

# Polypharmacy and Prescribing Quality in Older People

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**OBJECTIVES:** To evaluate the relationship between inappropriate prescribing, medication underuse, and the total number of medications used by patients.

**DESIGN:** Cross-sectional study.

**SETTING:** Veterans Affairs Medical Center.

**PARTICIPANTS:** One hundred ninety-six outpatients aged 65 and older who were taking five or more medications.

**MEASUREMENTS:** Inappropriate prescribing was assessed using a combination of the Beers drugs-to-avoid criteria (2003 update) and subscales of the Medication Appropriateness Index that assess whether a drug is ineffective, not indicated, or unnecessary duplication of therapy. Underuse was assessed using the Assessment of Underutilization of Medications instrument. All vitamins and minerals, topical and herbal medications, and medications taken as needed were excluded from the analyses.

**RESULTS:** Mean age was 74.6, and patients used a mean  $\pm$  standard deviation of  $8.1 \pm 2.5$  medications (range 5–17). Use of one or more inappropriate medications was documented in 128 patients (65%), including 73 (37%) taking a medication in violation of the Beers drugs-to-avoid criteria and 112 (57%) taking a medication that was ineffective, not indicated, or duplicative. Medication underuse was observed in 125 patients (64%). Together, inappropriate use and underuse were simultaneously present in 82 patients (42%), whereas 25 (13%) had neither inappropriate use nor underuse. When assessed by the total number of medications taken, the frequency of inappropriate medication use rose sharply from a mean of 0.4 inappropriate

medications in patients taking five to six drugs, to 1.1 inappropriate medications in patients taking seven to nine drugs, to 1.9 inappropriate medications in patients taking 10 or more drugs ( $P < .001$ ). In contrast, the frequency of underuse averaged 1.0 underused medications per patient and did not vary with the total number of medications taken ( $P = .26$ ). Overall, patients using fewer than eight medications were more likely to be missing a potentially beneficial drug than to be taking a medication considered inappropriate.

**CONCLUSION:** Inappropriate medication use and underuse were common in older people taking five or more medications, with both simultaneously present in more than 40% of patients. Inappropriate medication use is most frequent in patients taking many medications, but underuse is also common and merits attention regardless of the total number of medications taken. *J Am Geriatr Soc* 54: 1516–1523, 2006.

**Key words:** aged; drug utilization; quality of health care; polypharmacy; drug therapy

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In older persons with several chronic diseases, prescribing must balance competing tensions between limiting the number of medicines and using all medicines that may be beneficial.<sup>1–4</sup> The number of medicines might be limited, because the use of multiple medications is associated with higher likelihood of drug–drug interactions, adverse drug events, hospitalizations, and death.<sup>5–7</sup> Alternatively, more medicines might be prescribed, because evidence of efficacy and clinical guidelines support the use of a wide variety of drugs for common diseases such as ischemic heart disease, heart failure, and diabetes mellitus.<sup>2,8</sup>

Researchers and quality improvement programs have often established a set number of medications beyond which prescribing is considered to be “polypharmacy” and to merit extra attention for potential quality problems.<sup>9</sup> Several studies have demonstrated that the frequency of unnecessary or nonrecommended medication use is higher in patients taking many medications than in those taking few medications.<sup>6,10–14</sup> However, little systematic work has been done to assess the relationship between the total number of medications taken and the omission of drugs that

may be useful for a given patient (i.e., medication underuse).<sup>12</sup> As a result, efforts to improve prescribing quality lack information that could be used to target interventions.<sup>15,16</sup> In particular, understanding the relationship between inappropriate use, underuse, and the number of drugs taken can help determine how the focus of quality improvement interventions should differ for patients taking few versus many medications.

To investigate the relationship between inappropriate use, underuse, and total number of medications, data were used from a study of elderly veterans that included multiple measures of prescription quality. First, these data were used to determine the frequency of several types of prescribing problems, including use of medications that are ineffective, not indicated, or therapeutically duplicative; use of medications from a list of drugs that should be avoided in older people; and nonuse of beneficial medications. Next, analyses were performed to determine the association between the size of a patient's medication list and each of these outcomes and to compare the relative frequency of different prescribing problems in patients taking few versus many medications.

