THE UNIVERSITY OF SYDNEY

The association of medication regimen complexity on patient-related and clinical outcomes in end stage kidney disease

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Candidate's statement of originality

This is to certify that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

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Chapter 2 of this thesis has been submitted as Goh JX, Sud K, Tesfaye W, *et al.* The impact of medication regimen complexity on patient-related and clinical outcomes in kidney failure: A Systematic Review to the *Expert Opinion On Pharmacotherapy* journal and is undergoing peer review process at present.

I researched and systematically reviewed the literature, wrote the drafts of the manuscript, and currently managing the journal submission process. Associate Professor Ronald L Castelino, Dr. Wubshet Tesfaye and I conceived the study design. All authors were involved in critical editing and revision of the manuscript.

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Ethical clearance

The studies presented in Chapters 4 and 5 were approved by the Western Sydney Local Health District Human Research Ethics Committee (approval code: 2019/PID03039, approval date: 17 October 2023).

Abstract

Background: End stage kidney disease (ESKD) is the most severe form of chronic kidney disease (CKD), with increasing prevalence worldwide. At this stage, patients rely on dialysis and/or kidney transplantation to sustain life. Advances in ESKD treatment and pharmacotherapy have improved survival rates, but polypharmacy is inevitable due to multiple medications needed for comorbid conditions and metabolic disturbances.

Research gap: The impact of medication regimen complexity and burden on health outcomes in chronic diseases is known, but little is understood across different dialysis modalities, particularly beyond haemodialysis (HD). Inconsistencies in measuring medication regimen complexity complicate understanding its effect on outcomes in these vulnerable patients.

Aims & objectives: This thesis aims to quantify and compare medication regimen complexity in patients across different dialysis modalities (facility-based HD, home HD, peritoneal dialysis (PD)), and explores associations with patient-centred and clinical outcomes.

Methods: Three studies were conducted:

- **Study 1**: Literature review of assessment methods, outcomes related to medication regimen complexity, and effectiveness of interventions to address the complexity in ESKD.

- **Study 2**: Prospective study with retrospective component quantifying medication regimen complexity in 145 facility-based and home-based HD patients and comparing the outcomes between the two HD settings.
- **Study 3**: Similar study design for 131 PD patients, examining regimen complexity and outcomes.

Key findings:

- **Study 1:** Adverse health outcomes, including poor quality of life (QoL) and impaired medication adherence, are linked to regimen complexity in dialysis-dependent and kidney transplant patients.
- **Study 2:** Higher medication regimen complexity in home HD patients, but better QoL and hospitalisation outcomes compared to facility-based HD patients.
- **Study 3:** PD patients who were adherent to medications had better QoL and serum phosphate levels compared to non-adherent patients.

Conclusion: These studies enhance understanding of medication regimen complexity and its association on outcomes across different dialysis modalities. The findings provide a basis for future multi-centre studies to develop interventions to reduce medication complexity and improving outcomes in ESKD.

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2. Pharmaceutical Society of Australia (PSA) Conference 2024: POS-11 - The impact of medication regimen complexity on patient-related and clinical outcomes in patients undergoing haemodialysis [Poster presentation]
3. 82nd International Pharmaceutical Federation (FIP) World Congress of Pharmacy and Pharmaceutical Sciences 2024: HPS-017 - The impact of medication regimen complexity on patient-related and clinical outcomes in patients undergoing haemodialysis [Abstract poster acceptance]
4. Sydney Pharmacy School Higher Degree Research (HDR) Conference 2024: Medication Regimen Complexity and Patient-Centred Outcomes in Patients Undergoing Peritoneal Dialysis [Oral presentation]

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Abbreviations

AKI	Acute kidney injury
APD	Ambulatory Peritoneal Dialysis
BMI	Body mass index
BMQ	Brief Medication Questionnaire
CAPD	Continuous Ambulatory Peritoneal Dialysis
CKD	Chronic kidney disease
CVD	Cardiovascular disease
COPD	Chronic obstructive pulmonary disease
eMR	Electronic medical record
ESA	Erythropoiesis-stimulating agent
ESKD	End stage kidney disease
EQ-5D-5L	EuroQoL-5D-5L
EQ VAS	EuroQoL visual analogue scale
GFR	Glomerular filtration rate
GR-SMAQ-HD	GR-Simplified Medication Adherence Questionnaire – Haemodialysis
HD	Haemodialysis
HIV	Human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
HRQoL	Health-related quality of life
IDWG	Interdialytic weight gain
KDIGO	Kidney Disease: Improving Global Outcomes
KDQOL-36	Kidney Disease Quality of Life-36
KRT	Kidney replacement therapy
MMAS-4	4-item Morisky Medication-Taking Adherence Scale

MMAS-8	8-item Morisky Medication-Taking Adherence Scale
MMS	Medication Management Service
MRCI	Medication Regimen Complexity Index
PIM	Potentially inappropriate medication
PD	Peritoneal dialysis
QoL	Quality of life
SCr	Serum creatinine
SF-12	12-Item Short Form Health Survey
SF-36	36-Item Short Form Health Survey
TBQ	Treatment burden questionnaire
TCI	Therapeutic complexity index

Chapter 1:

Introduction

This chapter provides a brief introduction to chronic kidney disease (CKD) and end stage kidney disease (ESKD), presenting trends in the incidence, prevalence, and burden of the disease in Australia. An overview of the treatment options for ESKD is given, followed by a discussion on the complexity and adherence of medications among ESKD patients. The chapter concludes by outlining the aim and specific objectives of the research study.

1.1 Current trend of chronic kidney disease and end stage kidney disease

Chronic kidney disease (CKD) is a silent progressive condition profoundly impacting patients, their families, and the healthcare system. The irreversible loss of kidney function disrupts the body's chemical balance, leading to a build-up of toxic metabolic waste products due to the kidney's inability to filter blood, resulting in various complications [1, 2]. According to the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines, CKD is defined as abnormalities of kidney structure or function, present for a minimum of three months, with implications for health [3]. Kidney function is reflected by glomerular filtration rate (GFR) and estimated by measuring blood levels of serum creatinine (SCr), a degradative product of muscle protein [3].

Globally, more than 800 million people are affected by CKD making it one of the leading non-communicable diseases that leads to significant morbidity and mortality [4]. The initial stages of CKD often go unnoticed and are significantly underdiagnosed, as patients in CKD stages 1-2 are usually asymptomatic [5]. This is evident in the National Health Measures Survey (NHMS), which found that among the 1.7 million (approximately 1 in 10) Australian adults exhibiting biological indicators of CKD, only six percent self-reported having the condition, with the majority being in CKD stages 3-5 when symptoms became more apparent [6].

The prevalence of CKD increases rapidly with age, affecting around 4 in 10 Australians aged 75 and over, compared to younger age groups [7]. As of 2023, over 2 million Australian adults are living with CKD, with 31,000 (1.5%) experiencing end stage kidney disease (ESKD) and undergoing either kidney replacement therapy or conservative care [8]. Projections indicate a nearly 18% increase in the number of new ESKD cases by 2030 [8]. This rise is attributed to the shift in disease burden from infectious diseases to chronic lifestyle-related diseases, along with increased life expectancy in developed countries [9].

In primary care settings, kidney disease rarely develops in isolation and is often associated with two of Australia's major chronic diseases – diabetes and cardiovascular disease (CVD), including hypertension [8, 10]. Diabetes remains the predominant cause of ESKD in Australia, accounting for 36% of cases, followed by glomerulonephritis, high blood pressure, tubulointerstitial, and hereditary kidney disease [11]. Other risk factors for developing CKD include obesity, smoking, a family history of kidney failure, or a history of acute kidney injury (AKI), age over 60, and being a First Nations Australian aged over 18 [8, 10]. Along with these risk factors, variables such as the cause of CKD, GFR category, and the extent of albuminuria are used to classify CKD staging and determine its prognosis [3]. The rate of progression to ESKD varies by aetiology, albuminuria, exposures, and interventions. Therefore, early detection of CKD is crucial to address the associated risk factors and preserve kidney function. Moreover, the progression of CKD can be significantly slowed if identified early and managed well, leading to improved clinical and economic outcomes [8].

1.2 The burden of chronic kidney disease and end stage kidney disease

Living with CKD imposes a substantial burden on individuals, detrimentally affecting their health, quality of life, job employability, and increasing other care requirements [8, 12]. Impaired kidney function is also associated with numerous other conditions such as gout, peripheral artery disease, dementia, ischemic heart disease, and stroke [3, 13]. This is primarily due to the retention of uremic toxins that disrupt cellular and organ function, leading to uremic syndrome – a complex pathophysiologic cascade of interlinked events [14].

In the later stages of the disease, dialysis treatment or kidney transplantation takes an immense toll on patients with ESKD. The need for daily peritoneal dialysis or thrice-weekly haemodialysis treatments significantly impacts patients' ability to work, travel, and function independently. [15]. Furthermore, the burden of the disease extends beyond the individual, adding strain to the healthcare system and the nation's economy [8]. Due to the multiple complications and the necessity of dialysis and/or kidney transplantation, ESKD is one of the most complex and expensive non-communicable diseases to manage [16, 17]. A typical patient on dialysis has seven annual healthcare visits and at least three different prescribers [18], making the management of ESKD and its numerous comorbidities costly. In 2021, the average cost of CKD per patient in Australia was approximately $4,800 per year, which surged to more than $182,000 if they progressed to ESKD, primarily due to the high costs associated with kidney replacement therapy [8]. This accounts for an estimated total expenditure of $9.9 billion annually in Australia on CKD, with most of the cost attributed to managing people with ESKD [8].

CKD remains one of the leading causes of mortality, particularly among the older population aged 85 and over [13]. The latest statistics from the Australian Institute of Health and Welfare (AIHW) show a rising trend in CKD's contribution to the total disease

burden, increasing from 0.8% in 2003, to 1.1% in 2022 [13]. The loss of well-being among Australians impacted by CKD is measured by an estimated loss of 55,931 disability-adjusted life years (DALYs), which is comparable to other chronic illnesses such as blood and metabolic disorders, as well as reproductive and maternal conditions [8]. If medically suitable, patients with ESKD can either undergo a kidney transplant from a living kidney donor or wait for two to five years for a cadaveric donor kidney transplant [19]. While waiting for a suitable living or cadaveric kidney donor, patients must remain on dialysis [8].

Over the past two decades, CKD-related mortality has increased by 97% reaching around 20,000 deaths per year and accounting for 12% of all deaths in Australia [13]. CKD is often regarded as a contributing factor rather than the primary cause of death, as the condition itself may not directly lead to death [13]. During the COVID-19 pandemic, CKD was also recorded as the comorbid condition with the third-highest death rate among hospitalised COVID-19 cases [13]. Data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry indicate that mortality rates among the population with kidney failure depend on kidney replacement therapy modality, with those on dialysis experiencing a mortality rate approximately three times higher than those who have undergone kidney transplantation [20]. Therefore, early detection through regular health checks is crucial for those at risk of CKD, as it helps preserve kidney function, save lives, and reduce the strain on the healthcare system.

1.3 Treatments for end stage kidney disease

CKD can progress to ESKD characterised by a severe loss of kidney function, requiring extensive management with limited treatment options. According to the KDIGO Clinical Practice Guidelines, ESKD, is the terminal stage (stage 5) of CKD, diagnosed when the

estimated GFR falls below 15 mL/min/1.73m^2, with or without albuminuria [3]. At this stage, kidney replacement therapy (KRT), including dialysis or kidney transplantation, becomes a life-saving intervention. However, some patients, particularly the elderly, may opt for conservative kidney management, which focuses on individualised supportive care and symptom control to optimise quality of life (QoL) [21].

A systematic review conducted by Tonelli *et al.* highlighted kidney transplantation as the preferred treatment for ESKD, significantly reducing mortality and cardiovascular events while improving QoL compared to various dialysis modalities [22]. Despite the benefits of kidney transplantation, barriers such as limited donor availability, cultural attitudes towards donation, comorbidities, and access to the healthcare system impede its widespread adoption [22, 23]. Consequently, dialysis remains the most common KRT for patients with ESKD in Australia [13].

Dialysis therapies are long-term and invasive, requiring adherence to rigid treatment schedules and major lifestyle adjustments. The optimal timing for initiating dialysis is often debated and should consider each patient's clinical status, preferences, and the balance between treatment burden and disease burden, rather than relying solely on estimated GFR [15]. Typically, the high burden of uremic symptoms prompts the initiation of maintenance dialysis. Absolute indications for dialysis include severe manifestations of uremic syndrome, such as uremic pericarditis, uremic encephalopathy, severe uremic bleeding, recurrent hyperkalaemia unresponsive to medical management, severe fluid overload leading to pulmonary oedema, refractory nausea and vomiting, and severe metabolic acidosis [15]. Dialysis aims to maintain chemical and fluid balance by filtering out toxins, waste products and excess fluids via diffusion and ultrafiltration [24]. However,

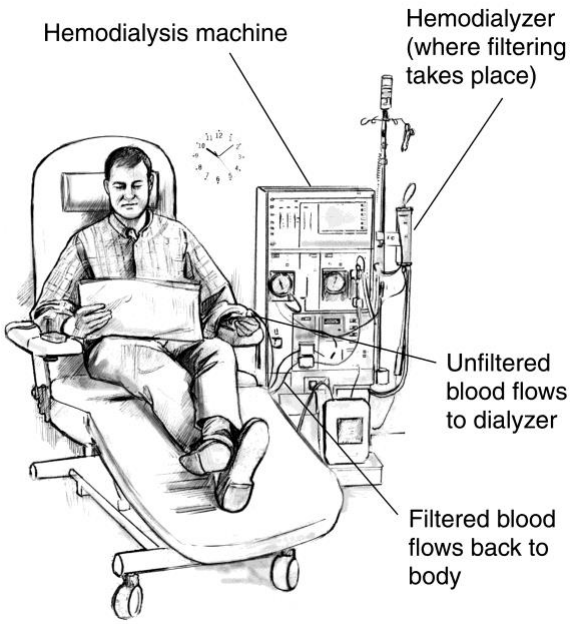
it does not fully replicate kidney function and does not restore normal kidney function [24, 25].

1.3.1 Dialysis modalities and considerations

Dialysis methods can be classified as either extracorporeal (haemodialysis, HD) or intracorporeal (peritoneal dialysis, PD) [23]. Globally, HD is the most widely used form of KRT, sustaining millions of lives post-kidney failure [26]. HD utilises an external filter (dialyser) with a semi-permeable membrane to remove metabolic waste products and excess water [24]. The counter-current flow gradient in the dialyser facilitates the diffusion of waste particles from the blood into the dialysate [24]. In PD, the body's peritoneal membrane acts as the natural semi-permeable membrane to filter waste and excess fluid into the dialysate, which is replaced multiple times a day [24]. In Australia, HD accounts for 83% of dialysis treatment, compared to 17% for PD in 2023 [11].

HD can be categorised as in-centre, satellite, or home HD. **Figure 1** illustrates the HD procedure [27].

Figure 1. Illustration of patient undergoing HD



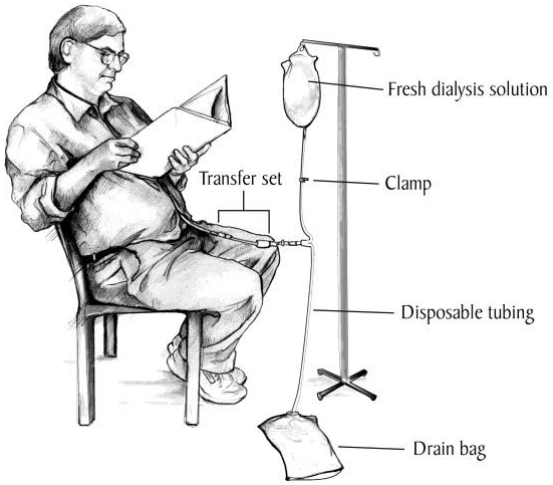
The dialysis machine pumps blood through the dialyser which filters out waste products, and returns the filtered blood to the patient's body (Source: U.S. National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health)

In-centre and satellite HD are provided in the hospital or community settings respectively, by healthcare professionals, typically involving thrice-weekly treatments of approximately four hours per session. Home HD is initiated in medically stable, independent patients after comprehensive education and training [28]. However, the absence of vascular access or severe cardiovascular instability are absolute contraindications for maintenance HD [28].

PD, on the other hand, is a gentler dialysis modality that uses the peritoneal membrane in the abdomen as a natural filter, offering greater flexibility and improved QoL especially for patients who work or travel [29]. PD also imposes a lower burden on the healthcare system due to its lower per-patient cost compared to HD [15]. Common PD options include Continuous Ambulatory Peritoneal

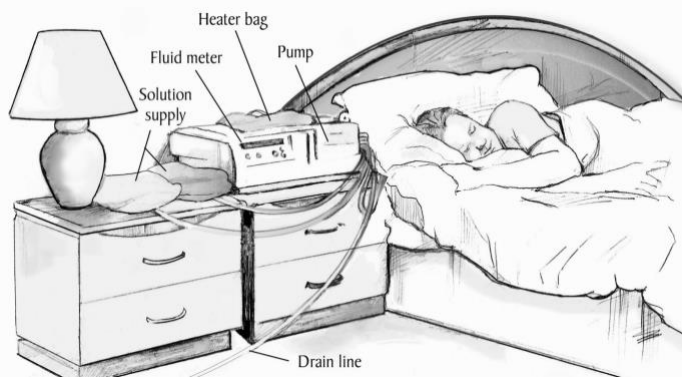
Dialysis (CAPD) and Automated Peritoneal dialysis (APD) [29]. CAPD involves manual exchanges of dialysate, while APD uses a machine called a cycler to assist with exchanges, typically overnight [30]. **Figure 2** illustrates the CAPD and APD procedures [31, 32].

Figure 2a. Illustration of patient undergoing CAPD



A machine-free dialysis procedure that uses gravity to drain the dialysis solution and involves manually emptying and replacing the dialysis solution several times daily (Source: U.S. National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health)

Figure 2b. Illustration of patient undergoing APD



A machine (cycler) is used to perform exchanges of the dialysate automatically, and it is repeated several times during the night (Source: U.S. National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health)

In Australia, most PD patients are treated with APD [11], often transitioning from CAPD as their bodies adjust to dialysis [33]. However, patients with diabetic kidney disease on PD generally report poorer outcomes compared to those on HD [34, 35]. Contraindications for PD include an obliterated peritoneal cavity, a non-functional peritoneal membrane, or the inability to obtain catheter access [28].

