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Consensus Guidelines for Oral Dosing of Primarily Renally Cleared Medications in Older Adults

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Abstract

Objectives—To establish consensus oral dosing guidelines for primarily renally cleared medications prescribed for older adults.

Design—Two-round modified Delphi Survey.

Participants—Expert panel of 11 geriatric clinical pharmacists.

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Measurements—After a comprehensive literature search and review by the investigative group of 6 physicians (2 from general internal medicine, 2 nephrologists, 2 geriatricians), 45 dosing recommendations for 30 medications at various levels of renal function were created. The expert panel rated their agreement with each of these 45 dosing recommendations using a 5-point Likert scale (1= strongly disagree to 5=strongly agree). Recommendation-specific means and 95% confidence intervals were estimated. Consensus was defined as a lower 95% confidence limit of >4.0 for the recommendation –specific mean score.

Results—The response rate was 81.8% (9/11) for the first round. All respondents that completed the first round also completed the second round. The expert panel reached consensus on 26 recommendations involving 18 (60%) medications. For 10 medications (chlorpropamide, colchicine, cotrimoxazole, glyburide, meperidine, nitrofurantoin, probenecid, propoxyphene, spironolactone, and triamterene), the consensus recommendation was not to use the medication in older adults below a specified level of renal function (e.g., creatinine clearance < 30 ml/min). For the remaining 8 medications (acyclovir, amantadine, ciprofloxacin, gabapentin, memantine, ranitidine, rimantadine, and valacyclovir), specific recommendations for dose reduction or interval extension were made.

Conclusion—An expert panel of geriatric clinical pharmacists was able to reach consensus agreement on a number of oral medications that are primarily renally cleared.

Keywords

aged; chronic kidney disease; suboptimal prescribing

INTRODUCTION

Chronic kidney disease (CKD) (Stage 3 CKD, defined as an estimated glomerular filtration rate (GFR) of <60ml/min) is a growing public health problem that disproportionately affects older adults.¹ Specifically, GFR decreases approximately 8 ml/min each decade of life after age 40.¹ Consequently, 7% of older adults between 60 and 69 years of age, and at least 26% of persons >70 years of age, have CKD.¹ CKD is often unrecognized in older adults because serum creatinine, a byproduct of muscle mass breakdown, may be in the normal laboratory range, while significant underlying impairment in GFR is present.¹

Medications are the most frequently used therapy for the management of problems in older adults. Unfortunately, these same medications are often prescribed in inappropriate doses. Studies have shown that up to two-thirds of older patients receive inappropriately high doses of primarily renally cleared medications.^{2,3} This may, in part, be due to unrecognized CKD, but could also be due to available conflicting dosing information. A recent study reported on the concordance between four different pharmacotherapy information sources regarding dosing information for 100 primarily renally cleared medications.⁴ They found that the four sources differed widely in their recommendations for adjustments of dosage and dosing interval for the medications examined. Moreover, the methods upon which the information was based, and references to original data, were rarely presented.

Given this background, the study objective was to establish consensus dosing guidelines for primarily renally cleared oral medications commonly taken by older adults using a two-stage modified Delphi survey of an expert panel of geriatric clinical pharmacists. In the absence of consistent evidence based drug dosing information, the Delphi survey methodology can be used to obtain consensus on the opinions of ‘experts’ through a series of structured questionnaires (commonly referred to as rounds).^{5–7} This technique gathers opinion without the need to bring panelists together physically, and the questionnaires are completed anonymously, allowing each panel member to present and react to ideas unbiased by the identities of other participants.

METHODS

Selection of Delphi Study Methodology

Our study involved the use of email to conduct a two-round, modified Delphi survey of experts in the field of geriatric clinical pharmacy. The Delphi methodology is a structured technique used to attain opinions with the object of obtaining a consensus from a group of experts.⁵⁻⁷ We selected the modified Delphi consensus method because previous studies by our group suggest that accurate and reliable assessments can be achieved by consulting a panel of experts and subsequently accepting the group consensus as the best estimate of the answer to a particular question.⁸⁻¹¹ The methodology used in this study differed from the Delphi process developed by the RAND Corporation that relies on face-to-face meetings to achieve consensus.¹² However, the modified method enables a group of experts to be contacted inexpensively, without geographic limitations.”

There are three distinct stages of the modified Delphi Technique: 1) comprehensive literature review and survey development, 2) expert panel selection, and 3) data collection and analysis.⁵⁻⁷ The methods employed for each of these three steps are described below.