## METHODS

### Subjects and Data

All data were obtained from baseline evaluations in the Enhanced Pharmacy Outpatient Clinic (EPOC) Study, a study conducted in 2001 through 2003 at the Iowa City Veterans Affairs (VA) Medical Center that enrolled veterans aged 65 and older who were using five or more medications.<sup>17</sup> Data on medication use were collected through in-person pharmacist interviews in which the patient was asked to bring in all medications whether prescribed in VA clinics or not. Demographic information, medical history, and other data were collected through a combination of patient interview and chart review.

For the present study, only patients with complete information necessary to calculate each measure of prescribing quality were included. Of a cohort of 503 subjects taking five or more medications, 224 were randomly selected for evaluation using the Medication Appropriateness Index, from which one of the quality measures was derived.<sup>18,19</sup> Two of these patients did not have the medical history information necessary to code the Beers criteria and were excluded. Finally, to maintain a common list of medications evaluated using each of the quality measures, 26 patients were excluded on the basis of having fewer than five medications evaluated using the Medication Appropriateness Index or more than two medications listed on the master medication list that were not evaluated using this instrument. For the remaining 196 patients, 100 drugs listed on the medication list that were not evaluated using the Medication Appropriateness Index were excluded. This left a final study sample of 1,582 medications taken by 196 patients.

### Definitions

For the purposes of this study, medications were defined as allopathic systemic drugs other than vitamins and minerals that are taken on a regular basis (not as-needed). Topical

and herbal medications were excluded, because they are often not included in traditional methods of assessing prescribing quality and were not routinely evaluated in the EPOC study's measures of prescribing quality. Vitamins and minerals and medications taken on an as-needed basis were also excluded because of inconsistent inclusion of these medication types in polypharmacy measures. For each patient, the medications that remained after these exclusions were counted and considered to be the total number of medications taken by that patient. This drug count was the primary independent variable in the analyses.

Using the list of medications defined above, several measures of suboptimal prescribing were assessed. The first of these corresponds to a concept of overuse (drugs that are not necessary and should be eliminated without substitution). To measure this construct, three items were used from the Medication Appropriateness Index, a 10-item instrument in which a pharmacist rater uses structured implicit review to assess each drug on a patient's regimen.<sup>18</sup> The three items used were "Is there an indication for the drug?" "Is the medication effective for the condition?" and "Is there unnecessary duplication with other drugs?" Medications that the rater judged to be not indicated or ineffective or that were judged to be unnecessary duplication were considered overused. Although the combination of these three questions has not been validated as a stand-alone measure, this grouping has been used in previous research,<sup>20</sup> and each of the three items has excellent inter- and intrarater reliability.<sup>18,21,22</sup>

The second measure—the 2003 update of the drugs-to-avoid criteria of Beers et al.<sup>23</sup>—roughly corresponds to a concept of misuse (drugs that may serve a reasonable therapeutic purpose but for which alternatives exist that are safer or more effective). These criteria were developed for elderly patients and include drugs that should rarely or never be used, doses of drugs that should not be exceeded, and drug-disease and drug-drug interactions that should be avoided. Each criterion is designated as low or high severity.

Finally, the Assessment of Underutilization of Medication was used to assess underuse (drugs that could be beneficial to a patient but which are not being used). The same pharmacist rater who scored the Medication Appropriateness Index applied this instrument, which uses implicit review based on clinical practice guidelines and clinical judgment.<sup>9,20</sup> To apply this instrument, the rater reviewed each patient's clinical history and chart and listed any drugs that should have been prescribed but were not present on the patient's medication list. This instrument is based on a measure developed earlier and has good interrater reliability.<sup>12,20</sup>

The demographic and clinical data listed in Table 1 were obtained from patient intake interviews and chart review. Diagnoses and diagnosis-related procedures were combined to define the conditions listed in Table 1 (e.g., patients were considered to have ischemic heart disease if they had a consistent diagnosis or had undergone percutaneous coronary angioplasty or coronary artery bypass grafting).

