Pharmacist-driven interventions in patients with chronic kidney disease and end-stage renal failure

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CHAPTER 1

General introduction

Section 1

Drug stewardship in patients with chronic kidney disease (CKD) and the role of the nephrology pharmacist

Chronic kidney disease (CKD) occurs in 10 to 15% of the population worldwide and is accompanied by renal and cardiovascular complications, leading to higher mortality [1,2]. Renal complications increase in number and frequency when CKD progresses and include anaemia, mineral-bone disorders, hyperkalaemia, and metabolic acidosis [3].

To slow disease progression and treat the renal and cardiovascular complications of CKD and comorbidities such as hypertension and diabetes, patients with CKD often use five or more different medications, which is called polypharmacy [4]. Polypharmacy occurs in more than 80% of the patients with CKD and around 90% of patients on haemodialysis [5,6]. Hyperpolypharmacy is defined as the use of at least ten different medications and occurs in 40-55% of CKD patients [5,6].

Treatment of CKD is complex due to the presence of multiple comorbidities, resulting in a multitude of prescribers and hyperpolypharmacy with complex medication regimens, which pose an increased risk of suboptimal medication management [7–11]. Suboptimal medication management may lead to medication-related problems (MRPs).

Patients with CKD often experience multiple MRPs at a time, increasing to three to four MRPs per patient for patients on haemodialysis, leading to negative consequences such as hospitalisation [12–15]. Other frequent reasons for hospitalisations in patients with CKD and on haemodialysis are cardiovascular disease, infections and fluid retention [11,16]. The clinical pharmacist is the pre-eminent medication expert and thereby perfectly suited to guide medication management in patients with CKD, to minimise MRPs[17]. It is known that on-ward pharmacist interventions in patients with CKD can reduce MRPs by 45 to 85% in hospitalised patients [18–21].

Although on-ward pharmacist interventions have been shown to reduce the number of MRPs, some research gaps remain. Long-term data on acceptance rate and clinical relevance of on-ward pharmacist interventions are lacking [18,19,21]. In studies with a follow-up of three months to one year, between 83% and 95% of

on-ward pharmacist interventions are generally accepted [22–24]. Clinical relevance is important for physicians' acceptance of pharmacist interventions [25]. However, the clinical relevance of pharmacist interventions is highly variable, with physicians assessing 30% to 56% of the interventions as clinically relevant [22,23,26,27]. Here too, follow-up is short with a maximum of one year.

Earlier data suggest that the acceptance rate and clinical relevance may change over time. A learning effect in both physicians and pharmacists may underlie these findings, resulting in an increase in acceptance rate and a decrease in the number of interventions during long-term participation of pharmacists in multidisciplinary ward rounds [28]. It is conceivable that this learning effect continues to exist for over a year, resulting in fewer but more clinically relevant pharmacist interventions with a higher acceptance rate. However, this hypothesis has not yet been confirmed in clinical studies.

Traditionally, the pharmacist's role in CKD care has mostly been reactive, consisting of advising and correcting prescribers, for example, in case of a medication overdose for a patient with reduced kidney function, or therapeutic drug monitoring for aminoglycosides and vancomycin, to optimise treatment efficacy and reduce (renal) toxicity. More recently, the pharmacist has become a more proactive member of the multidisciplinary team of healthcare professionals (HCPs) treating patients with chronic kidney disease [14,18,20,29–31]. In some hospitals in the Netherlands, nephrology pharmacists perform patient consultations as members of the multidisciplinary nephrology team. In CKD clinical practice in Europe, this new proactive role is gaining momentum, but it is still in the developing phase. Recent guidelines and position papers however foresee an important role for clinical pharmacists in CKD medication management and drug stewardship, which includes medication reconciliation, optimising medication impact, and reducing MRPs, for example as part of a medication review [17,32].

Besides reducing MRPs in patients with CKD, nephrology pharmacists may also improve medication management. Low-quality observational studies suggest that nephrology pharmacists can improve medication management in patients with CKD and on haemodialysis. The pharmacist-managed treatment of renal anaemia with erythropoietin-stimulating agents (ESA) is an example of the contribution of nephrology pharmacists to medication management in patients with CKD.

