MEDICATION USE AND FALLS IN OLDER ADULTS: A PHARMACOEPIDEMIOLOGIC APPROACH

by

Zachary Adam Marcum

Pharm.D., Butler University, 2008

M.S., University of Pittsburgh, 2011

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SCHOOL OF MEDICINE

This dissertation was presented

by

Zachary Adam Marcum

It was defended on

September 26, 2014

and approved by

Nicholas Castle, M.H.A., Ph.D., Professor, University of Pittsburgh Graduate School of Public Health

Joseph Hanlon, Pharm.D., M.S., Professor, University of Pittsburgh School of Medicine

Subashan Perera, PhD., Associate Professor, University of Pittsburgh School of Medicine

Joshua Thorpe, Ph.D., M.P.H., Associate Professor, University of Pittsburgh School of Pharmacy

Dissertation Advisor: Galen E. Switzer, Ph.D., Professor, University of Pittsburgh School of Medicine

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Zachary Adam Marcum, Pharm.D., M.S.

University of Pittsburgh, 2014

More than one-third of community-dwelling older adults fall each year. Falling is classified as a geriatric syndrome which has multiple contributing factors and an interaction between chronic predisposing diseases and impairments and acute precipitating insults. One potentially modifiable risk factor is medication use. While previous research has been conducted on medication-related falls, there are several gaps remaining in the literature, including the lack evidence on dose-response relationships across wide ranges of medication classes and falls as well as the frequent inability to address confounding by indication. Therefore, the overall purpose of this project was to determine—in a large, representative sample of community-dwelling older adults—associations between antihypertensive, anticholinergic, and antidepressant use and recurrent falls.

First, we found no increased risk of recurrent falls in antihypertensive users compared to non-users, or those taking higher doses or for longer durations. Only those using a loop diuretic were found to have a modest increased risk of recurrent falls. In conclusion, antihypertensive use overall was not associated with recurrent falls after adjusting for important confounders. Loop diuretic use may be associated with recurrent falls and needs further study.

Second, we found no statistically significant increased risk of recurrent falls in anticholinergic users, or those taking higher doses or for longer durations. In conclusion, increased point estimates suggest an association of anticholinergic use with recurrent falls, but

the associations did not reach statistical significance. Future studies are needed to examine other measures of anticholinergic burden, and their associations with other outcomes such as cognitive function.

Third, we found a statistically significant increased risk of recurrent falls in antidepressant users. An increased risk was also seen among those taking SSRIs, those with short duration of use, and those taking moderate doses. Among those with a history of falls/fracture at baseline, we found an increase in risk for any antidepressant use, but no increased risk was found in those without a history of falls/fracture.

Taken together, the findings from this proposal will provide clinicians and researchers with clinically-relevant information on potential harmful outcomes associated with chronic medication therapy among older adults.

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PREFACE

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"Time is your most precious gift because you only have a set amount of it. You can make more money, but you can't make more time. When you give someone your time, you are giving them a portion of your life that you'll never get back. Your time is your life. That is why the greatest gift you can give someone is your time." – Rick Warren

1.0 INTRODUCTION

Pharmacoepidemiology is the study of the use of and the effects of drugs in large numbers of people.[1] The potential contributions of pharmacoepidemiology include: (1) supplemental information to premarketing studies and better quantifying the incidence of known adverse and beneficial effects in certain populations not studied prior to marketing (e.g., elderly, children, or pregnant women); (2) new types of information not available from premarketing studies (e.g., undetected adverse and beneficial effects, patterns of utilization); and (3) reassurances about drug safety and fulfillment of ethical and legal obligations.[1] Overall, questions that pharmacoepidemiologic studies can answer include: (1) What are the beneficial and harmful outcomes of drug therapy?; (2) What interventions are effective in modifying the use and outcomes of drug therapy?; and (3) How and why is drug therapy being used/misused or prescribed?[1]

Moreover, medications are the most frequently used form of therapy for the medical problems of the aged.[2] Unfortunately, the frequent exclusion of this age group from premarketing clinical trials of new medications has limited our knowledge regarding the safety and efficacy and individual medications in this population.[2] Further, older patients often have various chronic conditions that may require long-term medications. Of potential concern is that multiple medication use (polypharmacy) can lead to problems in the medication use process and related health outcomes. Thus, pharmacoepidemiologic studies are critically important to

understand and improve the use of medications in older adults. One of the most important medication-related problems in older adults is falling.

More than one-third of community-dwelling older adults fall each year.[3] Approximately 10% of falls result in a major injury such as a fracture, serious soft tissue injury, or traumatic brain injury.[3] In addition, falls are major contributors to functional decline and health care utilization. Falls and fall injuries are among the most common causes of decline in the ability to care for oneself and to participate in social and physical activities. As with other conditions affecting older adults, falling is classified as a geriatric syndrome which has multiple contributing factors and an interaction between chronic predisposing diseases and impairments and acute precipitating insults.[3] One potentially modifiable risk factor is medication use.[4] While previous research has been conducted on medication-related falls, there are several gaps remaining in the literature, including the lack evidence on dose-response relationships across wide ranges of medication classes and falls as well as the frequent inability to address confounding by indication.

Using an existing data source available at the University of Pittsburgh, this proposal was an in-depth analysis of the first type of question answerable through a pharmacoepidemiologic approach (i.e., the harmful outcomes of drug therapy) which evaluated the association between three different medication classes and falls among community-dwelling older adults. All three analyses utilized data from the Health, Aging and Body Composition (Health ABC) Study. The proposed longitudinal analyses used data collected from 3,075 black and white men and women aged 70-79 enrolled in 1997/98 into the Health ABC Study and followed them from year 1 (baseline) to the year 7 follow-up.[5] Sample members representative of elders in Pittsburgh and Memphis initially reported no difficulty walking at least ¼ mile or up a flight of stairs. The

information sought over the seven year period included a battery of detailed physiologic and performance measurements and questionnaire material regarding sociodemographic characteristics, multiple aspects of the participants' physical health, and use of medications (at certain years). For medications, at baseline, years 2, 3, 5, and 6 participants were asked to bring to clinic all medications they had taken in the previous two weeks. In clinic, the interviewer gathered up all prescription and non-prescription drugs and transcribed from the medication container information about the drug name, strength, dosage form, prescription or non-prescription status, whether the drug was taken "prn" or as needed, the number of times the respondent reported taking the product the previous day, week, or month, and when they started the drug. The medication data collected for the Health ABC Study was edited, coded using the Iowa Drug Information System (IDIS) ingredient codes and entered into a computerized database.[6]

It is important to note that Health ABC is an ideal data source for conducting the proposed analyses. Previous studies assessing the association between medications and falls in older adults have been limited by their inability to control for the underlying indication for drug use, which Health ABC data will be able to address. In addition, prior research has been limited in terms of the medication data available such that they were frequently not able to look at the impact of dosage or duration of pharmacotherapy on the outcome of falls.[7] The proposed analyses were able to calculate robust medication variables including dosage and duration. Finally, a major strength of the Health ABC dataset is its inclusion of both prescription and over-the-counter medication information. Most medication datasets do not include over-the-counter medication data.

In conclusion, the overall purpose of this project was to determine—in a large, representative sample of community-dwelling older adults—associations between antihypertensive, anticholinergic, and antidepressant use and recurrent falls. The findings from this proposal provide clinicians and researchers with clinically-relevant information on potential harmful outcomes associated with chronic medication therapy among older adults.

2.0 ANTIHYPERTENSIVE USE AND RECURRENT FALLS IN COMMUNITY-DWELLING OLDER ADULTS: FINDINGS FROM THE HEALTH ABC STUDY

2.1 INTRODUCTION

Hypertension (especially systolic) is the most common chronic condition in older adults.[8] If un- or undertreated, hypertension can increase risk of stroke, heart failure and premature death.[8] Numerous randomized controlled trials demonstrate the effectiveness of thiazide diuretics, central alpha blockers, renin-angiotensin-aldosterone system inhibitors, and calcium channel blockers in reducing blood pressure in adults well into their eighties.[8] Even though these drugs are generally well tolerated, as few as 50% of elders with hypertension use antihypertensives, and fewer than 50% of these have adequate blood pressure control.[9]

Suboptimal blood pressure control may derive, in part, from concerns about adverse drug effects, including falls. Indeed, 18-40% of community-dwelling elderly fall yearly[10-12], of whom nearly 50% have recurrent falls.[12,13] Recurrent falls (as opposed to single falls) may be more clinically important since they can be a marker of physical and cognitive status problems, and other morbidity and mortality in the elderly.[12] A previous meta-analysis and a cohort study found antihypertensive use modestly increased risk of a single fall[14,15]; whether antihypertensive use is associated with recurrent falls and whether this risk varies by medication class, dose response, and duration response associations over time is relatively unknown.

Thus, the objective of the current longitudinal study was to assess the association of overall and specific classes of antihypertensive use, dose, and duration with recurrent falls in community-dwelling, initially well-functioning elders.

2.2 METHODS

2.2.1 Study design, data source, and sample

We used data from the Health, Aging, and Body Composition (Health ABC) study, a population-based, prospective, longitudinal observational study of community-dwelling older adults.[5] This study was approved by the University of California at San Francisco (UCSF), University of Pittsburgh, and University of Tennessee Memphis Institutional Review Boards, and informed consent was obtained from each participant prior to data collection. The baseline sample (1997/98) included 3,075 Black and White men and women aged 70-79 years who reported no difficulty walking ¼ mile, or climbing 10 steps and lived in specified zip codes surrounding Pittsburgh, PA and Memphis, TN.[5] The sample for the current analysis included 2,948 older adults at year 1 with complete medication use and fall data the following year followed through year 6 for antihypertensive medication exposure and year 7 for recurrent falls.

2.2.2 Data collection and management

Participants were seen annually during a clinic or home visit and detailed physiologic (including blood pressure) and self-report questionnaire measurements (including demographics, health behavior/status (including medications), and access to health care factors were collected.[5] Detailed medication data were collected in clinic or at home about products taken in the previous

month using a state of the art "brown bag" review method.[16,17] A similar data collection approach was used for telephone interviews if participants were unable to be seen in person. Studies have shown that medication use information collected by either "brown bag" or telephone methods are highly accurate and concordant with information about dispensed prescription drugs in claims data.[18,19] For all medications, the interviewer recorded the name, strength, dosage form, and the number of dosage forms the respondents said they had used the previous day, week, or month. The medication data collected for the Health ABC Study were edited and coded using the Iowa Drug Information System (IDIS) Drug Vocabulary and Thesaurus.[6] IDIS is a hierarchical coding system with 8 character unique codes for specific drug ingredients, chemical and therapeutic categories. The therapeutic category code allows drugs to be assigned to one of 20 major therapeutic classes and 200 sub-classes based on an expanded version of the American Hospital Formulary Services format.[20]

Teleform was used to create scannable forms for direct data entry. Missing and questionable values were highlighted by the software for visual review and online editing. Additional range checks and data cleaning were conducted at the UCSF Coordinating Center. De-identified SAS® permanent data files were created for analysis.

2.2.3 Primary outcome

The number of falls in which the participant landed on the floor or ground in the previous twelve months was assessed at the year following medication use data collection (e.g., year 1 antihypertensive use and previous year falls reported at year 2) for each wave (five waves). The primary outcome was recurrent falls (≥ two) in the ensuing 12 months following report of medication use. This method of fall recall (in the previous 12 months) has been shown to be

highly specific (91% – 95%) in comparison with that reported using more frequent assessments.[21]

2.2.4 Primary independent variable

Medications used to treat hypertension were grouped into therapeutic sub-classes: 1) *beta blockers* (IDIS codes:12160107, 12160114, 12160115, 12160123, 12160137, 12160145, 12160146, 12160150, 12160153, 12160167, 12160169); 2) *alpha blockers (peripheral and central)* (IDIS codes: 12160401, 12160404, 12160419, 24080006, 24080010, 24080063, 24080064, 24080084); 3) *loop diuretics* (IDIS codes: 40280401, 40280402, 40280405); 4) *thiazide diuretics* (IDIS codes: 40280025, 40280101, 40280106, 40280108, 40280110); 5) *potassium-sparing diuretics* (IDIS codes: 40280013, 40280016, 40280062); 6) *calcium channel blockers* (IDIS codes: 24120406, 24120410, 24120413, 24120415, 24120416, 24120421, 24120422, 24120449); 7) *angiotensin converting enzyme inhibitors (ACEI)* (IDIS codes: 24080202, 24080203, 24080206, 24080208, 24080213, 24080214, 24080216, 24080218, 24080223, 24080232); and 8) *angiotensin receptor blockers (ARBs)* (IDIS codes: 24080401, 24080402, 24080403, 24080405, 24080410, 24080412).[22] Too few participants were taking vasodilators so this class was not assessed. Any use was defined as the use of any medication from the 8 sub-classes. To evaluate the possibility of a dose-response relationship, the daily dose was calculated for current users for each individual antihypertensive medication by multiplying the number of dosage forms taken the previous day by the strength of the medication reported at the interview. The daily dose was then converted to a standardized daily dose (SDD) by dividing it by the ***maximum effective dose*** per day as noted in a standard reference.[22] Thus, a person taking 1.0 standardized antihypertensive drug unit would have taken the maximum

recommended effective daily dose for one agent. The standardized dose was summated for all antihypertensives, regardless of class, taken daily. Finally, to examine the impact of duration, long-term use was operationally defined as ≥ 2 years and short-term use as < 2 years.