### Analyses

For each patient, the number of problem drugs as assessed using each quality measure was tabulated. In the initial

**Table 1. Subject Characteristics**

Characteristic	Value
Age, mean $\pm$ SD	74.6 $\pm$ 5.4
Male, n (%)	194 (99)
White, n (%)	194 (99)
Drug copayment required, n (%) <sup>*</sup>	140 (72)
Comorbidities, n (%)	
Hypertension	175 (89)
Ischemic heart disease	111 (57)
Diabetes mellitus	88 (45)
Chronic obstructive pulmonary disease	51 (26)
Heart failure	23 (12)
Depression	22 (11)
Number of drugs, n (%) <sup>†</sup>	
$\leq 6$	63 (32)
7–9	84 (43)
$\geq 10$	49 (25)
Number of drugs, mean $\pm$ SD <sup>†</sup>	8.1 $\pm$ 2.5

<sup>\*</sup> Typically \$7.00 for a 30-day supply of each medication.

<sup>†</sup> Allopathic systemic drugs, not including vitamins and minerals, herbal medications, topical medications, or medications intended to be taken on an as-needed basis.

SD = standard deviation.

analyses, each measure is presented separately, although in clinical practice the concepts (and measures) of overuse and misuse may have substantial overlap. Thus, for the main analyses, these two measures were combined into a single measure of inappropriate medication use, and this was contrasted against the measure of medication underuse.

To evaluate the association between number of medications taken and number of problem medications, log-linear models with a Poisson distribution were employed. In these models, the number of medications was transformed using natural logarithms to improve model fit, which was assessed through visual inspection by plotting predicted values against a locally weighted regression line.<sup>24</sup> Tests for trend in categorical data were conducted using similar log-linear models in which the tertile of drug use was analyzed as a quantitative 1-2-3 variable. Finally, multivariable analyses without selection were conducted using the log-linear modeling methods described above, in which the number of problem medications was the dependent variable; the total number of medications was the primary independent variable; and age, medication copayment, and the diagnoses listed in Table 1 were secondary independent variables. (The limited number of women and nonwhites precluded the inclusion of patient sex and race in these analyses.) For each of the main analyses, sensitivity analyses were also conducted in which vitamins and minerals and as-needed medications were included in the total drug count. None of the results substantively changed (Appendix 1).

All analyses were conducted using Intercooled Stata 8.2 (Stata Corp., College Station, TX). The Committee on Human Research at the University of California at San Francisco, the institutional review board at the University of Iowa, and the Research and Development Committees at the Iowa City and San Francisco VA Medical Centers approved this research.

## RESULTS

Subjects were predominantly male and white, with a mean age of 74.6 (Table 1). Subjects used a mean of  $8.1 \pm 2.5$  medications, including a mean of  $1.4 \pm 1.0$  over-the-counter medications. Overall, medication use ranged from a study-imposed lower limit of five medications to a high of 17 medications per patient.

Of 196 subjects, 128 (65%) were taking one or more inappropriate medications. This included 112 (57%) patients who were taking a total of 171 medications that were ineffective, not indicated, or therapeutically duplicative and 73 (37%) patients taking a total of 91 medications deemed problematic according to the drugs-to-avoid criteria of Beers et al. (Table 2). Violations of the Beers criteria occurred at several levels, including 38 medications whose use in older people is never recommended; 28 medications contraindicated in the presence of certain diseases; and 25 violations of dosing criteria, drug-drug interactions, or combinations of problems. Overall, 62 of these 91 medication problems were classified as high severity. Over-the-counter agents accounted for 22 (10%) inappropriate drugs; approximately half of these were sedating antihistamines. The most common inappropriate drugs are listed in Table 3.

Underuse was present in 125 patients (64%), who were missing 199 medications considered useful and appropriate (Table 2). The majority of these 199 underused drugs were for cardiovascular conditions, including 49 antihypertensive medications, 29 anticoagulants (mostly aspirin), and 20 lipid-lowering agents (Table 3). Other commonly omitted medications were agents used for the prevention or treatment of gastrointestinal conditions, diabetes mellitus, osteoporosis, and obstructive pulmonary disease.

