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Prevalence of Unplanned Hospitalizations Caused by Adverse Drug Reactions Among Older Veterans

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AUTHOR CONTRIBUTIONS:

Dr. Marcum served as the first evaluator of potential ADRs and conceived of and designed the study, acquired the data, supervised the analyses and interpreted the data, and drafted the initial manuscript. Ms. Amuan preformed the analyses and assisted in the interpretation of data and preparation of the manuscript. Dr. Ruby helped develop the analysis plan, interpret the data, and prepare the final manuscript. Drs. Handler and Aspinall were involved in the development of the analysis plan, resolving any discordances with potential ADR evaluations, and assisted in the interpretation of data for this study and preparing the manuscript. Dr. Hanlon served as the second evaluator of potential ADRs, assisted in the design of the study, interpreted the data, and assisted in preparing the manuscript. Dr. Pugh was responsible for acquisition of the data and contributed to the design, analyses, and interpretation of data for this study and assisted in preparing the manuscript.

Conflict of Interest

Authors JH and SH are employed by the VA Pittsburgh Healthcare System. Author SA is employed by the VA Center for Medication Safety. Author MJP is employed by the South Texas Veterans Health Care System. Author MA is employed by the Edith Nourse Rogers Memorial VA. Dr. Hanlon has received research funding from National Institute on Aging grants (R01AG027017, P30AG024827, T32AG021885, K07AG033174, R01AG034056), a National Institute of Mental Health grant (R34 MH082682), a National Institute of Nursing Research grant (R01NR010135), an Agency for Healthcare Research and Quality grant (R01HS017695) and from VA HSR&D IIR-06-062. Dr. Handler has received research funding from the Agency for Healthcare Research and Quality grants (R01HS018721, R18HS018151), a National Institute on Aging grant (K07AG033174), a Pennsylvania Department of Aging grant, and from VA HSR&D IIR-06-062. Dr. Pugh has received research funding from VA HSR&D DHI 09-237 (PI); VA HSR&D IIR-06-062 PI, Epilepsy Foundation PI, VA HSRD PPO 09-295 PI, VA HSR&D IIR 02-274 PI. Pugh as co-I: VA HSR&D IIR 08-274, VA HSR&D SDR-07-042, IIR-05-121, IAF-06-080, IIR-09-335, SHP 08-140, TRX 01-091 Department of Defense CDMRP 09090014, NIH R01-NR010828, Pugh Speaker Honoraria: 2009 Kelsey Seybold Research Foundation \$400.

Abstract

Objectives—To describe the prevalence of unplanned hospitalizations caused by ADRs among older Veterans and examine the association between this outcome and polypharmacy after controlling for comorbidities and other patient characteristics.

Design—Retrospective cohort.

Setting—Veterans Affairs Medical Centers (VAMC).

Participants—678 randomly selected unplanned hospitalizations of older (age ≥ 65 years) Veterans between 10/01/03 and 09/30/06.

Measurements—Naranjo ADR algorithm, ADR preventability, and polypharmacy (0–4, 5–8, and ≥ 9 scheduled medications).

Results—Seventy ADRs involving 113 drugs were determined in 68 (10%) older Veterans' hospitalizations, of which 36.8% (25/68) were preventable. Extrapolating to the population of over 2.4 million older Veterans receiving care during the study period, 8,000 hospitalizations may have been unnecessary. The most common ADRs that occurred were bradycardia ($n=6$; beta blockers, digoxin), hypoglycemia ($n=6$; sulfonylureas, insulin), falls ($n=6$; antidepressants, ACE-inhibitors), and mental status changes ($n=6$; anticonvulsants, benzodiazepines). Overall, 44.8% of Veterans took ≥ 9 outpatient medications and 35.4% took 5–8. Using multivariable logistic regression and controlling for demographic, health status, and access to care variables, polypharmacy (≥ 9 and 5–8) was associated with an increased risk of ADR-related hospitalization (AOR 3.90, 95% CI 1.43–10.61 and AOR 2.85, 95% CI 1.03–7.85, respectively).