2.2.5 Control variables

To address potential confounding, we controlled for a number of demographic, health status/behavior, and access to care factors.[12,13] Demographic factors included age, sex, race, site, education (less than a high school education, high school graduate, and post-secondary education), and marital status (never married, married, previously married).

Health behaviors included smoking status and alcohol use. Health status factors included pulmonary disease, arthritis, urinary problems, cerebrovascular disease, bodily pain in the previous month, vision (excellent/good sight, fair sight, and poor to completely blind), and body mass index (underweight/normal, <24.9; overweight, 25.0-29.9; and obese, ≥30).[17,22] Self-rated global health was dichotomized as excellent/very good/good vs. fair/poor. In addition, time-varying covariates were created for depressive symptoms (Short Center for Epidemiologic Studies-Depression Scale >10), cognitive impairment (Modified Mini-Mental State Test [3MS] <80), exposure to any drug that increases the risk of falls (non-anticholinergic central nervous system medications, including benzodiazepines, antidepressants, antipsychotics, opioids), and the total number of prescription medications (excluding dugs that increase falls, and antihypertensive drugs) per participant.[13,23,24] Access to care factors included dichotomous variables for hospitalization in previous 12 months, private physician, prescription insurance, and flu shot in previous 12 months.[25]

Self-reported hypertension was sub-divided into controlled (>140/90 mmHg) and uncontrolled on a time-varying basis. Antihypertensives can be used for a number of comorbid conditions.[8,25] Therefore, to mitigate potential confounding by indication, we included self-reported peripheral artery disease, benign prostatic hyperplasia symptoms, coronary heart disease, congestive heart disease, and diabetes.

2.2.6 Statistical Analysis

We used appropriate descriptive statistics for summarization and generalized estimating equations (GEE) for eliciting the main findings.[26-28] First, we assessed the unadjusted association between antihypertensive use and recurrent falls over time. Second, *a priori* covariates that may affect recurrent falls were included: site, heart failure, benign prostatic hypertrophy, cognitive impairment, depressive symptoms, self-reported hypertension (controlled/uncontrolled), and other drugs that increase the risk of falls. Each antihypertensive sub-class was run as a separate model and controlled for antihypertensive sub-class use other than the sub-class being evaluated. Finally, additional covariates were selected using a forward stepwise selection approach applied separately for each of three domains of covariates (demographic, health status/behavior, and access to health care). Specifically, stepwise detected covariates and those deemed important *a priori* were included in the final model. We also conducted sensitivity analyses by restricting the sample to only those with hypertension (whether controlled or uncontrolled) at baseline, and stratifying the analysis by any falls history at baseline.

To address potential confounding, and make the comparisons between those with and without antihypertensive use as balanced as possible within the framework of existing data from an observational study, we created propensity scores for the baseline time point and used two

approaches. First, we used all demographic, health status/behavior, and access to health care variables to create propensity scores using backward selection; propensity scores were then used in regression (covariance) adjustment.[29] Specifically, we fit the primary model with any antihypertensive use as the independent variable and recurrent falls (yes/no) as the dependent variable, adjusting for propensity scores. Second, we stratified participants into quintiles based on the calculated propensity scores. Research has shown that stratification of propensity score balances all covariates that are used to estimate the propensity score, and often five sub-classes based on the propensity score will remove 90% of the bias in each of these covariates.[30] The primary analysis (i.e., any antihypertensive use) was performed within each of the five strata to compare odds ratios and 95% confidence intervals for recurrent falls for those who received an antihypertensive versus those who did not. All analyses were conducted using SAS® software (version 9.3; SAS Institute, Cary, NC).

2.3 RESULTS

At baseline, the mean (standard deviation) age was 73.6 (2.9) years, 51.6% were female, and 40.8% were black (**Table 1**). In addition, slightly more than half had self-reported hypertension, and nearly half of those with hypertension were uncontrolled.

Table 2 shows the prevalence of antihypertensive use over time. At baseline, over half reported the use of one or more antihypertensives, with calcium channel blockers being the most common class used (23%). At baseline, the overwhelming majority reported taking an antihypertensive for more than 2 years and in doses ≤ 2 SDDs. By year 6, 70% took one or more antihypertensives, with calcium channel blockers persisting as the most common class used (25.6%).

At baseline, 21.2% of participants reported any fall in the previous year. At year 2, 8% of participants reported having recurrent falls in the previous year. This rate remained somewhat stable over the next four waves (7.5 to 10.4%).

Table 3 shows the results from the multivariable model, controlling for demographic, health behavior/status, and access to care factors. We found no statistically significant increase in risk of recurrent falls in older antihypertensive users (adjusted OR 1.13, 95% CI 0.88-1.46), or those taking higher SDDs or for longer durations.

Of the eight sub-classes, only loop diuretics were found associated with recurrent falls (adjusted OR 1.50, 95% CI 1.11-2.03). Post hoc analyses revealed no significant dose-response

relationship among loop diuretic users (SDD ≥1 adjusted OR 1.53, 95% CI 0.88-2.65; SDD <1 adjusted OR 1.53, 95%CI 1.08-2.15). However, those taking a loop diuretic for ≥2 years had a significant increase in risk, but not for a shorter period of time (adjusted OR 1.64, 95%CI 1.10-2.45 and adjusted OR 1.38, 95% CI 0.94-2.03, respectively).

Multiple sensitivity analyses were conducted. Sensitivity analyses showed similar results when restricted to those with hypertension and when stratified by blood pressure control, and when stratified by those with a previous falls history at baseline (**Tables 4 and 5**). In addition, using the propensity scores in a covariance-adjusted model for the primary independent variable (i.e., any antihypertensive use) led to a similar overall finding (adjusted OR 1.07, 95% CI 0.81-1.41). Stratification of the propensity scores into quintiles also led to similar findings (quintile 1: adjusted OR 0.89, 95% CI 0.31-2.52; quintile 2: adjusted OR 1.56, 95% CI 0.74-3.30; quintile 3: adjusted OR 0.87, 95% CI 0.49-1.55; quintile 4: adjusted OR 0.79, 95% CI 0.45-1.38; quintile 5: adjusted OR 1.31, 95% CI 0.78-2.21).

2.4 DISCUSSION

This study assessed the association between antihypertensive use and recurrent falls in community-dwelling older adults. We found a non-significant 13% increase in risk of recurrent falls with any antihypertensive use, which is lower than the 24% increased risk of a single fall associated with any antihypertensive use reported in the meta-analysis by Woolcott et al.[14] Moreover, our main finding is also lower than the point estimates detected by Tinetti et al (Hazard Ratios, 1.28-1.40).[15] It is important to note our findings are robust in that our sensitivity analysis designed to address potential confounding by indication by restricting the sample to only those with hypertension (including whether or not it was controlled) found similar results. Unlike the study by Tinetti et al[15], we did not find an increased risk among those with a history of falls at baseline.

This study also explored both dose and duration response relationships with any antihypertensive use and recurrent falls and found no increased risk. This observation is consistent with Tinetti et al, who also failed to find a significant increase in risk of injurious falls in those in the high-intensity antihypertensive dose group (adjusted HR 1.28, 95% CI 0.91-1.80).[15] Neither did we find an increase in risk with respect to duration.

In examining whether recurrent falls risk was elevated with use of any of 8 antihypertensive sub-classes, we found a statistically significant 54% increase in risk of recurrent falls associated with loop diuretic use, but not with the remaining seven. A small, case-control

study similarly found over a two-fold increase in risk of falling in loop diuretic users versus the comparison group (31.1% versus 13.3%; $p<0.05$).[31] A nursing home study using a novel case-crossover design reported that nine persons with a loop diuretic change had a nearly 2.5 fold increased risk of a fall.[32] Few other studies have found this relationship, however. A prospective cohort study of women found no association between loop diuretic use and recurrent falls[33], and Tinetti's analysis of both men and women did not uncover this specific risk.[15] One explanation for the different findings may relate to duration of use, which we found to be an important factor. Further study is needed on the risk of falls with long-term loop diuretic use. One plausible explanation for this potential association is that loop diuretics can cause dehydration and/or hypotension, potentially causing dizziness and leading to a fall.

There are important potential limitations to our study. First, the main outcome of recurrent falls was retrospectively collected via self-report. However, it is a highly specific method in comparison to self-reporting of falls via diary.[21] Second, medication data were collected at fixed annual assessments, preventing us from documenting the exact date in which antihypertensive medications were initiated, changed, or discontinued. Third, while it is possible that there is residual confounding, we were mindful of potential confounding bias and adjusted for common indications for antihypertensive therapy. Moreover, our sensitivity analyses showed similar results when restricted to only those with hypertension and when stratified by those with a baseline falls history. Finally, our analysis focused on older, well-functioning community-dwelling Black and White men and women from the Memphis and Pittsburgh areas, and the generalizability to older adults in other regions or different care settings is unknown.

In conclusion, antihypertensive use overall was not associated with recurrent falls after adjusting for important confounders. Analyzed separately, however, loop diuretics were

significantly associated with recurrent falls. Future research is needed with larger sample sizes in both community and long-term care facility settings with older adults to improve the evidence base on about medication-related fall risk.

Table 1. Characteristics of the Sample at Baseline - Antihypertensives (n=2948)

Variables	**Mean ± SD or N, %**
Demographics	
Female gender	1522 (51.6)
Black race	1203 (40.8)
Site (Pittsburgh)	1466 (49.7)
Age	73.6 ±(2.9
Education Post secondary High school graduate < High school	 1260 (42.7) 954 (32.4) 727 (24.9)
Married	1531 (52.0)
Health Behaviors	
Current smoker	302 (10.2)
Alcohol use (≥1 drink per week)	847 (28.7)
Health Status	
Pulmonary disease	298 (10.1)
Arthritis	1650 (56.0)
Urinary problems	495 (16.8)
Cerebrovascular disease	231 (7.8)
Bodily pain (any in past 30 days)	1942 (65.9)

Table 1 (continued). Characteristics of the Sample at Baseline – Antihypertensives (n=2948)	
Variables	**Mean ± SD or N, %**
Vision problems	
Excellent/Good sight	2346 (79.6)
Fair sight	519 (17.6)
Poor to completely blind	81 (2.8)
Body Mass Index	
Underweight/Normal (<24.9)	947 (32.2)
Overweight (25.0-29.9)	1257 (42.6)
Obese (30+)	744 (25.2)
Excellent/Very good/Good self-rated health	2479 (84.1)
Depressive symptoms (Short CES-D≥10)*	168 (5.7)
Cognitive impairment (3MS<80)*	284 (9.6)
Drugs that increase risk of falls* (benzodiazepines, antipsychotics, opioids)	367 (12.5)
No. prescription medications*, †	1.8 ± 2.0
Health Status [conditions for which antihypertensives are prescribed]	
Self-reported hypertension*	
Controlled	775 (26.3)
Uncontrolled	723 (24.5)
Peripheral arterial disease	149 (5.1)
Benign prostatic hyperplasia	692 (23.5)

Table 1 (continued). Characteristics of the Sample at Baseline - Antihypertensives (n=2948)	
Variables	**Mean ± SD or N, %**
Coronary heart disease	631 (21.4)
Congestive heart disease	85 (2.9)
Diabetes	440 (14.9)
Access to Care	
Hospitalization in previous 12 months	435 (14.8)
Private physician	2319 (78.7)
Prescription Insurance	1861 (63.1)
Flu shot in previous 12 months	2039 (69.2)

*Time –varying

†Excluding drugs that increase falls and antihypertensives

Abbreviations: 3MS = Modified Mini-Mental Status Exam; CES-D = Center for Epidemiologic Studies Depression Scale; CNS= central nervous system; SD= standard deviation

