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Effect of Pharmacist-Led Medication Review on Medication Appropriateness in Older Adults with Chronic Kidney Disease

Abstract

This study evaluated the impact of pharmacist-led review on medication appropriateness in 204 older patients (aged ≥65 years) with chronic kidney disease (CKD) admitted to an Australian hospital. Medication appropriateness was evaluated using the Medication Appropriateness Index (MAI) prior to medication review, after review (assuming all recommendations were accepted by physicians) and after outcome (acceptance/non-acceptance) of recommendations.

Overall, 95 (46%) patients received a medication review by pharmacists. The median (interquartile range) MAI score significantly decreased from a baseline of 7 (3-12) to 5 (2-10) after medication review (p<0.001) and to 6 (2-10) after the outcome of recommendations (p<0.01). The MAI score also decreased from admission to discharge (6 [3-11] to 5 [2-9]; p<0.001) in patients with no medication review by a pharmacist. The MAI scores declined markedly in people with all the pharmacist-conducted medication review recommendations accepted (from 7 to 3; p<0.05).

Reassuringly, hospitalisation alone improved medication appropriateness. However, pharmacist-led medication review can further optimise medication appropriateness in older CKD patients, particularly when the recommendations are implemented.

Key words: Chronic kidney disease, Medication Appropriateness Index, potentially inappropriate medications

Introduction

Older adults with chronic kidney disease (CKD) are at increased risk of receiving inappropriate medications and experiencing adverse drug events.[1, 2] Moreover, aging and advanced CKD are associated with multiple chronic conditions and the use of a higher number of medications,[3,4] which in turn is associated with patient morbidity and mortality.[5] As such, measuring inappropriate medication use in older people is a research topic of significant interest. In line with this, various criteria, both implicit and explicit, have been developed in recent decades to assess the appropriateness of prescribing in older adults.[6]

Implicit criteria are generally thought to give a more comprehensive and holistic assessment of pharmacotherapy, mainly because of the detailed clinical information used, compared to their explicit counterparts.[7-9] The Medication Appropriateness Index (MAI) is one of the implicit measures used to evaluate medication appropriateness in older adults. This tool detects potentially inappropriate prescribing more frequently than other explicit criteria, with acceptable validity and intra- and inter-rater reliability.[10] The MAI has been used to assess the quality of prescribing in different health settings and was predictive of various health outcomes, including quality of life and medication-related hospitalisations.[10,11] The MAI was also previously applied to evaluate the impact of medication review conducted by pharmacists on medication appropriateness.[11-14]

In Australia, government-funded medication review services, in the form of home (HMRs) and residential medication management reviews (RMMRs), are important strategies to improve the appropriate use of medications.[15] These programs require a coordinated effort among general practitioners, pharmacists, and patients to identify and correct medication issues. Similarly, the Society of Hospital Pharmacists of Australia has a standard of practice in place for pharmacists to be involved in clinical services in hospitals, to optimise patient outcomes by aiming to

improve the quality use of medications.[16] It has been reported, however, that hospital pharmacists spend less than half of their time in providing clinical and drug information services.[15] Ideally, every patient should receive clinical pharmacy services during hospitalisation, yet limited funding and inadequate staffing may limit implementation in inpatient settings.[16] Therefore, pharmacists may need to prioritise the reviewing of patients based on their risk of medication-related problems.[16]

The implementation of clinical pharmacy services has contributed to the improvement of patient outcomes.[17,18] However, little is known about the impact of pharmacist-led medication review on the quality of prescribing in older adults with CKD. Therefore, we examined the impact of medication review by pharmacists during hospitalisation on medication appropriateness in older adults with CKD. We also identified the type of recommendations commonly given by pharmacists and the medications commonly implicated in medication-related problems.

Methods

Study participants, setting and data collection

This was a cross-sectional comparative study conducted retrospectively in a 500-bed Tasmanian tertiary care hospital. All older adults (aged ≥65 years) with CKD and not receiving any form of renal replacement therapy, who were consecutively admitted over a period of six months (January 2015 – June 2015), were included for analysis. For this study, CKD was defined based on an estimated glomerular filtration rate (eGFR) of 15-60 mL/min/1.73m^2, reported via the CKD Epidemiology Collaboration (CKD-EPI) equation,[19] present for at least three months.[20] People with acute kidney injury, those who did not have repeated eGFR measures for at least three months, had stayed in hospital briefly (<24 hours), were critically

ill/died during hospitalisation and those with incomplete medical records were excluded from the study.