Conclusion—ADRs determined by a validated causality algorithm are a common cause of unplanned hospitalization among older Veterans, are frequently preventable, and are associated with polypharmacy.

Keywords

adverse drug reactions; Veterans; aged; pharmacoepidemiology

INTRODUCTION

Adverse drug reactions (ADRs), defined as any noxious, unintended, and undesired effects of drugs, which occur at doses used in humans for prophylaxis, diagnosis, or therapy, are a significant public health concern as they are a major cause of morbidity and mortality, particularly among older adults (i.e., age ≥ 65 years).^{1–11} One of the worst consequences of ADRs in older adults living in the community is hospitalization and its related costs.^{2–11} Previous studies of ADR-related hospitalizations in older adults have reported a prevalence rate as high as 21%.^{2,4,8,11} Many of these studies are limited by the use of different methods used to define and assess ADRs and their inability to extrapolate their findings to the underlying patient population from which the ADR-related hospitalizations arose.

Polypharmacy, or multiple medication use, is common in community-dwelling older adults and has been shown to be the most consistent and strongest predictor of ADRs in older adults.^{2,4,12–16} It is not clear whether polypharmacy is just a proxy for severity of illness (i.e., comorbidities) such that sicker elders require more medication therapy. In addition, other patient characteristics inconsistently reported to be associated with ADRs include age, previous ADR, and female gender.^{2,4,12–16} Yet, few studies of ADR-related hospitalizations have examined the association with polypharmacy while also controlling for comorbidity and the above mentioned and other patient demographic, health status, and access to care factors.^{4,9}

Thus, the main objective of this study was to describe the prevalence of unplanned hospitalizations caused by ADRs among older Veterans using information drawn from an electronic health record system to examine the association between this outcome and polypharmacy after controlling for comorbidities and other patient demographic, health status, and access to care variables. Secondly, we aimed to describe the preventability of these hospitalizations to allow for extrapolation to the population of older Veterans who receive care within the Veterans Health Administration (VHA).

METHODS

Study Design, Setting, and Sample

A retrospective cohort study was conducted using data from older Veterans across all 152 Department of Veterans Affairs (VA) Medical Centers (VAMC). The overall cohort consisted of Veterans ≥ 65 years of age by October 1, 2003 (beginning Fiscal Year 2004 [FY04]) who received VA care (inpatient or outpatient) at least once in any year between FY03-FY06 ($n=2,430,186$). Furthermore, the sample for the current study included those Veterans who were hospitalized at a VAMC at least once between FY04-FY06 ($n=328,166$). From this sample, we randomly selected 1,000 hospitalizations. We included those patients who were hospitalized directly from an ambulatory care setting for an *unplanned* admission ($n=678$), which we operationally defined as those that excluded transfers, surgical procedures, and elective admissions because we were interested in ADRs as the reason for hospitalization. Only the first admission was included for those Veterans with more than one admission during the study period. The study was approved by the VA Institutional Review Board.

Data Sources

We obtained national VA inpatient, outpatient, and pharmacy data from FY03 through FY06 for individuals who were ≥ 65 years of age at the beginning of FY04. We created a merged database using information from the VA Medical SAS[®] datasets (contains all national inpatient and outpatient services provided) and outpatient pharmacy prescription data from the VA Pharmacy Benefits Management (PBM) database. Records were merged using an encrypted identifier that is consistent for each person across VA data sets.

Study Chart Abstracts and Screening and Evaluating Potential ADRs

A research assistant was trained by two of the investigators (JH, MP) on the procedures for study chart abstraction from national VA electronic health records using VistAWeb. The study chart abstracts included outpatient medications three months before and after the index hospitalization, allergies, medical problem lists, emergency department (ED) and hospital discharge summaries for the year prior to the index hospitalization, lab tests six months prior to and during the index hospitalization, admission history and physical note, and progress notes during the index hospitalization. A clinical pharmacist (ZM) established the number of medications that patients were taking just prior to hospitalization.

