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Prescribing Quality in Older Veterans: A Multifocal Approach

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BACKGROUND AND OBJECTIVE: Quality prescribing for older adults involves multiple considerations. We evaluated multiple aspects of prescribing quality in older veterans to develop an integrated view of prescribing problems and to understand how the prevalence of these problems varies across clinically important subgroups of older adults.

DESIGN AND PARTICIPANTS: Cross-sectional observational study of veterans age 65 years and older who received medications from Department of Veterans Affairs (VA) pharmacies in 2007.

MAIN MEASURES: Using VA pharmacy data linked with encounter, laboratory and other data, we assessed five types of prescribing problems.

KEY RESULTS: Among 462,405 patients age 65 and older, mean age was 75 years, 98 % were male, and patients were prescribed a median of five medications. Half of patients (50 %) had one or more prescribing problems, including 12 % taking one or more medications at an inappropriately high dose, 30 % with drug–drug interactions, 3 % with drug–disease interactions, and 26 % taking one or more Beers criteria drugs. In addition, 16 % were taking a high-risk drug (warfarin, insulin, and/or digoxin). On multivariable analysis, age was not strongly associated with four of the five types of prescribing issues assessed (relative risk < 1.3 across age groups), and comorbid burden conferred substantially increased risk only for drug–disease interactions and use of high-risk drugs. In contrast, the number of drugs used was consistently the strongest predictor of prescribing problems. Patients in the highest quartile of medication use had 6.6-fold to12.5-fold greater risk of each type of prescribing problem compared to patients in the lowest quartile ($P<0.001$ for each).

CONCLUSIONS: The number of medications used is by far the strongest risk factor for each of five types of prescribing problems. Efforts to improve prescribing should especially target patients taking multiple medications.

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INTRODUCTION

Prescribing for older adults is complex. The presence of comorbid diseases, multiple medications, and renal impairment requires careful attention to avoid a variety of prescribing pitfalls, including excessive medication doses, drug–disease interactions, drug–drug interactions, and use of any of a long list of medications that should typically be avoided in older adults.[1–4]

While many studies have documented the presence of these types of prescribing problems in older adults, the existing literature has notable limitations.[5–10] Nearly all previous research has evaluated the prevalence of one specific aspect of prescribing quality (for example, use of medications from the Beers drugs-to-avoid criteria), or global measures of quality as assessed by structured implicit review (for example, the Medication Appropriateness Index).[2,4] In contrast, much less work has been done on the simultaneous occurrence of different aspects of prescribing quality, a multifocal approach that more closely reflects the complicated reality of patients' clinical care.[11,12]

Some interventions have embraced this complexity, particularly comprehensive medication review by pharmacists with expertise in geriatric care.[13] While this model has been tested in research settings and incorporated into Medicare Part D's Medication Therapy Management program, the availability of in-depth, regular reviews for all patients who could benefit remains limited. In the absence of resources to conduct these regular, multifocal, and comprehensive reviews, improving prescribing in part depends on synthesizing the epidemiology of different types of prescribing misadventures. In particular, this synthesis can help prioritize attention to those problems that are most common and most serious, both for the population as a whole as well as for individual patients who may be at greater risk for a certain type of prescribing problem.

To address this important gap in the literature, we conducted a national study of five types of prescribing problems in older adults who receive care in the Department of Veterans Affairs (VA) health care system. In particular, we sought to assess the relative prevalence of different types of prescribing problems in this national population, and the extent to which potential risk factors vary across different types of prescribing issues.

METHODS

Subjects

Using national VA databases merged with data from the Medicare program, we identified all veterans age 65 years and older who were seen in VA primary care and/or medicine subspecialty clinics during Fiscal Year 2007, were receiving at least one medication from a VA outpatient pharmacy as of the first day of the FY2008 (1 October 2007), and were not residing in an inpatient facility on this date. Because patients receiving care from both VA and Medicare providers may receive drugs from either source, we excluded patients who received less than 80 % of their outpatient care through VA or were enrolled in Medicare Managed Care plans. This research was approved by the institutional review boards of the San Francisco VA Medical Center and the University of California, San Francisco.