Notwithstanding the emergence of HIF-PH-(hypoxia-inducible factor prolyl-hydroxylase) inhibitors as a new treatment option, ESA are still first-line therapy in the treatment of renal anaemia [33]. Renal anaemia is associated with adverse outcomes, such as a higher risk of coronary artery disease, heart failure, cardiovascular hospitalisations, and mortality [34–36]. However, a disadvantage of long-term use of ESA is the risk of thrombotic complications, particularly major adverse cardiovascular events (MACE). MACE comprise myocardial infarction, non-haemorrhagic stroke, and cardiovascular death, the latter being the leading cause of death in patients on haemodialysis. When using ESA, higher target levels for haemoglobin are associated with an increased risk of stroke, other MACE, and worsening hypertension [37–41]. To reduce this risk, the current (concept) guideline recommends targeting haemoglobin levels below 7.2 mmol/L in patients with CKD and on haemodialysis [33].

However, in clinical practice, it is challenging to maintain haemoglobin levels around this target level. Without the use of decision aids, only about 30% of haemodialysis patients in Europe have adequate haemoglobin values [42]. Several factors contribute to this finding, such as ESA hyporesponsiveness, infections, and suboptimal prescribing of ESA and iron [42,43]. As clinicians mainly focus on avoiding low haemoglobin levels and transfusions, high haemoglobin levels are still frequently overlooked. This leads to the erroneous continuation of (a too-high dose of) ESA, which occurs in more than a quarter of haemodialysis patients in Europe [42].

Pharmacist-managed renal anaemia may improve the attainment of haemoglobin target levels. Earlier systematic reviews on pharmacist interventions included studies on pharmacist-managed renal anaemia using ESA, but had a very broad scope. Their conclusions regarding the effects of pharmacist-managed renal anaemia were ambiguous due to a lack of high-quality studies and the large heterogeneity of pharmacist interventions [20,31,44]. The most recent systematic review concluded that pharmacist-managed renal anaemia increased haemoglobin by 0.47 mmol/L, but it included only studies from non-Western countries, and baseline haemoglobin values were low or very low [20]. In Western countries nowadays, during the treatment of renal anaemia with ESA, a high haemoglobin concentration might occur more often than a low haemoglobin concentration. These high haemoglobin concentrations, especially in the case

of high ESA dose, are associated with higher rates of cardiovascular disease and mortality [40,45–47]. Furthermore, these systematic reviews only reported on haemoglobin outcome parameters, whereas other relevant outcome parameters, such as ESA expenditure, were missing.

To conclude, the published systematic reviews on pharmacist-managed renal anaemia using ESA reported on a broad range of interventions but lacked an in-depth discussion of pharmacist-managed renal anaemia, and their conclusions regarding pharmacist-managed anaemia were ambiguous. To provide focus on pharmacist-managed renal anaemia, incorporating a broad range of outcomes, an updated systematic review is warranted.

As stated above, there is a paucity of high-quality studies on pharmacist-managed renal anaemia using ESA, including randomised controlled trials. Therefore, more high-quality studies, preferably randomised controlled trials, investigating haemoglobin and other relevant outcome parameters, are needed to strengthen the body of evidence in this field. Furthermore, the choice of haemoglobin outcome parameter is important, as a higher haemoglobin concentration does not necessarily improve patient outcomes. Therefore, the percentage in target range for haemoglobin might be a more suitable outcome parameter than the level of haemoglobin itself.

Section 2
Medication self-management and adherence in patients with CKD in relation to health literacy and the pharmacist's role in improving medication adherence

Pharmacists can contribute to and improve medication management. However, the patient also has a very important role in medication management, as the greatest part of the treatment of chronic diseases, including chronic kidney disease, takes place at home. At home, the patient has to take care of managing the disease, including its symptoms, lifestyle recommendations, and medication. This is called self-management. Patients with CKD often perceive self-management as difficult and report an increase in difficulty of self-management with the progression of CKD [10,48,49].

Medication self-management is part of self-management in chronic diseases in general and is defined as the range of tasks people have to undertake to successfully manage their therapeutic regimen and sustain the safe and appropriate use of medication [50]. As patients with CKD use approximately ten different medications [5,17], medication self-management is seen as critical in this patient group [38–40]. Adequate medication self-management results in taking medication correctly (i.e. medication adherence), which is essential for the treatment of chronic diseases [50–52].