To screen for potential ADRs, a trained clinical pharmacist (ZM) reviewed each chart abstract using previously established methods.¹⁷ This screening approach included looking for drug-disease interactions, discontinued medications, narrow therapeutic index medications, renally cleared medications, abnormal laboratory/medication combinations, and the use of specific high-risk medications.¹⁸⁻²² For chart abstracts that screened positive for a potential ADR, two trained clinical pharmacists (ZM, JH) separately evaluated whether the hospitalization was causally related to an ADR using the reliable and valid standardized Naranjo ADR algorithm.²³ Each confirmed ADR was also evaluated for preventability, defined as any *medication error* occurring in the prescribing, order communication,

dispensing, administering, or monitoring in the medication use process, or medication nonadherence.^{24,25} Evaluation discordances were resolved by consensus with a clinical pharmacist and a geriatrician (SA, SH). Inter-rater reliability measured using the κ statistic for both ADR events and preventability was adequate (0.81 and 0.73, respectively).²⁶

Primary Outcome

An ADR-related hospitalization (including all possible, probable, or definite ADRs based on the Naranjo ADR algorithm) was used as the dichotomous primary outcome of interest.

Primary Independent Variable

We defined polypharmacy as the use of five or more regularly scheduled systemic medications (i.e., excluding protectant/moisturizing topicals, moisturizing eye drops, and as-needed medications) prescribed by a VA physician just prior to the time of hospitalization.⁷ For analysis purposes, we created a categorical variable for polypharmacy for each patient (i.e., 0–4, 5–8, and ≥ 9 medications).

Control Variables

Previous research has shown various factors to be associated with the occurrence of ADRs in older adults, including specific demographic, health status, and access to care variables.^{2–11,27} Therefore, to examine the relationship between polypharmacy and any ADR, we controlled for these factors specified below.

Demographic Control Variables—We identified patient demographic characteristics (i.e., age in the year of admission, gender, and race/ethnicity) using data fields from VA administrative databases between FY03-FY06. We used a process in which we looked back in VA data for previous years and forward in the data in subsequent years to minimize missing data. Race was also included in the study to assess potential disparities.

Health Status Control Variables—In order to assess comorbidity, we used ICD9-CM codes (one inpatient or two outpatient) found in VA inpatient and outpatient data (i.e., FY03-FY05 – the year prior to admission) to identify individuals with physical and psychiatric conditions in the Selim comorbidity indices.²⁸ These indices were developed to control for disease burden in research studies involving Veterans.²⁸ For physical conditions, we used a continuous count of the number of chronic diseases from 30 possible conditions included in the Selim Physical Comorbidity Index. We also identified the following psychiatric conditions included in the Selim Psychiatric Comorbidity Index: schizophrenia, bipolar disorder, depressive disorder, post-traumatic stress disorder, substance abuse disorder, and anxiety disorders. Due to the highly skewed distribution of these data, we dichotomized this variable (0 vs. ≥ 1 psychiatric conditions). These measures of comorbidity have been previously associated with mortality, measures of health status, and potentially inappropriate prescribing.^{28,29}

Access to Care Control Variables—Access to care variables included measurements of copayment exemption, geriatric care and primary care utilization in the year prior, and an emergency department (ED) visit or hospitalization in the year prior to admission as well as the year of the index hospitalization. A dichotomous variable for copayment exemption was created using the VA priority group. Veterans with a service-connected disability $\geq 50\%$ or individuals who were catastrophically disabled, very low income, or had specific war-related experiences generally receive a waiver for copayments associated with VA care.³⁰ Individuals who received care in geriatric outpatient clinics or inpatient geriatric evaluation and management in the year prior were identified as having prior geriatric care using a

dichotomous measure.³¹ Furthermore, we included measures of health care utilization, including a categorical variable for the number of primary care visits (0–1, 2–4, and ≥ 5) in the previous year. In addition, we utilized dichotomous variables for an ED visit or hospitalization in the previous year. Finally, we controlled for the year of hospitalization (2004, 2005, or 2006).

