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ASSOCIATION BETWEEN CONCOMITANT USE OF BISPHOSPHONATES AND SEROTONIN REUPTAKE INHIBITORS AND INCREASED RISK OF OSTEOPOROTIC-RELATED FRACTURES: AMONG COMMUNITY-DWELLING POSTMENOPAUSAL WOMEN

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A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

by

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Dedication

This dissertation is dedicated to the following:

My parents, Mr&Mrs Agnes and Gideon Nyandege Bienda, who instilled in me the discipline to strive for success in academics.

My late grandparents, Mr& Mrs Francis and Kebubo Sibia Bienda, who emphasized the importance of education; and my late friend, Elizabeth Reid, who enjoyed listening to my research project in older adults and was supportive of my academic dream, but you did not live to see my accomplishments.

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ARR	Adjusted relative rates
AG	Adipogenesis
AIs	Aromatase inhibitors
ALN	Alendronate
ALN&vertF	Alendronate and the risk reduction of vertebral fracture (reference)
ATF-4	Activating transcription factor 4
Adrβ2	β2 adrenergic receptor
ADEs	Adverse drug events
Antidep	Antidepressant
AHRQ	Agency for Health Care Research and Quality
AnyFractc	Any fracture
BP	Bisphosphonate
BPs	Bisphosphonates
BISPH&AF	BPs use and the reduction of any fracture (this study)
Bisp&Hip	BPs use and the reduction of hip fracture (this study)
BISPH&Hip	BPs use and the risk reduction of hip fracture (reference)
BMD	Bone mineral density
CMS	Centers for Medicare and Medicaid Services
CCW	Chronic Condition Data WareHouse
CI	Confidence interval
CYP450	Cytochrome P-450 enzyme
CNS	Central Nervous System
CLO	clodronate
cAMP	Cyclic adenosine monophosphate
CREB	cAMP response element-binding
COPD	Chronic obstructive pulmonary disease
Cyc D1	Cyclin D1
CINAHL	Cumulative Index to Nursing and Allied Health
DDDs	Defined daily doses
DALYs	Disability-adjusted life years
ED_{50}	Concentration at which the protein exhibits 50% of its maximum activity
ED	Emergency department
FEHB	Federal Employees' Health Benefits
FDA	U.S Food and Drug Administration
FRAX®	Fracture Risk Assessment Tool
FPP	Farneslypyrophosphate synthase
GPCR	G-protein coupled receptor
GDS	Geriatric Depression Scale
GCs	Glucocorticoids
GERD	Gastroesophageal reflux disease
HRT	Hormone replacement therapy
5-HT	Serotonin
5-HTT	Serotonin transporter
HR	Hazard ratio
HipFractc	Concomitant use of BPs and SSRIs and risk of hip fracture (this study)
IRB	Institutional Review Board
ICD-9-CM	International Classification of Diseases, 9^{th} revision; Clinical Modification
IADLs	Instrumental Activities of Daily Living
IC_{50}	Inhibition concentration (half-maximal effect)
IRR	Incidence risk ratio
IBN&vertF	Ibandronate and the risk reduction of vertebral fracture (reference)
K_i	Dissociation constant
LT_4	Levothyroxine

MEPS	Medical Expenditure Panel Survey
MEPS-HC	MEPS-Household component
MeSH	Medical subject headings
MCBS	Medicare Current Beneficiary Survey
MAOIs	Mono amine oxidase inhibitors
MDD	Major depressive disorder
MCCs	Multiple chronic conditions
Mg/d	Milligram per day
NE	Norepinephrine
nM	Nanomolar
NIMH	National Institute of Mental Health
NSAIDS	Nonsteroidal anti-inflammatory drugs
NHIS	National Health Interview Survey
NCHS	National Center for Health Statistics
OR	Odds ratio
OCD	Obsessive compulsive disorder
PPIs	Proton pump inhibitors
PPAR-γ	Peroxisome proliferator-activated receptor γ
PTH	Parathyroid hormone
Pr	Probability
PSM	Propensity score method
PS	Propensity score
PSU	Primary sampling unit
PKA	Protein Kinase A
PDPs	Medicare stand-alone prescription drug plans
PIN	Unique personal identification number
QTc	Corrected QT interval
ResDAC	Research Data Assistance Center
RX	Prescription
RANK	Nuclear factor kappa B receptor
RANKL	Nuclear factor kappa B receptor ligand
RCTs	Randomized clinical trials
RR	Relative risk
RSN&vertF	Risedronate and the risk reduction of vertebral fracture (reference)
SSRIs	Selective serotonin reuptake inhibitors
SSRIAnyFs	SSRI use and increased risk of any fracture (this study)
SSRI&Fract	SSRI use and increased risk of fracture (reference)
SSRI&HIPs	SSRI use and increased risk of hip fracture (this study)
SNRIs	Serotonin norepinephrine reuptake inhibitors
SERM	Selective estrogen-receptor modulator
SES	Socioeconomic status
s.c	Subcutaneous
SD	Standard deviation
TSH	Thyroid stimulating hormone
TZDs	Thiazolidinediones
TNF	Tumor necrosis factor
TCAs	Tricyclic antidepressants
USPSTF	U.S Preventive Services Task Force
VrtFractc	Concomitant use of BPs and SSRIs and risk of vertebral fracture
WHO	World Health Organization
WHI	Women's Health Initiative

Abstract

ASSOCIATION BETWEEN CONCOMITANT USE OF BISPHOSPHONATES AND SEROTONIN REUPTAKE INHIBITORS AND INCREASED RISK OF OSTEOPOROTIC-RELATED FRACTURES: AMONG COMMUNITY-DWELLING POSTMENOPAUSAL WOMEN

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A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

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Osteoporosis and depression are prevalent among older postmenopausal women 65 years or older. Bisphosphonates (BPs) and selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) are commonly used medications to treat these conditions. Inhibitory effects of BPs on osteoclasts are responsible for the reduction in fracture risk. SSRIs, however, are associated with increased fracture risk through decreasing osteoblasts and increasing osteoclastic activity. These effects of SSRIs could attenuate the beneficial effects of BPs. This dissertation describes the concomitant use of BPs and SSRIs among postmeopausa

women and reports findings from examining the association between concomitant use of BPs and SSRIs and fracture risk.

Separate cross-sectional analyses were performed using data from the 2004-2008 Medical Expenditure Panel Survey (MEPS) and Medicare Part D prescriptions claims data (2008-2010) to examine usage patterns of BPs and SSRIs/SNRIs for women aged ≥45 years and ≥65 years, respectively. For our second objective, a nested-case control was conducted using Medicare claims data (2008-2010). Data from Medicare inpatient claims were linked to Medicare Part D data for all female BP users 65 years or older. We used Cox proportional hazards model to assess the increased risk of osteoporotic-related fractures among propensity score matched (1:1 ratio) cohorts of concomitant users of BPs and SSRIs and BP alone users.

Concomitant use of BPs and SSRIs was prevalent and increased with age for each timeframe examined. Findings showed that approximately 12% (using MEPS) and 28% (using Medicare data) of women on BPs were also on SSRIs. For the second objective, 4,214 propensity score matched pairs (average age=80.4 years) of subjects were analyzed. Findings showed that concomitant use of BPs and SSRIs was associated with statistically significant increased risk for any fracture (HR=1.29, 95% CI, 1.07-1.57), but statistically non-significant increased risk for hip (HR=1.16, 95% CI, 0.92-1.47) and vertebral fractures (HR=1.55, 95% CI, 0.97-2.48).

Current findings indicate that concomitant use of BPs and SSRIs is not uncommon among postmenopausal women and suggest potential attenuation of antifracture efficacy of BPs by SSRIs. Further studies are needed to understand the clinical impact of concomitant use of these medications among older postmenopausal women.

Chapter 1

1.0 INTRODUCTION

1.1 Overview of the document

This dissertation describes a pharmacoepidemiologic study to (1) describe the concomitant utilization pattern of selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) and bisphosphonates, examine (2) the increased risk of osteoporotic-related fractures associated with the concomitant use of SSRIs with bisphosphonate therapy, and (3) whether the risk of osteoporotic-related fractures is related to the role of serotonin in bone rather than the disease (depression). This chapter provides background on the basic understanding of osteoporosis and osteoporotic fractures and the associated risk factors, epidemiology, prevention and treatment of the disease, bisphosphonate therapy, and a brief statement on the safety concerns with simultaneous use of bisphosphonate therapy and SSRIs or SNRIs in postmenopausal women. Chapter 2 provides a more in depth overview of the literature of concomitant use of drugs and adverse drug events, concomitant use of drugs with bisphosphonates and risk of fractures, SSRIs or SNRIs and bone health, and pharmacoepidemiologic study design considerations. Chapter 3 provides details on a preliminary descriptive study to assess the utilization of these medications both separately and concomitantly using nationally-representative survey data in order to determine to what extent these medications are prescribed among women. Chapter 4 describes the methods used for this pharmacoepidemiologic study, whereas Chapter 5, Chapter 6, and Chapter 7 describe the results, and discussion and conclusions from the study, respectively.

1.2 Osteoporosis and osteoporotic-related fractures

1.2.1 Basic understanding

Bone is a highly specialized living supportive tissue with major functions of providing support for the body, protection of vital organs, providing an environment for marrow, and acts as a mineral reservoir for calcium homeostasis in the body. Bone is comprised of bone cells, an organic matrix of collagen and noncollagenous proteins (osteoid), and inorganic mineral matrix. Bone cells which include osteoblasts, osteocytes, and osteoclasts are concerned with the production, maintenance and modeling of osteoid (**Figure 1.1**).

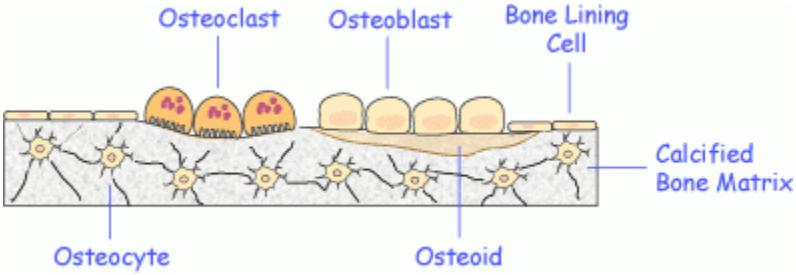

Figure 1.1. Bone cells
Source: www.iofbonehealth.org

Osteoblasts are bone-forming cells or they are the cells within bone that lay down the extracellular matrix and regulate its mineralization. Osteoclasts are bone degrading (resorption) cells at sites called Howship's lacunae. Osteocytes, smaller in size than osteoblasts, are mature osteoblasts which eventually become calcified bone. Osteocytes are the most abundant cells in bone (or are the principal cell in adult bone) and are thought to be important in responding to changes in physical forces upon bone and to transducer messages to the osteoblastic cells on the bone surface, directing them to initiate resorption or formation responses.[1,2]

Osteoporosis is a bone health disease characterized by the loss of bone mass (low bone mineral density) and strength that leads to an increased risk of fracture. Osteoporosis results from

the imbalance created in the process of bone remodeling, which is the major activity of bone cells in the adults skeleton.[3] Bone remodeling is a process by which old bone is continuously replaced by new tissue through resorption and formation, balanced at an equilibrium, so that the bone adapts to mechanical load and strain.[4] Diagnosis of osteoporosis is based on the World Health Organization (WHO) criteria for bone mineral density (BMD). Osteoporosis corresponds to BMD T-score of -2.5 or less compared to a normal, young adult population of the same gender (reference population) BMD T-score of -1.0 or higher. A T-score is useful to express BMD in a postmenopausal population and is expressed as standard deviation (SD) units.[5] Factors associated with osteoporosis (or low BMD) and increased risk of fractures included in a new Fracture Risk Assessment Tool (FRAX®) for evaluating fracture risk are listed in **Table 1.1**. FRAX® was developed by the WHO to evaluate a patient's 10-year probability of hip fracture and major osteoporotic fracture (i.e., clinical spine, forearm, hip, or shoulder fracture). Previously, clinicians could only estimate a 5-year fracture risk.[6]

Table 1.1. Risk factors for osteoporotic fracture used in FRAX®

- Age (50 to 90 years)
- Sex
- Body mass index
- Low femoral neck BMD
- Prior fragility fracture
- Parental fragility fracture
- Current tobacco smoking
- Long-term use of glucocorticoids
- Rheumatoid arthritis
- Other causes of secondary osteoporosis (e.g., medications and medical conditions)
- Alcohol intake of more than two drinks per day

Adapted from the North American Menopause Society, 2010.[6]

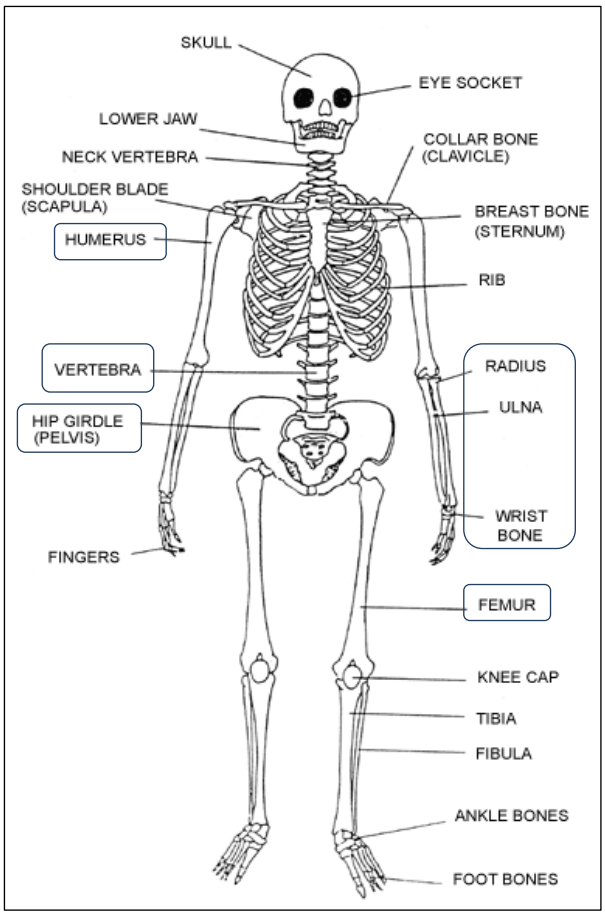

Figure 1.2. The human skeletal system highlighting common osteoporotic fracture sites.

In healthy postmenopausal women, BMD of both the entire skeleton and single anatomical sites have been shown to decrease progressively after the onset of menopause because of hormonal changes.[7] Specifically, the rapid bone loss in postmenopausal women results from low estrogen production.[8] Although postmenopausal osteoporosis affects the whole skeleton, vertebral fractures, hip fractures, and Colles' (wrist/forearm) fractures are the most common osteoporotic fractures.[9] Other osteoporotic fractures include pelvic, humeral, and other femoral fractures.[10] A schematic diagram of the human skeletal system is shown in **Figure 1.2** highlighting the most common osteoporotic fracture sites.

1.2.2 Epidemiology

Osteoporosis and its resulting problem of fractures among older adults are a major public health concern in the United States.[11] The proportion of osteoporosis is significantly higher in postmenopausal women compared with men of the same age.[12] The U.S. Preventive Services Task Force (USPSTF) recommends that women ≥65 years of age be screened routinely for osteoporosis, but there is no recommendation for or against routine osteoporosis screening in postmenopausal women who are younger than 60 years of age or in women 60 to 64 years of age who are not at increased risk for osteoporotic fractures.[13] The prevalence of osteoporosis rises from 4% in women ages 50 to 59 years to 52% in women age 80 years and older.[14] Thus, osteoporosis and osteoporotic fractures increases with age. This is further supported by the findings in a study of over 200,000 postmenopausal women. In this study, relative to women aged 50-54 years, the odds of having osteoporosis were found to be 5.9-fold higher in women aged 65-69 and 14.3-fold higher in women aged 75-79 years.[15] This information suggests that older postmenopausal women are more prone to suffer from osteoporosis and thus are at increased risk of osteoporotic fractures in their lifetime.

Roughly 4 in 10 white women age 50 years or older in the U.S. will experience a hip, vertebral, or wrist fracture sometime during the remainder of their lives and 13% of white men will suffer a similar fate. The estimated remaining lifetime risks after age 50 for hip, vertebral, and wrist/forearm fractures in women are 17.5%, 15.6%, and 16.0%, respectively.[10] In the U.S., the rates of osteoporosis and/or osteoporotic fractures are higher among white women compared with Asian or African American women.[16] It is estimated that 90% of all hip and vertebral fractures in white American women aged between 65 and 85 years old are attributed to osteoporosis.[17]

Of the most common osteoporotic fractures, hip and vertebral fractures are associated with pronounced burden on society and individuals in terms of clinical consequences and economic burden emphasizing the need for intervention in women at high risk.[18] Specific burdens include chronic pain, disability, depression, loss of independence or functional ability and psychosocial difficulty, increased mortality, and increased healthcare costs.[19] In 2005, osteoporosis-related fractures were responsible for an estimated $19 billion in costs in the U.S. By 2025, predictions show that these costs will rise to approximately $25.3 billion.[20] It has been estimated, assuming there will be no changes over a long period of time, that hip fractures, the most prevalent in older adults, are projected to increase progressively to 2.6 million by 2025 and to 4.5 million by 2050 worldwide.[21] The current annual cost to the U.S. health care system for patients with hip fractures is more than $12.6 billion (an average of $37,000 per patient). Only 25% of hip fracture patients will make a full recovery; 40% will require nursing home care; 50% will need a cane or walker; and 24% of those over age 50 will die within 12 months, hence, the future post-fracture cost may even be greater.[22]

As the U.S. population of older adults is projected to increase in the coming decades, a high prevalence of osteoporosis and/or osteoporotic-related fracture burden is expected. In fact, according to the U.S. Census Bureau, it is projected that by 2030, 20% of Americans will be aged 65 years and older and by 2050, the age group is projected to increase to 88.5 million from 38.7 million in 2008. Similarly, the 85 years and older population is expected to increase to 19 million by 2050 from 5.4 million in 2008.[23] Moreover, among older adults, the current proportion of females in the U.S and other countries is greater than males and will still remain so in the future. The United Nations suggests that, “in many cases, the difference is so large that concerns of the older population should in fact be viewed primarily as the concerns of older

women". The difference in this ratio is generally driven by the fact that average life expectancy is greater for females than for males.[24,25]

1.2.3 Prevention and treatment of disease

1.2.3.1 Background

Patients with osteoporosis and osteoporotic (or prevalent) fractures are offered opportunities for prevention (medication given to individuals with no prior fractures to prevent the onset of osteoporosis (i.e., further lowering of bone density and/or a first fracture) and treatment of disease (i.e., the person begins pharmacotherapy after having sustained fractures) to reduce the risk of new fractures. These opportunities involve both nonpharmacological and pharmacological therapy interventions.[26]

Nonpharmacological interventions involve measures such as falls prevention. Falls are defined as events which result in persons inadvertently coming to rest on the floor or ground or other lower level, excluding intentional change in position to rest in furniture, wall or other objects.[27] Risk factors for falls among older adults include medications (e.g., antidepressants, hypnotics and anxiolytics, any central nervous system drug, analgesics, any cardiovascular drug, any endocrine system drug, any respiratory system drug), chronic diseases (coronary heart disease, any circulatory disease, diabetes, thyroid disease, chronic obstructive pulmonary disease, depression, eye disease, arthritis),[28] and physical function in terms of one or more impairments of self-reported difficulty on five Instrumental Activities of Daily Living (IADLs, range 0-5) including walking two to three blocks, climbing up ten steps, preparing meals, doing heavy household chores, and shopping.[29]

Falls are a common and serious public health concern among older adults 65 years and older. It is estimated that one in every three adults 65 years and older fall each year.[30] Falls can

be especially injurious for this age group. About 20-30% of older people who fall suffer moderate to severe injuries (e.g., bruises, hip fractures, traumatic brain injuries, and upper limb injuries).[31,32] Injurious falls can lead to hospitalizations, disability and loss of independence, functional decline, reduced quality of life, and even premature death.[31-35] For example regarding hospitalization, a Statistical Brief presenting data from the Healthcare Cost and Utilization Project Nationwide Emergency Department Sample on emergency department (ED) visits among older adults in 2006 reported that of the more than 2.1 million visits to the ED for injurious falls, 29.6% of visits resulted in hospital admission. The most common injuries related to falls were fractures, which accounted for 41% of injurious fall-related ED visits.[33] Consistent with these findings, data from the National Center for Health Statistics showed that in 2007, there were 264,000 fall-related hip fractures and the rate for women was almost three times the rate for men.[36]

The preceding information further illuminates the fact that osteoporosis and osteoporotic fractures are a result of multifactorial factors (i.e., component causes for a sufficient cause).[37] In other words, any single approach to optimal bone health is not thought to be adequate to prevent the disease from occurring. In addition to the appropriate pharmacologic therapy, clinicians are urged to educate patients about the use of nonpharmacologic interventions/measures (e.g., fall prevention, use of hip protectors) to assist patients at risk of osteoporotic fractures.[38] A fall is neither necessary nor a sufficient cause of fracture.[39] Osteoporotic fractures (e.g., spine fractures) which are pathologic can occur spontaneously,[40] but a fall is considered the strongest single risk factor for fracture in an older adult.[38] Thus, of the nonpharmacologic interventions for osteoporosis, fall prevention represents the foundation of prevention and management of disease, without which patients are unlikely to achieve the full benefit of pharmacologic therapy.[41] The

Centers for Disease Control and Prevention recommends steps or interventions to reduce the risk of falling for older adults 65 years or older and these include using muscle strengthening exercise, being mindful of medications, keeping vision sharp, and eliminating hazards at home.[42]

With regards to pharmacologic therapy, the decision to intervene or selection of patients for treatment is based on the patient's level of fracture risk profile and skeletal health assessment involving clinical judgment, not just on BMD assessment and the efficacy and side-effects of drugs likely to be prescribed.[43,44] The National Osteoporosis Foundation recommends initiating therapy in postmenopausal women age 50 years and older presenting with a hip or vertebral (clinical or morphometric) fracture, BMD tests of T-score ≤-2.5 at the femoral neck or spine after appropriate evaluation to exclude secondary risk factors, T-score between -1.0 and -2.5 at the femoral neck or spine and a 10-year probability of a hip fracture ≥3% or a 10-year probability of a major osteoporosis-related ≥ 20% based on the U.S.-adapted WHO algorithm.[45]

1.2.3.2 Pharmacologic therapy options

Of the current U.S. Food and Drug Administration (FDA)-approved pharmacologic therapy options, bisphosphonates are widely prescribed[46] and recommended by the North American Menopause Society as first-line pharmacologic treatments in the management of osteoporosis for postmenopausal women.[6] The American College of Rheumatology recommends bisphosphonates as first-line therapy in medication-induced osteoporosis (e.g., in long-term users of glucocorticoids or oral corticocosteroids).[47] Other pharmacologic options include the selective estrogen-receptor modulator (SERM; also known as estrogen agonist/antagonist) raloxifene (marketed as Evista® oral tablets), parathyroid hormone (PTH) or its analogues such as

teriparatide (recombinant human PTH 1-34) (marketed as Forteo®), estrogens, calcitonin, and denosumab (marketed as Prolia®).

1.3 Bisphosphonates: FDA-approved

The current FDA-approved bisphosphonates in the management of osteoporosis for postmenopausal women in U.S. include alendronate (Fosamax®), ibandronate (Boniva®), risedronate (Actonel®), and zoledronic acid (Reclast®). **Table 1.2** and **Table 1.3** provide a list of these bisphosphonates with some additional information. It is unclear whether any of these drugs is more effective than any other. This is because there are no head-to-head clinical trials of bisphosphonates for the prevention of fractures.[48]

Table 1.2. List and dosage of FDA-approved bisphosphonates in the U.S.

Generic name	Brand name	Dosage, dosing interval, and formulation (s)	Original FDA approval year
Alendronate	Fosamax® or Fosamax Plus D®	Prevention (oral tablet of 5 mg daily or 35 mg weekly) and treatment (oral tablet of 10 mg daily or 70 mg weekly)	1995
Risedronate	Actonel®	Oral tablet doses of 5 mg daily, 35 mg weekly, 75 mg on 2 consecutive days once a month, or 150 mg monthly	1998
Ibandronate	Boniva®	2.5 mg oral tablet daily, 150 mg tablet monthly (for prevention and treatment), or intravenous injection of 3 mg every 3-months (for treatment)	2003
Zoledronic acid	Reclast®	5 mg intravenous injection yearly for treatment	2007

Table 1.3. List and description of FDA-approved bisphosphonates in the U.S.

Drug product	Indications	Contraindications	Geriatric use
Fosamax® (***Alendronate sodium***)	Treatment and prevention of osteoporosis in postmenopausal women, glucocorticoid-induced osteoporosis, and Paget's disease of bone	- Abnormalities of the esophagus (e.g., stricture or achalasia)-upper gastrointestinal adverse reactions - Severe renal impairment	Fosamax®-treated patients were at least 65 years of age in postmenopausal osteoporosis studies
Actonel® (***Risedronate sodium***)	Prevention of postmenopausal osteoporosis, treatment and prevention of glucocorticoid-induced osteoporosis, and Paget's disease	- Abnormalities of the esophagus (e.g., stricture or achalasia)-upper gastrointestinal adverse reactions - Hypocalcemia (mineral metabolism) - Severe renal impairment	Actonel®-treated patients were at least 65 years of age in postmenopausal osteoporosis studies
Boniva® (***Ibandronate sodium***)	Treatment and prevention of postmenopausal osteoporosis	- Upper gastrointestinal adverse reactions - Severe renal impairment	Boniva®-treated patients were at least 65 years of age in postmenopausal osteoporosis studies
Reclast® (***Zoledronic acid Injection***)	Treatment of postmenopausal osteoporosis, and Paget's disease of bone	- Severe renal impairment - Hypocalcemia (mineral metabolism)	Reclast®-treated patients were at least 65 years of age in postmenopausal osteoporosis studies

1.3.1 Bisphosphonates: Efficacy

Several studies have shown bisphosphonates to have beneficial clinical effects in reducing bone loss and the risk of fracture in older women.[49-51] However, a recent report based on research conducted by the Southern California Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality found that comparative benefits in fracture risk reduction among the treatments for low bone density vary. The strength of evidence is high for reducing vertebral fractures, non-vertebral fractures, and hip fractures among postmenopausal women with osteoporosis. In contrast, the evidence for treatments of wrist fractures is low. A summary of strength of evidence and conclusions from various studies is presented in **Table 1.4**.[48]

Table 1.4. Summary of comparative benefits of bisphosphonates in fracture reduction.[48]

Strength of evidence	Study design	Conclusion
High	Randomized clinical trials (RCTs)	Vertebral fractures: alendronate, risedronate, ibandronate, and zoledronic acid reduce the risk of vertebral fractures among postmenopausal women with osteoporosis
High	RCTs	Non-vertebral fractures: alendronate, risedronate, and zoledronic acid reduce the risk of nonvertebral fractures among postmenopausal women with osteoporosis
High	RCTs	Hip fractures: alendronate, risedronate, and zoledronic acid reduce the risk of hip fractures among postmenopausal women with osteoporosis. *The effect of ibandronate is unclear, since hip fracture risk reduction was not a separately reported outcome in trials reporting nonvertebral fractures.*
Low		Wrist: alendronate reduces the risk of wrist fractures among postmenopausal women with osteoporosis. *Risedronate in a pooled analysis of two trials was associated with a lower risk of wrist fractures, but did not quite reach the conventional level of statistical significance.*
Insufficient	Head-to-head trials	Data are insufficient from head-to-head trials of bisphosphonates to prove or disprove superiority for prevention of fractures for any agent

Table 1.5. Adherence to bisphosphonate therapy and fracture rates in osteoporosis.

	RR reduction in adjusted OR (%)
Compliant cohort	
Total fractures	21.1
Vertebral fractures	37.2
Hip fractures	37.3
Wrist fractures	9.2
Persistent cohort	
Total fractures	29.3
Vertebral fractures	40.0
Hip fractures	44.5
Wrist fractures	22.5

Adapted from Siris, 2006[51]

It is important to note that compliance and persistence to these medications is an important factor in order to achieve the expected benefits. For example, a study to characterize the relationships between adherence (compliance and persistence) to bisphosphonate (alendronate or risedronate) therapy and risk of fracture types in 35,537 postmenopausal women using 2 claims databases from 45 employers and 100 health plans in the continental U.S., showed

that adherence to bisphosphonate therapy was associated with significantly fewer fractures at 24 months (See **Table 1.5**).[51]

Also beneficial clinical effects have been shown in medication-induced osteoporosis (i.e., long-term users of glucocorticoids and/or oral corticosteroids) [52,53] and in those supplemented with vitamin D and calcium.[54] The American College of Rheumatology 2010 recommendations indicate pharmacologic treatment with bisphosphonates in postmenopausal women and men age ≥50 years with glucocorticoid treatment with an anticipated duration of ≥3 months, or prevalent glucocorticoid therapy of a duration of at least 3 months.[47] Glucocorticoid use is considered the most prevalent secondary risk factor for osteoporosis.[52]

1.3.2 Bisphosphonates: Structure and pharmacology

To appreciate the clinical benefits of bisphosphonates in osteoporosis and osteoporotic fractures, one needs to understand the molecular structure and mechanism of action at the molecular level. Bisphosphonates are characterized by their affinity for bone mineral because they bind to hydroxyapatite crystals,[55] and inhibitory effects on osteoclasts.[56] Bisphosphonates inhibit the aggregation of crystals and the crystal dissolution thereby inhibiting calcification. The attachment of bisphosphonates to crystalline hydroxyapatite is related to their structure. There are, however, differences among molecules in terms of configuration and the associated affinities. These molecules are ranked with respect to their affinities from lowest to highest as risedronate, ibandronate, alendronate, and zoledronic acid.[58] It is important to note that the four molecules are classified as nitrogen-containing bisphosphonates that act specifically by inhibiting the enzyme farneslypyrophosphate synthase (FPP)[57] within osteoclasts.

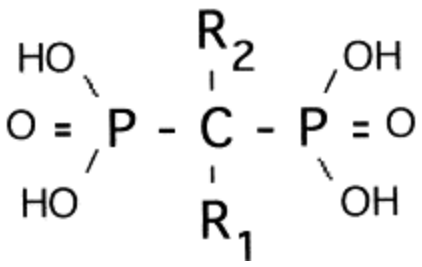

Figure 1.3. General structure of a bisphosphonate.

The general structure of a bisphosphonate is shown in **Figure 1.3**. The R_1 side chain is usually a hydroxyl, and R_2 side-chain contains the nitrogen group that is responsible for potency. In relation to potency, the following schematic representation (**Figure 1.4**)[58] summarizes the correlation between moieties and the potency, while **Table 1.6** shows the structure-activity relationship of the FDA-approved bisphosphonates in the US and bisphosphonate concentration that gives 50% inhibition (IC_{50}) for each compound.[59] As can be seen from the table, the antiresorptive relative potencies for osteoclast inhibition (from lowest to highest) are: alendronate, ibandronate, risedronate, and zoledronic acid.

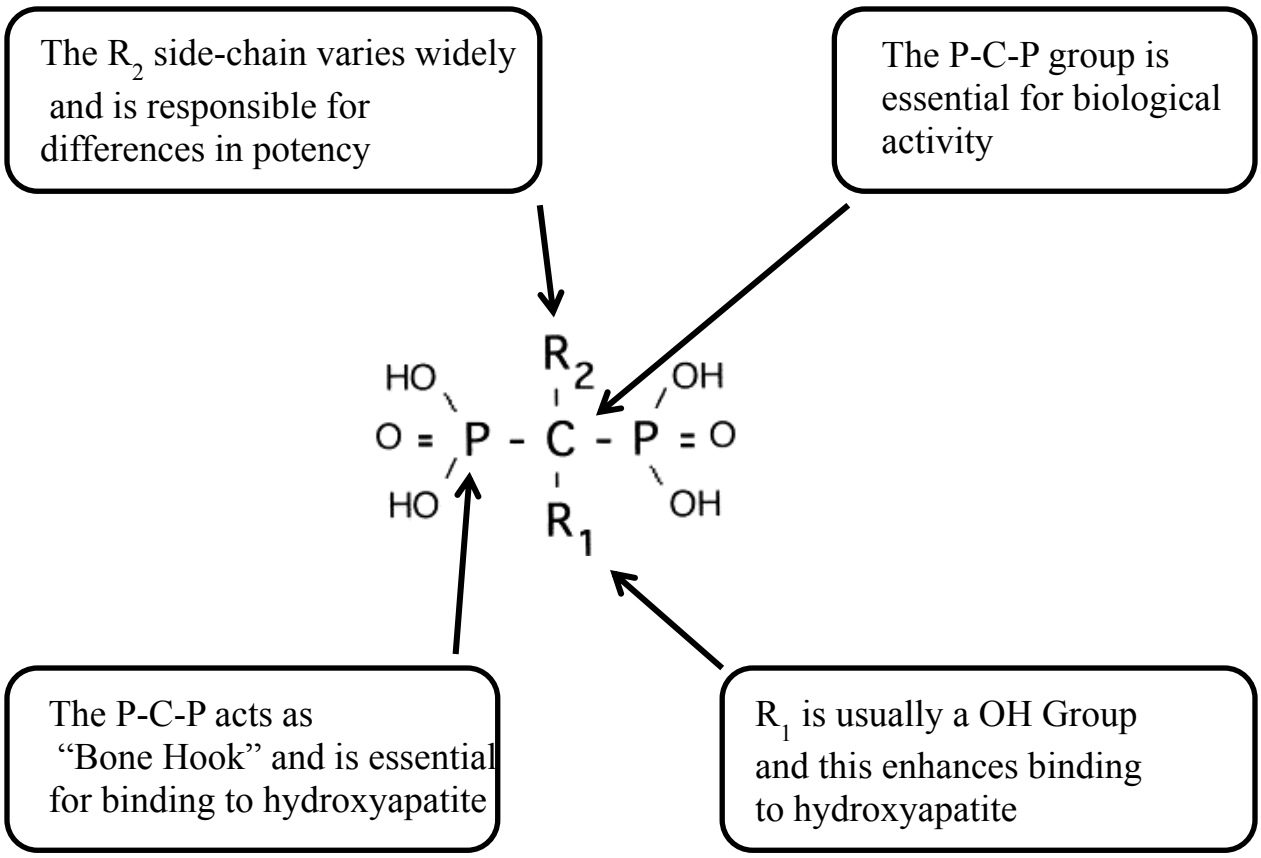

Figure 1.4. Bisphosphonate structure moieties and their role in potency for osteoclast inhibition.

Table 1.6. US-approved bisphosphonates and their structures with IC_{50} values for the inhibition of FPP synthase.[59]

Bisphosphonates	R_1	R_2	initial IC_{50} (nM)	final IC_{50} (nM)
Alendronate	-OH	$-(CH_2)_3NH_2$	2249±180	260.0±19.6
Risedronate	-OH	$-CH_2$-3-pyridine	452.9±16.6	5.7±0.54
Ibandronate	-OH	$-CH_2CH_2N(CH_3)$(pentyl)	1052±55.1	25.4±1.57
Zoledronic acid	-OH	$-CH_2$-imidazole	475.3±18.3	4.1±0.22

Both bisphosphonates' affinities for crystalline hydroxyapatite and inhibitory effects on osteoclasts are important pharmacological features. The high affinity for bone mineral allows bisphosphonates to achieve a high local concentration throughout the entire skeleton. Suppressed bone resorption after bisphosphonate initiation suggests bisphosphonate efficacy and potency in

promoting the apoptosis of osteoclasts actively engaged in degradation of mineral on the bone surface. Thus, bisphosphonates have become the primary therapy for managing skeletal conditions characterized by increased osteoclast-mediated bone resorption[60] (i.e., osteoporosis and/or osteoporotic fractures). Overall, these studies clearly demonstrate that bisphosphonates (nitrogen-containing bisphosphonates) produce their beneficial clinical effect through the mode of osteoclast inhibition. The half-life of bisphosphonates ranges between 5 and 10 years.[61]

Whether the potential differences in molecular structure and clinical efficacy factors are related to safety issues of bisphosphonate use remains to be determined. For example alendronate (second highest in affinity but with lowest relative potency) has a stronger prophylactic effect against fractures than risedronate (lowest affinity but high potency) in rheumatoid arthritis patients on long-term corticosteroid therapy.[53] In depth investigations of these differences and the safety of bisphosphonates with differences in molecular structures and potency are not the scope of this present study. However, the findings of this study suggest potential attenuating or negating effects of corticosteroid therapy (drug associated with increased risk of fracture) and the effects can be thought to be greater on risedronate than on alendronate therapy. Therefore, drugs that interfere with bone remodeling and associated with increased risk of fracture, and concomitant use of these drugs with bisphosphonates may alter the beneficial clinical effect of bisphosphonates and instead put the patients at increased risk of fracture. These are potential safety concerns that warrant further understanding and investigation.

1.4 Problem statement

Ideally, optimal efficacy of bisphosphonate therapy is expected to be achieved even in the presence of competing risk factors (e.g., medications) for osteoporosis and osteoporotic fractures (**Table 1.1**). There are two possible scenarios: 1) best case scenario: bisphosphonate therapy

supersedes the competing negative effects of risk factors for osteoporotic fractures and therefore treatment effects are beneficial, or 2) worst case scenario: the beneficial effects of bisphosphonate therapy are attenuated by the negative effects of risk factors for osteoporotic fractures and instead result in increased risk of new fracture. The second phenomenon is a serious safety issue and can be the case when bisphosphonate therapy is given concomitantly or simultaneously with medications that induce secondary osteoporosis such as SSRIs and SNRIs. Given that bone cell types possess a functional serotonin (5-HT) signal transduction mechanism (5-HT receptors and the serotonin transporters [5-HTT]) for both responding to and regulating the uptake of 5-HT suggest the involvement of 5-HT and 5-HTT in bone metabolism,[62,63] the safety of these agents is of particular interest for individuals with osteoporosis and/or osteoporotic fractures.

1.5 Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake Inhibitors: Use and Clinical Pharmacology

1.5.1 SSRIs

The first SSRI to be used clinically was fluoxetine (Prozac®) which was approved by the FDA in 1987.[64] Several other SSRIs have since become available including paroxetine (Paxil®), sertraline (Zoloft®), fluvoxamine (Luvox®), citalopram (Celexa®), and escitalopram (Lexapro®). **Table 1.7** provides a list of these SSRIs with some additional information.

Table 1.7. List and description of FDA-approved SSRIs in the U.S.