Table 2. Antihypertensive Use Over Time*

Antihypertensive Medication Use	**Year 1 (n=2948) N(%)**	**Year 2 (n=2811) N(%)**	**Year 3 (n=2679) N(%)**	**Year 5 (n=2489) N(%)**	**Year 6 (n=2388) N(%)**
Any use	1677 (56.9)	1636 (58.2)	1622 (60.5)	1676 (67.3)	1673 (70.1)
Long term (≥2 years) for any use	1143/1677 (68.2)	1084/1636 (66.3)	1073 (66.2)	1153/1676 (68.8)	1059/1673 (63.3)
SDD ≥2	283 (9.6)	289 (10.3)	253 (9.4)	300 (12.4)	305 (12.8)
SDD 1-2	546 (18.5)	555 (19.7)	584 (21.8)	668 (26.8)	662 (27.7)
SDD <1	820 (28.7)	774 (28.1)	770 (29.3)	703 (28.4)	695 (29.6)
Specific class use	--	--	--	--	--
Beta blockers	395 (13.4)	409 (14.5)	434 (16.2)	520 (20.9)	572 (24.0)
Alpha blockers	364 (12.4)	317 (11.3)	284 (10.6)	264 (10.6)	238 (10.0)
Loop diuretics	178 (6.0)	195 (6.9)	207 (7.7)	263 (10.6)	265 (11.1)
Thiazide diuretics	582 (19.7)	593 (21.1)	557 (20.8)	599 (24.1)	579 (24.3)
Potassium-sparing diuretics	258 (13.2)	257 (9.1)	239 (8.9)	230 (9.2)	208 (8.7)
Calcium channel blockers	678 (23.0)	662 (23.6)	642 (24.0)	631 (25.4)	611 (25.6)
ACE inhibitors	443 (15.0)	458 (16.3)	479 (17.9)	586 (23.5)	606 (25.4)
ARB	69 (2.3)	95 (3.4)	142 (5.3)	205 (8.2)	249 (10.4)
Vasodilators	35 (1.2)	20 (0.7)	18 (0.7)	9 (0.4)	10 (0.4)

Abbreviations: ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; SDD = standardized daily dose of antihypertensives

*No medication data were collected at year 4 in the Health ABC Study

Table 3. Association between Antihypertensive Use and Recurrent Falls Controlling for Covariates

Antihypertensive Medication Use[*]	**Adj. OR (95% CI)** [†]
Any use	1.13 (0.88-1.46)
Long duration (≥2 years)	1.15 (0.88-1.49)
Short duration	1.11 (0.83-1.49)
SDD ≥2	1.21 (0.82-1.78)
SDD 1-2	1.05 (0.78-1.42)
SDD <1	1.16 (0.88-1.52)
Specific Class Use[‡]	
Beta blockers	1.06 (0.82-1.36)
Alpha blockers	1.25 (0.94-1.67)
Loop diuretics	1.50 (1.11-2.03)
Thiazide diuretics	0.87 (0.68-1.10)
Potassium-sparing diuretics	0.81 (0.56-1.17)
Calcium channel blockers	1.06 (0.84-1.33)
ACE inhibitors	1.10 (0.85-1.42)
ARBs	1.17 (0.80-1.71)

Abbreviations: ACE = angiotensin converting enzyme; adj=adjusted; ARB = angiotensin II receptor blocker; CI=confidence interval; OR=odds ratio

[*]Reference group is No Use

[†]Controlling for variables forced into the model (i.e., site, heart failure, BPH, cognitive impairment, depressive symptoms, self-reported hypertension (controlled/uncontrolled), drugs that increase risk of falls) and those from forward selection procedures (i.e., education, age, marital status, alcohol use, cerebrovascular disease, diabetes, pulmonary disease, arthritis, urinary problems, vision problems, total number of prescription medications, syncope)

‡Each antihypertensive sub-class was run as a separate model and controlled for antihypertensive sub-class use other than the sub-class being evaluated.

Table 4. Multivariable Association between Antihypertensive Use and Recurrent Falls Restricted to those with Self-Reported Hypertension and Stratified by Blood Pressure Control

	Self-reported Hypertension (n=1498)	Controlled (n=775)	Uncontrolled (n=723)
Antihypertensive Medication Use*	**Adj. OR (95% CI)†**	**Adj. OR (95% CI)†**	**Adj. OR (95% CI)†**
Any use	0.99 (0.70-1.42)	0.90 (0.57-1.41)	1.02 (0.62-1.69)
Long duration (≥2 years)	0.96 (0.67-1.38)	0.89 (0.56-1.40)	1.00 (0.60-1.68)
Short duration	1.05 (0.71-1.56)	0.93 (0.55-1.57)	1.06 (0.60-1.85)
SDD ≥2	1.07 (0.68-1.67)	0.86 (0.47-1.57)	1.20 (0.66-2.20)
SDD 1-2	0.93 (0.63-1.36)	0.71 (0.43-1.16)	1.05 (0.60-1.84)
SDD <1	0.99 (0.68-1.46)	1.06 (0.65-1.72)	0.88 (0.51-1.52)
Specific Class Use‡			
Beta blockers	1.18 (0.90-1.54)	1.05 (0.72-1.52)	1.29 (0.88-1.91)
Alpha blockers	1.20 (0.87-1.66)	1.15 (0.76-1.73)	1.12 (0.70-1.96)
Loop diuretics	1.45 (1.02-2.06)	1.47 (0.92-2.37)	1.48 (0.90-2.44)
Thiazide diuretics	0.91 (0.71-1.16)	0.77 (0.54-1.11)	1.02 (0.72-1.44)
Potassium-sparing diuretics	0.76 (0.51-1.14)	0.72 (0.42-1.21)	0.88 (0.48-1.61)
Calcium channel blockers	1.04 (0.81-1.32)	0.87 (0.62-1.23)	1.18 (0.85-1.64)
ACE inhibitors	1.10 (0.83-1.45)	1.20 (0.83-1.73)	1.06 (0.73-1.53)
ARBs	1.19 (0.82-1.73)	0.94 (0.54-1.64)	1.31 (0.78-2.20)

Abbreviations: ACE = angiotensin converting enzyme; adj=adjusted; ARB = angiotensin II receptor blocker; CI=confidence interval; OR=odds ratio; MV=multivariable

*Reference group is No Use

[†]Controlling for variables forced into the model (i.e., site, heart failure, BPH, cognitive impairment, depressive symptoms, drugs that increase risk of falls) and those from forward selection procedures (i.e., age, alcohol use, cerebrovascular disease, diabetes, pulmonary disease, arthritis, vision problems, total number of prescription medications)

[‡]Each antihypertensive sub-class was run as a separate model and controlled for antihypertensive sub-class use other than the sub-class being evaluated.

Table 5. Multivariable Association between Antihypertensive Use and Recurrent Falls Stratified by History of Falls at Baseline (n=2948)

	History of Falls (n=632)	No History of Falls (n=2316)
Antihypertensive Medication Use*	**Adj. OR (95% CI) †**	**Adj. OR (95% CI) †**
Any use	0.93 (0.51-1.70)	0.68 (0.39-1.17)
Long duration (≥2 years)	0.83 (0.43-1.60)	0.80 (0.45-1.41)
Short duration	1.10 (0.54-2.22)	0.47 (0.23-0.96)
SDD ≥2	1.22 (0.50-3.01)	0.55 (0.23-1.33)
SDD 1-2	0.77 (0.35-1.70)	0.67 (0.34-1.30)
SDD <1	0.97 (0.51-1.86)	0.71 (0.39-1.26)
Specific Class Use‡		
Beta blockers	0.69 (0.33-1.43)	1.13 (0.63-2.03)
Alpha blockers	1.49 (0.69-3.23)	1.00 (0.50-2.02)
Loop diuretics	1.52 (0.93-2.48)	1.50 (1.00-2.23)
Thiazide diuretics	1.01 (0.54-1.92)	0.55 (0.31-0.99)
Potassium-sparing diuretics	0.90 (0.37-2.21)	0.90 (0.43-1.87)
Calcium channel blockers	1.31 (0.74-2.35)	1.14 (0.70-1.85)
ACE inhibitors	0.66 (0.31-1.42)	0.77 (0.43-1.39)
ARBs	0.97 (0.29-3.22)	1.55 (0.45-5.4)

Abbreviations: ACE = angiotensin converting enzyme; adj=adjusted; ARB = angiotensin II receptor blocker; CI=confidence interval; OR=odds ratio; MV=multivariable

*Reference group is No Use

†Controlling for variables forced into the model (i.e., site, heart failure, BPH, cognitive impairment, depressive symptoms, self-reported hypertension (controlled/uncontrolled), drugs that increase risk of

falls) and those from forward selection procedures (i.e., education, age, marital status, alcohol use, cerebrovascular disease, diabetes, pulmonary disease, arthritis, urinary problems, vision problems, total number of prescription medications, syncope)

‡Each antihypertensive sub-class was run as a separate model and controlled for antihypertensive sub-class use other than the sub-class being evaluated.

3.0 ANTICHOLINERGIC USE AND RECURRENT FALLS IN COMMUNITY-DWELLING OLDER ADULTS: FINDINGS FROM THE HEALTH ABC STUDY

3.1 INTRODUCTION

Anticholinergic medication use has been reported to be as high as 25% among community-dwelling older adults.[34-36] Older adults may be more susceptible to anticholinergic adverse effects due to several reasons. One is decreased systemic clearance of many anticholinergic drugs. For example, because of age-related decreases in hepatic metabolism and systemic clearance, the half-life of cyclobenzaprine in older adults, a well-known skeletal muscle relaxant with strong anticholinergic effects, is nearly twice as long as that seen in their younger counterparts.[37] Another reason is the decrease in central cholinergic activity due to decreased levels of acetylcholine synthesis or the number of acetylcholine receptors. This may account for the increased pharmacodynamic sensitivity seen in older adults with anticholinergic exposure.[38] In addition, there is evidence of increased blood-brain barrier permeability to drugs, including anticholinergics, in older adults. Finally, there is a reduction in P-glycoprotein activity as an efflux pump to transport drugs, including anticholinergics, out of the aged brain.[39] These reasons make older adults more vulnerable to anticholinergic adverse effects.

One such adverse effect that may occur from anticholinergic use is falling. Of note, 18-40% of community-dwelling elderly fall yearly[10-12], of whom nearly 50% have recurrent

falls.[12,13] While it is generally accepted that anticholinergic use can lead to a fall, to date the results from studies assessing the association between anticholinergic use and falls are mixed.[35,40-42] More specifically, direct evidence of the association between the use of anticholinergic medications and falls among community-dwelling older adults is limited.[35,42] Furthermore, because in the US over-the-counter (OTC) medication data are not available in administrative pharmacy claims, there is limited prior literature taking this type of medication exposure into account. Thus, a definitive answer to the association between the use of anticholinergic medications and falls in older patients deserves further study. Accordingly, the immediate objective is to conduct a thorough longitudinal analysis to assess the association between anticholinergic use across multiple anticholinergic sub-classes and recurrent falls.

3.2 METHODS

3.2.1 Study design, data source, and sample

This longitudinal study used data from the Health, Aging, and Body Composition (Health ABC) study, a population-based, prospective, observational study of community-dwelling older adults. This study was approved by the University of California at San Francisco (UCSF), University of Pittsburgh, and University of Tennessee Memphis Institutional Review Boards, and informed consent was obtained from each participant prior to data collection. The baseline sample included 3,075 Black and White men and women aged 70-79 years who reported no difficulty walking ¼ mile, or climbing 10 steps and lived in specified zip codes surrounding Pittsburgh, PA and Memphis, TN.[5] The sample for the current analysis included 2,948 older adults at year 1

with complete medication use and fall data the following year followed through year 6 for anticholinergic medications and year 7 for recurrent falls.

3.2.2 Data collection and management

Participants were seen annually during a clinic or home visit and detailed physiologic and self-report questionnaire measurements (including demographics, health behavior/status (including medications), and access to health care factors) were collected.[5] Detailed medication data were collected in clinic or at home about products taken in the previous month using a state of the art "brown bag" review method.[16,17] A similar data collection approach was used for telephone interviews if they were unable to be seen in person. Studies have shown that medication use information collected by either the "brown bag" or telephone methods is highly accurate and concordant with information about dispensed prescription drugs in claims data.[18,19] For all medications, the interviewer recorded the name, strength, prescription type (prescription or over-the-counter), dosage form, and the number of dosage forms the respondents said they had used the previous day, week, or month. The medication data collected for the Health ABC Study were edited and coded using the Iowa Drug Information System (IDIS) Drug Vocabulary and Thesaurus.[16] IDIS is a hierarchical coding system with 8 character unique codes for specific drug ingredients, chemical and therapeutic categories. This therapeutic category code allows drugs to be assigned to one of 20 major therapeutic classes and 200 sub-classes that are based upon an expanded version of the American Hospital Formulary Services format.[20]

Teleform was used to create scannable forms for direct data entry. Missing and questionable values were highlighted by the software for visual review and online editing.