1.3.2 Choosing the right modality

Ideally, a home dialysis modality is preferred when feasible. Nonetheless, several factors must be considered, including patient age, fragility, home facilities, support from family members or caregivers, overall health, lifestyle, and the local availability of expertise and resources [15, 33]. Selecting a dialysis modality is a complex decision requiring collaboration between clinicians, patients, and their families to balance life expectancy and QoL. Previous studies emphasise the importance of incorporating patient priorities when choosing a dialysis modality to improve health outcomes [36].

1.4 Medication complexity and pill burden in end stage kidney disease

As kidney function declines, ESKD is characterised by additional comorbidities such as CVD and metabolic disorders, along with complications like anaemia, acidosis, hypertension, bone mineral disorders, hyperkalaemia and hyperlipidaemia [3, 37, 38]. These comorbidities often lead to poor sleep quality, depression, pain, frailty, and cognitive impairment, particularly in older populations [39]. The need to manage these conditions results in highly complex medication regimens, with numerous studies demonstrating a high prevalence of polypharmacy among dialysis patients [40-42]. HD patients, in particular, have significantly higher Medication Regimen Complexity Index (MRCI) scores compared to non-kidney failure patients, correlated with increased regimen complexity [43].

The higher medication utilisation pattern among HD patients compared to pre-dialysis patients is linked to a higher perceived treatment burden, which impairs QoL [44]. Medication and lifestyle change burden are the highest perceived treatment-related burdens among kidney disease patients, followed by administrative, social, and financial burdens [45]. It is not unusual for ESKD patients to require an average of 10-12 medications each day, including but not limited to phosphate binders, erythropoiesis-stimulating agents (ESAs), iron and vitamin D supplements, calcimimetics, antihypertensives, and antidiabetics [37, 46]. This is higher than the medication burden for patients with CKD or human immunodeficiency virus (HIV) [47-49]. The complex medication regimen also places patients with ESKD at higher potential for medication-related problems such as drug interactions [50].

Phosphate binders, which must be taken with each meal, account for nearly half of the daily pill burden and contribute significantly to the medication administration burden [50,

51]. This affects medication adherence and HRQoL [50]. Studies have shown that increasing the number of phosphate binders prescribed for hyperphosphatemia does not correlate with better serum phosphate control [50]. Hence, reducing mineral and bone disorder medications could simplify regimens and improve health outcomes [52].

1.4.1 Comparison across dialysis modalities

The importance of studying medication regimen complexity across different dialysis modalities lies in the unique challenges of medication management and outcomes associated with each modality. Evidence comparing medication complexity across different dialysis modalities is limited and there is no standardised approach to defining medication regimen complexity. Patients receiving HD and PD would face varying degrees of medication burden due to differences in comorbidities and treatment protocols [53]. Generally, PD and facility-based HD patients have higher pill burden compared to home HD patients [53]. Chronic PD patients often have a higher burden of orally administered medications, possibly due to the need for oral administration of medications like vitamin D receptor activators, which can be given intravenously to HD patients during dialysis sessions [50]. However, some studies show that HD patients overall have a higher mean number of prescribed medications, particularly for symptomatic and complication management [54]. Medication burden increases with dialysis vintage in both HD and PD patients [54].

When transitioning from in-centre HD to nocturnal home HD therapy, MRCI scores rise significantly, possibly due to the shift in administration of medications such as ESAs, intravenous iron, and vitamin D analogues from in-centre to home settings, along with increased reliance on oral medications [52]. Vitamin and supplement

use also increases due to greater removal of water-soluble vitamins in home HD [52]. Post-transplant, pill burden can reach up to 25 pills per day one month post-transplant and 16 pills per day by one year post-transplant, making it one of the highest among chronic conditions [55].

Although polypharmacy is ubiquitous among patients with kidney failure, it does not necessarily indicate overprescribing or poor medical management but rather reflects the need to manage multiple concomitant medical conditions [41]. Medication regimen complexity is further increased by the different dosages, forms, frequencies, and administration instructions. The complexity predisposes patients to a higher risk of medication-related issues, such as non-adherence and adverse drug reactions, contributing to suboptimal outcomes and higher treatment costs [37, 41]. Furthermore, an Australian study identified the impact of polypharmacy on QoL and the need for regimen simplification as top research priorities among patients undergoing HD [56]. Understanding the differences of medication regimen complexity among different dialysis modalities is crucial for developing targeted interventions to address medication complexity and improve patient-related and clinical outcomes among patients with ESKD.

1.5 Adherence in end stage kidney disease patients

1.5.1 Definition and importance of adherence

According to the World Health Organisation, adherence is “the extent to which a person’s behaviour – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a healthcare provider” [57]. Poor medication adherence in patients with chronic diseases is a global issue, leading to poor health outcomes and increased economic burden [57]. Medication

non-adherence can be broadly categorised into intentional and unintentional non-adherence [56]. Intentional non-adherence occurs when patients consciously decide to follow or refuse professional recommendations [58]. In contrast, unintentional non-adherence results from passive processes such as lack of understanding, memory issues, or access to medications, which are less influenced by beliefs and values [58]. Nonetheless, both types of non-adherence ultimately lead to less desirable treatment outcomes.

1.5.2 Medication adherence in end stage kidney disease

Given the complexity of medication regimens in patients with ESKD, medication adherence is crucial. Unsurprisingly, medication non-adherence is common in both pre-dialysis and dialysis patients, leading to serious consequences such as anaemia, hyperphosphatemia, hyperkalaemia, hypertension, and fluid retention, all of which increase morbidity and mortality [39, 59, 60]. Poor adherence also results in unnecessary dosage adjustment, additional blood tests, follow up visits, and emergency or hospital admissions, thereby increasing treatment costs [61]. In addition to medication adherence, adherence to dialysis treatment involves strict fluid and dietary restrictions, particularly concerning potassium and phosphate intake [60].

Non-adherence in dialysis patients is often defined as interdialytic weight gain (IDWG) > 1.5kg, pre-dialysis serum potassium levels > 5.5 mEq/L (5.5 mmol/L), and serum phosphate levels > 6 mg/dL (1.94 mmol/L) [61]. In HD patients, pill burden is a significant risk factor for high IDWG, which is associated with increased mortality [62]. Medication adherence rates are around 50% among HD patients [63, 64], with lower rates reported in home PD patients, though the reasons are unclear

[61]. Studies have shown that non-adherent PD patients experience higher peritonitis incidence and longer hospital stays [65]. After kidney transplantation, adherence issues persists due to the higher pill burden, including immunosuppressive drugs and prophylactic antimicrobials [61].

A systematic review found wide variation in non-adherence rates to phosphate binders, with 22-74% of patients with ESKD not adhering to therapy, increasing the risk of uncontrolled hyperphosphatemia and cardiovascular effects [66]. Long-term serum phosphate levels > 6.5 mg/dL (2.10 mmol/L) increase the risk of death in HD patients due to soft tissue and vascular calcification [67]. On the other hand, ESAs are crucial for managing anaemia in ESKD, with the KDIGO guidelines recommending specific haemoglobin and haematocrit levels [3]. While facility-based HD patients receive ESA from dialysis nurses, home HD and PD patients self-administer ESAs subcutaneously, with adherence rates around 45% among PD patients [68]. Furthermore, non-adherent patients were shown to have lower average haematocrit levels [68].

1.5.3 Factors influencing medication adherence

Medication non-adherence in patients with ESKD is multifactorial, similar to other chronic diseases, and includes demographic, clinical, and psychosocial factors [64, 66]. Factors such as age, sex, health beliefs, motivation, depression, perceived treatment benefits, forgetfulness, education level, race, ethnicity, treatment cost, side effects, dosage frequency of medications, and socioeconomic status affect adherence [61]. The number of medications, pill burden, and administration burden also impact adherence to varying extents, alongside the demanding dialysis schedule. For instance, patients with difficulty swallowing struggle with

high pill burdens, while those with memory issues face medication administration challenges [52]. For some patients who face financial difficulties, the number of medications is the most crucial factor affecting adherence, even for motivated patients [52].

1.5.4 Role of healthcare providers

Healthcare providers play a crucial role in motivating patients to adhere to treatment. Interventions such as simplifying medication regimens, de-prescribing unnecessary medications, selecting drugs with fewer dosing frequencies and adverse effects, and assisting patients develop medication-taking cues can improve adherence and management in ESKD [61].

1.6 Rational for this thesis

Once an ESKD patient begins dialysis, the therapeutic goal shifts to focus primarily on treating complications such as anaemia and bone and mineral disease, which require lifestyle modifications and good medication adherence for effective management [47]. However, actual medication adherence is often poorer than perceived, largely due to the complexity of medication regimens among patients with ESKD. Hence, it is important for healthcare providers to recognise and address medication complexity to ensure that patients with ESKD receive the full benefits of their treatment.

There are significant limitations in the current evidence regarding the association between medication regimen complexity and patient-related and clinical outcomes among patients with ESKD. Firstly, there is a lack of consistency in the measurement of medication regimen complexity and a standardised definition of what constitutes a complex medication regimen. Many studies that utilise pill burden or number of

prescribed medications often overlook critical factors such as the dosing frequency, which can add to the administration burden for patients. The MRCI developed by George *et al.* is a widely used tool that provides an objective assessment of regimen complexity in patients [69]. With translated and validated versions for other languages, it is often considered the gold standard for assessing medication regimen complexity [70]. However, its applicability to all patient populations remains uncertain, and only a few studies have used the MRCI tool to assess regimen complexity in patients with ESKD.

Secondly, most evidence on the association between medication regimen complexity and outcomes is primarily focused on HD patients, thus failing to capture the comprehensive picture across different dialysis modalities. With the advent of patient-centred care in CKD management and considering that medication regimen is a modifiable determinant of health outcomes, it is essential to examine the link between medication-related factors and patient-centred outcomes such as HRQoL, medication adherence, and hospital admissions. These outcomes were selected because they are critical indicators and captures the overall well-being of patients with ESKD. HRQoL reflects the patients' perceived physical, mental, and social domains of health, medication adherence is an essential determinant of treatment success, and hospital admission rates are a key measure of patient stability and health system utilisation. Therefore, investigating medication regimen complexity in dialysis patients and understanding its variation across different dialysis modalities is the key to designing tailored interventions that ensure optimal medication use and ultimately improve patient-centred and clinical outcomes.

1.7 Aim

The overarching aim of this study is to compare medication regimen complexity in patients across different dialysis modalities including facility-based HD, home HD, and long-term PD, and understand the association between medication regimen complexity and patient-centred and other clinical outcomes.

1.8 Objectives

The specific objectives of the study include:

1. To quantify and compare the level of regimen complexity in people on different modalities of dialysis (facility-based HD, home HD, and PD).
2. To measure medication adherence (both self-reported and objective evidence, for example phosphate levels) in people on different dialysis modalities.
3. To examine the association between medication regimen complexity and patient-related and clinical outcomes including the incidence of hospitalisation over a 12-month period and HRQoL.
4. To compare the differences in patient-related and clinical outcomes across the two HD settings.
5. To compare differences in patient-related and clinical outcomes among PD patients based on their medication adherence.

1.9 Hypotheses

This research hypothesised that the medication regimen complexity will vary across dialysis modalities, each with varied clinical implications. It is also hypothesised that higher medication regimen complexity will lead to poorer health outcomes, such as lower quality of life, poor medication adherence, and a higher incidence of hospital admissions.

1.10 Structure of this thesis

Table 1. Structure of this thesis

Chapter	Description
1 Introduction	This chapter provides an overview of the current trends and burden of CKD and ESKD, treatment options for ESKD, and medication regimen complexity and adherence among patients with ESKD. It also presents the aim, objectives, and hypotheses of this study.
2 Medication regimen complexity and patient-centred outcomes in ESKD: A Systematic Review	This chapters offers a detailed review of the methods used in current literature to assess medication regimen complexity among adults with kidney failure, the associated patient-reported and clinical outcomes, and the effectiveness of interventions to address regimen complexity.
3 Methodology	This chapter explains the rationale for the methodologies used in this study.
4 The impact of medication regimen complexity on patient-related and clinical outcomes in patients undergoing haemodialysis	This chapter presents findings on medication regimen complexity among facility-based and home-based HD treated patients, its impact on patient-related and clinical outcomes, and a comparison of outcomes across these two HD settings.
5 Medication regimen complexity and patient-	This chapter presents findings on medication regimen complexity among patients undergoing PD, including

centred outcomes in patients undergoing peritoneal dialysis	patient-centred outcomes such as medication adherence and its determinants.
6 Discussion	This chapter discusses the research impact of the work from the perspective of clinical practice and kidney research. It concludes the thesis with remarks around the essential findings and recommendations for future research directions.

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Chapter 2:

Medication regimen complexity and patient-centred outcomes in ESKD: A Systematic Review

In this chapter, a detailed review of the methods used in existing literature to assess medication regimen complexity amongst adults with kidney failure, the associated patient-reported and clinical outcomes, as well as the effectiveness of interventions to address regimen complexity are presented.

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I researched and systematically reviewed the literature, wrote the drafts of the manuscript, and currently managing the journal submission process. Associate Professor Ronald L Castelino, Dr Wubshet Tesfaye and I conceived the study design. All authors were involved in critical editing and revision of the manuscript.

Abstract

Introduction: Kidney failure is a life-limiting condition that profoundly impacts an individual's quality of life. The significant medication burden on patients required to manage the comorbidities and complications of kidney failure can have implications for patient-reported and clinical outcomes.

Areas covered: This work systematically reviewed methods used to assess medication regimen complexity amongst adults with kidney failure, the associated patient-reported and clinical outcomes, and the effectiveness of interventions to address regimen complexity. A comprehensive search of PubMed, Embase, Web of Science, and Scopus covering all relevant literature up until November 2023 was performed.

Expert opinion: The findings of this review suggest that patients with kidney failure are prescribed complex medication regimens, which have implications for both clinical and patient-related outcomes. A significant link was found between regimen complexity and poor health outcomes, particularly in the dialysis-dependent patient population. These outcomes included poor quality of life, medication non-adherence, frailty, hospitalisation, and mortality. Interventions to improve medication regimen complexity included de-prescribing tools and pharmacist-led medication management services. Future research should consider well-designed prospective longitudinal studies that develop more comprehensive and standardised definitions of medication regimen complexity. Additionally, multifaceted interventions are needed to address the complex medication regimen to improve outcomes in patients with kidney failure.

Keywords**:** dialysis; interventions; kidney failure; medication regimen complexity; medication burden; transplant

Article highlights

- Patients with kidney failure have a high medication burden and are prescribed complex medication regimens that have implications on both clinical and patient-related outcomes, highlighting the need for a tailored approach to address it.
- There was a significant heterogeneity in the measures and definitions of medication regimen complexity, as well as the tools used to assess it, making it challenging to compare results across studies.
- There was a significant link found between medication regimen complexity and poor health outcomes, particularly in the dialysis-dependent patient population.
- These outcomes included poor quality of life, poor medication adherence and attendance at haemodialysis sessions, as well as higher prevalence of depression, interdialytic weight gain, serum phosphate levels, frailty, malnutrition, fall episodes, hospitalisation, and mortality.
- De-prescribing tools and pharmacist-led medication management services were among the interventions implemented to improve medication regimen complexity associated with positive outcomes.
- Future research should consider well-designed prospective longitudinal studies that develop comprehensive and standardised definitions of medication regimen complexity. Additionally, multifaceted interventions are needed to address the high medication burden and medication regimen complexity to improve outcomes in patients with kidney failure.

1. Introduction

Chronic kidney disease (CKD) has emerged as one of the leading causes of mortality that affects approximately 10% of the population worldwide [1]. The 2021 Global Burden of Disease study highlighted that diabetes and kidney disease are closely associated and pose rising threats to public health all over the world [2]. Of note, CKD was projected to be the 5th leading cause of years of life lost globally by 2040 [3].

As CKD progresses to kidney failure, patients require kidney replacement treatment (KRT) such as dialysis and/or kidney transplantation to sustain life. While a kidney transplantation is associated with improved outcomes and more freedom [4, 5], the average wait for a donor kidney in Australia is 2-3 years [6]. During this time patients need to commence on dialysis which is repetitive and intrusive that requires patients to undertake several major lifestyle adaptations as well as adhere to rigid and complex treatment schedules [7]. In addition, exposure to a complex medication regimen seems inevitable as patients with kidney failure (including kidney transplant recipients) invariably require multiple medications to correct or manage the ensuing metabolic disturbances and complications of uraemia, as well as their coexisting comorbid conditions [8, 9]. Whilst medication regimen complexity is recognised as a major challenge among patients with kidney failure, the frequent changes in medications and their doses adds further complexities in this patient group [10, 11]. This undoubtedly increases the risk of polypharmacy and high pill burden among this patient population. With a mean burden of 8.2 pills per day before kidney transplantation increasing to 18.0 pills per day immediately after transplantation, this cohort has one of the highest pill burden as compared to patients with other chronic illnesses [9]. Consequently, these complex medication regimens predispose patients to high risk of medication-related problems including adverse drug events and non-adherence, resulting in suboptimal treatment outcomes [12, 13]. Even

after successful kidney transplantation, polypharmacy remains an issue that negatively impacts the quality of life of these patients [14].

However, to date, published literature on patients with dialysis-dependent kidney failure has not provided clear and consistent definition of medication regimen complexity, and has not thoroughly examined the association between medication regimen complexity and outcomes. There is neither a standardised definition of medication complexity in patients with kidney failure, nor a comprehensive review of literature summarising the complexity of medication regimen in this patient group and its effect on outcomes. Further, there has been no review of interventions for improving medication regimen complexity. Therefore, this systematic review aims to:

i. identify and summarise various methods used to assess medication regimen complexity in patients with kidney failure;
ii. understand the association between medication regimen complexity and patient-reported and other clinical outcomes in patients with kidney failure; and
iii. explore any interventions implemented to optimise medications by improving medication regimen complexity parameters in patients with kidney failure and the outcomes associated with these interventions.

2. Methods

2.1 Design and study selection

This systematic review was registered in PROSPERO (CRD42024532986) and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [15]. The PRISMA checklist is supplied in Appendix S1. Articles were evaluated for inclusion by an independent reviewer, and later checked by two reviewers. Any uncertainties or disagreements between reviewers were resolved

through discussion. A web-based collaboration software platform – Covidence was used for the management of the removal of duplicate articles and screening of search outputs [16].