Drug product	Indications	Contraindications	Geriatric use
Lexapro® (*Escitalopram*)	-Acute and maintenance treatment of Major Depressive Disorder (MDD) -Acute treatment of generalized anxiety disorder	-****Serotonin Syndrome especially when co-administered with other serotonergic agents (including triptans, TCAs, fentanyl, lithium, tramadol, tryptophan, buspirone and St. John's Wort) or using of MAOIs such as linezolid or intravenous methylene blue -Concomitant use of pimozide	The number of elderly patients in controlled trials of Lexapro® in MDD was insufficient to adequately assess for possible differential efficacy and safety measures on the basis of age (approximately 6% of the 1144 patients were 60 years of age or older)
Celexa® (*Citalopram*)	Treatment of depression	-**** (see Lexapro®) -Concomitant use of pimozide	-No overall differences in safety or effectiveness were observed between older subjects and younger subjects -Precautions-Hyponatremia
Prozac® (*Fluoxetine*)	-Maintenance treatment of MDD -Treatment of Obsessive Compulsive Disorder (OCD) -Acute treatment of panic disorder	-**** (see Lexapro®) -Coadministration of pimozide, thioridazine due to QTc prolongation -Concomitant use of olanzapine	No overall differences in safety were observed between geriatric and younger patients (approved for use)
Luvox® (*Fluvoxamine*)	Treatment of OCD	-**** (see Lexapro®) -Coadministration of tizanidine, thioridazine, alosetron, pimozide	No overall differences in safety were observed between geriatric and younger patients (approved for use)
Paxil ® (*Paroxetine*)	-MDD -OCD -Panic Disorder -Social Anxiety Disorder -Generalized Anxiety Disorder -Posttraumatic Stress Disorder	-**** (see Lexapro®) -Concomitant use with thioridazine-produces prolongation of the QTc interval-associated with ventricular arrythmias -Concomitant use of pimozide	Premarketing clinical trials with Paxil® (17% of patients treated with Paxil® were 65 years of age or older). No overall differences in the adverse event profile and effectiveness between elderly and younger subjects
Zoloft ® (*Sertraline*)	-MDD -OCD -Panic Disorder -Posttraumatic Stress Disorder -Social anxiety disorder	-**** (see Lexapro®) -Concomitant use of pimozide -with ANTABUSE® (disulfiram) due to the alcohol content of the concentrate	-No overall differences in pattern of adverse reactions and efficacy were observed in the U.S. geriatric clinical trial subjects relative to younger subjects

For over a decade now, SSRIs have been the most popular psychotropic medications in treating depression[65] with a better safety and tolerability profile than older agents of

antidepressants (e.g., tricyclic antidepressants [TCAs], monoamine oxidase inhibitors [MAOIs]).[66] SSRIs are considered first-line drug treatment in older patients,[67] especially in relieving depression in women.[68] In addition, SSRIs are useful in a variety of other medical conditions which include possible management of chronic painful rheumatologic conditions such as fibromyalgia,[69] diabetic peripheral neuropathic pain,[70] anxiety and panic disorders,[71] and treatment of vasomotor symptoms such as hot flashes.[72-74] Hot flashes have been reported to be persistent into the late postmenopausal years.[75]

The clinical benefit of SSRIs is believed to derive from increasing the synaptic levels of 5-HT by antagonizing the 5-HTT to block neuronal 5-HT reuptake from the extracellular space and thereby prolonging 5-HT receptor activation.[76] Despite the better safety profile and tolerability of SSRI use, they are not completely devoid of adverse effects. Examples of adverse effects include, but are not limited, to bleeding, serotonin syndrome, hyponatremia, sleep disturbances, nausea, diarrhea, and bone loss (or osteoporosis)- a risk factor for osteoporotic-related fractures.[77,78]

1.5.2 SNRIs

Serotonin norepinephrine reuptake inhibitors have been associated with bone loss (or bone resorption) thus potentially increasing the risk of fracture in older adults.[71,79] SNRIs are dual action antidepressants that inhibit both 5-HT and norepinephrine (NE) transporters. The FDA-approved SNRIs include venlafaxine (Effexor®), duloxetine (Cymbalta®), desvenlafaxine (Pristiq®), which is an active metabolite of venlafaxine, and levomilnacipran (Fetzima®).[64]

1.6 Significance

Increased risk of osteoporotic fractures associated with use of SSRIs, and potentially SNRIs, introduces additional clinical consequences of concern about bone health in postmenopausal women. Concomitant SSRIs or SNRIs with bisphosphonate (BP) utilization may continue to rise in postmenopausal women because of the projected future increase in the population of older adults. Therefore, results from this study could add to the gap in the current body of literature and be useful for physicians treating osteoporosis and/or osteoporotic fractures by highlighting possible safety concerns that may be important to consider when optimizing patient care. Currently, there are no specific guidelines for the management of bone loss observed with antidepressants, yet considerable evidence suggests SSRIs and SNRIs have an effect on bone health. Results from this study may provide useful information to be integrated into the monitoring of the routine care for osteoporosis and/or osteoporotic-related fractures in the same way that other drug-related risk factors for osteoporosis (e.g., glucocorticoids)[47] are monitored. Also these results might be relevant to policymakers concerned with meeting the needs of aging Americans, especially the health of older women.

1.7 Objectives of the study

There are three specific aims for this study:

1. To describe the concomitant utilization pattern of SSRIs and SNRIs with BPs.
2. To assess the risk of osteoporotic-related fractures associated with the concomitant use of BPs and SSRIs.
3. To assess the increased risk of osteoporotic-related fractures associated with the concomitant use of BPs and SNRIs and whether the risk of osteoporotic-related fractures is related to the role of 5-HT in bone rather than the disease (depression).

1.8 Hypotheses

The following null hypotheses are being tested in this study:

$H_{0(1)}$ Concomitant use of SSRIs with BPs will have no effect on the risk of fractures compared to use of BPs alone (i.e., HR=1)

$H_{0(2)}$: Concomitant use of SNRIs with BPs will have no effect on the risk of fractures compared to use of BPs alone (i.e., HR=1)

Like many observational studies, confounding is a common threat in this study. Confounding will be controlled at the design stage using propensity score matching. Propensity score is defined as the probability of receiving treatment rather than the control for a patient conditional on observed baseline covariates.[80] Details of motivation to use propensity score method in the design of a pharmacoepidemiologic study are provided in **Section 2.8** of Chapter 2.

1.9 Summary

Osteoporosis and osteoporotic-related fractures are serious public health burdens in postmenopausal women. The burden is expected to rise due to the projected future increase in the population of older adults. Pharmacologic therapy using BPs in prevention and treatment is currently a popular option. However, SSRIs and, potentially SNRIs, are associated with increased risk of fracture and might potentially attenuate the beneficial effects of bisphosphonate therapy. These serious safety concerns have not been investigated yet.

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Chapter 2

2.0 LITERATURE REVIEW

2.0.1 Overview

This chapter will provide 1) a brief understanding of the motivation to concomitant drug use and adverse drug events as a consequence, 2) a detailed literature review of concomitant use of specific drugs with BPs and potential adverse drug events such as increased risk of fracture, 3) description of concomitant use of SSRIs with bisphosphonates and increased risk of fracture and suggested supporting evidence, 4) the description to determine the role of depression versus 5-HT in bone health, and 5) pharmacoepidemiologic study design considerations.

2.1 Concomitant Use of Osteoporosis-Inducing Medications with Bisphosphonates and Increased Risk of Fracture

2.1.1 Introduction

The number of older Americans suffering with multiple chronic health conditions (multimorbidity)[1] is large and growing over time. Estimates have shown that 68.4% of Medicare beneficiaries have two or more chronic conditions and 36.4% have four or more chronic conditions. Moreover, these multiple chronic conditions (MCCs) increase with age and are more prevalent among women than men across all age groups.[2] For example, in 2010, in a study of Medicare fee for service beneficiaries, over 70% of women had two or more chronic conditions compared with 65% of men.[3] The 15 common chronic conditions (and their proportions) that are available in the 2010 CMS Chronic Condition Warehouse research files include hypertension/high blood pressure (58%), high cholesterol (45%), ischemic heart disease (31%), arthritis (29%), diabetes (28%), heart failure (16%), chronic kidney disease (15%), depression

(14%), chronic obstructive pulmonary disease (12%), Alzheimer's disease (11%), atrial fibrillation (8%), cancer (8%), osteoporosis (7%), asthma (5%), and stroke (4%).[3] This list corresponds with a list of chronic conditions used to define MCCs by the Department of Health and Human Services Strategic Framework on Multiple Conditions.[4]

With regard to the trend of MCCs, findings from the 1998, 2004, and 2008 waves of the Health and Retirement Study (a nationally representative survey of older adults over 50 years in the U.S.) showed that the proportion reporting one or more chronic diseases increased from 86.9% in 1998, to 91.2% in 2004, and 92.2% in 2008.[5] Similarly, recent estimates using data from the National Health Interview Survey found that the percentage of adults aged 45 years and over with two or more of nine self-reported chronic conditions increased from the 1999/2000 collection period to the 2009/2010. During that 10-year period, the percentage of adults aged 45-64 years who had been diagnosed with two or more chronic conditions rose from 16% to 21%, and rose from 37% to 45% among adults aged 65 years or older.[6] The increasing prevalence of MCCs has significant impact for the aging population. People with MCCs are particularly vulnerable to suboptimal quality care, have more physician contacts, fill more prescription drugs, and are more likely to be hospitalized each year than those with only one chronic condition.[7,8] Therefore, care management of MCCs requires heightened coordination of complex medical and longitudinal psychosocial care, and management of prescribed drugs.[6]

Medication management of MCCs is a challenging task. As the number of chronic conditions increases, the number of medications prescribed also increases. According to the National Center for Health Statistics, the percentage of persons who used two or more prescription drugs (concomitant use) increased from 25% in 1999-2000 to 31% in 2007-2008.[9] Women use more prescriptions than men, and this increases with age suggesting that women are

at a greater likelihood of experiencing an adverse drug event (ADE).[10,11] It is important to note, however, that the association of ADEs and age is a complex issue that can, in part, be explained by pharmacokinetic and pharmacodynamic changes, patient-specific physiologic and functional characteristics that occur with aging, and pharmacoeconomics rather than simple chronologic age.[12,13]

Medication management of postmenopausal osteoporosis is the particular focus of this review. Postmenopausal osteoporosis is a result of reduced production of estrogen after menopause and increases the risk of fracture.[14] The National Osteoporosis Foundation reports that about 80% of the estimated 10 million Americans with osteoporosis are women. In addition, approximately one in two women age 50 years and older will break a bone because of osteoporosis.[15] Bisphosphonates are widely prescribed[16] and recommended by the North American Menopause Society as first-line pharmacologic treatment in the management of osteoporosis for postmenopausal women.[17] Bisphosphonates are characterized by their affinity for bone mineral through binding to hydroxyapatite crystals[18] and inhibitory effects on osteoclasts.[19]

Examples of chronic conditions that can exist in osteoporotic postmenopausal women older than 50 years of age include diabetes, depression, chronic inflammatory joint disease, chronic inflammatory bowel disease, and breast cancer. These chronic conditions may increase the severity of osteoporosis and often affect the management of osteoporosis by increasing the risk of fracture.[20] Other factors include medications such as glucocorticoids (GCs) for the treatment of chronic inflammatory joint disease. Management of both osteoporosis and chronic inflammatory joint disease is an example of management for MCCs that requires concomitant use of medications and could also affect the management of osteoporosis. This is of concern

because concomitant uses of medications have the potential for clinically important interactions that may result in ADEs leading to patient harm.

In a study using the 2000-2002 National Ambulatory Medical Care Survey to examine 25 clinically important drug-drug interactions, Aparasu et al. found that patients over 44 years of age, especially older adults, Medicare beneficiaries, and those prescribed multiple medications, were at risk of receiving concomitant medications with the potential for a clinically important drug-drug interaction when compared to patients less than 25 years of age. Moreover, the study showed that the annualized visit rates involving interacting medications were high among persons over 64 years vs. less than 64 years, females vs. males, and whites vs. others. Interestingly, of the examined potentially interacting medications, none of the combinations included osteoporosis treatment agents such as bisphosphonates.[21] The U.S. Department of Human Services framework to address the population with MCCs highlights that recognizing drug-drug interactions and potential ADEs from complex medication regimens is one of the strategies for medication management.[22]

Drug-drug interactions occur when one therapeutic agent alters the absorption, distribution, metabolism, and/or excretion of another drug (pharmacokinetic interactions) or the biological effect of another agent (pharmacodynamic interactions). In the case of pharmacodynamic interactions, the two drugs act at the same or interrelated receptor sites and may behave in an additive, synergistic, or antagonistic fashion.[23] Pharmacokinetic interactions often occur via the cytochrome P-450 (CYP450) enzymes, which is the most common pathway for drug-drug interactions.[24] Transporter-based interactions (analogous to drug interactions mediated by P450 enzymes) have also been documented in recent years. Transporters can play a role in drug absorption, distribution, metabolism (in concert with metabolizing enzymes), and excretion.[25]

With regard to osteoporosis treatment agents, **Table 2.1** outlines drug-drug interactions involving BPs and the potential outcomes sourced from the FDA prescribing and labeling information; however, there is evidence in the literature of additional possible interactions that are not documented in the product label. For example, within the past 10 years, studies have suggested that medications associated with increased risk of fracture (see **Table 2.2**), such as proton pump inhibitors (PPIs), might attenuate the beneficial effects of BPs when used concomitantly. Drug-drug interactions between BPs and medications, which result in negative effect on bone strength leading to increased risk of fracture, have been hypothesized to be a pharmacodynamic interaction.[26] In support of this hypothesis, an explanation follows.

Table 2.1. Bisphosphonate-drug interactions and ADEs from the FDA prescribing and labeling information.

Bisphosphonate drug	Co-administered drug (s)	Outcome
Fosamax® (alendronate sodium), Boniva® (ibandronate sodium), Actonel® (risedronate sodium)	Calcium supplements/Antacids	Interference with absorption of drugs
Fosamax® (alendronate sodium), Boniva® (ibandronate sodium), Actonel® (risedronate sodium)	Aspirin/ Nonsteroidal anti-inflammatory drugs (NSAIDS)	May worsen gastrointestinal irritation
Boniva® (ibandronate sodium), Actonel® (risedronate sodium)	H_2 blockers and PPIs	May affect oral bioavailability, but interactions are not considered to be clinically relevant
Reclast® (zoledronic acid)	Nephrotoxic drugs	Renal failure
Reclast® (zoledronic acid)	Aminoglycosides	May have additive effect to lower serum calcium for prolonged periods
Reclast® (zoledronic acid)	Loop diuretics	May increase risk of hypocalcemia

Pharmacologic actions of bisphosphonates are osteoclast-mediated. Bisphosphonates inhibit bone resorption by preventing osteoclast recruitment, differentiation and activity, and inducing osteoclast apoptosis.[19] Therefore, suppression of osteoclast bone resorption is the

pharmacodynamic effect of bisphosphonates. On the other hand, medications associated with osteoporosis and increased risk of fracture such as GCs and PPIs affect bone by inhibiting osteoblast differentiation and activity, bone formation, and/or increasing bone resorption.[27,28] In this case, concomitant GC/PPI and bisphosphonate use may increase the risk of osteoporosis/bone loss through the antagonizing or attenuating effects of GC/PPI on any beneficial effects of bisphosphonates. The pharmacodynamic interaction of these combinations would result in attenuation of bisphosphonate effects, hence increasing the risk of fracture for the patient.

Table 2.2. Medications associated with increased risk of fracture in older people.

Medication class	Generic drug examples
Oral GCs	Hydrocortisone, prednisone, dexamethasone
Aromatase inhibitors	Letrozole, anastrozole
SSRIs	Citalopram, fluoxetine, paroxetine
PPIs (acid suppressive drug).	Esomeprazole, omeprazole, lansoprazole
Thiazolidinediones	Rosiglitazone, pioglitazone
Thyroid hormones	Levothyroxine
Anticoagulants	Heparin, warfarin
Anticonvulsants	Phenobarbital, oxcarbazepine, valproic acid
Benzodiazepines	Lorazepam, triazolam
Atypical antipsychotics	Olanzapine, quetiapine, risperidone
Opioid analgesics	Hydrocodone, oxycodone, morphine
Loop diuretics	Furosemide, bumetanide
Methotrexate	Methotrexate

Although **Table 2.2** includes a number of medications associated with osteoporosis and/or increased risk of fracture in older people, this review focuses only on five selected medication classes (GCs, PPIs, SSRIs, aromatase inhibitors, and thiazolidinediones) and one medication (levothyroxine). The rationale for the selection is because there is supportive evidence in the literature suggesting that the biological mechanisms of these drug effects can influence bone metabolism and increase the risk of fracture (i.e., have negative effects on normal bone remodeling process). Medications that were not reviewed are those with poorly understood

pharmacological actions on bone (e.g., anticonvulsants)[29] and/or that the pharmacodynamic effect of increased risk of fracture may be explained primarily through increased risk of falls (e.g., anticonvulsants[30] and benzodiazepines[31]). Similar to these drug examples, it is worth mentioning that the association between SSRIs and increased risk of fractures can be fall-related, for example through sedating effects of SSRIs.[32] However, SSRIs have been included for review because there is sufficient evidence that the biological mechanisms of these drug effects can influence drug metabolism. We review the literature and outline the results of the clinical outcomes of concomitant use of these agents with BPs and increased risk of fracture through potential attenuation of BPs. Furthermore, we summarize the pharmacology of these agents and potential harm on the bone and suggest future areas of research.

2.1.2 Literature search strategy

We performed a Medline search for articles published from January 2003 to January 2013. The following medical subject headings (MeSH) terms were used: bisphosphonates (formerly termed diphosphonates) OR bone density conservation agents OR glucocorticoids OR acid-suppressive drugs/proton pump inhibitors OR levothyroxine OR thiazolidinediones OR aromatase inhibitors OR selective serotonin uptake inhibitors AND bone fractures. CINAHL and PsychINFO databases were also searched for any additional relevant publications. The abstracts of all potential articles were reviewed for relevancy. Other references were obtained from citations from retrieved articles. Studies were included if they specifically reported results of concomitant use of any of these medications with bisphosphonates and risk of fractures, focused on women, and were published in the English language. Articles that focused generally on use of one of the listed medications and fractures without particular emphasis on use with bisphosphonates and potential antifracture efficacy or attenuation of bisphosphonates were excluded. There were no

studies of concurrent use in the literature to review thiazolidinediones, aromatase inhibitors, and SSRIs and therefore studies suitable for conducting this review only focused on acid-suppressive drugs, GCs, and levothyrozine. Following is a review of these medications in more detail.

2.1.2.1 Proton pump inhibitors

Acid-suppressive drugs, such as PPIs, may be associated with increased risk of fractures. In a pooled analysis of PPI use, Kwok et al. showed significant risk for spine fractures (4 studies, OR:1.50; 95% CI, 1.32-1.72) and hip fractures (10 studies, OR:1.23; 95% CI, 1.11-1.36). Where duration of follow up was reported, this ranged from a median of 6.5 weeks to a mean of 7.8 years. Longer duration of exposure (typically >3 years, pooled result of 6 studies) was associated with higher increased risk of fracture (OR:1.40; 95% CI, 1.14-1.72) when compared with the increased risk of fracture (OR:1.23; 95% CI, 1.19-1.27) at shorter duration of exposure (<12 months, pooled result of 5 studies).[33] PPIs are the most effective pharmacological option for managing gastrointestinal disorders such as gastroesophageal reflux disease (GERD).[34] BP drugs have been shown to cause upper gastrointestinal adverse events such as GERD,[35] thus resulting in the concomitant use of BPs and PPIs. Concomitant use of PPIs with BPs may increase the risk of fracture by reducing the antifracture efficacy of bisphosphonates. With regard to this hypothesis, three studies were identified.

De Vries et al. conducted a retrospective cohort study using the UK General Practice Research Database in patients who started either acid-suppressive medication (PPIs or H_2 receptor blockers) or BP therapy (alendronate, risedronate, ibandronate, or etidronate) between 1988 and 2007. The primary objective was to assess the association between concomitant use of BPs and acid suppressants and attenuated fracture risk in patients aged 40 years and older. Concomitant use of acid suppressants was defined as a prescription within 6 months before start

of 3 month-long BP episodes. The periods of follow-up (defined from the first BP or acid-suppressive medication prescription) was divided into periods of current (the period from the prescribing date up to 91 days after the estimated end of the prescription) and past exposure for BPs and acid suppressive medication. In the BP cohort, the findings indicated a significant association between current concomitant use of H_2 receptor blockers and BPs and risk of vertebral fracture (ARR: 1.56; 95% CI, 1.24-1.96); concomitant use of PPIs and BPs and increased risk of any fracture (ARR:1.08; 95% CI, 1.01-1.16) and hip fracture (ARR:1.24; 95% CI, 1.08-1.42), when compared with current users of BP alone (i.e., patients who never used acid suppressants or who stopped taking acid suppressants for at least 6 months before the start of the BPs). Further investigations on these data showed that the risk of fracture was observed to be dose-dependent with fracture risk increasing as daily dose increased. The authors concluded that these findings suggest that BP use does not counteract the increased risk of fracture seen with acid-suppressive medication use.[36]

In a cohort study using Danish national health care data from 38,088 people from 1996 to 2005, Abrahamsen et al. found that concomitant PPI use with alendronate was associated with a dose-dependent attenuation of risk reduction against hip fracture in patients aged 70 years and older. Based on theoretically complete (100%) refill compliance, the risk reduction in PPI users was not significant (19%; HR: 0.81; 95% CI, 0.64-1.01), but there was a 39% risk reduction (HR: 0.61; 95% CI, 0.52-0.71) in patients who were not PPI users. The attenuation of the risk reduction depended on the cumulative PPI dose. A cumulative PPI dose of 1 to 359 defined daily doses (DDDs) had no impact on the treatment response at the hip, but the authors demonstrated no risk reduction with alendronate in patients exposed to more than 360 DDDs of a PPI. No such effects were observed with concomitant histamine H_2 receptor blockers.[37] A previous case-

control study also showed that PPIs (calculated as cumulative DDDs) were found to be associated with an increase in fracture risk while H_2 receptor blockers were not, but the reasons were unclear.[38] Both H_2 receptor blockers and PPIs are potent antisecretory agents[39] and this would seem to suggest that acid suppression is not the mechanism for the effects on bone. Yang et al. have proposed that the increased risk associated with PPIs may be linked to a decreased in calcium absorption.[28]

In contrast to the preceding studies, Roux et al. found that concomitant PPI use did not demonstrate canceling effects of anti-fracture efficacy of BPs. This study was a recent post hoc analysis of a subset of patients who had participated in three prospective, randomized, placebo-controlled clinical trials (Vertebral Efficacy with Risedronate Trial-MultiNational, Vertebral Efficacy with Risedronate Trial-North America, and the risedronate Hip Intervention Program) with durations of up to 3 years. In this post hoc analysis, it was found that concomitant PPI use with risedronate was not associated with incident vertebral fractures, when compared to PPI non-users. The vertebral fracture rate was similar among PPI users (16.1%) and PPI non-users (16.9%). Overall findings from this study showed that risedronate reduced fracture risk of new vertebral fractures in PPI users (RR:0.43; 95% CI,0.23-0.81) and PPI non-users (RR:0.62; 95% CI, 0.52-0.73).[40]

The evidence on concomitant use of PPIs and bisphosphonates and antifracture efficacy of bisphosphonates is conflicting. Two cohort studies indicated a significant antifracture efficacy of bisphosphonates with concomitant PPIs and bisphosphonates use, but the randomized clinical trial (RCT) did not indicate significant association. Although the cohort studies were of good quality (e.g., sample size, generalizability of the databases, and follow-up periods long enough to capture the outcomes being evaluated) and controlled for measurable confounders, the studies

are subject to selection bias making it difficult to determine if the attenuation of BPs are because of PPIs or some source of bias. On the other hand, the RCT by Roux et al. may reflect a true causal-relationship of non-significant attenuation of BPs due to PPIs because they eliminate selection bias.[41] From an methodological standpoint, RCTs are superior to observational studies, such as cohort studies, and are thus considered a gold standard for determining causal relationships.[42] This is because in observational studies participants are not randomized to a treatment or control group, but differences in outcomes (between participants with varying characteristics) are observed after treatment decisions. In contrast, in RCTs, participants are randomly assigned to a treatment or control group, thus participants under study are expected to have the same characteristics. Findings from the RCT above would be considered "stronger" than findings from the two cohort studies. However, two important concerns about this particular RCT are noted. First, the trials included relatively healthy postmenopausal women with osteoporosis or radiographically identified vertebral fractures and had no recent use of drugs known to affect bone (e.g., BPs), and had no major illness. Applying these exclusion and inclusion criteria limits the generalizability of the findings from RCT populations as they are not representative of broader populations included in observational studies. Second, the Roux et al. study was a post hoc analysis of a subset of patients who had participated in prospective RCTs. The initial hypothesis in these RCTs was not PPI effects on bisphosphonates. In such case one could argue that all of the methodological benefits of an RCT do not necessarily apply. Both of these reasons could explain why the RCT and the two cohort studies did not arrive at the same conclusions. Given this conflicting evidence and the methodological challenges, it is premature to conclude one way or the other based on these few studies. Additional well-designed studies are needed to help determine valid conclusions.

2.1.2.2 Glucocorticoids

Glucocorticoids (GC) (also called corticosteroids) used in the management of many inflammatory conditions are considered the most prevalent secondary risk factor for osteoporosis.[43] Van Staa et al. in a prospective study using data from two large, prospective, randomized, controlled trials, showed that postmenopausal oral GC users have considerably higher fracture risk compared to nonusers (adjusted RR:5.67; 95% CI, 2.57-12.54) at similar baseline levels of bone mineral density (BMD).[44] Chronic treatment with GC in postmenopausal women can independently result in significant reduction in BMD.[45]

In a population-based, case-control study using a hospital discharge registry in Denmark, Vestergaard et al. found an association between cumulative GC use (more than an average dose of approximately 71 mcg prednisolone per day) and increased risk of hip fracture compared with never users.[46] Using the same database in a large community-based sample in Denmark, Vestergaard et al. later conducted a case-control study to examine the risk of fractures in subjects exposed to systemic and topical GCs and found an increased risk of fracture among oral GC users at dosages higher than 2.5 mg prednisolone equivalents per day (adjusted OR:1.15; 95% CI, 1.09-1.22 for dosages of 2.5-7.49 mg/day, and adjusted OR:1.59; 95% CI, 1.49-1.70 for dosages of ≥7.5 mg/day).[47] Manuel et al. conducted a cross-sectional study of 513 men and women in Spain and found that the use of oral GCs over a 3-month period at doses higher than 7.5 mg/day of prednisone or equivalent was associated with risk of non-vertebral fractures (a prevalence of 28.3%).[48] In a case-control study using patients within the Dutch PHARMO-RLS database, De Vries et al. found that current use of oral GCs was associated with an increased risk of hip/femur fracture (adjusted OR:1.43; 95% CI, 1.22-1.67) in patients 50 years and older, especially at higher daily dosages.[49]

It is evident that oral GCs used for a longer duration are associated with increased risk of fracture and the risk is dose dependent. Bisphosphonates are recommended as first-line therapy in these patients.[50] This is in agreement with the current guidelines and recommendations developed by the American College of Rheumatology. In addition, the American College of Rheumatology recommends calcium and vitamin D supplementation counseling for all patients beginning GC therapy.[51] Bisphosphonates have been shown to be beneficial in medication-induced osteoporosis such as in long term users of oral GCs[43,52] and in those supplemented with vitamin D and calcium.[53] Maintenance of sufficient calcium and vitamin D is needed for optimal benefits of bisphosphonates.[54]

Concomitant use of GCs with BPs has been reported. A recent descriptive study using the 1999-2008 U.S. National Health and Nutrition Examination Survey found that the prevalence of GC use in the U.S. general population 20 years and older is 1.2% (95% CI, 1.1-1.4), corresponding to 2,513,259 persons, but the prevalence rate increases with age. Women (53.3%, 95% CI, 47.2-59.4) represented a larger proportion of oral GC users than men. Oral GC users reported concomitant use of BPs (8.6%), hormone replacement therapy (5.9%), calcium (22.7%), vitamin D (18.5%), and other medications (37.9%). Women reported greater concomitant use of all antiosteoporosis pharmaceutical interventions.[55] Despite the current recommendations for BPs use in GC-induced osteoporosis and the prevalent concomitant use, the potential for GCs to attenuate the effects of BPs and any resulting increased risk of fracture remains unclear in the literature.

A review of case series and case reports conducted by a taskforce of the American Society for Bone Mineral Research to assess reports of atypical femoral fractures in patients receiving long-term BPs suggests that concomitant use of medications such as GCs might be an

important risk factor for these atypical femoral fractures. The taskforce recommended that assessment of concomitant use of GCs is one of the key areas for the evidence when evaluating the long-term use of BPs and atypical femoral fractures.[56,57] Similarly, Giusti et al. conducted a systematic literature review of postmenopausal women treated with BPs who sustained subtrochanteric/diaphyseal fractures and found that concomitant use of GC therapy might be an important risk factor.[58] Evidence from case series and reports may constitute only a small percentage of the total number of cases that exist. Larger studies have yet to be conducted to examine this potential attenuating effect of GC on BPs and increased risk of fracture.

Considering that oral GCs are widely accepted risk factors for fracture, it is not our intention to suggest that large studies on oral GCs and their contribution to the increased risk of fracture are lacking in the current literature; however, through our review we found that none of the large studies we identified and reviewed that demonstrate strength of association between oral GCs and fractures investigated an interaction with bisphosphonates. In other words, concomitant use of oral GCs and bisphosphonates was not investigated as an independent risk factor. Instead, bisphosphonate use was either not assessed at baseline[44,47-49] or was only adjusted for as a potential confounder.[46]

2.1.2.3 Levothyroxine

The prevalence of thyroid diseases (i.e., hyperthyroidism and hypothyroidism) increase with age and is more common among older women than men. Women are five times more likely than men to have thyroid problems.(www.thyroid.org) A recent review of studies from Europe, Japan, and the U.S. shows that the prevalence ranges between 0.6 and 12 per 1000 in women and between 1.3 and 4.0 per 1000 in men.[59] Levothyroxine (LT_4) replacement therapy is the treatment of choice for hypothyroidism in postmenopausal women. The goal of LT_4 treatment is

to normalize serum thyroid stimulating hormone (TSH) values.[60] Both hyperthyroidism, defined as suppressed TSH, and suppressive T_4 treatment are associated with a reduction in BMD and an increased risk of fracture in postmenopausal women and in men aged 50 years and older.[61] It is worth noting that the effects of thyroid hormone on bone are related to the dose. Excess thyroid hormone increases the risk of fracture, therefore it is recommended that the lowest possible dose of thyroid hormone be used to correct the medical problem being addressed.[62] The patient fact sheet provided by the American College of Rheumatology also recognizes excess thyroid hormone replacement in those taking medications for low thyroid or hypothyroidism as an important risk factor for osteoporosis. One of the steps suggested to prevent, treat, or manage osteoporosis and/or increased risk of fracture is to use bisphosphonates.[63] The important question, however, is whether anti-fracture efficacy of BPs can be counteracted when levothyroxine is given concomitantly with BPs. Two relevant articles were available in the current literature for review.

Panico et al. conducted a prospective cohort study involving seventy four postmenopausal women aged 52-65 years with low BMD (T-score $\leq$ -2.5) and thyroid carcinoma using long-term LT_4 therapy (3-9 years) versus non-users. Effectiveness of alendronate on BMD in this study was observed to be worsened as the duration of LT_4 treatment increased when measured at 12 and 24 months.[64] Specifically, changes in BMD were significantly less in alendronate-treated osteoporotic women who had been on TSH-suppression therapy for 9 years than those receiving therapy for 3 years or those who had not been taking LT_4 (i.e., controls). Patients treated for 3 years showed an increase of BMD at the lumbar level by 7.88%, those treated for 6 years by 4.63%, and those treated for 9 years by 0.86% from their baseline BMD measurements. Similarly, the increase of BMD at the femoral level was 4.62% in those treated

for 3 years, 3.01% in those treated for 6 years, and 0.95% in those treated for 9 years.[64] In the control group (women who had not been taking LT_4 and were treated with BPs) BMD increased 8.2%. These findings suggest that LT_4 may have attenuated the beneficial effects of alendronate and potentially other BPs when the two agents are co-administered.

Turner et al. conducted a nested case-control study consisting of 213,511 adults aged 70 and over prescribed LT_4 between April 2002 and March 2007 and followed them for fractures until March 2008. Descriptive results showed that a total of 22,236 (10.4%) people sustained at least one fracture and of these cases 20,514 (92.3%) were current users of LT_4 at the index date (the date of admission to hospital for the first fracture). Of particular interest, the authors reported that cases were more likely than controls to have a diagnosis of osteoporosis (27% vs. 22%) and to use BP (28% vs. 23%). Despite this, the association between concomitant LT_4 and BP use and increased risk of fracture was not examined. Bisphosphonate use was adjusted for as a potential confounder. Nevertheless, when the association between LT_4 and increased risk of fracture was examined, current use (if the duration of their prescription encompassed the index date) of LT_4 when compared with remote use (if the prescription ended more than 180 days before the index date) was associated with a higher risk of fracture in women (adjusted OR:1.98; CI, 1.80-2.19) than men (adjusted OR:1.42; CI, 1.15-1.76). Among current users, high cumulative doses of LT_4 (>0.093 mg/day) were associated with an increased risk of fractures (adjusted OR:3.45; CI, 3.27-3.65) compared with low doses (<0.044 mg/day).[65]

2.2 Selected medications and pharmacology on bone

The mechanisms of action of medications associated with increased risk of fracture are via their impact on osteoblasts and osteoclasts. These effects have an overall influence on the

balance of the bone remodeling process. As pointed out in this review, there is some clinically significant evidence in the literature suggesting possible attenuating effects of PPIs, oral GCs, or LT_4 on BPs. This interaction might also be clinically significant between SSRIs, aromatase inhibitors, or thiazolidinediones and BPs. Currently there is a lack of evidence in the literature on these latter medications with regard to these potential interactions. To provide insight into the potentially similar pharmacodynamic interaction of attenuation of BPs and increased risk of fractures when these medications are co-administered with BPs, we briefly outline the proposed mechanisms of action on bone for PPIs, GCs, LT_4, SSRIs, aromatase inhibitors, and thiazolidinediones in **Table 2.3.**

Table 2.3. Medications likely to be prescribed concomitantly with bisphosphonates that can influence bone metabolism and increase the risk of fracture.

Medication type	Proposed mechanism	Reference
PPIs	Gastric acid suppression can result in hypergastrinemia and may cause malabsorption of calcium and vitamin B_{12}. Decreased calcium absorption leads to decreased plasma Ca^{2+} concentration leading to elevated levels of parathyroid hormone, followed by increased bone resorption, decreased volumetric BMD, and consequently decreased bone strength. Vitamin B_{12} is involved in osteoblast activity and bone formation. Deficiency of vitamin B_{12} can result in a sequence of events which includes decreased osteoblastic activity, decreased bone formation, and decreased volumetric BMD that finally results in decreased bone strength. Another potential pathway to decreased bone strength is that deficiency of Vitamin B_{12} can induce homocysteinemia by interfering with collagen cross-linking. Decreased bone strength leads to increased risk of fracture.	Yang Y-X, et al. 2010.[28]
GCs	The GC effect is mediated via the GR. GR is present in osteoblasts and is required for inhibition of bone formation and, consequently, bone loss. Suppression of osteoblast differentiation and inhibition of bone formation may be central to the association between GC and increased risk of fractures.	Rauch, et al., 2010.[27]
LT_4	Physiological variation in normal thyroid status is related to BMD, with hyperthyroid status resulting in decreased BMD (increased bone resorption), and leading to increased risk of fractures.	Murphy et al. 2010.[66]
SSRIs	Osteocytes and osteoblasts possess a functional 5-HT signal transduction mechanism (5-HT receptors and the 5-HTT) for both responding to and regulating the uptake of serotonin. 5-HT uses one predominant receptor, Htr1b, to affect osteoblast biology. Brain-derived high levels of 5-HT binds to 5-HT receptors on osteoblasts which in turn negatively controls osteoblast proliferation via molecular clock Cyclin (Cyc D1) gene cascade leading to decreased bone formation. The binding of 5-HT also positively regulates bone resorption via activation of a protein kinase A/ATF4-dependent pathway, leading to increased synthesis of RANKL, an activator of osteoclast differentiation and function.	Bliziotes et al. 2001, Takeda et al. 2002, Karsenty 2006.[67-69]

Table 2.3. …..CONTINUED

Medication type	Proposed mechanism	Reference
Aromatase inhibitors (AIs)	AIs act by blocking the peripheral conversion of estrogen from androgen precursors and thus lowering tissue and circulating estrogen levels. Estrogen deficiency leads to the development of osteoporosis and increased risk of fracture. Estrogen receptors and aromatase are both expressed in bone. Normally, estrogen has suppressive, antiresorptive effects on osteoclasts during remodeling by stimulating the expression of antiresorptive factors such as osteoprotegerin. This results in the attenuation of RANK and RANKL signaling, leading to inhibition of osteoclastogenesis and decreased bone resorption. Therefore, the presence of AIs leads to estrogen deficiency, which in turn leads to increased synthesis of RANKL.	Gaillard et al. 2011.[70]
Thiazolidinediones (TZDs)	Users of TZDs are at increased risk of low BMD and fractures which result from bone marrow AG. Bone marrow AG is stimulated from the switch of mesenchymal stem cells into the fat lineage via activation of PPAR-γ and this leads indirectly to suppression of osteogenesis. TZD-mediated activation of PPAR-γ accelerates osteoblast differentiation and is ultimately followed by increased osteoblast apoptosis. This concept builds the molecular basis for clinically observed bone marrow AG, diminished bone formation, and increased fracture rate in TZD-treated patients.	Bruedigam et al. 2010.[71]

Abbreviations: GR, glucocorticoid receptor; 5-HT, serotonin; 5-HTT, serotonin transporters; ATF-4, activation transcription factor protein 4; RANKL, receptor activator of nuclear factor kappa B ligand; RANK, nuclear factor kappa B receptor; AG, adipogenesis; PPAR-γ, peroxisome proliferator-activated receptor γ.

2.3 Conclusions and recommendations

Available literature suggests that concomitant PPIs, GCs, or LT_4 with BPs could lead to increased risk of fracture through the attenuation of beneficial effects of BPs. This attenuation could be because of the negative/antagonistic pharmacodynamic interaction. Although we did not find sufficient evidence in the literature to suggest that SSRIs, AIs, or TZDs might attenuate the effects of BPs when given concomitantly, we hypothesize the possibility of this phenomenon. Potentially, there may be a common underlying mechanism for attenuation effects. What these drugs have in common is that they result in bone loss and increased risk of fracture via inhibition

of osteoblastic activity and bone formation and/or increased bone resorption caused by increased osteoclast differentiation and function. This similarity of negative effects on bone might suggest analogous evidence (and may have a biologic rationale) to demonstrate a potentially clinically important association between concomitant use of SSRIs, AIs, or TZDs with BPs and attenuation of antifracture effects of BPs.