Statistical Analysis

Descriptive statistics were used to summarize the primary dependent, independent and control variables for the sample. To retain those individuals with missing data in the final analyses, we created dummy variables for a “missing” category. For descriptive purposes, ADRs were categorized by the major organ system/condition using ICD-9-CM codes and the medication involved using the VA Drug Class Index.³² We were also interested in describing whether two Healthcare Effectiveness and Data and Information Set (HEDIS) quality of prescribing measures, use of Drugs to Avoid in the Elderly and potentially harmful Drug-Disease interactions in the Elderly, were potential causes of an ADR-related hospitalization.^{21,22} These explicit measures represented a subset of drug-related problems developed by Fick *et al* and Lindblad *et al*.^{18,33} For analysis purposes, the percentage of patients with one or more ADRs was calculated.

Bivariate analyses were conducted to assess the association of the primary independent variable (polypharmacy) and other control variables with the primary outcome (ADR-related hospitalization) using chi-square and t-tests as appropriate. Multivariable logistic regression models were fit with the ADR measure as the dichotomous dependent variable and the categorical polypharmacy measure as the primary independent variable. We forced into the final model demographic, health status, and access to care control variables shown to be associated with ADRs in other published studies.^{2–11} The underlying statistical assumption of collinearity was evaluated using variance inflation factors, and the regression diagnostic of goodness-of-fit was verified using Hosmer-Lemeshow testing.³⁴ All statistical analyses were conducted using SAS[®] version 9.2 (SAS[®] Institute, Inc., Cary, NC).

RESULTS

The mean age of the cohort ($n=678$) was 76.4 years, and polypharmacy was common (i.e., 44.8% took ≥ 9 outpatient medications and 35.4% took 5–8) (Table 1). Most Veterans were white (75.5%) and male (98.5%). In addition, the mean number of chronic comorbid conditions (measured using the Selim Physical Comorbidity Index) was approximately four while almost one-fourth of the cohort had ≥ 1 psychiatric condition (measured using the Selim Psychiatric Comorbidity Index).

As seen in Table 2, 70 ADRs were associated with hospitalization. These ADRs occurred in 68 (10%) Veterans' hospitalizations involving 113 drugs; of these ADR-related hospitalizations, 36.8% (25/68) were found to be preventable. The most common ADRs that occurred were bradycardia ($n=6$), hypoglycemia ($n=6$), falls ($n=6$), and mental status changes ($n=6$). Only one HEDIS drug-disease interaction (lorazepam/dementia) was found to be associated with ADR development. Moreover, we found one HEDIS high-risk medication (hyoscyamine) associated with ADR development. The most common reason for a preventable ADR was due to suboptimal prescribing (13/25; 52.0%). Patient nonadherence to the medication regimen (7/25; 28.0%) and suboptimal monitoring (3/25; 12.0%) were the next most common reasons for a preventable ADR-related hospitalization.

On bivariate analysis, only polypharmacy was significantly associated with the occurrence of an ADR-related hospitalization ($P = 0.01$) (Table 1). None of the control variables were shown to be significantly related to ADRs. Using multivariable logistic regression and

controlling for demographic, health status (including comorbidity), and access to care factors, polypharmacy (≥ 9 and 5–8 medications) continued to be the only significant factor associated with an ADR-related hospitalization (adjusted odds ratio [AOR] 3.90, 95% confidence interval [CI] 1.43–10.61 and AOR 2.85, 95% CI 1.03–7.85, respectively) (Table 3). No modeling diagnostic problems with collinearity were detected, and adequate model fit was found ($\chi^2=12.46$; $df=8$; $P = 0.13$).

