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Potentially Inappropriate Prescribing of Primarily Renally Cleared Medications for Older Veterans Affairs Nursing Home Patients

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Abstract

Background—Inappropriate prescribing of primarily renally cleared medications in older patients with kidney disease can lead to adverse outcomes.

Objectives—To estimate the prevalence of potentially inappropriate prescribing of 21 primarily renally cleared medications based on 2 separate estimates of renal function and to identify factors associated with this form of suboptimal prescribing in older VA nursing home (NH) patients.

Design—Longitudinal study

Participants—Participants were 1304 patients, aged 65 years or older, admitted between January 1, 2004, and June 30, 2005, for 90 days or more to 1 of 133 VA NHs.

Main Measures—Potentially inappropriate prescribing of primarily renally cleared medications determined by estimating creatinine clearance using the Cock-croft Gault (CG) and Modification of Diet in Renal Disease (MDRD) equations and applying explicit guidelines for contraindicated medications and dosing.

Key Results—The median estimated creatinine clearance via CG was 67 mL/min, whereas it was 80 mL/min/1.73m^2 with the MDRD. Overall, 11.89% patients via CG and only 5.98% via MDRD had evidence of potentially inappropriate prescribing of at least 1 renally cleared medication. The most commonly involved medications were ranitidine, glyburide, gabapentin, and nitrofurantoin. Factors associated with potentially inappropriate prescribing as per the CG were

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age older than 85 (adjusted odds ratio [AOR] 4.24, 95% confidence interval [CI] 2.42–7.43), obesity (AOR 0.26, 95% CI 0.14–0.50) and having multiple comorbidities (AOR 1.09 for each unit increase in the Charlson comorbidity index, 95% CI 1.01–1.19).

Conclusions—Potentially inappropriate prescribing of renally cleared medications is common in older VA NH patients. Intervention studies to improve the prescribing of primarily renally cleared medications in nursing homes are needed.

Chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73m^2, is a growing public health problem that disproportionately affects older individuals.[1–3] Older adults have a higher incidence of CKD because the GFR decreases by approximately 8 mL/min with each decade of life after age 40.[2] The underlying pathophysiology of CKD in older adults is attributable to an age-related loss of renal mass and a reduction in the number and size of nephrons, the high prevalence of chronic disease states such as diabetes and hypertension, and increased susceptibility of the older kidney to drug-induced damage.[2–5] Consequently, 7% of older adults between 60 and 69 years of age, and at least 26% of persons 70 years or older, have CKD.[6] Because CKD is highly prevalent and associated with many comorbid medical conditions, it is one of the top 10 causes of death in older adults.[7]

Despite its high prevalence and association with mortality, CKD is often unrecognized in older adults because serum creatinine, a by-product of muscle mass breakdown, is an unreliable marker of renal function in older adults. In older adults, lean muscle mass is reduced so that a measured serum creatinine that is reported to be in the normal laboratory range frequently represents unrecognized renal insufficiency.[2] Measured creatinine clearance with a 24-hour urine collection provides the most accurate clinically available measurement of renal function. Unfortunately, this measurement often is difficult or impractical to obtain in the elderly. Therefore, to potentially improve the identification of CKD, clinical laboratories have recently begun to report the eGFR, which is based on the patient's serum creatinine, race, age, and gender using the 4-variable Modification of Diet in Renal Disease (MDRD) equation.[8]

It is essential to consider renal function when prescribing primarily renally excreted medications in nursing home patients so as to avoid adverse outcomes. Nursing home patients are at greater risk for adverse outcomes because they are older, have multiple comorbidities, and take numerous medications. Previous studies found that a high proportion of older long-term care facility residents were inappropriately prescribed a primarily renally cleared medication given their reduced estimated creatinine clearance (eCrClr) based on the patient's serum creatinine, age, weight, and gender using the Cockcroft-Gault (CG) equation.[9,10] However, these studies did not apply evidence-based consensus criteria for dosing, or avoiding, primarily renally cleared drugs in patients with renal impairment. This is important, as a recent study found conflicting recommendations for the renal dosing of medications in 4 different pharmacotherapy information sources.[11] Finally, the preferred method for estimating renal function (ie, eGFR/1.73m^2 versus eCrClr), and subsequently dosing renally cleared medications, has recently been debated.[12,13]

