine /Trazodone, Mirtazapine
Combo17	231	.	323	241	323	persist	Other	Citalopram /Amitriptyline, Trazodone
Combo18	300	.	.	72	300	persist	SSRI	Fluoxetine/Trazodone, Bupropion

* This categorization may result in misclassification of the subgroups.

Subgroup category: SSRI=SSRI/SNRI; Other=TCA/Other antidepressant

Appendix C. Persistence status and classified subgroup in patients who switched medications

No	Duration of Therapy					Persistence Status	Subgroup Category	Comments (Switching From-To)
	SSRI	SNRI	TCA	Other	Therapy Days			
Switching-1	211	.	.	.	211	persist	SSRI	SSRI - SSRI
Switching-2	30	.	.	23	53	non-persist	SSRI	Other - SSRI
Switching-3	.	.	30	30	60	non-persist	Other	TCA - Other
Switching-4	252	.	.	117	365	persist	SSRI	SSRI - Other
Switching-5	43	96	.	.	137	non-persist	SSRI	SNRI - SSRI
Switching-6	30	.	.	30	60	non-persist	Other*	Other - SSRI
Switching-7	270	.	.	.	270	persist	SSRI	SSRI - SSRI

* This categorization may result in misclassification of the subgroups.

Subgroup category: SSRI=SSRI/SNRI; Other=TCA/Other antidepressant

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