DISCUSSION

To the best of our knowledge, this is one of the first studies to describe the prevalence of unplanned hospitalizations caused by ADRs determined by use of a reliable and valid algorithm among older Veterans using a population-based sample. These findings are relevant because they come from a nationally representative sample, allowing for extrapolation to the entire older Veteran population in the United States (US). Most previous studies of ADRs leading to hospitalization in older adults have been limited by the use of a sample from a more select population (e.g., individual hospital or region).^{3,15} Moreover, these findings were drawn from VA electronic health records, which have been shown to enhance ADR detection.³⁵ The VA's advanced computer system has wide implications for improving the detection of drug-related problems, which is an essential step in determining future areas for intervention.

We found that 10% of unplanned hospitalizations were caused by ADRs and that over one-third of these hospitalizations were preventable. Between FY04–FY06, 2,430,186 older Veterans received care in a VHA facility, of whom 13.5% ($n=328,166$) were hospitalized at least once. Given this, we can extrapolate using our data that two-thirds of these hospitalizations were unplanned and that 10% of these hospitalizations were due to ADRs. Further applying our ADR-related hospitalization preventability rate of 36.8%, it is estimated that over 8,000 admissions would be preventable during this timeframe. Using the average length of stay from the Veteran population of 7.4 days and applying conservative FY04 acute inpatient admission daily costs (\$1,880 per day; personal communication with VA Health Economics Resource Center), then ADRs cost the VA over \$110 million from preventable hospitalizations.³⁶ These healthcare costs may also be applicable to non-VA settings.

Previous individual studies in non-VA settings on ADR-related hospitalizations have reported higher rates up to 21%^{2,4,8,11}, including a subgroup analysis of 17 studies of elderly patients from a larger meta-analysis (68 observational studies total) that reported a 16.6% prevalence rate of hospitalizations caused by ADRs.³ However, our finding of 10% of hospitalizations caused by ADRs is consistent with more recently published research. A literature review examining the relationship between study factors and the prevalence of medication-related hospital admissions reported a prevalence of 10.8% for ADR-related admissions across 3 studies where patients were admitted to a ward for care of the elderly.¹¹ Moreover, a systematic review of prospective observational studies assessing the prevalence of hospitalizations associated with ADRs reported a median ADR prevalence rate of 10.7% across 5 studies of elderly patients (age > 60 years).¹⁵

It is important to compare our finding of the association between polypharmacy and ADR-related hospitalizations with previous studies. After controlling for physical and psychiatric measures of comorbidity, polypharmacy was found to be significantly associated with ADR-related hospitalization in both bivariate and adjusted analysis. This finding is consistent with a multicenter cross-sectional study of older adults (mean age 70 years) in academic hospitals throughout Italy that assessed the prevalence of ADR-related hospital admission in older adults. In this previous study, Onder *et al* found that the number of drugs was the most

important risk factor associated with ADR-related hospitalization (OR 1.24, 95% CI 1.20–1.27 for each drug increase).⁴ However, it is essential to recognize that polypharmacy is influenced by the complexity of prescribing for older adults with multiple comorbid conditions who often have varying social situations and fluctuating goals and priorities of care.³⁷ Because of this, clinicians, together with their patients, are often faced with making difficult trade-offs between achieving the intended benefits and avoiding the potential harms of medication use in complex older adults. Evidence of the need for such personalized clinical decision-making comes from a study that demonstrated interindividual variability in health priorities among older adults when faced with competing outcomes (i.e., cardiovascular event vs. fall injury vs. medication-related symptoms).³⁸ Moreover, it has been shown that primary care clinicians who care for older adults with multiple medical conditions also display variability in their beliefs regarding the benefits and harms of following guideline-directed care.³⁹ Thus, more research is needed to determine how to best equip clinicians with informed decision-making tools across conditions in older adults who often receive polypharmacy.