Demographic and Clinical Information

Demographic data were assessed using VA outpatient files and the Medicare denominator file. To assess comorbid conditions, we compiled ICD9 codes for 23 common conditions among veterans based on established methodology.[14]

Renal function was assessed using the most recent test results from VA clinical laboratories prior to 1 October 2007, excluding results obtained during or within 3 days before or after hospitalization. For patients in whom estimated glomerular filtration rate (eGFR) was not directly reported, we used the CKD-EPI equation to estimate GFR based on the patient's serum creatinine.

Medication Use

Using VA outpatient pharmacy records, we assessed prevalent medication use as of 1 October 2007. A medication was considered to be in active use on that date if the last dispensing of the medication provided sufficient days supply to last until or beyond the index date, or if the drug's medication possession ratio was 80 % or greater prior to the index date and the patient continued to receive the medication after the index date.[15] Although we assessed all medications dispensed to study patients, where appropriate we only analyzed medications given orally or otherwise designed for systemic absorption (e.g., excluding topical medications, eye drops, and so forth).

Markers of Prescribing Quality

We evaluated several markers of prescribing quality. Because quality issues can apply to thousands of types of medications, for reasons of feasibility we used queries of national VA data and results of a VA medication research study to identify the 132 medications most commonly dispensed by VA outpatient pharmacies for oral use.[16] We applied each of our quality measures to these 132 drugs, and also to insulins, since they are frequently used and are a common cause of adverse drug events in older adults. Together, these drugs accounted for 78 % of all drugs dispensed by VA pharmacies over the study period, and 98 % of subjects in the sample were taking at least one such drug (Appendix 1, available online). In addition, for each quality indicator, we supplemented our list of 132 drugs with additional medications particularly relevant to that indicator, as described below.

Beers Criteria. We applied the 2012 update of the Beers criteria, a list of drugs that are considered potentially inappropriate in older adults.[4] We accounted for the contextual factors that apply to many of these criteria (e.g., dose and duration restrictions, use of concurrent drugs, and so forth).

Drug Dosing. We evaluated whether the patient exceeded the maximum recommended daily dose for the 132 most commonly dispensed drugs, using dosage information listed in a pharmacy reference guide.[17] We also evaluated the maximum recommended dose of medications that require adjustment in patients with impaired renal function, applying these dosing criteria for each individual patient's eGFR. These renal dosing criteria included drugs that require lower doses and those that are contraindicated entirely below a threshold of renal function. For this analysis, we supplemented the list of 132 drugs with a consensus list of other medications that require dose adjustment in older adults with renal insufficiency.[18]

Finally, we used criteria from the pharmacy reference guide to determine dose adjustments or drug contraindications in patients with hepatic impairment, using ICD9 codes for cirrhosis and portal hypertension to identify the presence of moderate or severe hepatic dysfunction.[19]

Drug–Drug Interactions. We used several complementary approaches to identify clinically significant drug–drug interactions. First, we assessed all drug–drug interactions

involving each of the 132 most common drugs in VA that were listed in a pharmacy reference source as Risk Level D (close monitoring advised) or Risk Level X (avoid the interaction).[17] Second, we evaluated interactions from a consensus paper that defined common and clinically important drug–drug interactions in older adults.[20] Third, we assessed which of our top 132 drugs produced moderate or marked inhibition or induction of metabolic pathways, and which of these drugs were metabolized by these pathways. In addition, we identified drugs listed in a widely cited reference source as producing or being affected by CYP450-mediated changes in drug metabolism.[21] Using this information, we identified all metabolism-associated drug–drug interaction pairs present among patients in our sample. To check the clinical importance of these interactions, we entered each pair into a drug–drug interaction assessment tool, and counted only those interactions classified as Risk Levels D or X.[17] Because of the prohibitive volume of pairs that needed checking, we focused on the top 175 interaction pairs that involved inhibition of metabolic pathways, and all interaction pairs that involved induction of metabolic pathways.