Given this background, the objectives of this study were to estimate the prevalence of potentially inappropriate prescribing (use of a contraindicated medication or greater than maximum daily dosage based on renal function) of one or more primarily renally cleared medications based on 2 separate estimates of renal function and to identify factors associated with this form of suboptimal prescribing in older Department of Veterans Affairs (VA) nursing home (NH) patients.

METHODS

Study Design, Setting, and Sample

This was a longitudinal study of 3480 patients admitted to any one of the 133 VA NHs (now called Community Living Centers) located in the United States between January 1, 2004, and June 30, 2005. A total of 1531 patients were included because they were 65 years of age or older at the time of admission, were long-stay patients (resided for ≥90 days), had at least 2 serum creatinine measurements within the previous 180 days, and received 1 of 21 primarily renally cleared medications (Appendix 1). Patients who were dialysis dependent, had unstable renal function (serum creatinine increased by either ≥ 0.25 mg/dL or > 25% from previous value within 180 days), or had inadequate height or weight information were excluded. The final sample was 1304 patients. This study was approved by the Pittsburgh VA Institutional Review Board and Research and Development Committees.

Data Sources

We recently described in detail the development of a merged database that included Minimum Data Set (MDS) and medication-dispensing information from the VA Pharmacy Benefits Management Services (PBM).[14] Briefly, all veterans receiving care in a VA NH were evaluated using the MDS. MDS version 2.0 is a reliable standardized tool to identify the functional, psychological, and health status needs of residents, and to evaluate the quality of care for these residents.[15] All MDS data were collected via resident interviews, staff interviews, and from reviews of resident records. For all NH patients, the MDS was completed at admission (within 14 days of admission), quarterly thereafter (within 90 days of previous evaluation), and with any significant change in status (eg, major change in cognitive function or functional status decline). The VA PBM provided all prescription data for the defined study cohort. These data included the following information for each drug dispensed: (1) start date; (2) drug name; (3) strength; (4) directions for use; (5) VA therapeutic class; and (6) amount dispensed. To the merged database mentioned previously, we also added serum creatinine lab results from the VA Decision Support System (DSS) national data extracts and ICD-9 codes for in-patient and outpatient diagnoses from the VA National Patient Care Database (NPCD) records. We used this merged database for the present analysis.

Main Outcome Measure

The main outcome was the presence or absence of a potentially inappropriately prescribed primarily renally cleared medication (operationally defined for the purpose of this study as the use of a contraindicated medication or greater than maximum daily dosage based on renal function). For all eligible patients, we used actual body weight, age, gender (derived from the MDS), and the most recent serum creatinine measurements obtained in the 180 days before the prescription date to calculate an eCrCl using the original Cockcroft-Gault equation.[16] The Cockcroft-Gault equation is:

$$\text{eCrCl (mL/ min) (for males)} = \frac{(140 - \text{age}) \text{ (actual body weight in kilograms)}}{(72) \text{ (patient serum creatinine)}}$$

(for females) = Multiply above results by 0.85

For comparison purposes only, we estimated the patient's GFR using the 4-variable MDRD equation.[8] The MDRD equation is:

$$eGFR = 186 \times (SCr)^{-1.154} \times (age)^{-0.203} * (0.742 \text{ if females}) * (1.212 \text{ if African American})$$