Several other interesting findings deserve mention. First, we only detected one case in which the use of a HEDIS high-risk drug was implicated in an ADR-related hospitalization (i.e., hyoscyamine associated with constipation).²² This low rate compares favorably to a nationally representative study of US older adults in 2004–2005 that assessed whether ED visits due to adverse drug events (ADEs) were due to potentially inappropriate medication use determined by Beers criteria.^{7,33} They also found low numbers of ED visits for ADEs due to potentially inappropriate medication use (i.e., 3.6% of all visits for ADEs). In addition, we found only one HEDIS drug-disease interaction (i.e., lorazepam/dementia) and three additional drug-disease interactions defined by other explicit criteria (i.e., diltiazem/heart failure; terazosin, nortriptyline/pre-syncope, postural hypotension; and hyoscyamine/constipation) that were associated with hospitalization.¹⁸ This low rate of drug-disease interactions could be due to the fact that many patients with drug-disease interactions were successfully treated in the ED setting and did not require subsequent hospital admission.

It is also important to note that the use of a few medication classes accounted for a majority of ADR-related hospitalizations. Specifically, we found that four medication classes (i.e., cardiovascular, central nervous system, antithrombotic, and endocrine) accounted for almost 80% of all the drugs implicated with ADRs (data not shown), which is consistent with prior research.^{25,40} In particular, among those ADR-related hospitalizations deemed to be preventable, narrow therapeutic range drugs (e.g., digoxin and theophylline) were implicated in 4 of 25 preventable admissions, and dysglycemia accounted for 5 of the 25 admissions (data not shown). Given that it is well-documented that older adults often take unnecessary medications and that narrow therapeutic range drugs may be improperly monitored, this suggests that future reductions in ADR-related hospitalizations may be possible and could reduce unnecessary health care expenditures.^{41–43}

What is the clinical value of these research findings? This information should be useful to clinicians in that it highlights possible areas for intervention (e.g., reducing unnecessary polypharmacy) to decrease preventable ADR-related hospitalizations. This may be particularly important for patients who have been recently hospitalized and in whom the rate of taking one or more unnecessary drugs at discharge ranges from 44–59%.^{44,45} One approach to reduce polypharmacy in older adults that has been published recently is the Good Palliative-Geriatric Practice algorithm, which outlines a systematic approach to evaluate medication regimens with a focus on discontinuing certain drug therapies not immediately essential for life.⁴⁶ While this approach has been shown to be successful in the nursing home setting as well as in community-dwelling older adults in Israel,⁴⁶ future studies are needed to evaluate this algorithm in other populations of older adults such as

those residing in VA nursing homes. Moreover, using a careful, stepwise approach to discontinuing medications while also incorporating the goals of care of the patient, their social situation, and the most current pharmacotherapy evidence base should aid in the successful discontinuation of potentially unnecessary medications.⁴⁷ It is also important for clinicians to be aware of the clinically relevant potential for adverse drug withdrawal events (ADWEs) when discontinuing medications. While ADWEs are relatively rare, it is notable that they may present as either physiologic withdrawal reactions (e.g., beta blockers) or return of the underlying disease (e.g., worsening of hypertension upon stopping an anti-hypertensive).⁴⁸

There are several potential limitations worth discussing. First, this study relied heavily on information from electronic health records to assess ADRs, and we may have underestimated problems if the information was missing, incorrectly entered, or not recorded in the chart. We did, however, use a reliable and valid ADR algorithm to assess ADR events that were related to the hospital admission.⁴⁹ In addition, it is possible that unmeasured confounding could account for the association between polypharmacy and ADRs. To minimize this threat to validity, we controlled for a number of variables shown in other studies to be related to the outcome measure, including comorbidity. Moreover, the sample consisted mostly of older male Veterans living in the community and may not generalize to older females or non-Veteran populations. Indeed, this study found that older Veterans have multiple comorbid conditions and that 80% took ≥ 5 regularly scheduled prescription medications. However, it is important to note that our findings may be relevant to the one-third of community-dwelling older adults who reported using ≥ 5 regularly scheduled prescription medications in a nationally representative study.⁵⁰