Drug–Disease Interactions. We used a consensus list of common and clinically important drug–disease interactions defined by Lindblad et al.[22] ICD9 codes were used to identify relevant conditions, following the methods of comorbidity assessment described earlier for measuring comorbid conditions.

High-Risk Drugs. We evaluated use of three drugs (warfarin, insulin, digoxin) that are among the most common cause of emergency room visits for adverse drug events in older adults.[23,24] Although use of these drugs is not intrinsically problematic, their high risk of causing serious adverse events makes them a source of scrutiny and caution.

Analyses

We used log binomial regression to evaluate the independent association between patient characteristics and the rate of prescribing problems for each patient, except for analyses of drug–disease interactions, in which we used Poisson regression with robust error variance due to lack of convergence in the log binomial models.[25] In each case, we dichotomized each type of prescribing problem as absent or present (e.g., one or more problems) per patient. Results were similar when data were analyzed retaining the actual number of prescribing problems; e.g. 0, 1, 2, etc. per patient. Pairwise comparisons of the association between different types of prescribing quality were assessed through relative risk estimation using log binomial regression. Analyses were conducted using SAS 9.2 (SAS Corp, Cary, NC).

RESULTS

Characteristics of Patients

Characteristics of patients are shown in Table 1. Mean age was 75 years, 53 % had three or more common comorbid conditions, and patients used a median of five (interquartile range, three to eight) medications.

Prevalence of Prescribing Problems

Table 2 shows the prevalence of different types of prescribing problems in veterans age 65 years and older. Overall, 50 % of patients had at least one prescribing problem identified. The most common type of prescribing problem was drug–drug interactions, present in 30 % of patients, including 4 % of patients with one or more Risk Class X interactions. The next most common types of problems were use of Beers criteria medications (26 % of patients) and use of the high-risk medications warfarin, insulin, and/or digoxin (16 %), which are not considered intrinsically problematic, yet are associated with high rates of adverse drug events. The most common medications for each type of prescribing problem are shown in Table 3.

Table 1. Characteristics of Subjects

	N (%) *N*=462,405
Age (years)	
65–74	265,826 (58)
75–84	164,049 (36)
≥85	32,530 (7)
Male sex	452,427 (98)
Race / ethnicity	
White, non-Hispanic	380,539 (82)
Black, non-Hispanic	62,135 (13)
Other, non-Hispanic	11,597 (3)
Hispanic	8,134 (2)
Comorbid conditions	
Ischemic heart disease	93,661 (20)
Heart failure	32,536 (7)
Diabetes	145,354 (31)
Arthritis	52,829 (11)
COPD / asthma	68,904 (15)
Number of combined conditions recorded (out of 23)	
0	64,895 (14)
1–2	152,715 (33)
3–5	188,155 (41)
≥6	56,640 (12)
Estimated glomerular filtration rate (eGFR; ml/min/1.73M^2)	
≥60	221,802 (48)
30–59	159,135 (34)
15–29	12,041 (3)
<15	2,023 (0)
Not available	67,404 (15)
Moderate or severe impairment in hepatic function	587 (0)
Number of medications used (on index date)	
1–2	80,351 (17)
3–5	152,755 (33)
6–10	163,526 (35)
>10	65,773 (14)
Hospitalized in Fiscal Year 2007 (VA or Medicare)	86,264 (19)
Number of primary care and medicine subspecialty visits over Fiscal Year 2007 (including VA and Medicare); median(IQR)	4 (2, 7)