Comprehensive patient, medical and laboratory information, including both regular and 'as needed' medications, was collected from the digital medical record at hospital admission and discharge. Medications that were used for a short period, such as acutely used antibiotics and medications prescribed for in-hospital use, were excluded from the evaluation of medication appropriateness. Medical progress notes were thoroughly examined by the principal investigator (WHT) for pharmacists' reviews and recommendations during hospitalisation.

Medication appropriateness was evaluated using the MAI prior to medication review by pharmacists, after review (assuming all recommendations were accepted by physicians) and after the outcome of recommendations (i.e. acceptance or non-acceptance by physicians). This tool has ten components, assessing indication, effectiveness, dosage appropriateness, directions of use and their practicality, drug-drug and drug-disease interactions, expense, duplication of therapy and duration of treatment. Each criterion has special rating instructions, operational definitions, and referential guides to rate the degree of appropriateness.[10] These criteria have weighted scores and the MAI score for an individual drug ranges between 0 and 18. Patient MAI scores are the sum of the scores of their individual medications, and higher scores are indicative of high level of medication inappropriateness.[21] For the purpose of this study, after trialling the tool on 10 patients, the investigators agreed to remove two components: 'practicality of directions' and 'expense'. Therefore, the MAI scores for medications in our study ranged between 0 and 15. The comorbidity status of patients was also evaluated using the Charlson's comorbidity index (CCI).[22] The MAI rating was performed by the primary investigator (WHT).

Ethics

Ethics approval was obtained from the Tasmanian Health and Medical Human Research Ethics Committee (H0016044).

Statistical analyses

Data were checked for normality of distribution via Shapiro-Wilk's *p*-value of > 0.05 and visual inspection of histograms. Continuous variables were reported as mean ± SD for parametric data or median (interquartile range [IQR]) for non-parametric data. Frequency (percentage) was used to report proportions for categorical variables.

Patients were included in the medication review group when there were documented recommendations/notes given by pharmacists during hospitalisation. A chi-square test was used to compare categorical variables in people with or without medication review, whereas the independent-samples t test and Mann-Whitney U test were applied for continuous variables. For the medication review group, the baseline MAI scores were compared with the scores after medication review, (a) assuming all recommendations were accepted and (b) after outcome (acceptance or non-acceptance) of recommendations by physicians, using Wilcoxon signed ranks test. Similarly, the MAI scores at hospital admission and discharge were compared using the same test for the patients without medication review. Finally, in people with (i) at least one recommendation and (ii) all recommendations accepted by physicians, the MAI before medication review was compared with the one after medication review. Analyses were performed using SPSS, version 23 (Armonk, NY: IBM Corp.).

Results

A total of 204 patients consecutively admitted to the study hospital for medical (75%) and surgical reasons (25%) were retrospectively categorised into two groups as follows: medication review (n=95) and no medication review (n=109). The baseline characteristics of patients are presented in Table 1. There were no significant differences between the two groups.

The impact of medication review on medication appropriateness

In the medication review group, the median (IQR) baseline MAI score of patients declined after medication review (7 [3-12] to 5 [2-10]; $p<0.001$) and after the outcome of recommendations (7 [3-12] to 6 [2-10]; $p<0.01$). The median MAI score also decreased significantly from admission to discharge (6 [3-11] to 5 [2-9]; $p<0.001$) in patients with no medication review. Table 2

Of patients who had received medication review by pharmacists, at least one recommendation was accepted by physicians in almost half of the patients (47%). In patients with at least one recommendation accepted, a marked improvement in medication appropriateness – a 3-unit cumulative decline in median MAI score, (7 to 4; $p<0.01$) – was observed. Similarly, in people whose recommendations were all accepted, a median MAI reduction of 4 units was observed (7 to 3; $p<0.05$). Table 2

Characteristics of recommendations given by pharmacists

Table 3 shows the type of recommendations given by pharmacists and the medications implicated in drug-related problems. Nearly half of the recommendations given by pharmacists had an impact on MAI (46%). Dosage adjustment (51%) and medication cessation (38%) were the most common recommendation types with an impact on MAI. These recommendations were also more likely to be accepted by physicians; 92% of medication cessation and 63% of dosage adjustment recommendations were accepted. Specifically, dosage adjustment recommendations related to anticoagulant medications had a high acceptance rate by physicians (8 out of 11 recommendations). Similarly, among recommendations for medication cessation, medications advised to be avoided in older people (e.g. benzodiazepines and amiodarone) and those that need adjustment or avoidance in severe renal impairment (e.g. dabigatran and spironolactone) were among recommendations often accepted by physicians.