Additional ranges checks and data cleaning were conducted at the UCSF Coordinating Center. De-identified SAS® data files were created for purposes of analyses.

3.2.3 Primary outcome

The number of falls in which the participant landed on the floor or ground in the previous twelve months was assessed at the year following medication use data collection (e.g., year 1 antihypertensive use and year 2 falls) for each wave (five waves). The primary outcome was recurrent falls (≥ two) in the ensuing 12 months following report of medication use. This method of fall recall (in the previous 12 months) has been shown to be highly specific (91% – 95%) in comparison with that reported using more frequent assessments.[21] Recurrent falls (as opposed to single falls) may be more clinically important since they can be a marker for those with an increased risk of physical and cognitive status problems, and other morbidity and mortality in the elderly.[12]

3.2.4 Primary independent variable

Medications with anticholinergic properties were grouped based on the 2012 AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults into the following therapeutic classes: 1) *antiemetic / antivertigo / antihistamine* (IDIS codes: 4000003, 4000006, 4000010, 4000012, 4000018, 4000054, 4000061, 4000068, 4000078, 4000079, 4000083, 4000084, 4000091, 4000099, 12080009, 28160807, 56220003, 56220005, 56220096); 2) *antidepressant / antipsychotic* (IDIS codes: 28160601, 28160602, 28160650, 28160681, 28160688, 28160689, 28160695, 28160702, 28160836, 28160858, 28160912, 28160913, 56220089); 3)

gastrointestinal / urinary antispasmodics (IDIS codes: 12080001, 12080005, 12080008, 12080009, 12080039, 12080047, 12080079, 52240008, 86000004, 86000047); and 4) miscellaneous (skeletal muscle relaxants, antiparkinson agents, and cardiac) (IDIS codes: 12080802, 12080804, 12080806, 12200009, 24040024).[43] Any use was defined as the use of any medication contained in these 4 classes. To evaluate the possibility of a dose-response relationship, we used a previously published approach; the daily dose was calculated for current users for each individual anticholinergic medication by multiplying the number of dosage forms taken the previous day by the strength of the medication reported at the interview.[13] The daily dose was then converted to a standardized daily dose (SDD) by dividing it by the ***minimum effective dose*** per day as noted in standard references.[44] Thus, a person taking 1.0 standardized anticholinergic drug unit would have taken the minimum recommended effective daily dose for one agent. The standardized dose was summated for all anticholinerigcs, regardless of class, taken daily. Finally, to examine the impact of duration, long-term use was operationally defined as $\geq$ 2 years and short-term use as < 2 years.[13]

3.2.5 Control variables

To address potential confounding, we controlled for a number of demographic, health status/behavior, and access to care factors.[12,13] Demographic factors included age, sex, race, site, education (less than a high school education, high school graduate, and post-secondary education), and marital status (never married, married, previously married).

Health behavior factors included current smoking status and alcohol use. Health status factors included self-reported pulmonary disease, urinary problems, coronary heart disease, congestive heart disease, cerebrovascular disease, diabetes, hypertension, peripheral artery

disease, hearing impairment, vision (excellent/good sight, fair sight, and poor to completely blind), and body mass index (underweight/normal, <24.9; overweight, 25.0-29.9; and obese, ≥30). Self-rated global health was dichotomized as excellent/very good/good vs. fair/poor. We created a time-varying dichotomous variable for exposure to any drug that increases the risk of falls (***non-anticholinergic*** central nervous system medications, including benzodiazepines, antipsychotics, opioids).[13] A continuous time-varying variable was created for the total number of prescription medications (excluding dugs that increase falls, and anticholinergic drugs) per participant. Access to care factors included dichotomous variables for hospitalization in previous 12 months, private physician, prescription insurance, and flu shot in previous 12 months.[25]

Anticholinergics can be used for a number of conditions. Therefore, to control for potential confounding by indication we created time-varying dichotomous variables for depressive symptoms (Short Center for Epidemiologic Studies-Depression Scale ≥10) – for which tricyclic antidepressants may be used[23]; cognitive impairment (The Modified Mini-Mental State Test [3MS] <80) – for which antipsychotics may be used to treat the behavioral symptoms of cognitive impairment[24]; back pain in past 12 months – for which skeletal muscle relaxants may be used; anxiety symptoms – for which several anticholinergic agents may be used; and sleep problems – for which antihistamines may be used.[13]

3.2.6 Statistical analysis

We used appropriate descriptive statistics for summarization and generalized estimating equations (GEE) for eliciting the main findings.[26-28] First, we assessed the unadjusted association between anticholinergic use and recurrent falls over time. Second, *a priori* covariates that may affect recurrent falls were included: site, cognitive impairment, depressive symptoms, non-

anticholinergic drugs that increase the risk of falls, urinary problems, back pain, and sleep problems. Each anticholinergic sub-class was run as a separate model and controlled for anticholinergic sub-class use other than the sub-class being evaluated. Finally, additional covariates were selected using a forward stepwise selection approach applied separately for each of three domains of covariates (demographic, health status/behavior, and access to health care). Specifically, stepwise detected covariates and those deemed important *a priori* were included in the final GEE model. All analyses were conducted using SAS® software (version 9.3; SAS Institute, Cary, NC) with GENMOD procedure to obtain main results.

3.3 RESULTS

At baseline, the mean (standard deviation) age was 73.6 (2.9) years, 51.6% were female, and 40.8% were black (**Table 6**). In addition, approximately 40% reported back pain in the past 12 months, and the vast majority had excellent/very good/good self-reported health. Baseline characteristics of anticholinergic users versus nonusers are shown in Table 1. The groups were found to have several differences. For example, anticholinergic users were more likely to have fair/poor self-rated health, urinary problems, back pain the past 12 months, sleep problems, anxiety symptoms, and depressive symptoms.

Table 7 shows the prevalence of anticholinergic use over time. At baseline, 16% reported the use of one or more anticholinergics, with antiemetic / antivertigo / antihistamine being the most common class used (9.8%). At baseline, half took an anticholinergic for $\geq$ 2 years and half for < 2 years, with three-fourths taking them in doses $\leq$ 2 SDDs. By year 6, the prevalence of anticholinergic use remained consistent at 15.8%, with antiemetic / antivertigo / antihistamine

remaining the most common category used (6.6%). Moreover, at year 2, 8% of participants reported having ≥ 2 falls in the previous year. This rate remained somewhat stable over the next four waves (7.5 to 10.4%).

Table 8 shows the results of the multivariable GEE analyses, controlling for potential demographic, health status/behavior, and access to care factors. Adjusted modeling revealed no statistically significant increase in risk of recurrent falls in older anticholinergic users (adjusted OR 1.34, 95% CI 0.93-1.93). Similarly, no increase in risk was found among those taking higher SDDs or those with longer duration of use. In addition, none of the 3 anticholinergic sub-classes were found to be significantly associated with recurrent falls. Finally, **Table 9** shows the results of the multivariable GEE analyses, controlling for key covariates forced into the model, including and not including the important variable, cognitive impairment. Similar point estimates were seen compared to the fully adjusted model as well as between these two models.

3.4 DISCUSSION

This study presents some of the first data to longitudinally assess the association between anticholinergic use – measured via detailed dosage and duration data and including both prescription and OTC drug use – and recurrent falls in community-dwelling older adults. We found no statistically significant association between any anticholinergic use and recurrent falls after adjusting for important potential confounders. In addition, we did not find a statistically significant association between anticholinergic dose or duration response and recurrent falls.

These findings are consistent with a study of community-dwelling older Canadians using 10 years of prospective data from the Canadian Multicentre Osteoporosis Study (MaMos).[42]

Fraser et al sought to determine if anticholinergic medication use was associated with falls in 7,753 participants (mean age, 71.1 years for anticholinergic users vs. 66.7 years for nonusers).[42] They found that unadjusted anticholinergic use was associated with falls (OR=1.50, 95% CI=1.14-1.98), but the association was no longer significant after covariate adjustment (adjusted OR=1.25, 95% CI=0.91-1.72).[42] Similar results occurred at years 5 and 10. It is important to note that this study used any fall as the primary outcome, whereas our study used recurrent falls, and that the Fraser et al study conducted three cross-sectional analyses without using longitudinal analyses (e.g., GEE).[42] Despite these differences, our findings are essentially the same.

Previous studies have reported anticholinergic use to be significantly associated with falls in older adults[40,41], and there is biologic plausibility to support the mechanism by which this could occur. For example, anticholinergic medications are known to cause dizziness and lightheadedness, and pharmacokinetic/ pharmacodynamic changes in older adults increase their risk for such side effects. Thus, a logical explanation exists for an association between anticholinergic use and falls in older adults, which has been perpetuated for years in clinical and research settings. However, the literature on the association between anticholinergic use and falls in community-dwelling older adults is mixed.[35,40-42] One possible reason for this lack of clarity may be because previous studies have not controlled for underlying medical conditions for which anticholinergic medications are used (e.g., back pain, depression, cognitive impairment). The potential for confounding by indication is a major threat to studies assessing medication use in older adults. To address this, we controlled for key conditions for which older adults might use anticholinergics. Taken together, our findings in addition to the results from Fraser et al suggest that after controlling for these important underlying medical conditions for which anticholinergic medications might be used, there is no statistically significant association between

anticholinergic drugs and falls in community-dwelling elders.[42] Simply put, while anticholinergic drugs should generally be avoided in the elderly, individual risks and benefits for each patient should be considered.[35]

Moreover, although we did not assess drug-disease interactions in this study, one could presume that the older adults at highest risk for falls are those with underlying medical conditions that independently increase the risk of falling (e.g., depression, cognitive impairment). Therefore, older adults with these conditions should be carefully monitored if they are receiving an anticholinergic medication. This approach is supported by the AGS Beers Criteria, which identify important drug-disease interactions involving anticholinergic medications.[43]

There are important potential limitations to our study. First, the question of statistical power may be a concern. In order to assess the power available in the current study, we conducted a power assessment. We base the power assessment on a test of unadjusted association between the measure of any anticholinergic use and the primary outcome, previously published literature, and our prior analyses of Health ABC Study data. We had found that medication data with subsequent falls data (the following year) had been available for 2948, 2811, 2679, 2489, and 2449 participants at years 1, 2, 3, 5, and 6, respectively. The proportion of any anticholinergic drug use was 14-16% at any given year, and 7-10% of participants had experienced recurrent falls. Due to the potential correlation between the years of the same participants, we conservatively assumed the above 13,376 observations effectively contain information from half as many independent observations or 6,688 (i.e., design effect of 2). Given these parameters, we would have been able to detect statistical significance of an odds ratio as small as 1.35 with 80% power in a two-tailed test at the alpha=0.05 level for the any anticholinergic use measure and the primary outcome. Given that the point estimate for our main

finding was also 1.34 and the fact that we did not observe the combination of a high odds ratio and a very wide confidence interval, it is unlikely that lack of statistical power played a major role in arriving at our conclusion. However, a prospectively designed study with adequate statistical power is needed to arrive at definitive conclusions.

Second, the main outcome of recurrent falls was retrospectively collected via self-report. However, it is a highly specific method in comparison to self-reporting of falls via diary.[21] Third, medication data were collected at fixed annual assessments, preventing us from documenting the exact date in which anticholinergics were initiated, changes, or discontinued. Fourth, while it is possible that there is residual confounding, we were mindful of potential confounding bias and adjusted for common indications for anticholinergic therapy. Finally, our analysis focused on older, well-functioning community-dwelling Black and White men and women from the Memphis and Pittsburgh areas, and the generalizability to older adults in other regions or different care settings is unknown.

In conclusion, increased point estimates suggest an association of anticholinergic use with recurrent falls, but the associations did not reach statistical significance. Future studies are needed to examine other measures of anticholinergic burden, and their associations with other outcomes such as cognitive function.