2.2 Eligibility criteria

Studies were included if they fulfilled the following inclusion criteria:

(1) conducted in patients with kidney failure ≥ 18 years of age, undergoing dialysis or having undergone kidney transplantation, and included measure(s) of medication regimen complexity;

(2) a definition of the medication regimen complexity measure was provided, the extent of the complexity was reported, and patient-related and clinical outcomes were related with medication regimen complexity;

(3) interventional studies to address or improve medication regimen complexity that presented outcome(s) associated with the intervention.

Studies were excluded when:

(1) they included patients who opted out of dialysis and were on a kidney supportive care pathway;

(2) medication regimen complexity could not be determined or was limited to one class of medication;

(3) they did not relate medication regimen complexity to patient-centred outcomes; or

(4) they were reviews articles, editorials, letters to the editor, commentaries, case-reports, or case studies.

2.3 Search strategy and sources

Embase, Web of Science, PubMed/Medline and Scopus were searched for peer-reviewed articles published in English until November 2023. The search was undertaken using the combinations of Medical Subject Heading (MeSH) terms and truncated keywords like “kidney failure/end-stage kidney disease”, “dialysis”, “kidney transplant”, “medication regimen complexity”, “polypharmacy”, and “pill/drug burden”. Details of the initial search strategy are provided in Appendix S2. A manual search of the references cited in the publications from the electronic database search was also conducted to identify additional relevant articles. After de-duplication, the titles and abstracts were screened to identify potentially relevant studies based on the predefined inclusion and exclusion criteria. The full articles of the selected abstracts were then screened to confirm their eligibility for inclusion in the review.

2.4 Data extraction and analysis

Data from the included studies were extracted by an independent reviewer followed by verification by the second reviewer. Information extracted included the name of authors, year of publication, country of study, study design, patient treatment modality, number of patients, age, medication regimen complexity measure, patient-reported outcomes associated with medication regimen complexity, as well as interventions to address medication regimen complexity and its associated outcome(s). The following outcomes were considered: all-cause mortality, hospitalisation, quality of life (QoL), medication adherence and frailty. Since the identified studies were of heterogenous nature, data analysis involved a descriptive summary of included studies. The data extraction template and collected data are provided in Appendix S3.

2.5 Quality assessment

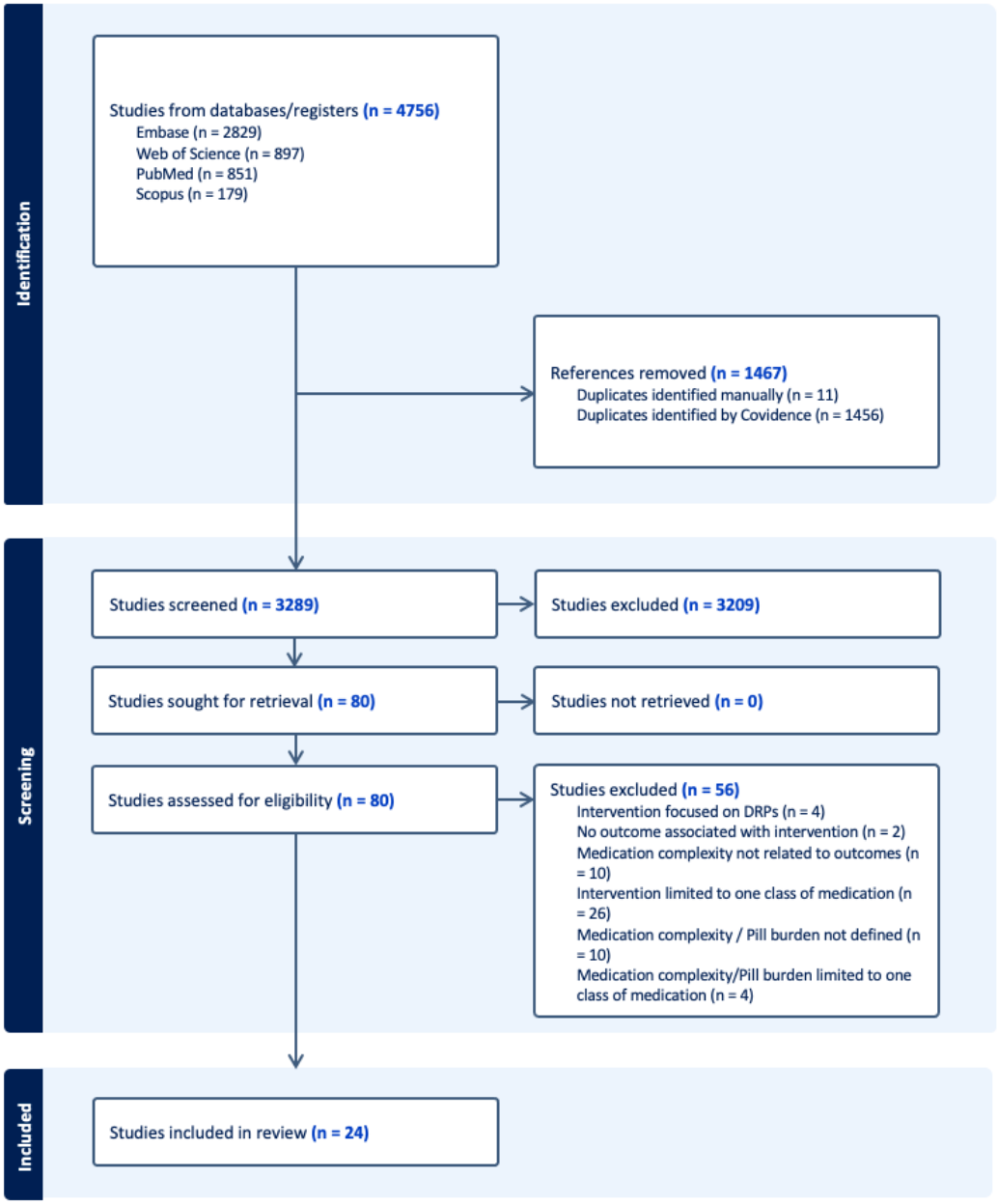
Eligible studies were assessed for methodological quality using the Joanna Briggs Institute's (JBI) critical appraisal tool for cross sectional studies, cohort studies, prevalence studies, and quasi-experimental studies (see Appendix S4) [17]. These included items of study design (inclusion criteria, study setting and exposure measurement method), statistical analysis (calculation of sample size and adjustment for potential confounding factors) and results (losses to follow up) relevant to the study type.

3. Results

3.1 Study selection

Overall, 3289 potentially relevant articles were screened, and 80 articles were reviewed in full-text. Of these, 24 studies were included in this systematic review based on the pre-defined inclusion/exclusion criteria (Figure 1).

Figure 1. PRISMA flowchart of study selection.



Abbreviation: DRP, drug-related problem

3.2 Description of included studies

There were 21 studies [8, 14, 18-36] that reported the association between the various indicators of medication regimen complexity and patient-reported outcomes - addressing objectives 1 and 2 of this systematic review, whilst the other three studies [37-39] implemented interventions to address or improve medication regimen complexity and

associated outcomes - addressing objective 3 of this systematic review. The characteristics of the included studies are summarised in Appendix S3.

More than half of the included studies (*n* = 14) were cross-sectional in design [8, 14, 18, 22-26, 29-31, 33-35], four were cohort studies [19-21, 27], another four were non-experimental studies [32, 37-39], and the other two were prevalence studies [28, 36]. The studies were conducted in 15 different countries, predominantly in Asia (*n* = 11) [18-20, 23, 24, 27-30, 37, 38], five in Europe [8, 14, 22, 34, 35], five in North America [21, 31, 32, 36, 39], two in South America [25, 26], and one study was performed in Australia [33].

The sample size varied from a minimum of 35 participants [32, 39] to a maximum of 1,238 participants [35]. Over half (*n* = 18) of the included studies had a sample size of more than 100 participants [8, 14, 18-28, 30, 31, 34, 35, 37]. Moreover, the study with the greatest number of participants was carried out across 54 haemodialysis (HD) centres in Italy [35]. Of the studies on medication regimen complexity and its associated outcomes, nearly all the studies were conducted in patients receiving HD and/or peritoneal dialysis treatment [8, 18-23, 25-27, 29-35], whilst only four studies focused on patients who had undergone kidney transplantation [14, 24, 28, 36]. On the other hand, the interventional studies to address medication complexity were all carried out among patients receiving HD treatment [37-39].

3.3 Assessment of medication regimen complexity

There was a wide variation in the definitions used to assess medication regimen complexity measures. During our analysis, we found the two most commonly used assessment methods are pill burden (*n* = 12) [19, 22, 23, 28-36] and number of medications (*n* = 9) [8, 14, 19-21, 24, 25, 31, 32]. Three studies utilised the medication

regimen complexity index (MRCI) [32-34], two studies determined the prevalence of polypharmacy [26, 27], and the remaining studies used the therapeutic complexity index (TCI) [26], treatment burden questionnaire (TBQ) [18], perceived burden of oral therapy [35] and medication administration burden [32] to determine medication regimen complexity. Although most studies included all drug formulations (i.e. tablets, capsules, injections, inhalations, etc.) in the assessment of medication complexity, several studies only included oral medications in the assessment [28, 30, 34, 35]. Furthermore, seven studies applied two or more assessment methods to determine medication regimen complexity [19, 26, 31-35].

3.4 Clinical and patient-reported outcomes associated with medication regimen complexity

Eight studies reported QoL assessed using validated questionnaires: 12-Item Short Form Health Survey (SF-12) [8], 36-Item Short Form Health Survey (SF-36) [18, 25, 26, 31, 32] or Kidney Disease Quality of Life (KDQOL-36) Instrument [14, 22]. Most studies concluded that higher medication regimen complexity was associated with lower scores on the various components of the QoL surveys among both dialysis-dependent patients [8, 18, 25, 31] and kidney transplant recipients [14]. Patients' self-rated health assessed by the EuroQoL-5D-5L (EQ-5D-5L) utility score was also reported to be 1.5 points lower for each additional medication. Additionally, a greater dialysis symptoms burden was observed with a higher number of medications [8]. On the contrary, Alikari et al. [22] found a positive correlation between the number of pills with well-being and interpersonal dimensions of QoL, while Cardone et al. [32] and Alves et al. [26] reported no correlation between the medication regimen complexity measures and QoL in patients undergoing HD.

The second most reported outcome was medication adherence based on different self-reported measures: 4-item Morisky Medication-Taking Adherence Scale (MMAS-4) [26, 28, 33, 35], 8-item Morisky Medication-Taking Adherence Scale (MMAS-8) [34], Brief Medication Questionnaire (BMQ) [26], or GR-Simplified Medication Adherence Questionnaire – Haemodialysis (GR-SMAQ-HD) [22]. Interestingly, three out of six studies highlighted no association between regimen complexity and self-reported adherence to medications [28, 33, 34], while two studies reported that a higher pill burden was associated with poorer medication adherence [22, 35], and one study found a slight association between complexity of medications and adherence to pharmacotherapy [26]. Furthermore, Chiu et al. investigated adherence specifically to phosphate binders based on objective measure (pill count) and found a significant inverse relationship between adherence to phosphate binders and pill burden from phosphate binders [31].

Ten studies on patients with kidney failure undergoing dialysis reported the association between polypharmacy or regimen complexity and a range of patient-reported and clinical outcomes like higher perceived treatment burden [23], prevalence of depression [25], interdialytic weight gain [29, 30], serum phosphate levels [31, 33], frailty [19, 21], malnutrition and fall episodes [19], hospitalisation [19, 27], mortality [19, 20], and poor attendance at HD sessions [22]. Nevertheless, there was one study that found no correlation between polypharmacy and all-cause mortality at admission or discharge [27], and another that found no significant relationship between pill burden with thirst and xerostomia [29]. One study conducted among kidney transplant recipients found that a higher pre-transplantation pill burden was associated with poorer kidney function after transplantation [36]. Moreover, hyperpolypharmacy (use of $\geq$ 10 medications) was also associated with frailty in this cohort of patients [24].

3.5 Interventions to address or improve medication regimen complexity and its associated outcomes

Among the three studies that presented outcomes associated with the interventions targeting medication regimen complexity, two implemented de-prescribing tools for patients undergoing HD [37, 39] and one carried out a Geriatric Medication Management Service (MMS) [38]. The de-prescribing tool developed by McIntyre et al. [39] was specifically designed for use in an outpatient HD population which targeted five classes of medications – quinine, diuretics, α_1-blockers, proton pump inhibitors (PPIs), and HMG-CoA reductase inhibitors (statins). After four weeks, 31 of 40 (78%) target medications were successfully deprescribed in 35 patients, and six months after deprescription, only 5 of 31 (16%) medications discontinued were represcribed. At the end of the study, over half (57%) of patients were taking fewer medications than at baseline, and no adverse events were observed [39]. On the other hand, the active de-prescription program specific for HD patients formulated and implemented by George et al. [37] successfully reduced the number of medications from 11 (IQR 8–13.25) to 8 (IQR 6–9) ($p < 0.001$) and the number of pills from 16 (IQR 12.75–21.25) to 11 (IQR 8–14.25) ($p < 0.001$) among patients undergoing HD. The study also assessed pill burden using Living with Medication Questionnaire-Visual Analogue Scale whereby the score reduced from 7 (IQR 5–8) to 4 (IQR 3–5) ($p < 0.001$) after de-prescription. Furthermore, a significant improvement in drug adherence after deprescription was seen via the Modified Medication Adherence Rating Scale (MARS) score increasing from 7 (IQR 5–9) to 8 (IQR 7–9), ($p = 0.02$) [37].

Under the Geriatric MMS program implemented by Kim et al. [38], pharmacists evaluated drug-related issues, including medication adherence, effectiveness of medications, current or past adverse drug reactions, drug–drug interactions, patient dependency on medications, and the necessity for de-prescribing among elderly patients

with CKD, including patients on HD on a weekly basis. After providing Geriatric MMS, the total number of medications decreased from 13.5 ± 4.3 to 10.9 ± 3.8 ($p < 0.001$), and the proportion of patients with excessive polypharmacy (use of ≥ 10 medications) reduced from 85.1% to 59.8% ($p < 0.001$). The study also examined outcomes in terms of the number of potentially inappropriate medications (PIMs) per patient, which decreased from 1.6 ± 1.4 to 1.0 ± 1.2 ($p < 0.001$), while the proportion of patients who used at least one PIM and three or more PIMs significantly decreased from 77.0% to 59.8% and 23.0% to 10.3%, respectively ($p < 0.001$). Additionally, the anticholinergic burden score, determined using the Korean Anticholinergic Burden Scale (KABS), decreased from 2.7 ± 2.6 at baseline to 1.8 ± 2.2 after providing Geriatric MMS ($p < 0.001$) [38].

3.6 Study quality

Based on the JBI critical appraisal tool, all studies had medication regimen complexity measured in a valid and reliable way, and clear characteristics of participants' treatment modality. Seventeen out of 18 (94%) of the cross sectional and cohort studies had confounding factors identified, out of which 16 (89%) articles presented strategies to deal with the confounding factors. The majority (23/24; 96%) of the studies had a statistical plan with appropriate statistical analysis used. Nonetheless, two studies did not clearly define the sample inclusion criteria [14, 26], and one did not describe the study setting in detail [14]. The sample sizes of both the prevalence studies were unclear as sample size calculation and analysis were not conducted [28, 36]. The three quasi-experimental studies included also had no control group [37-39].

4. Discussion

This is the first comprehensive systematic review to summarise the various methods used to assess medication regimen complexity in patients with kidney failure, and its

associated patient-reported and other clinical outcomes. The present review summarised findings from 24 studies over a period of one and a half decades, with most of the studies conducted within the past five years, indicating a growing concern of medication regimen complexity in kidney research. This review is unique in including studies conducted among patients on dialysis and those who have undergone kidney transplantation, as medication regimen complexity seems to remain an ongoing issue before and after kidney transplantation. In addition, this review included studies with diverse patient-reported and clinical outcomes associated with medication regimen complexity in patients with kidney failure. A previous work on a similar topic included a smaller number of studies (*n* = 10) and was limited to studies that involved dialysis-dependent patients with kidney failure [40].

Assessment of Medication Regimen Complexity

Given the absence of a unified standardised approach to define medication regimen complexity, the current review observed several methods that were used to measure medication regimen complexity in patients with kidney failure. While only 4 studies utilised calculation tools to evaluate the complexity [26, 32-34], discrepancies in the definitions were observed among studies that used pill burden [19, 22, 23, 28-36] and number of medications [8, 14, 19-21, 24, 25, 31, 32]. Pill burden was mostly defined as the total number of pills, including tablets, capsules, injections, inhalations, topical formulations, etc. that the patients were prescribed to take daily or weekly, excluding medications prescribed on an as-needed basis [23, 32, 33, 36]. However, in some studies, only orally administered medications were included in the pill burden count [28, 30]. The number of medications refers to the count of different prescribed medications self-administered by the patients [8, 14, 19-21, 24, 25, 31, 32]. The use of 5 or more medications per day is commonly considered as polypharmacy [8, 19, 26], whilst hyperpolypharmacy often refers to the use of 10 or more medications in a day [19, 24].

MRCI is a 65-item tool developed by George et al. to assess medication complexity based on a weighted scoring system by considering three different components: (i) dosage form, (ii) dosing frequency and (iii) additional directions concerning administration [41]. As the total score increases in line with the increase in regimen complexity, there is no established maximum MRCI score. Similarly, the TCI assessment method utilised by Alves et al. also included measurements of the number of medications, frequency, and type of actions required for self-administration [26]. On the other hand, while the TBQ was designed to capture a more holistic treatment burden that incorporates five dimensions (medication burden, administrative burden, financial burden, lifestyle change burden, and social burden) [18], the perceived burden of oral therapy questionnaire focused on the extent of patients being bothered by their medication regimen in terms of the number, size, frequency and adverse effects of the pills prescribed [35]. Additionally, Cardone et al. defined medication administration burden as the number of administrations per day required for a prescribed drug regimen [32].

Owing to these inconsistent definitions, a variation in the reported complexity measures were observed and this variation highlights the importance of having a consensus on standard definitions to better assess medication regimen complexity. Medication complexity measures such as pill burden and medication count that focus primarily on the quantity of pills or medications may neglect other critical factors such as the dosing frequencies of medications. Complexity measures such as MRCI and TCI would evaluate a medication regimen more thoroughly by taking into account not only the number of medications, but also various other aspects including the dosage forms, dosing frequencies, and special instructions of the medications. Nevertheless, the calculations of these scores can be time-consuming and may require additional training for clinicians to accurately interpret the complexity, creating a challenge for implementation in clinical

practice. Furthermore, these complexity measures often do not consider individual patient factors such as health literacy and cognitive function, as well as the financial burden associated with the medications which are important factors that can affect medication management. Hence, more studies are needed to fill the knowledge gap of identifying more practical, accurate and comprehensive tools to assess medication regimen complexity.