CONCLUSION

In conclusion, unplanned hospitalizations caused by ADRs are common in older Veterans, are frequently preventable, and are associated with polypharmacy. The implications of these findings should encourage further population-based research of ADR-related morbidity, including the risk of increased healthcare utilization (e.g., ED visits⁷ and hospitalizations) in older adults. Our study findings and the suggested further research should be useful to clinicians and health policy makers to highlight possible areas for future interventions (e.g., reducing inappropriate prescribing using computerized physician order entry with decision support⁵¹) to improve these important and preventable medication safety problems.

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The sponsor of this research had no role or influence in matters relating to research design, methods, subject recruitment, data collection, analysis and/or preparation of the paper.

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Table 1

Comparison of Characteristics by ADR Group (n=678)

	Without ADR, n (%) (n=610)	With ADR, n (%) (n=68)	P value
<i>Primary Independent Variable</i>			
Number of regularly scheduled medications			0.01
0–4	129 (21.1)	5 (7.4)	--
5–8	217 (35.6)	23 (33.8)	--
≥ 9	264 (43.3)	40 (58.8)	--
<i>Demographic Control Variables</i>			
Age (years)			0.47
65–74	243 (39.8)	30 (44.1)	
75–84	305 (50.0)	29 (42.7)	
≥ 85	62 (10.2)	9 (13.2)	
Female	9 (1.5)	1 (1.5)	0.99
Race/Ethnicity			0.22
White	455 (74.6)	57 (83.8)	--
Black	78 (12.8)	9 (13.2)	--
Hispanic	41 (6.7)	1 (1.5)	--
Other	6 (1.0)	0 (0)	--
Unknown/Missing	30 (4.9)	1 (1.5)	
Unmarried	318 (52.1)	29 (42.6)	0.14
<i>Health-Status Control Variables</i>			
Selim Physical Comorbidity Index, mean (SD)	3.9 (2.2)	4.3 (2.6)	0.28
Selim Psychiatric Comorbidity Index (% with ≥ 1)	145 (23.8)	15 (22.1)	0.75
<i>Access to Care Control Variables</i>			
Non-exempt copayment status	74 (12.1)	10 (14.7)	0.54
Geriatric Evaluation & Management clinic visit in previous year	45 (7.4)	5 (7.4)	0.99
Number of primary care visits in previous year			0.22
0–1	84 (13.8)	9 (13.2)	--
2–4	241 (39.5)	34 (50.0)	--
5	285 (46.7)	25 (36.8)	--
Emergency Department visit in previous year	307 (50.3)	37 (54.4)	0.52
Hospitalization in previous year	192 (31.5)	26 (38.2)	0.26

Abbreviations: ADR: adverse drug reaction; SD: standard deviation

Table 2

ADRs Causing Hospitalization (by Major Condition and Therapeutic Class) among Older Veterans (n=678)