Table 6. Characteristics of the Sample at Baseline - Anticholinergics (n=2948)

Variables	**Anticholinergic use, mean ± SD or N (%)** (n = 467)	**No anticholinergic use, mean ± SD or N (%)** (n = 2481)	**P value**
Sociodemographics			
Female gender	308 (65.9)	1214 (48.9)	<0.0001
Black race	160 (34.3)	1043 (42.0)	0.002
Age, mean (SD)	73.6 (2.8)	73.6 (2.9)	0.71
Pittsburgh site	189 (40.5)	1277 (51.5)	<0.0001
Education Post secondary High school graduate < High school	 211 (45.2) 153 (32.8) 102 (21.8)	 1049 (42.3) 801 (32.3) 625 (25.2)	0.274
Married	208 (44.5)	1323 (53.3)	<0.001
Health Behaviors/Status			
Current smoker	52 (11.1)	250 (10.1)	0.493
Alcohol use (≥1 drink per week)	126 (27.0)	721 (29.1)	0.363
Pulmonary disease	60 (12.9)	238 (9.6)	0.032
Urinary problems*	213 (45.6)	928 (37.4)	0.001
Coronary heart disease	94 (20.1)	537 (21.6)	0.459
Congestive heart disease	11 (2.4)	74 (3.0)	0.463
Cerebrovascular disease	43 (9.2)	188 (7.6)	0.229

Diabetes	70 (15.0)	370 (14.9)	0.974
Hypertension	232 (49.7)	1266 (51.0)	0.593
Peripheral arterial disease	21 (4.5)	128 (5.2)	0.522
Hearing impairment	42 (9.0)	220 (8.9)	0.923
Vision problems Excellent/good sight Fair sight Poor to completely blind	 375 (80.3) 85 (18.2) 7 (1.5)	 1971 (79.4) 434 (17.5) 74 (3.0)	0.193
Body Mass Index Underweight/normal (<24.9) Overweight (25.0-29.9) Obese (30+)	 158 (33.8) 183 (39.2) 126 (27.0)	 789 (31.8) 1074 (43.3) 618 (24.9)	0.256
Self-rated health Excellent/very good/good Fair/poor	 378 (80.9) 89 (19.1)	 2101 (84.7) 376 (15.2)	0.035
Drugs that increase risk of falls (benzodiazepines, antipsychotics, opioids)[*]	167 (35.8)	218 (8.8)	<0.0001
Number of prescription medications[*,†]	2.1 (2.4)	1.7 (1.9)	0.0001

Health Status [conditions for which anticholinergics are prescribed]			
Depressive symptoms (Short CES-D≥10)*	40 (8.6)	128 (5.2)	0.003
Cognitive impairment (3MS<80)*	29 (6.2)	255 (10.3)	0.006
Back Pain in past 12 months*	224 (48.0)	1017 (41.0)	0.005
Anxiety symptoms*	100 (21.4)	314 (12.7)	<0.0001
Sleep problems*	135 (28.9)	556 (22.4)	0.002
Access to Health Care			
Hospitalization in previous 12 months	89 (19.1)	346 (14.0)	0.004
Private physician	382 (81.8)	1937 (78.1)	0.071
Prescription insurance	294 (63.0)	1567 (63.2)	0.939
Flu shot in previous 12 months	339 (72.6)	1700 (68.5)	0.081

*Time-varying

†Excluding drugs that increase risk of falls and anticholinergic drugs

Abbreviations: 3MS = Modified Mini-Mental Status Exam; CES-D = Center for Epidemiologic Studies Depression Scale; CNS= central nervous system; SD= standard deviation

Table 7. Anticholinergic Use over Time*

Anticholinergic Medication Use	**Year 1 (n=2948) n, %**	**Year 2 (n=2811) n, %**	**Year 3 (n=2679) n, %**	**Year 5 (n=2489) n, %**	**Year 6 (n=2388) n, %**
Any Use	471 (16.0)	402 (14.3)	375 (14.0)	384 (15.4)	378 (15.8)
ACSD ≥2	120 (25.5)	118 (29.4)	102 (27.2)	79 (20.6)	95 (25.1)
ACSD 1-2	161 (34.2)	150 (37.3)	163 (43.5)	189 (49.2)	188 (49.7)
ACSD <1	190 (40.3)	134 (33.3)	110 (29.3)	116 (30.2)	95 (25.1)
Long term use (≥2 years)	232 (49.3)	180 (44.8)	160 (42.7)	187 (48.7)	160 (42.3)
Short term use	239 (50.7)	222 (55.2)	215 (57.3)	197 (51.3)	218 (57.7)
Specific class use*	--	--	--	--	--
Antiemetic / antivertigo /	290 (9.8)	197 (7.0)	183 (6.8)	177 (7.1)	158 (6.6)
antihistamines	118 (4.0)	112 (4.0)	109 (4.1)	99 (4.0)	107 (4.5)
Antidepressants /	70 (2.4)	106 (3.8)	94 (3.5)	127 (5.1)	138 (5.8)
antipsychotics	26 (0.9)	23 (0.8)	23 (0.9)	15 (0.6)	15 (0.6)
GI / urinary antispasmodics					
Miscellaneous: SMR /					
Antiparkinson / Cardiac					

*Medication data were not collected at year 4 in the Health ABC Study

Abbreviations: ACSD: anticholinergic standardized dose; GI: gastrointestinal; SMR: skeletal muscle relaxant

Table 8. Association between Anticholinergic Use and Recurrent Falls Controlling for Covariates

Anticholinergic Medication Use*	**Adjusted OR (95% CI)†**
Any Use	1.34 (0.93-1.93)
Long duration (≥2 years)	1.36 (0.84-2.21)
Short duration	1.32 (0.83-2.10)
SDD – ≥2	1.54 (0.84-2.82)
SDD – 1-2	1.40 (0.80-2.45)
SDD – <1	1.17 (0.68-2.00)
Specific Class Use‡	
Antiemetic / antivertigo / antihistamines	1.40 (0.91-2.13)
Antidepressants / antipsychotics	1.14 (0.59-2.18)
Gastrointestinal / urinary antispasmodics and Miscellaneous	1.26 (0.64-2.48)

Abbreviations: OR=odds ratio; CI=confidence interval

*Reference group is No Use

†Controlling for variables forced into the model (i.e., site, cognitive impairment, depression, drugs that increase the risk of falls, urinary problems, back pain, and sleep problems) and those from forward selection procedures (i.e., smoking, alcohol use, cerebrovascular disease, diabetes, vision problems, anxiety, and total number of prescription medications)

‡Each anticholinergic sub-class was run as a separate model and controlled for anticholinergic sub-class use other than the sub-class being evaluated

Table 9. Association between Anticholinergic Use and Recurrent Falls Controlling for Key Covariates – Including and Not Including Cognitive Impairment

Anticholinergic Medication Use*	**Including Cognitive Impairment – Adjusted OR (95% CI)†**	**Not Including Cognitive Impairment – Adjusted OR (95% CI)†**
Any Use	1.40 (0.99-1.99)	1.40 (0.99-1.98)
Long duration (≥2 years)	1.42 (0.90-2.22)	1.41 (0.90-2.22)
Short duration	1.39 (0.89-2.19)	1.38 (0.88-2.17)
SDD – ≥2	1.82 (1.02-3.23)	1.82 (1.02-3.23)
SDD – 1-2	1.42 (0.83-2.43)	1.42 (0.83-2.42)
SDD – <1	1.16 (0.69-1.97)	1.15 (0.68-1.95)
Specific Class Use‡	--	--
Antiemetic / antivertigo / antihistamines	1.38 (0.92-2.07)	1.37 (0.92-2.06)
Antidepressants / antipsychotics	1.23 (0.66-2.31)	1.24 (0.66-2.31)
Gastrointestinal / urinary antispasmodics and Miscellaneous	1.59 (0.83-3.04)	1.58 (0.83-3.03)

*Reference group is No Use

†Controlling for variables forced into the model (i.e., site, depression, drugs that increase the risk of falls, urinary problems, back pain, and sleep problems)

‡Each anticholinergic sub-class was run as a separate model and controlled for anticholinergic sub-class use other than the sub-class being evaluated

4.0 ANTIDEPRESSANT USE AND RECURRENT FALLS IN COMMUNITY-DWELLING OLDER ADULTS: FINDINGS FROM THE HEALTH ABC STUDY

4.1 INTRODUCTION

Falls and depressive symptoms are common in older adults and pose a significant burden on the healthcare system and society.[45] Prevalence of mild depressive symptoms in older adults has been estimated to be 15% for community populations; major clinical depression is less common, with a prevalence of 0.4% to 2%.[45] Several studies have reported associations between depressive symptoms and falls in older adults, and it has been suggested that common pathways for both conditions can explain such associations. Although many older adults with symptoms of depression are not treated, the pharmacologic treatment for depression with antidepressants has also been consistently associated with risk of falls.[46] Antidepressants are thought to contribute to falls through several different mechanisms although the exact mechanisms are not known. While selective serotonin reuptake inhibitors (SSRIs) were originally thought to be safer alternatives to the tricyclic antidepressants (TCAs) regarding falls risk, the literature is mixed on their relative safety.[47]

Furthermore, the magnitude of the increased risk of falling with an antidepressant is about the same as the excess risk found in patients with untreated depression.[47] Moreover, when an antidepressant is necessary, the clinician needs to estimate the risk of falls consequent upon

prescribing or continuing with it, and to estimate the relative risks of falls with difference classes of drug. Many patients with a history of depression are maintained on an antidepressant over the long term but might be able to manage without drug treatment. In cases where the depression has been a major illness or has been recurrent, it may be necessary to continue with antidepressants, whatever the falls risk.[47] Moreover, recurrent falls (as opposed to single falls) may be more clinically important since they can be a marker for those with an increased risk of physical and cognitive status problems, and other morbidity and mortality in the elderly (6). However, it is not clear what the comparative risk of falls is for various antidepressant agents among community-dwelling older adults who have a history of a fall/fracture (i.e., those at the highest risk of future falls). Thus, a thorough longitudinal analysis is needed to assess the association between antidepressant use and the important outcome of recurrent falls, particularly among those with a history of falls/fractures.

4.2 METHODS

4.2.1 Study design, data source, and sample

This longitudinal study used data from the Health, Aging, and Body Composition (Health ABC) study, a population-based, prospective, observational study of community-dwelling older adults. This study was approved by the University of California at San Francisco (UCSF), University of Pittsburgh, and University of Tennessee Memphis Institutional Review Boards, and informed consent was obtained from each participant prior to data collection. The baseline sample included 3,075 Black and White men and women aged 70-79 years who reported no

difficulty walking ¼ mile, or climbing 10 steps and lived in specified zip codes surrounding Pittsburgh, PA and Memphis, TN.[5] The sample for the current analysis included 2,948 older adults at year 1 with complete medication use and fall data the following year followed through year 6 for antidepressant medications and year 7 for recurrent falls.

4.2.2 Data collection and management

Participants were seen annually during a clinic or home visit and detailed physiologic and self-report questionnaire measurements (including demographics, health behavior/status (including medications), and access to health care factors) were collected.[5] Detailed medication data were collected in clinic or at home about products taken in the previous month using a state of the art "brown bag" review method.[16,17] A similar data collection approach was used for telephone interviews if they were unable to be seen in person. Studies have shown that medication use information collected by either the "brown bag" or telephone methods is highly accurate and concordant with information about dispensed prescription drugs in claims data.[18,19] For all medications, the interviewer recorded the name, strength, dosage form, and the number of dosage forms the respondents said they had used the previous day, week, or month. The medication data collected for the Health ABC Study were edited and coded using the Iowa Drug Information System (IDIS) Drug Vocabulary and Thesaurus.[6] IDIS is a hierarchical coding system with 8 character unique codes for specific drug ingredients, chemical and therapeutic categories. This therapeutic category code allows drugs to be assigned to one of 20 major therapeutic classes and 200 sub-classes that are based upon an expanded version of the American Hospital Formulary Services format.[20]

Teleform was used to create scannable forms for direct data entry. Missing and questionable values were highlighted by the software for visual review and online editing. Additional ranges checks and data cleaning were conducted at the UCSF Coordinating Center. De-identified SAS® data files were created for purposes of analyses.

4.2.3 Primary outcome

The number of falls in which the participant landed on the floor or ground in the previous twelve months was assessed at the year following medication use data collection (e.g., year 1 antihypertensive use and year 2 falls) for each wave (five waves). The primary outcome was recurrent falls (≥ two) in the ensuing 12 months following report of medication use. This method of fall recall (in the previous 12 months) has been shown to be highly specific (91% – 95%) in comparison with that reported using more frequent assessments.[21]

4.2.4 Primary independent variable

Antidepressant medications were grouped as follows: 1) selective serotonin reuptake inhibitors (SSRI) (IDIS codes: 28160701, 28160703, 28160704, 28160705, 28160702, 28160711); 2) tricyclic antidepressants (TCA) (IDIS codes: 28160601, 28160602, 28160650, 28160681, 28160688, 28160689, 28160695); and 3) others (bupropion, venlafaxine, mirtazapine, trazodone, phenelzine) (IDIS codes: 28160505, 28160434, 28160458, 28160617, 28160415). Any use was defined as the use of any medication contained in these 3 sub-classes. To evaluate the possibility of a dose-response relationship, the daily dose was calculated for current users for each individual antidepressant medication by multiplying the number of dosage forms taken the

previous day by the strength of the medication reported at the interview. The daily dose was then converted to a standardized daily dose (SDD) by dividing it by the ***minimum effective dose*** per day as noted in standard references.[44] Thus, a person taking 1.0 standardized antidepressant drug unit would have taken the minimum recommended effective daily dose for one agent. The standardized dose was summated for all antidepressants, regardless of class, taken daily. Finally, to examine the impact of duration, long-term use was operationally defined as ≥ 2 years and short-term use as < 2 years.[13]

4.2.5 Control variables

To address potential confounding, we controlled for a number of demographic, health status/behavior, and access to care factors.[12,13] Demographic factors included age, sex, race, site, education (less than a high school education, high school graduate, and post-secondary education), and marital status (never married, married, previously married).