Using dispensing information provided by VA PBM, we calculated the total daily dose by multiplying the strength of the medication by the number of dosage forms administered per dose and the number of times the doses were administered per day. We then applied explicit prescribing recommendations for 18 drugs developed by consensus using a Delphi survey of an expert panel of geriatric clinical pharmacists.[17] We supplemented these with evidence-based prescribing recommendations for 3 additional newer medications (ie, duloxetine, tramadol, levetiracetam) taken from VA/Department of Defense (DoD) CKD guidelines published after the Delphi survey manuscript (Appendix 1).[18]

Independent Variables

Based on previous literature, our independent variables included demographics, health status, and psychiatric/neurological diseases for which many of the potentially inappropriately prescribed medications could have been indicated.[9,10] Using data from the MDS, categorical variables were created for age (65–74, 75–84, 85+), race (Black or White), gender (male or female), and educational level (less than high school, high school, greater than high school).

Regarding health status factors, measured weight and height from the admission MDS were used to calculate body mass index (BMI) (defined as weight [kg]/height [m^2]). Patients were categorized as underweight (BMI ≤ 18.5), normal weight (BMI 19.0 to <25.0), overweight (BMI 25.0 to 29.9), and obese (BMI ≥30.0).[19] Normal weight was the referent group. We created a continuous variable for a comorbidity index based on the methods of Charlson et al.[20] The method used by Deyo et al[21] creates a score (range 0–34) that is calculated based on the presence of 18 chronic conditions documented in the electronic medical record via ICD-9-codes. Higher scores denote greater levels of comorbidity. For functional status, we created a continuous variable with a range from 0 to 20 points that identifies the amount of assistance needed from staff for 5 activities (bathing, dressing, grooming, toileting, and eating) based on a previously validated measure.[22] We also quantified the number of prescribed drugs at admission (excluding those 21 renally cleared target drugs). We also examined dichotomous variables for 4 individual diseases (ie, hypertension, arthritis, cardiac dysrhythmia, and osteoporosis) not included in the Charlson comorbidity index and documented in admission MDS data.

Psychiatric/neurological disease variables were created to further address potential confounding by indication.[23] Using MDS data, we created dichotomous variables for the following psychiatric/neurological diseases: (1) anxiety disorder, (2) bipolar disease, (3) depression, (4) dementia, (5) Parkinson's disease, (6) schizophrenia, and (7) seizure disorder. Data from the admission MDS evaluation were also used to create a categorical variable for cognitive function (ie, Cognitive Performance Score [CPS]—intact, mild/moderate, severe).[24] To supplement the neurological/psychiatric problems, data from the admission MDS evaluation were used to create a dichotomous variable for depressive symptoms using the Depression Rating Scale (DRS). The DRS considers 7 items, and scores of 3 or higher indicate a high likelihood of depression.[25] Finally, a dichotomous variable was created to indicate moderate or severe pain experienced by the patient at admission as determined from the MDS.

Statistical Analyses

We used descriptive statistics (percentages, means, and standard deviations) to characterize the independent and outcome variables at the patient level. For descriptive purposes, we calculated the number of patients who were prescribed 1 of the individual 21 renally cleared drugs and how often they were prescribed a potentially inappropriate medication using the Cockcroft-Gault (eCrClr in mL/min) and MDRD (eGFR in mL/min/1.73m^2) equations. We also determined the prevalence of patients prescribed any contraindicated medication or prescribed too high a dosage of any renally cleared medications.

We used multivariable logistic regression analyses to identify factors associated with patients being prescribed one or more potentially inappropriate primarily renally cleared medications as identified by the Cockcroft-Gault equation. We used a backward selection approach (alpha = 0.15) to identify those health status factors and psychiatric/neurological conditions to be added to the 4 demographic variables in the final model. Goodness of fit was assessed using the Hosmer-Lemeshow test statistic.[26] We also conducted collinearity diagnostic testing. All statistical analyses were performed using SAS software (version 9; SAS, Cary, NC).