The Bradford Hill criterion of analogy[72] can be useful in evaluating causal associations in pharmacoepidemiology.[73] The criteria may be applied in this situation because all the listed medications in **Table 2.3** have similar pharmacological actions on bone and are associated with increased risk of bone loss and fracture in patients. Therefore, given the analogy to pharmacological actions of drugs such as PPIs, it is plausible to suppose that the phenomenon of attenuation of BPs might exist among concomitant users of medications associated with increased risk of fracture with BPs for the treatment of postmenopausal osteoporosis. This is an important drug safety issue concerning prescribing and use of BPs that has not been addressed in clinical guidelines commonly used by clinicians.

Recommendations developed in the current Clinician's Guide to Prevention and Treatment of Osteoporosis on the drug safety issues of BPs include side effects of BPs (e.g., atrial fibrillation), contraindications in certain patients, osteonecrosis of the jaw, and atypical femoral fractures associated with long-term use of bisphosphonates.[74] Furthermore, currently there are no ongoing or documented safety review reports of concomitant use of PPIs, GCs, TZDs, AIs, SSRIs, or LT_4 with BPs and potential increased risk of fracture by the FDA. With this gap in the current clinical guidelines, and lack of ongoing drug safety reviews by the FDA regarding the concomitant use of BPs with any of the aforementioned drugs, it calls for more research to investigate this hypothesis by conducting pharmacoepidemiologic studies to

investigate which pharmacodynamic interactions might be clinically important and have the potential for harm on the bone, and if necessary, prompt further prospective pharmacodynamic studies of these drug combinations. These future research efforts add to prescribers' knowledge of potential safety issues during the process of medication management of MCCs, especially, comorbid osteoporosis. This current study focuses on concomitant use of SSRIs or SNRIs with BPs and increased risk of fracture. This phenomenon has not been reported yet.

2.4 SSRIs Use and Icreased Risk of Fractures in Postmeopausal Women

2.4.1 Literature review results

A number of prospective studies and studies based on administrative databases have demonstrated the association between SSRIs use and increased risk of fracture, especially among postmenopausal women. The results are discussed as follows.

In a large United Kingdom (UK) case-control and case series study using data from the UK General Practice Research Database involving 16,341 cases, 79% women of mean age 79 years old with a recorded diagnosis of hip fracture or fractured neck of femur, analysis of the data showed a strong association of prior SSRI exposure and hip fracture (OR=1.42; 95% CI 1.28-1.58). However, the authors noted that the results were probably overestimated because of selection and indication bias. The case-series design ascertained the true adverse impact of antidepressants on hip fracture risk through removing the influence of factors that varied between individuals, such as frailty and severity of depression.[75]

Bolton et al. performed a case-control study involving 15,792 cases (70.3% females) of persons aged 50 years and older using a population based administrative health data in Canada aimed at determining the effects of individual psychotropic medications (SSRIs, other monoamine antidepressants, lithium, typical antipsychotics, atypical antipsychotics, or

benzodiazepines) and increased risk of osteoporotic fractures. The findings showed that of the current psychotropic medications used, SSRIs had the strongest positive association with fractures (OR=1.45; 95% CI 1.32-1.59; p<0.01) in a multivariable model and showed a significant trend of increasing fracture with increasing dose.[76] These two studies based on administrative database are in agreement with other prospective studies.

Ensrud and colleagues[77] conducted a prospective Study of Osteoporotic Fractures from August 4, 1992 to July 31, 1994 involving 9,704 women 65 years and older who were CNS active medication users. Among the antidepressant users, 103 (21%) were SSRIs users (fluoxetine, paroxetine, and sertraline). Findings from the study showed women using SSRIs had moderate increased risk of hip fracture (multivariable HR= 1.54; 95% CI, 0.62-3.82) compared with central nervous system (CNS) medication nonusers. However, the results were not statistically significant[38] possibly because of the small sample size.

Diem et al.[78] in a prospective Study of Osteoporotic Fractures involving 9,704 women aged 65 years and older (of whom 198 [7.3%] were SSRI users), found that women taking SSRIs experienced a higher age-adjusted rate of bone loss at the total hip than nonusers (-0.77% vs -0.49% per year; p=0.005) and the results were not significantly altered in a multivariable model. Overall, the authors concluded that at any of the sites (hip, femoral neck, or trochanter), the adjusted rate of bone loss among SSRI users was at least 1.6-fold higher than that among nonusers of antidepressants.[78]

Similar results by Williams et al. in a retrospective cohort study have been reported. The study aimed at investigating the effect of SSRIs use on BMD among older women with a lifetime history of depressive disorder. The results showed that BMD among SSRIs users was 5.6% lower at the femoral neck (p=0.03), 6.2% lower at the trochanter (p=0.04), and 4.4% lower at the

mid-forearm (p=0.03) sites compared with nonusers.[79] Loss of BMD has been associated with increased risk of hip and spine fracture incidence in postmenopausal women.[80]

Richards et al.[81] found that postmenopausal women on SSRIs exhibited bone loss and had a two-fold increase in the risk of fragility fracture. The study involved a prospective cohort of 5008 community-dwelling adults 50 years and older aimed at investigating the effect of daily SSRI use on the incidence of clinical fragility fracture. Daily SSRI use was associated with increased risk of fragility fracture (adjusted hazard ratio [HR], 2.1; 95% CI 1.3-3.4). A dose effect of SSRIs on clinical fragility fracture was also noted (HR, 1.5; 95% CI 1.1-2.1). The clinically relevant sites were 40% forearm, 21% ankle and foot, 13% hip, 13% rib, 9% femur, and 4% back. Furthermore, daily SSRI users demonstrated decreased fracture-free survival compared with nonusers.[81]

Spangler et al. in a prospective cohort study of 93,676 postmenopausal women, found that compared with women using other types of antidepressants, women using SSRIs had increased adjusted risk of any fracture (HR=1.30; 95% CI 1.20-1.41), clinical spine (HR=1.25;95% CI 0.96-1.63), wrist (HR=1.29; 95% CI 1.07-1.56), and fractures at other sites (HR=1.32;95% CI 1.21-1.45). Statistical significance was not achieved at the hip (HR=1.33; 95% CI 0.95-1.86). Also, it can be seen that the confidence intervals for clinical spine included 1.0, but the authors did not mention whether this was an issue for their findings. This was probably because antidepressants were associated with increased risk of clinical spine fracture (HR=1.36; 95% CI 1.14-1.63) and the study was primarily looking at antidepressant use or depressive symptoms as primary exposures.[82]

Diem et al.[83] in a recent study based on a 10-year follow-up medication-use data involving the same population of 9,704 women aged 65 years and older recruited in the prospective Study

of Osteoporotic Fractures, showed that of these women 2,809 experienced an incident nonspine fracture over the follow-up period, including 936 with a hip fracture and 582 with a wrist fracture. Women taking SSRIs experienced a higher age-adjusted risk of nonspine fracture compared with nonusers (HR=1.36, 95% CI 1.11-1.67) and was not substantially altered after adjusting for other covariates (HR=1.38, 95% CI 1.10-1.72) in a multivariable model. The risk of wrist fracture was HR=1.54 (95% CI 1.01-2.36) for SSRIs users compared with nonusers. The risk of hip fracture was close to 1.0 (HR=1.01, 95% CI 0.71-1.44) for SSRIs users compared with nonusers secondary to potential confounding factors.[83]

The results provided above are from single studies. In order to provide reliable and a more generalizable summary of the results, meta-analysis becomes useful for reviewing and combining research results. Meta-analyses keeps researchers from relying on the results of a single study in attempting to understand a phenomenon. Thus, meta-analysis helps us to see the similarities and differences among the methodologies and the results of multiple studies.[84] It is in this effort that studies aimed at understanding the phenomenon of SSRIs and fracture risk have demonstrated more reliable evidence though meta-analysis. Summary of the results of the three most recent meta-analyses are presented as follows.

The Wu et al. results showed that overall, SSRIs use was associated with a significantly increased risk of fracture (RR=1.72;95% CI, 1.51-1.95, $p<0.001$).[85] Eom et al. in a meta-analysis based on 12-observational studies showed that the overall risk of fracture was higher among people using SSRIs (adjusted OR=1.69, 95% CI 1.51-1.90).[86] Rabenda et al., based on a total of 34 studies, found that use of SSRIs showed systematically a higher increase in the risk of fractures of all types, non-vertebral, and hip fractures than studies investigating TCA use.[87] Clearly, evidence from the meta-analyses adds more weight to the literature from single studies

discussed in this section. To the best of our knowledge, based on this evidence, we can conclude that indeed SSRIs may be associated with increased risk of fracture.

2.5 Serotonin System and Bone Health and Potential Attenuating Effects of SSRIs on Bisphosphonates

2.5.1 Serotonin and bone health

The link between SSRIs and bone health is based on the adverse effects of 5-HT on the bone remodeling process. The bone is comprised of bone cells, an organic matrix of collagen and noncollagenous proteins (osteoid), and inorganic mineral matrix. Of particular interest in this study is that bone cells (i.e., osteocytes, osteoblasts, and osteoclasts) possess a functional 5-HT signal transduction mechanism (5-HT receptors and the 5-HTT) for both responding to and regulating the uptake of 5-HT.[67,88]

Preclinical *in vitro* and *in vivo* studies support the potential for direct skeletal effects of SSRIs through 5-HTT inhibition.[89] In an earlier study by Warden and colleagues, the authors showed that inhibition of 5-HTT has significant detrimental effects on bone mineral accrual in the mouse skeleton. This study aimed to investigate the impact of 5-HTT inhibition on bone mineral accrual in the growing mouse skeleton. The study was achieved by assessing: 1) mice with a null mutation in the gene encoding for the 5-HTT, and 2) normal growing mice treated with a SSRI. The findings showed that the null mutation of the gene encoding for 5-HTT resulted in a consistent skeletal phenotype of reduced mass, altered architecture, and inferior mechanical properties. Moreover, inhibition of 5-HTT using SSRI resulted in reduced bone mineral accrual during growth.[90]

Similar findings on the effects of SSRI on mouse skeleton were later reported in another study by Warden and colleagues. The study involved adult female mice. Findings showed that

daily introduction of fluoxetine hydrochloride 5 and 20 mg/kg/d, equivalent with the standard (20 mg/d) and maximum (40-80 mg/d) recommended fluoxetine doses used to treat depression in humans, for four weeks reduced gains in lower extremity and vertebral BMD and negatively altered trabecular architecture within both the distal femur and L5 vertebra, independent of estrogen deficiency. The authors further suggested that these findings might support clinical data demonstrating SSRI use to be associated with decreased bone loss after menopause.[91] Further studies have demonstrated that the negative skeletal effects associated with pharmacological 5-HTT inhibition are independent of drug effects on animal physical activity levels and not supposedly altered skeletal loading.[92] Although there are still inconsistencies between some reported animal studies, most animal studies have reported convincing data to demonstrate skeletal effects of SSRIs.[93]

Since 5-HTT is a transporter, 5-HT needs to be present locally within the skeleton for the 5-HTT to influence bone cell activity.[89] 5-HT acts through binding on the 5-HT receptors. There are 14 genetically, pharmacologically, and functionally distinct 5-HT receptors belonging to seven families termed 5-HT_1 through 5-HT_7. 5-HT receptors belong to the G-protein coupled receptor (GPCR) family, with the exception of the 5-HT_3 receptor, which is a ligand-gated ion channel.[94] A number of these receptors have been located in bone cells. Three serotonin receptors: 5-Htr1b, 5-Htr2a, and 5-Htr2b, are expressed in osteoblasts.[88]

In a study by Westbroek et al., the presence of 5-Htrb receptors was reported in fetal chicken bone tissue and isolated bone cells (i.e., osteocytes, osteoblasts, and periosteal fibroblasts [a population containing osteoblast precursor cells]).[95] It has been demonstrated that 5-HT via 5-Htrb receptors is a peripheral modulator of osteoblast recruitment in bone formation

in aging mice.[96] These studies suggest that 5-HT and 5-HTT may be involved in bone metabolism and the potential consequences on bone health.

5-HT uses one predominant receptor Htr1b, to affect osteoblast biology. In gut-derived 5-HT on osteoblasts, binding of 5-HT to 5-Htr1b, which is linked to the $G_{\alpha i}$ protein, inhibits adenylyl cyclase which in turn inhibits second-messenger cAMP production and protein kinase A (PKA)-mediated cAMP response element-binding (CREB) phosphorylation. Most of the actions of cyclic AMP are carried out by protein kinase A, which phosphorylates specific sites on downstream effector processes. This process leads to decreased expression of *Cyclin* (Cyc D1) genes and decreased osteoblast proliferation. As a result, bone formation is slowed down.[68] In other words, higher 5-HT levels secondary to inhibition of 5-HTT by SSRI, contributes to the decrease in bone formation.

In brain-derived 5-HT on osteoblast, serotonergic neurons of the dorsal raphe signal to ventromedial hypothalamic nuclei neurons via the Htr2c receptor to inhibit the synthesis of epinephrine and thereby decrease sympathetic tone. This decrease is relayed in osteoblasts by decreased signaling via the β2 adrenergic receptor (Adrβ2), which negatively controls osteoblast proliferation via molecular clock gene (Cyc D1) cascade and positively regulates bone resorption via activation of a PKA/ATF4-dependent pathway (ATF-4: a transcription factor protein), leading to increased synthesis of receptor activator of nuclear factor kappa B ligand (*Rankl)*, an activator of osteoclast differentiation and function.[69] In other words, 5-HT activation can also directly produce RANKL in addition to the RANKL produced during normal bone remodeling process. In normal bone remodeling in healthy physiologic systems, bone stromal cells, including cells of the osteoblast lineage, provide a limited amount of RANKL, which leads to

osteoclast differentiation, survival, and activation and subsequent bone resorption. Resorption is balanced by osteoblast-dependent new bone formation.[97]

Treatment of homozygous *oim*/*oim* mice (the *oim*/*oim* mouse is an established model of moderate to severe osteoporosis) with either a bisphosphonate (alendronate) or *Rankl* inhibitor (*Rank-Fc*) causes similar decreases in fracture incidence.[98] This data suggests a link between SSRIs-*Rankl*-bisphosphonates. Similarly, Sutherland et al. in an *in vitro* study using rabbit osteoclasts treated with 100 μM clodronate or alendronate for up to 48 hours in the absence or presence of 100ng/mL RANKL found that RANKL significantly attenuated (or antagonized) the ability of both clodronate (CLO) and alendronate (ALN) to induce osteoclast apoptosis and inhibit bone resorption (Figure 2.1). The number of apoptotic rabbit osteoclasts was significantly lower in cultures treated for 48 hrs with ALN or CLO in the presence of RANKL than in cultures treated with the bisphosphonates alone. The authors conclude that RANKL protects osteoclasts from the apoptosis-inducing and anti-resorptive effects of bisphosphonates *in vitro*. [99]

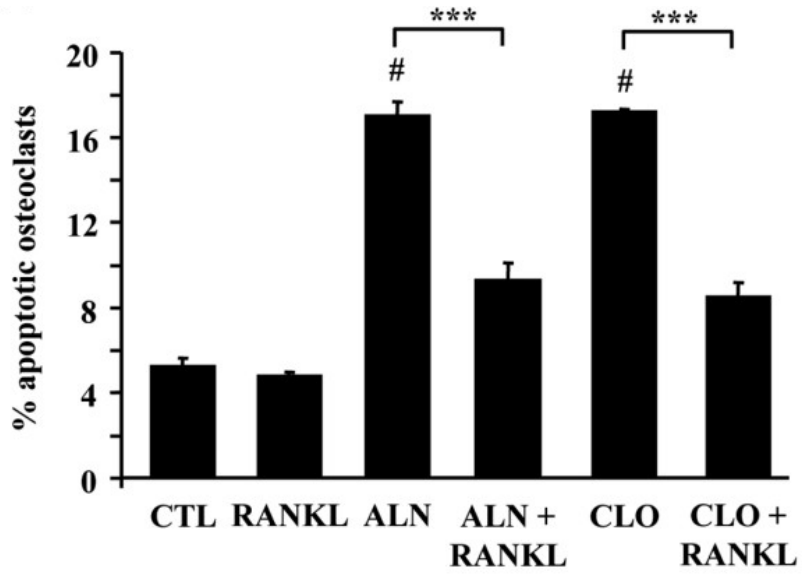

Figure 2.1. The percentage of non-apoptotic and apoptotic osteoclasts. Data are expressed as the mean ± SEM (n = 3 replicates). ***P = 0.001 compared with ALN or CLO alone (analysis of variance). #Treatment with ALN or CLO alone caused a significant decrease in osteoclast number compared with control (CTL) cultures (P = 0.01) and a significant increase in osteoclast apoptosis compared with control cultures (P = 0.001).[99] (*Disclaimer: This is an open access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited*)

2.5.2 Potential attenuating effects of SSRIs on bisphosphonates

Based on Bradford Hill causal criteria of plausibility (refers to the biological plausibility of the hypothesis) and the evidence from laboratory experiments on animals,[72] SSRIs and skeletal effect association can be considered to be causal. However, Rothman and coworker[100] warns that, "evidence from human experiments, however, is seldom available for most epidemiologic research questions, and animal evidence relates to different species and usually to levels of exposure very different from those humans experience." Despite this limitation, he adds that, "logically, however, experimental evidence is not a criterion but a test of the causal hypothesis, a test that is simply unavailable in most circumstances."[35] This underscores our hypothesis and provides a plausible reasoning to conduct this current study. Steps in which SSRIs might negate the beneficial effects of bisphosphonate therapies are given in **Figure 2.2**.

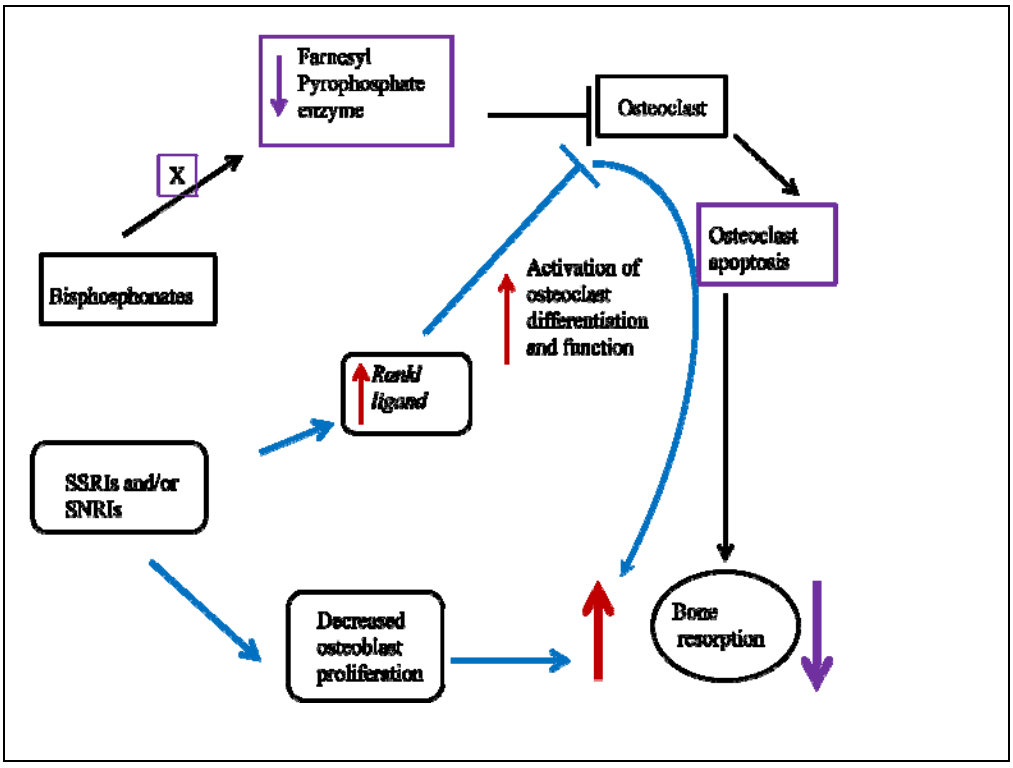

Figure 2.2. Schematic representation of the proposed model tested in this study.

2.6 Role of Depression versus Serotonin System on Bone Health

2.6.1 Depression and increased risk of fracture

Although the preceding discussion demonstrates that SSRIs, commonly used for the treatment of depression, increases the risk of fracture through the 5-HT transporter inhibition, it is still unclear whether the ADE of increased risk of fracture is associated with burden of the disease (depression) or the serotonin transporter system.

Depression is thought to be an independent risk factor for osteoporosis or decreased BMD, with depressed women, particularly those who are postmenopausal, showing a higher risk than men.[101] Diem and colleagues have shown that depressive symptoms are associated with higher bone loss, leading to low BMD, in older women with Geriatric Depression Scale score (GDS) of at least 6 independent of antidepressants.[79] Silverman et al. found that postmenopausal women

with prevalent vertebral fracture reported more symptoms as assessed by the GDS than women without prevalent vertebral fracture (1.54 vs 1.26; p=0.001).[102] Tolea et al. found that high depressive symptoms were associated with increased risk of osteoporosis (OR=1.39, 95% CI, 1.02-1.91) and new fractures (OR=1.39, 95% CI, 1.01-1.95) among Mexican American women aged 65 years and older.[103]

In contrast to these findings, Spangler and colleagues in a cohort study of 93,676 postmenopausal women found no statistical significant association between depressive symptoms and mean change in 3-year BMD at the hip or spine. Similarly, no significant association was found between the use of antidepressants and 3-year changes in hip, spine, or whole body BMD. Moreover, depressive symptoms were not associated with increased risk for hip, spine, or wrist fracture, but were only associated with minimal increased risk for any fracture.[83] Therefore, not only is the association between depression and osteoporosis and/or fractures uncertain, but also the causal relationship has not been fully elucidated.[68] This presents challenges in need of further investigations.

To investigate this dilemma, we compare the association of concomitant SNRIs with bisphosphonates users and concomitant SSRIs with bisphosphonates users and increased risk of fracture. Selective serotonin reuptake inhibitors and, possibly SNRIs, are associated with osteoporosis and increased risk of fracture.[104] Currently there are no specific studies on the association between SNRIs and fracture.[105] However, studies on antidepressants other than SSRIs and fracture might implicate SNRIs. Vestergaard et al. found that venlafaxine (an example of a SNRI) was associated with statistically significant increased risk of forearm fracture at a dose of >0.5 DDD/day (OR=1.54 95% CI 1.12-2.12) and spine fracture at a dose of ≤0.25 DDD/day (OR=1.97; 95% CI 1.18-3.29). There were no statistically significant results for hip or

any fracture or at other drug doses.[106] (One DDD is the dose thata person on average uses of the drug in 1 day. The amount of DDD was calculated from the number of prescriptions, the number of tablets prescribed, and the dose of the pills in the actual prescription).[www.whocc.no/atcddd/] Vardel et al. found that non-SSRI/non-TCA antidepressants drugs (including venlafaxine) were associated with osteoporotic fracture (OR=1.40; 95% CI 1.06-1.85).[107] Why the comparison? This is because of the binding characteristics and selective nature of SNRIs on 5-HT receptors.

2.6.2 Selective nature of SNRIs and bone health

Serotonin norepinephrine reuptake inhibitors are dual action antidepressants that inhibit both serotonin (5-HT) and norepinephrine (NE) transporters. The FDA-approved SNRIs include venlafaxine (Effexor®), duloxetine (Cymbalta®), and desvenlafaxine (Pristiq®) which is an active metabolite of venlafaxine, and levomilnacipran (Fetzima®).[108] The ability of these drugs to block 5-HT and NE transporters *in vitro* and *in vivo* has been reported.

Duloxetine potently inhibits binding to the human 5-HT (K_i=0.8 nM) and NE transporters (K_i=7.5 nM). Venlafaxine, however, inhibiting binding to the human 5-HT was 106 times less potent (K_i=82 nM) than duloxetine and also inhibits binding to NE transporters (K_i=2480 nM). Thus venlafaxine binds to NE transporter with 331 times lower affinity than duloxetine. Results from *in vitro* studies showed that duloxetine inhibited 5-HT (K_i=4.6 nM) and NE (K_i=16), whereas venlafaxine inhibited 5-HT and NE with 17- and 34-fold lower potency. Furthermore, duloxetine blocked *ex vivo* 5-HT and NE transporter binding with ED_{50} values of 0.03 and 0.7 mg/kg subcutaneous (s.c). Venlafaxine was 67 and 77-fold less potent than duloxetine at inhibiting 5-HT and NE *ex vivo* transporter binding. These findings indicate that higher doses of venlafaxine were needed to block the NE transporter.[109]

Desvenlafaxine has higher affinity for the human 5-HT transporter (K_i=40.2 nM) compared with NE transporter (K_i=3385 nM). In addition, assays indicate that desvenlafaxine is approximately 10-fold more potent at inhibiting 5-HT uptake (IC_{50}=47.3) than NE uptake (IC_{50}=531.3).[110] Despite the findings from different assays, the findings suggest that the relative potencies for 5-HT transporter inhibition relative to NE transporter inhibition is in the order (low to high): venlafaxine, desvenlafaxine, duloxetine, and levomilnacipran.

Of particular interest is that venlafaxine acts as a SSRI at lower doses (75 mg/day, FDA labeling recommended starting dose), and a SNRI at higher doses (150-225 mg/day).[111] This mode of action might also be observed with desvenlafaxine and duloxetine in relation to the relative potencies. Higher doses of venlafaxine for the treatment of a severe depressive episode are well tolerated.[112] The recommended therapeutic dosage for desvenlafaxine is 50 mg/day for MDD patients and higher doses (50-400 mg/day) are well tolerated.[113] On the other hand, the recommended and with demonstrated efficacy dose for duloxetine in the treatment of MDD is 60 mg/day and higher doses can be tolerated up to 120 mg/day.[114]

The important question is whether the selectivity of SNRIs on 5-HT vs. NE transporters is clinically relevant as drug doses are increased with respect to the effects of SNRIs[115] and increased risk of osteoporotic fracture. A dose-dependent effect of SSRI use on fracture cases has been observed. Vestergaard et al. has shown that users of SSRIs reported an increased risk of any fracture (OR from 1.1 at doses <0.15 daily defined dose (DDD)/day to 1.4 at doses ≥0.75 DDD).[106] This dose-effect (in the opposite direction than what might be expected) may or may not be observed with SNRIs use. We hypothesize that if the risk of fracture is the same between SSRIs vs. SNRIs, then the increased risk of fracture may be related to the role of depression. In contrast, if the risk of fracture differs, and is greater among SSRIs users compared to SNRIs

users, then there is a higher likelihood of 5-HT playing a role but, not depression, in increased risk of fracture. Findings from this investigation can add new knowledge to understand the role of depression as an important risk factor for fracture as opposed to 5-HTT.

2.7 Summary

Bisphosphonates are effective in the prevention and treatment of osteoporosis and/or osteoporotic fractures in postmenopausal women. However, safety concerns of potential attenuation of BPs with concomitant use of medications with skeletal effects (e.g., SSRIs) and increased risk of fracture have been raised. Literature review has demonstrated the association of SSRI use with increased risk of fracture among postmenopausal women. However, these studies did not report fracture outcome comparisons between concomitant SSRIs with bisphosphonate users and nonusers (BP alone users). Most studies investigating the effect of SSRIs on bone in postmenopausal women exclude users of BP medications or BP use was not examined as a specific risk factor/ exposure of interest. Instead, it was just adjusted for,[75-83] thus missing the opportunity to investigate this potential event of possible attenuation of BPs by SSRIs and eventual increased risk of fracture.

Since BPs are considered a mainstay of pharmacologic therapy for the prevention and treatment of osteoporosis and/or osteoporotic-related fractures, it is highly likely that postmenopausal women prescribed BPs would be using SSRIs as well, if needed. A descriptive study using a large U.S. claims database (from 1999 to 2004) of women aged ≥50 years has shown that concomitant medications are used by women receiving daily or weekly BP therapy and this increased with age. The study did not include monthly or yearly BP therapies. Furthermore, of the medications that were concomitantly used with BPs, SSRIs or SNRIs were not described, highlighting a gap in the literature.[116] Descriptive concomitant use of

SSRIs/SNRIs with bisphosphonates is explored and results are provided in Chapter 3 and Chapter 5. In order to assess the association between concomitant use (section VI) and the role of 5-HT in bone (section VII), a pharmacoepidemiologic study was conducted and results and discussion are presented in Chapter 6 and Chapter 7, respectively.

2.8 Study design considerations

2.8.1 Background

This study focuses on the effects of concomitant SSRIs/SNRIs with bisphosphonates in large numbers of patients, which is the definition of pharmacoepidemiology, a discipline that applies epidemiological principles and methods. Pharmacoepidemiological studies are often conducted after approval for drug marketing has been granted. These studies are classified as observational in nature.[117] Observational research involves the direct observation of individuals (rather than manipulated [e.g., through randomization]) in their natural setting.[118] For example, studies using Medicare claims data are observational because the investigator is observing the subjects' health care utilization without any contact or involvement with the subjects.[118] Unlike clinical trials where individuals are randomized to receive an intervention or not, in observational studies, receiving an intervention or not is determined by individual preferences, practice patterns, or policy decisions.[119]

The most commonly used study design types for observational pharmacoepidemiologic studies include cohort studies, case-control studies, crossover studies,[120] and nested case-control studies[121]. In order to attribute a particular effect to the use of a drug, one of the key components to consider is the study design. Studies designed to minimize confounding bias (e.g., experimental designs), provide the most convincing evidence for a causal relationship between exposure and outcome of interest.[117] Confounding bias is of particular concern in observational

epidemiologic studies of drug effects.[122] In observational designs, the researcher must identify and measure potentially confounding variables, or the internal validity of the study will be undermined. As a consequence of lacking internal validity, conclusions about relationships are incorrect, and any generalization, regardless of the level of external validity, is meaningless.[123] Therefore, it is important to identify and handle confounding in observational studies.

2.8.2 Identification of confounders

Confounding is defined as the mixing effects between an exposure (X), an outcome (Y), and a third extraneous variable known as a confounder. As such, confounders are factors (exposures, interventions, treatments, etc.) that explain or produce all or part of the difference between the measure of association and the measure of effect that would be obtained with a counterfactual ideal.[100] The ideal comparison group in a cohort study consists of exactly the same individuals in the exposed group had they not been exposed. The ideal comparison would help to answer the question of what would have happened to those who did receive treatment, if they had not received treatment. Practically, this ideal comparison is unobservable and only an estimate of them can be created. Thus, the ideal comparison is referred to as counterfactual ideal.[100]

There are three criteria that must be met in order for a variable to be considered a confounder: 1) that the variable must be associated with the exposure in the population that produces the cases, 2) the variable must be an independent cause or predictor of the disease, and 3) the variable cannot be an intermediate step in the causal pathway between the exposure and disease. **Figure 2.3** depicts the relationship between the confounder, the exposure, and the disease and **Figure 2.4** depicts a variable that is a step in the causal pathway between exposure and a disease.[124]

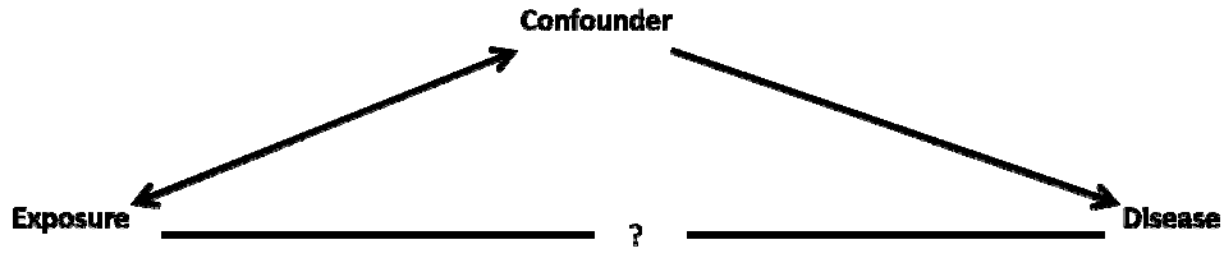

Figure 2.3. Schematic representation of the association between the confounder with both the exposure and disease.

Figure 2.4. Schematic representation of the variable that is a step in the causal pathway between the exposure and the disease.

With regards to osteoporotic fractures, **Table 2.4** shows potential risk factors associated with osteoporosis (or low BMD) and increased risk of fractures included in a new Fracture Risk Assessment Tool (FRAX®) for evaluating fracture risk. FRAX® was developed by the WHO to evaluate a patient's 10-year probability of hip fracture and major osteoporotic fracture (i.e., clinical spine, forearm, hip, or shoulder fracture).[17] Assuming one of the risk factors is considered an exposure (X), then the remainder of the risk factors are considered as the third extraneous variables known as confounders.

Table 2.4. Risk factors for osteoporotic fracture used in FRAX®.

- Age (50 to 90 years)
- Sex
- Body mass index
- Low femoral neck BMD
- Prior fragility fracture
- Parental fragility fracture
- Current tobacco smoking
- Long-term use of glucocorticoids
- Rheumatoid arthritis
- Other causes of secondary osteoporosis (e.g., medications and medical conditions)
- Alcohol intake of more than two units daily

Adapted from The North American Menopause Society, 2010.[17]

2.8.3 Handling confounding

2.8.3.1 Background

The central target of most health sciences research studies is the elucidation of cause-effect relationships among variables of interest and outcomes.[125] In epidemiology, variables of interest are commonly referred as exposure or treatment. When a statistical association is reported in an epidemiology study, it is stated with the hope of using the association measures to give insight into a causal-effect relationship.[126] Confounding is termed a "causal concept"[125] and thus can be an impediment to elucidation about true causal effects. In other words, recognizing confounding, one ought to understand what is meant by causal effect. A causal-effect can be defined as the effect due to a certain treatment or exposure.[126]

For illustration, suppose $Y_{a=1}$ is the outcome variable that would have been observed under exposure value a=1, and $Y_{a=0}$ the outcome variable that would have been observed under the exposure value a=0. The exposure has a causal effect in the population if $\Pr[Y_{a=1}=1] \neq \Pr[Y_{a=0}=1]$, where the probability $\Pr[Y_{a=1}]$ is the proportion of subjects that would have developed the outcome Y had all the subjects in the population of interest received exposure

value *a*. Note that the risk $\Pr[Y_{a=1}]$ is computed using all subjects of the population had they received the counterfactual exposure *a* (that is, it is an unconditional or marginal probability).[127]

On the other hand, exposure or treatment and outcome are associated if $\Pr[Y=1|A=1] \neq \Pr[Y=1|A=0]$. Where the probability $\Pr[Y=1|A=a]$ is the proportion of subjects that developed the outcome Y among those subjects in the population of interest that happened to receive exposure value *a* (that is, it is a conditional probability). In other words, the distribution of *Y* conditional on variable *A* is defined as examining the distribution of *Y* within levels of variable *A.* The symbol "|" denotes conditional relations. Therefore, the definition of association involves two disjoint subsets of the population determined by subjects' actual exposure value, whereas causation involves the same subset (for example, the entire population) under two potential exposure values. Hence the cliché "association is not causation." In ideal randomized experiments (assuming no loss to follow-up, full compliance with assigned treatment, and blind assignment), association is causation.[127]

In non-randomized (e.g., observational) studies association is not necessarily causation because of the potential lack of exchangeability of exposed and unexposed subjects. Exchangeability means that the risk under the potential exposure value *a* among the exposed, equals the risk under the potential exposure value *a* among the unexposed.[127] Therefore, pharmacoepidemiologic research aimed at assessing cause-effect relationships would prefer randomized experiments as the gold standard method of design. Unfortunately, randomized experiments are not always feasible because of cost, ethical, or practical reasons.[128,129] Therefore, even though exchangeability is not guaranteed, conducting observational studies is the only option available to pharmacoepidemiologists to identify associations or relationships and determine causal-effect relationships using observational data and statistical analyses.

Correlation, regression, risk ratio, and odds ratio are examples of associational concepts whereas confounding and randomization are examples of causal concepts. Bias or confounding exists when an association measure differs from the corresponding effect measure that would prevail under ideal experimental conditions and this is the case with non-randomized (observational studies).[125] This highlights the challenges pharmacoepidemiologists face when they draw conclusions about effects of drugs in large populations. How do we explain this challenge?

The fundamental problem of addressing a causal-effect research question is how to reconstruct outcomes that are not observed (counterfactuals or potential outcomes) because they are not what happened. The outcome can be observed only (or more precisely, at most) under one, and not under both conditions. Hence, reconstructing the counterfactuals is crucial to estimate unbiased causal-effects. The treatment that an individual actually does not receive is called counterfactual treatment.[130] How can we address this problem? One approach would be to reconstruct counterfactuals using propensity score method (PSM).