Health behavior factors included smoking status and alcohol use. Health status factors included pulmonary disease, arthritis, urinary problems, cerebrovascular disease, peripheral artery disease, benign prostatic hyperplasia, coronary heart disease, congestive heart disease, diabetes, vision (excellent/good sight, fair sight, and poor to completely blind), body mass index (underweight/normal, <24.9; overweight, 25.0-29.9; and obese, ≥30), self-reported hypertension, and cognitive impairment (The Modified Mini-Mental State Test [3MS] <80).[24] Self-rated global health was dichotomized as excellent/very good/good vs. fair/poor.

To control for potential confounding by indication we created a time-varying dichotomous variable for depressive symptoms (Short Center for Epidemiologic Studies-Depression [CES-D] Scale ≥10).[23] We also included a self-reported variable for history of

depression, bodily pain in the past 30 days, sleep problems, anxiety symptoms, and exposure to any drug that increases the risk of falls (central nervous system medications, including benzodiazepines, antipsychotics, and opioids).[13,23,24] A continuous time-varying variable was created for the total number of prescription medications (excluding dugs that increase falls, and antidepressant drugs) per participant. Access to care factors included dichotomous variables for hospitalization in previous 12 months, private physician, prescription insurance, and flu shot in previous 12 months.[25]

4.2.6 Statistical Analysis

We used appropriate descriptive statistics for summarization and generalized estimating equations (GEE) for eliciting the main findings.[26-28] First, we assessed the unadjusted association between antidepressant use and recurrent falls over time. Second, *a priori* covariates that may affect recurrent falls were included: site, depressive symptoms, self-reported depression, non-antidepressant drugs that increase the risk of falls, bodily pain, sleep problems, and anxiety symptoms. Each antidepressant sub-class was run as a separate model and controlled for antidepressant sub-class use other than the sub-class being evaluated. Finally, additional covariates were selected using a forward stepwise selection approach applied separately for each of three domains of covariates (demographic, health status/behavior, and access to health care). Specifically, stepwise detected covariates and those deemed important *a priori* were included in the final GEE model.

To address potential confounding, we ran sensitivity analyses. First, we ran bivariate and multivariable analyses stratified by presence of a history of falls and/or fracture (after age 45) at baseline. Then, we modified our measure of depressive symptoms (CES-D) by isolating those

items assessing somatic and non-somatic depressive symptoms.[48] We then ran bivariate and multivariable analyses stratified by presence of depressive symptoms using the original measure (including both somatic and non-somatic depressive symptoms; CES-D $\geq$10) and the modified measure (including only non-somatic depressive symptoms; CES-D $\geq$5). All analyses were conducted using SAS® software (version 9.3; SAS Institute, Cary, NC) with GENMOD procedure to obtain main results.

4.3 RESULTS

At baseline, the mean (standard deviation) age was 73.6 (2.9) years, 51.6% were female, and 40.8% were black (**Table 9**). In addition, 5.7% had evidence of serious depressive symptoms, and 37.0% had a history of falls/fractures. Baseline characteristics of antidepressant users versus nonusers are shown in Table 1. The groups were found to have several differences. For example, antidepressant users were more likely to have urinary problems, sleep problems, anxiety symptoms, and a hospitalization in the previous 12 months. Moreover, raw scores for the CES-D items assessing non-somatic depressive symptoms at baseline are presented in **Table 10**, and the prevalence of depressive symptoms per the CES-D with and without items assessing somatic symptoms over time are presented in **Table 11**.

Table 12 shows the prevalence of antidepressant use over time. At year 1, 5.8% reported antidepressant use. The most common class used was SSRIs, 55.3% were short-term users, and 57.1% of users took 1-2 SDDs. By year 6, the prevalence of antidepressant use increased to 9.8%, with SSRIs remaining the most common category used (6.6%). The mean (standard deviation) SDDs for each of the three sub-classes are as follows: SSRI, 1.74 (0.94); TCA, 3.45

(2.63); and Other, 2.49 (1.98) (data not shown). Moreover, at year 2, 8% of participants reported having ≥ 2 falls in the previous year. This rate remained somewhat stable over the next four waves (7.5 to 10.4%).

Table 13 shows the results of the multivariable GEE analyses, controlling for demographic, health status/behavior (including depressive symptoms and self-reported depression), and access to care factors. Adjusted modeling found a statistically significant increase in risk of recurrent falls in antidepressant users (adjusted odds ratio=AOR=1.48; 95% confidence interval=CI=1.12-1.96). We also found an increase in risk among those taking SSRIs (AOR=1.62, 95% CI=1.15-2.28), those with short duration of use (AOR=1.47, 95% CI=1.04-2.00), and those taking 1-2 SDD (AOR=1.59, 95% CI=1.15-2.18).

Regarding sensitivity analyses, among those with a history of falls/fracture at baseline, we found an increase in risk for any antidepressant use (AOR=1.83, 95% CI=1.28-2.63), but no increased risk was found in those without a history of falls/fracture (**Table 14**). The stratified analysis across years by somatic and non-somatic depressive symptoms revealed similar point estimates as the main analysis (CES-D <10, AOR=1.51, 95% CI=1.09-2.10; CES-D ≥10, AOR=1.39, 95% CI=0.83-2.30) (**Table 15**). Repeating the same analysis but only assessing non-somatic depressive symptoms showed similar results (CES-D <5, AOR=1.54, 95% CI=1.11-2.13; CES-D ≥5, AOR=1.47, 95% CI=0.90-2.39) (**Table 16**).

4.4 DISCUSSION

This study presents some of the first data to longitudinally assess the association between antidepressant use – measured via detailed dosage and duration data – and recurrent falls in community-dwelling older adults. Consistent with prior literature, we found a statistically significant association between any antidepressant use and recurrent falls after adjusting for important potential confounders.[45,46,49] For example, Kerse et al found that antidepressant use was significantly associated with multiple falls and injury but not having sustained a single fall (OR 1.46, 95% CI 1.25-1.70).[45] Moreover, a previous study by Ensrud et al of community-dwelling older women found that antidepressant use overall was associated with a 54% increased risk of frequent falling.[50] However, unlike our findings, they found the risk of falling among antidepressant users to be similar in women with and without a fall in the previous year.[50] We found an increased risk for recurrent falls among those using moderate doses, short duration, and in those with a history of falls/fracture. This latter finding highlights the importance of measuring and improving drug-disease interactions in older adults.[43]

Previous investigations over the past several years have reported a significant association between users of specific classes of antidepressants and falls in older adults. For example, Quach et al found a statistically significant association between SSRIs and outdoor falls in community-dwelling elders.[46] Similar to our findings, TCAs and other types of antidepressants were not found to be associated with falls, which the authors attributed to the small number of users with insufficient statistical power.[46]

Any study of antidepressant use risk must address the role of depressive symptoms. This is particularly important because meta-analyses are consistent in that the presence of depressive symptoms increases the risk of falling by a factor of almost 1.5.[47] We paid special attention to this potential bias in the current analyses. Ensrud et al stratified analyses by the presence or absence of depressive symptoms and found the risk of falls in antidepressant users was similar in women with and without depressive symptoms.[50]Our sensitivity analysis revealed similar results to the main findings.

There are important potential limitations to consider for this study. First, the main outcome of recurrent falls was retrospectively collected via self-report. However, it is a highly specific method in comparison to self-reporting of falls via diary.[21] Second, medication data were collected at fixed annual assessments, preventing us from documenting the exact date in which antidepressants were initiated, changed, or discontinued. Third, while it is possible that there is residual confounding, we adjusted for common indications for antidepressant therapy. Finally, our analysis focused on older, well-functioning community-dwelling Black and White men and women from the Memphis and Pittsburgh areas, and the generalizability to older adults in other regions or different care settings is unknown.

In conclusion, antidepressant use overall, SSRI use, short duration of use, and moderate dosage were associated with recurrent falls after adjusting for important confounders. Moreover, those with a history of falls/fracture had an even greater risk for recurrent falls.

Table 10. Characteristics of the Sample at Baseline - Antidepressants (n=2948)

Variables	Overall mean ± SD or N (%)	Antidepressant use, mean ± SD or N (%) (n=170)	No antidepressant use, mean ± SD or N (%) (n=2778)	P value
Demographics				
Female gender	1522 (51.6)	107 (62.9)	1415 (50.9)	0.002
Black race	1203 (40.8)	41 (24.1)	1162 (41.8)	<0.001
Pittsburgh site	1466 (49.7)	77 (45.3)	1389 (50.0)	0.23
Age	73.6 (2.9)	73.4 (2.70)	73.6 (2.88)	0.37
Education Post secondary High school graduate < High school	 1260 (42.7) 954 (32.4) 727 (24.7)	 87 (51.2) 49 (28.8) 33 (19.4)	 1173 (42.2) 905 (32.6) 694 (25.0)	 0.08
Married	1531 (52.0)	96 (56.5)	1435 (51.7)	0.36
Health Behaviors				
Current smoker	302 (10.2)	20 (11.8)	282 (10.2)	0.75
Alcohol use (≥1 drink per week)	847 (28.7)	41 (24.1)	806 (29.0)	0.37
Health Status				
Pulmonary disease	298 (10.1)	18 (10.6)	280 (10.1)	0.83
Arthritis	1650 (56.0)	106 (62.4)	1544 (55.6)	0.22
Urinary problems	495 (16.8)	40 (23.5)	455 (16.4)	0.02
Cerebrovascular disease	231 (7.8)	18 (10.6)	213 (7.7)	0.17
Peripheral arterial disease	149 (5.1)	6 (3.5)	143 (5.2)	0.64
Benign Prostatic Hyperplasia	692 (23.5)	36 (21.2)	656 (23.6)	0.47
Coronary heart disease	631 (21.4)	35 (20.6)	596 (21.5)	0.20
Congestive heart disease	85 (2.9)	6 (3.5)	79 (2.8)	0.55
Diabetes	440 (14.9)	21 (12.4)	419 (15.1)	0.57
Vision problems Excellent/Good sight Fair sight Poor to completely blind	 2346 (79.6) 519 (17.6) 81 (2.8)	 136 (80.0) 30 (17.7) 4 (2.4)	 2210 (79.6) 489 (17.6) 77 (2.8)	 0.97
Body Mass Index Underweight/Normal (<24.9) Overweight (25.0-29.9) Obese (30+)	 947 (32.2) 1257 (42.6) 744 (25.2)	 61 (35.9) 63 (37.1) 46 (27.1)	 886 (31.9) 1194 (43.0) 698 (25.1)	 0.31
Excellent/Very good/Good self-rated health	2479 (84.1)	134 (78.8)	2345 (84.4)	0.12

Self-reported hypertension[*] Controlled Uncontrolled	 775 (26.3) 723 (24.5)	 48 (28.2) 36 (21.2)	 727 (26.2) 687 (24.7)	 0.56
Cognitive impairment (3MS<80)[*]	284 (9.6)	13 (7.7)	271 (9.8)	0.45
Drugs that increase risk of falls[*] (benzodiazepines, antipsychotics, opioids)	248 (8.4)	49 (28.8)	199 (7.2)	<0.001
No. prescription medications[*,†]	1.8 (2.0)	2.33 (2.13)	1.76 (1.99)	<0.001
Health Status [conditions for which antidepressants are prescribed]				
Self-reported depression	277 (9.4)	88 (51.8)	189 (6.8)	<0.001
Depressive symptoms (Short CES-D≥10)[*]	168 (5.7)	27 (15.9)	141 (5.1)	<0.001
Bodily pain (any in past 30 days)	1942 (65.9)	120 (70.6)	1822 (65.6)	0.38
Sleep problems	691 (23.4)	111 (65.3)	1579 (56.8)	0.03
Anxiety symptoms	414 (14.0)	47 (27.7)	367 (13.2)	<0.001
Access to Care				
Hospitalization in previous 12 months	435 (14.8)	35 (20.6)	400 (14.4)	0.03
Private physician	2319 (78.7)	139 (81.8)	2180 (78.5)	0.31
Prescription insurance	1861 (63.1)	116 (68.2)	1745 (62.8)	0.16
Flu shot in previous 12 months	2039 (69.2)	124 (72.9)	1915 (68.9)	0.27