RESULTS

Table 1 shows the characteristics of patients receiving one or more primarily renally cleared medications. Most patients were male and had multiple comorbidities. One in 5 patients were obese (BMI >30). Of these latter, only 22 of 271 had a BMI greater than 40. CKD was present in 26.22% of patients. The median estimated renal function using the Cockcroft-Gault and MDRD equations were 67 mL/min and 80 mL/min/1.73m^2, respectively. When compared with the Cockcroft-Gault equation, the mean estimated renal function was also higher with the MDRD equation (66.66 + 27.34 versus 79.61+ 32.80, respectively).

Table 2 shows the number of patients who were prescribed renally cleared medications during the study period. The table also shows the number of patients who received individual renally cleared medications considered potentially inappropriate as a function of the equation used to assess renal function (ie, eCrClr or eGFR). The most common potentially inappropriately prescribed medications to patients were ranitidine, glyburide, gabapentin, and nitrofurantoin.

Table 3 shows that when the Cockcroft-Gault (eCrClr) equation was used to estimate renal function, 11.89% of patients had evidence of potentially inappropriate prescribing of at least one renally cleared medication. Only 7 patients had 2 or more potentially inappropriate medications. When the MDRD (eGFR) equation was used to estimate renal function, considerably fewer patients (5.9%) had evidence of potentially inappropriate prescribing. Slightly less than 5% of patients were identified as taking a potentially inappropriate medication by both equations. The more common prescribing problem was using too high of a dose for the patient's renal function.

Table 4 shows the results of the multivariable logistic regression analyses. Hosmer-Lemeshow goodness-of-fit test indicated no lack of fit, and no collinearity problems were detected. Factors associated with an increased risk of potentially inappropriate prescribing were age 85 or older, obesity, and having multiple comorbidities.

DISCUSSION

This study showed that more than 1 in 10 older long-stay patients in VA nursing homes had potentially inappropriate prescribing of primarily renally cleared medications when

evidence-based, consensus-derived criteria were used. This is considerably less than the 42% rate of prescribing problems found in 456 patients prescribed 1 of 20 primarily renally cleared drugs reported in the study by Papaioannou et al[9] in 4 long-term care facilities in 3 Canadian cities. It is also less than the 46% of 56 patients with a prescribing problem involving 1 of 27 medications from 2 nursing homes in Georgia.[10] We suspect that our study findings represent the lower bounds of prescribing problems with primarily renally cleared medications for older nursing home patients for several reasons. First, our sample was restricted to those with adequate (ie, not dialysis-dependent) or stable (no recent change between 2 serum creatinine values) renal function, which reduced the at risk pool for prescribing problems. Moreover, we applied a consensus list of oral-dosing guidelines for 21 primarily renally cleared medications, and of these, only 7 were part of the Rahimi et al[10] (2008) list. Only 5 were in the study from Papaioannou et al.[9] This discrepancy suggests that many of the drugs rated as being inappropriately prescribed (eg, angiotensin-converting enzyme inhibitors) in the Rahimi et al[10] and Papaioannou et al[9] studies may have contributed to an overestimation of the prescribing problem. Finally, our lower rate may in part be attributable to the availability of an electronic medical record system in the VA nursing homes, which allows for the easy retrieval of information necessary for the calculation of CrCl (eg, age, weight, and recent serum creatinine values) and the use of a collaborative practice model between on-site pharmacists and prescribers in many VA nursing homes.

It is of interest that both our study and the study by Papaioannou et al[9] reported that ranitidine and glyburide were among the most common drugs with prescribing problems. It is well known that histamine 2 blockers such as ranitidine, when given in higher doses than necessary, can lead to problems with cognitive impairment in older adults.[27] Glyburide has been associated with an increased risk of severe hypoglycemia compared with other sulfonylureas.[28–30] In addition, renal insufficiency, advanced age, dose, concomitant medications, and the initiation of therapy are well-known predisposing factors to hypoglycemia with sulfonylureas.[29,31] Given the increased risk of hypoglycemia, especially in the elderly and those with renal impairment, VA Pharmacy Benefits Management Services recommends the use of glipizide instead of glyburide in patients with an estimated creatinine clearance less than 50 mL/min who require a sulfonylurea for control of their diabetes and is actively working with providers to decrease glyburide use in this patient population.