Comprehensive Literature Review and Survey Development of Preliminary List of Primarily Renally Cleared Oral Medications

Multiple steps were taken in order to ensure the preliminary list of primarily renally cleared medications was based on published data. The first step was for two clinical pharmacist researchers (JTH, SLA) to conduct a comprehensive literature search to identify published articles and abstracts from the scientific literature on the topics of inappropriate prescribing of renally cleared medications in renal failure. Medline and International Pharmaceutical Abstracts databases were searched from January 1, 1966 to April 1, 2007. A search of the World Wide Web, National Quality Measures Clearinghouse, National Committee for Quality Assurance, National Guideline Clearinghouse, and Centers for Medicaid and Medicare Services was also conducted using these terms as practice guidelines and quality indicators may not be referenced in typical scientific literature databases. These investigators also conducted a manual search of the reference lists from these identified articles, articles from the investigators’ files, and recent reviews and book chapters to identify additional relevant publications. This first search identified two studies on the epidemiology of inappropriate prescribing of renally cleared medications in older adults.^{2,3}

The second step involved a search of the above mentioned sources to identify widely accepted measures of appropriate prescribing in older adults. Two sets of explicit criteria published in the scientific literature were found.^{7,9} They were the Assessing Care of Vulnerable Elders and Beers criteria.^{13,14}

Third, three clinical pharmacist investigators (JTH, SLA, TS) examined the above mentioned articles and compiled a preliminary list of primarily renally cleared medications. The clinical pharmacist investigators then used Micromedex®, 2007 (Micromedex® Healthcare Series: Thomson Micromedex, Greenwood Village, Colorado) to confirm that those medications are prescribed orally and are primarily renally cleared. Medications were excluded if: 1) they could be measured via serum concentrations (e.g., digoxin, lithium, primidone, procainamide); 2) were known to exacerbate CKD (e.g., nonsteroidal anti-inflammatory drugs); 3) are given parenterally; or, 4) have a particularly wide therapeutic index (e.g., penicillins and cephalosporins). Angiotensin converting enzyme inhibitors (ACEIs) were also excluded since they are often considered the medication class of choice in CKD and they are dosed to the desired effect.¹ Using this process, a total of 36 unique medications were identified.

The fourth step was to develop the modified Delphi survey instrument using an approach similar to those previously published.^{7,9} The clinical pharmacists (JTH, SLA, TS) conducted comprehensive searches of Medline and International Pharmaceutical Abstracts databases from 1966 to 2007 to identify evidence-based primary scientific literature (i.e., randomized controlled pharmacokinetic studies comparing patients with normal and reduced renal function) for each of the 36 medications. Three reviewers (JTH, SLA, TS) independently assessed each identified article to derive initial dosing recommendations for specific levels of creatinine clearance. Guidelines for medication dosing were based on creatinine clearance and not the Modification of Diet in Renal Disease (MDRD) formula.¹ The MDRD was not selected to estimate GFR as the Food and Drug Administration and the National Kidney Disease Education Program does not recommend using this estimate because the clinical impact on medication dose adjustment has not been studied.¹ In the absence of direct evidence as defined above, the two reviewers consulted the two articles on inappropriate prescribing for elders with renal failure, two sets of explicit criteria for inappropriate prescribing, and two books for dosing.^{2,3, 13–16}

The fifth step was for a 6 member physician panel (2 from general internal medicine, 2 nephrologists, 2 geriatricians) to independently review the primary literature and consider the preliminary dosing recommendation prior to evaluation by the geriatric clinical pharmacists. The physician panel felt there was insufficient information to formulate specific recommendations for several medications (e.g., methotrexate for rheumatoid arthritis, sulfasalazine, risperidone, tolterodine). Also excluded were two bisphosphonates (i.e., alendronate and risedronate), because there was sufficient evidence supporting their use in older adults with age-related reduced renal function available prior to the beginning of the study.^{17–19} The final list of 30 medications with 45 specific dosing recommendations was presented to the geriatric clinical pharmacist expert panel (a copy of first round survey and supporting references is available upon request from the first author).

Expert Panel Selection of Participants

An expert panel of 11 geriatric clinical pharmacists were asked to participate in the modified Delphi survey. Geriatric clinical pharmacists were chosen because they are involved in monitoring the dosing of all the medications that were part of the survey. Appendix I lists these experts and their current affiliations.