Table 2. Prevalence of Types of Prescribing Problems

Problem class	Problem	N (%) of patients with the problem N=462,405
Any problem	Any of the problems listed in this table	252,113 (54.5)
	Any of the problems listed in this table not including high-risk drugs (warfarin, insulin, or digoxin)	229,791 (49.7)
Dosing	Inappropriately high dosing (any type)	53,407 (11.6)
	Inappropriate dosing (general)	27,722 (6.0)
	Inappropriate dosing for renal function	28,034 (6.1)
	Inappropriate dosing for hepatic function	199 (0.0)
Drug–drug interactions	Any drug–drug interaction	139,807 (30.2)
	Risk D interaction	138,671 (30.0)
	Risk X interaction	20,463 (4.4)
Drug–disease interactions	Any drug–disease interaction	14,828 (3.2)
Beers criteria	Any Beers criteria drug	120,136 (26.0)
High risk drug	Any high-risk drug	74,212 (16.1)
	Warfarin	34,872 (7.5)
	Insulin	33,473 (7.2)
	Digoxin	19,036 (4.1)

Relationship Between Patient Characteristics and Prescribing Problems

Most types of drug-related problems did not vary substantially by age, although use of Beers criteria medications decreased from 27 % among patients age 65–69 years to 19 % of patients age 90 and older ($P<0.001$) and the frequency of drug–disease interactions increased across this age range ($P<0.001$; see Figure 1 and Appendix 2, available online). Declining renal function and increasing number of comorbid conditions were both associated with increasing risk of drug-related problems (Fig. 1). However, the number of medications used was the strongest predictor of each type of medication-related problem (Fig. 1).

These patterns were even more pronounced on multivariable analyses (Table 4). The number of medications used by the patient was strongly associated with each type of prescribing problem. Patients in the highest quartile of medication use (eight or more medications) had a 6.7-fold to 12.5-fold increased risk of each type of prescribing issue compared with those in the lowest quartile of medication use (one to three medications). In contrast, most other patient characteristics did not confer substantially increased risk for the five types of prescribing problems we assessed. For example, age was not associated with major differences in risk for four of the five types of prescribing problems we studied (i.e., relative risk < 1.3 for difference in frequency of the prescribing problem between age groups). Similarly, comorbid burden was not substantially associated with three of the five types of prescribing problems we evaluated, although higher levels of comorbid burden were associated with a roughly twofold to threefold increase in risk for drug–disease interactions and use of high-risk drugs (see Table 3).

Patients with one type of prescribing problem were more likely to have another type of prescribing problem, with a relative risk of 1.5 to 3.0 for each possible pairwise

Table 3. Most Common Problem Medications

Problem	Most common problem drugs / drug combinations	N (%) of patients with prescribing problem	N (%) of patients taking the drug (with or without prescribing problem)
Inappropriate dosing [a]	Lisinopril	10,906 (2.4)	168,044 (36.3)
	Allopurinol	8,248 (1.8)	19,738 (4.3)
	Ranitidine	6,438 (1.4)	30,154 (6.5)
	Enalapril	4,355 (0.9)	6,858 (1.5)
	Docusate	3,603 (0.8)	28,479 (6.2)
Drug–drug interactions [b]	Alpha1 Blockers—Beta Blockers	51,276 (11.1)	–
	Allopurinol—ACE Inhibitors	11,654 (2.5)	–
	Gemfibrozil—HMG CoA Reductase Inhibitors	10,709 (2.3)	–
	Simvastatin—Diltiazem	9,549 (2.1)	–
	Clopidogrel—Proton Pump Inhibitors	8,006 (1.7)	–
Drug–disease interactions	Glucocorticoids (Steroids)—Diabetes	2,690 (0.6)	7,703 (1.7)
	Diltiazem—Congestive Heart Failure	2,557 (0.6)	20,519 (4.4)
	Benzodiazepines—Dementia	1,854 (0.4)	22,170 (4.8)
	Aspirin—Peptic Ulcer Disease	1,569 (0.3)	67,969 (14.7)
	Antihistamines—Dementia	1,488 (0.3)	24,326 (5.3)
Beers criteria drugs	NSAIDs (non-COX selective)	38,161 (8.3)	38,161 (8.3)
	Sulfonylureas, Long Duration	37,531 (8.1)	37,531 (8.1)
	Benzodiazepines	14,183 (3.1)	14,183 (3.1)
	Antihistamines	10,816 (2.3)	10,816 (2.3)
	Tertiary Tricyclic Antidepressants	8,371 (1.8)	8,371 (1.8)
High-risk drugs	Warfarin	34,872 (7.5)	34,872 (7.5)
	Insulins	33,473 (7.2)	33,473 (7.2)
	Digoxin	19,036 (4.1)	19,036 (4.1)