Inappropriate medication use and underuse often coexisted in the same patient, yet the presence of inappropriate use was not correlated with the presence of underuse ( $P = .91$ , chi-square). Eighty-two patients (42%) were simultaneously using one or more inappropriate medications and not using one or more indicated medications, whereas 25 patients (13%) had neither inappropriate use nor underuse. The remaining patients were evenly divided between having inappropriate use of at least one drug without any underuse (46 patients; 23%) and having at least one instance of underuse without any inappropriate use (43 patients; 22%).

### Drug Count and Prescribing Quality

Use of inappropriate medications rose sharply with increases in the total number of medications taken (log-linear beta coefficient = 1.68, 95% confidence interval (CI) = 1.23–2.12). Patients taking five to six medications used a mean of 0.4 inappropriate drugs, compared with a mean of 1.1 inappropriate drugs in patients taking seven to nine medications and 1.9 inappropriate drugs in those taking 10 or more medications ( $P < .001$  by test for trend). Similar patterns were observed for both components of this measure. Patients taking five to six medications used a mean of 0.4 ineffective, nonindicated, or therapeutically duplicative drugs, compared with a mean of 0.9 such drugs in patients taking seven to nine medications and 1.4 such drugs in patients taking 10 or more medications ( $P < .001$ ). Similarly, a

**Table 2. Frequency and Examples of Prescribing Problems**

Prescribing Problem	Problem Medications*	Patients with $\geq 1$ Problem Medications*	Examples (With Criterion Description and Reviewer Comments)
	n (%)	n (%)	
Inappropriate medications <sup>†</sup>	214 (14)	128 (65)	
Ineffective, not indicated, or therapeutically duplicative	171 (11)	112 (57)	Ineffective: digoxin—“diastolic dysfunction” No indication: furosemide—“no documented indication in chart” Duplication: ibuprofen—“[also taking] rofecoxib”
Drugs to avoid (Beers criteria)	91 (6)	73 (37)	Almost never indicated: amitriptyline, cimetidine Drug-disease contraindication: oxybutynin and prostatic hypertrophy; propranolol and chronic obstructive pulmonary disease
Underused medications	199 (N/A)	125 (64)	Omitted drug: thiazide—“BP not at goal” angiotensin-converting enzyme inhibitor—“with DM and CAD”

\* In 196 patients taking 1,582 medications.

<sup>†</sup> Of 214 medications identified as inappropriate, 43 (20%) were identified using the Beers criteria only, 123 (57%) were identified using the ineffective/not indicated/therapeutically duplicative measure only, and 48 (22%) were identified using both.

BP = blood pressure; DM = diabetes mellitus; CAD = coronary artery disease.

mean of 0.2, 0.5, and 0.8 medications from the drugs-to-avoid list of Beers et al. were used in these three groups, respectively ( $P < .001$ ).

In contrast, underuse of medications remained constant across the range of medication use, averaging 1.0 underused

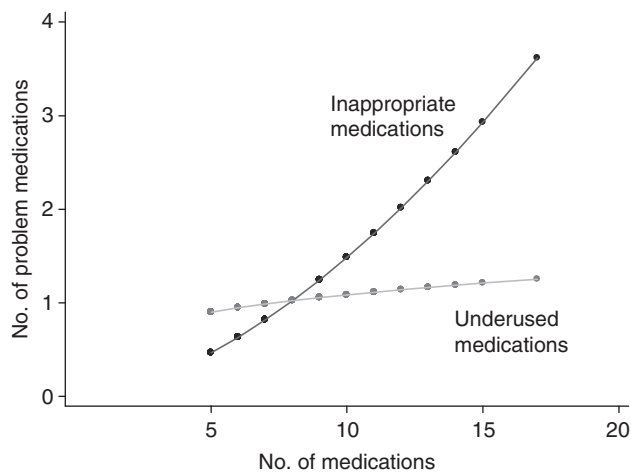
drugs per patient in patients taking few or many medications (beta coefficient = 0.27, 95% CI = -0.20-0.74, corresponding to  $P = .26$  for association between number of omitted medications and total number of medications taken). The type of drugs omitted did not vary in patients tak-