Results from studies of this review showed that the pill burden ranged from a mean of 9.7 to 19.7 among patients undergoing HD [30, 33], and a median range of 15 to 17 before kidney transplantation and 14 to 16 one year after transplantation [28, 36]. Only one study from Hong Kong reported a mean pill burden of 15.5 ± 8.5 among patients undergoing PD [19]. On the other hand, the mean number of medications prescribed ranged from a mean of 10 to 12.2 medications per day among HD patients [21, 32], which is higher than that of kidney transplanted patients prescribed with 6.6 to 9.4 medications each day [14, 24] and patients undergoing PD with an average of 7.5 ± 2.6 medications daily [19]. These findings of pill burden and number of medications prescribed in patients with kidney failure were found to be higher than those of patients with other chronic illnesses such as HIV (4.3 to 8 medications and 8 pills daily) [42, 43], asthma (7.8 ± 0.1 medications/day) [44] and psychiatric illnesses (4.5 ± 2.7 medications/day) [45]. Based on the MRCI scores ranging from 20.5 in pre-dialytic kidney failure patients and up to 28.3 in patients undergoing HD, patients with kidney failure were shown to have more complex sets of medications compared to patients with diabetes, HIV, COPD and psychiatric disorders (MRCI range 6.9 – 16.0) [46-49]. Several factors including gender, comorbidity, BMI and kidney function were identified from the included studies, which were associated with medication burden or regimen complexity [14, 34].

Outcomes Associated with Medication Regimen Complexity

In addition to dietary restrictions and significant lifestyle modifications, the need for multiple medications and frequent medication doses can overwhelm patients with kidney failure, creating a burden for patients to adhere and a challenge for clinicians to optimise their treatment regimens [50]. As identified in our review, there is a significant link between medication regimen complexity and poor health outcomes, particularly in the dialysis-dependent patient population. These outcomes included poor QoL, medication adherence and attendance at HD sessions, as well as higher prevalence of depression, interdialytic weight gain, serum phosphate levels, frailty, malnutrition and fall episodes, hospitalisation and mortality [8, 18-22, 25-27, 29-31, 33, 35]. Although fewer studies were conducted among patients who had undergone kidney transplantation and one study presented conflicting results [28], medication regimen complexity was similarly associated with poorer QoL, frailty, and increased serum creatinine in this patient population [14, 24, 28, 36], suggesting medication regimen complexity remains as an ongoing issue before and after kidney transplantation. The findings of this review were also consistent with previous studies conducted among patients with heart failure, whereby medication regimen complexity led to adverse outcomes such as rehospitalisation, lower medication adherence, and poor QoL [51].

Several health outcomes resulting from medication regimen complexity were often found to be interlinked. As an example, the complex medication regimen that led to impaired medication (phosphate binder) adherence could result in uncontrolled serum phosphate levels [31]. In turn, physicians may respond by prescribing additional number of phosphate binders, increasing the pill burden to compensate for the non-adherence [31], while medication non-adherence was also found to be associated with poor QoL and mortality [22, 50]. Patients who were prescribed a greater number of medications and had

high pill burden were found to have significantly higher perceived treatment burden [23], in which higher treatment burden was also strongly correlated with lower QoL [18]. Although previous literature reported better health outcomes such as QoL and survival when comparing patients receiving PD or kidney transplant receipts versus patients receiving HD in general [4, 5, 52, 53], it is unclear if the variation in medication regimen complexity among these subgroups of patients on different treatment modalities have an implication on patient-centred outcomes.

Most studies had strengths of medication regimen complexity measured in a valid and reliable way, clear characteristics of participants' treatment modality, confounding factors identified and adjusted, as well as appropriate statistical analysis used to determine the association of medication complexity and its outcomes. However, several studies had limitation around defining the types of medication included in the respective measures of medication regimen complexity [14, 21, 22, 24, 25, 27, 29]. Additionally, most of the available evidence on association between medication regimen complexity and outcomes are largely based on cross-sectional data. Patients with kidney failure often have their treatment regimen adjusted to manage multiple comorbidities and dynamic changes in their health status. Hence, measuring medication regimen complexity at a single timepoint may not fully capture the complexity and potentially lead to an over- or under-estimation of medication regimen complexity, limiting the conclusions drawn with the associated outcomes. Therefore, further research utilising longitudinal study design is needed to provide more conclusive evidence on the association between medication regimen complexity and its outcomes, as well as potentially investigating how and which medications and medication-related factors affect outcomes.

Interventions Targeting Medication Regimen Complexity

Three studies investigated the effectiveness of interventions in addressing or improving medication regimen complexity among patients with kidney failure, either directly by using de-prescribing tools or as part of a wider strategy through MMS, as detailed in Appendix S3, Table S3. There was one study that also carried out de-prescribing [54], while another implemented medication review clinic led by pharmacists [55] to improve medication regimen complexity among HD patients. However, these studies were excluded as there were no outcomes presented with the interventions. Our findings indicated that an interprofessional collaborative approach involving health workers such as nurses, pharmacists and nephrologist can improve overall medication burden, which subsequently lead to reduction of the number of PIMs and improvement of anticholinergic burden particularly patients with kidney failure in the geriatric population. De-prescribing implementation, in general, had been shown to improve health outcomes across different settings and patient populations [56]. Specific de-prescribing tool formulated for patients with kidney failure, although at single centres in existing literatures, is an important initial step to address medication regimen complexity in kidney research [37, 39]. Moreover, the medication management service conducted by Kim at el. had shown that the role of pharmacists in evaluating drug-related issues is crucial to improve medication regimen complexity in kidney failure [38]. Nevertheless, the most common potential sources of biases among these studies were that the outcomes of interventions were not compared with a control group. Hence, this warrants future research to consider this limitation as well as to recruit larger sample sizes involving multiple study centres to allow extrapolation of the results to other dialysis units or transplant clinics. Further studies are also needed to explore interventions in kidney transplant setting and on long-term outcomes.

Study Limitations

Whilst this systematic review provides comprehensive evidence on medication regimen complexity in adults with kidney failure across different treatment modalities, the work has several limitations. The findings from this review should be interpreted with caution due to the difference in quality among the studies included, as well as the majority of the reviewed studies were cross-sectional in design, hence limiting the suitability for assessing medication regimen complexity. We only presented evidence on medication regimen complexity in adults with kidney failure; thus, the findings may not be generalisable to paediatric or adolescent population. In addition, we did not assess the impact of complexities of dialysis regimens (that are especially relevant to patients on home dialysis) on patient-related or clinical outcomes. The inclusion of only studies published in English may have led to missing studies from non-English literature.

5. Conclusion

The evidence from this review suggests that patients with kidney failure are prescribed with complex medication regimens, which can have implications for both clinical and patient-reported outcomes. Adverse health outcomes including poor QoL and impaired medication adherence have been linked to medication regimen complexity in both dialysis-dependent patients and kidney transplant recipients. Although only less than a handful of studies were conducted to assess the outcomes associated with the intervention to address medication regimen complexity, the promising results should serve as reference for future studies and implementation in practice involving collaboration of all healthcare professionals. The findings also emphasise the need for further research to identify more comprehensive tool to standardise the assessment of medication regimen complexity, which would be able to assist in specific interventions targeted to improve patient and clinical outcomes.

6. Expert opinion

The advances in understanding kidney disease, its complications, and the ensuing increase in pharmacotherapy armamentarium have led to longer life expectancy among patients with kidney failure in recent decades. Nevertheless, this systematic review has found that the resultant exposure to polypharmacy and complex medication regimens that may seem unavoidable for patients with kidney failure, is associated with various medication-related problems and undesirable clinical and patient-reported outcomes. Nevertheless, as our review has indicated, structured de-prescribing interventions still have a role in mitigating this issue, that can result in improvement in patient-reported and clinical outcomes. Many of the studies included in this review were published in the last five years, indicating medication regimen complexity is a growing concern in kidney research. It is important to note that despite the rising prevalence of kidney failure worldwide, most of the studies looking into medication regimen complexity among patients with kidney failure as well as interventional studies to address complexity with associated outcomes were largely limited to patients undergoing HD. In fact, our literature review shows that despite kidney transplantation, medication regimen complexity remains an ongoing issue for patients and is associated with negative consequences. It is therefore important for more studies to be conducted to address medication regimen complexity tailored to kidney transplanted patients given that this highly vulnerable cohort of patients are still marginally studied despite the number of medications including immunosuppressants they are prescribed.

Moreover, it would be interesting to conduct a longitudinal prospective study to examine the impact of medication regimen complexity on patient-reported and clinical outcomes across patients undergoing different dialysis modalities as well as kidney transplant recipients recruited from multiple dialysis and transplant centres. This prospective study

would address the limitation of measuring medication regimen complexity at a single time point and account for the frequent adjustment of treatment regimens in managing the multiple comorbidities and dynamic changes in health status of this patient population. While the complexity associated with dialysis treatment regimen is an important factor that can affect patient outcomes, we have decided to only include studies examining the complexity of the medication aspect as the assessment of kidney replacement treatment complexities including dialysis regimen is beyond the scope of our study.

Meanwhile practice-wise, one of the major weaknesses in the current evidence base is the lack of consistent reporting of medication regimen complexity assessment measures. Therefore, given the drawbacks of the existing methods, we strongly advocate the development and use of a standardised and practical assessment method of medication regimen complexity specifically in this patient population, thereby allowing future interventions to target specific aspects of medication regimens that are associated with negative health outcomes. In our opinion, the understanding and identification of these specific factors can lead to the development of more effective and patient-centred medication management strategies. These strategies may be incorporated into future recommendations within the next five to ten years, providing healthcare providers with higher quality and more conclusive evidence-based guidance than currently available. Additionally, despite the implementation of several interventional approaches led by different healthcare professionals such as nurses, pharmacists, and nephrologists to mitigate inappropriate polypharmacy, there is limited evidence on the clinical relevance of improving regimen complexity for better health outcomes, highlighting a research gap that also needs to be explored in future studies.

Statements and Declarations

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The authors declare that they have no relevant financial interests.

Competing interests

KS is on the Fresenius Medical Advisory Board for Australia and New Zealand and has received speaker's honoraria from Baxter Healthcare, Roche and Fresenius Medical Care.

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Chapter 3:

Methodology

This chapter provides an overview of the study design and patient cohort. It explains the rationale behind each method used to assess medication regimen complexity and details the approaches employed to evaluate patient-related and clinical outcomes.

The study is summarised below in **Figure 1**.

145 haemodialysis & 131 peritoneal dialysis patients at Blacktown Hospital

Medication-related factors (medication count & complexity)	Self-reported & clinical outcomes via interviews & eMR	Medication adherence, HRQoL & incidence of hospitalisation(s)

Figure 1. Overview of study methodology

3.1 Study design and patient cohort

This research is structured into two sub-studies based on patients' dialysis treatment modalities: HD and PD. The studies include both prospective and retrospective components. The prospective component assesses the relationship between medication-related factors (such as medication count and regimen complexity) and self-reported and clinical outcomes (including medication adherence, HRQoL and random serum phosphate levels). The retrospective component determines the incidence of hospitalisation and the number of hospital admissions in the preceding 12 months, using self-report and electronic medical records (eMR).

All the patients undergoing dialysis at Blacktown Regional Dialysis Centre in New South Wales, Australia were approached to participate in the study. Patients who were temporarily undergoing HD, those receiving only kidney-supportive or end of life care, and those with language barriers or cognitive impairment were excluded from the studies. Interested participants, upon receiving consent, were provided with the Participant Information Sheet (**Appendix B**) before inclusion in the study. Patients undergoing home therapies (home HD and PD) were interviewed via phone or during their follow-up appointments at the dialysis centre. A total of 145 HD and 131 PD patients were recruited for the respective studies. This study was approved by the Western Sydney Local Health District (WSLHD) Human Research Ethics Committee (2019/PID03039) (See **Appendix B** for the Ethics Approval Letter).

3.2 Variable measures

3.2.1 Medication regimen complexity index (MRCI)

The MRCI is a validated 65-item tool developed by George et al. [1] in Australia to evaluate the complexity of a patient's medication regimen. Initially used in patients with COPD, the MRCI has since been translated and validated for use in other languages and various chronic conditions [1-6]. Previous studies in CKD and ESKD have also utilised the MRCI to determine medication regimen complexity [7-10]. The tool requires approximately 2-8 minutes to assess a regimen, and the complexity is calculated based on factors such as the number of medications, dosage forms, dosing frequencies, and additional instructions related to the medications [1]. The total score is the sum of the three individual sections: (A) dosage form; (B) dosing frequency; and (C) additional directions related to the medication. There is no established maximum score; a higher total score indicates a more complex medication regimen. **Table 1** provides details of

each subsection and an example of the MRCI calculation. See **Appendix B** for the full version of the MRCI tool adapted from the original article [1].

Table 1. Details of MRCI subsections and example of the MRCI calculation

Subsection	Explanation
Subsection A: Dosage form	Tablets / capsules administered orally have the lowest weighting of 1 point as they are the simplest to administer correctly. The weighting increases for medications administered via other routes or with devices, such as nasal spray (2 points), eye drops (3 points), MDI (4 points), and injections (3 or 4 points depending on injection type). Each dosage form contributes only once to the weighting calculation.
Subsection B: Dosing frequency	Medications taken multiple times a day contribute additional points for each medication. A dosing frequency of 'as needed' has a base weighting of 0.5 points, increasing to 1 point for once daily, 2 points for twice daily, etc. Medications with specifically timed doses (e.g., every 8 hours) are scored higher than those administered without specific timings (e.g., three times daily), with scores of 3.5 and 3 points respectively.
Subsection C: Additional directions	Special instructions, such as breaking or crushing the tablet (1 point), dissolving the tablet or powder (1 point), or tapering / increasing / alternating doses (2 points), also contribute additional points to the complexity score.

Total score	Each medication's score is determined by summing of the subsections (A+B+C). The total MRCI score for a medication regimen is the sum of scores for all medications in the regimen.

Calculation example:

	Subsection			Total
Medication regimen	**A**	**B**	**C**	
Calcitriol 2 capsules daily	1	1	1[b]	3
Esomeprazole 1 tablet twice daily	0[a]	2	0	2
Furosemide 2 tablets in the morning	0[a]	1	2[c]	3
Levothyroxine 1 tablet in the morning on non-dialysis days	0[a]	1	3[d]	4
Sevelamer 2 tablets twice daily with meals	0[a]	2	2[e]	4
Darbepoetin alfa 60mcg subcutaneous injection every 3 weeks	3	2	0	5
MRCI total				**21**

Abbreviation: MDI, metered dose inhaler; MRCI, medication regimen complexity index

[a]No additional points are added for the subsequent medications as tablets/capsules.

[b]Additional point assigned for 'multiple units at one time'.

[c]Additional points assigned for 'multiple units at one time' and 'take/use at specific time/s'.

[d]Additional points assigned for 'take/use at specific time/s' and 'alternating dose'.

[e]Additional points assigned for 'multiple units at one time' and 'relation to food'.

3.2.2 Pill burden, medication count, and polypharmacy

Pill burden refers to the number of pills a patient takes on a regular basis. Both pill burden and the number of prescribed medications have been widely used as key indicators for assessing medication regimen complexity among patients with various chronic conditions, including CVD, diabetes, HIV, and liver disease [12-17]. Studies have linked higher pill burden or number of prescribed medications to poorer outcomes such as lower medication adherence, reduced QoL, increased hospitalisations, and a higher perceived burden of disease [12, 13, 15, 17, 18]. Pill burden and medication count are also associated with polypharmacy. Although definitions vary, a systematic review identified the use of five or more medications as the most common definition of polypharmacy [19].

As identified in the systematic review in Chapter 2 of this thesis, pill burden and number of medications were the most utilised methods to assess medication regimen complexity and associated outcomes among patients with ESKD. Although these methods do not account for other important aspects of a medication regimen, such as dosing schedules or administration requirements that contribute to complexity, they were employed in this research due to their ease of implementation and to facilitate comparison of findings across other studies.

3.3 Outcome measures

3.3.1 Medication adherence

Medication adherence was evaluated via both subjective and objective measures in this research. Self-reported medication adherence was evaluated using the 4-item Morisky-Green-Levine Scale (MGLS), initially developed to determine

medication adherence among adults with hypertension [20]. This tool has subsequently been validated and widely used in diverse patient populations with various chronic conditions, making it a common choice in clinical practice and research [21-24]. The 4-item MGLS was selected for this research due to its simplicity and ease of use. It consists of four questions with dichotomous (yes/no) response options: *Do you ever forget to take your medicine? Are you careless at times about taking your medicine? When you feel better, do you sometimes stop taking your medicine? Sometimes if you feel worse when you take the medicine, do you stop taking it?* Participants were deemed non-adherent if they responded 'yes' to any of the four questions.

Hyperphosphatemia, a common complication in ESKD due to impaired phosphate excretion by the kidneys, is associated with greater cardiovascular and all-cause mortality in dialysis patients [25]. Dialysis or dietary restriction alone is often insufficient for adequate phosphate control, making phosphate binder medication therapy critical in managing hyperphosphatemia [26]. Since poorly controlled serum phosphate levels indicate poor adherence to phosphate binders [27], random serum phosphate levels were used in this research as an objective measure to further confirm medication adherence among the study participants.

3.3.2 Health-related quality of life (HRQoL)

The EuroQol 5-dimension 5-level (EQ-5D-5L) tool, developed by the EuroQol group, was used to assess HRQoL among participants in this research (registration ID: 61889) [28]. This version that has been validated and widely used across multiple diseases and locations, providing a simple yet comprehensive assessment of a person's HRQoL [29].

The EQ-5D-5L comprises two parts: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS) (see **Appendix B**). The descriptive system assesses health in five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has five response levels, starting with no problem, slight problems, moderate problems, severe problems, and extreme problems, indicating a patient's health state. Responses for each dimension corresponds to a standard index value ranging from -0.3 to 1, where 1 reflects the most optimal state of health. These values are used to derive an EQ-5D summary index, with higher scores indicating better health states.

The EQ VAS, the second part of the questionnaire, requires patients to rate their perceived general health on a visual analogue scale from 0 (the worst imaginable health) to 100 (the best imaginable health). This scale is used alongside the descriptive system as a quantitative measure of health outcome based on a person's self-perceived health status [28].