Major Diagnosis Category (n)*	Most Common Conditions in Each Diagnosis Category (n)	Most Common Therapeutic Classes (n)†
Circulatory system (18)	Bradycardia/Heart Block (6)	Beta-blockers (6) Digitalis glycosides (2) Calcium channel blockers (1)
	Congestive Heart Failure (3)	Blood glucose regulation agents (TZD) (2) Calcium channel blockers (1)
	Hypotension (3)	Alpha blockers (2) ACE Inhibitors (1) Loop diuretics (1) Thiazide diuretics (1) Tricyclic antidepressant (1)
	Arrhythmia/Tachycardia (3)	Antiarrhythmics (1) Xanthine-derivative bronchodilators (2)
Endocrine, nutritional, metabolic, and immunologic (16)	Hypoglycemia (6)	Oral hypoglycemic agents (5) Insulin (2) Anti-infectives, other (FQ) (1) Blood glucose regulation agents (TZD) (1)
	Hyponatremia (3)	Thiazide diuretics (3) Loop diuretics (1) Potassium-sparing diuretics (1)
	Acidosis (2)	Blood glucose regulation agents (2)
	GI Bleed (5)	Anticoagulants (3) Platelet aggregation inhibitors (3)
Gastrointestinal/Genitourinary (12)	Ulcer (2)	Platelet aggregation inhibitors (2) NSAIDs (1)
	Fall (6)	Antidepressants (3) ACE Inhibitors (2) Anticonvulsants (2) Alpha blockers (1) Antineoplastics (1) Beta-blockers (1) Loop diuretics (1) Non-opioid/opioid analgesics (1)
Musculoskeletal and connective tissue (7)		
Cognitive (7)	Mental Status Changes (6)	Anticonvulsants (2) Antidepressants (2) Benzodiazepines (2) Antiemetics (1) Opioid analgesics (1)
Hepatic/Renal (5)	Acute Kidney Injury (4)	Non-steroidal anti-inflammatory analgesics (3) ACE Inhibitors (1) Loop diuretics (1) Platelet aggregation inhibitors (1) Sulfonamides (1)
Other (5)	<i>Clostridium difficile</i> (3)	Beta-lactam antimicrobials (2) Anti-infectives, other (FQ) (1) 1 st generation cephalosporins (1)
Overall (70)	--	--

Abbreviations: ACE: angiotensin converting enzyme; ADR: adverse drug reaction; FQ: fluoroquinolone; NSAIDs: nonsteroidal anti-inflammatory drugs; TZD: thiazolidinedione

* Some Veterans may have experienced an ADR in >1 diagnostic category.

† Some Veterans experienced an ADR from >1 class of medications or an ADR from multiple medications in a single class. ADRs from multiple medications within a single major medication class were counted only once per veteran.

Table 3

Factors Associated with ADR-Related Hospitalizations in Older Veterans (n=678)

Variable	Adjusted OR	95% CI	P value
<i>Primary Independent Variable</i>			
Number of regularly scheduled medications			
0–4	1.0 (<i>Reference</i>)	--	--
5–8	2.85	1.03–7.85	0.04
≥ 9	3.90	1.43–10.61	<0.01
<i>Demographic Control Variables</i>			
Age (years)			
≥ 85	1.0 (<i>Reference</i>)	--	--
65–74	0.76	0.33–1.74	0.51
75–84	0.62	0.27–1.41	0.25
Female	1.15	0.13–10.26	0.90
Race/Ethnicity			
White	1.0 (<i>Reference</i>)	--	--
Black	0.86	0.40–1.84	0.69
Hispanic	0.21	0.03–1.60	0.13
Unmarried	0.71	0.41–1.20	0.20
<i>Health-Status Control Variables</i>			
Selim Physical Comorbidity Index	1.01	0.87–1.18	0.86
Selim Psychiatric Comorbidity Index	0.85	0.45–1.60	0.61
<i>Access to Care Control Variables</i>			
Non-exempt copayment status	1.31	0.61–2.82	0.49
Geriatric Evaluation & Management clinic visit in previous year	1.39	0.50–3.90	0.53
Number of primary care visits in previous year			
0–1	1.0 (<i>Reference</i>)	--	--
2–4	1.20	0.53–2.74	0.66
5	0.62	0.25–1.54	0.30
Emergency Department visit in previous year	1.09	0.57–2.08	0.80
Hospitalization in previous year	1.24	0.60–2.58	0.57
Year of hospital admission			
2006	1.0 (<i>Reference</i>)	--	--
2004	1.01	0.51–1.99	0.98
2005	0.68	0.38–1.23	0.20

Abbreviations: ADR: adverse drug reactionHosmer and Lemeshow Goodness-of-Fit Test: $\chi^2=12.46$; $df=8$; $p=0.13$