Data Collection and Analysis of the Survey

For round 1, the panel members were sent an Excel® spreadsheet by e-mail containing the 30 medications and corresponding doses for a given degree of renal impairment. For each medication, the panelists were asked to rate their level of agreement with the dosing recommendations using a five-point Likert scale (1= strongly disagree, 2=disagree, 3=equivocal, 4= agree, 5=strongly agree).^{8,9} The panel was also given the opportunity to provide comments and additional suggestions for dosing recommendations for renally cleared medications not on the list. A priori we decided to include new drugs and/or dosing recommendations if they were suggested by two or more panel members.

After round 1, scores were compiled and a mean score and 95% confidence interval (CI) for each dosing recommendation was computed. Based on previously published work, the lower and upper limits of the 95% CIs were examined, and then each recommendation was classified into one of three categories: consensus agreement (defined as those having a score with a lower-limit 95% CI of ≥ 4.0); consensus disagreement (defined as those having a score with an upper-limit 95% CI of < 3.0); or equivocal (defined as those having a score with a lower-limit 95% CI between 3.0 and 3.9, indicating the need for reevaluation).^{8,9} We chose not to reevaluate items that reached consensus disagreement or consensus agreement after round one because a

previous study by our group found good intra-rater reliability between round one and two responses (kappa statistic=0.73).¹⁰

In round 2, only the equivocal criteria from round 1 were included. For each equivocal signal, each participant was provided with his or her round 1 individual score and the round 1 mean group score to aid in the consensus-building process. After round 2, the processes of compiling scores and computing mean scores and 95% CIs was repeated. Again criteria were classified as accepted if they had a lower-limit 95% CI of ≥ 4.0 (indicating consensus agreement). All other criteria were rejected.

For all statistical analyses, SAS ® version 9 for Windows (SAS Institute, Inc., Cary, NC) was used. The University of Pittsburgh Institutional Review Board approved the study as exempt.

Results

The response rate was 81.8% (9/11) for the first round. All respondents that completed the first round also completed the second round. Overall, 55.5% of expert panel members were male.

After the first round of the survey, consensus was reached for 10 dosing recommendations involving 8 medications (Table 1). Twenty-two of the dosing recommendations were rated as equivocal and none were rejected. There were no recommendations/comments made by two or more of the panelists during the first round. After the second round of the survey, an additional 16 dosing recommendations associated with 10 medications reached consensus (Table 1). For 10 medications (chlorpropamide, colchicine, cotrimoxazole, glyburide, meperidine, nitrofurantoin, probenecid, propoxyphene, spironolactone, and triamterene), the consensus recommendation was not to use the medication in older adults below a specified level of renal function (e.g., creatinine clearance < 30 ml/min). For the remaining 8 medications (acyclovir, amantadine, ciprofloxacin, gabapentin, memantine, ranitidine, rimantadine, and valacyclovir), specific recommendations for dose reduction or interval extension were made. The three medications with the highest consensus mean value and the tightest 95% CIs were chlorpropamide, meperidine and propoxyphene.

Consensus could not be reached for a total of 19 dosing recommendations associated with 12 medications (Table 2). The two medications with the lowest mean value and the widest 95% CI's were allopurinol and metformin.

DISCUSSION

This study found that expert geriatric clinical pharmacists could achieve consensus agreement with dosing recommendations for the majority (60%) of a list of primarily renally cleared oral medications commonly used by older adults. The rate of consensus agreement is consistent with those reported by previous Delphi surveys to establish prescribing guidelines.¹⁴ The two most common medication classes for which consensus was reached were anti-infectives (seven medications) and central nervous system medications (four medications).

It is interesting to note the agreement between the medication dosing recommendations determined by this modified Delphi Survey and those published by other investigators. Wong et al. in a study of older inpatients from the United Kingdom also identified chlorpropamide, ranitidine, colchicine, and cotrimoxazole as medications whose dosing should be adjusted for varying levels of renal function.² Papaioannou et al. in a study of older nursing home patients also identified glyburide, nitrofurantoin, ranitidine, and spironolactone as requiring dose adjustments in CKD.³ Finally, the final list was in concordance with the medications included in the Renal Drug Guidelines developed by Kaiser Permanente Colorado (Personal Communication with Marsha Raebel, PharmD). The specific medications in common between

the two lists include acyclovir, amantadine, chlorpropamide, ciprofloxacin, colchicine, gabapentin, glyburide, nitrofurantoin, cotrimoxazole, and spironolactone. A medication of particular importance is glyburide which has been shown to have the greatest risk of drug induced hypoglycemia than any other sulfonylurea, especially in older adults.²⁰

Spironolactone is another medication that should be used cautiously in older adults. It is well documented that there is a high risk of hyperkalemia in older adults receiving this medication for heart failure, especially in those taking a concomitant angiotensin converting enzyme inhibitor or an angiotensin II receptor blocker.²¹