*Time-varying

[†]Excluding drugs that increase risk of falls and antidepressants

Abbreviations: 3MS = Modified Mini-Mental Status Exam; CES-D = Center for Epidemiologic Studies Depression

Scale; CNS= central nervous system; SD= standard deviation

Table 11. CES-D Items Assessing Non-somatic Symptoms at Baseline (n=2948)

CES-D Item	N	N missing	Mean	Median	SD	Min.	Max.
I was depressed.	2925	23	0.189	0	0.505	0	3
I felt hopeful about the future.	2872	76	0.569	0	0.922	0	3
I felt fearful.	2923	25	0.104	0	0.369	0	3
I was happy.	2893	55	0.422	0	0.760	0	3
I felt lonely.	2929	19	0.237	0	0.566	0	3
Overall	2939	9	1.488	1.00	2.009	0	15.00

Abbreviations: CES-D = Center for Epidemiologic Studies Depression Scale; max: maximum; min: minimum; SD: standard deviation

Table 12. Prevalence of Depressive Symptoms per the CES-D with and without Items Assessing Somatic Symptoms Over Time

	Year 1 (n=2948) n, %	**Year 2 (n=2811) n, %**	**Year 3 (n=2679) n, %**	**Year 5 (n=2489) n, %**	**Year 6 (n=2388) n, %**
CES-D $\geq$ 10 (including items assessing somatic symptoms)	168 (5.7)	--	321 (12.0)	336 (13.5)	329 (13.8)
CES-D $\geq$ 5 (**not** including items assessing somatic symptoms)	250 (8.5)	--	501 (18.7)	475 (19.1)	417 (17.5)

Table 13. Antidepressant Use over Time*

Antidepressant Medication Use	**Year 1 (n=2948) n, %**	**Year 2 (n=2811) n, %**	**Year 3 (n=2679) n, %**	**Year 5 (n=2489) n, %**	**Year 6 (n=2388) n, %**
Any Use	170 (5.8)	189 (6.7)	219 (8.2)	220 (8.8)	235 (9.8)
SDD ≥2	67 (2.3)	78 (2.8)	75 (2.8)	74 (3.0)	88 (3.7)
SDD 1-2	97 (3.3)	120 (4.3)	156 (5.8)	176 (7.1)	189 (7.9)
SDD <1	11 (0.4)	19 (0.7)	26 (1.0)	22 (0.9)	27 (1.1)
Long Term use (≥2 years)	74 (2.5)	100 (3.6)	104 (3.9)	119 (4.8)	122 (5.1)
Short Term Use	94 (3.2)	98 (3.5)	129 (4.8)	117 (4.7)	144 (6.0)
Specific Class Use	--	--	--	--	--
SSRI	73 (2.5)	90 (3.2)	123 (4.6)	139 (5.6)	158 (6.6)
TCA	70 (2.4)	71 (2.5)	59 (2.2)	44 (1.8)	44 (1.8)
Others†	31 (1.1)	41 (1.5)	51 (1.9)	49 (2.0)	44 (1.8)

*Medication data not available at year 4

†Others: trazodone, bupropion, venlafaxine, mirtazapine, phenelzine

Abbreviations: SDD: standardized daily dose; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant

Table 14. Association between Antidepressant Use and Recurrent Falls, with and without Controlling for Covariates (Including Depressive Symptoms)

Antidepressant Medication Use*	**Bivariate OR (95% CI)**	**Adjusted OR (95% CI)†**
Any Use	1.99 (1.60-2.48)	1.48 (1.12-1.96)
Long duration (≥2 years)	1.77 (1.31-2.40)	1.31 (0.88-1.95)
Short duration	1.79 (1.36-2.36)	1.47 (1.04-2.00)
SDD – ≥2	1.35 (0.90-2.02)	1.03 (0.64-1.65)
SDD – 1-2	1.91 (1.47-2.49)	1.59 (1.15-2.18)
SDD – <1	1.57 (0.81-3.04)	1.18 (0.49-2.87)
Specific Class Use§	--	--
SSRI	2.23 (1.68-2.97)	1.62 (1.15-2.28)
TCA	1.61 (1.08-2.40)	1.27 (0.76-2.13)
Others‡	1.79 (1.07-3.00)	1.34 (0.72-2.50)

Abbreviations: OR=odds ratio; CI=confidence interval; SDD: standardized daily dose; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant

*Reference group is No Use

†Controlling for variables forced into the model (i.e., site, drugs that increase the risk of falls, self-reported depression, depressive symptoms per CES-D 10, bodily pain, sleep problems, and anxiety symptoms) and those from forward selection procedures (i.e.,
age, pulmonary disease, arthritis, urinary problems, cerebrovascular disease, diabetes,
vision problems, hospitalization in previous 12 months, and private physician)

‡Others: trazodone, bupropion, venlafaxine, mirtazapine, phenelzine

§Each antidepressant sub-class was run as a separate model and controlled for antidepressant sub-class use other than the sub-class being evaluated

Table 15. Bivariate and Multivariable Association between Antidepressant Use and Recurrent Falls Stratified by History of Falls and/or Fracture (after age 45) at Baseline

	History of Falls/Fracture (n=1092)		No History of Falls/Fracture (n=1856)	
Antidepressant Medication Use*	**Crude OR (95% CI)**	**Adj. OR (95% CI)†**	**Crude OR (95% CI)**	**Adj. OR (95% CI)†**
Any use	2.02 (1.51-2.69)	1.83 (1.28-2.63)	1.83 (1.30-2.59)	0.97 (0.60-1.56)
Long duration (≥2 years)	1.61 (1.09-2.39)	1.38 (0.82-2.30)	1.84 (1.15-2.95)	1.30 (0.69-2.42)
Short duration	1.85 (1.30-2.64)	1.77 (1.17-2.68)	1.61 (1.03-2.51)	0.79 (0.42-1.48)
SDD ≥2	1.39 (0.81-2.40)	1.06 (0.57-1.97)	1.13 (0.63-2.06)	0.98 (0.48-2.01)
SDD 1-2	1.80 (1.26-2.57)	1.99 (1.31-3.01)	1.97 (1.34-2.88)	1.17 (0.71-1.93)
SDD <1	1.16 (0.41-3.31)	0.75 (0.18-3.05)	2.22 (0.99-4.93)	1.89 (0.67-5.36)
Specific Class Use§	--	--	--	--
SSRI	2.12 (1.49-3.02)	1.92 (1.24-2.97)	2.21 (1.40-3.48)	1.11 (0.62-2.01)
TCA	1.86 (1.11-3.09)	1.47 (0.77-2.82)	1.25 (0.64-2.41)	0.86 (0.35-2.13)
Others‡	1.90 (0.90-4.01)	2.22 (0.99-4.94)	1.65 (0.80-3.40)	0.76 (0.27-2.12)

Abbreviations: OR: odds ratio; CI=confidence interval; SDD: standardized daily dose; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant

*Reference group is No Use

†Controlling for variables forced into the model (i.e., site, drugs that increase the risk of falls, self-reported depression, depressive symptoms per CES-D 10, bodily pain, sleep problems, and anxiety symptoms) and those from forward selection procedures (i.e., age, pulmonary disease, arthritis, urinary problems, cerebrovascular disease, diabetes, vision problems, hospitalization in previous 12 months, and private physician)

‡Others: trazodone, bupropion, venlafaxine, mirtazapine, phenelzine

§Each antidepressant sub-class was run as a separate model and controlled for antidepressant sub-class use other than the sub-class being evaluated

Table 16. Bivariate and Multivariable Association between Antidepressant Use and Recurrent Falls Stratified by Time-Varying Depressive Symptoms per CES-D 10

	CES-D ≥ 10		CES-D < 10	
Antidepressant Medication Use*	**Crude OR (95% CI)**	**Adj. OR (95% CI)†**	**Crude OR (95% CI)**	**Adj. OR (95% CI)†**
Any use	1.88 (1.27-2.80)	1.39 (0.83-2.30)	1.88 (1.43-2.47)	1.51 (1.09-2.10)
Long duration (≥2 years)	1.67 (0.92-3.02)	1.31 (0.66-2.61)	1.99 (1.37-2.88)	1.43 (0.92-2.23)
Short duration	1.74 (1.11-2.72)	1.42 (0.79-2.54)	1.52 (1.06-2.18)	1.47 (0.99-2.19)
SDD ≥2	1.32 (0.61-2.83)	1.12 (0.53-2.40)	1.13 (0.64-2.00)	0.99 (0.54-1.85)
SDD 1-2	1.88 (1.18-2.99)	1.69 (0.97-2.94)	1.79 (1.28-2.50)	1.56 (1.07-2.29)
SDD <1	0.83 (0.23-2.93)	0.50 (0.08-3.12)	2.20 (1.02-4.76)	1.68 (0.66-4.31)

Abbreviations: CES-D = Center for Epidemiologic Studies Depression Scale; CI=confidence interval; OR: odds ratio; SDD: standardized daily dose; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant

*Reference group is No Use

†Controlling for variables forced into the model (i.e., site, drugs that increase the risk of falls, self-reported depression, bodily pain, sleep problems, and anxiety symptoms) and those from forward selection procedures (i.e., age, pulmonary disease, arthritis, urinary problems, cerebrovascular disease, diabetes, vision problems, hospitalization in previous 12 months, and private physician)

Table 17. Bivariate and Multivariable Association between Antidepressant Use and Recurrent Falls Stratified by Time-Varying Depressive Symptoms per CES-D with Items Assessing Non-somatic Symptoms

	CES-D ≥ 5		CES-D < 5	
Antidepressant Medication Use*	**Crude OR (95% CI)**	**Adj. OR (95% CI)†**	**Crude OR (95% CI)**	**Adj. OR (95% CI)†**
Any use	2.18 (1.49-3.18)	1.47 (0.90-2.39)	1.91 (1.45-2.53)	1.54 (1.11-2.13)
Long duration (≥2 years)	2.04 (1.21-3.45)	1.42 (0.74-2.72)	2.00 (1.38-2.90)	1.53 (0.98-2.37)
Short duration	1.92 (1.24-2.96)	1.52 (0.87-2.63)	1.50 (1.02-2.20)	1.37 (0.89-2.11)
SDD ≥2	1.36 (0.65-2.87)	0.97 (0.45-2.08)	1.19 (0.70-2.03)	1.11 (0.62-1.97)
SDD 1-2	2.20 (1.43-3.40)	1.95 (1.17-3.27)	1.78 (1.26-2.53)	1.53 (1.02-2.27)
SDD <1	0.87 (0.29-2.68)	0.31 (0.06-1.74)	2.42 (1.12-5.23)	2.14 (0.87-5.22)

Abbreviations: CES-D = Center for Epidemiologic Studies Depression Scale; CI=confidence interval; OR: odds ratio; SDD: standardized daily dose; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant

*Reference group is No Use

†Controlling for variables forced into the model (i.e., site, drugs that increase the risk of falls, self-reported depression, bodily pain, sleep problems, and anxiety symptoms) and those from forward selection procedures (i.e., age, pulmonary disease, arthritis, urinary problems, cerebrovascular disease, diabetes, vision problems, hospitalization in previous 12 months, and private physician)

5.0 DISCUSSION

I believe the findings from this dissertation contribute to a better understanding of recurrent medication-related falls in community-dwelling older adults. First, we found that antihypertensive use overall was not associated with recurrent falls after adjusting for important confounders. However, we reported that loop diuretic use may be associated with recurrent falls, and this finding needs further study. Second, while increased point estimates suggested an association of anticholinergic use with recurrent falls, none of them reached statistical significance. This finding is consistent with prior literature showing no significant association between anticholinergic use and recurrent falls in community-dwelling elders. Third, we were able to replicate prior studies' findings showing a statistically significant association between antidepressant use and recurrent falls. Importantly, we found an even greater risk among those with a history of a fall or fracture, suggesting that this could be a high-risk group to target future interventions. In addition, SSRI use, short duration of use, and moderate dosage were associated with recurrent falls after adjusting for important confounders. Moreover, sensitivity analyses using a sample stratified by a time-varying measure of depressive symptoms found an increased risk of recurrent falls.