In contrast, dosage adjustment recommendations related to metformin, allopurinol, moxonidine, and epleronone were among recommendations that were not accepted by physicians. In particular, only half of the recommendations for metformin dose adjustment were accepted (3 out of 6). The recommendations that were not accepted by physicians were all made in patients with eGFR between 30 and 60mL/min/1.73m^2. Moreover, although they had no impact on MAI, more than half of recommendations related to initiation of therapy were not accepted by physicians (55%). These included initiations of prophylaxis for venous thromboembolism and deep vein thrombosis, addition of antihypertensives, such as ramipril and atenolol, and supplementation of vitamin D.

Discussion

Almost half of the older adults with CKD had a pharmacist-conducted medication review during their hospital stay. People who had a medication review by pharmacists were not different from those with no medication review in terms of important patient characteristics. In both groups, after hospitalisation, an improvement in medication appropriateness, as assessed with the MAI, was observed. Reassuringly, this demonstrates that hospital admission alone and the associated clinical care improved medication appropriateness. Although not significantly different, there was a trend indicating that people with pharmacist-conducted medication review had greater improvement. Importantly, a considerable median reduction in MAI was observed in patients with at least one recommendation accepted by physicians. The reduction was even higher in patients whose recommendations were fully accepted.

The observed reduction in MAI after physicians' acceptance of pharmacist recommendations was comparable to other hospital studies that evaluated medication appropriateness in older adults using the MAI.[14,23] However, this reduction is much lower than that observed from medication review studies in community settings.[12,13] This could be because, in accordance

with the eligibility criteria for medication management reviews,[24] patients targeted by HMRs are typically those on more medications. Therefore, these patients may have an increased risk of medication-related problems necessitating a substantial review by pharmacists, leading to a marked reduction in MAI.

The improvement in medication appropriateness, especially after acceptance of pharmacists' recommendations by physicians, is indicative of the positive role pharmacists can play in potentially reducing adverse drug events. Pharmacist-led medication review has been linked to a reduction in medication-related hospitalisations and improved healthcare service utilisation.[25,26] Nevertheless, more than half of the patients included in this study did not receive medication review by pharmacists. Implementing a standard clinical pharmacy service for all hospitalised patients may result in a better improvement in medication appropriateness.

The most common recommendations by pharmacists with an impact on MAI were dosage adjustment and medication cessation. Other studies also reported medication cessation as the most common type of recommendation.[12,13,27] The recommendations related to dosage adjustment in our study, while not surprising, also indicate pharmacists' recognition of the poor renal function in these patients. Despite the need to recognise medications that need dosage adjustment in renal impairment, CKD patients have complex regimens that require a thorough medication appropriateness assessment. For example, patients will benefit if pharmacists assess other important factors, such as drug-drug and drug-disease interactions. The recommendations given by pharmacists were accepted in nearly half of patients with medication review (47%). Previous studies have reported acceptance rates ranging between 45% and 69%, depending on the study setting and population targeted.[12,13,23,27]

It was interesting to note that pharmacists' recommendations were perhaps less likely to be accepted when based on evidence that was limited or changing; for instance, the risk of lactic

acidosis in patients treated with metformin and the need for dosage reduction in mild to moderate CKD has been seemingly overemphasised in the past.[28,29]

Limitations

The relatively small number of patients from a single site limited the statistical power to show significant differences and may have influenced the generalisability of the study. Despite the use of various explicit instructions, applying the MAI requires clinical judgment from the evaluator, which could pose a concern of reliability. However, the fact that the rating was performed by the same investigator had an advantage of avoiding potential inconsistencies. The validity of the MAI without the two subcomponents, 'practicality of instructions' and 'expense', has not been investigated. Nevertheless, the individual components of the MAI were found to be valid and reliable.[30] As a retrospective study, the MAI was evaluated based on secondary data at baseline and after medication review by pharmacists. Therefore, the pharmacists were not trained on how to use MAI and they were most likely not using this tool during the medication review. Further, we relied on information that was documented in the medical progress notes to examine the impact of medication review; it is possible we may have missed other recommendations because of poor documentation or because they were given verbally to physicians. Finally, we did not fully evaluate the evidence base and clinical rationale for each of the pharmacists' recommendations but suspect that the uptake of recommendations and the improvement in medication appropriateness were greatest when these were strongest.

Conclusion

This study demonstrates that medication review by pharmacists, especially upon acceptance by physicians, can improve medication appropriateness in older hospitalised adults with CKD. Future studies should investigate if the pharmacist-led improvement in medication

appropriateness translates to positive clinical outcomes in these patients. Moreover, it is important to investigate the quality of recommendations given by pharmacists and the reasons for non-acceptance of some of the recommendations by physicians.