The results of this study provide consensus dosing recommendations for five unique medications which have not been reported in the aforementioned studies. These medications include memantine, rimantadine, probenecid, propoxyphene, meperidine and triamterene. It is likely that memantine reached consensus in this study because the primary pharmacokinetic data in renal failure was not published until recently.²² There is face validity with both propoxyphene and meperidine appearing on the final list as they have active renally cleared metabolites that can accumulate and have been associated with adverse drug reactions.²³ In general, their use is not recommended in older adults.¹⁴

It should be noted that consensus was not reached for 19 dosing recommendations associated with 12 unique medications. One of these medications was allopurinol whose active metabolite, oxypurinol, is primarily renally cleared. Perhaps the lack of consensus was due to the panel being aware of data that shows that toxicity is uncommon when using doses greater than recommended based on creatinine clearance to reduce uric acid.^{24,25} Some might also question the lack of consensus for the most commonly used thiazide diuretic, hydrochlorothiazide. While it is commonly assumed that thiazide diuretics are ineffective in patients with creatinine clearances of less than 30 ml/min, in fact, studies have shown these medications to be effective alone or in combination with loop diuretics at this level of renal dysfunction.^{26,27} Another surprise for some may be the lack of consensus for metformin. The primary concern with metformin use in CKD is the occurrence of lactic acidosis. Nevertheless, the literature suggests that this is a relatively rare adverse drug reaction even in the presence of CKD.²⁸ Currently, the dosing guidelines in the drug package insert are vague, stating that metformin is contraindicated in patients with renal disease as indicated by males with a serum creatinine > 1.5mg/dl or females with a serum creatinine > 1.4 mg/dl or an abnormal creatinine clearance (Glucophage® package insert, Bristol Meyer Squibb). What should the clinician do when facing this situation? One approach is to calculate an estimated creatinine clearance using the Cockcroft Gault equation.²⁹ Assuming a female aged 80 years of age with a weight of 70 kilograms, applying the Cockcroft Gault equation would give an estimated creatinine clearance of approximately 35ml/min. Using the same age and weight for a male, the estimated creatinine clearance would be approximately 40ml/min. Therefore, one might conclude that using metformin in older men and women with a creatinine clearance above 40 ml/min may be reasonable.

Limitations

This study had several potential limitations. First, our list of medications may not have included every possible oral drug that was primarily renally cleared. For example, we did not evaluate pregabalin or loratadine. For these medications, the parent drug or active metabolite, respectively, is primarily renally cleared. Although, it is important to note though that the only study of pregabalin in older adults was published after our literature search was completed.

³⁰ Moreover, previous studies of loratadine, which is primarily metabolized by the liver to an active renally cleared metabolite, have shown no differences in half-lives when comparing young adult volunteers with older adults or those with renal failure.^{31,32} Second, a convenience sample of geriatric clinical pharmacists was used in the modified Delphi survey.

As a result, the majority of respondents were affiliated with an academic institution. Third, face-to-face meetings of the panelists, a practice that is not always done with Delphi surveys, were not held due to the costs being prohibitive.^{5–7} Bringing panelists together allows individual respondents to incorporate the perspectives of others, and may have resulted in further refinement of the dosing guidelines for primarily renally cleared medications, while facilitating the consensus process. However, in person meetings might have limited the broad geographic representation we were able to achieve with the use of e-mail. Finally, as new research contributes additional information about safe and effective medication dosing in the elderly, the list of drugs and associated prescribing information will likely need to be updated.

Implications and Further Research

Further development and research is needed in several areas. First, programmers need to develop computerized provider order entry (CPOE) with clinical decision support systems (CDSS) that incorporate a standardized set of dosing guidance (such as contained within this study) for older adults with renal insufficiency. Although some researchers have developed advanced systems that incorporate dosing guidance for patients with renal insufficiency, the dosing guidance was developed primarily from a limited number of reference textbooks rather than the primary literature or expert consensus. Furthermore, the studies that have been conducted were either in a tertiary care hospital or an academic nursing home.^{33,34} Second, CPOE with CDSS have been shown to improve the quality, efficiency, and cost of healthcare.^{35–37} Formal assessments of CPOE with CDSS containing dosing guidance for older adults with renal insufficiency should be formally evaluated to determine the potential impact on patient outcomes such as adverse drug reactions and healthcare utilization. ”

Conclusion

Despite these potential limitations, the modified Delphi process identified consensus on 18 primarily renally cleared medications used by older adults including five new recommendations for wider consideration. As new research contributes more information about medication safety, the list of medications will need to be updated. Further clinical research is needed to assess the impact on health outcomes that inappropriate prescribing, as defined by the consensus dosage recommendations, has in these patients.