3.3.3 Incidence of hospitalisations

Complex medication regimens can increase the likelihood of confusion and improper administration of medications, leading to higher rates of hospitalisation directly or indirectly caused by medication non-adherence [30-32]. Previous studies have reported that higher MRCI scores are associated with longer intensive care unit stays and are significant predictors of hospital readmission [2, 33]. Therefore, understanding the relationship between medication regimen complexity and the incidence of hospitalisation across different dialysis treatment modalities is crucial for improving patient-centred care in ESKD.

The incidence of hospitalisations in the preceding 12-month period was obtained from eMRs. Only unplanned admissions were included in the study, while elective admissions and admissions with stays of less than 24 hours were excluded. Data on the number of hospital admissions was also collected for participants who were admitted during the preceding 12-month period.

3.4 Statistical analysis

All study data were tested for normality using the Shapiro–Wilk test. Continuous variables that were normally distributed were presented as mean ± standard deviation (SD), whereas non-normally distributed variables were presented as median (interquartile range [IQR]) (25–75%). Frequency (percentage) was used to report proportions for categorical variables.

Participant characteristics such as demographic profile, medication complexity, number of medications, pill burden, and outcomes (medication adherence, HRQoL, incidence, and number of hospitalisation(s)) were compared between patients on facility-based HD and home HD in the HD study, and between adherent and non-adherent group of participants in the PD study. Comparisons between continuous variables with normal distribution were performed using the Student's *t*-test, while the Mann–Whitney *U* test was used for nonnormally distributed variables. The Chi-squared test was used for the comparison of categorical variables.

In the study involving PD participants, study variables with p values < 0.1 for the univariate analyses and the MRCI were entered into the binary logistic regression model to identify predictors of medication non-adherence. Effect sizes were reported using odds ratios (ORs) and 95% confidence intervals (CIs). Statistical significance at a two-

sided *p*-value of <0.05 was set for all analyses. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS version 29.0.1.0, Armonk, NY: IBM Corp).

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Chapter 4:

The impact of medication regimen complexity on patient-related and clinical outcomes in patients undergoing haemodialysis

This chapter presents the findings on the comparison of medication regimen complexity between facility-based and home-based HD treated patients. The impact of regimen complexity on patient-related and clinical outcomes is also reported and compared between the two HD settings.

The manuscript of this chapter, titled 'The impact of medication regimen complexity on patient-related and clinical outcomes in patients undergoing hemodialysis' by Goh JX, Tesfaye W, Van C, *et al.,* has been submitted to the journal *Hemodialysis International* and is currently undergoing peer review. This chapter is formatted as the final version submitted to *Hemodialysis International*.

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Author contributions:

Associate Professor Ronald L Castelino, Dr Wubshet Tesfaye and I conceived the study design. I collected and analysed the data, interpreted the results, wrote the drafts of the manuscript, and currently managing the journal submission process. All authors were involved in critical editing and revision of the manuscript.

Abstract

Introduction: There is limited data on medication regimen complexity on outcomes in patients with kidney failure receiving haemodialysis (HD) in different settings. This study aims to quantify medication regimen complexity and assess its impact on patient-related and clinical outcomes in facility-based and home-based HD treated patients.

Methods: This study targeted patients undergoing HD at a large metropolitan dialysis centre in Australia. Baseline data and hospitalisations were recorded through retrospective audit of electronic medical records whilst other outcome data were collected prospectively. Medication regimen complexity was assessed using the 65-item Medication Regimen Complexity Index (MRCI), patient outcomes were evaluated with 4-item Morisky-Green-Levine Scale (MGLS), EQ-5D-5L and EQ VAS.

Findings: Of 174 eligible adults, 145 (80 facility-based and 65 home HDs) patients participated. Participants of both facility-based and home HD were predominantly men (65% and 75.4%, respectively) with a mean age of 62±13 years and 56±12 years, respectively. Home HD participants had higher median MRCI than those on facility-based HD [26.0 (IQR 20.6-33.0) vs 20.8 (IQR 13.6-28.4), respectively; p=0.005]. Whilst there was no significant difference in the non-adherence rate, home HD participants had higher scores for both EQ-5D-5L [0.917 (IQR 0.745-0.984) vs 0.798 (IQR 0.302-0.956), respectively; p=0.006] and EQ VAS [60 (IQR 50-75) vs 50 (IQR 40-70), respectively; p=0.034]. Home HD participants also had fewer number of hospitalisations in prior one-year [0 (IQR 0-1) vs 1 (IQR 0-1), respectively; p=0.042).

Discussion: The higher complexity of medication regimen for home HD compared to facility-based HD participants may be due to the shift in dose administration responsibility of several parenteral medications. Despite the higher complexity, home HD patients had better outcomes, including HRQoL and hospitalisations compared to facility-based HD patients.

Keywords

Kidney failure; medication regimen complexity index; polypharmacy; adherence; health-related quality of life

1. Introduction

Chronic kidney disease (CKD) is a life-limiting condition that has profound impact on an individual's quality of life (QoL). Due to its silent nature, it is often only detected when the condition progresses to more advanced, burdensome, and costly stages where the symptoms become more apparent and patients are close to needing kidney replacement treatments (including dialysis and kidney transplantation) to sustain life. Patients with kidney failure requiring dialysis often have complex medication regimens to manage a myriad of comorbidities and complications including but not limited to bone mineral diseases, anaemia, and hypertension [1, 2]. This cohort has one of the highest pill burden among cohort of patients with other chronic illnesses, with a mean burden ranging from 8.2 pills per day before kidney transplantation to 18.0 pills per day immediately after transplantation [3]. These medications are often prescribed by multiple different clinicians, adding on to the complexity of patients' medication regimens and increasing the risk of medication non-adherence. High prevalence of polypharmacy among kidney failure patients has been associated with poorer medication adherence, and poorer patient outcomes [1, 4].

However, to date most of the evidence on the association between medication regimen complexity, adherence and outcomes are largely limited to people using facility-based HDs and there are insufficient evidence exploring the impact of medication regimen complexity on patient-related and clinical outcomes among kidney failure patients across the different dialysis modalities and settings. Thus, this study aims to (i) quantify and compare the level of medication regimen complexity in people on HD in different HD settings (facility-based HD and home HD); (ii) evaluate the patient-related and clinical outcomes including medication adherence, health-related quality of life (HRQoL), and incidence of hospitalisation(s) over the preceding 12-months period in people on HD in different settings; and (iii) compare differences in patient-related and clinical outcomes across these two HD settings.

2. Methods

2.1. Study design, setting and population

This study combined a retrospective audit of relevant clinical information of patients undergoing HD recruited at a large metropolitan dialysis centre in New South Wales, Australia, with a prospective evaluation of patient-related outcomes. The dialysis centre comprises of 22 HD chairs providing daytime facility-based HD sessions as well as a large home HD training and outreach unit with 90-100 patients on home-based HDs at any given time. Purposive sampling was employed targeting all patients undergoing HDs at this centre between August 2023 to January 2024. Patients were approached by the renal pharmacist or research pharmacist for participation in the study and provided with the Participant Information Sheet and consented before inclusion in the study. Facility-based HD patients' medications, HRQoL, and medication intake behaviour were obtained via interviews during the HD sessions whilst patients on home HD were interviewed via phone. Participants' characteristics (age, gender, primary language, marital status, ethnic group, smoking status, alcohol consumption, laboratory values and comorbidities) were obtained from the patients' electronic medical records. Patients who had language barrier, cognitive impairment, undergone a kidney transplantation, and those receiving only kidney supportive care/end of life care were excluded from the study.

2.2. Measures

Variables

Medication-related information was obtained from clinical charts and electronic medical record, and this was verified with participants during the interview and/or correlated with dispensing history provided by their community pharmacy, if required. The medication list included both prescription and non-prescription medications. Medications for short-term use (e.g. antibiotics) were excluded from the medication list.

Discrepancies between participants' medication lists and the electronic medical record or pharmacy's dispensing history were resolved through discussion between the renal pharmacist and the patient.

Medication regimen complexity was quantified using the Medication Regimen Complexity Index (MRCI) [5] and pill burden assessment. MRCI has 65 items and considers three different components: (i) dosage form, (ii) dosing frequency and (iii) additional directions concerning administration. Each medication was coded based on the weighted scoring system, with a base score of 1 given to (each) a tablet/capsule dosage form and a once daily dosing frequency. The individual component scores were then summed to a total score for medication complexity and there is no established maximum score as the total score increases in line with the increase in regimen complexity. An electronic data capture and coding tool for MRCI developed by Libby *et al.* was used to calculate the total MRCI scores of all participants [6]. Parenteral medications such as erythropoiesis-stimulating agents (ESAs) and intravenous iron that were administered by nursing staff at the dialysis centre were excluded for participants on facility-based HDs. Pill burden was defined as the total number of orally administered medications taken daily by the participants. For medications that were not taken daily i.e. once or several times a week, the total pill burden for a week was divided by 7. Non-orally administered medications such as eye drops, injections, topical or inhaled formulations, were excluded. Medications administered "as needed" were also excluded.

Outcomes

Medication adherence was self-reported by participants using the 4-item Morisky-Green-Levine Scale (MGLS) [7]. This is a reliable, validated and widely used tool in different chronic conditions including CKD [4, 8-10], and consists of four questions with

'yes' or 'no' answers to measure adherence. Participants were deemed not adherent if they responded 'yes' to any of the questions. Medication adherence was also further confirmed via objective assessment of random serum phosphate level closest to the interview date.

HRQoL was assessed via EQ-5D-5L and EQ VAS developed by EuroQol (registration ID: 61889) [11]. EQ-5D-5L consists of five dimensions – mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 response levels, starting with no problem, slight problems, moderate problems, severe problems and extreme problems. Each dimension represents an index score ranging from -0.3 to 1, whereby 1 is the most optimal state of health. EQ VAS served as a quantitative measure of participants' perception towards their overall health. It comprises a visual analogue scale, whereby participants were required to rate their overall health on a scale of 0 – 100.

The incidence of hospitalisation(s) 12-months prior to interview was obtained from electronic medical records. Only unplanned admissions were included in the study data, while elective admissions and admissions of <24 hours stay in the hospital were excluded.

2.3. Statistical analyses

Data were tested for normality using the Shapiro-Wilk test and normally distributed continuous data were reported as mean ± standard deviation (SD) values, whereas non-normally distributed data were reported as median (interquartile range [IQR]) (25-75%) values. Frequency (percentage) was used to report proportions where appropriate.

Participant characteristics such as demographic profile, medication complexity, number of medications, pill burden, and outcomes (medication adherence, HRQoL, incidence and number of hospitalisation(s)) were compared between patients on facility-based HD and home HD. The comparisons between continuous variables with normal distribution were performed using the Student's *t*-test, while the Mann-Whitney U test was used for nonnormally distributed variables. The Chi-square test was used for comparison of categorical variables. Statistical significance at a two-sided *p*-value of <0.05 was set for all analyses. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS version 29.0.1.0, Armonk, NY: IBM Corp).

3. Results

Overall, 174 eligible individuals (88 facility-based HD and 86 home HD patients) were invited to participate in the study. Of these, 145 patients (83%) agreed to participate. The baseline sociodemographic and medical characteristics of study participants are reported in Table 1.

Table 1. Sociodemographic and medical characteristics of study participants.

Variables	**Overall (*n* = 145)**	**Facility-based HD (*n* = 80)**	**Home HD (*n* = 65)**	***p* value**
Sociodemographic				
Mean age, years (SD)	59.46 (13.08)	62.45 (13.24)	55.78 (11.99)	0.002*
Male gender, *n* (%)	101 (69.7)	52 (65.0)	49 (75.4)	0.176
Primary language, *n* (%)				

English	103 (71.0)	58 (72.5)	43 (66.2)	
Tagalog	10 (6.9)	2 (2.5)	8 (12.3)	
Arabic	9 (6.2)	5 (6.3)	4 (6.2)	
Level of education (year 12 or less), *n* (%)	66 (45.5)	40 (50.0)	26 (40.0)	0.229
Married/de facto, *n* (%)	93 (64.1)	39 (48.8)	54 (83.1)	<0.001*
Clinical				
Smoking (former/current), *n* (%)	67 (46.2)	42 (52.5)	25 (38.5)	0.092
Alcohol consumption (former/current), *n* (%)	67 (46.2)	28 (35.0)	39 (60.0)	0.003*
Total number of comorbid conditions, median (IQR)	6 (5-8)	7 (5-9)	6 (4-8)	0.043*
Common comorbidities, *n* (%)				
Hypertension	131 (90.3)	74 (92.5)	57 (87.7)	0.330
Diabetes mellitus	74 (51.0)	48 (60.0)	26 (40.0)	0.017*
Atherosclerotic disease	62 (42.8)	45 (56.3)	17 (26.2)	<0.001*
Malignant neoplasm	18 (12.4)	7 (8.8)	11 (16.9)	0.138
Laboratory				
Haemoglobin (g/L), median (IQR)	110 (100-119)	110 (98-119)	111 (103-120.5)	0.508
Ferritin (µmol/L), median (IQR)	251 (127-415)	244 (137-401)	257 (109-467)	0.785
Medications				

No. of medications, median (IQR)	10 (7-13)	10 (7-12)	10 (8-13)	0.319
≥ 5 medications, *n* (%)	135 (93.1)	73 (91.3)	62 (95.4)	0.329
≥ 10 medications, *n* (%)	73 (50.3)	40 (50.0)	33 (50.8)	0.927
Daily pill burden, median (IQR)	13.0 (9.2-18.2)	14.0 (9.6-19.0)	12.7 (9.0-17.2)	0.438
MRCI, median (IQR)	24.0 (17.0-32.0)	20.8 (13.6-28.4)	26.0 (20.6-33.0)	0.005*
A/ dosage form	4.0 (1.0-8.0)	3.0 (1.0-5.0)	8.0 (4.5-8.0)	<.001*
B/ dosing frequency	14.5 (10.5-19.5)	13.3 (8.6-18.5)	14.5 (11.8-20.0)	0.078
C/ additional directions	4.0 (2.0-7.0)	4.5 (2.0-7.0)	4.0 (3.0-6.0)	0.504

Abbreviations: IQR, interquartile range; MRCI, medication regimen complexity index; SD, standard deviation.

*Statistical significance

Participants of both facility-based and home HD were predominantly men (65% vs 75%, respectively), with a higher mean age of 62 (SD 13) years for the facility-based HD group as compared to 56 (SD 12) years for the home HD group (p=0.002). The home HD group had a significantly higher number of participants who were married/de facto (n=54; 83.1%) compared to the facility-based HD participants (n=39; 48.8%). There were no significant differences in sociodemographic characteristics such as gender, level of education and smoking, as well as laboratory parameters (haemoglobin and ferritin levels) between the two groups. In general, the study participants had a relatively high comorbidity burden,

with those receiving facility-based HDs having a slightly higher level of comorbidity than home HD participants (7 vs 6, IQR 5-9 vs 4-8, respectively; *p*=0.043). Compared to those on home HD, a significant proportion of participants undergoing facility-based HDs had diabetes mellitus (40% vs 60%) and atherosclerotic disease (26.2% vs 56.3%).

Only 10 (6.9%) participants were prescribed fewer than five individual medications, with the vast majority (>90%) of the overall participants experiencing polypharmacy (use of ≥5 medications). There was no significant difference in terms of pill burden between participants receiving facility-based and home HD (14.0 vs 12.7, IQR 9.6-19.0 vs 9.0-17.2, respectively). Of note, the median MRCI score for participants of home HD modality was higher than that of the facility-based HD participants (26.0 vs 20.8, IQR 20.6-33.0 vs 13.6-28.4, respectively; *p*=0.005). Whilst there were no significant differences in the specific MRCI components of dosing frequency and additional instructions, the dosage form component was found to be significantly higher in the home HD compared to the facility-based HD group (8.0 vs 3.0, IQR 4.5-8.0 vs 1.0-5.0, respectively; *p*=<0.001).

Table 2. Clinical and patient-related outcomes.

Variables	**Overall (*n* = 145)**	**Facility-based HD (*n* = 80)**	**Home HD (*n* = 65)**	***p* value**
EQ-5D-5L index, median (IQR)	0.857 (0.503-0.956)	0.798 (0.302-0.956)	0.917 (0.745-0.984)	0.006*
EQ VAS, median (IQR)	60 (50-75)	50 (40-70)	60 (50-75)	0.034*
Non-adherence, *n* (%)	60 (41.4)	29 (36.3)	31 (47.7)	0.164

Serum phosphate level (mmol/L), median (IQR)	1.66 (1.34-1.98)	1.69 (1.39-2.10)	1.59 (1.31-1.90)	0.185
Hospital admission(s) 1 year prior to baseline, *n* (%)	65 (44.8)	41 (51.3)	24 (36.9)	0.084
Number of hospital admission(s), median (IQR)	0 (0-1)	1 (0-1)	0 (0-1)	0.042*

Abbreviations: IQR, interquartile range; EQ-5D-5L, EuroQol-5 dimensions-5 level; EQ VAS, EuroQol visual analogue scale.

*Statistical significance

Table 2 presents the patient-related and clinical outcomes of the study participants. While there was no significant difference in medication non-adherence rate between the two groups, both the EQ-5D-5L index and EQ VAS scale showed similar trends of higher scores among home HD participants (p=0.006 and p=0.034, respectively). There was also a significant difference between the number of hospital admission(s), whereby the home HD participants had fewer hospitalisations in the one-year prior to the date of interview (0 vs 1, IQR 0-1 vs 0-1, respectively; p=0.042). As for the objective assessment of serum phosphate level, no statistically significant difference was found between facility-based and home HD participants (1.69 vs 1.59, IQR 1.39-2.10 vs 1.31-1.90, respectively).

4. Discussion

In this first study assessing the impact of medication regimen complexity on patient-related and clinical outcomes in facility-based and home-based HD patients, we found a higher median MRCI score of home HD participants compared to that of facility-based HD

participants (p=0.005). A significant increase in MRCI over time was also reported in another study when patients were switched from facility-based HD to nocturnal home HD, despite a profound decrease in pill burden for certain classes of medications [12]. Parenteral medications such as ESAs and intravenous iron that are usually administered by nursing staff at the dialysis unit were self-administered by home HD participants. This would account for the discrepancies of the total MRCI scores between the two groups as facility-based HD participants were not responsible for administering these medications and hence excluded in the analysis. On the other hand, there were no statistically significant differences in the number of medications used, prevalence of polypharmacy, and daily pill burden between facility-based and home HD participants. This is in contrast to a previous study reporting that home HD patients had significantly reduced pill burden compared to facility-based HD and peritoneal dialysis patients [13].