However, suboptimal medication adherence occurs in approximately 50% of all patients with CKD [53,54]. Patients with CKD and on haemodialysis experience several barriers to adhering to their medication. These barriers are present in a large proportion of patients and are related to disease-specific factors such as the high prevalence of multimorbidity, hyperpolypharmacy, dietary restrictions, the large quantity of information, and the high disease burden. Other causative factors are medication-specific, such as the occurrence of side effects, a high pill burden and a complex medication regimen [49,55,56]. Limited health literacy skills may also impede medication adherence [50,57,58].

Health literacy (HL) skills are the personal, cognitive and social skills which determine the ability of individuals to gain access to, understand, appraise, and apply health information to make well-informed health and treatment decisions [59–61]. Medication-related health literacy skills are essential for adequate and safe medication use. For example, patients need to be able to perform numeric tasks in understanding and using medication information with numbers, tables, graphs, and statistics [62]. They also need skills to recognise and respond to a lack of treatment effect as well as possible side effects. Furthermore, adequate health literacy skills are essential for patients to understand the aim of the medication, the expected treatment effects and side effects, and specific user instructions.

However, limited health literacy (HL) is present in at least 25% of patients with CKD [63]. Limited HL is associated with the onset of CKD, and individuals with worse renal function are more likely to have limited HL [64]. In most chronic diseases, limited HL is associated with reduced adherence to treatment, including adherence to medication [50,52,57,58,65–71]. In CKD, however, data regarding this association are conflicting, and no clear association has been found [69,72–74].

To date, no studies have been published on medication-related health literacy in patients with CKD and on haemodialysis. As health literacy is content and context-specific [75], it is important to investigate and describe medication-related HL (content) in the context of haemodialysis treatment.

One of the medication groups for which HL is extremely relevant is phosphate-binding medication (PBM). As the use of PBM requires a complex treatment regimen with extensive user instructions, adequate health literacy skills are needed to correctly interpret all treatment information.

PBM is used to treat a high serum phosphate concentration, one of the most common complications of CKD. Elevated serum phosphate concentrations contribute to secondary hyperparathyroidism, bone disease, and the development of atherosclerotic heart disease by inducing cardiovascular calcifications and are independently associated with a 20% to 40% increase in mortality risk among patients with end-stage renal disease (ESRD) [76,77]. Among PBM, sevelamer is the first-choice agent as it is associated with lower all-cause mortality [78].

Besides phosphate-binding medication, diet and dialysis are used to lower serum phosphate concentrations [79]. However, self-management of a high serum phosphate concentration, including medication self-management of PBM, is very complex and demanding for patients. Besides dietary adjustments, taking into account the protein and phosphate content of different foods and drinks, a correct intake of phosphate-binding medication (PBM) is essential to keep the serum phosphate concentration within the target range [79].

However, patients encounter several barriers to adequate intake of PBM. They consider the high pill burden and the complex pharmacotherapeutic treatment regimen with extensive user instructions to be particularly challenging. This often results in medication non-adherence, which is reported to occur in at least 50% of the patients on PBM [80–83]. When serum phosphate concentration remains uncontrolled, and adherence is suboptimal, this often triggers a vicious treatment circle in which the nephrologist continues to increase the PBM dose, and the patient becomes less and less satisfied with PBM treatment, with adherence diminishing further [84]. This may explain the finding of a higher PBM pill burden being associated with lower PBM adherence [82,85].

Nephrology pharmacists are perfectly suited to guide patients in addressing barriers to adhering to PBM [29,86,87]. Several adherence-improving pharmacist interventions have been investigated in patients with CKD using PBM. Individualised, multi-component interventions targeting knowledge and skills mostly improved adherence to PBM and the percentage of patients within target range, but did not reduce phosphate concentrations [88–92] . Furthermore, the positive effects of these interventions on adherence are often short-lived, and little is known about how long the effect on adherence remains after discontinuing the intervention.