This study also identified that advancing age was associated with an increased risk of inappropriate dosing of renally cleared drugs. This finding is consistent with results from the study by Papaioannou et al[9] and underscores the need for health professionals to be aware that a serum creatinine within the laboratory reference range (ie, “normal”) does not necessarily reflect normal renal function in elders because of age-related changes in lean muscle mass and turnover. We also found, as did Papaioannou et al,[9] that the risk of inappropriately prescribing of these renally cleared medications decreases as weight increases. One possible explanation for this finding is that estimated creatinine clearance is often overestimated in obese individuals. Alternatively, it is possible that doses for obese individuals are given greater scrutiny. Last, an increased risk of inappropriate prescribing in those with multiple comorbidities is clinically sensible and consistent with previous studies of suboptimal prescribing in older veterans cared for in other clinical care settings.[32,33]

Practice Implications

What should clinicians do about these findings? First, CrClr should be estimated using the Cockcroft-Gault equation for all older nursing home patients being prescribed these target drugs. The rationale is that to date most pharmacokinetic studies of drugs that are primarily renally cleared used the Cockcroft-Gault equation.[13,34] Although the use of actual body

weight is recommended for most patients, one might consider substituting lean body weight (LBWmale = 9270 * total body weight/6680 + 216 * BMI; LBWfemale = 9270 * total body weight/8780 + 244 * BMI) as suggested by Demirovic et al,[35] for those who are morbidly obese because actual body weight will overestimate creatinine clearance in these patients. It is also important to note that clinical laboratories are beginning to use the new serum creatinine assay, which results in creatinine values that are 5% less and leads to higher estimated creatinine clearances. To address this, one group of authors recently suggested the use of a revised Cockcroft-Gault equation[14] (changes italicized): eCrCl = 140 − age*weight/*68** serum creatinine. However, this approach has not yet been validated in pharmacokinetic studies of drugs that are primarily renally cleared.

Second, until more convincing data are available, clinicians who provide care for older patients should reject the recent recommendations from the Food and Drug Administration (FDA), the National Kidney Disease Education Program (NKDEP), and the *National Institute of Diabetes and Digestive and Kidney* Diseases (NIDDK) that the MDRD can be used in place of the Cockcroft-Gault for dosing renally cleared medications.[34,36] These recommendations are based primarily on one cross-sectional study involving 5504 participants from 6 research and 4 clinical sites.[37] The study objective was to determine the concordance between kidney function and dosing recommendations for 15 drugs as per eGFR via MDRD corrected for body surface area (BSA) and eCrClr via CG with measured GFR via I-125 iothalmate clearance. Study investigators found that the MDRD had better concordance than CG with measured (mGFR) kidney function. They also found that the MDRD had better concordance than the CG with dosing recommendations determined by mGFR. However, it must be noted that there are numerous limitations precluding the application of these study findings to elderly patients including the following: (1) only 13% of the sample was 65 years or older, and no information was provided separately for those 85 or older or frail; (2) GFR was measured using a method that is not used routinely in clinical practice; (3) eGFR reported by laboratories is not routinely corrected by BSA and has not been validated; (4) no drugs to avoid were included (eg, glyburide < 50 mL/min); and (5) the study conducted a data simulation and not a pharmacokinetic study.[38] This latter point is important after considering the findings of a pharmacokinetic study of gentamicin, a narrow therapeutic range primarily renally cleared medication, in 68 older inpatients from Australia.[39] Study investigators found that the MDRD equation overestimated gentamicin clearance by 29% as opposed to the Cockcroft-Gault equation, which underestimated gentamicin clearance by 10%. This discordance was even more pronounced in those 80 or older where the bias for the MDRD was 69% higher and the Cockcroft-Gault equation was 4% lower.[39] Using the MDRD may therefore result in an overestimation of renal function and could lead to potentially inappropriate dosing and associated adverse drug events. Therefore, at the present time, we would recommend that clinicians use the Cockcroft-Gault equation to estimate kidney function and consult pharmacotherapy references for dosing guidelines for primarily renally cleared medications.[17,18,40]