There are several strengths of these three analyses. First, all study designs were longitudinal, which allowed for a more robust assessment of risk over time compared to a cross-sectional analysis. Second, we used state-of-the-art methods to calculate medication dosage

variables, filling a gap in the previous literature. Third, we assessed various sub-class analyses to examine drug risk at a more granular level. Finally, we used sophisticated statistical methods to account for the longitudinal nature of the study and conducted multiple sensitivity analyses to assess the robustness of our findings. There are, of course, important limitations to this work as well, which have been previously described within the individual manuscripts.

Looking forward, important questions remain. First, very little is known about shared risk factors between falls and fractures in older adults. Are certain medications associated with only falls, only fractures, or both? In addition, very little is understood about medication-related mechanisms to cause falls in older adults. Moreover, many new antidepressants have reached the market in the past few years, and it is not clear which individual agent(s) (as opposed to sub-class) is/are the safest for older adults to take in terms of falls risk. Additional comparative effectiveness research is needed using more recent data and including these newer agents. Finally, there is a great need for feasible and scalable interventions to reduce medication-related falls in community-dwelling older adults. Unfortunately, there is no clear evidence currently available for an effective intervention to be widely implemented.[51] Health information technologies are a promising approach to reducing the risk of falls in older adults through alerts for risky medications.[51] Until more effective interventions are available, the following quote from a thought leader in the field summarizes a practical approach to reducing medication-related falls risk: "By eliminating unnecessary medications and reducing the dose of necessary medications, it is often possible to treat coexisting conditions while minimizing risk of medication-related fall or injury."[3]

BIBLIOGRAPHY

1. Strom BL. What is Pharmacoepidemiology? In: Storm BL, Kimmel SE, Hennessy S, eds. *Pharmacoepidemiology*. 5 ed. England: John Wiley & Sons Ltd; 2012:3-22.

2. Marcum ZA, Peron E, Hanlon JT. Medication use in older adults. In: Newman A, Cauley J, eds. *The Epidemiology of Aging*. New York: Springer Publishing Company; 2013:317-327.

3. Tinetti ME, Kumar C. The patient who falls: "It's always a trade-off". *JAMA*. 2010;303(3):258-266.

4. Weiner DK, Hanlon JT, Studenski SA. Effects of central nervous system polypharmacy on falls liability in community-dwelling elderly. *Gerontology*. 1998;44(4):217-221.

5. Newman AB, Haggerty CL, Kritchevsky SB, Newvitt MC, Simonsick EM; Health ABC Collaborative Research Group. Walking performance and cardiovascular response: associations with age and morbidity--the Health, Aging and Body Composition Study. *J Gerontol A Biol Sci Med Sci*. 2003;58(8):715-720.

6.Pahor M, Chrischilles EA, Guralnik JM, Brown SL, Wallace RB, Carbonin P. Drug data coding and analysis in epidemiologic studies. *Eur J Epidemiol*. 1994;10(4):405-411.

7. Hartikainen S, Lönnroos E, Louhivouri K. Medication as a risk factor for falls: critical systematic review. *J Gerontol A Biol Sci Med*. 2007;62(10):1172-1181.

8. Aronow WS, Fleg JL, Pepine CJ, Artinian NT, Bakris G, Brown AS, Ferdinand KC, Ann Forciea M, Frishman WH, Jaigobin C, Kostis JB, Mancia G, Oparil S, Ortiz E, Resin E, Rich MW, Schocken DD, Weber MA, Wesley DJ. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. *J Am Coll Cardiol*. 2011;57(20):2037-2114.

9. Ostchega Y, Dillon CF, Hughes JP, Carroll M, Yoon S. Trends in hypertension prevalence, awareness, treatment, and control in older U.S. adults: data from the National Health and Nutrition Examination Survey 1988 to 2004. *J Am Geriatr Soc*. 2007;55(7):1056-1065.

10. Hanlon JT, Landerman LR, Fillenbaum GG, Studenski S. Falls in African American and white community-dwelling elderly residents. *J Gerontol A Biol Sci Med Sci*. 2002;57(7):M473-478.

11. de Rekeneire N, Visser M, Peila R, Nevitt MC, Cauley JA, Tylavsky FA, Simonsick EM, Harris TB. Is a fall just a fall: correlates of falling in healthy older persons. The Health, Aging and Body Composition Study. *J Am Geriatr Soc*. 2003;51(6):841-846.

12. King MB. Falls. In: Halter J, Ouslander J, Tinetti M, Studenski S, High K, Asthana S, eds. *Hazzard's Geriatric Medicine and Gerontology*. 6 ed. New York:McGraw-Hill; 2009:659-670.

13. Hanlon JT, Boudreau RM, Roumani YF, Newman AB, Ruby CM, Wright RM, Hilmer SN, Shorr RI, Bauer DC, Simonsick EM, Studenski SA. Number and dosage of central nervous system medications on recurrent falls in community elders: the Health, Aging and Body Composition study. *J Gerontol Med Sci*. 2009;64(4):492-498.

14. Woolcott JC, Richardson KJ, Wiens MO, Patel B, Marin J, Khan KM, Marra CA. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med*. 2009;169(21):1952-1960.

15. Tinetti ME, Han L, Lee DS, McAvay GJ, Peduzzi P, Gross CP, Zhou B, Lin H. Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. *JAMA Intern Med*. 2014;174(4):588-595.

16. Psaty BM, Lee M, Savage PJ, Rutan GH, German PS, Lyles M. Assessing the use of medications in the elderly: methods and initial experience in the Cardiovascular Health Study. The Cardiovascular Health Study Collaborative Research Group. *J Clin Epidemiol*. 1992;45(6):683-692.

17. Marcum ZA, Perera S, Donohue JM, Boudreau RM, Newman AB, Ruby CM, Studenski SA, Kwoh CK, Simonsick EM, Bauer DC, Satterfield S, Hanlon JT; Health, Aging and Body Composition Study. Analgesic use for knee and hip osteoarthritis in community-dwelling elders. *Pain Med*. 2011;12(11):1628-1636.

18. Pit SW, Byles JE, Cockburn J. Accuracy of telephone self-report of drug use in older people and agreement with pharmaceutical claims data. *Drugs Aging*. 2008;25(1):71-80.

19. Caskie GI, Willis SL, Warner Schaie K, Zanjani FA. Congruence of medication information from a brown bag data collection and pharmacy records: findings from the Seattle longitudinal study. *Exp Aging Res*. 2006;32(1):79-103.

20. McEvoy GK, ed. *AHFS Drug Information*. Bethesda, MD: American Society of Hospital Pharmacists; 2011.

21. Ganz DA, Higashi T, Rubenstein LZ. Monitoring falls in cohort studies of community-dwelling older people: effect of the recall interval. *J Am Geriatr Soc*. 2005;53(12):2190-2194.

22. National Institutes of Health, National Heart, Lung, and Blood Institute. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Available at: http://www.nhlbi.nih.gov/guidelines/archives/jnc6/jnc6_archive.pdf. Accessed July 7, 2014.

23. Radloff LS. The CES-D scale: a self-report depression scale for research use in the general population. *Appl Psych Measur*. 1977;1:385-401.

24. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry*. 1987;48:314-318.

25. Rooks RN, Simonsick EM, Klesges LM, Newman AB, Ayonayon HN, Harris TB. Racial disparities in health care access and cardiovascular indicators in Black and White older adults in the Health ABC study. *J Aging Health*. 2008;20(6):599-614.

26. Liang K, Zeger S. Longitudinal data analysis using generalized linear models. *Biometrika*. 1986;73:13–22.

27. Diggle PJ. An approach to the analysis of repeated measures. *Biometrics*. 1988;44:959-971.

28. Diggle PJ, Heagerty P, Liang K, Zeger S, eds. *Analysis of Longitudinal Data*, 2 ed. New York City, NY: Oxford University Press; 2002.

29. D'Agostino RB. Propensity scores in cardiovascular research. *Circulation*. 2007;115(17):2340-2343.

30. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. *J Am Stat Assoc*. 1984;79:516-524.

31. Sobel KG, McCart GM. Drug use and accidental falls in an intermediate care facility. *Drug Intell Clin Pharm*. 1983;17:539-542.

32. Berry SD, Mittleman MA, Zhang Y, Solomon DH, Lipsitz LA, Mostofsky E, Goldense D, Kiel DP. New loop diuretic prescriptions may be an acute risk factor for falls in the nursing home. *Pharmacoepidem Drug Saf*. 2012;21(5):560-563.

33. Lim LS, Fink HA, Blackwell T, Taylor BC, Ensrud KE. Loop diuretic use and rates of hip bone loss and risk of falls and fractures in older women. *J Am Geriatr Soc*. 2009;57(5):855-862.

34. Rémillard AJ. A pharmacoepidemiological evaluation of anticholinergic prescribing patterns in the elderly. *Pharmacoepidemiol Drug Saf*. 1996;5(3):155-164.

35. Ness J, Hoth A, Barnett M, Shorr RI, Kaboli PJ. Anticholinergic medications in community-dwelling older veterans: prevalence of anticholinergic symptoms, symptom burden, and adverse drug events. *Am J Geriatr Pharmacother*. 2006;4(1):42-51.

36. Sumukadas D, McMurdo ME, Mangoni AA, Guthrie B. Temporal trends in anticholinergic medication prescription in older people: repeated cross-sectional analysis of population prescribing data. *Age Ageing*. 2014;43(4):515-521.

37. Winchell GA, King JD, Chavez-Eng CM, Constanzer ML, Korn SH. Cyclobenzaprine pharmacokinetics, including the effects of age, gender, and hepatic insufficiency. *J Clin Pharmacol*. 2002;42(1):61-69.

38. Bowie MW, Slattum PW. Pharmacodynamics in older adults: a review. *Am J Geriatr Pharmacother*. 2007;5(3):263–303.

39. McLachlan AJ, Hilmer SN, Le Couteur DG. Variability in response to medicines in older people: phenotypic and genotypic factors. *Clin Pharmacol Ther*. 2009;85(4):431-433.

40. Berdot S, Bertrand M, Dartiques, FourrierA, Tavernier B, Ritchie K, Alpérovitch A. Inappropriate medication use and risk of falls--a prospective study in a large community-dwelling elderly cohort. *BMC Geriatr*. 2009;9:30.

41. Wilson NM, Hilmer SN, March LM, Cameron ID, Lord SR, Seibel MJ, Mason RS, Chen JS, Cumming RG, Sambrook PN. Associations between drug burden index and falls in older people in residential aged care. *J Am Geriatr Soc*. 2011;59(5):875-880.

42. Fraser LA, Adachi JD, Leslie WD, Goltzman D, Josse R, Prior J, Kaiser S, Kreiger N, Kovacs CS, Anastassiades TP, Papaioannou A; for the CaMos Research Group. Effect of anticholinergic medications on falls, fracture risk, and bone mineral density over a 10-year period. *Ann Pharmacother*. 2014;48(8):954-961.

43. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2012;60(4):616-631.

44. Reuben DB, Herr KA, Pacala JT, Pollock BG, Potter JF, Semla TP, eds. *Geriatrics At Your Fingertips*. 15 ed. New York: American Geriatrics Society;2013.

45. Kerse N, Flicker L, Pfaff JJ, Draper B, Lautenschlager NT, Sim M, Snowdon J, Almeida OP. Falls, depression and antidepressants in later life: a large primary care appraisal. *PLoS ONE*. 2008;3(6):e2423.

46. Quach L, Yang FM, Berry SD, Newton E, Jones RN, Burr JA, Lipsitz LA. Depression, antidepressants, and falls among community-dwelling elderly people: the MOBILIZE Boston study. *J Gerontol Med Sci*. 2013;68(12):1575-1581.

47. Kvelde T, McVeigh C, Toson B, Greenaway M, Lord SR, Delbaere K, Close JC. Depressive symptomatology as a risk factor for falls in older people: systematic review and meta-analysis. *J Am Geriatr Soc*. 2013;61(5):694-706.

48. Kohout FJ, Berkman LF, Evans DA, Cornoni-Huntley J. Two shorter forms of the CES-D (Center for Epidemiological Studies Depression) depression symptoms index. *J Aging Health*. 1993;5(2):179-192.

49. Darowski A, Chambers SCF, Chambers DJ. Antidepressants and falls in the elderly. *Drugs Aging*. 2009;26(5):381-394.

50. Ensrud KE, Blackwell TL, Mangione CM, Bowman PJ, Whooley MA, Bauer DC, Schwartz AV, Hanlon JT, Newvitt MC; Study of Osteoporotic Fractures Research Group. Central nervous system-active medications and risk for falls in older women. *J Am Geriatr Soc*. 2002;50(10):1629-1637.

51. Huang AR, Mallet L, Rochefort CM, Equale T, Buckeridge DL, Tamblyn R. Medication-related falls in the elderly: causative factors and preventive strategies. *Drugs Aging*. 2012;29(5):359-376.