It is well known that HD patients are prescribed with numerous medications which consequently lead to high pill burden and a complex medication regimen [13-15]. Polypharmacy has been commonly defined as the use of ≥ 5 medications, which applies to 93% of our cohort. When compared to patients with other chronic diseases such as cardiovascular and mental diseases, a higher proportion of participants in our study were prescribed with ≥ 5 medications [16]. The median overall MRCI score of participants in our study was also higher than that of patients with HIV, hypertension and diabetes [6]. A regression analysis to determine the association between medication-related factors and outcomes was not conducted in this study, as prior studies had demonstrated the impact of high medication regimen complexity and pill burden on outcomes including poor adherence and QoL in kidney failure patients [10, 13-15].

The current study indicated a significantly better HRQoL for home HD participants in terms of EQ-5D-5L index and EQ VAS. This is consistent with the data from a systematic review showing better HRQoL when comparing home HD to facility-based HD-treated patients [17]. We noted that the home HD participants in our study were significantly younger and had fewer comorbidities such as diabetes and atherosclerotic disease compared to their facility-based counterparts. It is not surprising that home HD patients have better QoL as they tend to have better family support, health literacy and motivation to self-manage dialysis compared to facility-based HD patients, which in turn also lead to lower mortality risk [17, 18]. Additionally, the flexibility provided by home HD compared to facility-based HD in terms of tailored dialysis regimen has been linked in previous studies to benefits such as improvement in sleep quality, restless legs symptoms and HRQoL [19, 20]. In our study, there was no significant difference in the medication non-adherence rate between the two groups of participants. Nevertheless, the overall non-adherence rate found among our participants (41.4%) was higher compared to patients with other chronic illnesses such as hypertension (31%) and asthma (29.95%) [21, 22]. In contrast to previous findings that demonstrated higher serum phosphate level among facility-based HD compared to home HD participants [23, 24], our data showed no significant difference in the phosphate levels between the two groups. Previous studies have attributed their findings to a higher dose of dialysis received in the home setting that is difficult to achieve in a facility-based setting because of constraints related to nursing shifts [12, 24]. There was a significant difference in the median number of hospital admission(s) between facility-based and home HD participants. Previous literature that focused on hospitalisation rate showed no statistically significant effect with home HD in general, although, a reduced duration of hospitalisation with home HD was observed [17].

There are only limited number of studies comparing medication regimen complexity, number of medications and pill burden, as well as patient-related and clinical outcomes between HDs delivered in different settings. Furthermore, this study was conducted in one of the large dialysis centres in Australia, with existing local literatures on dialysis patients featuring smaller sample sizes. To minimize the potential inaccuracy of patients' medication lists, we have obtained the medication list from several sources to consolidate the best possible medication history. Nevertheless, this study is not without limitations. Medication regimen complexity and pill burden were only measured at a single timepoint, which is at the time of recruitment into the study. Despite the use of an objective outcome measure (i.e. serum phosphate level), it may not accurately reflect patient outcomes related to medication complexity as other factors including dietary adherence will also influence serum phosphate level. Another caveat is that self-reported adherence method may not be reliable and participants may under-estimate non-adherence due to recall and social desirability bias. However, the 4-item MGLS is commonly adopted given its ease of implementation in practice.

In conclusion, the higher complexity of medication regimen for home HD compared to facility-based HD participants may be due to the shift in dose administration responsibility of several parenteral medications. Nevertheless, home HD, compared to facility-based HD, showed significantly better patient-related and clinical outcomes in terms of HRQoL and number of hospitalisation(s). The outcomes of this study may also provide an insight into the choice of dialysis modality tailored to both patients' medical and non-medical factors, considering patients' ability to self-manage the more complex medication regimen in relation to the better outcomes associated with home HD. Future research should be conducted with a larger sample of patients encompassing multiple dialysis centres and

dialysis modalities, as well as interventional studies to address or improve medication complexity among HD patients.

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Ethics approval and consent to participate

This study was performed in accordance with the principles of the Declaration of Helsinki. Approval was granted by the Western Sydney Local Health District Human Research Ethics Committee (2019/PID03039). Informed consent was obtained from all participants included in the study.

Availability of data and materials

The datasets generated and analysed are available upon request.

Authors contributions

RLC and WT conceptualised and designed the study. JXG conducted the methodology, performed the analyses, and drafted the manuscript. WT, CV, KS, ST, SS and RLC contributed to extensive review and editing of the paper. All authors have read and approved the final manuscript for publication.

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Competing interests

KS is on the Fresenius Medical Advisory Board for Australia and New Zealand and has received speaker's honoraria from Baxter Healthcare, Roche and Fresenius Medical Care.

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Chapter 5:

Medication regimen complexity and patient-centred outcomes in patients undergoing peritoneal dialysis

This chapter presents the findings on the level of medication regimen complexity among patients receiving PD, the differences in self-reported patient-centred outcomes among PD patients based on their medication adherence, as well as the determinants of medication adherence in this cohort of patients.

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Associate Professor Ronald L Castelino, Dr. Wubshet Tesfaye and I conceived the study design. I collected and analysed the data, interpreted the results, and wrote the drafts of the manuscripts. All authors were involved in critical editing and revision of the manuscript.

Abstract

Introduction: Although patients undergoing peritoneal dialysis typically have complex treatment needs, the effect of medication regimen complexity on patient outcomes has not been thoroughly evaluated. This study aims to quantify medication regimen complexity and evaluate patient-centred outcomes including medication adherence and its determinants in patients undergoing PD.

Methods: This study combined a retrospective audit of baseline data with a prospective evaluation of patient-related outcomes among patients undergoing PD at a large metropolitan dialysis centre in Australia. Medication regimen complexity was assessed using the 65-item Medication Regimen Complexity Index (MRCI), while patient outcomes were evaluated with validated self-reported questionnaires, including the 4-item Morisky–Green–Levine Scale (MGLS), EQ-5D-5L and EQ VAS.

Findings: A total of 131 patients participated [median age 67 (IQR 57–74) years]. Patients on PD were found to have complex medication regimens with an average MRCI score of 28.6 ± 11.4. Over half of the participants were deemed to be adherent to their prescribed medications as measured by the MGLS (*n* = 79; 60.3%). Male participants were more likely to be non-adherent to medications compared to female participants (OR 2.465; 95% CI 1.055–5.759). Participants with higher serum phosphate levels were 2.5 times more likely to report non-adherence to their medications (OR 2.523; 95% CI 1.247–5.104), while a higher health-related quality of life (HRQoL) was associated with medication adherence (OR 0.151, 95% CI 0.031–0.732).

Discussion: Patients on PD are prescribed complex medication regimens in addition to PD treatments that they perform at home. Patients on PD who were adherent to their medications had significantly better outcomes in terms of HRQoL and serum phosphate levels compared to non-adherent patients.

Keywords: kidney failure; peritoneal dialysis; medication regimen complexity index; adherence; health-related quality of life

1. Introduction

Peritoneal dialysis is the preferred form of kidney replacement therapy for many people with kidney failure, as it is delivered at home. Several countries have adopted a 'PD-first' or 'PD-favoured' approach because PD requires less personnel and infrastructure [1]. According to the latest data from the Australia and New Zealand Dialysis and Transplant Registry, there were 2657 (17%) PD patients in Australia, of which the majority (73%) were receiving automated peritoneal dialysis (APD) in 2022 [2].

It has been suggested that PD confers several advantages over haemodialysis (HD) in terms of preserving residual kidney function, as well as providing a better health-related quality of life (HRQoL) [3]. Nevertheless, regardless of the dialysis treatment modality, polypharmacy is an issue in patients with kidney failure since patients invariably require multiple medications to alleviate the symptoms associated with kidney failure and to manage multiple comorbidities and complications such as hypertension, cardiovascular diseases, bone mineral diseases and anaemia [4]. Recent studies have shown that patients undergoing PD treatment have a similar medication burden to those receiving facility-based HD treatments [5, 6]. As most of the evidence to date has focused on patients on HD, with limited studies on patients undergoing PD, little is known about the medication regimen complexity, medication adherence and patient-centred outcomes in this population with kidney failure. Thus, this study aims to (i) quantify the level of medication regimen complexity in people undergoing PD; (ii) evaluate patient-centred outcomes including HRQoL and the incidence of hospitalisation(s) over the preceding 12-month period in people on PD; and (iii) compare differences in self-reported patient-centred outcomes among PD patients based on their medication adherence.

2. Materials and Methods

2.1. Study Design, Setting and Population

This was a retrospective audit of relevant clinical information, and a prospective evaluation of patient-related outcomes among patients undergoing PD recruited from a large metropolitan dialysis centre in New South Wales, Australia. The PD service provides care and patient training for approximately 325 patients on PD. Patients were approached for participation in the study between March 2024 and May 2024. We excluded patients who were temporarily undergoing HD, and those receiving kidney-supportive care/end of life care while on PD. Patients who had a language barrier or cognitive impairment were also excluded from the study. After informed consent, participants' characteristics—age, gender, primary language, marital status, ethnic group, smoking status, alcohol consumption, laboratory values, comorbidities and medications—were obtained from the patients' electronic medical records, while HRQoL and medication intake behaviour were obtained via phone interviews or during their follow up appointment at the PD clinic. Complexity of prescribed PD regimens or adherence of PD treatments at home were not assessed. This study was approved by the Institutional Human Research Ethics Committee (2019/PID03039).

2.2. Measures

2.2.1. Variables

A list of the participants' medications was obtained from the electronic medical record (eMR). The accuracy of these medication lists was verified with participants during the interview and/or correlated with dispensing history provided by their community pharmacy, if required. The medication list included both prescription and over-the-counter medications. Medications such as antibiotics for short-term use and herbal supplements were excluded from the medication list. If necessary, to resolve any discrepancies between participants' medication lists and the eMR or pharmacy's dispensing history, a discussion between the renal pharmacist, research pharmacist and the patient was conducted.

The Medication Regimen Complexity Index (MRCI) [7] and daily pill burden assessment were used to quantify medication regimen complexity. The MRCI is a 65-item tool developed

to evaluate the complexity of a patient's drug therapy by considering three different components: (i) dosage form, (ii) dosing frequency and (iii) additional directions concerning administration. Based on a weighted scoring system, each medication was scored on the three different components, and the individual component scores were then summed to create a total score for medication complexity. A base score of 1 was given to (each) a tablet/capsule dosage form and a once daily dosing frequency. There was no established maximum score as the total score increases in line with the quantity of medications and the increase in regimen complexity. An electronic data capture and coding tool developed by Libby et al. was used to compute the total MRCI scores for each participant [8]. Pill burden was determined as the total number of medications taken orally by the participants each day. For medications that were not taken daily, i.e., once or several times a week, the total pill burden for a week was divided by 7. Medications administered on an "as needed" basis and non-orally administered medications such as topical, injectable and inhaled formulations were excluded from the pill burden count. Medications were classified as per the World Health Organisation Anatomical Therapeutic Chemical (ATC) Classification system.

2.2.2. Outcomes

Self-reported medication adherence was evaluated using the 4-item Morisky–Green–Levine Scale (MGLS) which consists of four questions with binary (yes/no) response options [9]. It is a validated, reliable and widely used instrument in the clinical setting for different chronic illnesses including chronic kidney disease (CKD) [10-14]. Participants were classified as non-adherent if they responded 'yes' to any of the four questions. An objective assessment of a random serum phosphate level close to the interview date was also carried out to further confirm medication adherence.

EQ-5D-5L and EQ VAS developed by EuroQol were used to measure HRQoL (registration ID: 61889) [15]. EQ-5D-5L comprises five dimensions—mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 response levels of

perceived problems, starting with level 1 indicating no problem, to level 5 indicating extreme problems. Each dimension represents a standard index score ranging from −0.3 to 1, where 1 reflects the most optimal state of health. EQ VAS forms part of the EQ-5D-5L that served as a quantitative assessment of participants' overall health status. It is a visual analogue scale on which participants are required to rate their general health from 0 to 100.

The incidence of hospitalisation(s) 12 months prior to interview was obtained from electronic medical records. Only unplanned admissions were included in the study data, while admissions resulting in an <24 h stay in the hospital and elective admissions were excluded.

2.3. Statistical Analyses

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS version 29.0.1.0, Armonk, NY, USA: IBM Corp). All study data were tested for normality using the Shapiro–Wilk test. Continuous variables that were normally distributed were presented as the mean ± standard deviation, whereas non-normally distributed variables were presented as the median (interquartile range [IQR]) (25–75%). Frequency (percentage) was used to report proportions for categorical variables.

Participant characteristics such as sociodemographic and medical profile, medication regimen complexity, number of medications, pill burden and outcomes (HRQoL, serum phosphate level, incidence and number of hospitalisation(s)) were compared between adherent and non-adherent groups of participants. Student's *t*-test was used to compare the means of normally distributed continuous variables, while the comparison between nonnormally distributed variables were performed using the Mann–Whitney U test. Categorical variables were compared using the Chi-square test. Study variables with *p* values < 0.1 for the univariate analyses (gender, serum phosphate level, EQ-5D-5L index and EQ VAS) as well as the MRCI were entered into the binary logistic regression model to identify predictors of medication non-adherence. Effect sizes were reported using odds ratios (ORs) and 95% confidence intervals (CIs). A two-sided *p*-value of <0.05 was considered statistically significant.

3. Results

Overall, 131 [71 automated peritoneal dialysis (APD) and 60 continuous ambulatory peritoneal dialysis (CAPD)] patients consented to the study (response rate 65.5%). More than half of the patients were deemed adherent to their prescribed medications as assessed by the MGLS (*n* = 79; 60.3%). The baseline sociodemographic and medical characteristics of study participants are reported in **Table 1**.

Table 1. Study characteristics based on participant self-reported medication adherence.

Variables	Total Cohort (*n* = 131)	Adherent (*n* = 79)	Non-Adherent (*n* = 52)	*p* Value
Sociodemographic				
Median age, years (IQR)	67 (57–74)	67 (58–74)	67 (54–74)	0.422
APD modality, *n* (%)	71 (54.2)	40 (50.6)	31 (59.6)	0.313
Male gender, *n* (%)	85 (64.9)	45 (57.0)	40 (76.9)	0.019 *
Primary language, *n* (%)				
English	63 (48.1)	38 (48.1)	25 (48.1)	
Tagalog	16 (12.2)	9 (11.4)	7 (13.5)	
Mandarin	8 (6.1)	4 (5.1)	4 (7.7)	
Married/de facto, *n* (%)	89 (67.9)	54 (68.4)	35 (67.3)	0.900
Level of education (year 12 or less), *n* (%)	71 (54.2)	41 (51.9)	30 (57.7)	0.515
Clinical				
Total number of comorbid conditions, median (IQR)	6 (5–8)	6 (5–8)	6 (5–9)	0.476
Common comorbidities, *n* (%)				
Hypertension	123 (93.9)	72 (91.1)	51 (98.1)	0.105
Diabetes mellitus	75 (57.3)	42 (53.2)	33 (63.5)	0.244
Atherosclerotic disease	47 (35.9)	25 (31.6)	22 (42.3)	0.213
Congestive heart failure	26 (19.8)	18 (22.8)	8 (15.4)	0.299
Malignant neoplasm	13 (9.9)	8 (10.1)	5 (9.6)	0.924

Smoking (former and current), *n* (%)	47 (35.9)	28 (35.4)	19 (36.5)	0.898
Alcohol consumption (former and current), *n* (%)	46 (35.1)	25 (31.6)	21 (40.4)	0.305
Laboratory				
Haemoglobin (g/L), median (IQR)	108 (98–117)	108 (99–117)	104 (96–117)	0.192
Ferritin (µmol/L), median (IQR)	290 (151–473)	295 (154–460)	278 (145–545)	0.976
Medications				
No. of medications, median (IQR)	11 (8–14)	11 (9–14)	11 (7–14)	0.549
≥5 medications, *n* (%)	127 (96.9)	76 (96.2)	51 (98.1)	0.542
≥10 medications, *n* (%)	87 (66.4)	56 (70.9)	31 (59.6)	0.181
Patient prescribed with phosphate binder(s), *n* (%)	100 (76.3)	57 (72.2)	43 (82.7)	0.165
Prescribed medications by drug categories, *n* (%)				
Cardiovascular system	460 (31.4)	268 (29.8)	192 (33.8)	
Alimentary tract and metabolism	455 (31.0)	281 (31.3)	174 (30.6)	
Blood and blood forming organs	194 (13.2)	118 (13.1)	76 (13.4)	
Daily pill burden, median (IQR)	14.5 (10.0–21.0)	15.0 (10.1–21.4)	14.2 (10.0–20.6)	0.358
MRCI, mean	28.6 (11.4)	28.7 (11.3)	28.6 (11.7)	0.962
A/dosage form	4.9 (2.5)	4.9 (2.5)	4.9 (2.5)	0.958
B/dosing frequency	17.2 (7.1)	17.8 (7.3)	16.4 (6.8)	0.279
C/additional directions	6.6 (4.1)	6.1 (3.4)	7.4 (4.9)	0.093

Abbreviations: APD, automated peritoneal dialysis; IQR, interquartile range; MRCI, medication regimen complexity index; SD, standard deviation. * Statistical significance.

3.1. Characteristics of Study Participants

The study participants were predominantly men (*n* = 85; 64.9%), with a median age of 67 (IQR 57–74) years. More than half of the participants were treated with the APD modality (*n* = 71; 54.2%). There was no significant difference in adherence between the different PD modalities. There were also no significant differences in sociodemographic characteristics

such as marital status, level of education, alcohol consumption and smoking, as well as laboratory parameters (haemoglobin and ferritin levels), between the adherent and non-adherent groups of participants. In general, the study participants had a relatively high comorbidity burden, with a median of six (IQR 5–8) comorbid conditions. The most common comorbidities were hypertension (*n* = 123; 93.9%), followed by diabetes mellitus (*n* = 75; 57.3%), and atherosclerotic disease (*n* = 47; 35.9%).

Participants were prescribed a median of 11 (IQR 8–14) medications, with a daily pill burden of 14.5 (IQR 10.0–21.0). Only four (3.1%) participants were prescribed fewer than five medications, indicating that the vast majority of participants (96.9%) experienced polypharmacy (use of ≥5 medications). In line with the common comorbidities present in this cohort of participants, we identified that the most prescribed drug class was from the cardiovascular system pharmacological group (31.4%), followed by the alimentary tract and metabolism (31.0%), and the blood and blood-forming organs (13.2%) group of medications. The mean MRCI score of the study population was 28.6 (SD 11.4), with the dosing frequency component contributing the most to the total score. The number of medications prescribed, daily pill burden, total MRCI and individual MRCI component scores did not significantly differ between the adherent and non-adherent participants.