It has been suggested that a reduction in PBM pill burden might improve PBM adherence [82,93]. This strategy might be key to breaking the vicious treatment circle in the treatment with PBM. However, this hypothesis has not yet been tested in patients with CKD and on haemodialysis. As the most effective adherence-improving interventions are multi-component, individualised interventions [88,91,92,94,95], it would be logical to combine a reduction in pill burden with addressing individual barriers to adherence to PBM.

In patients with hypertension and diabetes, a multi-component, individualised intervention addressing individual barriers to adherence has been investigated [96,97]. This intervention was feasible in clinical practice but did not improve self-reported medication adherence. To augment the effectiveness of the intervention, the authors recommended specifically targeting this intervention at patients with a high risk of or proven suboptimal adherence [96]. The combination of this multi-component, individualised pharmacist intervention with reducing PBM pill burden may be the way to go in improving adherence to PBM and thereby reducing a high serum phosphate concentration.

When an intervention has been proven effective in studies, data regarding the implementation of the intervention are often lacking. Furthermore, interventions are often poorly implemented in clinical practice, leading to suboptimal effects [98]. All in all, it often remains unknown how well a specific intervention was performed and what barriers and facilitators may have influenced its implementation. This lack of information impedes the effective implementation of adherence-improving interventions in clinical practice.

The implementation fidelity (IF) theory can be used to address the extent to which an intervention has been performed as designed, and what its barriers and facilitators for implementation in clinical practice are [99]. One framework often used for studying implementation fidelity is Carroll's Conceptual Framework for Implementation Fidelity (CFIF) [99]. The CFIF identifies several elements of implementation fidelity: adherence to the intervention, moderating factors, and key elements of the intervention. The IF of several pharmacist interventions has been studied using the CFIF [100–103]. The results of these studies show that the CFIF can help improve research on and the development and improvement of pharmacist interventions in two ways: 1) IF acts as a moderator between the intervention as designed and the effects of the intervention in research and clinical practice, which is why it is important to study it, and 2) in studying IF barriers and facilitators for the implementation of the intervention are identified, and, recommendations can be provided for the implementation of the intervention in clinical practice taking these barriers and facilitators into account.

To conclude, several research gaps remain regarding the role of the nephrology pharmacist in patients with chronic kidney disease, including those on haemodialysis, in drug stewardship and medication self-management and adherence in relation to health literacy.

Aim and outline of this thesis

The overall aim of this thesis is to investigate how the interventions of a specialised nephrology pharmacist can contribute to rational, safe, and effective medication use in patients with CKD and, more specifically, in patients on haemodialysis. Health literacy and implementation fidelity will also be investigated in this thesis as they are important drivers of the effectiveness of pharmacist interventions. With the studies reported in this thesis, the position of pharmacists can be strengthened by demonstrating how the pharmacist can help to improve overall CKD outcomes as an essential member of the renal care team. The pharmacist-managed treatment of renal anaemia is discussed in Chapters 2 and 3. Chapter 2 contains the results of a systematic review of the effectiveness of pharmacist-managed and algorithm-managed renal anaemia on several outcome parameters.

In Chapter 3, a randomised controlled trial is described in which the effect of pharmacist-managed renal anaemia on haemoglobin outcomes is investigated.

Trends in acceptance rate, number, and clinical relevance of nephrology pharmacist interventions during multidisciplinary nephrology ward rounds over five years are discussed in Chapter 4.

In Chapter 5, the medication-related health literacy (HL) of haemodialysis patients using phosphate-binding medication (PBM) and its association with self-reported medication adherence is presented.

Chapters 6 and 7 contain the results of a prospective study in which we investigate a multi-component Pharmacist Intervention with Dose Optimisation of Phosphate-binding medication, the PIDO-P intervention, in haemodialysis patients with uncontrolled hyperphosphatemia and a high PBM pill burden. The goal of this intervention was to improve hyperphosphatemia. With the intervention, we address patient barriers to adherence and aim to improve adherence by reducing the pill burden. In Chapter 6, we describe the results of this intervention on phosphate concentration. Chapter 7 discusses the implementation fidelity of this intervention with a mixed methods design. Moderating factors, such as barriers and facilitators for implementation, are assessed.

In the general discussion (Chapter 8), we reflect upon the implications of the main study results and provide recommendations for clinical practice and future research.

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