**Table 3. Most Common Inappropriate and Underused Medications**

Drug Class*	Drugs n (%)	Most Common Individual Drug (n)
<b>Inappropriate (n = 214)<sup>†</sup></b>		
Histamine antagonists	18 (8)	Ranitidine (10)
Digitalis glycosides	16 (7)	Digoxin (16)
Loop diuretics	12 (6)	Furosemide (11)
Proton pump inhibitors	11 (5)	Rabeprazole (6)
Tricyclic antidepressants	10 (5)	Amitriptyline (8)
Urinary antispasmodics	10 (5)	Oxybutynin (7)
Nasal antiinflammatories	10 (5)	Beclomethasone nasal MDI (10)
Sedating antihistamines	9 (4)	Diphenhydramine (5)
Nonsteroidal antiinflammatory drugs	8 (4)	Ibuprofen (3)
<b>Underused (n = 199)</b>		
Antihypertensives	49 (25)	—
Anticoagulants	29 (15)	Aspirin (26)
Lipid-lowering agents	20 (10)	Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) (16)
Sublingual nitroglycerin	17 (9)	—
Proton pump inhibitors	13 (7)	—
Hypoglycemic agents	9 (5)	—
Calcium	8 (4)	—
Bronchodilators (anticholinergic)	7 (4)	Ipratropium (7)
Bronchodilators (sympathomimetic)	6 (3)	Albuterol (6)

\* Arranged by Department of Veterans Affairs (VA) drug class codes. Class descriptions are modified from the original VA terminology to best reflect the specific drugs within each category. In categorizing underused medications, VA drug classes were combined when the reviewer suggested a choice of medications from different classes (e.g., angiotensin-converting enzyme (ACE) inhibitor or beta-blocker for a patient with hypertension, insulin or thiazolidinedione for a patient with diabetes mellitus). Antihypertensive medications include ACE inhibitors, beta-blockers, calcium-channel blockers, and thiazide diuretics; hypoglycemic agents include insulin, thiazolidinediones, and sulfonylureas.

<sup>†</sup> Ineffective, not indicated, therapeutically duplicative, or in violation of the drugs-to-avoid criteria of Beers et al.



**Figure 1.** Number of medications and frequency of problem medication use. Lines show frequency of inappropriate medication use and underused medications according to log-linear models.

ing few versus many medications; patients taking fewer than nine medications versus nine or more medications were equally likely to underuse cardiovascular, gastrointestinal, endocrine, and pulmonary drugs ( $P > .50$ , chi-square for each medication category).

Next, the linear models of inappropriate use and underuse were overlaid to evaluate the relative frequency of different prescribing problems across the spectrum of medication use (Figure 1). On average, patients taking fewer than eight medications were more likely to be missing a useful medication than to be taking an inappropriate drug. The converse was true in patients taking more than eight medications.

The unadjusted association between the total number of medications and each of the measures of problem prescribing persisted in multivariable analyses that controlled for potential confounders. After controlling for patient age, copayment, and diagnoses, the number of medications remained strongly associated with the frequency of inappropriate medication use and unassociated with the frequency

of medication underuse (Table 4). The two components of the inappropriate drug use measure had similar results as the combined measure. The frequency of ineffective, not indicated, or therapeutically duplicative medications was positively associated with the total number of medications (beta coefficient = 1.97, 95% CI = 1.44–2.51), negatively associated with the presence of hypertension (beta coefficient =  $-0.67$ , 95% CI =  $-1.07$  to  $-0.26$ ), and trended toward a negative association with ischemic heart disease (beta coefficient =  $-0.30$ , 95% CI =  $-0.61$ – $0.02$ ). Similarly, the frequency of Beers criteria medications was positively associated with the total number of medications (beta coefficient = 1.69, 95% CI = 0.94–2.43) and negatively associated with the presence of ischemic heart disease (beta coefficient =  $-0.47$ , 95% CI =  $-0.90$  to  $-0.04$ ).

## DISCUSSION

In this study of elderly veterans, inappropriate medication use rose rapidly as the length of patients' medication lists grew longer. In contrast, underuse of medications was common and constant at all levels of medication use, with an average of one underused medication per patient regardless of whether that patient was taking few or many medications. Overall, patients taking fewer than eight medications were more likely to be underusing a potentially useful medication than to be taking a drug that was unnecessary, not indicated, therapeutically duplicative, or not recommended for older people.