Conflicts of interests:

The authors declare that they have no conflicts of interests.

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Table 1. Baseline characteristics of patients with and without pharmacist medication review

Characteristics	Medication review (n=95)	No medication review (n=109)	*p*-value
Age, years, mean (SD)	84 (8)	82 (10)	0.564
Male gender, n (%)	55 (58)	70 (64)	0.416
Serum creatinine, µmol/L, median (IQR)	132 (113-160)	136 (116-164)	0.638
eGFR, mL/min/1.73m^2, mean (SD)	37 (10)	37.2 (9.9)	0.828
CCI, median (IQR)	4 (3-5)	4 (3-5)	0.747
Length of hospitalisation, days	5 (3-9)	4 (2-7)	0.109
Admission medications, mean (SD)	10 (4)	10 (4)	0.660
Discharge medications, mean (SD)	11 (4)	10 (4)	0.116
Admission MAI, median (IQR)	7 (3-12)	6 (3-11)	0.633
Discharge MAI, median (IQR)	6 (2-10)	5 (2-9)	0.749
Causes of hospitalisation (ICD-10 codes), n (%)			
Circulatory	40 (42)	44 (40)	
External causes and their consequences (falls and fractures)	15 (16)	14 (13)	
Mental and behavioural	7 (7.4)	0	
Infections	7 (7.4)	14 (13)	
Digestive	4 (4.3)	5 (4.6)	
Nervous system	2 (2)	5 (4.6)	
Drug-induced	5 (5.3)	8 (7.3)	

Abbreviations: CCI, Charlson's comorbidity index; eGFR, estimated glomerular filtration rate; ICD-10, International Classification of Diseases (tenth edition); IQR, interquartile range; MAI, Medication Appropriateness Index; SD, standard deviation.

Table 2. The change in MAI scores in people with and without medication review and in patients whose recommendations were accepted by physicians

	Median MAI (IQR)	*p* value[¥]
People with no medication review (n=109)		
At hospital admission	6 (3-11)	
At hospital discharge	5 (2-9)	<0.001
People with medication review (n=95)		
Before review	7 (3-12)	
After review[a]	5 (2-10)	<0.001
After outcome of recommendations[b]	6 (2-10)	0.001
People with at least one recommendation accepted (n=47)		
Before review	7 (3-14)	
After outcome of recommendations	4 (2-11)	0.004
People with all recommendations accepted (n=19)		
Before review	7 (2-12)	
After outcome of recommendations	3 (1-8)	0.032

[¥]Wilcoxon Signed Rank Test
[a]MAI was measured assuming all recommendations by pharmacists were accepted
[b]MAI was measured after outcome (acceptance or non-acceptance) of recommendations by physicians

Table 3. Type of recommendations given by pharmacists and medications implicated

Total recommendations (N=141)	N	Medications implicated
Recommendations with an impact on MAI (n=65)		
Dose adjustment	33	Atorvastatin, apixaban, allopurinol, enoxaparin, prednisolone, epleronone, metformin, pregabalin, moxonidine, rivaroxaban, gliclazide, furosemide, lercanidipine, propantheline, warfarin
Cessation of medications	25	Digoxin, pregabalin, irbesartan, simvastatin, lercanidipine, tramadol, prednisolone, ramipril, indapamide, temazepam, aspirin, oxybutynin, travoprost, diazepam, mirtazapine, prazosin, atorvastatin, amiodarone, spironolactone, furosemide, potassium, dabigatran
Drug-drug/-disease interaction	7	Atorvastatin, apixaban, diltiazem, irbesartan, moclobemide, moxonidine, pseudoephedrine, tramadol, spironolactone
Drug change	5	Dabigatran, felodipine, perindopril, ranitidine
Recommendations with no impact on MAI (n=76)		
Initiation of medications	18	Beta blockers, ramipril, dual antiplatelet therapy, iron, flunitrazepam, metformin, vitamin D, enoxaparin, magnesium, warfarin, esomeprazole
Monitoring patients based on laboratory parameters, particularly renal function	34	Enoxaparin, epleronone, isosorbide mononitrate, gliclazide, pregabalin, moxonidine, lercanidipine, furosemide, ramipril, warfarin
Medication adherence	15	Aspirin, bisoprolol, ezetimibe, iron, isosorbide mononitrate, metoprolol, oxybutynin, simvastatin, travatan
Others	4	Carvedilol, rivaroxaban, spironolactone

Abbreviation: MAI, Medication Appropriateness Index