[a] *Lisinopril and docusate identified for inappropriately high dose regardless of renal function; allopurinol, enalapril, ranitidine noted for inappropriately high dose given impaired renal function*

[b] *Each drug–drug interaction listed is risk class D (monitoring advised for adverse effects of drug–drug interaction), except clopidogrel-proton pump inhibitors (Class X, avoid combination, although this recommendation is controversial)*

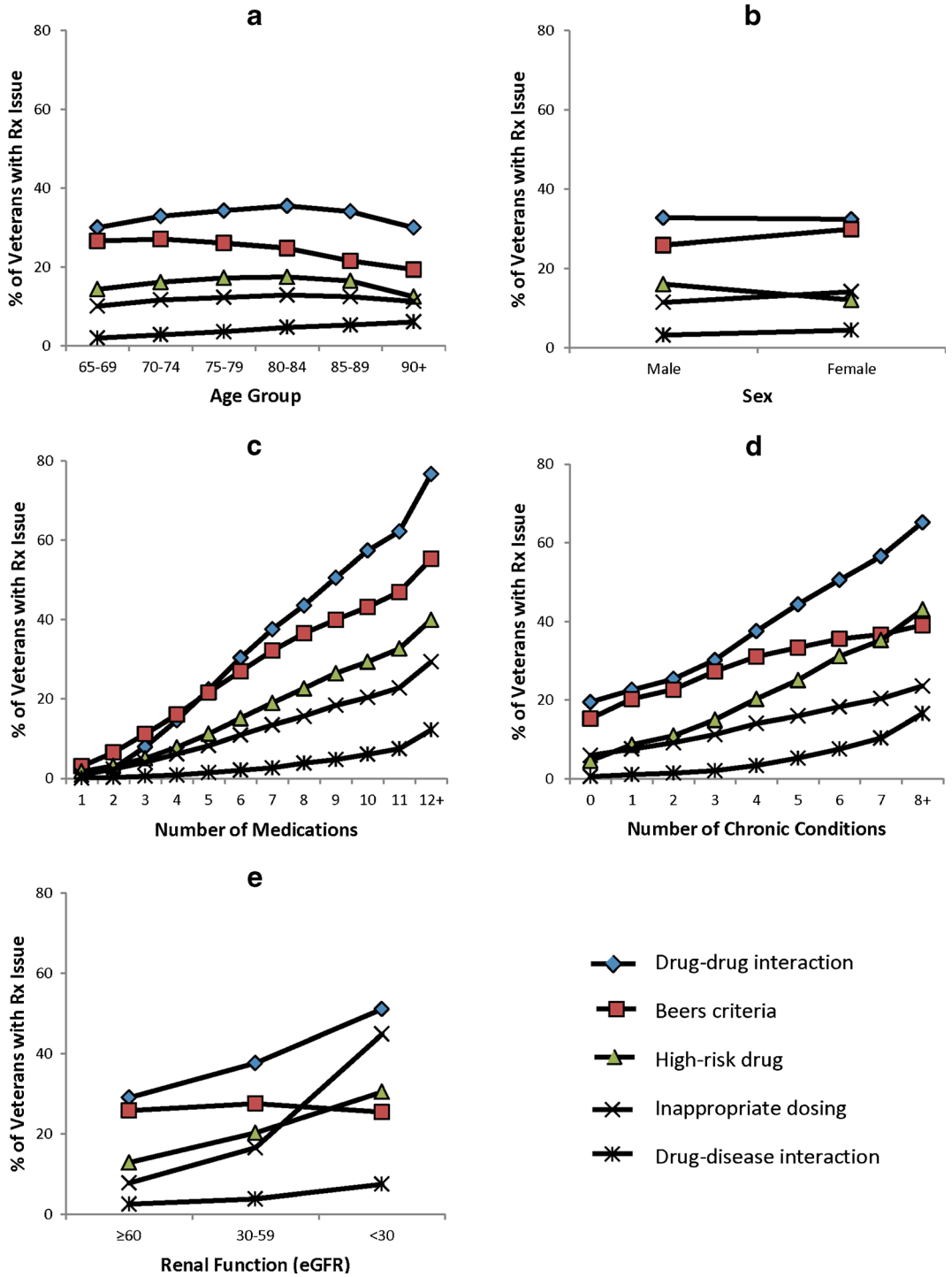

Figure 1. Bivariate associations between patient characteristics and prescribing problems. Each panel shows the relationship between a different patient characteristic and five types of prescribing issues, as indicated in the legend. Patient characteristics include age (panel A), sex (panel B), number of medications used (Panel C), number of chronic conditions (panel D), and renal function as assessed by estimated glomerular filtration rate (Panel E).

comparison of prescribing problems (see Appendix 3, available online). For example, patients with one or more drug–drug interactions were 2.2 times as likely (95 % CI, 2.2–2.3) to have one or more dosing problems than patients with no drug–drug interactions. Adjusting for number of medications substantially attenuated these relationships. After adjusting for number of medications, the relative risk for each possible pairwise comparison ranged from 0.9 to 1.5, with more than three-quarters of these relative risks ranging from 0.9 to 1.2 (Appendix 3, available online).

DISCUSSION