These findings highlight the complexity and potential limitations of polypharmacy (use of multiple medications) as a marker of prescribing quality. The steep rise in inappropriate medication use with increasing numbers of drugs provides a striking confirmation of the potential harms and need for extra vigilance in patients with polypharmacy. These findings are consistent with previous reports that have found associations between multiple medication use and several undesirable process and outcome measures in older people, including worse scores on measures of inappropriate prescribing, a higher likelihood of adverse drug events, and higher rates of hospitalization and death.<sup>6,9,14,25–28</sup>

**Table 4.** Factors Associated with Problem Prescribing—Multivariable Analyses

Factor	Inappropriate Use (Combined Measure)	Underuse
	Log-Linear Beta Coefficient (95% Confidence Interval)*	
Number of drugs <sup>†</sup>	1.95 (1.47–2.42)	$-0.06$ ( $-0.59$ – $0.47$ )
Patient age	NS	NS
Drug copayment required	NS	NS
Hypertension	$-0.49$ ( $-0.87$ to $-0.12$ )	$-0.68$ ( $-1.06$ to $-0.30$ )
Ischemic heart disease	$-0.31$ ( $-0.59$ to $-0.03$ )	NS
Diabetes mellitus	NS	0.46 (0.16–0.76)
Chronic obstructive pulmonary disease	NS	0.48 (0.17–0.80)
Heart failure	NS	NS
Depression	NS	NS

\* Coefficients greater than 0 represent a positive association between the predictor and the number of problem medications; coefficients less than 0 represent a negative association. Coefficients near 0 reflect the absence of an association between the predictor and number of problem medications. Aside from the primary predictor variable (number of drugs), coefficients with  $P$ -value  $> .10$  are not reported.

<sup>†</sup> Transformed using natural logarithms.

NS = nonsignificant.

Although these associations are important, a focus on the errors of commission that accompany multiple medication use can divert attention from errors of omission—that is, the underuse of important drugs.<sup>2,29,30</sup> In the current study, omissions of useful drugs were common and as prevalent in patients taking multiple medications as in those taking few. Although it is difficult to assess the clinical effect of these omissions, approximately half of omitted drugs were cardiovascular agents, which are often used to treat diseases with major effects on morbidity and mortality. Furthermore, the distribution of omitted drugs was similar in patients taking more or fewer medications, suggesting that similar types of problems were being undertreated in both populations. One caveat to this finding is that the study design did not permit assessment of underuse in patients taking fewer than five medications. However, an earlier report found no differences in underuse in patients taking fewer than five versus five or more medications.<sup>12</sup>

This tension between avoiding errors of commission and errors of omission is familiar to primary care physicians, particularly those who care for older people with multiple comorbidities. In this population, the use of multiple medications has the potential to provide substantial clinical benefit and to cause substantial harm.<sup>1,4</sup> Unfortunately, few tools exist to guide prescribers seeking the proper balance for their patients.<sup>2</sup> For example, most clinical practice guidelines provide little guidance on the treatment of older people in general, and fewer still discuss how to balance and prioritize medication use in older people with multiple comorbidities.<sup>8</sup> Increasing the number of prescribed medications does not guarantee inappropriate prescribing, nor does trimming a patient's medication list necessarily result in clinically important omissions. Nonetheless, physicians operate in a system in which the clinical needs of patients often overwhelm the time available for management.<sup>31</sup> As a result, physicians may not routinely review medication lists<sup>30</sup> and can have difficulty prioritizing among the many interventions that may be applicable to their patients.<sup>32</sup>

In this light, these findings provide a framework for thinking about ways to maximize prescribing quality in older people. In particular, the prevalence of medications that were unnecessary, not indicated, therapeutically duplicative, or contraindicated in older people was low in persons at the lower range of medication use. This suggests that a focus on potentially omitted drugs in such patients is most likely to yield improvements in prescribing quality. Patients taking many drugs had substantially higher numbers of errors of commission; therefore their medication lists merit closer scrutiny for potentially inappropriate medications in addition to problems of omission. Of note, the threshold beyond which overuse and misuse became more common is eight medications, similar to the cutoff of nine medications at which the Centers for Medicare and Medicaid Services requires greater scrutiny of medication lists for nursing home patients.<sup>9</sup>