This study has potential limitations. The study sample included mostly older male patients, whereas in most non-VA nursing homes, most patients are older females. The use of some medications may be different in VA versus non-VA settings, but these renally cleared drugs are commonly used in the elderly. Also, renal function was estimated and not directly measured. However, the collection of 24 hours of urine output is often impractical in older frail nursing home patients. As a result, most practitioners rely on calculated estimates of renal function in clinical practice.

Despite the potential limitations listed previously, we conclude that prescribing problems with primarily renally cleared medications were common. Future studies should focus on developing and assessing the impact of computerized provider order entry, combined with

clinical decision support systems, on improving the prescribing of primarily renally cleared medications and associated patient outcomes such as adverse drug reactions.

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Table 1

Characteristics of the Sample (n = 1304)

Variables	n	%	Mean (SD)
Demographics			
Age			
65–74	388	29.75	
75–84	697	53.45	
85+	219	16.79	
White race	1148	88.04	
Male gender	1275	97.88	
Education			
Below high school	411	31.52	
High school	598	45.86	
Above high school	287	22.01	
N/A	8	0.61	
Health Status			
Body Mass Index			
Underweight	101	7.75	
Normal	562	43.10	
Overweight	370	28.37	
Obese	271	20.78	
Charlson Comorbidity Index			3.10 (2.20)
ADL dependence (range 0–20)			9.01 (6.51)
Number of medications			10.22 (6.44)
Hypertension	898	68.87	
Arthritis	338	25.92	
Cardiac dysrhythmias	217	16.64	
Osteoporosis	82	6.29	
Psychiatric/Neurological Problems			
Anxiety	119	9.13	
Depression diagnosis	374	28.68	
Depressive symptoms (DRS>3)	81	6.21	
Bipolar disease	43	3.30	
Schizophrenia	99	7.59	
Parkinson’s disease	67	5.14	
Dementia	437	33.51	
Cognitive Performance Scale			
Intact	763	58.51	
Mild/Moderate	374	28.68	
Severe	141	10.81	
N/A	26	1.99	
Seizure Disorder	77	5.90	

Variables	n	%	Mean (SD)
Moderate/Severe pain	381	29.22	

DRS, Depression Rating Scale; N/A, not available.

Table 2

Patients Prescribed a Potentially Inappropriate Renally Cleared Medication

Medication	No. of Patients Prescribed Medication	Inappropriate by eCRClr (n = 1304)	Inappropriate by eGFR (n = 1304)
Acyclovir	22	1 (0.08)	1 (0.08)
Amantadine	49	4 (0.31)	1 (0.08)
Chlorpropamide	0	0 (0.00)	0 (0.00)
Ciprofloxacin	245	3 (0.23)	2 (0.15)
Colchicine	61	0 (0.00)	0 (0.00)
Duloxetine	2	0 (0.00)	0 (0.00)
Gabapentin	221	24 (1.84)	15 (1.15)
Glyburide	175	42 (3.22)	23 (1.76)
Levetiracetam	13	2 (0.15)	1 (0.08)
Memantine	90	1 (0.08)	0 (0.00)
Meperidine	5	2 (0.15)	1 (0.08)
Nitrofurantoin	57	21 (1.61)	13 (1.00)
Probenecid	1	0 (0.00)	0 (0.00)
Propoxyphene	12	0 (0.00)	0 (0.00)
Ranitidine	345	52 (3.99)	19 (1.46)
Rimantidine	26	3 (0.23)	1 (0.08)
Spironolactone	96	2 (0.15)	1 (0.08)
Sulfamethoxazole/Trimethoprim	258	5 (0.38)	3 (0.23)
Tramadol	137	0 (0.00)	0 (0.00)
Triamterene	39	0 (0.00)	0 (0.00)
Valacyclovir	3	1 (0.08)	0 (0.00)