2.8.3.2 Propensity score method

PSM allows researchers to reconstruct counterfactuals using observational data, a situation similar to random assignment, albeit only with respect to observed variables.[131] Propensity score method does this by reducing the bias due to the measured confounders.[132] The strategy does not control for hidden biases.[131] Using PSM it is possible to duplicate one crucial feature of randomized experiment of designing an observational study without access to the outcome data. In experiments design, the way data will be collected is decided before observing the outcome data which is a tremendous stimulus for "honesty" in experiments and can be in well-designed observational studies as well.[133]

Propensity score method was introduced by Rosenbaum and Rubin and was defined as the probability of treatment assignment conditional on observed baseline covariates: $e_i=\Pr(Z_i=1|X_i)$, where Z=1 for treated and Z=0 for control. The propensity score (e_i) exists in both randomized experiments and in observational studies. Like all probabilities, a propensity score ranges from 0 to 1. In randomized experiments, the propensity score is known and is defined by the study, whereas in an observational study, it must be estimated from the data on indicator for received treatment (treated and controls) and observed covariates. The propensity is most often estimated using a logistic regression model.[134]

Given random assignment to treatment or control in randomized experiments (e.g., tossing a coin), each person has a 50% chance of being in treatment. Thus, each person has a true propensity score of 0.5. In non-randomized quasi experimental studies where the investigators have no control over the treatment assignment, the probabilities of receiving treatment (e_i) are a function of individual characteristics and are likely to vary from 0.50. For example, consider treatment assignments Z=1 and Z=0, then e_i above 0.50 would mean the person was more likely to select into treatment than control, and score below 0.50 would mean the opposite.[135]

In observational studies, propensity scores are used primarily to reduce bias and increase precision. There are four different PSMs researchers can use for removing the effects of confounding when estimating the effects of treatment on outcomes which involve balancing of nonequivalent groups. These include propensity score matching, stratification on the propensity score, covariance adjustment, or inverse probability of treatment weighting using the propensity score.[136] In this research project, the focus was on propensity score matching. Propensity score matching is the commonly used in the medical literature.[137] Furthermore, previous research has

demonstrated that matching on propensity score can result in a greater reduction in treatment selection bias than stratification on propensity score.[138]

2.8.3.3 Propensity score matching

The propensity score (PS) is a potential matching variable because it does not depend on response information that will be collected after matching.[134,139] Propensity score matching refers to pairing of treatment and control subjects, to form matched sets, with similar values (or distribution) of PS so that treated subjects are similar to the control subjects with respect to background variables (or covariates) measured on all subjects, just like in a randomized experiment. Thus, two matched subjects (one in treated and one in control group), with the same propensity score, are imagined to be 'randomly' assigned to each group in the sense of being equally likely to be treated or control. It is important to note that PS achieves balance in observed covariates whereas randomization in experimental studies achieves balance in all covariates (observed and unobserved).[134,136,139]

The implication of the balancing property of the propensity score in all observed covariates is that, when matching on PS, any differences in outcomes between treated and control subjects cannot be due to observed covariates. In other words, matching on PS tends to produce unbiased estimates of the treatment effects when treatment is strongly ignorable. Treatment assignment is considered strongly ignorable if the treatment assignment, Z, and the response, Y, are known to be conditionally independent given the covariates, X. Moreover, these design efforts, which result in more balanced distributions of covariates across treatment groups, make subsequent model-based adjustments (e.g., covariance adjustments, instrumental variables) more reliable.[133,134]

There are advantages for designing this pharmacoepidemiologic study using the PS matching strategy. First, a matched data set allows for simple, transparent analysis. Second, a matched analysis based on a well-formulated propensity score has the advantage of deleting from analysis those subjects with measurable contra-indications (or absolute indications) for treatment who have no available treated (or untreated) comparison subject. Confounding by indication is often the main challenge to validity in pharmacoepidemiology and the PS focuses directly on the indications for use and non-use of the drug under study.[140] For example, Zoledronic acid (Reclast®) is contraindicated in patients with severe renal impairment (i.e., creatinine clearance less than 35 ml/min) or in patients with evidence of acute renal impairment. A complete list of indications, contraindications, and geriatric use information for BPs is shown in **Table 1.7** in **Chapter 1**. Third, matched or stratified analyses do not make strong assumptions of linearity in the relationship of propensity with the outcome which is the assumption made when PS is included in a multivariate model together with actual treatment.[140] The estimated treatment effects can be biased if this assumption does not hold.[134]

The most common approach to PS matching is 1:1 matching and this research project used 1:1 matching strategy, where each treatment subject is matched to its 1 nearest neighbor. Matching at ratios of 1:n can increase statistical efficiency in case-control[141] and cohort studies.[142] However, it should be noted that 1:n matching increases bias because it is likely that less similar cases are matched with increasing number of matches.[142] Upon matching, balance of the covariates is assessed and then the treatment effect is estimated directly comparing outcomes between treatment and control groups in the matched sample.

2.8.3.4 Sensitivity test

The sensitivity test is the final step used to investigate whether causal effect estimated from PSM is susceptible to the influence of unobserved covariates. There are three approaches for conducting a sensitivity test: 1) changing the specification in the equation, 2) using the instrumental variable, and 3) use of Rosenbaum Bounding approach.[126]

2.9 Summary

Concomitant uses of medications are associated with ADEs. Literature shows that concomitant use of medications known to induce osteoporosis (e.g., GCs, PPIs, or LT_4) with BPs have potential attenuating effects of BPs resulting in increased risk of fracture. SSRIs are associated with increased risk of fracture and might also have potential attenuating effects. Also, the role of depression versus 5-HT on bone is unclear. Both of these latter hypotheses will be investigated in this study. To ensure internal validity of estimated effects, confounding bias of observed covariates will be handled using the PSM.

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Chapter 3

3.0 Preliminary study

3.1 Abstract

Title: Utilization patterns of bisphosphonates and selective serotonin reuptake inhibitors from 2004 to 2008 among women

Introduction: Comorbid osteoporosis and/or fractures and depression is prevalent in older postmenopausal women in the United States. Both conditions might require pharmacologic therapy. The most popularly used are antidepressants of the SSRIs or SNRIs and BPs. SSRIs and SNRIs have been associated with increased risk of osteoporosis and/or osteoporotic fractures. SSRI, SNRIs, and BPs utilization has become more common over time among women. The potential for attenuation of the effect of BPs by SSRIs/SNRIs and increased risk of fracture has not been investigated yet. Before the investigations, it was important to explore the extent to which these medications are prescribed concomitantly.

Specific aims: 1) to examine the proportion of BP users who are also on SSRIs/SNRIs and patterns of use over time, and 2) to explore the relationship between concomitant use and patient age among women aged 45 years and older.

Methods: A cross-sectional analysis was performed using data from the 2004-2008 Medical Expenditure Panel Survey (MEPS) to examine usage patterns of BPs and SSRIs/SNRIs for women aged ≥45 years. Analyses were based on yearly consolidated data and prescribed medicines files. Weighted descriptive statistics were used to evaluate patterns of medications use

and proportions were reported. Age was categorized into four groups: 45-54, 55-64, 65-74, and 75-85 years old.

Results: Of the survey respondents, proportions of women 45-64 years old were higher compared to those women 65-85 years old. Also, for each year about 80% of the respondents were white women. In the timeframe examined, 8.9% of women in 2004, 9.9% in 2005, 10.3% in 2006, 9.8% in 2007, and 10.0% in 2008 received bisphosphonates. In the same period, 13% of women in 2004, 12.7% in 2005, 12.8% in 2006, 12.2% in 2007, and 11.9% in 2008 received SSRIs. In addition, 2.7% of women in 2004, 3.3% in 2005, 3.0% in 2006, 3.9% in 2007, and 4.6% in 2008 received SNRIs. Concomitant use (BPs+SSRIs) was observed in 11.7% of women in 2004, 12.1% in 2005, 13.3% in 2006, 14.1% in 2007, and 13.5% in 2008. Overall, the trend of concomitant use of BPs+SSRIs increased across the five-year period (slope=0.56; p-value=0.04). In the same timeframe examined, no statistically significant trend in concomitant use of BPs+SNRIs was observed (slope=0.33; p-value>0.05). Furthermore, no structured odds ratios were observed for the association of age and concomitant use of BPs+SSRIs.

Conclusion: Concomitant use of BPs and SSRIs in adult women ≥45 years is not uncommon and might be higher in older postmenopausal women. The observed concomitant use presents drug safety challenges surrounding the bone health of postmenopausal women. Studies are needed to investigate the potential interactive effects of SSRIs on BP therapy.

3.2 Introduction

Osteoporosis and depression are known to coexist and it is still unclear the association between these two chronic conditions.[1] Also, these two conditions can exist together as comorbidities of other diseases such in patients with chronic obstructive pulmonary disease.[2]

Comorbid osteoporosis and depression is prevalent in patients 65 years and older.[3] The prevalence is higher in women (postmenopausal) than men.[1] The interaction between osteoporosis and depression is complex and as such single interventions are unlikely to be effective in improving outcomes in patients with these coexisting conditions.[4] Management of both conditions often requires pharmacologic therapy interventions and these include antiresorptives for osteoporosis and antidepressants for depression.

Of the current FDA-approved antiresorptives, BPs are recommended as first-line pharmacologic therapy in the management of osteoporosis and/or fractures, especially in older postmenopausal women.[5] Bisphosphonates have become the primary therapy for managing skeletal conditions characterized by increased osteoclast-mediated bone resorption[6] such as osteoporosis (or low bone mineral density). Bisphosphonates have been shown to reduce fracture risk by 40-50% in patients with low BMD.[7] The pharmacological features of BPs include a high affinity for crystalline hydroxyapatite in the bone and inhibitory effects on osteoclasts. The high affinity for bone mineral allows BPs to achieve a high local concentration throughout the entire skeleton.[6]

The use of antiresorptive treatment (e.g., BPs) appears to be fairly common, with one study reporting that 43% of premenopausal women (mean age 37± 8) have used BPs.[8] Perreault et al. in a study to determine use of antiresoptives (bone-specific drugs [BP, calcitonin, raloxifen] and hormone replacement therapy) among older women who had an osteoporotic fracture or were at risk of osteoporic fracture found that the use of these agents was reported to have increased over time—from 1.9 per 100 person-years in 1995 to 31 per 100 person-years in 2000 among those with prior osteoporotic-related fracture and 0.5 per 100 person-years in 1995 to 11 in 2000 for controls.[9] Gold et al. in a study using a large U.S. patient claims database accessed

through Wolters Kluwer Health found that female BP recipients increased from 78,909 in 1999 to 250,286 in 2004.[10] Also, other studies showed a significant reduction in hormone replacement therapy (HRT) utilization and a corresponding increase in newer anti-osteoporosis medications or nonhormonal therapy (e.g, BPs) after release of the Women's Health Initiative study[11] in 2002 that reported an association between HRT and increased risk of cardiovascular health disease and breast cancer among postmenopausal women.[12,13,14] Alternative medications to HRT for postmenopausal symptoms include clonidine, SSRIs, SERMs, and BPs.[15]

On the other hand, with a better safety and tolerability profile than older classes of antidepressants, SSRIs and SNRIs have become the most popular medications in treating depression and are considered first-line drug treatment in older patients.[16,17] An analysis of the Medical Expenditure Panel Survey (MEPS) has reported that SSRI and SNRI use has become more common (54.8% of antidepressant use in 1996 and 66.89% of antidepressant use in 2005) over time. Use of newer agents which include SNRIs has also been shown to be common over time (23.6% of antidepressant use in 1996 and 37.9% of antidepressant use in 2005). Of the individuals in the MEPS analysis, general antidepressant use (rates per 100 persons treated) was highest among those aged 50 years or older in women (7.62% in 1996 and 13.42% in 2005) than men (3.96% in 1996 and 6.68% in 2005).[18] In agreement, a recent Medicare Current Beneficiary Survey by Akincigil et al. showed that use of SSRIs and SNRIs increased over a period of 10 years (between 2002-2005 compared to 1992-1995) and was higher in females.[19]

The studies discussed above demonstrate an increasing trend of utilization of BPs and SSRIs /SNRIs. Whether this trend can also be observed for concomitant SSRIs or SNRIs with BPs remains an open question. Because of comorbid osteoporosis and depression,[1] BPs and SSRIs or SNRIs could be prescribed together. In the study by Caughey et al., the authors

determined the prevalence of potentially inappropriate medicines and treatment conflicts, for older people dispensed an antidepressant. In this study, patients with comorbid osteoporosis (already at-risk population for fractures), almost half were dispensed a SSRI and were at even higher risk for decreased bone density over time and increased risk of fracture.[3] Treatment for osteoporosis was not addressed. To the best of our knowledge, no studies have been reported describing the utilization pattern of concomitant SSRIs or SNRIs with BPs. Therefore, the primary objective of this study was to examine the proportion and use over time of BP users who are also on SSRIs or SNRIs and to explore the relationship between concomitant use and patient age among women aged 45 years and older.

3.3 Methods

3.3.1 Data sources and patient population

Data from the 2004-2008 MEPS was used to examine usage patterns of BPs and SSRI/SNRI antidepressants for women aged 45 years or older. MEPS, a survey cosponsored by the Agency for Health Care Research and Quality (AHRQ) and the National Center for Health Statistics (NCHS), is a relatively large, longitudinal study of health care use among the U.S. civilian, non-institutionalized population (e.g., not in prisons or nursing homes). The survey is conducted as a national probability survey using a complex stratified multistage area probability design.[20] The National Health Interview Survey (NHIS), another large ongoing Federal health survey conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, serves as the sampling frame for MEPS.

The MEPS household component collects information on demographic and socio-economic characteristics, health care use, expenditures, respondent's health status, sources of payment, and health insurance coverage for all the members of the household. The survey is designed such that certain groups, including racial minorities (Blacks, Hispanic, and Asian individuals), and low-income households, are oversampled from the NHIS. Data from the MEPS household participants are collected over a two and half year period. Each new MEPS annual sample is referred to as a panel. The MEPS conducts the survey annually and employs an overlapping panel design to collect data whereby each year a new panel of households is selected from among those households that participated in the previous year's NHIS. This design provides data which can be combined and used for cross-sectional or longitudinal analysis.[20,21]

3.3.2 Identification of exposure

Concomitant use was defined as receipt of at least one prescription of a bisphosphonate and a SSRI or SNRI antidepressant during a calendar year. The assigned Multum Lexicon Drug Database values (Cerner Multum Inc., Denver, CO, USA; http://multum.com/Lexicon.htm) were used to identify drug products in the MEPS survey. The Multum Therapeutic category values are 217 (BPs), 208 (SSRI antidepressants), and 308 (SNRI antidepressants).

3.3.3 Statistical analysis

Analyses were based on yearly consolidated data, and prescribed medicines files. The demographic characteristics (including age, race, health insurance coverage, socio-economic status, marital status, and education) and prescribed medicines information of the qualified participants was obtained from the Full Year Consolidated Data, and the Prescribed Medicines Files respectively of the 2004-2008 MEPS household components. Weighed descriptive statistics were used to evaluate patterns of medication use and proportions were reported. Respondents

who self-identified as “White” were categorized as “White” and also “Black” respondents were classified as “Black”. However, respondents who self-identified as either “American Indian/Alaskan Native” or “Asian” or “Native Hawaiian/Pacific Islander” or “Multiple races” were re-classified as “Other”.

Based on age, and race, first, the proportions of women aged ≥45 years old who filled at least one SSRI or SNRI antidepressants, and BPs, both separate were calculated. Second, the analysis was limited to only women who were on BPs. The proportions of BP users who are also on SSRI or SNRI antidepressants were calculated for each calendar year and these proportions were further analyzed by age-groups: 45-54, 55-64, 65-74, and 75-85 years old. Age was defined as age at the end of each calendar year. All estimates were calculated using the survey procedures (PROCSURVEYFREQ) of the software SAS 9.3 version (SAS Institute, Cary, NC) including variables for generating weighted national estimates and for use of the Taylor series linearization method for variance estimation for complex survey designs. These variables are: person-level weight (PERWT0xF); stratum (VARSTR); and cluster/psu (VARPSU).[22,23]

For trend analysis, the frequencies of overall utilization and utilization by age of SSRIs or SNRIs with BPs were calculated for each year. Then, any change in these frequencies across the 5-year period were described and analyzed for statistical significance. A linear regression was performed using the proportions of BP+SSRI/SNRI use from 2004 to 2008 to test for significant linear trend across the 5 survey years for concomitant users.

Logistic regression was used to examine the relationship between increasing age and utilization of BPs+SSRIs/SNRIs and whether the relationship was linear. The categorized age groups (categorical variable) were thought of as ordered. Thus a Cochran-Armitage trend test

was performed to test whether there was a linear relationship. Odds ratios were reported for the age group categories in the model. For all analyses statistical significance was set at $p<0.05$.

3.4 Results

3.4.1 Summary descriptive statistics

In the time frame examined in this study, there were a total of 34,403 observations in 2004, 33,961 observations in 2005, 34,145 observations in 2006, 30,964 observations in 2007, and 33,066 observations in 2008. The demographic information of women ≥45 years are presented in Table 3.1 for MEPS 2004-2008. In addition, the population patterns of these participants are presented in Figure 3.1 which parallels the actual annual estimates from the U.S. Census Bureau in Figure 3.2.[24] The proportion of women ≥45 years during a calendar year increased gradually and steadily, from 19.5 percent in 2004 to 20.4 percent in 2008 (Table 3.1 and Figure 3.1). Of these participants, White women accounted for the largest proportions followed by African American women and the rest were of other racial backgrounds.

Table 3.1. Demographic information of U.S. women aged 45 years and older for MEPS 2004-2008.

Year	2004	2005	2006	2007	2008
Total	N (5846)	N (5834)	N (6113)	N (5550)	N (5574)
Characteristic	%	%	%	%	%
Age					
45-54	2058 (34.0)	2088 (34.2)	2168 (34.4)	1941 (33.3)	2005 (33.4)
55-64	1624 (28.8)	1646 (29.2)	1737 (29.2)	1665 (30.4)	1690 (30.5)
65-74	1098 (18.5)	1030 (17.5)	1103 (17.4)	1001 (17.9)	1003 (18.0)
75-85	1066 (18.6)	1070 (19.2)	1105 (19.0)	943 (18.4)	876 (18.1)
Race					
White	4626 (83.7)	4528 (83.5)	4704 (83.5)	4240 (83.4)	3960 (83.1)
Black	874 (10.7)	952 (10.6)	1037 (10.6)	919 (10.7)	1124 (11.1)
Other	365 (5.6)	368 (5.9)	384 (5.9)	407 (5.9)	517 (5.8)
Marital status					
Married	2986 (54.5)	2988(55.1)	3184 (55.9)	3020 (55.7)	2994 (55.3)
Divorced/Separated	1160 (18.1)	1172 (18.1)	1229 (18.2)	1110 (19.4)	1103 (19.0))
Widowed	1310 (21.5)	1265 (20.8)	1256 (19.6)	1033 (18.5)	1021 (19.0)
Never Married	389 (5.8)	409 (6.0)	444 (6.2)	387 (6.2)	456 (6.7)
Family income					
Low income or below	2211 (29.4)	2245 (29.1)	2348 (28.3)	1975 (28.6)	1970 (29.6)
Middle income	1633 (29.0)	1586 (28.5)	1673 (28.6)	1574 (27.7)	1653 (27.7)
High income	2002 (41.6)	2003 (42.5)	2092 (43.1)	2001 (43.8)	1951 (42.7)
Insurance type					
Private	3617 (70.8)	3553 (70.4)	3690 (70.2)	3418 (68.6)	3370 (65.9)
Public	1633 (22.0)	1639 (22.0)	1719 (21.4)	1498 (22.9)	1523 (25.0)
Uninsured	596 (7.2)	642 (7.6)	704 (8.4)	634 (8.6)	681 (9.2)
Education					
<High school	1542 (17.3)	1479 (16.8)	1548 (17.1)	1292 (16.3)	1293 (15.5)
High school	2869 (53.2)	2878 (53.2)	2941 (51.2)	2689 (50.9)	2680 (52.2)
>4 years college+	1435 (29.4)	1477 (30.0)	1624 (31.6)	1569 (32.8)	1601 (32.3)

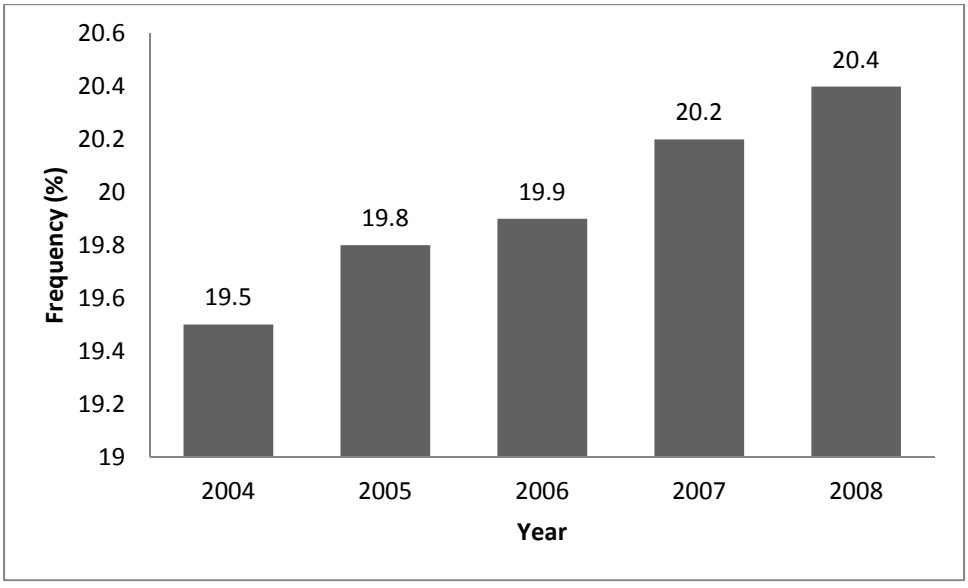

Figure 3.1. Plot of population patterns of US women aged 45 years and older, MEPS 2004-2008.

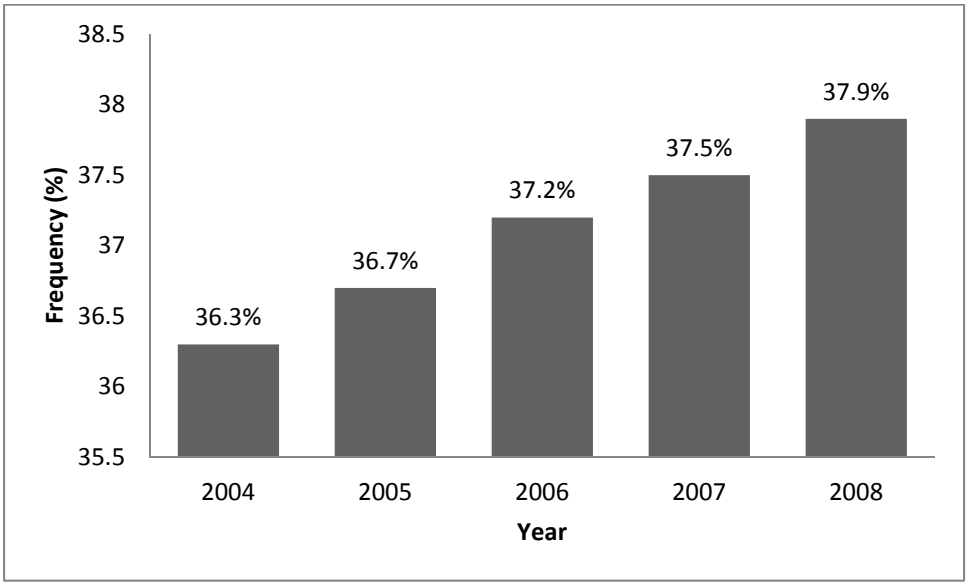

Figure 3.2. Annual estimates of the U.S. resident population of women aged 45-85 years: July 1, 2004 to July 2008.[24]

Table 3.2 shows the proportions of those women 45 years or older reporting use of BPs, SSRIs, SNRIs by year. According to the MEPS-HC for 2004-2008, 8.9 percent of women in 2004, 9.9 percent in 2005, 10.3 percent in 2006, 9.8 percent in 2007, and 10.0 percent in 2008 were using BPs. In the same period, 13.0 percent of women in 2004, 12.7 percent in 2005, 12.8 percent in 2006, 12.2 percent in 2007, and 11.9 percent in 2008 were using SSRI antidepressants. 2.7 percent of women in 2004, 3.3 percent in 2005, 3.0 percent in 2006, 3.9 percent in 2007, and 4.6 percent in 2008 were using SNRI antidepressants.

Table 3.2. Utilization patterns of bisphosphonates and SSRIs in U.S. women aged 45 years and older for 2004-2008.

Year	**2004**	**2005**	**2006**	**2007**	**2008**
Total	N (5846)	N (5834)	N (6113)	N (5550)	N (5574)
Medication use	%	%	%	%	%
Bisphosphonates (BPs)	8.9	9.9	10.3	9.8	10.0
SSRIs	13.0	12.7	12.8	12.2	11.9
SNRIs	2.7	3.3	3.0	3.9	4.6

3.4.2 Overall concomitant use of BPs and SSRIs or SNRIs

Among those women who were using BPs, concomitant SSRIs with BPs use was observed in 11.7 percent of women in 2004, 12.1 percent in 2005, 13.3 percent in 2006, 14.1 percent in 2007, and 13.5 percent in 2008 (Table 3.3). Graphic representations of these findings are shown in Figure 3.3. A steady increase in BPs+SSRIs concomitant use was observed between 2004 and 2007 and then decreased slightly in 2008 (Table 3.3 and Figure 3.3). Whereas, for BPs+SNRIs utilization, an increase in concomitant use was observed from 2004 to 2005, followed by a downward utilization trend in 2006 and then a steady upward trend in 2007 and 2008 (Table 3.4 and Figure 3.3). Overall, between 2004 and 2008, the utilization rate of BPs+SSRIs increased (from 117 to 135 concomitant use per 1000 persons) and this increase had a significant linear trend (slope=0.56;p=.04). When weighted, this increase represented an increase of 0.66 million BPs+SSRIs users in 2004 to 0.86 million in 2008. On the other hand, a non significant increase in utilization rate (from 25 in 2004 to 43 concomitant use per 1000 persons in 2008) was observed for concomitant BPs+SNRIs (slope=0.33; p>0.05).

Table 3.3. Utilization patterns of concomitant use of bisphosphonates and SSRIs by age in U.S. women aged 45 years and older for MEPS 2004-2008.

Year	2004	2005	2006	2007	2008
Total	N=497	N=519	N=556	N=496	N=466
BPs+SSRIs use					
45-54 years, n (%)	6 (12.6)	10 (16.5)	8 (16.2)	5 (10.8)	11 (26.9)
55-64 years, n (%)	20 (18.4)	24 (19.4)	20 (9.8)	23 (13.3)	9 (7.3)
65-74 years, n (%)	12 (7.5)	11 (6.6)	25 (16.2)	19 (13.0)	15 (12.3)
75-85 years, n (%)	14 (8.8)	17 (9.5)	27 (13.4)	26 (16.6)	27 (15.9)
All, n (%)	52 (11.7)	62 (12.1)	80 (13.3)	73 (14.1)	62 (13.5)

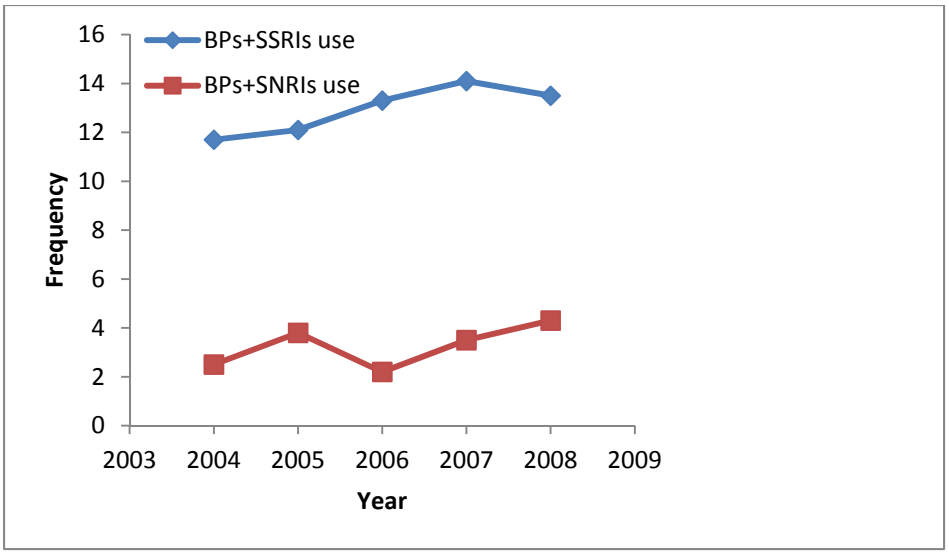

Figure 3.3. A plot of utilization patterns for concomitant use of BPs+SSRIs, and BPs+SNRIs in U.S. women aged ≥45 years, MEPS 2004 to 2008.

Table 3.4. Utilization patterns of concomitant use of bisphosphonates and SNRIs by age in U.S. women aged 45 years and older for MEPS 2004-2008.

Year	2004	2005	2006	2007	2008
Total	N=497	N=519	N=556	N=496	N=466
BPs+SNRIs use					
45-54 years, n (%)	1 (5.5)	4 (12.1)	1 (2.3)	1 (3.0)	4 (11.5)
55-64 years, n (%)	3 (3.0)	4 (4.0)	4 (3.3)	10 (5.9)	6 (5.1)
65-74 years, n (%)	2 (1.6)	6 (4.0)	3 (1.5)	0 (0)	5 (4.8)
75-85 years, n (%)	3 (1.9)	1 (1.1)	3 (1.7)	6 (3.8)	2 (2.1)
All, n (%)	9 (2.5)	15 (3.8)	11 (2.2)	17 (3.5)	17 (4.3)

3.4.3 Concomitant use of BPs and SSRIs/SNRIs by age and year

When concomitant use of SSRIs with BPs use was examined by age group in each calendar year (Table 3.5 and Figure 3.4), we observed a significant linear trend (slope=2.1; p=0.01) of concomitant use among women aged between 75-85 years which increased steadily between 2004 and 2008. Although a similar upward trend was observed among women aged 65-74 years, the linear trend was nonsignificant (slope=1.6; p>0.05). In the group aged 65-74 years, utilization decreased between 2004 and 2005, increased sharply in 2006, and then decreased in

2007 and 2008. Of the qualified participants in this study, interesting findings were observed among women aged 55-64 years. Among women of this age group, unstable ("zigzag") downward, but nonsignificant, trend (slope=-2.8; p=0.06) was observed from 2004 to 2008. A look at year to year utilization pattern shows an increase from 2004 to 2005 then decreased sharply in 2006, increased sharply in 2007 and then decreased in 2008. Finally, a non significant overall upward utilization trend (slope=2.3; p>0.05) was observed among women aged 45-54 years old. In this age group, the utilization trend increased upward from 2004 to 2005 then remained almost unchanged in 2006, decreased in 2007, and then increased sharply in 2008.

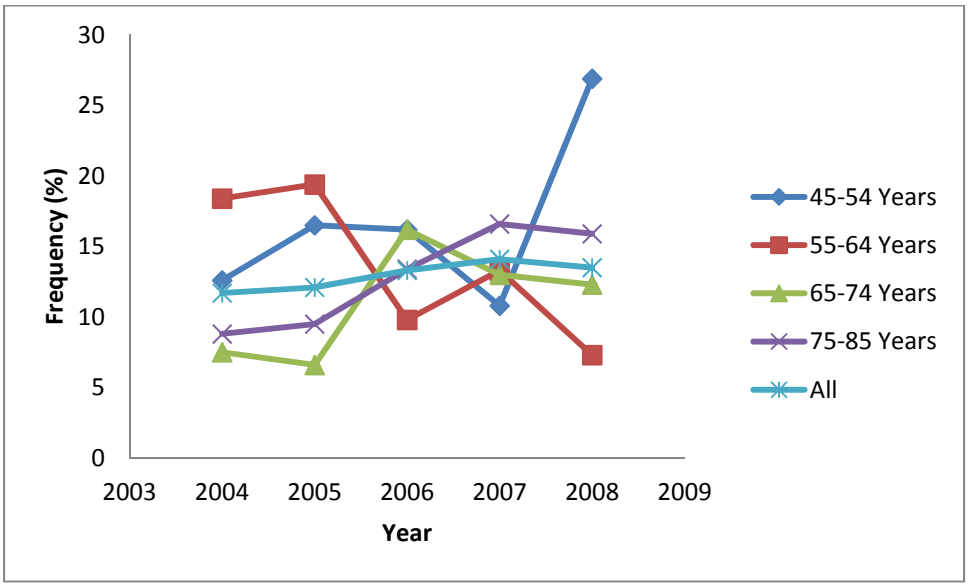

Figure 3.4. Plot of utilization patterns of concomitant BPs+SSRIs use by age of U.S. women age ≥45 years and older, MEPS 2004-2008.

Table 3.5. Trend analysis for concomitant SSRIs use with BPs.

Year	2004	2005	2006	2007	2008	Slope; p-value
Total	N=467	N=519	N=556	N=496	N=466	
BPs + SSRIs use						
45-54 (%)	12.6 (7.04-18.24)	16.5 (15.81-17.11)	16.2 (14.10-18.22)	10.8	26.9 (0.16-53.59)	2.3; p>0.05
55-64 (%)	18.4 (16.01-20.87)	19.4 (14.53-24.26)	9.8 (7.21-12.30)	13.3 (10.31-16.26)	7.3 (3.46-11.04)	-2.8; p>0.05
65-74 (%)	7.5 (2.57-12.41)	6.6 (4.12-9.10)	16.2 (12.85-19.52)	13.0 (10.66-15.32)	12.3 (8.67-16.02)	1.6; p>0.05
75-85 (%)	8.8 (7.53-10.00)	9.5 (6.33-12.59)	13.4 (8.69-18.06)	16.6 (12.47-20.81)	15.9 (12.03-19.78)	2.1; p=0.01
All, n (%)	11.7 (8.67-14.74)	12.1 (9.56-14.73)	13.3 (10.57-16.01)	14.1 (11.57-16.72)	13.5 (10.37-16.56)	0.56; p=0.04

Note: The denominator for age categories is the total number of women in that particular age group and for that particular year, whereas the denominator for "All" is the "Total" number of women in that year.

When concomitant use of BPs+SNRIs was examined by age group in each calendar year (Table 3.6 and Figure 3.5), we observed a positive, but nonsignificant linear trend across all age groups of concomitant use between 2004 and 2008 (slope range=+0.24 to +0.61; p >0.05).

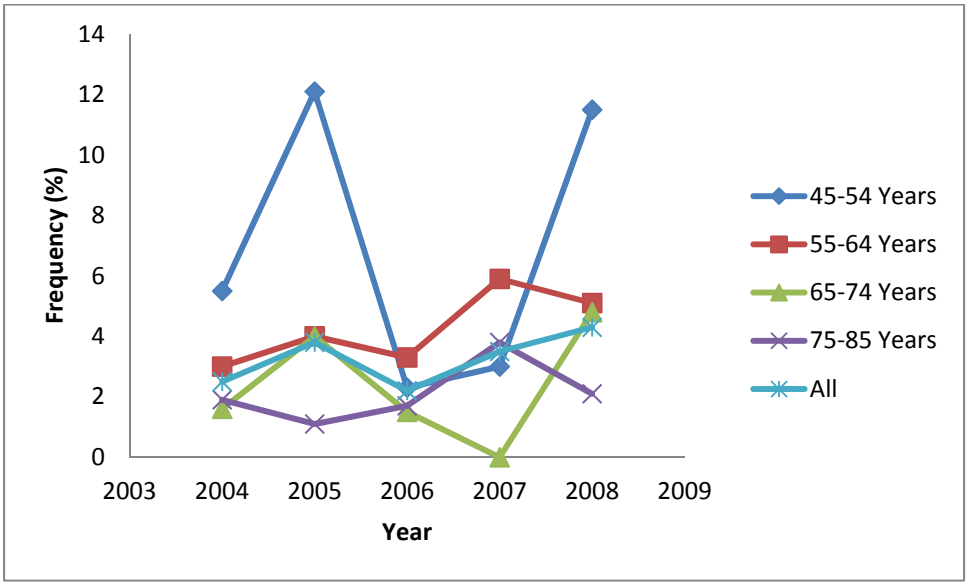

Figure 3.5. Plot of utilization patterns of concomitant BPs+SNRIs use by age of U.S. women age ≥45 years, MEPS 2004-2008.

Table 3.6. Trend analysis for concomitant SNRIs use with BPs.

Year	2004	2005	2006	2007	2008	Slope; p-value
Total BPs+SNRIs use	N=467	N=519	N=556	N=496	N=466	
45-54 (%)	5.5 (5.21-5.78)	12.1 (11.67-12.63)	2.3 (1.98-2.55)	3.0	11.5 (5.79-17.24)	0.29p>0.05
55-64 (%)	3.0 (1.37-4.56)	4.0 (1.05-6.90)	3.3 (1.58-4.99)	5.9 (4.44-7.41)	5.1 (1.14-9.13)	0.61;p>0.05
65-74 (%)	1.6 (0-4.23)	4.0 (1.85-6.20)	1.5 (0.20-2.85)	0	4.8 (2.67-6.93)	0.24;p>0.05
75-85 (%)	1.9 (1.72-2.06)	1.1 (0-3.24)	1.7 (0-3.68)	3.8 (1.24-6.42)	2.1 (1.96-2.23)	0.31;p>0.05
All, n (%)	2.5 (0.76-4.26)	3.8 (1.87-5.76)	2.2 (1.05-3.29)	3.5 (2.38-4.71)	4.3 (1.55-7.05)	0.33;p>0.05

Note: See Table 3.5

3.4.4 Relationship between concomitant use of BPs+SSRIs and age

The findings from examining whether age is associated with utilization pattern of concomitant use of BPs+SSRIs (Table 3.7) shows no structured pattern of odds ratios, overall. However, we noticed the highest odds of concomitant use with increasing age in the year 2007 (odds ratios ranging from 1.24 to 1.66). Also, we observed that the pattern of odds ratios were similar in the years 2005 and 2008 which might suggest a need for further investigations.

A time-trend analysis of the age effect shows a statistically non significant decreasing probability trend for BPs+SSRIs concomitant use in 2004 ($p>0.05$) and a statistically significant decreasing trend in 2005 ($p<0.05$), a statistically non significant increasing trends in 2006 to 2008 ($p>0.05$). See Table 3.8.

Table 3.7. BPs+SSRIs concomitant utilization odds ratio (and 95% confidence interval) for age, by year; MEPS 2004-2008.

Year	2004	2005	2006	2007	2008
Total	N=467	N=519	N=556	N=496	N=466
BPs+SSRIs use					
Age					
45-54	1.00	1.00	1.00	1.00	1.00
55-64	1.56 (0.76, 3.20)	1.22 (0.59, 2.54)	0.56 (0.26, 1.24)	1.27 (0.46, 3.55)	0.21 (0.07, 0.62)
65-74	0.56 (0.22, 1.43)	0.36 (0.14, 0.90)	1.00 (0.48, 2.11)	1.24 (0.46, 3.35)	0.38 (0.16, 0.94)
75-85	0.66 (0.32, 1.39)	0.53 (0.24, 1.16)	0.80 (0.35, 1.85)	1.66 (0.63, 4.36)	0.52 (0.25, 1.08)

Table 3.8. Cochran-Armitage Trend test of concomitant use of BPs+SSRIs for age, by year; MEPS 2004-2008.

Year	2004	2005	2006	2007	2008
Statistic (Z)	1.438	2.547	-0.229	-0.699	-0.319
0ne-sided p-value	0.075	0.005	0.410	0.242	0.375
Trend ('1')	**decrease**	**decrease**	increase	increase	increase

3.5 Discussion

This study described national estimates across five-year period of concomitant SSRIs/SNRIs with BPs and the trend over time. We also screened the effects of age on utilization patterns in order to provide information that might be useful in supporting the need for further detailed investigations. Both overall utilization patterns of concomitant use as well as utilization for four age categories were presented.

3.5.1 Overall utilization and trends of concomitant use

We found that overall concomitant SSRIs with BPs use is prevalent and increased slightly across the five-year period among the study population. Although we observed concomitant SNRIs with BPs use, based on the National Center for Health Statistics minimum standard for reliability of estimates,[25] overall patterns of use across the five-year period were

considered too small for any meaningful interpretations and therefore concomitant SNRIs with BPs use findings are not discussed further. The low cell sizes can be attributed to the fact that SSRIs are widely used than SNRIs. Although SSRIs and SNRIs are both most popular antidepressants with comparable efficacy,[26] all SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) but only one SNRI (venlafaxine) are the most commonly used medications for depression. This was according to the 2000 American Psychiatric Association practice guideline for the treatment of patients with major depressive disorder. These medications are likely to be optimal in terms of the patient's acceptance of side effects, safety, and quantity and quality of clinical data.[27] Also, the 2001 expert consensus panel recommended venlafaxine as an alternative to SSRIs as a first-line treatment for depression in older adults.[28]

With regards to the overall increasing trend of concomitant SSRI with BP use, it is unclear why the simultaneous use of these agents increased across the five-year period and what might explain the effects of age on patterns of use. Since this present study did not intend to determine the predictive factors influencing the patterns of use, we explored the literature in an effort to suggest explanations for our findings. Three suggested explanations are provided and these include, 1) increasing population of women in the US and demographic factors, 2) increasing diagnosis of osteoporosis or fractures and/or depression, 3) side effects associated with HRT use and the influence on alternative therapies, and 4) newer indications for both BPs and SSRIs in women.