In this study of older veterans, half had one or more prescribing problems, ranging from 30 % with drug–drug interactions to 3 % with drug–disease interactions. Age, comorbid burden, and renal function were associated with selected prescribing problems, albeit in contrasting ways. However, by far the strongest and most consistent predictor of prescribing problems was the number of medications used by patients. After controlling for key patient characteristics, the rate of each type of prescribing problem was 6.7-fold to 12.5-fold higher in patients with the highest quartile of medication use (eight or more medications) than in patients with the lowest quartile of use (one to three medications).

Our results have implications for caring for older adults who may have a variety of different types of medication-related problems. Efforts to improve prescribing quality often focus narrowly on one type of potential problem. In doing so, these efforts can miss the mark in identifying which patients have the highest burden of prescribing problems overall, and thus might be most likely to benefit from intervention. This is particularly important for interventions that involve comprehensive medication review, which by design are able to take a more holistic view of the patient's medication regimen and potential problems with it.[26,27] Our results provide support for focusing on the number of medications taken by a patient as the key risk factor for identifying medication-related problems, regardless of the type of problem. It is important to note that being in the upper reaches of age (e.g., age 80 years and older) was associated with a neutral to lower risk of most types of prescribing problems on both bivariate (Fig. 1) and multivariable (Table 4) analyses. Studies of adverse drug events have found a similar pattern, whereby advanced older age is not consistently associated with a higher rate of adverse drug events, particularly after accounting for numbers of medications taken and comorbid burden.[28–30]