It is important to note that the clinical effect of different types of prescribing problems may vary in importance between patients, being highly contextual to the drug in question and to the circumstances and treatment goals of the patient. In addition, evidence about the outcomes of prescribing errors is often difficult to interpret. For example,

there are limited data about the effectiveness of guideline-recommended therapies in older people, and observational studies that have documented links between inappropriate medication use and adverse clinical outcomes may have been substantially confounded by unmeasured characteristics of patients and prescribing physicians and the reasons the drugs were prescribed (confounding by indication).<sup>33–35</sup> This framework should thus be construed as a guide to understanding the relative frequency of errors of omission and commission. Quantifying the importance of these errors to patient outcomes largely remains a matter of clinical interpretation and context.

Several methodological limitations of the study deserve mention. Measures of nonindicated, unnecessary, and duplicative medication use, although derived from subscales of the Medication Appropriateness Index, have not been independently validated as stand-alone measures, nor has the Assessment of Underutilization of Medication undergone extensive validation. Nevertheless, each of these measures has face validity and moderate to high interrater reliability.<sup>18,20–22</sup> Furthermore, it is unlikely that the application of these measures would vary across different levels of medication use, thus minimizing the potential for bias in the relationship between number of medications used and assessment of prescribing quality. The applicability of the results to patients taking fewer than five medications is unknown. In particular, in patients taking fewer than five medications, an association between number of medications and underuse cannot be excluded. Direct assessment of the relationship between the number of inappropriate medications and the number of appropriate medications could provide further insight, but it was not possible to perform this analysis, because the nature of the sample (ascertained on the basis of the total number of medications taken) would have resulted in biased conclusions. Finally, the study was conducted among veterans at a single medical center who were predominantly male and white, and the generalizability of the findings cannot be extended to other populations.

Prescribing is a complex phenomenon, with multiple attributes of quality.<sup>36</sup> This complexity can interfere with efforts to improve the quality of pharmacological care that patients receive, because improvements in some quality domains can inadvertently cause harm in others. For example, prescribing of a guideline-recommended medication can cause an adverse drug reaction or difficulties with adherence. Although findings from this study cannot address these issues in detail, they shed light on the relative importance of different types of quality problems in patients taking few versus many medications and thus may help to guide the prioritization of different types of quality improvement efforts. In patients taking few medications, clinical vigilance and quality efforts should place particular focus on the underuse of medications. In contrast, in patients taking large numbers of medications, it is important to expand—but not substitute—the focus to include inappropriate medication use.

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**Author Contributions:** Study concept and design (MAS, CSL, GER, PJK), acquisition of subjects and data (GER, DB, PJK), analysis and interpretation of data (MAS, CSL, GER, SS, PJK), preparation of the manuscript (MAS), and critical review of the manuscript (all authors).

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**Appendix 1. Sensitivity Analyses: Key Results When Including Vitamins and Minerals and As-Needed Medications**

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Each patient used a mean of 1.2 vitamins and minerals (SD 1.3, range 0–6 per patient). When these agents were also counted as medications, neither the unadjusted nor adjusted relationship between volume of medication use and number of problem medications was substantially changed for either of the primary quality measures. In unadjusted analyses, the beta coefficient for number of medications was 1.59 (95% confidence interval (CI) = 1.16–2.01) for association with inappropriate drug use and 0.33 (95% CI = – 0.12–0.79) for association with drug omissions. In adjusted analyses, the beta coefficient for number of medications was 1.79 (95% CI = 1.33–2.35) for association with inappropriate drug use and 0.09 (95% CI = – 0.40–0.59) for association with drug omissions.

In addition, patients used a mean of 1.3 medications prescribed on as as-needed basis (SD 1.4, range 0–10 per patient). Similarly, inclusion of as-needed medications did not substantially change any of the observed relationships. In unadjusted analyses, the beta-coefficient for number of medications was 1.60 (95% CI = 1.22–1.98) for association with inappropriate drug use and 0.08 (95% CI = – 0.35–0.50) for association with drug omissions. In adjusted analyses, the beta coefficient for number of medications was 1.93 (95% CI = 1.50–2.35) for association with inappropriate drug use and – 0.29 (95% CI = – 0.81–0.22) for association with drug omissions.

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