Population increase is an important factor to consider when assessing changes in trend of drug utilization, and in the present study concomitant SSRIs with BPs use. In our study we observed that overall the female population increased in numbers from 2004 (36%) to 2008 (40%) (see Figure 3.2).[24] Utilization can increase if the chances that more females begin taking

medications increases. This can be supported by the fact that females are more likely to visit their healthcare providers than males and this has an overall influence on medication utilization.[29] Furthermore, of the women surveyed, we observed a large number of white women compared to other races across the five year period. The old National Osteoporosis Foundation Guide, last updated in 2005, applied only to postmenopausal white women[30] and this might have influenced both the patient preference and physician prescribing habits in shared decision-making.

Another perspective related to population increase might be the increase in the incidence of osteoporosis or fractures and/or depression. This is an important factor that could result in an overall increased demand for prescription drugs. The incidence of osteoporosis and risk of fractures in postmenopausal women continues to increase over time. It is estimated that 10 million individuals in the United States have osteoporosis, eight million are women and two million are men.[31] According to estimated figures, osteoporosis was responsible for more than 2 million osteoporotic fractures in 2005. Due to specialized tests for diagnosis there has been a five-fold increase in office visits for osteoporosis (from 1.3 to 6.3 million) based on data from 1996 to 2006. This data suggests that improved diagnosis can lead to therapeutic follow-up to treat or prevent osteoporosis and/or risk of fractures through administering antiresorptives (e.g., bisphosphonates) and this will have an overall impact of increasing utilization of such medications. Low BMD in combination with low-trauma fracture or fracture risk factors (smoking and weight) remains the strongest predictor or drivers of BPs use in postmenopausal women.[32,33]

The WHO suggests that major depression is the leading cause of burden of disease in the Americas accounting for 7.5% of total disability-adjusted life years (DALYs) and is expected to

be leading worldwide by year 2030 accounting for 6.2% of total DALYs. Moreover, the WHO report indicates that depression is the leading cause of disease burden in young women (15-44 years).[34] As with younger women, among older persons, the burden of depression is higher in older women than older men, but is less common during the postmenopausal years.[35,36] For example in the study by Barry et al. it was found that among those who were non-depressed, women were more likely to transition to a depressed state, with an adjusted odds ratio of 2.02 (95% CI;1.39-2.94).[36] It is important to note that depression in older adults is not directly associated with advancing age[37], but rather is considered a disorder co-morbid with other illnesses associated with aging.[38]

According to the Agency for Healthcare Research and Quality (AHRQ), about 60% of depressed outpatients have at least one other chronic medical condition as well. The challenge of treating depression is a big issue in older adults. AHRQ research comparing older adult patients with and without depression in a primary care clinic found that the depressed patients had almost 1.5 more ambulatory care visits per year, over 12 percent more visits to the emergency department, and 5% more hospitalizations.[39] Despite the complexity of treatment of patients with comorbidity, patients with cormobid disorders continue to receive treatment to improve the quality of care.[40] With the high prevalence of depression in postmenopausal women attributed to improved diagnosis through increased contacts with the healthcare system, antidepressant prescriptions are likely to be driven up as result in order to meet the desired goal of improving the quality of care for patients with depression. This is in agreement with previous literature which found that guideline concordance (guideline of the 1999 Canadian Network for Mood and Anxiety Treatments) increased prescribing physician visits in the year following diagnosis. In this study 2,742 patients (mean age 42 years; 64% female patients) met the study criteria. Of the

beneficiaries to whom psychoactive medication was dispensed, 2,047 (75%) received an antidepressant as the initial starting drug and 1958 (71%) received a recommended first-line antidepressant. In a multivariable model, recommended first-line medication (z=6.17, df 11, p=0.001), starting dose (z=5.70, df 11, p=0.001), and duration (z=9.49, p=0.001) were associated with more visits to prescribing physicians.[41]

Another factor that might have influenced use of bisphosphonates and/or SSRIs/SNRIs is the study by the Women's Health Initiative (WHI) about the adverse effects of estrogen in women. In 2002, data from a WHI study was published highlighting the side effects (breast cancer and cardiovascular disease) of estrogen plus progestin in healthy postmenopausal women.[42] In response to these concerns, use of alternative therapies increased. This is evident from the reported increase in nonhormonal options as alternatives to estrogen, given with and without progestin (or HRT), for postmenopausal symptoms such as osteoporosis and hot flushes that respond only to prescription medications following WHI study. The North American Menopause Society released a position statement in 2003 recommending options for women with concerns or contraindications relating to estrogens. The nonhormonal options included antidepressants such as venlafaxine (SNRI), paroxetine, and fluoxetine (both of which are SSRIs). This statement in now retired.[43] Huot et al. showed a decrease in HRT and increase in bisphosphonate prescriptions from 2004 to 2006 in women aged 50 years and older.[44] Vegter et al. showed that those who stopped HRT received more nonhormonal therapies for menopausal symptoms from 2002 to 2006 compared to those who continued hormonal therapy; incidence risk ratio (IRR) of bisphosphonates was significant (IRR=2.54, 95% CI 1.16-5.55) and overall IRR of antidepressants was not statistically significant (IRR=1.34, 95% CI 0.97-1.86).

Antidepressant use was increased for both tricyclic antidepressants and SSRIs, but not for other types of antidepressants (including SNRIs).[45]

Another way through which side effects of HRT use may influence alternative therapy choices could be to increase healthcare costs. The long-term safety concerns of breast cancer associated with HRT use increases management costs for HRT users because women are more likely to get excess rates of resource utilization for uterine- and breast-related diagnostic and treatment procedures, thus, increasing the healthcare cost pressures.[46] Considering that the current US Preventive Service Task Force guidelines recommend alternatives such as bisphosphonates for osteoporosis therapy,[47] these recommendations plus the induced additional healthcare-related cost pressures might have reinforced the need to consider therapeutic alternatives to HRT.

Consensus guidance recommendations support new indications for BPs or SSRIs and the new indications may contribute to expanded utilization of either or both drugs. Additional indications for bisphosphonate use include reducing skeletal complications of many malignancies, including multiple myeloma, breast and prostate cancer, and other solid tumors, and palliation of cancer-associated bone pain.[48] Data from the Surveillance, Epidemiology, and End Results from 2004-2008 showed that the trend of cancer incidence for females of all races remained stable with an annual percentage change of 0.4%. (www.seer.cancer.gov) In addition, data from the Centers for Disease Control (2004-2008) indicate that the site with the highest incidence rate (about 120 per 100,000 population) was of the female breast followed by the lung. The highest death rate among females was from lung cancer (www.apps.nccd.cdc.gov). Other indications for SSRIs include, generalized anxiety disorder, social anxiety, panic disorder, posttraumatic stress disorder, obsessive compulsive disorder, and eating disorder.(www.fda.gov)

Given that some of the commonly associated health conditions in the postmenopausal years include osteoporosis, depression, diabetes, and cancer (www.menopause.org), it is plausible to suggest that coexistence of osteoporosis and depression or osteoporosis and other indications for SSRIs or depression and other indications for BPs, or other indications for both BPs and SSRIs are prevalent. Coexistence of any of these diseases can influence overall expanded utilization of simultaneous SSRIs with BPs use.

3.5.2 Utilization patterns and trend of concomitant use with age

The main reason to further classify patients into age groups is that age-related characteristics (e.g., clinical) are heterogeneous.[49] As a result, age-related differences might influence health services and medications utilization. The differences are especially significant among women within the older age groups 65 years and older.[50] In this present study, the tabulated results by year for each age category showed increasing utilization of concomitant SSRIs with bisphosphonates use among respondents 65 years and older across the five-year period and the pattern might be time-dependent. This was further explained by looking at the age-specific odds ratios. Although the odds ratios showed no structured pattern, the observed highest odds ratios of older respondents with simultaneous use of BPs+SSRIs in 2007 is probably because 90% of older adults 65 years and older had regular source of health care regardless of other factors and the use of physician services was found to be high among this population.[51] The higher contact with healthcare providers could have had an overall influence in medications use. In addition, major policy changes of year 2006 following the implementation of The Medicare Modernization Act Prescription Drug Benefit (Part D)[52] made it possible for older adults 65 years or older to voluntarily subscribe to drug coverage which in turn resulted in modest increase in average drug utilization.[53] Another primary contributor to upward drug trend

in this age group is the decline in unit costs of medications due to entry of lower-cost options (generic drugs).[54] Zoloft® (sertraline) was one of the generic drugs introduced in mid-2006.[55]

In 2005 and 2008 the similar low odds ratios observed suggested important factors that might have impacted utilization of medications. In 2005 Gunnell et al. reported that SSRIs use was associated with increased risk of suicidality in older adults.[56] It is probably in response to these concerns that SSRIs prescribing and hence utilization growth declined. In addition to the implementation of Medicare Part D prescription drug coverage in 2006 which resulted in increased drug utilization among older adults 65 years and older, the first generic bisphosphonate, Fosamax® (alendronate), that is approved to treat osteoporosis was introduced in 2008.[57] As would be expected, the introduction of generic bisphosphonate into the pharmaceutical market would decrease the unit costs of the most popular bisphosphonate drug. Both the guaranteed prescription drug coverage and decreased unit costs were expected to further drive the utilization of medications upwards and possible increased likelihood of simultaneous SSRIs with BPs users. Instead, a decline in utilization was observed and there are two suggested contributing factors: 1) the safety and effectiveness concerns related to medications for postmenopausal osteoporosis published in 2007, and 2) the economic downturn-related factors in 2008.

Of the medications that have been proven to be effective in decreasing the risk of osteoporotic-related fractures in postmenopausal women, bisphosphonates are the most popular. Suboptimal compliance and persistence with bisphosphonate treatment was associated with increased fracture risk. However, the benefits of oral bisphosphonates use over extended period of time were unclear suggesting that decisions on optimal clinical effectiveness achieved during indefinite use of bisphosphonates could not be supported.[58] In a randomized, double-blind trial

conducted at 10 U.S. clinical centers that participated in the Fracture Intervention Trial of postmenopausal women using alendronate, findings showed that discontinuation of alendronate for up 5 years does not appear to significantly increase fracture risk but therapy beyond 5 years was recommended for women at high risk of clinical vertebral fractures.[59] Considering that the journal has a high impact factor, looking at the time of publication of this article (December 2006) the findings might have created confusion among physicians and patients as well during the year 2007.

At about the same time of publication of the article by Black et al.[59] a review by Briot et al. which assessed optimal treatment duration of use of bisphosphonates determined that there was no proof that these drugs prevented fractures after the first 4 to 5 years of treatment and so, long-term use of these drugs was recommended for 4-5 years.[60] Additional articles with consistent conclusions have since been reported. During the year 2007, these findings were widely publicized which also may have spilled over to 2008. As a result, it is plausible to suppose that the negative impact on physician prescribing habits and patient preference was unavoidable and, thus, had an overall influence in the decline in utilization of bisphosphonates.

As was mentioned earlier, the second suggested contributing factor to changes in utilization of concomitant SSRIs with BPs was the impact of the economic crisis in 2008. The economic crisis in 2008 was quite devastating for many families. Investments were devalued, people lost jobs, and budget cuts were made in the government as well as the private sector and this could strongly and negatively impact overall spending on basic needs including healthcare-related utilization. A recent study by Piette et al.[61] found that among chronically ill patients in 2008, rates of medication-cost problems associated with recent economic recession impacted all

age groups including those >65 years of age and eligible for Medicare Part D. Rates were especially high among adults aged 40-64 years.

3.5.3 Relationship between concomitant SSRIs with BPs and age

The relationship between concomitant SSRIs with BP use and age was not consistent across the five year-period. Overall, concomitant use decreased with age from 2004 to 2005 but increased from 2006 to 2008. This can, in part, be explained by the confusion in age-related treatment options driven by the age-dependent bone density change[62] and safety of hormonal treatments of menopause-related health outcomes.[63] In younger postmenopausal women (after 50 years old), increase in bone loss (osteoporosis) is related to a sharp drop in estrogens and thus hormonal therapy might be beneficial.[62,63] Although HRT is associated with heart disease in postmenopausal women, complications of therapy occur in women many years after the start of menopause.[64] In 2004, Anderson et al. released an updated interpretation of the WHI study (in comparison to the previous 2002 WHI study) that was supportive of estrogen use in the younger postmenopausal women below the age of 60 years.[65] SERMs are considered first-line therapy in younger postmenopausal women at lower risk for hip fracture.[5] Use of SERMs results in a 55% reduction in vertebral fractures but lacks advantage when looking at nonvertebral fractures.[66] In older postmenopausal years (65 years and older), there is accelerated bone loss beginning at 70 years old[62] and bisphosphonates are the first-line therapy for osteoporosis.[5] In reference to SSRIs, the downward trend from 2004 to 2005 was probably due to a fall in utilization. For example, Chen et al. in a study using Medicaid data found that the total number of antidepressant prescriptions increased from 1991 to 2004 (from 6.8 million to 35 million scripts), but then fell

in 2005 to 32.7 million prescriptions. SSRI prescriptions were 20.8 million in 2004 but fell to 19.5 million in 2005.[67]

The National Osteoporotic Foundation suggests age as one of the factors to consider when choosing a treatment. The foundation states that "some medicines may be more appropriate for younger postmenopausal women while others are more appropriate for older women."[68] This statement is likely to have an overall influence on physician prescribing habits, patient preferences, or healthcare systems. Under this confusion, some physicians might switch their patients to a safer alternative, or some might use their clinical judgment and experiences to wait and switch their patients later, patients' preference might influence physician prescribing, or healthcare systems might tailor their formularies. In summary, the factors discussed above might be responsible to explain a downward (2004-2005) and upward (2006-2008) trend of concomitant SSRIs with BPs use with age in our present study.

3.5.4 Strengths and limitations

There are strengths and limitations in this study. Strengths: First, MEPS consists of patient-level data and is nationally representative of the U.S. civilian, non-institutionalized population. It was therefore suitable to use this dataset to describe national estimates of medication use. Secondly, self-reporting bias is minimal. This is because MEPS does seek permission from the respondents to verify medications use from their respective pharmacies. Limitations: Following age categorizations and medications use, all cell sizes for BPs+SSRIs use were small (less than 30). According to the National Center for Health Statistics, estimates determined to be statistically reliable are generally based on sample size (cell size greater than or equal to 30) and relative standard error (less than 30%).[25] Therefore, interpretations of data under age categories is not representative of national estimates and caution is advised.

3.6 Conclusions

We conclude that concomitant SSRIs with BPs use in adult women ≥45 years is not uncommon and might be higher in older postmenopausal women. The trend of concomitant use may be time-dependent and the utilization pattern over time may be influenced by patient-, provider/physicians-, and health-care system-level factors that determine prescribing of medications to particular patients. Unfortunately this study did not attempt to assess these factors but only suggested possible explanations from literature. As such there is still need to further investigate the impact of these factors on the utilization patterns of SSRIs with BPs using a large sample size and longitudinal data. Moreover, the observed concomitant use presents drug safety challenges surrounding the bone health of postmenopausal women. Studies are needed to investigate the potential interactive effects of SSRIs on BP therapy.

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Chapter 4

4.0 METHODS

4.1 Study design

A nested case-control study was performed to examine 1) the association between concomitant use of SSRIs or SNRIs with bisphosphonates and increased risk of osteoporotic-related fractures, and 2) whether the risk of osteoporotic-related fractures is related to the role of serotonin in bone rather than the disease (depression).

4.1.1 Rationale

One of the prime purposes of a pharmacoepidemiologic study is to determine whether drug exposure causes an adverse drug event (health outcome). Typically, the sequence of discovery of causal association between exposure and outcome using epidemiologic approaches involves five steps which include the analytic methods such as nested-case control study design (or the case-control in a cohort study).[1] Nonetheless, many population-based case-control studies can be thought of as nested within an enumerated source population.[2] This design is based on a sampling approach known as incidence density sampling or risk set sampling. In the nested-case control study, cases of the outcome of interest that occur in a defined cohort are identified, a risk set (i.e., that could become a case) corresponding to the cases is formed and, for each, a specified number of matched controls is randomly selected for each risk set from among those in the cohort who have not developed the outcome by the time of the outcome occurrence in the case.[3]

By using this strategy, cases occurring later in the follow-up are eligible to be controls for earlier cases.[4]

Strengths exist in support of this study design strategy. First, the design combines some of the features and advantages of both cohort (i.e., limiting selection bias) and the efficiency of case-control designs approach. The likelihood of selection bias tends to be diminished in comparison with the traditional case-based case-control study. This is because cases and controls are selected from the same (defined) source cohort and because (as in any traditional cohort study) exposures are assessed before the disease occurs.[4] In addition, this study approach can be relatively quicker and less expensive than cohort or experimental studies, primarily because the control group is a sample of the source population. Also, the design strategy involves potentially less complex analysis. Second, when the outcome being studied occurs rarely and/or is suspected to be a latent effect of the exposure, cohort studies become impractical and case-control studies become a useful and efficient alternative. This is because fewer subjects are needed than for cohort studies.[2,5] Third, the likelihood of survival bias tends to be diminished in comparison with the traditional case-based case control study. Survival bias is a potential problem in a case-based case-control study carried out "cross-sectionally" because only cases with long survival after diagnosis (best prognosis) are included in the case group.[4] Fourth, the study design is better in quantification of exposure with respect to time.[3] Sampling is the equivalent of matching cases and controls on duration of follow-up (or respect to time), thus if time is related to exposure, the resulting data should be analyzed as matched data.[2,4]

4.2 Data sources

We used the random 5% sample data from the entire Medicare administrative claims data (see Table 4.1 for a description of the data obtained) from 2008 to 2010. (Part A Medicare claims

were of persons enrolled in fee-for-service because claims from these sources provide information needed for research purposes.) These data are available back to January 2006, when the program was implemented. The Centers for Medicare and Medicaid Services (CMS) administer Medicare. All requests for CMS research-identifiable Medicare Part D data was developed and reviewed with the assistance of the Research Data Assistance Center (ResDAC), a CMS contractor that provides free assistance to academic, government and nonprofit researchers.[6]

4.2.1 Rationale

Pharmacoepidemiologic research on the beneficial and adverse events of medications among older adults has used databases such as Medicare Current Beneficiary Survey (MCBS) or Medicare Expenditure Panel Survey (MEPS). However, these databases are limited by smaller sample sizes, which can limit statistical power.[7] MCBS is a continuous, multipurpose survey (collected since 1991) of a representative sample of the Medicare population designed to aid the CMS administration, monitoring and evaluation of the Medicare program.[8] Unlike the databases mentioned above, Medicaid database has a relatively large sample size of older adults and has been used for drug safety related studies.[9] The specific limitation of this database is its generalizability. Those older adults who are not classified as of low income are not covered under the Medicaid program and so are not represented in findings based on this database.

The use of Medicare Part D data, like other administrative databases such as Medicaid data[10] is faced with methodological challenges such as verifying data validity, confounding, and logistic problems. A central limitation with many implications is that such databases are collected for administrative rather than research purposes. These limitations are an important

source of bias in the results of most studies. Based on this understanding, new methods relating to data analysis approaches applicable to administrative claims data, such as Medicare Part D data, have been suggested. These efforts are geared towards improving the usefulness of these important data sources to evaluate drug safety and effectiveness.[11] For example, recently, Graham et al.[12] determined the increased risk of cardiovascular events by rosiglitazone compared with pioglitazone among 227,571 Medicare beneficiaries aged 65 years or older through a Medicare Part D prescription drug plan from July 2006-June 2009. The results showed that the prescription of rosiglitazone was associated with increased risk of cardiovascular events.[12]

This underscores the statement noted by Strom[13] that "Medicare Part D is one potential data source, which, when linked to other Medicare claims data, will be a unique resource on a massive and stable population".[13] Thus the main advantage of using this source of data is its large, nationally representative population of older adults. Also due the fact that out-of-pocket spending was reduced with this plan among older adults, prescription drug use increased significantly[14] suggesting that Medicare Part D data potentially captures large numbers of users of prescription drugs. Medicare Part D provided an opportunity for those beneficiaries who had no drug coverage that were not poor and frail. Also, in a similar perspective, Platt and Ommaya[15] noted that linked Medicare Part D data presents a valuable resource to assess drugs under real-life conditions, particularly in this vulnerable population, which is often excluded or underrepresented in clinical trials. Therefore, use of information from Medicare administrative claims data will be important because our preliminary studies using MEPS (see **Chapter 3**) have been limited by smaller sample sizes and have not provided statistically reliable findings.

Table 4.1. Description of CMS data files and key variables needed for analysis.

Study objective	Data variable (s)	CMS data file (s) needed
To examine the association of concomitant use of SSRIs/SNRIs, glucocorticoids, or PPIs and bisphosphonates and increased risk of osteoporosis-related fracture in adult women aged ≥65 years	Individual claims (e.g., fracture) submitted for each inpatient stay at a Medicare-approved facility (e.g., hospital)	Medicare Part A (inpatient)
	CCW Encrypted Part D Event Number, CCW Encrypted Beneficiary ID Number, Patient Date of Birth, Gender, RX Service Date (DOS), Encrypted Plan Contract ID, Compound Code, Quantity Dispensed, Days Supply, Dispensing Status Code, Patient Pay Amount, Medicare Part D formulary tier identifier	Medicare Part D (prescription drug event)
	CCW Encrypted Part D Event Number, CCW Encrypted Beneficiary ID Number, Brand Name, Generic Name, Drug Strength Description, Dosage Form Code, and Dosage Form Code Description	Medicare Part D (drug characteristics file)
	Provides a summary of the beneficiary's use of various Medicare categories and prior history of various chronic conditions (e.g., myocardial infarction, depression, etc.)	Beneficiary annual summary file
	Provides basic beneficiary demographic and geographic data, as well as enrollment and eligibility information	Beneficiary summary file

4.2.2 Data elements

The data elements from this database included a coded patient identifier (Medicare patients have a unique personal identification number (PIN) through which all health system encounters are tracked); patient demographics (age, race, and socioeconomic status); procedure/diagnostic codes (or medical diagnoses); claim admission codes and dates, and pharmacy claims details (National Drug Codes, drug names, date of drug dispensing, quantity

dispensed, number of days supplied, and refill status).[96] See **Table 4.1** for a description of the data variables obtained.

4.3 Study population

4.3.1 Inclusion criteria

Cases and controls were eligible for inclusion in the study if they were females and aged 65 years or older. Cases were defined as women with a first osteoporotic-related fracture matching with the fracture index date. The fracture index date (date of experiencing a fracture) was defined as the first documentation of an osteoporotic-related fracture during the study period (January 2008 to December 2010) associated with hospitalization. Fracture identification was based on the *International Classification of Diseases*, *9th revision; Clinical Modification (ICD-9-CM)* codes for fracture at six of the most common fracture sites from inpatient encounters: hip, spine, distal radius/ulna, tibia/fibula or ankle, and humerus from inpatient encounters (**Table 4.2**). Only patients using bisphosphonates were included in the study.

Table 4.2. Description of osteoporotic fracture sites included in the study.

Fracture site	Fracture type	ICD-9-CM	
Hip or pelvis fracture	Closed	Pathologic	733.14
		Transcervical	820.0x
		Pertrochanteric	820.2x
		Unspecified hip	820.8x
		Acetabulum	808.0x
		Pubis	808.2x
		Other specified	808.4x
		Unspecified	808.8x
Femur	Closed	Pathologic	733.15
		Shaft/unspecified	821.0x
		Lower end	821.2x
Vertebral (without spinal cord injury)	Closed	Pathologic	733.13
		Cervical	805.0x, 806.0x
		Thoracic/Dorsal	805.2x, 806.2x
		Lumbar	805.4x, 806.4x
		Sacrum & coccyx	805.6x, 806.6x
		Unspecified	805.8x, 806.8x
Radius / ulna or wrist	Closed	Pathologic	733.12
		Upper end	813.0x
		Shaft	813.2x
		Lower end	813.4x
		Unspecified	813.8x
Humerus	Closed	Pathologic	733.11
		Upper end	812.0x
		Shaft/unspecified	812.2x
		Lower end	812.4x
Tibia/fibula or ankle	Closed		823.0x, 823.2x, 823.4x 823.8x, 824.0x, 824.2x 824.4x, 824.6x, 733.16

4.3.2 Exclusion criteria

Cases and controls were excluded if they had a history of prior fracture. History of prior fracture was defined by any fracture in the first 6 months of observation if multiple fracture events are noted during the study period, only the first event was included in the study. Women with any fracture that was listed as "open" (e.g., 813.1x: fracture of radius/ulna, upper end, open) was excluded since open fractures are more likely the result of a major trauma rather than

osteoporosis. The complete list of open fractures is as follows: those with open fractures of the hip, ICD-9-CM codes: 820.1x (transcervical), 820.3x (pertrochanteric), and 820.9x (unspecified part of neck of femur); open wrist or radius/ulna fracture, ICD-9-CM codes: 813.1x (upper end), 813.3x (shaft), 813.5x (lower end), and 813.9x (unspecified part of radius/ulna), and open vertebrae fracture with or without spinal code injury, ICD-9-CM codes: 805.1x, 806.1x (cervical), 805.3x, 806.3x (thoracic), 805.5x, 806.5x (lumbar), 805.7x, 806.7x (sacrum & coccyx), and 805.9x, 806.9x (unspecified part). Other exclusions were those women taking calcitonin (Miacalcin), parathyroid hormone teriparatide (Forteo), selective estrogen-receptor modulators (Evista), and also those women with diagnosis of Paget's disease, or disabled people under 65 years of age. These patients are at a much higher risk for adverse bone health.

4.4 Exposure to concomitant use

Assessments of the drug exposure as identified by their brand or generic names were as follows. The primary exposure variable was the concomitant use of SSRIs or SNRIs with bisphosphonates and was defined as having received at least one prescription for a bisphosphonate and a SSRI or SNRI (with no dispensing medication gap for a SSRI or SNRI of more than 90 days whereas users of bisphosphonates were those patients who were exposed for at least 180 days in the 360 day period). SSRI users were defined as women reporting SSRI use but no other antidepressants at a given visit. Likewise, SNRI users were defined as women reporting SNRI use but no other antidepressants at a given visit.[16] Information on SSRI or SNRI use was classified as either 'current', 'recent', or 'past' users. A schematic representation is shown in **Figure 4.1**. *Current users* were defined as those individuals with a total of 90 day supply for a SSRI or SNRI and within 90 days (1 to 90) prior to the index date of sustained fracture. *Recent users* were defined as those individuals with a total of 90 day supply for a SSRI

or SNRI and within 91 days and 180 days prior to the index date of sustained fracture. *Past users*-those individuals who were not current users or recent users and had a supply for a SSRI or SNRI dispensed more than 180 days in the 360 day period prior to the index date of sustained fracture. These definitions have been used in a previous study to assess the association between antidepressants and risk of fracture of the hip or femur. In this study, compared with individuals who had never used an SSRI, the risk of hip/femur fracture increased with current use of SSRIs (adjusted OR=2.35, 95% CI 1.94-2.84), recent use (adjusted OR=1.48; 95% CI 1.14-1.93), and past use (adjusted OR=1.23; 95% CI 1.07-1.42).[17]

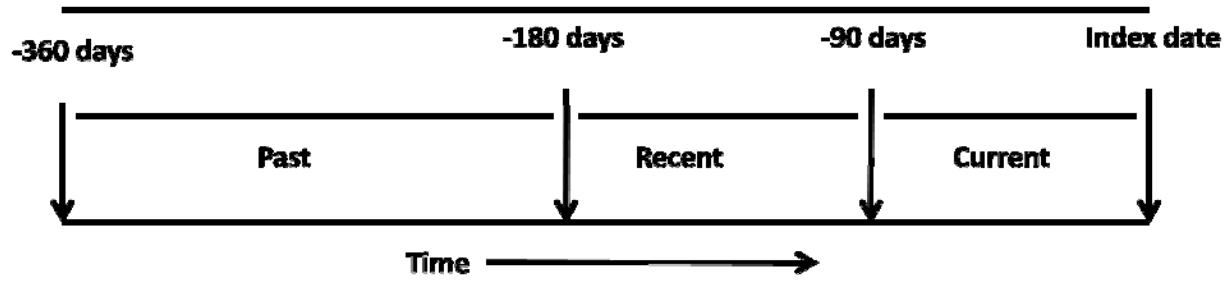

Figure 4.1. Timing of SSRI or SNRI use.

4.5 Regulatory approval

This study was reviewed and approved by the Institutional Review Board (IRB) at Virginia Commonwealth University.

4.6 Statistical plan

4.6.1 Selection of subjects:

Flow charts for the selection of subjects eligible for analysis are shown in Figure 4.2 (Specific Aim 1) and Figure 4.3 (Specific Aim 2).

4.6.2 Dependent and independent variables:

Dependent (or response) variable: increased risk of osteoporotic-related fractures

Independent (treatment or explanatory) variables: Concomitant use of SSRIs or SNRIs and bisphosphonates.

4.7 Strategic framework to control for confounding

A multivariable logistic regression model was developed to calculate the propensity score of individual patients. (Refer to more information on propensity score method in Chapter 2 Section IX). Propensity score is defined as the probability of receiving treatment rather than the control for a patient conditional on observed baseline covariates.[18] In this study, the propensity score is the probability of receiving concomitant SSRIs or SNRIs with bisphosphonates versus bisphosphonate alone users as a function of all the potential confounders listed in **Table 4.4**. Medicare beneficiaries who were identified as "White" or "Black", or "Hispanic" were categorized as "White", or "Black", or "Hispanic" respectively. However, beneficiaries who were identified as either "North American Native" or "Asian" or "Other" or "Unknown" were re-classified as "Other". To quantify patients' comorbidities included in the logistic regression model, two potential comorbidity indices: Functional or Deyo-adapted Charlson Comorbidity Index can be used for this pharmacoepidemiologic study. Both of these indeces are described next, but we calculated the comorbidity scores using the Deyo-adapted Charlson Comorbidity index. The rationale for the comorbidity index choice is provided in the following description.

Table 4.3. Baseline patient characteristics of all antidepressant initiators.

Characteristic
Demographic
Age (within 5 year bands): Aging is characterized by changes in pharmacokinetic and pharmacodynamic processes. These processes when altered increase the risk of adverse drug events, and increased sensitivity to medications.[1]
Race (White, Black, Hispanic, or Other)
SES (based on low income subsidy of the beneficiary, as a proxy for socioeconomic status)
Health service-use intensity or Health care utilization factors
Comorbidity score
Number of unique prescribed medications
Medical conditions
Rheumatoid arthritis/ Osteoarthritis
Osteoporosis
Kidney disease
Anxiety or sleep disorder
Epilepsy
Movement disorders (e.g., Parkinson's disease)
Cognitive dysfunction (e.g., Alzheimer's disease or other diagnosis of dementia)
Hypertension
Congestive heart failure
Diabetes mellitus
Chronic obstructive pulmonary disease (COPD)
Hyperparathyroidism
Depression
Orthostatic hypotention
Use of other medications that may modify fracture risk
Oral glucocorticoid use/oral corticosteroid use
Proton pump inhibitor use
Aromatase Inhibitors
Thiazolidinediones use
Estrogen use (or hormone replacement therapy)
Warfarin use
Anticonvulsant use
Thyroid medication use
Opioid use
Antihypertensive use (thiazide diuretics, angiotensin II converting enzymes inhibitors, angiotensin II receptor blockers, beta-adrenergic blockers, or calcium channel blockers)
Loop diuretic use (e.g. furosemide)
Antipsychotics use, Methotrexate, and Lithium

[1]Corsonello A, Pedone C, Incalzi RA. Age-related pharmacokinetic and pharmacodynamic changes and related risk of adverse drug reactions. *Curr Med Chem*. **2010**;17(6):571-584.

4.7.1 Comorbidity score

4.7.1.1 Functional comorbidity index

A functional comorbidity index is an index of comorbid diseases with physical function. The functional comorbidity index contains 18 diagnoses scored by adding the number of "yes" answers, with a score of 0, indicating no comorbid illnesses.[19] The reason to use this index is because SSRIs are one of the examples of medications associated with drug-related falls.[20] SSRIs-related falls can be injurious and result in fractures. For example, in an observational study of 368 subjects (SSRI users, n=129; non-SSRIs, n=40; non-antidepressants, n=199) conducted in a nursing home setting showed high rate of falling in SSRIs users (24%, OR of 1.9 or greater) and high rate of injurious falls (OR, 1.73) that resulted in fractures and/or hospitalization from a series of adjusted models compared with other two groups of subjects.[21] Also, French et al.[22] in a national veterans study using outpatient medication data to assess fall-related hip fracture hospitalization showed that usage of SSRIs was 2-fold higher in hip-fracture patients compared to the control groups.[22] However, risk factors for falls and/or a fracture in older adults are multifactorial such as comorbid diseases and physical function. The diseases include but are not limited to diabetes mellitus, dementia, high blood pressure, chronic obstructive pulmonary disease, and arthritis.[23] In fact, the diseases are all included in the functional comorbidity index.

Overall physical functioning is one of the intrinsic factors associate with falls recommended to be assessed in an older patient reporting a fall.[24] Therefore, the suggested index might be appropriate in quantifying comorbidities and physical function on fracture outcomes.

4.7.1.2 Charlson comorbidity index

There are thirteen different methods to assess comorbidity: one disease count and 12 indices. Of these, the Charlson index is the most extensively studied comorbidity index.[25] The Charlson comorbidity index is a summary score based on 19 major medical conditions including myocardial infarction, pulmonary disease, cancer, diabetes, renal disease, hepatic disease, HIV infection, etc. A score of 0 represents absence of comorbidity, and a higher score indicates a greater number of comorbid conditions. The index was originally developed and validated in 1987 to classify prognostic comorbidity for patients enrolled in longitudinal studies; developed based on the inception cohort study of 604 patients admitted to the medical service at New York Hospital during 1 month in 1984 and then was tested for its ability to predict risk of death from comorbid disease in a cohort of 685 patients who were treated for primary breast cancer at Yale New Haven between 1962 and 1969. Its performance was compared to the method of classifying comorbid disease developed by Kaplan and Feinstein.[26] In later studies, it was validated for a proposed age-comorbidity index in a different cohort of patients who had essential hypertension or diabetes and who were undergoing elective general surgery for diagnoses such as peripheral vascular disease and aortic aneurysm.[27]

Deyo et al. adapted Charlson comorbidity index, designed for use with clinical records, for research relying on International Classification of Diseases (ICD-9-CM) diagnosis and procedure codes to examine the association of the adapted index with health outcomes and resource utilization. Data of all Medicare claims for beneficiaries who underwent lumbar spine surgery in 1985 (n = 27,111) was used. This was based on Part A Medicare claims. The study findings concluded that the Charlson index can be valuable in studies of disease outcome and resource utilization when used with ICD-9-CM administrative databases.[28] In further support,

other studies have also validated use of Charlson index with administrative databases. D'Hoore et al. adapted Charlson comorbidity index to ICD-9 codes to perform analysis on 1990-1991 MED-ECHO database (Québec) with 36,012 patient admissions with ischemic heart disease and associated in-hospital death. The study concluded that the Charlson comorbidity index may be an efficient approach to risk adjustment from administrative databases.[29]

Following validation of Charlson comorbidity index with administrative databases, the index has gained popular use in epidemiologic research. For example, the Deyo-adapted Charlson Comorbidity index has been used to quantify patients' comorbidities and scores used in a propensity score method to estimate the incidence rates and hazard ratios of subtrochanteric and femoral fractures in elderly patients treated with oral biphosphonates compared with those treated with either raloxifene or calcitonin.[30] Since this dissertation project uses Medicare claims data (administrative database), which was used to validate Charlson comorbidity index, then the rationale for using the index is strongly justified and therefore Charlson comorbidity index was adapted instead of the functional comorbidity index. Another reason is that obesity and/or body mass index is one of the 18 diagnoses scored in the functional comorbidity index. Medicare claims data does not provide information for these variables.

4.7.2 Propensity score matching

The primary analysis used a greedy algorithm for 1:1 propensity score matching to control for confounding. Users of SSRIs were matched to potential users of SSRIs based on the estimated propensity scores. All potential confounders included in the propensity-score model are provided in Table 4. To assess achieving balance in baseline covariates between treatment groups, standardized difference was used.[31]

4.8 Statistical analysis

4.8.1 Descriptive analysis

After the propensity score matching, subjects were then analyzed. Descriptive statistics comparing the baseline characteristics of the cases and the controls was performed. Continuous variables were expressed as mean ± SD, 95% CI and categorical data was reported as proportions. The characteristics of patients in each group were compared before and after the propensity score matching. Baseline characteristics included sociodemographic characteristics (age, race/ethnicity, and socioeconomic status), distinct prescription drugs (excluding SSRIs) and co-morbidities (including depression), and prior and current use of exposures of interest (**Table 4**).

4.8.2 Multivariable analysis

Using bisphosphonate-alone users as our comparison group (controls), Cox proportional hazard models were constructed to assess the risk of osteoporotic-related fractures among bisphosphonates, SSRIs, and SNRIs users separately and among concomitant users of bisphosphonates with SSRIs or SNRIs. Hazard ratios (HRs) and 95% CI were estimated. Since we matched the groups on propensity scores containing potential confounders, the Cox regression models contained only a variable for exposure of interest, with bisphosphonate-alone users as the reference/comparison exposure.

The software SAS 9.3 version (SAS Institute, Cary, NC) was used and the level of significance of α=0.05 was considered for all statistical tests.