A major challenge in comparing results across studies of prescribing quality is that the observed prevalence of prescribing problems varies widely depending on the measures and definitions used, as well as characteristics of the cohort, such as clinical setting and illness burden. Our study was designed to help overcome some of these challenges by evaluating several prescribing problems in the same cohort. Notwithstanding the limitations of comparing results across studies, our results are generally consistent with prior research on the prevalence of prescribing problems in community-dwelling older adults. Drug–drug interactions occurred in 30 % of our cohort, which is substantially higher than the 4–11 % prevalence

Table 4. Multivariable Predictors of Each Type of Prescribing Problem[a]

	Patients in subgroup N (%)	Any problem RR (95 % CI)	Dose adjustment RR (95 % CI)	Drug–drug interaction[b] RR (95 % CI)	Drug–disease interaction RR (95 % CI)	Beers criteria RR (95 % CI)	High-risk drugs RR (95 % CI)
By age group	–	–	–	–	–	–	–
65–74	265,826 (58)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
75–84	164,049 (36)	0.98 (0.98–0.98)	0.92 (0.91–0.94)	0.99 (0.99–1.00)	1.42 (1.37–1.47)	0.89 (0.88–0.90)	0.94 (0.93–0.95)
85+	32,530 (7)	0.95 (0.94–0.95)	0.83 (0.81–0.85)	0.96 (0.95–0.97)	1.86 (1.77–1.96)	0.76 (0.75–0.78)	0.84 (0.81–0.86)
By sex	–	–	–	–	–	–	–
Male	452,427 (98)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Female	9,978 (2)	0.99 (0.98–1.00)	1.13 (1.08–1.18)	0.95 (0.93–0.98)	1.34 (1.22–1.46)	1.13 (1.10–1.16)	0.73 (0.69–0.77)
By number of meds	–	–	–	–	–	–	–
Lowest quartile	131,314 (28)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
2nd quartile	101,792 (22)	2.72 (2.68–2.76)	2.58 (2.48–2.68)	3.33 (3.24–3.43)	2.57 (2.32–2.86)	2.54 (2.49–2.60)	2.40 (1.32–2.49)
3rd quartile	116,212 (25)	4.17 (4.12–4.22)	4.43 (4.27–4.59)	6.46 (6.28–6.64)	5.10 (4.63–5.62)	4.28 (4.19–4.37)	4.17 (4.05–4.31)
Highest quartile	113,087 (25)	5.24 (5.18–5.31)	7.41 (7.14–7.68)	11.07 (10.77–11.38)	12.45 (11.33–13.69)	6.70 (6.56–6.84)	6.63 (6.43–6.84)
By number of conditions	–	–	–	–	–	–	–
Lowest quartile	133,388 (29)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
2nd quartile	84,222 (18)	1.02 (1.01–1.03)	1.01 (0.98–1.04)	0.97 (0.96–0.99)	1.33 (1.23–1.44)	1.01 (1.00–1.03)	1.30 (1.27–1.34)
3rd quartile	148,321 (32)	1.05 (1.04–1.06)	1.01 (0.99–1.03)	1.00 (0.99–1.01)	1.70 (1.59–1.81)	1.03 (1.01–1.04)	1.59 (1.55–1.62)
Highest quartile	96,474 (21)	1.09 (1.08–1.09)	0.98 (0.96–1.00)	1.13 (1.12–1.15)	3.59 (3.36–3.84)	0.99 (0.98–1.01)	2.13 (2.09–2.18)
By renal function[c]	–	–	–	–	–	–	–
eGFR≥60	221,802 (48)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
eGFR 30–59	159,135 (34)	1.05 (1.04–1.05)	1.82 (1.79–1.86)	1.08 (1.07–1.09)	0.95 (0.91–0.98)	0.93 (0.92–0.93)	1.25 (1.24–1.27)
eGFR<30	14,064 (3)	1.07 (1.07–1.08)	3.88 (3.79–3.97)	1.13 (1.11–1.15)	1.07 (1.00–1.14)	0.71 (0.69–0.73)	1.35 (1.32–1.39)
Unknown	67,404 (15)	1.00 (0.99–1.00)	0.72 (0.069–0.74)	1.03 (1.02–1.05)	1.00 (0.95–1.06)	0.93 (0.92–0.95)	1.12 (1.09–1.14)