3.2. Outcomes and Determinants of Medication Non-Adherence

Table 2 presents the patient-centred outcomes of the study participants. Of note, participants who were adherent to their prescribed medications had a higher EQ-5D-5L score compared to their non-adherent counterparts [0.926 (IQR 0.755–0.968) vs. 0.734 (IQR 0.333–0.928), respectively; *p* = 0.002]. Similarly, the EQ VAS score was significantly higher among those who were adherent compared to the non-adherent group of participants [70 (IQR 50–80) vs. 50 (IQR 40–80), respectively; *p* = 0.017]. Unsurprisingly, the objective assessment of serum phosphate level among adherent participants was shown to be lower compared to non-adherent participants [1.61 (IQR 1.36–2.06) vs. 1.80 (IQR 1.50–2.33), respectively; *p* = 0.019].

Nevertheless, there were no significant differences in the incidence and number of hospitalisation(s) 12 months prior to the date of interview between the two groups of participants.

Table 2. Clinical and patient-related outcomes.

Variables	Total Cohort (*n* = 131)	Adherent (*n* = 79)	Non-Adherent (*n* = 52)	*p* Value
EQ-5D-5L, median (IQR)	0.889 (0.566–0.961)	0.926 (0.755–0.968)	0.734 (0.333–0.928)	0.002 *
EQ VAS, median (IQR)	60 (50–80)	70 (50–80)	50 (40–80)	0.017 *
Serum phosphate level (mmol/L), median (IQR)	1.69 (1.43–2.19)	1.61 (1.36–2.06)	1.80 (1.50–2.33)	0.019 *
Hospital admission(s) 1 year prior to baseline, *n* (%)	65 (49.6)	37 (46.8)	28 (53.8)	0.432
Number of hospital admission(s), median (IQR)	0 (0–2)	0 (0–2)	1 (0–2)	0.409

Abbreviations: IQR, interquartile range; EQ-5D-5L, EuroQol-5 dimensions-5 level; EQ VAS, EuroQol visual analogue scale. * Statistical significance.

When examining the predictors of medication non-adherence using the binary logistic regression model (**Table 3**), we found that male participants were more likely to be non-adherent to medications compared to female participants (OR 2.465; 95% CI 1.055–5.759; p = 0.037). Participants with a higher serum phosphate level were 2.5 times more likely to report non-adherence to their medications (OR 2.523; 95% CI 1.247–5.104; p = 0.010). On the other hand, a higher HRQoL was associated with medication adherence (OR 0.151, 95% CI 0.031–0.732; p = 0.019).

Table 3. Predictors of medication non-adherence using logistic regression analysis.

Variables	Adjusted OR (95% CI)	*p* Value
Male gender	2.465 (1.055–5.759)	0.037 *
MRCI (total score)	0.969 (0.933–1.007)	0.104
Serum phosphate level, per 1 mmol/L	2.523 (1.247–5.104)	0.010 *
EQ-5D-5L	0.151 (0.031–0.732)	0.019 *
EQ VAS	0.988 (0.967–1.011)	0.309

Abbreviations: EQ-5D-5L, EuroQol-5 dimensions-5 level; EQ VAS, EuroQol visual analogue scale; MRCI, medication regimen complexity index. * Statistical significance.

4. Discussion

This is the first study assessing medication regimen complexity, medication adherence and patient-centred outcomes focusing on patients receiving PD. We found that patients with kidney failure undergoing PD had complex medication regimens with an average MRCI score of 28.6 ± 11.4, which was notably higher than that reported for patients with pre-dialysis CKD (median MRCI 19.0) [12] as well as other chronic illnesses such as diabetes mellitus, HIV and psychiatric disorders (mean MRCI range 6.9–16.0) [16-18]. The MRCI scores of participants in this study were found to be comparable to studies involving patients undergoing facility-based [19, 20] and home HD [21] treatments. Interestingly, at our dialysis centre, we found that the MRCI scores of participants undergoing PD were higher than those undergoing facility-based HD (median MRCI 20.8) (author's unpublished study—currently under review). This may be due to a shift in the dose administration responsibility for several parenteral medications such as erythropoiesis-stimulating agent. The adherence rate among participants in this study (65.5%) was also shown to be slightly better compared to previous reports conducted among facility-based HD patients (≤50%) [19, 21]. This could be attributed to several reasons as patients receiving PD are generally younger, more educated and have fewer comorbidities compared to patients treated with HD [22]. As a result, PD patients would be more independent

in dealing with the challenges of managing their own treatment at home, hence their better motivation and commitment to their care plan. Nevertheless, the previous literature indicated the medication non-adherence rate in PD patients varied from 3.9% to 85% [23]. Differences in adherence assessment tools, patient demographics, healthcare systems and settings may contribute to such discrepancies.

Of note, the current study reported a significantly better HRQoL measured using the EQ-5D-5L index and EQ VAS among the adherent compared to the non-adherent group of participants. This finding is congruent with the findings of previous studies conducted among patients with pre-dialysis CKD [12] and in patients who underwent kidney transplantation [24]. In general, patients receiving PD have been shown to have a better QoL and other clinical outcomes compared to patients receiving HD [3, 22], but a comparison of PD versus HD and the associated outcomes was not part of this study's objectives. Compared to our study, which showed that male gender, serum phosphate levels and HRQoL were determinants of medication non-adherence, several other factors such as younger age and being from racial minority and lower socioeconomic groups were also identified as predictors of poorer medication adherence across all CKD stages [25]. Despite similar findings from a previous study suggesting poorer outcomes in males with CKD due to a lower adherence to treatment [26], the reasons for gender differences influencing medication adherence are multifactorial and could include sociodemographic, psychological and other factors. Furthermore, since a poor HRQoL has been well documented to be associated with increased morbidity and mortality, the enhancement of a patient's HRQoL is increasingly important when monitoring the quality and effectiveness of kidney care, and is currently considered a high priority area in kidney research [27]. On another note, adherent participants in our study had lower random serum phosphate levels compared to non-adherent participants, indicating better phosphate control possibly due to a better phosphate binder and/or dietary adherence. This was also shown in previous studies conducted among patients undergoing HD [28, 29]. Lower serum

phosphate levels, in turn, were found to be a predictor of medication adherence in our study, further indicating the importance of the relationship between both outcomes in patients treated with PD. Since a limited amount of phosphate is removed through the peritoneal membrane, PD patients frequently develop hyperphosphatemia and are often prescribed phosphate binder medications to reduce dietary phosphate absorption [30]; phosphate binder adherence is crucial to reduce the risk of cardiovascular morbidity and mortality among PD patients.

The present study failed to show significant differences in measures of medication regimen complexity including the MRCI scores, number of medications prescribed and daily pill burden between the adherent and non-adherent groups of PD participants. Ghimire et al. and Parker et al. have also reported no association between medication complexity and adherence in both pre-dialytic and patients on dialysis [19, 20], in contrast with other studies that indicated an inverse relationship between medication complexity and adherence in a similar patient group [13, 31]. The lack of a standardised definition of medication regimen complexity would most likely account for the differences in findings between the studies. Nevertheless, the use of different medication regimen complexity assessment methods and MRCI as the main measure in our study, which includes comprehensive aspects of a medication regimen, enabled us to compare between the outcomes of different studies. Whilst there were no significant differences in the outcomes of hospital admission(s) one-year prior to baseline and the median number of hospitalisation(s) between the adherent and non-adherent groups of participants, the hospitalisation rate in PD participants in our study was found to be lower than that in a recent study comparing the hospitalisation rates between PD and HD patients [32].

This is the first study from Australia conducted among PD patients on medication regimen complexity and pill burden, as well as patient-centred outcomes. Additionally, in contrast to existing local literature [19] on dialysis patients featuring a smaller sample size (n < 60), this study was carried out in the largest PD centre in Australia with a sample size of n >

100. To obtain the best possible medication history and to minimise the potential inaccuracy of participants' medication lists, we have obtained the lists of medications from several sources including the electronic medical record, verification with participants' community pharmacy and confirmation during patient interview. Nonetheless, this study is not without limitations. Although this study was conducted in a large centre that caters to people from diverse background, this may not be representative of the entire Australian population. The use of a self-reported adherence tool may lead to an under-estimation of non-adherence due to recall and social desirability bias. However, the 4-item MGLS that was used in this study is commonly adopted in clinical practice due to its ease of implementation. Additionally, the use of serum phosphate level as an objective outcome measure may be influenced by other factors including dietary adherence, and hence may not accurately reflect patient outcomes related to medication complexity. Another caveat is that medication regimen complexity was only measured at a single timepoint, when participants were recruited into the study. This may not fully capture the complexity, potentially leading to an over- or under-estimation of medication regimen complexity as patients with kidney failure frequently have their treatment adjusted to manage multiple comorbidities which can cause dynamic changes in their health status. Such limitations of a cross-sectional study design could be addressed in future studies by incorporating a longitudinal study design to gain a better understanding of medication complexity among patients receiving PD. Finally, we have not assessed the impact of the complexity of prescribed PD regimens or adherence to PD treatments at home on patient-related outcomes as this was beyond the scope of our study.

5. Conclusions

Despite the complex medication regimens, PD patients who were adherent to their medications had significantly better patient-centred outcomes in terms of HRQoL and serum phosphate levels compared to non-adherent patients. This reinforces the importance of enhancing patient adherence as one of the main focuses in the practice of daily care for

patients with kidney failure. Future research should consider interventional studies to address or improve medication adherence and regimen complexity among PD patients, and should recruit a larger sample of patients from multiple dialysis centres and various dialysis modalities.

Author Contributions

Conceptualization, J.X.G. (research pharmacist) and R.L.C. (renal pharmacist); Formal analysis, J.X.G. and R.L.C.; Methodology, J.X.G. and R.L.C.; Writing—original draft, J.X.G. and R.L.C.; Writing—review and editing, K.S., W.T., C.V., S.S., S.T. and R.L.C. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

This study was performed in accordance with the principles of the Declaration of Helsinki. Approval was granted by the Western Sydney Local Health District Human Research Ethics Committee (approval code: 2019/PID03039, approval date: 17 October 2023).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The datasets generated and analysed are available upon request.

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Conflicts of Interest

K.S. is on the Fresenius Medical Advisory Board for Australia and New Zealand and has received speaker's honoraria from Baxter Healthcare, Roche and Fresenius Medical Care.

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Chapter 6:

Discussion, Future Work and Conclusions

In this chapter, a summary of the main findings of this thesis is provided along with a discussion on the research impact of this work from the perspective of clinical practice and the strengths and limitations of this research. Finally, a conclusion with remarks around the essential findings of this work, and recommendations for future research directions are provided in this chapter.

6.1 Summary of main findings

The findings of this thesis have addressed the aims by examining medication regimen complexity across patients with ESKD receiving different dialysis modalities and understanding its association with patient-related and clinical outcomes.

Chapter 2 (*Medication regimen complexity and patient-centred outcomes in ESKD: A Systematic Review*) summarised, via a systematic review, the methods used to assess medication regimen complexity amongst adults with ESKD in the current literature, as well as the association between regimen complexity and patient-reported and clinical outcomes. Whilst medication burden among patients with dialysis-dependent CKD has been previously reviewed, our study provided detailed information on medication regimen complexity among patients on dialysis and those who have undergone kidney transplantation. It included studies with diverse patient-reported clinical outcomes associated with complexity. Additionally, the effectiveness of interventions implemented in addressing regimen complexity is also summarised.

This review identified significant heterogeneity in the measures and definitions of medication regimen complexity, as well as the tools used to assess it. Furthermore, a significant link was found between medication regimen complexity and poor health outcomes, particularly in the dialysis-dependent patient population. The review also

identified several interventions aimed at improving medication regimen complexity, which were associated with positive outcomes among patients with ESKD.

Chapter 4 (*The impact of medication regimen complexity on patient-related and clinical outcomes in patients undergoing haemodialysis*) examined medication regimen complexity among facility-based and home-based HD treated patients and its impact on patient-related and clinical outcomes using a combined retrospective audit of relevant clinical information and prospective evaluation of the outcomes. Medication regimen complexity and outcomes were also compared across the two HD settings, in which the main findings of this study include:

- Home HD participants had higher median MRCI compared to those on facility-based HD.
- Whilst there was no significant difference in the medication non-adherence rate, home HD participants had better HRQoL and fewer number of hospitalisations in prior one-year, despite the higher complexity of medication regimen.
- The higher complexity of medication regimen for home HD compared to facility-based HD participants may be due to the shift in dose administration responsibility of several parenteral medications.

Chapter 5 (*Medication regimen complexity and patient-centred outcomes in patients undergoing peritoneal dialysis*) evaluated medication regimen complexity among patients undergoing PD, differences in self-reported patient-centred outcomes among PD patients based on their medication adherence, as well as the determinants of medication adherence in this cohort of patients. The key results of this study are as follows:

- Patients on PD are prescribed complex medication regimens in addition to PD treatments that they perform at home.

- Over half of the participants were deemed to be adherent to their prescribed medications, and male participants were more likely to be non-adherent to medications compared to female participants.
- Patients on PD who were adherent to their medications had significantly better outcomes in terms of HRQoL and serum phosphate levels compared to non-adherent patients.

6.2 Clinical and research implications

These findings partially confirm our hypotheses that medication regimen complexity varies across patients receiving different dialysis modalities and has varied clinical implications. Although we also hypothesised that high medication regimen complexity would lead to poor health outcomes, our data shows that home HD patients, despite having more complex medication regimens, had better outcomes in terms of HRQoL and hospitalisations compared to patients undergoing facility-based HD.

6.2.1 Medication regimen complexity in dialysis-dependent ESKD patients

The findings of this research are similar to previous studies indicating that patients receiving different forms of dialysis experience polypharmacy and high pill burden due to the complex medication regimens prescribed [1-14]. We identified that patients receiving home dialysis (PD and home HD) have more complex medication regimens compared to patients undergoing facility-based HD. This may be due to the shift in dose administration responsibility for several parenteral medications, such as ESAs, from nursing staff at the dialysis unit to home dialysis patients.

While other chronic conditions such as HIV, asthma, COPD, and psychiatric illnesses may also involve complex medication regimens [15-18], the greater complexity in

EKSD is driven by the need to manage co-existing comorbidities and complications among this cohort of patients [19, 20]. Although medication regimen complexity among HD patients assessed by MRCI in our study is similar to that found by Parker et al., it is unclear if patients undergoing home HD were included in their study [13]. Nevertheless, Ghimire et al. found higher MRCI scores among patients undergoing facility-based HD compared to our study [12], while the average MRCI score among PD participants in this research is higher than that found by Parker et al., which only involved a small number (n = 19) of PD participants [13].

The differences in findings between the studies may be due to slight variations in the medications defined for inclusion in the MRCI calculations, as well as interstudy differences in population and sample sizes. These factors contribute to challenges in comparing the findings between studies.

6.2.2 The association of medication regimen complexity on patient-centred outcomes

From our systematic review, it is apparent that medication regimen complexity is linked to various adverse health outcomes among the dialysis-dependent ESKD patients. These outcomes included poor quality of life, medication adherence, frailty, hospitalisation, and mortality [1-4, 7, 10, 14, 21-24]. While previous studies that utilised the MRCI to assess medication regimen complexity either included only a single dialysis modality [12] or analysed the association of medication complexity among different dialysis modalities as a combined variable against outcomes [13], our research, which compared the complexity and outcomes between HDs delivered in different settings, showed significantly better patient-related and clinical outcomes in terms of HRQoL and hospitalisations among the home HD cohort.

Additionally, this research has shown that PD patients who were adherent to their medications had better HRQoL, which aligns with the findings from previous studies conducted among patients with pre-dialysis CKD [25] and in patients who underwent kidney transplantation [26]. The medication non-adherence rate among patients undergoing HD and PD were similar in our studies (~40%), which were higher than that of patients with other chronic conditions such as hypertension (31%) and asthma (30%) [27, 28].

The data from this research provide an overview of medication regimen complexity among both HD and PD patients, as well as new evidence of medication regimen complexity assessed by MRCI in a large cohort of PD patients. These findings address the knowledge gap of medication complexity among different dialysis modalities and could provide a basis for future interventional studies to address or improve the complexity.

The use of MRCI as a tool to assess medication regimen complexity in this research has shown that the dosing frequency significantly contributes to the medication complexity of both patients undergoing HD and PD. These findings can influence clinical practice in terms of designing targeted interventions such as medication reviews focusing on dosing frequency as the key factor in simplifying regimens and improving medication adherence. Understanding specific challenges related to medication complexity allows for more personalised and practical strategies to be implemented, as well as enhanced monitoring and support to manage complex regimens. An interdisciplinary approach involving pharmacists, nephrologists, nurses and other health professionals would ensure a comprehensive care for patients with ESKD.

Furthermore, the findings from this research can provide insights for clinicians when deciding on the choice of dialysis modality tailored to both patients' medical and non-medical factors. It is important to consider patients' and/or caretakers' ability to self-manage not only the dialysis treatment at home, but also the more complex medication regimen associated with home dialysis treatments to achieve better health outcomes, as shown in this research.

6.3 Strengths and limitations of the research

This is the first study to compare medication regimen complexity, the number of medications, and pill burden, as well as patient-related and clinical outcomes between HDs delivered in different settings and among patients receiving PD. Additionally, this study was conducted in one of the large dialysis centres in Australia, with sample sizes of $n > 100$, in contrast to existing local literature on facility-based HD patients, which feature smaller sample sizes ($n < 60$) [12]. We thoroughly obtained patients' medication list by consolidating the best possible medication history from several sources to minimise the potential inaccuracy of patients' medication lists. Compared to many other studies that utilised pill burden or medication count to evaluate complexity, the strength of our approach using the MRCI led to a more comprehensive assessment by considering not only the number of medications, but also various other aspects, including the dosage forms, dosing frequencies, and special instructions.

Nevertheless, this study is not without limitations. Although it was conducted in a large dialysis centre that caters to people from diverse background, the findings may not be representative of the entire Australian population. We only presented findings on medication regimen complexity in adults with ESKD; hence, the results may not be generalisable to paediatric or adolescent populations. The use of a self-reported

adherence tool may lead to an underestimation of non-adherence due to recall and social desirability bias. However, the 4-item MGLS that was used in this research is commonly adopted in clinical practice due to its ease of implementation. Additionally, the use of serum phosphate level as an objective measure of medication adherence may be influenced by other factors, including dietary adherence and dialysis dose, and hence may not be the best parameter to reflect patient outcomes in relation to medication complexity.