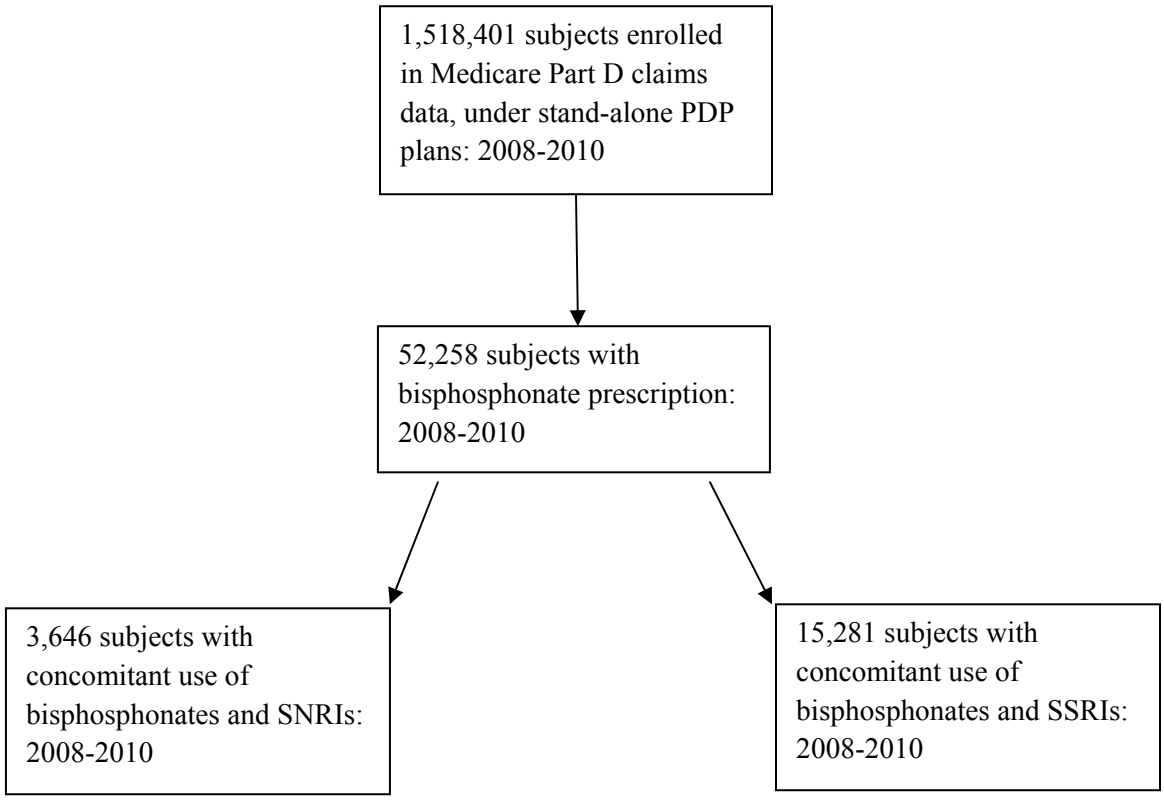

Figure 4.2. Flow chart showing selection of subjects from the Medicare part D, under stand-alone prescription drug plan eligible for analysis (Specific Aim 1): 2008-2010.

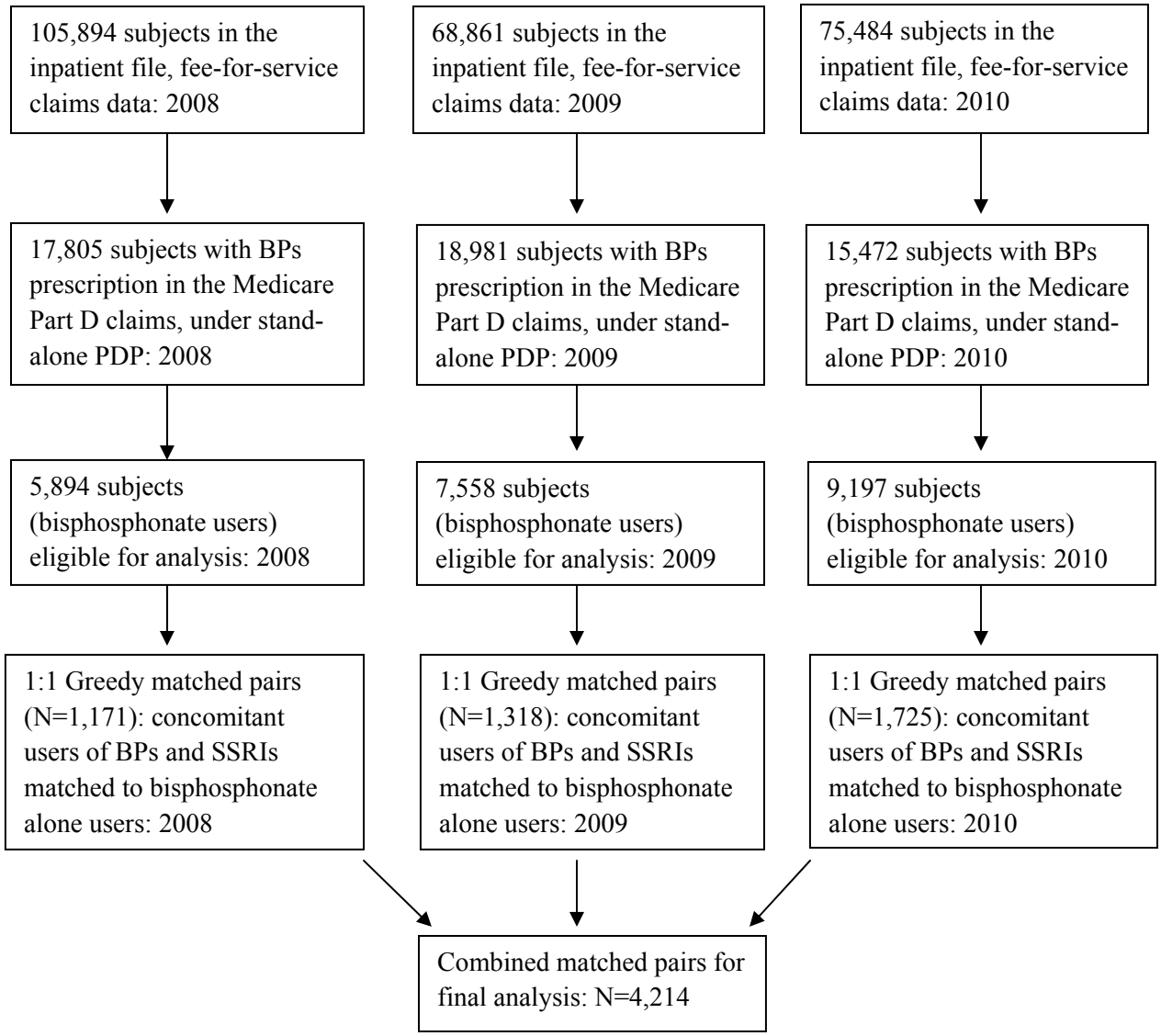

Figure 4.3. Flow chart showing selection of subjects from the Medicare Part A, fee-for-service and Medicare part D, under stand-alone prescription drug plan (Specific Aim 2): 2008-2010.

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Chapter 5

5.0 Specific Aim 1: Results and Discussion

5.1 Descriptive statistics

5.1.1 Overall summary

Descriptive statistics for the study population across the 3 year period are shown in **Table 5.1** and **Table 5.2**. During the time period examined (2008-2010), there were 17,805 (3.5%) patients aged 65 years or older who were bisphosphonate users in 2008, 18,981 (3.8%) patients in 2009, and 15,472 (3.1%) in 2010. Of these bisphosphonate users 28.4% also used SSRIs in 2008, 28.8% in 2009, and 30.7% in 2010 (**Table 5.1**), whereas 6.7% used SNRIs in 2008, 6.9% in 2009, and 7.5% in 2010 (**Table 5.2**).

Table 5.1: Descriptive statistics of Medicare PDP concomitant users of BPs and SSRIs.

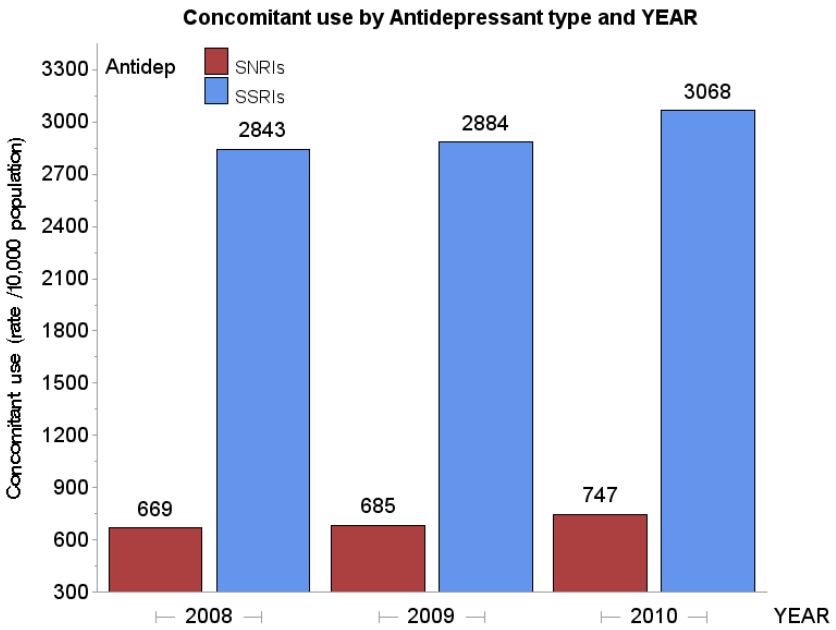
Characteristic	2008	2009	2010
Composite PDP Enrollees, n	510,861	504,574	502,966
Bisphosphonate users, n (%)	17,805 (3.5)	18,981 (3.8)	15,472 (3.1)
Concomitant users, n (%)	5061 (28.4)	5474 (28.8)	4746 (30.7)
Age, n (%)			
65-69	557 (11.0)	692 (12.6)	634 (13.4)
70-74	828 (16.4)	852 (15.6)	713 (15.0)
75-79	959 (18.9)	997 (18.2)	865 (18.2)
80-84	1109 (21.9)	1214 (22.2)	1012 (21.3)
85+	1608 (31.8)	1719 (31.4)	1522 (32.1)
Race, n (%)			
White	4366 (86.2)	4730 (86.4)	4013 (84.6)
Black	165 (3.3)	181 (3.3)	175 (3.7)
Hispanic	389 (7.7)	429 (7.8)	409 (8.6)
Other	141 (2.8)	134 (2.5)	149 (3.1)
Socioeconomic status, n (%)			
Low	2443 (48.3)	2706 (49.4)	2462 (51.9)
High	2618 (51.7)	2768 (50.6)	2284 (48.1)

Abbreviations: PDPs, Medicare stand-alone prescription drug plans

Table 5.2. Concomitant use of bisphophonates and SNRIs.

Characteristic	2008	2009	2010
Composite PDP Enrollees, n	510,861	504,574	502,966
Bisphosphonate users, n (%)	17,805 (3.5)	18,981 (3.8)	15,472 (3.1)
Concomitant users, n (%)	1191 (6.7)	1300 (6.9)	1155 (7.5)
Age, n (%)			
65-69	189 (15.8)	214 (16.5)	237 (20.5)
70-74	220 (18.5)	238 (18.3)	213 (18.4)
75-79	225 (18.9)	260 (20.0)	210 (18.2)
80-84	265 (22.3)	264 (20.3)	225 (19.5)
85+	292 (24.5)	324 (24.9)	270 (23.4)
Race, n (%)			
White	1049 (88.1)	1125 (86.5)	1013 (87.7)
Black	33 (2.8)	34 (2.6)	34 (2.9)
Hispanic	73 (6.1)	100 (7.7)	82 (7.1)
Other	36 (3.0)	41 (3.2)	26 (2.3)
Socioeconomic status, n (%)			
Low	577 (48.5)	679 (52.2)	618 (53.5)
High	614 (51.5)	621 (47.8)	537 (46.5)

It appears that concomitant use of bisphosphonates and SSRIs/SNRIs among Medicare beneficiaries increased from 2008 through 2010, but utilization was observed to be more prevalent among SSRI than SNRI users (**Figure 5.1**). Among those patients who were bisphosphonate users, the proportions of SSRI use in the year 2010 was 2.3% points higher than in the year 2008 (30.7% vs. 28.4%) and 1.9% points higher than in the year 2009 (30.7% vs. 28.8%). On the other hand, the proportions of SNRI use in the year 2010 was 0.8% points higher than in the year 2008 (7.5% vs. 6.7%) and 0.6% points higher than in the year 2009 (7.5% vs. 6.9%). However, linear trends in the standardized rates (**Table 5.3** and **Table 5.4**) were not statistically significant and thus no evidence for change in concomitant use of bisphosphonates and SSRIs (slope: +112.5, *p-value*: 0.2227) or SNRIs (slope: +38.8, *p-value*: 0.2082) from 2008 to 2010. This may not be surprising since a 3-year period is relatively short.



Abbreviations: Antidep, antidepressant

Figure 5.1. Overall concomitant use of bisphosphonates and SSRIs or SNRIs.

Table 5.3: Concomitant use of bisphosphonates (BPs) and SSRIs rates.

	BPs + SSRIs users	**All BPs users**	**Rate/10,000**	**95% CI**
2008	5061	17,805	2842.5	2764.2-2920.8
2009	5474	18,981	2883.9	2807.5-2960.3
2010	4746	15,472	3067.5	2980.2-3154.8

Rate=2706.3 + 112.5year; *p-value*=0.2227

Table 5.4: Concomitant use of bisphosphonates and SNRIs rates.

	BPs + SSRIs users	**All BPs users**	**Rate/10,000**	**95% CI**
2008	1191	17,805	668.9	630.9-706.9
2009	1300	18,981	684.9	647.7-722.1
2010	1155	15,472	746.5	703.1-789.6

Rate=622.5 + 38.8year; *p-value*=0.2082

Summary of concomitant use by demographic subgroups showed variations in concomitant use across the 3 years by age, socioeconomic status (SES), race, and geographic location (by states). Notably, concomitant use showed an increasing trend with increasing age,

concomitant use increased among those of low SES but showed decreasing trend among those of higher SES over time, and overall concomitant use was highest among white women compared to other races. However, these differences were more pronounced for concomitant use of bisphosphonates and SSRIs than with SNRIs. Small proportions of concomitant use (especially with SNRIs) as well as usage by race which were highly skewed were not described further in detail. Therefore, following is a further description of concomitant use of bisphosphonates and SSRIs by selected demographic characteristics (age, SES, and geographic location).

5.1.2 Concomitant use by age

Overall, we observed a steady and increasing trend of concomitant use across the 5 age groups and across the 3 years (**Figure 5.2**). Older adults over 85 years or older were about 2.5 times as likely to have used bisphosphonates and SSRIs as those who were 65-69 years old (31.8% vs. 11.0% in 2008, 31.4% vs. 12.6% in 2009, and 32.1% vs. 13.4% in 2010). Findings from the year to year trend within age groups showed that concomitant use increased from 2008 to 2010 for the 65-69 age groups, but we observed unstructured pattern of concomitant use for other age groups across the 3 years.

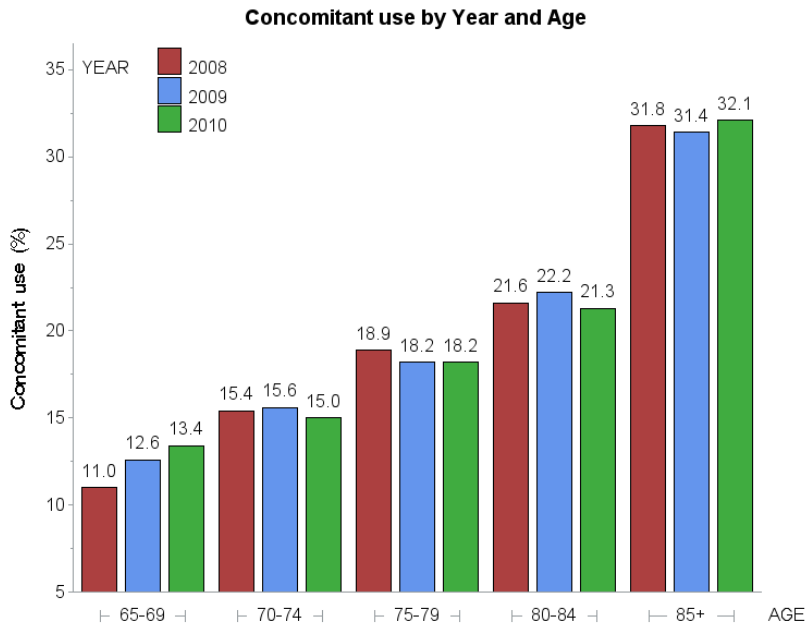


Figure 5.2. Proportions of concomitant use by age.

5.1.3 Concomitant use by socioeconomic status and age

We observed that concomitant use varied by SES and also by age within the two groups of SES (**Figure 5.3**). For all ages, concomitant use was slightly higher among women of higher SES (50.2%) than those of lower SES (49.8%). In terms of trend, we observed increasing pattern of concomitant use across age groups for those of higher SES, but decreasing pattern for those of lower SES. The proportions ranged between 56.6% (age group: 65-69) to 46.5% (age group: 85+) among women of lower SES and between 43.4% (age group: 65-69) to 53.5% (age group: 85+) among those women of higher SES. When we observed concomitant use by SES across the 3 year period (**Figure 5.4**), we found that concomitant use among women of lower SES increased (from 48.3% in 2008 to 51.9% in 2010), whereas that of higher SES decreased (from 51.7% in 2008 to 48.1% in 2010) over time.

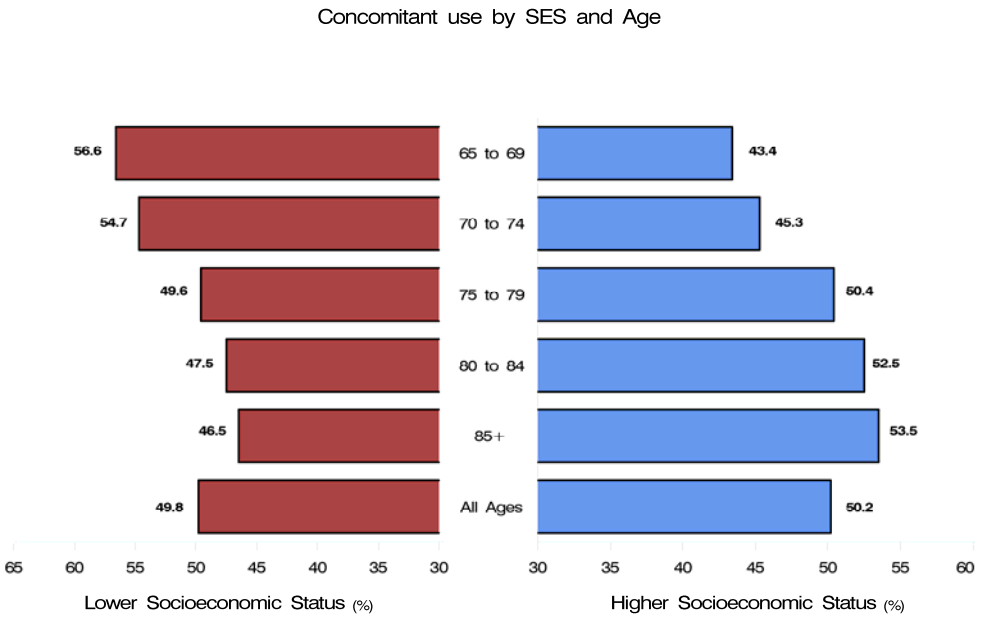


Figure 5.3. Proportions of concomitant use by socioeconomic status and age.

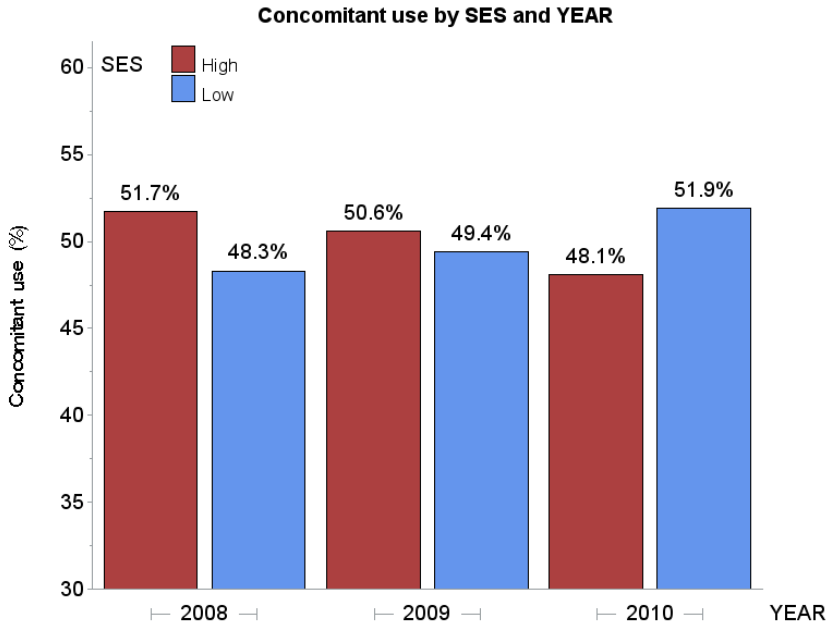


Figure 5.4. Proportions of concomitant use by SES and year of enrollment.

5.1.4 Utilization by state

Overall, we observed that concomitant use of bisphosphonates and SSRIs varied by state (Figure 5.5). The frequency of use appears to be higher in the South and North East regions of the U.S. compared to Western regions of the U.S.

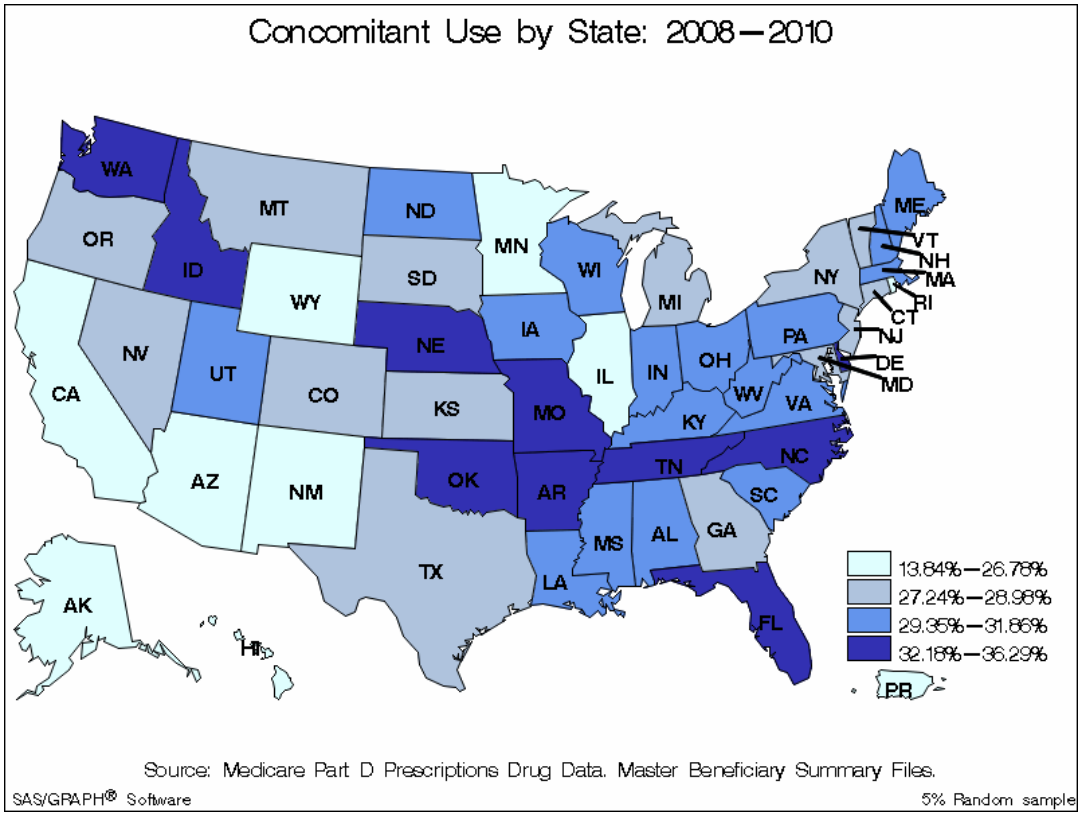
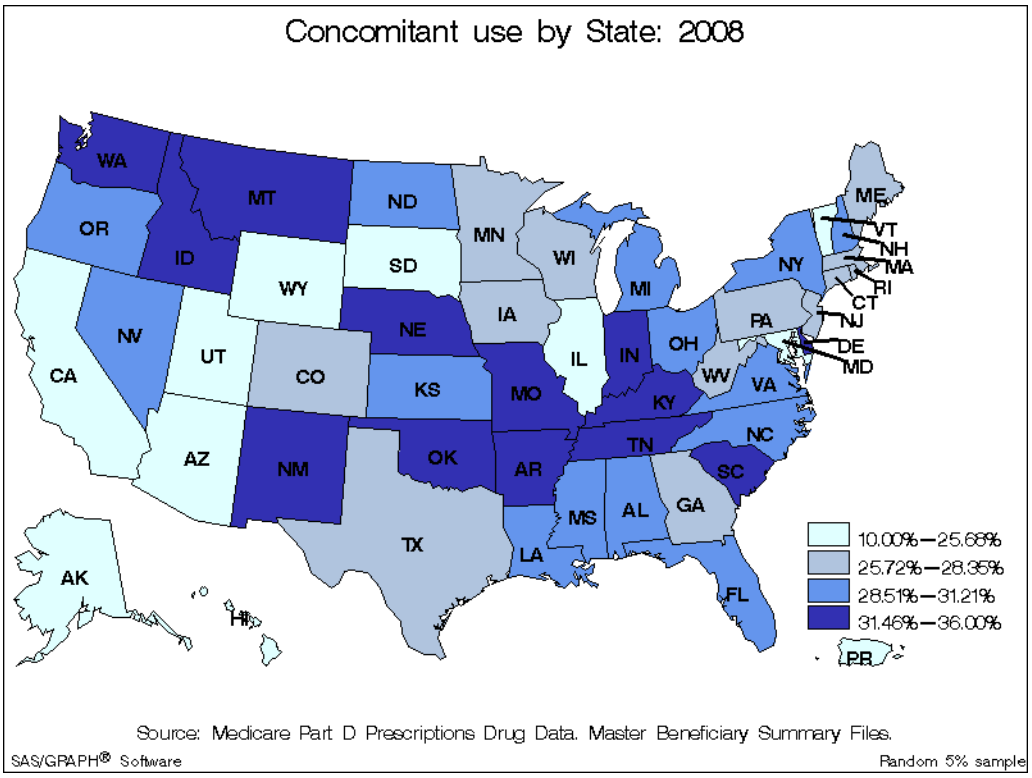


Figure 5.5. Overall variation in concomitant use of bisphosphonates and SSRIs: 2008-2010.

Figures 5.6-5.8 shows the proportion of concomitant and bisphosphonate alone users by state across the 3 year period. The plots are placed side by side for each year. Overall, we observed that the number of Medicare beneficiaries who were bisphosphonate users or were concomitant users varied by states and across the years. Quartile ranking in bisphosphonate use by state for most of the states did not follow a similar pattern as the ranking in concomitant use.

The concomitant use proportions ranged between 10.0%-36.0% in 2008, 14.9%-36.2% in 2009, and 8.7%-49.9% in 2010. The bottom 3 states with the lowest proportion of concomitant users in 2008 were Washington, D.C. (10.0%), Puerto Rico (12.5%), and Hawaii (16.4%) and the top 3 states with the highest proportion of concomitant use were Washington (34.3%), Tennessee (34.5%), and Delaware (36.0%). In 2009, the bottom 3 states were Hawaii (14.9%), Alaska (17.4%), and Washington, D.C. (19.0%) and the top 3 states were West Virginia (34.4%), Missouri (34.9%), and Tennessee (36.2%). In 2010 the bottom 3 states were Puerto Rico (8.7%), New Mexico (20.6%), and Hawaii (20.6%) and the top 3 states were Tennessee (38.5%), Alaska (46.7%), and Idaho (49.0%). Overall, we noted that Hawaii had consistently lower concomitant users in the 3 years, whereas the state of Tennessee had higher and slightly increased over time. These data suggested that concomitant use is influenced by multiple factors that vary from state to state.



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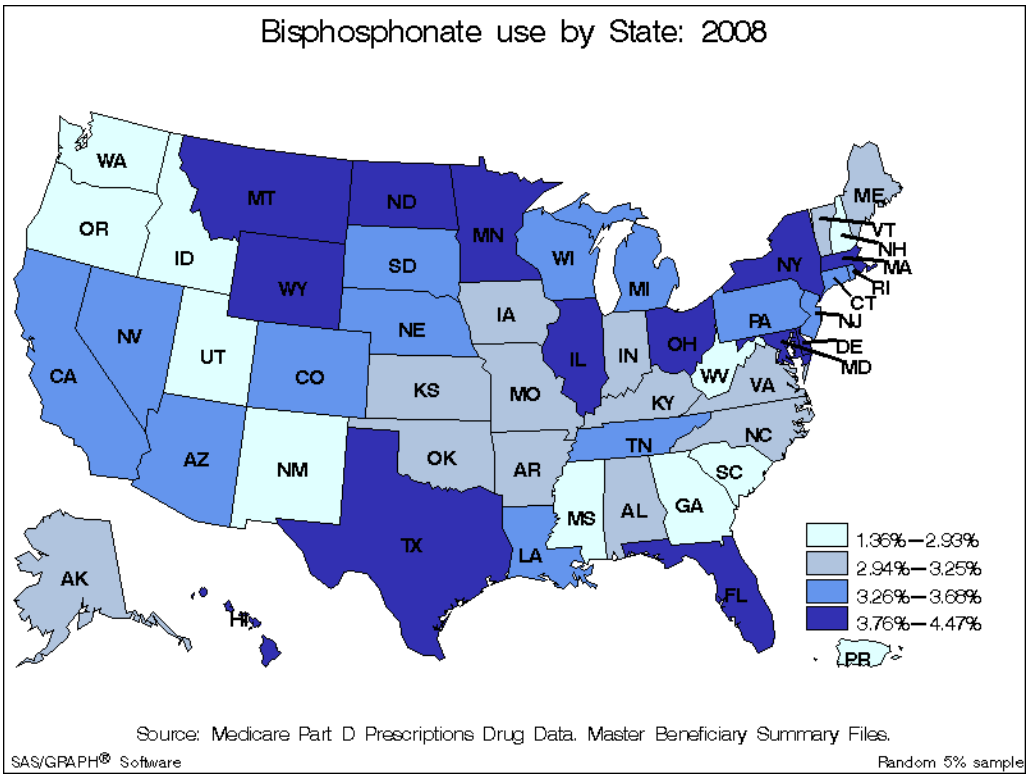
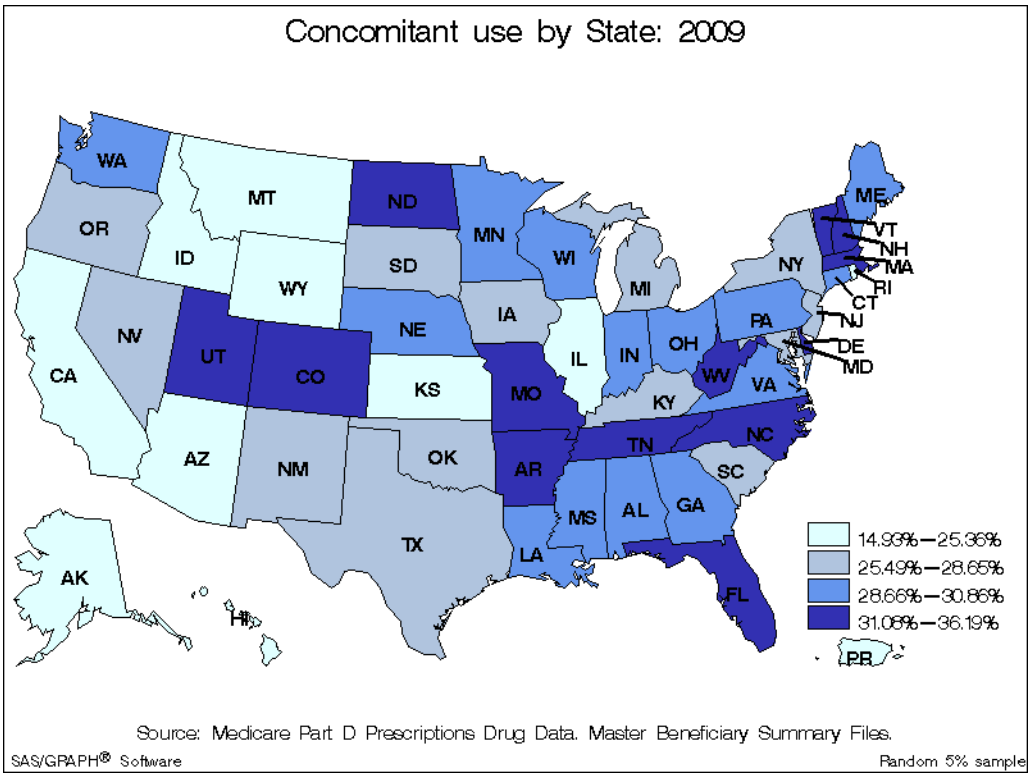


(*b*)

Figure 5.6. Quartiles of concomitant and bisphosphonate alone use by state in 2008. Figure 5.6a shows variation in concomitant use, whereas figure 5.6b shows variation of bisphosphonate use.

(*a*)



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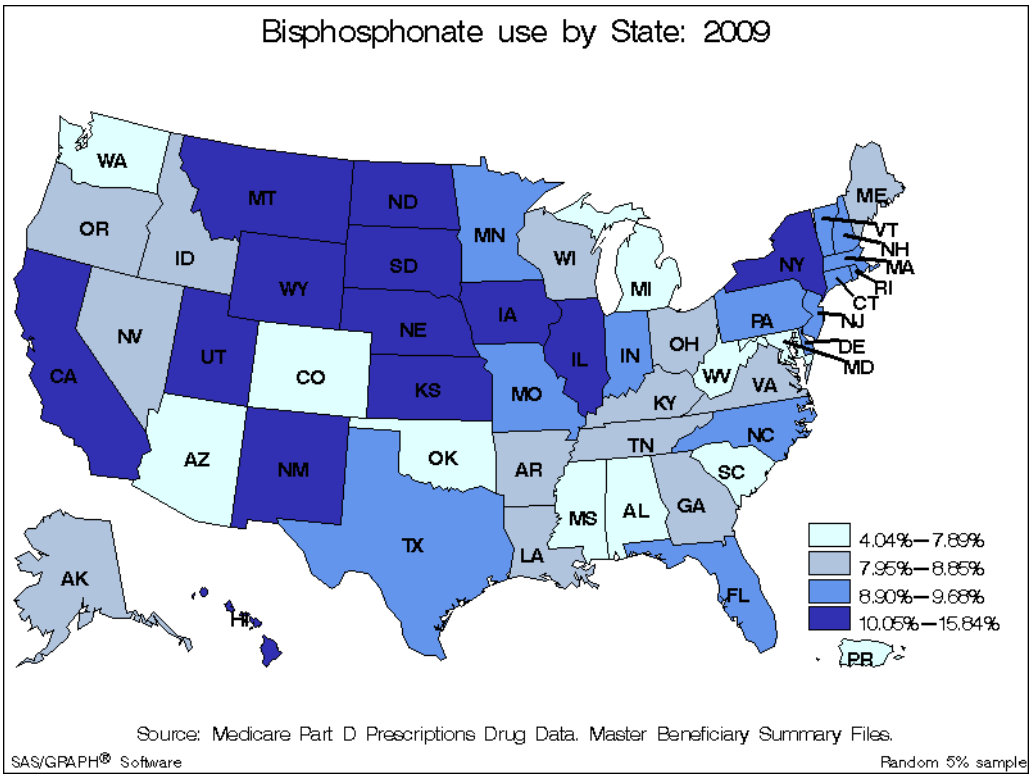
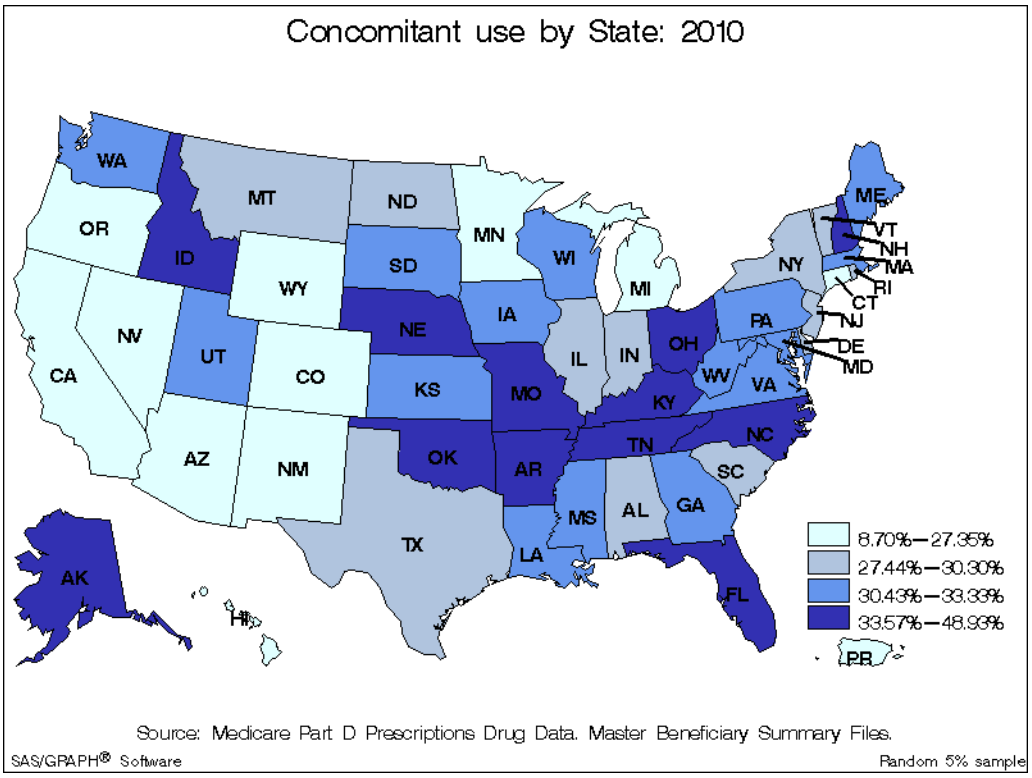


Figure 5.7. Quartiles of concomitant and bisphosphonate alone use by state in 2009. Figure 5.7a shows variation in concomitant use, whereas figure 5.7b shows variation of bisphosphonate use.