Table 3

Summary of Prescribing Problems for Primarily Renally Cleared Medications

Variables	Using eCrClr n (%)	Using eGFR n (%)	Abnormal by Both n (%)
Any contraindicated medication	65 (4.98)	38 (2.91)	26 (1.99)
Any high dosage problem	92 (7.06)	42 (3.22)	37 (2.84)
Any of the above problems	155 (11.89)	78 (5.98)	62 (4.75)

eCrClr, estimated creatinine clearance via the Cockcroft-Gault equation; eGFR, estimated glomerular filtration rate via the Modification of Diet in Renal Disease equation.

Table 4

Multivariable Logistic Regression Model of Factors Associated with Patient's Prescribed a Potentially Inappropriate Primarily Renally Cleared Medication*

Factor	Adjusted OR	95% CI (n = 1304)
Age		
65–74	1.00	—
75–84	2.32	1.40–3.83
85+	4.24	2.42–7.43
Black Race	1.29	0.78–2.15
Female Gender	2.11	0.75–5.99
Education		
Below high school	1.00	referent
High school	0.91	0.62–1.34
Above high school	0.61	0.36–1.03
N/A	2.28	0.43–12.0
Body Mass Index		
Underweight	0.96	0.52–1.78
Normal	1.00	referent
Overweight	0.64	0.42–0.96
Obese	0.26	0.14–0.50
Charlson Comorbidity Index (for each unit increase)	1.09	1.01–1.19

CI, confidence interval; OR, odds ratio; N/A, not available.

*Hosmer and Lemeshow Goodness-of-fit test *P* value =.34 (df =8).

Appendix 1

Prescribing Recommendations for Primarily Renally Cleared Medications*

Medication	Creatinine Clearance, mL/min	Maximum Dosing Recommendation, mg
Acyclovir (zoster)	10–29	800 every 8 hours
Acyclovir (zoster)	<10	800 every 12 hours
Amantadine	30–59	100 daily
Amantadine	15–29	100 every 48 hours
Amantadine	<15	100 every 7 days
Chlorpropamide	<50	Avoid use
Ciprofloxacin	<30	500 every 24 hours
Colchicine	<10	Avoid use
Duloxetine†	<30	Avoid use
Gabapentin	30–59	600 twice daily
Gabapentin	15–29	300 twice daily
Gabapentin	<15	300 daily
Glyburide	<50	Avoid use
Levetiracetam†	50–80	500–1000 every 12 hours
Levetiracetam†	30–50	250–750 every 12 hours
Levetiracetam†	<30	250–500 every12 hours
Memantine	<30	5 twice daily
Meperidine	<50	Avoid use
Nitrofurantoin	<60	Avoid use
Probenecid	<50	Avoid use
Propoxyphene	<10	Avoid use
Ranitidine	<50	150 daily
Rimantidine	<50	100 daily
Sulfamethoxazole/Trimethoprim	15–29	800/160 daily
Sulfamethoxazole/Trimethoprim	<15	Avoid use
Spironolactone	<30	Avoid use
Tramadol†	<30	50–100 every 12 hours
Triamterene	<30	Avoid use
Valacyclovir	30–49	1000 every 12 hours
Valacyclovir	10–29	1000 every 24 hours
Valacyclovir	<10	500 every 24 hours

*All based on criteria from Hanlon et al[17] unless otherwise indicated.

†Based on criteria from VA/DOD Clinical practice guidelines.[18]