[a] *Analyses are adjusted for all variables shown in the table (age, sex, number of medications, number of conditions, and renal function)*
[b] *Includes drug–drug interactions of either Risk Class D (monitoring advised) or Risk Class X (avoid use)*
[c] *eGFR = estimated glomerular filtration rate, ml/min/1.73 m2*

observed in similar cohorts.[9,31,32] The difference may be due to the fact that our criteria for detecting drug–drug interactions were generally more comprehensive and less restrictive than criteria used in the comparator studies. Drug–disease interactions have been reported to occur in 1–30 % of older adults.[6,9,10,22,32–37] Our relatively unselected patient population and use of explicit criteria suitable to administrative data likely explain why our findings are at the lower end of this range, and are similar to findings from studies using similar methods.[10,33] Beers criteria violations occurred in 26 % of our cohort, similar to findings in a variety of previous studies of community-dwelling older adults.[8,9,32,38] The proportion of older veterans taking the high-risk medication warfarin is also similar to findings from other population-based surveys.[39] Finally, our finding that the number of medications used is a dominant risk factor across a range of prescribing problems is consistent with prior research, which has also found strong associations of this type.[33,34,40–43]

Our findings should be considered in light of the clinical importance of the medication-related problems that we identified. All explicit measures of prescribing quality face the challenge of reducing widely disparate clinical scenarios into a simple measure.[44] Even though we took steps to exclude items of minor clinical significance, our results include medication-related problems of both greater and lesser importance. In addition, it is important to note that criteria for different types of prescribing problems vary in their comprehensiveness. Thus, our results should not be interpreted as definitively identifying the true prevalence of each of these types of problems. Rather, our results are most useful when viewed as illuminating the extent to which different types of prescribing problems share a common set of risk factors, and thus might be present in similar or different groups of patients.

Our study has several limitations. First, we were unable to assess medications purchased over-the-counter or drugs obtained from non-VA sources. However, by restricting the cohort to include only patients who received the strong majority (or all) of their health care within VA, the likelihood of substantial non-VA prescription drug use is low. Second, our cohort consisted mostly of men, consistent with the population demographics in VA. However, given the national scope of the study, there were sufficient numbers of women to reliably evaluate sex differences in the risk of different types of prescribing problems (e.g., Table 3). Third, we cannot know the extent to which our findings generalize to other health care systems, although VA's leadership in geriatrics, team-based care, electronic medical records, and quality improvement suggests that the problems we identified may be equally if not more prevalent in non-VA settings.[45] Finally, the observation that number of medications strongly correlates with the likelihood of prescribing problems is consistent with what one would expect based on simple probability—that is, the more medications a patient takes, the more chances there are that something will go wrong. Nonetheless, understanding these relationships, even if expected, provides an important tool for identifying and intervening on patients at high risk of prescribing misadventures.

In summary, half of older veterans have one or more types of prescribing problems, and the strongest risk factor for each type of problem was the number of medications taken. As a result, efforts to identify patients at high risk of medication misadventures should focus predominantly on those that use multiple medications. Since patients taking multiple medications who have one type of prescribing problem are also at elevated risk of other types of problems, a comprehensive approach to assessing medication use in these patients may be particularly useful for reducing the totality of prescribing misadventures among older adults.

Conflict of Interest: *The authors declare that they do not have a conflict of interest.*

Author Contributions: *Study conception and design: Steinman, Schwartz, Boscardin*
Data acquisition: Miao, Steinman, Boscardin
Analyses: Miao, Steinman, Boscardin, Komaiko
Authorship of manuscript: Steinman, Komaiko
Review for critical intellectual content: Miao, Komaiko, Boscardin, Schwartz
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