(*a*)



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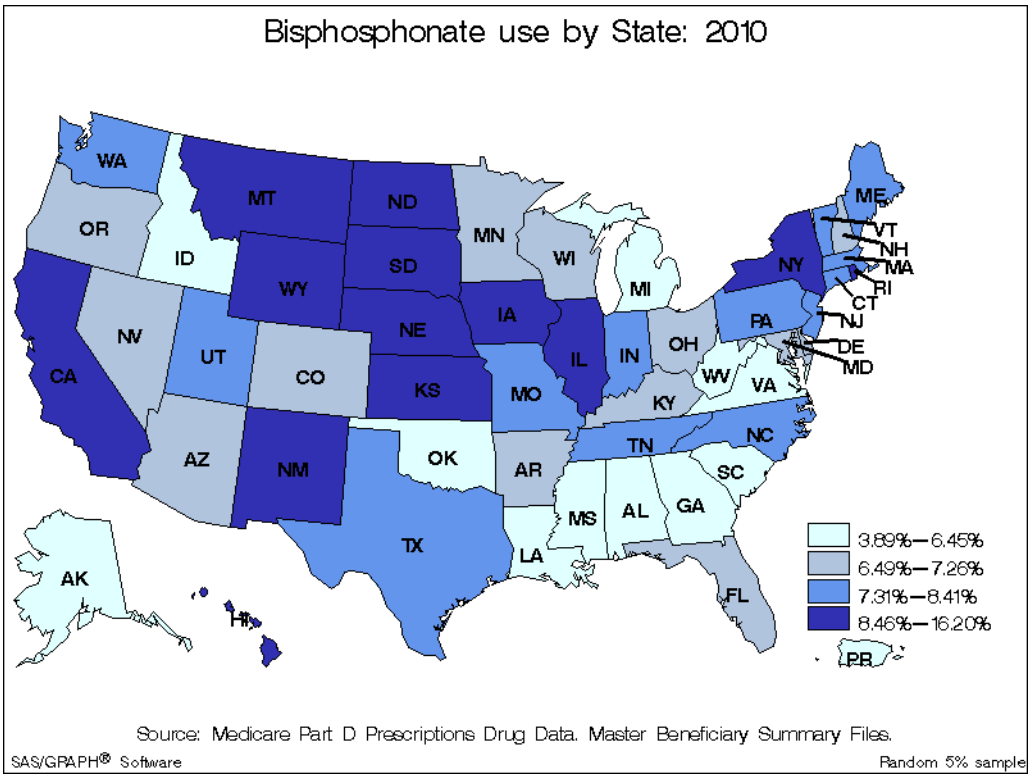

Figure 5.8. Quartiles of concomitant and bisphosphonate alone use by state in 2010. Figure 5.8a shows variation in concomitant use, whereas figure 5.8b shows variation of bisphosphonate use.

5.2 Discussion

This study examined utilization patterns of concomitant use of bisphosphonates and SSRIs among older postmenopausal women from 2008 to 2010. Our findings confirm that concomitant use of bisphosphonates and SSRIs is prevalent. Since this study was limited to Medicare Part D data, indications for these concomitant medications can only be inferred. As indicated earlier bisphosphonates are the most widely FDA-approved pharmacologic agents for treatment of postmenopausal osteoporosis.[1] On the other hand, SSRIs are the most popular medications in treating depression.[2] Therefore our findings suggest that exposure to concomitant use is most likely due to the prevalent comorbid osteoporosis and depression among older postmenopausal women. There is a strong positive relationship between osteoporosis and depression, and both diseases are more prevalent among women than men.[3] Although it is still unclear the association between these two chronic conditions,[3] existing research shows that depression is associated with increased risk for both low bone mineral density and fractures.[4] On the other hand, fractures which can be clinical consequences of osteoporosis can also cause psychological symptoms, most notably depression.[5]

Given the high prevalence of osteoporosis and depression among older women, the use and pattern of concomitant use of bisphosphonates and SSRIs was not surprising. Our findings further showed that concomitant use varied with demographic characteristics, notably age, race, socioeconomic status, and geographic locations in the United States. Medicare beneficiaries under study were more likely to be concomitant users as they aged, if they were of Caucasian race or of higher socioeconomic status. It has been shown that relative to women aged 50-54, the odds of having osteoporosis is 5.9-fold higher in women aged 65-69 and 14.3-fold higher in women aged 75-79.[6] On the other hand, although the prevalence of depression is lower among

older adults than younger people, aging people experience changes in their health and their lifestyles (considered risk factors) that make an older adult more vulnerable to becoming depressed. These risk factors for depression can include changes in physical health or fumctioning, mental health, or circumstances or social support.[7] The increasing trend of osteoporosis with age and the susceptibility of depression with aging are therefore reflective of our findings that concomitant use increases with age.

The higher proportions of concomitant use among the white women could be attributed to the high prevalence of osteoporosis and the propensity to receiving antidepressant treatment compared to minority groups. Osteoporosis is more frequent in white women than other races. In the U.S, the rates of osteoporosis and/or osteoporotic fractures are higher among white women compared to Asian or African American women.[8] Similarly, white race has been found to be a strong predictor of antidepressant use over time. White patients with major depression were found to be more likely than African Americans to receive antidepressant medications.[9] A previous study had also showed that persons from racial or ethnic minority groups were more likely than whites to report major depression and less likely to receive treatment.[10]

The observed concomitant use that varied with socioeconomic status over time was probably influenced by the economic downturn beginning in 2008 and might have impacted cost-related non-adherence among those considered to be of higher SES. This is consistent with a study by Piette et al. that found substantial increase in medication-cost problems was associated with the economic crisis in 2008 especially among chronically ill older adults. Those aged 65 or older reported delayed filling a prescription because of financial reasons despite the availability of Medicare Part D benefits.[11] On the other hand, existing research suggests that socioeconomic status is associated with negative impact on the psychological health of aging

individuals. Those at the lower levels of socioeconomic status are often most likely to be afflicted with disorders such as depression.[12] The financial crisis probably worsened the situation and thus increasing the incidence of depression. Therefore, our findings were consistent with the existing research that patients of low SES were more likely to be prescribed SSRIs for depressive symptoms beginning 2008 and thus having an overall influence on concomitant usage over time. Another explanation that could explain the reversed trend over time is that, the financial crisis beginning in 2008 qualified more beneficiaries to be considered of low SES over time shifting them from higher SES to lower SES.

With regards to the findings for concomitant use by state, the usage pattern primarily indicates that the prevalence of use is a nationwide problem. For some states, however, the prevalence and pattern of use varied across the 3 years. In addition, ranking on quartiles showed that for most of the states the proportions of concomitant use did not parallel the proportions of bisphosphonate alone use suggesting that comorbid osteoporosis and depression varies by state. Because of the haphazard pattern of concomitant and bisphosphonates alone use, it is unclear what factors might have influenced the pattern that we observed. Using secondary analysis results, we did not observe a clear pattern with SES status of the patients across the states. Although it might be obvious that the care that Medicare beneficiaries receive will vary depending on where they live and their physicians and hospitals, more research is needed to investigate predictors of use across states.

Overall, the steady rates (2842.5 per 10,000 populations in 2008, 2883.9/10,000 in 2009, and 3067.5/10,000 in 2010) and non-significant trend of concomitant use did not mirror the count of those females enrolled with Part D coverage provided under PDPs during the same period. Using the CMS reported statistics for the actual proportions of female beneficiaries who

were Part D enrolled for 100% of Medicare beneficiaries during the same period, the female counts dropped in 2009 and then increased sharply in 2010 compared to 2008. The proportions enrolled were 59.5% females in 2008, 59.1% in 2009, and 58.8% in 2010 (**Table 5.5**). [13] Their corresponding estimated counts were 11,192,051 females with Part D coverage under PDPs in 2008, 11,172,347 females in 2009, and 11,304,283 females in 2010. This lack of parallel trend suggests that not only did the prevalence rates of concomitant use of bisphosphonates and SSRIs (a proxy of comorbid osteoporosis and depression prevalence) not change over time, but also was less impacted by changes in population of older postmenopausal women.

Despite the non-significant trend of concomitant use across the 3 years, our findings suggest that large numbers of older postmenopausal women prescribed bisphosphonates are also on SSRIs. These findings were consistent with our preliminary study using MEPS data (see Chapter 3). Following extrapolation of our estimates to all Medicare beneficiaries with Part D coverage under PDPs, our findings suggest that there were 391,721 (3.5%) females who were bisphosphonate users in 2008, 424,549 (3.8%) females in 2009, and 350,432 (3.1%) females in 2010. Of these bisphosphonate users, there were 111,248 (28.4%) females who were also on SSRIs in 2008, 122,270 (28.8%) females in 2009, and 107,582 (30.7%) in 2010. The positive side of this is that patients with potential comorbid osteoporosis and depression are receiving respective therapies for treatment. The National Institute of Mental Health (NIMH) recommends that treatment of depression (commonly using SSRIs or SNRIs) can help patients manage their osteoporosis and improve overall health.[14] The NMIH also adds that while currently available common treatments for depression are generally well tolerated and safe, some medications, including some antidepressants (such as SSRIs or SNRIs), can increase a patient's risk for osteoporosis.[14]

Table 5.5. CMS Chronic Condition Data Warehouse: Medicare Part D Beneficiary Counts for 2008 through 2010.

Beneficiary Demographics	2008	2009	2010
Part D Enrolled			
Total	27,529,528	28,722,645	29,740,680
Part D Plan Type			
PDP	18,810,171	18,904,141	19,224,972
Gender			
Female, n (%)	16,377,483 (59.5)	16,976,321 (59.1)	17,493,688 (58.8)
Age			
65-74	10,966,227	11,591,840	12,069,321
75-84	7,674,907	7,855,991	7,995,935
85+	3,575,116	3,704,040	3,813,281

Selective serotonin reuptake inhibitors or SNRIs have been documented to be associated with increasing a patient's risk for osteoporosis. Two meta-analysis studies have summarized these findings. Wu et al. results showed that overall, SSRIs use was associated with a significantly increased risk of fracture (RR=1.72;95% CI, 1.51-1.95).[15] Eom et al. in a meta-analysis based on 12-observational studies showed that the overall risk of fracture was higher among people using SSRIs (adjusted OR=1.69, 95% CI 1.51-1.90).[16] This evidence is troubling especially considering that the patients in reference are those already on bisphosphonates or will be prescribed bisphosphonates at some point in their lifetime. This situation presents a prime example of potentially risky bisphosphonate-drug combinations with potential interaction resulting in increased risk of fracture.

Although there is a paucity of documented reports on these particular interactions, research has suggested that medications associated with increased risk of fracture might attenuate the beneficial effects of bisphosphonates when used concomitantly. Concerns about this phenomenon has focused on medications such as proton pump inhibitors[17,18], glucocorticoids[19,20], and levothyroxine[21], but the interaction of bisphosphonates and SSRIs or SNRIs has not been

investigated yet. The common aspect about proton pump inhibitors, glucocorticoids, levothyroxine, and SSRIs is that all of these medications are associated with increased risk of fracture.[1] So, SSRIs or SNRIs also have the potential of demonstrating similar attenuating effects, but this phenomenon in currently unknown. Animal studies have shown that increased levels of nuclear factor kappa ligand (RANKL) due to high blood levels of serotonin significantly attenuated (or antagonized) the ability of clodronate and alendronate to induce osteoclast apoptosis and inhibit bone resorption.[22] In normal bone remodeling in healthy physiologic systems, bone stromal cells, including cells of the osteoblast lineage, provide a limited amount of RANKL, which leads to osteoclast differentiation, survival, and activation and subsequent bone resorption. Resorption is balanced by osteoblast-dependent new bone formation.[23] Clearly we can see that there is need for randomized clinical trials or observational studies to investigate further the interaction between bisphosphonates and SSRIs. The evidence following this research will be important to the clinicians and the older adult patients with comorbid osteoporosis and depression to aid in developing optimal care strategies. When presented with patients with osteoporosis and other comorbidies (such as depression), the clinician should consider the common disease-disease and drug-disease interactions, and screen for or treat these as appropriate to the patient's goals and preferences.[24]

Similarly, The American Geriatrics Society expert panel has documented an approach by which clinicians can care optimally for older adults with multimorbidity (multiple chronic conditions). In this document the society acknowledges that clinicians need a better management approach to clinical decision- making. One example of such an approach would require an assessment of patient preferences for all clinical decisions. The first step in the process of eliciting patient preference is to recognize when the older adult with multimorbidity is facing a

"preference sensitive" decision. In this step the clinician tries to understand what is most important to the patient to determine the best option.[25] An example would be medications that may improve one condition but make coexisting condition worse for example inhaled corticosteroids to treat chronic obstructive pulmonary disease may worsen osteoporosis.[26] Clearly, the tradeoff between managing depressive symptoms and worsening osteoporosis varies from patient to patient. Given supportive evidence from research about whether SSRIs may worsen osteoporosis when given concomitantly with bisphosphonates, clinicians will have new information that will aid optimal care for these patients. More emphasis for optimal care will be among postmenopausal women as they advance in age, those who are of white race, and/or of low socioeconomic status.

5.2.1 Strengths and limitations of the study

5.2.1.1 Strengths

The strengths of our study are that to the best of our knowledge, this study is the first to describe concomitant use of bisphosphonates and SSRIs or SNRIs among older postmenopausal women. Also this study used Medicare Part D data, which is a large national database with prescription drug data primarily for older adults 65 years or older. Therefore this dataset was suitable to describe national estimates of medications use for older postmenopausal women 65 years or older and are more generalizable.

5.2.1.2 Limitations

The use of Medicare Part D data, like other administrative databases is faced with methodological challenges such as verifying data validity. A central limitation with many implications is that such databases are collected for administrative rather than research purposes. These limitations are an important source of bias. For example the complexity of preparing

claims data (prescribing, dispensing, and the third party payer adjudication and entering into the computer system for billing purposes) can result in misclassification bias. Misclassification of bisphosphonate or SSRIs or SNRIs could bias estimates of proportions of concomitant use in this study.

Another bias introduced into the Medicare Part D data that is a limitation to our findings is the bias of limited generalizability and information bias. This bias is a limitation because of the assumption that the dataset is accurate and also that the data includes every encounter with health professionals. Generalizability or external validity is defined as the validity of the inferences as they pertain to people outside the source population.[27] In this study the referred people outside the source population are those women aged ≥ 65 years old but are not Medicare part D beneficiaries. By using Medicare Part D data, we have made the assumption that the database captures every encounter of women aged ≥ 65 years. Although Medicare Part D offers prescription coverage to all those eligible for Medicare, not all beneficiaries are enrolled in a part D plan. Of those who were Medicare eligible between 2008 and 2010, 57.5% were enrolled in a part D plan in 2008, 58.7% in 2009, and 59.4% in 2010. The rest were not covered by part D and with no credible coverage or with other credible coverage, or were enrolled in retirement drug subsidy.[13] Credible coverage sources are required to have approval from Medicare as being equivalent or better than part D plans. Examples include the U.S. Department of Veterans Affairs, the military health plan (TRICARE), the Federal Employees' Health Benefits (FEHB) or are active workers under employer sponsored programs.

Furthermore, our findings may not be generalizable to all women ≥ 65 years old including the more affluent and employed and also those who might be healthier. The healthier lifestyle could be promoted by insurance under the wellness programs- a feature of the consumer

driven healthcare which is typical for the employed.[28] Finally, exclusion of men in our study can also be considered a limitation of generazability to the entire older adult population. Although comorbid osteoporosis and depression is more prevalent among women than men,[3] the safety of concomitant use of bisphosphonates and SSRIs or SNRIs is as important to men as it is to women.

5.3 Conclusions

In summary, this study determined that concomitant use of bisphosphonates and SSRIs is prevalent and varies with demographic characteristics and geographic location in the U.S. Concomitant use seems to increase with aging, among the white race and those who are of low socioeconomic status. The prevalence and variation of concomitant use is troubling because of the potential interaction between SSRIs and bisphosphonates with potential antifracture efficacy of bisphosphonates. With this growing concern, understanding the number of patients exposed to the concurrent medication use will be used to initiate further studies to assess the potential consequence of the problem, if any. Given that the population of older adults is high and is projected to increase in the future, the prevalence of use is expected to grow exponentially and the associated economic impact of antifracture efficacy of bisphosphonates on the U.S. healthcare system will be enormous. Potential antifracture efficacy will result in worsened osteoporosis and greater risk of fractures suggesting more hospitalizations for expensive bone related procedures, and wasted resources on prescriptions that are suboptimal. This underscores the need for research to investigate the effect of SSRIs on the beneficial effects of bisphosphonates which may be useful for physicians to integrate in clinical decision-making for optimal care of older postmenopausal women with multimorbidity.

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Chapter 6

6.0 Specific Aim 2: Results and Discussion

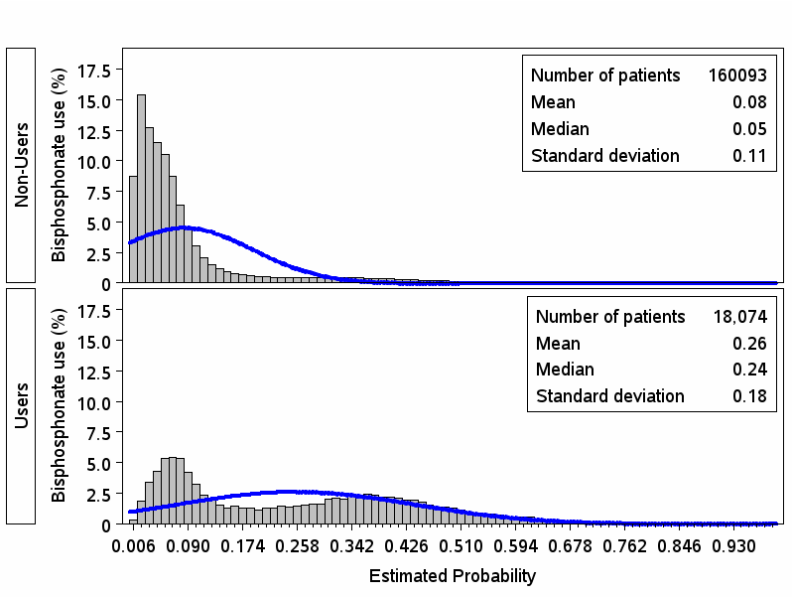
6.1 Bisphosphonates and fracture reduction

6.1.1 Matching process and patient characteristics

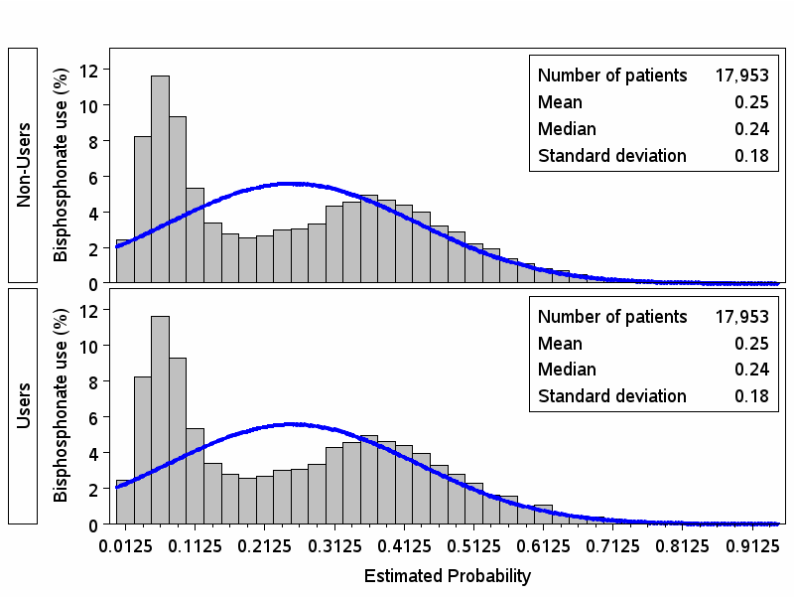
A total of 178,167 postmenopausal female Medicare beneficiaries between 2008 and 2010 were eligible for analysis after application of the inclusion and exclusion criteria. Of these Medicare beneficiaries, 18,074 were bisphosphonate (BP) users. **Figure 6.1a** shows the distributions of propensity scores for the 160,093 BP non-users and the 18,074 BP users before matching. We can see that the distribution before matching shows a good discrimination between the two groups of patients. The distributions of propensity scores between the two groups after 1:1 matching are shown in **Figure 6.1b**. The distributions of the propensity scores for the matched groups were similar suggesting that treated subjects (BP users) are similar to the control subjects (BP non-users) with respect to background variables (or covariates) measured on all subjects, as would be expected in a randomized experiment. Thus, two matched subjects (one in treated and one in control group), with the same propensity score, are imagined to be 'randomly' assigned to each group in the sense of being equally likely to be treated or control.[1] Previous research has demonstrated that matching on propensity score can result in a greater reduction in treatment selection bias than stratification on propensity score.[2]

Table 6.1 shows the baseline characteristics of the two groups after matching and the standardized differences (<0.1) between them. The average age of those who were BP users was 80.6 ± 7.7 (SD) years and that of BP non-users was 80.8 ± 8.4 (SD) years. For both treatment

groups, there were more white women than other minority races and also within the age groups, the proportions of older adults 85 years or older was the highest compared to other age groups. The proportions of both BP users and non-users were higher for women of higher socioeconomic status and lower for those of lower socioeconomic status.



(6.1a)



(6.1b)

Figure 6.1. Distribution of propensity scores: (6.1a) shows the distribution for 178,167 patients before matching and (6.1b) shows the distribution for 17,953 patients after matching. The curved lines are normal distribution curves.

Table 6.1. Baseline patient characteristics of propensity score matched cohort.

Characteristic	Bisphosphonate users (N=17,953)	Bisphosphonate non-users (N=17,953)	Standardized differences
Demographic			
Age , mean ± SD	80.6 (7.7)	80.8 (8.4)	0.021
65-69	1706 (9.5)	2079 (11.6)	
70-74	2638 (14.7)	2548 (14.2)	
75-79	3476 (19.4)	3228 (18.0)	
80-84	4193 (23.4)	3779 (21.1)	
85+	5940 (33.1)	6319 (35.2)	
Race, n (%)			
White	14928 (83.2)	15187 (84.6)	
Black	905 (5.0)	809 (4.5)	
Hispanic	1170 (6.5)	1114 (6.2)	
Other	950 (5.3)	843 (4.7)	
Socioeconomic status, n (%)			
Low income	6794 (37.8)	6605 (36.8)	
Higher income	11159 (62.2)	11348 (63.2)	
Health care utilization factors, mean (SD)			
Comorbidity score	2.2 (2.0)	2.2 (2.0)	0.001
Number of unique prescribed medications	12.2 (6.7)	12.3 (7.5)	0.002
Medical conditions, n (%)			
Osteoporosis	10494 (58.5)	10453 (58.2)	0.005
Rheumatoid arthritis/ Osteoarthritis	10206 (56.9)	10279 (57.3)	0.008
Depression	3095 (17.2)	3059 (17.0)	0.005
Hyperparathyroidism	4838 (27.0)	4775 (26.6)	0.008
Kidney disease	4680 (26.1)	4661 (26.0)	0.002
Diabetes mellitus	5499 (30.6)	5366 (29.9)	0.016
Chronic obstructive pulmonary disease	4651 (25.9)	4693 (26.1)	0.005
Congestive heart failure	6435 (35.8)	6493 (36.2)	0.007
Hypertension	15701 (87.5)	15645 (87.1)	0.009
Anxiety	474 (2.6)	467 (2.6)	0.002
Parkinson's disease	260 (1.5)	233 (1.3)	0.013
Alzheimer's disease	1994 (11.1)	1883 (10.5)	0.02
Epilepsy	260 (1.5)	252 (1.4)	0.004
Orthostatic hypotension	726 (4.0)	737 (4.1)	0.003
Medications, n (%)			
Oral glucocorticoid use	4217 (23.5)	4257 (23.7)	0.005
Proton pump inhibitor use	6124 (34.1)	6161 (34.3)	0.004
Aromatase inhibitors	413 (2.3)	408 (2.3)	0.002
Thiazolidinediones use	674 (3.8)	692 (3.9)	0.005
Hormone replacement therapy	1284 (7.2)	1292 (7.2)	0.002
Antihypertensive use	11306 (63.0)	11415 (63.6)	0.013
Anticonvulsant use	2795 (15.6)	2831 (15.8)	0.006
Thyroid medication use	4862 (27.1)	4864 (27.1)	0.0
Warfarin use	2531 (14.1)	2514 (14.0)	0.003
Loop diuretic use	4781 (26.6)	4846 (27.0)	0.008
Opioid use	7382 (41.1)	7535 (42.0)	0.017
Antipsychotics use	824 (4.6)	814 (4.5)	0.003
Lithium	41 (0.2)	37 (0.2)	0.005
Methotrexate	467 (2.6)	429 (2.4)	0.014

6.1.2 Bisphosphonates use and risk of fracture: Minor findings

Table 6.2. Cox proportional hazard model for risk of fractures among BP users and non-users.

	Non-Bisphosphonate users	Bisphosphonate users
Total number of patients	17,953	17,953
Any fracture		
Total events	1031	922
Hazard Ratio (95% CI)	1.00 (Reference)	0.89 (0.81, 0.97)
Hip/Pelvis/Femur fracture		
Total events	678	592
Hazard Ratio (95% CI)	1.00 (Reference)	0.87 (0.77, 0.97)
Vertebral fracture		
Total events	164	153
Hazard Ratio (95% CI)	1.00 (Reference)	0.93 (0.75, 1.16)
Humerus		
Total events	80	75
Hazard Ratio (95% CI)	1.00 (Reference)	-
Radius/Ulna		
Total events	39	41
Hazard Ratio (95% CI)	1.00 (Reference)	-
Tibia/Fibula		
Total events	70	61
Hazard Ratio (95% CI)	1.00 (Reference)	-

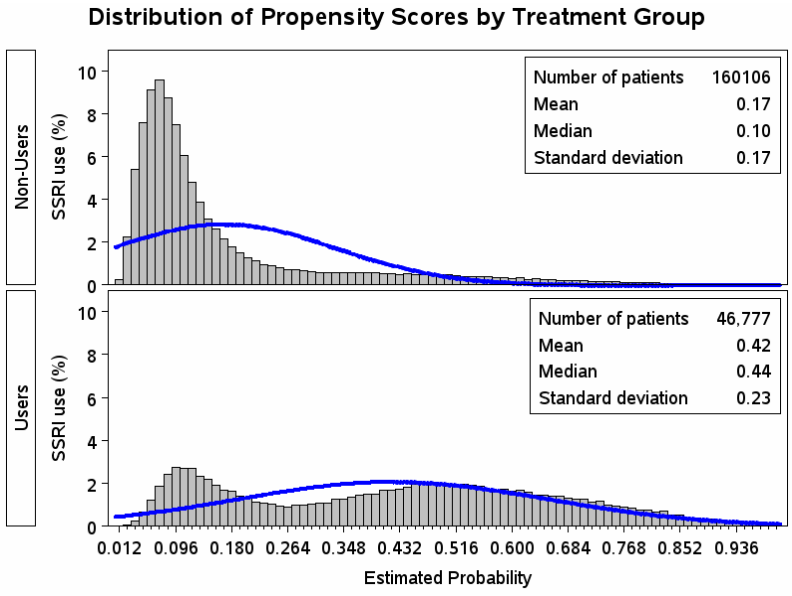
Table 6.2 presents results from the Cox proportional hazards model. Among the propensity score matched patients, 922 bisphosphonate users experienced at least one first fracture of the hip, vertebral, humerus, radius/ulna, or tibia/fibula, whereas 1,031 BP non-users experienced at least one first fracture during the 3 year period (2008 – 2010). Of these patients, 592 BP users and 678 BP non-users experienced a hip fracture.

With regards to the hazard ratios, we observed that BP use was associated with statistically significant reduction of any fracture (HR=0.89, 95% CI, 0.81-0.97) and hip fracture (HR=0.87, 95% CI, 0.77-0.97), and statistically non-significant reduction for vertebral fracture (HR=0.93, 95% CI, 0.75-1.16). There were no results obtained for the humerus, radius/ulna, or tibia/fibula fractures because of very small sample size.

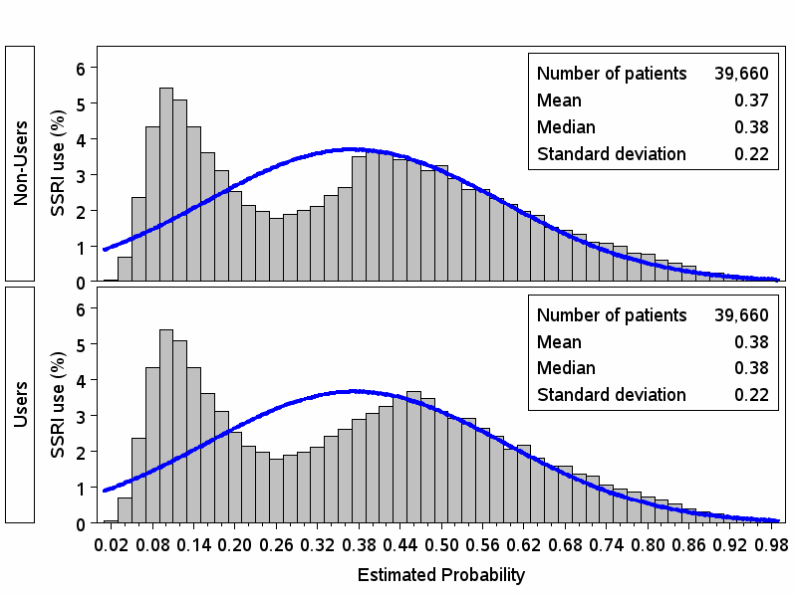
6.2 SSRIs and increased risk of fracture

6.2.1 Matching process and patient characteristics

A total of 206,883 postmenopausal female Medicare beneficiaries between 2008 and 2010 were eligible for analysis after application of the inclusion and exclusion criteria. Of these Medicare beneficiaries, 46,777 were SSRI users. **Figure 6.2a** shows the distributions of propensity scores for the 160,106 SSRI non-users and the 46,777 SSRI users before matching. We can see that the distribution before matching shows a good discrimination between the two groups of patients. The mean age was 79.0 ± 8.4 (SD) years for SSRI users and 79.3 ± 8.5 (SD) years for SSRI non-users. The distributions of propensity scores between the two groups after 1:1 matching are shown in **Figure 6.2b**. The mean age was 79.1 ± 8.5 (SD) years for SSRI users and 79.1 ± 8.4 (SD) years for SSRI non-users. **Table 6.3** shows the baseline characteristics of the two groups after matching and the standardized differences between them. All the standardized differences were < 0.10 suggesting a balance between the two groups on observed covariates.



(6.2a)



(6.2b)

Figure 6.2. Distribution of propensity scores: (6.2a) shows the distribution for 206,883 patients before matching and (6.2b) shows the distribution for 39,660 patients after matching.

6.2.2 SSRI use and increased risk of fracture: Minor findings

Our findings showed that SSRI use was associated with statistically significant increased risk for any fracture (HR=1.17, 95% CI, 1.09-1.26), hip fracture (HR=1.16, 95% CI, 1.06-1.26), and for Tibia/fibula fracture (HR=1.33, 95% CI, 1.05-1.68). We also observed increased risk for vertebral fracture (HR=1.10, 95% CI, 0.89-1.36), but statistical significance was not achieved. (see **Table 6.4**)

Table 6.3. Baseline patient characteristics of propensity score matched cohort.

Characteristic	SSRI users (N=39,660)	SSRI Non-users (N=39,660)	Standardized differences
Demographic			
Age , mean ± SD	79.1 (8.5)	79.1 (8.4)	0.002
65-69	6609 (16.7)	6392 (16.1)	
70-74	6677 (16.8)	6708 (16.9)	
75-79	7148 (18.0)	7354 (18.5)	
80-84	7651 (19.3)	7756 (19.6)	
85+	11575 (29.2)	11450 (28.9)	
Race, n (%)			
White	33859 (85.4)	34067 (85.9)	
Black	2838 (7.2)	2784 (7.0)	
Hispanic	2286 (5.8)	2204 (5.6)	
Other	677 (1.7)	605 (1.5)	
Socioeconomic status, n (%)			
Low income	19691 (49.6)	19550 (49.3)	
Higher income	19969 (51.4)	20110 (50.7)	
Health care utilization factors, mean(SD)			
Comorbidity score	2.6 (2.1)	2.6 (2.1)	0.001
Number of unique prescribed medications	13.4 (6.8)	13.3 (7.6)	0.023
Medical conditions, n (%)			
Osteoporosis	6286 (15.9)	6219 (15.7)	0.005
Rheumatoid arthritis/ Osteoarthritis	21660 (54.6)	21626 (54.3)	0.002
Depression	23483 (59.2)	23660 (59.7)	0.009
Hyperparathyroidism	10711 (27.0)	10760 (27.1)	0.003
Kidney disease	12456 (31.4)	12481 (31.5)	0.001
Diabetes mellitus	16621 (41.9)	16671 (42.0)	0.003
Chronic obstructive pulmonary disease	12770 (32.2)	12898 (32.5)	0.007
Congestive heart failure	17418 (43.9)	17406 (43.9)	0.001
Hypertension	35614 (89.8)	35668 (89.9)	0.005
Anxiety	2114 (5.3)	2239 (5.7)	0.014
Parkinson's disease	780 (2.0)	738 (1.9)	0.008
Alzheimer's disease	7829 (19.4)	7736 (19.5)	0.006
Epilepsy	651 (1.6)	642 (1.6)	0.002
Orthostatic hypotension	1542 (3.9)	1539 (3.9)	0.0
Medications, n (%)			
Oral glucocorticoid use	9118 (22.9)	9093 (22.9)	0.001
Proton pump inhibitor use	16800 (42.4)	16849 (42.5)	0.002
Aromatase inhibitors	538 (1.4)	537 (1.4)	0.0
Thiazolidinediones use	1866 (4.7)	1856 (4.7)	0.001
Hormone replacement therapy	2878 (7.2)	2957 (7.5)	0.008
Antihypertensive use	25204 (63.6)	25470 (64.2)	0.014
Anticonvulsant use	8138 (20.5)	8301 (20.9)	0.01
Thyroid medication use	11247 (28.4)	11304 (28.5)	0.003
Warfarin use	5691 (14.4)	5736 (14.5)	0.003
Loop diuretic use	13455 (33.9)	13437 (33.9)	0.001
Opioid use	18991 (47.9)	19120 (48.2)	0.007
Antipsychotic use	4942 (12.4)	4643 (11.7)	0.023
Lithium	155 (0.4)	177 (0.5)	0.009
Methotrexate	432 (1.1)	443 (1.1)	0.003

Table 6.4. Cox proportional hazard model for risk of fractures among SSRI users and non-users.

	SSRI non-users	SSRI users
Total number of patients	39,660	39,660
Any Fracture		
Total events	1,443	1,675
Hazard Ratio (95% CI)	1.00 (Reference)	1.17 (1.09, 1.26)
Hip/Pelvis/Femur fracture		
Total events	994	1,141
Hazard Ratio (95% CI)	1.00 (Reference)	1.16 (1.06, 1.26)
Vertebral fracture		
Total events	163	179
Hazard Ratio (95% CI)	1.00 (Reference)	1.10 (0.89, 1.36)
Humerus		
Total events	116	143
Hazard Ratio (95% CI)	1.00 (Reference)	1.23 (0.97, 1.58)
Radius/Ulna		
Total events	51	54
Hazard Ratio (95% CI)	1.00 (Reference)	-
Tibia/Fibula		
Total events	119	158
Hazard Ratio (95% CI)	1.00 (Reference)	1.33 (1.05, 1.68)

6.3 Concomitant use of bisphosphonates and SSRIs and increased risk of fracture

6.3.1 Matching process and patient characteristics

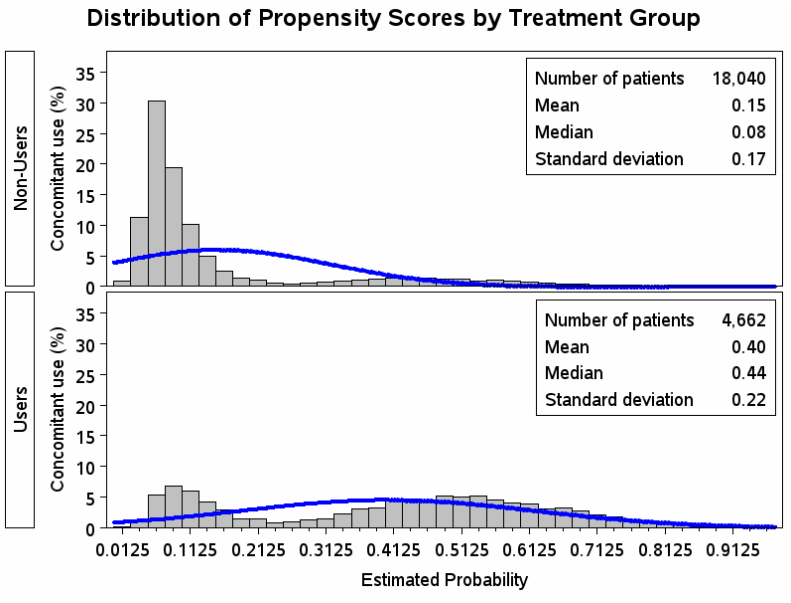
A total of 22,702 postmenopausal female Medicare beneficiaries who were BP users between 2008 and 2010 were identified after application of the inclusion and exclusion criteria. Alendronate (overall: 61.9%), 70 mg (58.2%) was the most frequently prescribed BP followed by risedronate (overall: 24.4%), 35 mg (20.6%) and ibandronate 150 mg (13.7%). Of these BP users, 4,662 were also on SSRIs and 18,040 were BP alone users. **Table 6.5** shows baseline characteristics of all BP users who were eligible for analysis. The average age of those who were concomitant users of BPs and SSRIs was 80.2 ± 8.0 (SD) years and that of BP alone users was 80.6 ± 7.7 (SD) years. For both treatment groups, there were more white women than other minority races and also within the age groups, the proportions of older adults 85 years or older

was the highest compared to other age groups. Concomitant users were equally distributed among women of lower and higher socioeconomic status, but BP alone users of higher socioeconomic status (62.0%) were almost twice that of low socioeconomic status (38.0%).

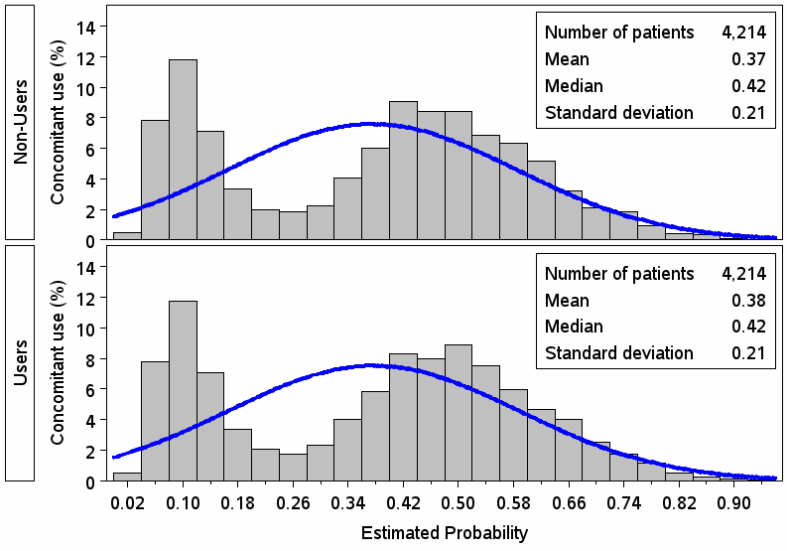
Figure 6.3a shows the distributions of propensity scores for the 18,040 BP alone users and the 4,662 concomitant users of BPs and SSRIs before matching. We can see that the distribution before matching shows a good discrimination between the two groups of patients. The distributions of propensity scores between the two groups after 1:1 matching are shown in **Figure 6.3b**. The distributions of the propensity scores for the matched groups were similar suggesting that treated subjects (concomitant users) are similar to the control subjects (concomitant non-users) with respect to background variables measured on all subjects, just like in a randomized experiment.