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Appendix I. Geriatric Clinical Pharmacists Expert Panel

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Table 1

Geriatric Clinical Pharmacist Expert Panel Consensus Recommendations for Primarily Renally Cleared Medications for Older Adults

Medication	Creatinine Clearance (ml/min)	Maximum Dosing Recommendation (milligrams)	Group Mean Score* (95% CI)
Acyclovir (for Zoster)	10–29	800 every 8 hours	4.44 (4.10–4.79)
”	<10	800 every 12 hours	4.44 (4.10–4.79)
Amantadine	30–59	100 daily	4.67 (4.34–4.99)
”	15–29	100 every 48 hours	4.67 (4.34–4.99)
”	<15	100 every 7 days	4.56 (4.21–4.90)
Chlorpropamide [†]	<50	Avoid use	4.89 (4.67–5.11)
Ciprofloxacin [†]	<30	500 every 24 hours	4.78 (4.49–5.07)
Colchicine	<10	Avoid use	4.67 (4.20–5.13)
Cotrimoxazole	15–29	1 DS tablet daily	4.44 (4.10–4.79)
”	<15	Avoid use	4.44 (4.10–4.79)
Gabapentin (for Pain)	30–59	600 twice daily	4.00 (4.00–4.00)
”	15–29	300 twice daily	4.11 (4.00–4.11)
”	<15	300 daily	4.11 (4.00–4.33)
Glyburide [†]	<30	Avoid use	4.78 (4.49–5.07)
Memantine	<30	5 twice daily	4.33 (4.01–4.66)
Meperidine [†]	<50	Avoid use	4.89 (4.67–5.11)
Nitrofurantoin [†]	<60	Avoid use	4.56 (4.21–4.90)
Probenecid	<50	Avoid use	4.44 (4.10–4.79)
Propoxyphene [†]	<10	Avoid use	4.89 (4.67–5.11)
Ranitidine [†]	<50	150 daily	4.44 (4.10–4.79)
Rimantidine	<50	100 daily	4.33 (4.01–4.66)
Spironolactone	<30	Avoid use	4.11 (4.00–4.33)
Triamterene	<30	Avoid use	4.22 (4.00–4.51)
Valacyclovir (for Zoster) [†]	30–49	1000 every 12 hours	4.56 (4.21–4.90)
”	10–29	1000 every 24 hours	4.56 (4.21–4.90)
”	<10	500 every 24 hours	4.56 (4.21–4.90)

* Recommendations with lower 95% confidence interval of > 4.0

[†] Accepted after first round

Abbreviations: CI= confidence interval; min=minute; ml=milliliters

Table 2

Primarily Renally Cleared Medications for Older Adults That Did Not Reach Consensus by a Geriatric Clinical Pharmacist Expert Panel

Medication	Creatinine Clearance (ml/min)	Maximum Dosing Recommendation (milligrams)	Group Mean Score (95% CI)
Allopurinol	10–50	200 daily	3.56 (3.08–4.03)
Allopurinol	<10	100 daily	3.67 (3.10–4.33)
Atenolol	15–35	50 daily	3.67 (3.20–4.13)
Atenolol	<15	25 daily	3.67 (3.20–4.13)
Cetirizine	10–30	5 daily	4.22 (3.79–4.66)
Cetirizine	<10	Avoid use	4.22 (3.68–4.77)
Cimetidine	<50	Avoid use	4.22 (3.79–4.66)
Famciclovir (for Zoster)	30–59	500 every 12 hours	4.11 (3.72–4.50)
Famciclovir (for Zoster)	<30	500 every 24 hours	4.00 (3.43–4.57)
Famotidine	10–50	20 daily	4.11 (3.72–4.50)
Famotidine	<10	20 every 48 hours	3.89 (3.38–4.40)
Fexofenadine	<80	60 daily	4.22 (3.79–4.66)
Hydrochlorothiazide	<30	Avoid use	3.78 (3.34–4.21)
Metformin	<60	Avoid use	3.56 (2.82–4.29)
Metoclopramide	<40	Avoid use	3.78 (3.34–4.21)
Sotalol (for Afib)	<40	Avoid use	4.13 (3.68–4.57)
Topiramate (for Epilepsy)	<70	100 twice daily	4.11 (3.60–4.62)

Abbreviations: CI= confidence interval; min=minute; ml=milliliters