Table 6.5. Baseline patient characteristics of all bisphosphonate users eligible for analysis.

Characteristic	Concomitant users (n=4,662)	Non concomitant users (n=18,040)
Demographic		
Age , mean ± SD	80.2 (8.0)	80.6 (7.7)
65-69	552 (11.8)	1718 (9.5)
70-74	705 (15.1)	2657 (14.7)
75-79	847 (18.2)	3493 (19.4)
80-84	1040 (22.3)	4218 (23.4)
85+	1518 (32.6)	5954 (33.0)
Race, n (%)		
White	4,041 (86.7)	14,953 (82.9)
Black	139 (3.0)	906 (5.0)
Hispanic	366 (7.9)	1179 (6.5)
Other	116 (2.5)	1002 (5.6)
Socioeconomic status, n (%)		
Low income	2350 (50.4)	6860 (38.0)
Higher income	2312 (49.6)	11,180 (62.0)
Health care utilization factors, mean (SD)		
Comorbidity score	2.4 (2.0)	2.2 (2.0)
Number of unique prescribed medications	16.0 (7.6)	12.3 (6.8)
Medical conditions, n (%)		
Osteoporosis	2727 (58.5)	10588 (58.7)
Rheumatoid arthritis/ Osteoarthritis	2854 (61.2)	10271 (57.0)
Depression	3214 (68.9)	3111 (17.3)
Hyperparathyroidism	1365 (29.3)	4872 (27.0)
Kidney disease	1394 (29.9)	4716 (26.1)
Diabetes mellitus	1564 (33.6)	5540 (30.7)
Chronic obstructive pulmonary disease	1603 (34.4)	4686 (26.0)
Congestive heart failure	1965 (42.2)	6473 (35.9)
Hypertension	4123 (88.4)	15783 (87.5)
Anxiety	242 (5.2)	475 (2.6)
Parkinson's disease	134 (2.9)	266 (1.5)
Alzheimer's disease	1096 (23.5)	2000 (11.1)
Epilepsy	103 (2.2)	265 (1.5)
Orthostatic hypotension	196 (4.2)	729 (4.1)
Medications, n (%)		
Oral glucocorticoid use	1296 (27.8)	4265 (23.6)
Proton pump inhibitor use	2236 (48.0)	6186 (34.3)
Aromatase inhibitors	101 (2.2)	421 (2.3)
Thiazolidinediones use	208 (4.5)	678 (3.8)
Hormone replacement therapy	362 (7.8)	1291 (7.2)
Antihypertensive use	2869 (61.5)	11,385 (63.1)
Anticonvulsant use	1051 (22.5)	2831 (15.7)
Thyroid medication use	1405 (30.1)	4897 (27.2)
Warfarin use	633 (13.6)	2537 (14.1)
Loop diuretic use	1529 (32.8)	4806 (26.6)
Opioid use	2326 (49.9)	7413 (41.1)
Antipsychotics use	671 (14.4)	827 (4.6)
Lithium	27 (0.6)	41 (0.2)
Methotrexate	125 (2.7)	488 (2.7)



(6.3a)



(6.3b)

Figure 6.3. Distribution of propensity scores: (6.3a) shows the distribution for 22,702 patients before matching and (6.3b) shows the distribution for 4,214 patients after matching.

Table 6.6. Baseline patient characteristics of propensity score matched cohort.

Characteristic	Concomitant users (N=4,214)	Non concomitant users (N=4,214)	Standardized differences
Demographic			
Age , mean ± SD	80.2 (8.0)	80.4 (7.9)	0.025
65-69	500 (11.9)	476 (11.3)	
70-74	628 (14.9)	594 (14.1)	
75-79	765 (18.2)	774 (18.4)	
80-84	926 (22.0)	958 (22.7)	
85+	1395 (33.1)	1412 (33.5)	
Race, n (%)			
White	3653 (86.7)	3620 (85.9)	
Black	133 (3.2)	151 (3.6)	
Hispanic	313 (7.5)	322 (7.6)	
Other	115 (2.7)	121 (2.9)	
Socioeconomic status, n (%)			
Low income	2043 (48.5)	2083 (49.4)	
Higher income	2171 (51.5)	2131 (50.6)	
Health care utilization factors, mean(SD)			
Comorbidity score	2.4 (2.0)	2.4 (2.0)	0.01
Number of unique prescribed medications	15.5 (7.2)	15.5 (7.9)	0.005
Medical conditions, n (%)			
Osteoporosis	2476 (58.8)	2420 (57.4)	0.027
Rheumatoid arthritis/ Osteoarthritis	2574 (61.1)	2592 (61.5)	0.009
Depression	2767 (65.7)	2767 (65.7)	0.0
Hyperparathyroidism	1224 (29.1)	1238 (29.4)	0.007
Kidney disease	1245 (29.5)	1245 (29.5)	0.0
Diabetes mellitus	1405 (33.3)	1395 (33.1)	0.005
Chronic obstructive pulmonary disease	1397 (33.2)	1398 (33.2)	0.001
Congestive heart failure	1725 (40.9)	1781 (42.3)	0.027
Hypertension	3725 (88.4)	3743 (88.8)	0.013
Anxiety	208 (4.9)	213 (5.1)	0.005
Parkinson's disease	113 (2.7)	109 (2.6)	0.006
Alzheimer's disease	920 (21.8)	912 (21.6)	0.005
Epilepsy	84 (2.0)	88 (2.1)	0.007
Orthostatic hypotension	170 (4.0)	173 (4.1)	0.004
Medications, n (%)			
Oral glucocorticoid use	1153 (27.4)	1168 (27.7)	0.008
Proton pump inhibitor use	1934 (45.9)	1976 (46.9)	0.02
Aromatase inhibitors	96 (2.3)	90 (2.1)	0.01
Thiazolidinediones use	172 (4.1)	182 (4.3)	0.012
Hormone replacement therapy	316 (7.5)	331 (7.9)	0.013
Antihypertensive use	2593 (61.5)	2623 (62.1)	0.015
Anticonvulsant use	927 (22.0)	953 (22.6)	0.015
Thyroid medication use	1254 (29.8)	1243 (29.5)	0.006
Warfarin use	589 (14.0)	589 (14.0)	0.0
Loop diuretic use	1349 (32.0)	1392 (33.0)	0.022
Opioid use	2046 (48.6)	2101 (49.9)	0.026
Antipsychotics use	553 (13.1)	520 (12.3)	0.023
Lithium	21 (0.5)	28 (0.7)	0.022
Methotrexate	109 (2.6)	114 (2.7)	0.007

Table 6.6 shows the baseline characteristics of the two groups after matching and the standardized differences (difference in means of continuous variables or proportions of binary variables divided by standard error) between them. The standardized difference effect size can be treated as equivalent to a Z-score of a standard normal distribution which can suggest non-overlap in distributions between two study groups (treatment and control groups).[3] Standardized difference of ≥ 0.10 are commonly used to indicate important imbalance between treatment groups.[4] Overall, good balance was achieved on observed variables that entered the propensity score, with the largest standard difference being equal to 0.027 which is well below the suggested threshold (< 0.10).

6.3.2 Concomitant use and risk of fractures: Major findings

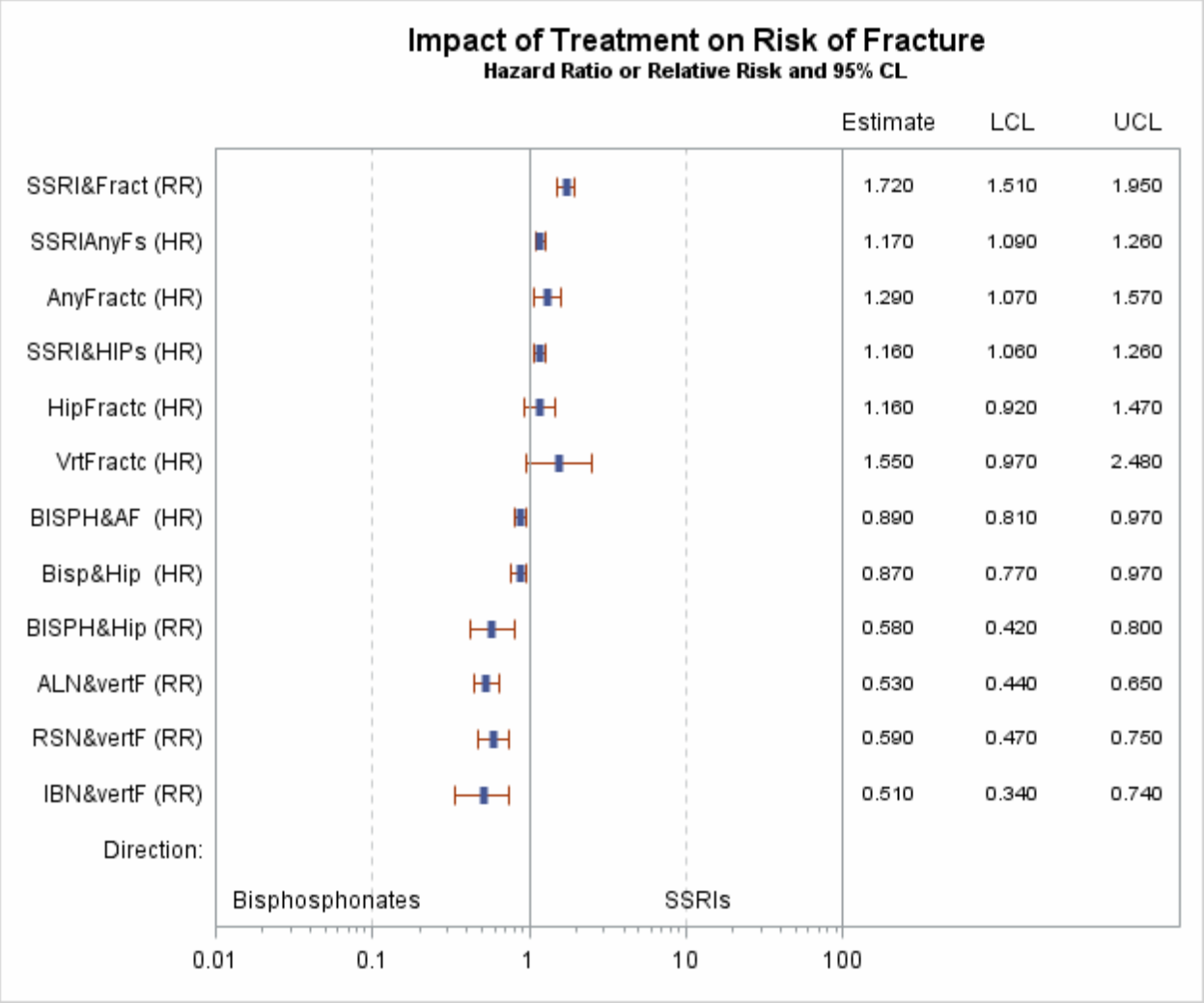
Among the patients who were eligible for analysis before matching, there were a total of 1,213 patients with the fracture outcome of interest. Specific fractures were hip/pelvis/femur (762), vertebral (194), humerus (92), radius/ulna or wrist (50), and tibia/fibula fracture (85). **Table 6.7** presents results from the Cox proportional hazards model. Among the propensity score matched patients, 256 concomitant users and 201 BP alone users experienced at least one first fracture of the hip, vertebral, humerus, radius/ulna, or tibia/fibula during the 3 year period (2008 – 2010). Of these patients, 161 concomitant users and 140 BP alone users experienced a hip fracture. Overall, concomitant users of BPs and SSRIs had slightly higher number of fracture outcomes for individual fracture subtypes of the hip, vertebral, humerus, radius/ulna, and tibia/fibula.

With regards to the hazard ratios, we observed that concomitant use was associated with statistically significant increased risk for any fracture (HR=1.29, 95% CI, 1.07-1.57), but not

with statistically significant increased risk for hip fracture (HR=1.16, 95% CI, 0.92-1.47) and vertebral fracture (HR=1.55, 95% CI, 0.97-2.48). No results were obtained for the humerus, radius/ulna, or tibia/fibula fractures because of very small sample size. The estimated results were graphically presented using a forest plot shown in **Figure 6.4**. The plot also includes treatment effects of BPs and risk reduction of any, hip, and vertebral fractures, SSRIs and increased risk of fracture. These treatment effects serve as references and were obtained from pooled results of meta-analysis studies[5-7] as well as BP use and fracture reduction results and SSRI use and increased risk of fracture from this study.

Table 6.7. Cox proportional hazard model for risk of fractures among concomitant users of BPs and SSRIs.

	Non concomitant users	**Concomitant users**
Total number of patients	4,214	4,214
Any Fracture		
Total events	201	256
Hazard Ratio (95% CI)	1.00 (Reference)	1.29 (1.07, 1.57)
Hip/Pelvis/Femur fracture		
Total events	140	161
Hazard Ratio (95% CI)	1.00 (Reference)	1.16 (0.92, 1.47)
Vertebral fracture		
Total events	29	45
Hazard Ratio (95% CI)	1.00 (Reference)	1.55 (0.97, 2.48)
Humerus		
Total events	15	17
Hazard Ratio (95% CI)	1.00 (Reference)	-
Radius/Ulna		
Total events	7	11
Hazard Ratio (95% CI)	1.00 (Reference)	-
Tibia/Fibula		
Total events	10	22
Hazard Ratio (95% CI)	1.00 (Reference)	-



Abbreviations: RR, Relative risk; HR, Hazard ratio; SSRI&Fract, SSRI use and increased risk of fracture (reference)[5]; SSRIAnyFs, SSRI use and increased risk of any fracture (this study); AnyFractc, Any fracture (this study); SSRI&HIPs, SSRI use and increased risk of hip fracture (this study); HipFractc, concomitant use of BPs and SSRIs and risk of hip fracture (this study); VrtFractc, concomitant use of BPs and SSRIs and risk of vertebral fracture (this study); BISPH&AF, BPs use and the reduction of any fracture (this study); Bisp&Hip, BPs use and the reduction of hip fracture (this study); BISPH&Hip, BPs use and the risk reduction of hip fracture (reference)[6]; ALN&vertF, Alendronate and the risk reduction of vertebral fracture (reference); RSN&vertF, Risedronate and the risk reduction of vertebral fracture (reference); IBN&vertF, Ibandronate and the risk reduction of vertebral fracture (reference)[7]. Note: Details and references are provided under the discussion section.

Figure 6.4. Forest plot of treatment effects and risk of fracture

Our findings indicate that concomitant users of BPs and SSRIs have a 1.29 times chance of experiencing any fracture compared to BP alone users at any given time. These findings

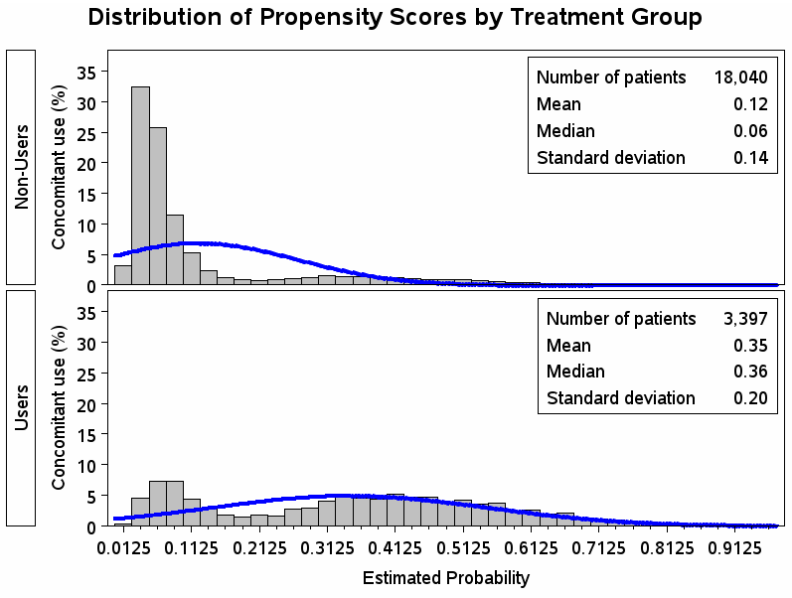
suggest that SSRIs might be associated with attenuation of antifracture efficacy of bisphosphonates. Based on the non-significance of our results for hip and vertebral fracture, we cannot determine the attenuation of the risk reduction associated with concomitant use of BPs and SSRIs, but we cannot rule out subtle attenuating effects.

6.3.3 Sensitivity analysis

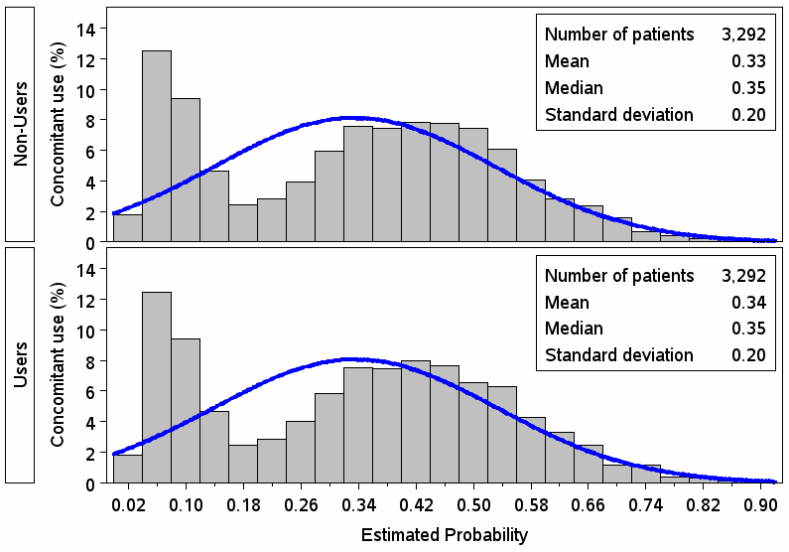
Two sensitivity analyses were performed to assess the robustness of our findings. First, we conducted a separate analysis among the same patients for the primary analysis, except that we redefined the exposure of concomitant use. Concomitant use of SSRIs with BPs was defined as having received at least one prescription for a BP and a SSRI (with no dispensing medication gap for a SSRI of more than 30 days whereas users of BPs were still defined as those patients who were exposed for at least 180 days in the 360 day period). The distributions of propensity scores between the two groups after 1:1 matching are shown in **Figure 6.5b**. **Table 6.8** shows the fracture outcomes from this analysis. The results were similar to the primary analysis, except that we observed slightly stronger associations and we also observed statistically significant risk for vertebral fracture. However, the wide confidence interval suggests that these results might have not had enough events for statistically reliable estimates.

In the second sensitivity analysis test, we used the matched data from the primary analysis but instead assessed the effect of short or long term exposure to SSRIs prior to a fracture event. The durations were exposure to SSRIs up to 90 days versus greater than 90 days. The fracture outcome results are shown in **Table 6.9a** and **Table 6.9b**. The results were similar to the primary analysis. Both of the durations of concomitant use showed no statistically significant association between concomitant use and increased risk of any fracture and were still non-significant for the hip fracture. However, the results for vertebral fracture were unstable. The

association was statistically significant when the duration of exposure was less than 90 days (but with wide confidence interval), but statistically non-significant when the exposure was greater than 90 days. This instability may be due to small sample size.



(6.5a)



(6.5b)

Figure 6.5. Distribution of propensity scores: (6.5a) shows the distribution for 21,437 patients before matching and (6.5b) shows the distribution for 3,292 patients after matching.

Table 6.8. Cox proportional hazard model for risk of fractures among concomitant users of bisphosphonates and SSRIs: Sensitivity analysis 1.

	Non concomitant users	Concomitant users
Total number of patients	3,292	3,292
Any fracture		
Total events	160	211
Hazard Ratio (95% CI)	1.00 (Reference)	1.35 (1.09, 1.68)
Hip/Pelvis fracture		
Total events	116	139
Hazard Ratio (95% CI)	1.00 (Reference)	1.21 (0.94, 1.55)
Vertebral fracture		
Total events	17	35
Hazard Ratio (95% CI)	1.00 (Reference)	2.13 (1.17, 3.85)

Table 6.9a. Cox proportional hazard model for risk of fractures among concomitant users of bisphosphonates and SSRIs (concomitant use ≤90 days before fracture): Sensitivity analysis 2.

	Non concomitant users	Concomitant users
Any Fracture		
Hazard Ratio (95% CI)	1.00 (Reference)	1.38 (1.08, 1.75)
Hip/femur/pelvis fracture		
Hazard Ratio (95% CI)	1.00 (Reference)	1.25 (0.93, 1.68)
Vertebral fracture		
Hazard Ratio (95% CI)	1.00 (Reference)	1.88 (1.02, 3.44)

Table 6.9b. Cox proportional hazard model for risk of fractures among concomitant users of bisphosphonates and SSRIs (concomitant use >90 days before fracture): Sensitivity analysis 2.

	Non concomitant users	Concomitant users
Any fracture		
Hazard Ratio (95% CI)	1.00 (Reference)	1.39 (1.04, 1.86)
Hip//pelvis fracture		
Hazard Ratio (95% CI)	1.00 (Reference)	1.27 (0.89, 1.81)
Vertebral fracture		
Hazard Ratio (95% CI)	1.00 (Reference)	1.23 (0.59, 2.56)

6.4 Discussion

This study assessed potential attenuation of the beneficial effects of BPs by SSRIs and increased risk of fracture. Given the popularity of BPs as the first-line therapy for the treatment of postmenopausal osteoporosis and reduction of fracture risk,[8] the potential antifracture efficacy of BPs is a major concern. Due to the high prevalence of comorbid osteoporosis and depression among women,[9] concomitant use in these patients is not uncommon. Indeed, our study found that of the BP users eligible for analysis in the study, the overall proportion of those patients who were reported with both depression and osteoporosis was 17.5% (i.e., 19.3% in 2008, 15.6% in 2009, and 17.9% in 2010). Furthermore, of the BP users, 20.5% were also on SSRIs.

Overall, our estimates showed an increased risk of fracture for any, hip, and vertebral fractures which suggested attenuation of BP, but the associations were not statistically significant for the hip and vertebral fracture. In other words, among all those already prescribed BPs, the risk of hip and vertebral fractures was not significantly different between those who added on SSRIs in their medication regimen compared to those who were only users of BPs, but the risk of any fracture was significantly different between these groups. These findings suggested that overall there is a potential antifracture efficacy of BPs but the effect was not significantly different between users and non users of concomitant use for individual fracture subtypes. Furthermore, sensitivity analysis results were similar: non-significant for hip and vertebral fracture and were still significant for the any fracture. These results suggested that the period of SSRIs exposure prior to a fracture event and a wider gap (up to 90 days between dispensing dates of BPs and SSRIs) did not affect the fracture outcome.

Bisphosphonates have been shown in randomized clinical trials to be beneficial in the reduction of fracture. A recent meta-analysis study found that oral BPs (i.e., alendronate, etidronate, risedronate, and clodronate) are effective in reducing the risk of hip fracture by 42%.

The pooled estimate of relative risk based on the Bayesian random-effects model was 0.58 (95% CI, 0.42-0.80).[6] Also pooled results as obtained with the network meta-analysis to evaluate the efficacy of BPs in the prevention of vertebral, hip, and nonvertebral-non hip fractures in postmenopausal women with osteoporosis found that vertebral fracture reduction with alendronate was RR=0.53, 95% CI, 0.44-0.65, risedronate: RR=0.59, 95% CI, 0.47-0.75, and ibandronate: RR=0.51, 95% CI, 0.34-0.74. The risk reduction for nonvertebral-non hip fractures for alendronate was RR=0.88, 95% CI, 0.77-1.00, risedronate: RR=0.62, 95% CI, 0.43-0.88, and ibandronate: RR=1.11, 95% CI, 0.80-1.52.[7] In this study, we also established antifracture efficacy of BPs for any and hip fracture.

A possible explanation for the variability observed in antifracture efficacy is that the antiresorptive relative potencies for osteoclast inhibition leading to increased bone mineral density and fracture risk reduction is related to their molecular structures.[10] Both BPs affinities' for crystalline hydroxyapatite and inhibitory effects on osteoclasts are important pharmacological features. The high affinity for bone mineral allows BPs to achieve a high local concentration throughout the entire skeleton. Suppressed bone resorption after BP initiation suggests BP efficacy and potency in promoting the apoptosis of osteoclasts actively engaged in degradation of mineral on the bone surface.[11] Antiresorptive therapies that produce larger increases in bone mineral density tend to have greater antifracture efficacy.[12] It is also important to note that improved BP treatment persistence and compliance are factors that have an overall influence on fracture risk reduction.[13]

We hypothesized that the established antifracture efficacy of BPs would be attenuated through an interaction with SSRIs. We observed this potential phenomenon and increased risk of any fracture. Although we were not able to determine with statistical certainty that SSRIs may

attenuate the antifracture efficacy of BPs and increased risk of fracture for hip and vertebral fracture (may be because of sample size issues), we cannot completely rule out subtle counteractive effects due to the well-established association of SSRIs and decreased BMD leading to increased risk of fracture. Using data for this study, we found strong association between SSRI use and increased risk of any and hip fracture. Both findings were consistent with reports from two prospective studies on the associations of SSRIs and increased risk of fracture. Spangler et al. in a prospective cohort study of 93,676 postmenopausal women, found that compared to women using other types of antidepressants, women using SSRIs had increased adjusted risk of any fracture (HR=1.30, 95% CI, 1.20-1.41) and hip fracture (HR=1.33, 95% CI, 0.95-1.86), but statistical significance was not achieved at the hip.[14] Diem et al. in a recent study based on a 10-year follow-up medication-use data involving 9,704 women aged 65 years and older recruited in the prospective Study of Osteoporotic Fractures, showed that of these women, 2,809 experienced an incident nonspine fracture over the follow-up period, including 936 with a hip fracture. Women taking SSRIs experienced a higher adjusted risk of nonspine fracture compared with nonusers (HR=1.38, 95% CI, 1.10-1.72) in a multivariable model. The risk of hip fracture was close to 1.0 (HR=1.01, 95% CI, 0.71-1.44) for SSRI users compared with nonusers due to potential confounding factors.[15] Overall, in a meta-analysis study, a summary of pooled estimates of risk associated with SSRI use in cohort and case-control studies has demonstrated that SSRI use is associated with a significantly increased risk of fracture (RR=1.72, 95% CI, 1.51-1.95).[5]

The link between SSRIs and bone health is based on the adverse effects of serotonin on the bone remodeling process. Bone cells (i.e., osteocytes, osteoblasts, and osteoclasts) possess a functional serotonin (5-HT) signal transduction mechanism (5-HT receptors and the serotonin

transporters [5-HTT]) for both responding to and regulating the uptake of serotonin.[16-20] These reports further suggested that serotonin may be involved in bone metabolism and the potential consequences on bone health. For example the study by Gustafsson et al. examined the *in vitro* effects of 5-HT and 5-HTT inhibitor fluoxetine (Prozac®) and found that serotonin as well as fluoxetine increased the total number of differentiated human osteoclasts as well as osteoclast activity. Fluoxetine was also found to increase receptor activator of nuclear factor kappa B ligand (RANKL) release.[20]

Possible bone metabolism pathways have also been proposed. In gut-derived 5-HT on osteoblasts, binding of 5-HT to 5-HT1B, which is linked to the $G_{\alpha i}$ protein, inhibits adenylyl cyclase which in turn inhibits second-messenger cAMP production and protein kinase A (PKA)-mediated cAMP response element-binding (CREB) phosphoslylation. This process leads to decreased expression of *Cyclin* (Cyc D1) genes and decreased osteoblast proliferation. As a result, bone formation is slowed. On the other hand, in brain-derived 5-HT on osteoblasts, binding of 5-HT negatively controls osteoblast proliferation via the molecular clock gene (Cyc D1) cascade and positively regulates bone resorption via activation of a PKA/ATF4-dependent pathway (ATF-4: a transcription factor protein), leading to increased synthesis of RANKL, an activator of osteoclast differentiation and function.[21,22] In other words, 5-HT activation can also directly produce RANKL in addition to the RANKL produced during normal bone remodeling process.

During normal bone remodeling in healthy physiologic systems, bone stromal cells, including cells of the osteoblast lineage, provide a limited amount of RANKL, which leads to osteoclast differentiation, survival, and activation and subsequent bone resorption. Bone resorption is balanced by osteoblast-dependent new bone formation.[23] RANKL is a member of

the tumor necrosis factor (TNF) superfamily, produced and secreted by osteoblasts.[24] RANKL stimulates osteoclasts through its own receptor RANK, which is a membrane-bound protein present on osteoclast precursors, inducing the formation of osteoclasts and subsequent bone resorption.[25] Increased RANKL expression has been shown to be present in bone marrow cells from postmenopausal women.[26]

How does this role of 5-HT-RANKL in bone metabolism relate to its potential attenuating effects of BPs? The elevation of RANKL because of 5-HT probably reflects a mechanism counter-regulating excessive bone resorption and increased risk of fracture. Treatment of homozygous *oim*/*oim* mice (the *oim*/*oim* mouse is an established model of moderate to severe osteoporosis) with either a BP (alendronate) or RANKL inhibitor (*Rank-Fc*) has been reported to cause decreases in fracture incidence.[27] Although research findings have suggested that treatment with BPs does not change RANKL serum levels,[28] Sutherland et al. has demonstrated that RANKL can attenuate the beneficial effects of bisphosphonates. In an *in vitro* study using rabbit osteoclasts treated with the bisphosphonates clodronate or alendronate for up to 48 hours in the absence or presence of RANKL found that RANKL significantly attenuated (or antagonized) the ability of both clodronate and alendronate to induce osteoclast apoptosis and inhibit bone resorption. The authors conclude that RANKL protects osteoclasts from the apoptosis-inducing and anti-resorptive effects of BPs *in vitro*.[29] This is an example of a pharmacodynamic drug interaction.

In pharmacodynamic interactions, the two drugs act at the same or interrelated receptor sites and may behave in an additive, synergistic, or antagonistic fashion.[30] Suppression of osteoclast bone resorption is the pharmacodynamic effect of BPs and so are the elevated levels of RANKL which in turn leads to osteoclast differentiation, survival, and activation and subsequent

bone resorption the pharmacodynamic effect of SSRIs. Concomitant BP and SSRI use may increase the risk of osteoporosis/bone loss and fracture through the antagonizing or attenuating effects of SSRIs on the beneficial effects of BPs. The pharmacodynamic interaction of these combinations would result in attenuation of BP effects, hence increasing the risk of fracture for the patient. However, our study provided evidence which only suggests the possibility of this phenomenon for any fracture, but was not well powered to determine the treatment effects for individual skeletal sites. So, further investigations are needed to provide more understanding.

An alternative explanation to our findings is that what we have demonstrated could be potential good news to patients on SSRIs and also prescribed BPs. It is possible that BPs are actually protective against SSRI-induced osteoporosis and increased risk of fracture and treatments effect estimates would have shifted toward less than 1.0. However, due to the potential for residual confounding bias for fracture not measured in Medicare claims data but are measured in Medicare Current Beneficiary Survey (MCBS) data (e.g., current tobacco smoking, alcohol intake, body mass index, or activities of daily living score, cognitive impairment, and Rosow-Breslau physical impairment scale)[31] which we did not control for in this study, both concomitant users of BPs and SSRIs and those on BPs alone probably had an equal probability of increased risk of fracture. Hence, the lack of substantial difference in increased risk of hip and vertebral fractures.

To ascertain this alternative hypothesis, further sensitivity analysis can be performed with an aim to correct effect estimates for unmeasured confounding using external information such as MCBS that contains additional survey information for some of the patients that were included in our study.[32] The MCBS is a continuous, multipurpose survey (collected since 1991) of a representative sample of the Medicare population designed to aid the CMS administration,

monitoring and evaluation of the Medicare program.[33] This sensitivity analysis technique has been used to investigate the association between selective COX-2 inhibitor use and the incidence of myocardial infarction.[34] With regards to concomitant use of BPs and SSRIs, findings favoring antifracture efficacy of BPs than antifracture attenuating effects of SSRIs could be welcome research findings as far as caring for older postmenopausal women that would need long term use of SSRIs.

6.4.1 Strengths and limitations of the study

6.4.1.1 Strengths

There are two key aspects that contributed to the strengths of findings from this study. These include the use of Medicare data and the study design strategy. The use of a large, nationally representative database for older adults 65 years or older is a source of strength because the findings are more generalizable to the population of older postmenopausal women. As for the design strategy, we believe that potential confounding of observed variables was well accounted for through propensity score matching. Confounding bias is of particular concern in observational epidemiologic studies of drug effects.[35] Using propensity score method it is possible to duplicate one crucial feature of randomized experiment of designing an observational study without access to the outcome data.[36] Propensity score method allows researchers to reconstruct counterfactuals using observational data, a situation similar to random assignment, albeit only with respect to observed variables.[37] Another strength in our design strategy is that the study design is better in quantification of exposure with respect to time.[38] Sampling is the equivalent of matching cases and controls on duration of follow-up (or respect to time).

6.4.2.2 Limitations

On the other hand, our study findings were also faced with some limitations. One key limitation in this study was the small number of fractures by anatomical site and so the study had insufficient power to detect treatment effect as statistically significant.[39] This can be explained in part by the existing imbalance in enrollment in Medicare Part A and Part D. Although Medicare Part D offers prescription coverage to all those eligible for Medicare, not all beneficiaries are enrolled in a Part D plan. Of those who were Medicare eligible between 2008 and 2010, 57.5% were enrolled in a Part D plan in 2008, 58.7% in 2009, and 59.4% in 2010. The rest were not covered by Part D and with no credible coverage or with other credible coverage, or were enrolled in a retirement drug subsidy.[40] This limitation significantly resulted in the exclusion of many Medicare Part A patients who had no medication history available from the study cohorts. For example, of the 7,757 patients with hip/pelvis/femur fractures enrolled in Medicare Part A and were eligible for this study, only 762 (9.8%) patients with hip fracture were enrolled in both plans (before matching). Also, vertebral fractures are frequently undetected by physicians[41] and so this can lead to the pronounced problem of too small number of events in the 5% random sample. Both of these issues could be dealt with by obtaining a 10% or greater sample from CMS rather than a 5% sample.

Second, we lacked precise information about when patients first initiated BPs. The period after initiating therapy of BPs ($\geq$ 3 months) plays a role in the antifracture efficacy of these medications and this was the basis for our inclusion and exclusion criteria.[42] However, due to the limitations of the data, patients on BPs for at least 6 months were assumed to be continuous users. It is likely that BPs would be significantly attenuated among those who are new users than those who have been on BPs for longer periods of time.

Third, our study is faced with the increased possibility of bias because of the retrospective nature of the data collection. Bias may entirely account for any weak associations that we may have observed. Potential misclassification bias, also called measurement error, is probably the most common form of bias in epidemiologic research.[43] Misclassification can occur for both drug exposure and the outcome of interest. With respect to drug exposure with outpatient prescription claims, a greater number of opportunities for misclassification in the direction of not exposed exist given the multiple channels by which members can receive their medications outside of the reimbursement arrangements of Medicare program, for example physician samples. In addition, one of the tips for Medicare Part D patients to avoid the coverage gap is the recommendation that patients pay cash for selected medications and request that the pharmacy not bill the Part D plan if cash prices are less than the co-payment. Discount generic programs (e.g., $4 generic prescription programs) are one of the recommended strategies.[44] SSRI medications in the generic programs include citalopram, fluoxetine, and paroxetine and BPs include alendronate.[45] Another potential misclassification bias of exposure is the assumption we made in our study that patients in Medicare data with records of dispensed BPs or SSRIs actually took them even though they may not have. In this case, patients who were non persistent and/or adherent were misclassified as exposed, thereby biasing our estimates. With respect to outcomes, misclassification of diagnostic codes can result due to ambiguity in diagnoses for example a self-reported fracture that is not adjudicated with radiographic reports.[46]

Fourth, coding of claims and filing of complete claims is done by the coding staff. During this aspect of data generation potential sources of bias introduced are miscoding of primary and secondary diagnoses and procedures and also failure to file claims properly and hence possible under-reporting of diagnoses. Finally, the temporal relationship between exposure and disease

may be difficult to establish given the fact that the study is retrospective.[43] This is especially so if important information may be missing on intermediate clinical outcomes such BMD and RANKL measurements.

6.5 Conclusions

In summary, we did not observe a significant association of antifracture efficacy of BPs with SSRIs for hip and vertebral fracture but significance was achieved for any fracture. Because this is the first study to investigate this phenomenon, further studies are needed to provide more understanding on the clinical impact of concomitant use of BPs and SSRIs among older postmenopausal women. Especially further studies that could prospectively assess changes in biochemical markers of bone turnover (e.g., RANKL) and BMD would provide better understanding of the potential attenuation of antifracture efficacy of BPs by SSRIs. Currently there are no clinical guidelines for the treatment of SSRI–related bone loss and such information would be important to be integrated in its development. It is probable to suggest that future concomitant use of BPs and SSRIs will continue to rise in this population due to the projected future increase in population of older adults. Therefore, results from studies such as this could add to the current body of literature and be useful for physicians treating osteoporosis and/or osteoporotic fractures by highlighting possible safety concerns that may be important to consider when optimizing patient care. Also these results might be relevant to policymakers concerned with meeting the needs of aging Americans, especially the health of older women.

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Chapter 7

Specific Aim 3: To assess the increased risk of osteoporotic-related fractures associated with the concomitant SNRIs with BPs use and whether the risk of osteoporotic-related fractures is related to the role of serotonin in bone rather than the disease (depression).

7.0 Results

We did not report findings for this specific aim. This is because we failed to determine the effects of concomitant use of bisphosphonates and SNRIs and increased risk of fracture. Although there were enough number of events to investigate the composite effect of SNRIs on the antifracture effects of bisphosphonates, the events were not sufficient enough to investigate a dose response effect which was our primary goal (see Table 7.1). SNRIs are less popularly used for the treatment of depression compared to SSRIs. Indeed, findings from Chapter 5 found that the prevalence of concomitant bisphosphonates and SSRIs use was higher than SNRIs. This limitation suggests that for future studies involving SNRIs and increased risk of fracture in older adults should use a larger sample of the Medicare claims data. If possible we recommend >5% to 100% samples of the Medicare claims data to be able to capture all the associated events with use of SNRIs.

Table 7.1. Descriptive statistics of matched concomitant users of bisphosphonates and SNRIs, dosage, and fracture events.

	Dosage			
Description	≤ 37 mg	> 37 - ≤ 60 mg	>60 - ≤ 75 mg	>75 mg
Concomitant users	590	511	377	205
Hip fracture	36	42	34	21
Vertebral Fracture	10	3	5	1
Humerus	5	2	3	4

Vita

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