Another caveat is that medication regimen complexity and pill burden were only measured at a single timepoint, which is at the time of recruitment into the study. This may not fully capture the complexity, potentially leading to an over- or underestimation of medication regimen complexity, as patients with ESKD frequently have their treatment adjusted due to the dynamic changes in their health status caused by the multiple co-existing comorbidities. Despite the aforementioned advantages of using the MRCI to assess medication complexity, several limitations of the MRCI were noticed in the research studies. The MRCI did not account for patient factors such as health literacy, cognitive function, the presence of caregiver support, and other social determinants of health, which could affect patients' abilities to manage their medication regimen. For instance, a patient with poor health literacy or impaired cognitive functioning may struggle managing their medication intake despite having a simple medication regimen prescribed, and incorrect administration of medications could potentially lead to adverse health outcomes. Finally, we have not assessed the impact of the complexities of prescribed dialysis regimens or adherence to dialysis treatments (that are especially relevant to patients on home dialysis) on patient-centred outcomes, as this was beyond the scope of our study.

6.4 Considerations for future work

Advances in understanding kidney disease and its complications have contributed to the development of promising pharmacotherapy for treating and preventing the progression of CKD. Despite increasing research in recent years around medication complexity among patients with ESKD, most studies focus on patients receiving facility-based HD, and there is still limited awareness among clinicians regarding medication complexities across different dialysis modalities. Hence, future research should be directed towards recruiting larger sample sizes of patients undergoing home dialysis treatments across multiple dialysis centres to gain a better understanding of medication complexities among this cohort and provide more generalisable findings. A longitudinal prospective study would be ideal for overcoming the limitations of assessing medication regimen complexity at a single time point and for accounting for frequent treatment adjustments. Longitudinal studies could help identify causal links between medication regimen complexity and patient health outcomes. While randomised controlled trials, on the other hand, could also be considered to provide more robust evidence by reducing bias, controlling confounding variables and directly testing the effects of interventions aimed at reducing medication regimen complexity.

We strongly advocate the development and use of a standardised and pragmatic assessment tool to evaluate medication regimen complexity among patients with ESKD. Large-scale studies could be conducted to validate existing tools, such as the MRCI, across diverse ESKD populations to ensure their reliability and applicability among this cohort of patients. Additionally, a more comprehensive assessment tool that captures additional dimensions of medication complexity, including patient-reported and clinical outcomes, could also be developed based on the outcomes of this research. The development and implementation of this standardised tool could be advocated at a policy

level to improve medication management and enhance patient care and outcomes among patients with ESKD.

The current findings could serve as a starting point and extend to explore strategies for addressing complexities to be implemented into routine practice tailored to the local context. In Australia, medication reviews conducted by accredited pharmacists with referrals from physicians are subsidised by Medicare. This would be beneficial for people with ESKD in simplifying their medication regimens and providing clinicians the opportunity to carefully consider the risk-benefit ratio of individual drugs and doses for each patient.

The strategies or tools developed could assist clinicians in better identifying inappropriate prescribing situations during medication reviews and provide interventions to improve safe medication prescribing and health outcomes among patients with ESKD. It could also potentially be incorporated into electronic health record systems to identify polypharmacy and complex medication regimens, flag potentially inappropriate prescribing, and incorporate a deprescribing algorithm to simplify a patient's medication regimen.

Additionally, the findings from this research could be further explored by conducting larger multicentre studies that incorporate a detailed analysis of prognostic factors such as cognition, frailty, and comorbidities to provide a deeper understanding of the complex relationships among ESKD, dialysis treatment, symptoms, and HRQoL. Such research could lead to the development of evidence-based guidelines that promote comprehensive care for patients with ESKD.

6.5 Conclusions

In summary, the studies in this thesis highlighted the variation in medication regimen complexities among patients undergoing facility-based HD, home HD, and PD. The higher medication complexities among patients receiving home dialysis could be attributed to the shift in dose administration responsibility of several parenteral medications. Despite this higher complexity, home HD patients had significantly better patient-related outcomes in terms of HRQoL and number of hospitalisations compared to facility-based HD patients. PD patients who were adherent to their medications also had significantly better patient-centred outcomes regarding HRQoL and serum phosphate levels compared to non-adherent patients. This reinforces the importance of encouraging patient adherence as a key focus in the daily care for this highly vulnerable group of patients. Last but not least, the findings from these studies could provide the foundational knowledge for future multi-centre interventional studies to address medication regimen complexities and improve outcomes in patients with ESKD.

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Appendix A:

Supplementary material for Chapter 2

- Medication regimen complexity and patient-centred outcomes in ESKD: A Systematic Review

S1 Appendix – PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title Page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Eligibility criteria
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Search strategy and sources
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	S2 Appendix
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Design and study selection
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Design and study selection
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Data extraction and analysis
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	S3 appendix

Section and Topic	Item #	Checklist item	Location where item is reported
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Quality assessment
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	S3 appendix
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	S3 appendix
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Not reported
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	S3 appendix
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	N/A
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Quality assessment
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Study selection
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Interventions to address complexity
Study characteristics	17	Cite each included study and present its characteristics.	S3 Appendix

Section and Topic	Item #	Checklist item	Location where item is reported
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	S4 Appendix; Study quality
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	S3 Appendix
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	N/A
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Discussion
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Study quality
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion
	23b	Discuss any limitations of the evidence included in the review.	Study limitations
	23c	Discuss any limitations of the review processes used.	Not reported
	23d	Discuss implications of the results for practice, policy, and future research.	Conclusion
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A

Section and Topic	Item #	Checklist item	Location where item is reported
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Statements & declarations
Competing interests	26	Declare any competing interests of review authors.	Statements & declarations
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Methods

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

S2 Appendix – Search strategies

Table S1. Search strategies for different databases combining the following two concepts.

#CONCEPT1	#CONCEPT2
Kidney failure	Medication regimen complexity
Renal failure	Medication regimen complexity index
End-stage kidney disease	MRCI
End stage kidney disease	Regimen complexity
End-stage renal disease	Treatment complexity
End stage renal disease	Medication complexity
End-stage kidney failure	Medication complexity index
End stage kidney failure	Medication complexity score
End-stage renal failure	Polypharmacy
End stage renal failure	Hyperpolypharmacy
ESRD	Pill burden
ESKD	Drug burden
ESRF	Treatment burden
ESKF	Medication related burden
Kidney disease	Treatment related burden
Renal disease	Drug related burden
Renal insufficienc*	
Kidney insufficienc*	
Chronic kidney failure	
Chronic renal failure	
Dialysis	
H#emodialysis	
Peritoneal dialysis	
Renal transplant*	
Kidney transplant*	

PubMed	
#1	"kidney failure"[All Fields] OR "renal failure"[All Fields] OR "end stage kidney disease"[All Fields] OR "end stage kidney failure"[All Fields] OR "end stage renal disease"[All Fields] OR "end stage renal failure"[All Fields] OR "esrd"[All Fields] OR "esrf"[All Fields] OR "eskd"[All Fields] OR "eskf"[All Fields] OR "kidney disease"[All Fields] OR "renal disease"[All Fields] OR "renal insufficiency"[All Fields] OR "kidney insufficiency"[All Fields] OR "renal insufficiencies"[All Fields] OR "kidney insufficiencies"[All Fields] OR "chronic renal failure"[All Fields] OR "chronic kidney failure"[All Fields] OR "dialysis"[All Fields] OR "haemodialysis"[All Fields] OR "hemodialysis"[All Fields] OR "peritoneal dialysis"[All Fields] OR "kidney transplant"[All Fields] OR "kidney transplantation"[All Fields] OR "renal transplant"[All Fields] OR "renal transplantation"[All Fields]

#2	"medication regimen complexity"[All Fields] OR "medication regimen complexity index"[All Fields] OR "mrci"[All Fields] OR "regimen complexity"[All Fields] OR "treatment complexity"[All Fields] OR "medication complexity"[All Fields] OR "medication complexity index"[All Fields] OR "medication complexity score"[All Fields] OR "polypharmacy"[All Fields] OR "hyperpolypharmacy"[All Fields] OR "pill burden"[All Fields] OR "drug burden"[All Fields] OR "treatment burden"[All Fields] OR "medication related burden"[All Fields] OR "treatment related burden"[All Fields] OR "drug related burden"[All Fields]
#3	#1 AND #2
Embase (via Ovid)	
#1	(Kidney failure.mp. or kidney failure/) or Renal failure.mp. or End stage kidney disease.mp. or (End stage renal disease.mp. or end stage renal disease/) or End stage renal failure.mp. or End stage kidney failure.mp. or ESKD.mp. or ESRD.mp. or ESRF.mp. or ESKF.mp. or (Kidney disease.mp. or kidney disease/) or Renal disease.mp. or (Renal Insufficiency, Chronic/ or Renal Insufficiency/ or Renal insufficienc*.mp.) or Kidney insufficienc*.mp. or (Chronic kidney failure.mp. or chronic kidney failure/) or Chronic renal failure.mp. or (home dialysis/ or extended daily dialysis/ or dialysis/ or Dialysis.mp.) or (H#emodialysis.mp. or hemodialysis/ or continuous hemodialysis/ or hemodialysis patient/) or (peritoneal dialysis.mp. or peritoneal dialysis/) or (transplantation/ or kidney graft/ or Kidney transplant*.mp. or kidney transplantation/) or Renal transplant*.mp.
#2	Medication regimen complexity.mp. or Medication regimen complexity index.mp. or MRCI.mp. or Regimen complex*.mp. or Treatment complex*.mp. or Medication complex*.mp. or Medication complexity index.mp. or Medication complexity score.mp. or (inappropriate polypharmacy/ or polypharmacy/ or Polypharmacy.mp. or Hyperpolypharmacy.mp. or Pill burden.mp. or Drug burden.mp. or Treatment burden.mp. or Medication related burden.mp. or Treatment related burden.mp. or Drug related burden.mp.
#3	#1 AND #2
Web of Science	
#1	ALL=("Kidney failure" OR "Renal failure" OR "End-stage kidney disease" OR "End stage kidney disease" OR "End-stage renal disease" OR "End stage renal disease" OR "End-stage kidney failure" OR "End stage kidney failure" OR "End-stage renal failure" OR "End stage renal failure" OR "ESRD" OR "ESKD" OR "ESRF" OR "ESKF" OR "Kidney disease" OR "Renal disease" OR "Renal insufficienc*" OR "Kidney insufficienc*" OR "Chronic kidney failure" OR "Chronic renal failure" OR "Dialysis" OR "Hemodialysis" OR "Peritoneal dialysis" OR "Renal transplant*" OR "Kidney transplant*")
#2	ALL=("Medication regimen complexity" OR "Medication regimen complexity index" OR "MRCI" OR "Regimen complexity" OR "Treatment complexity" OR "Medication complexity" OR "Medication complexity index" OR "Medication complexity score" OR "Polypharmacy" OR "Hyperpolypharmacy" OR "Pill burden" OR "Drug burden" OR "Treatment burden" OR "Medication related burden" OR "Treatment related burden" OR "Drug related burden")
#3	#1 AND #2
Scopus	

#1	(kidney AND failure OR renal AND failure OR end AND stage AND renal AND disease OR end AND stage AND kidney AND disease OR end AND stage AND renal AND failure OR end AND stage AND renal AND disease OR end-stage AND renal AND disease OR end-stage AND kidney AND disease OR end-stage AND renal AND failure OR end-stage AND renal AND disease OR esrd OR esrf OR eskd OR eskf OR kidney AND disease OR renal AND disease OR renal AND insufficienc* OR kidney AND insufficienc* OR chronic AND kidney AND failure OR chronic AND renal AND failure OR dialysis OR h?modialysis OR peritoneal AND dialysis OR renal AND transplant* OR kidney AND transplant*)
#2	(medication AND regimen AND complexity OR medication AND regimen AND complexity AND index OR mrci OR regimen AND complexity OR treatment AND complexity OR medication AND complexity OR medication AND complexity AND index OR medication AND complexity AND score OR polypharmacy OR hyperpolypharmacy OR pill AND burden OR drug AND burden OR treatment AND burden OR medication AND related AND burden OR treatment AND related AND burden OR drug AND related AND burden)
#3	#1 AND #2

S3 Appendix – Study characteristics

Table S2. Characteristics of medication regimen complexity studies included in systematic review

Study, Year	Region	Patients (% Male)	Mean Age (Years)	Treatment modality	Medication regimen complexity assessment method(s)	Description	Clinical/patient-related outcomes	Outcome results	Study design
Colombijn et al., 2021 [1]	Netherlands	162 (65.0)	58 (17)	In-centre HD (*n* = 130) and PD (*n* = 32)	Number of medications; prevalence of polypharmacy (use of ≥ 5 medications)	The mean number of medications was 12.2 ± 4.5, and 98% of the patients met the criteria for polypharmacy.	Number of dialysis-related symptoms (range 0-30)	Patients in the highest tertile of medications reported 4.1 more symptoms than in the lowest tertile (95% CI: 1.5-6.6; *p* = 0.002).	Multi-centre cross-sectional study
							HRQoL (measured with the Short Form-12)	In adjusted analyses, Physical Component Summary (PCS) was 0.6 point lower for each additional medication (95% CI: −0.9 to –0.2; *p* = 0.002). Mental Component Summary (MCS) was 4.9 point lower (95% CI: −8.8 to –1.0; *p* = 0.01) and 1.0 point lower (95% CI: −5.1–3.1; *p* = 0.63) for the highest (14-27 medications) and middle (11-13 medications) tertiles of medications, respectively, than for the lowest (2-10 medications) tertile.	
							Self-rated health	Patients with highest tertile (14–27 medications) reported 0.19 (95% CI: −0.28 to −0.09)	

							(measured with EQ-5D-5L)	point lower scores than patients with lowest tertile (2–10 medications). Self-rated health was 1.5 point lower for each medication (95% CI: −2.2 to –0.7; $p < 0.001$).	
Woźniak at el., 2018 [2]	Poland	136 (54.4)	Mean range of 47-54 (three groups of patients being compared based on number of prescribed drugs)	Kidney transplant-ation	Number of medications	The mean number of medications was 6.6 (range 2-16). 37 patients received ≤ 4 medications (group 1), 76 patients received 5-9 medications (group 2), and 23 patients with ≥ 10 medications (group 3).	QoL (assessed with KDQOL-36)	Patients treated with ≥10 drugs, compared to patients from the 2 other groups, had presented lower subscales results concerning the physical functioning (65.9 vs 84.5 in group 1 and 83.4 in group 2, $p < .001$ for both comparisons), pain (57.2 vs 82.7 and 76.5, respectively, $p < .001$ for both), social function (66.8 vs 82.1 and 80.4, respectively, $p = .04$ for both), and energy/fatigue (54.8 vs 67.7, $p = .03$ and 65.4, $p < .05$). Multivariate regression analysis revealed that the number of drugs independently influenced physical functioning, pain, and social function subscales.	Cross-sectional
Al-Mansouri et al., 2021 [3]	Qatar	280 (54.6)	59 (19)	HD ($n = 223$) and pre-dialysis ($n = 57$)	TBQ	The median (IQR) TBQ global score was 40.5 (38). HD patients experienced	HRQoL (assessed with KDQOL-36)	There was a strong, negative correlation between TBQ score and KDQOL-36 score [rs (251) = − 0.616, $p < 0.001$]. The higher the treatment-related burden, the lower the patients' QoL.	Single centre cross-sectional study

						significantly higher treatment burden compared to pre-dialysis patients with a median (IQR) of 45 (36) versus 25 (33), respectively (p < 0.001).			
Chan et al., 2022 [4]	Hong Kong, China	573 (55.1)	60.2 (11.9)	PD	Number of medications; daily pill load	Each patient took 7.5 ± 2.6 medications with 15.5 ± 8.5 tablets/day. Poly- (>5 concurrent medications) and hyper-polypharmacy (>10 concurrent medications) were present in 378 (66.0%) and 124 (21.6%) patients respectively.	All-cause mortality	Patients who took > 5 medications had the worst survival (71.6% vs 83.6%). In multivariate Cox regression model, medication number predicted mortality significantly (p = 0.005).	Single centre cohort study
							Fall, fracture and hospitalisation	Medication number predicted fall episodes (p = 0.02) and frailty progression (p = 0.002). Both medication number and daily pill load correlated with emergency room attendance rate (medication number: r = 0.22, p < 0.001; pill load: r = 0.15, p < 0.001), hospitalisation episodes (medication number: r = 0.23, p < 0.001; pill load: p = 0.16, p < 0.001) and period (medication number: r = 0.24,	

								$p < 0.001$; pill load: r = 0.17, $p < 0.001$). In multivariate linear regression model, medication number predicted fall episodes (unstandardised B 0.02, 95% CI 0.003 – 0.03, $p = 0.02$). Medication number ($p = 0.02$) and baseline FQ ($p < 0.001$) also predicted hospitalisation episodes. However, daily pill load did not predict hospitalisation.	
							Change in Frailty Score (FQ) and Subjective Global Assessment (SGA)	Medication number, but not daily pill load predicted baseline FQ ($p = 0.004$) and SGA ($p = 0.03$). One additional medication use conferred a 27.8% (OR, 95% CI: 1.15 – 1.42) increase in risk of being classified as frail (i.e., total FQ score above 6). There were significant correlations between medication number with FQ (r = 0.20, $p < 0.001$) but not with SGA ($p = 0.8$). Daily pills load weakly correlated with FQ only (r = 0.13, $p < 0.001$), but did not correlate with SGA ($p = 0.2$).	
Kitamura et al., 2021 [5]	Japan	339 (57.0)	67.3 (13.3)	HD	Number of prescribed medications	The mean numbers of prescribed essential[a] and	All-cause mortality	After adjusting for patient characteristics, the number of regularly prescribed medicines (10.0 ± 4.0) was	Retro-spective single centre

						non-essential medicines were 10.0 ± 4.0 and 7.9 ± 3.6, respectively. 55.5% of the patients were prescribed with ≥ 10 medications.		not correlated with prognosis (HR: 1.01, 95% CI 0.97–1.05, p = 0.60). However, the number of non-essential medicines (7.9 ± 3.6) was correlated with prognosis (HR: 1.06, 95% CI 1.01–1.10, p = 0.009). Adjusting for patient characteristics, patients who were prescribed > 10 non-essential medicines were found to have a significantly higher probability of mortality than those prescribed less than five non-essential medicines, with a relative risk of 2.01 (p = 0.004).	cohort study
Kimura et al., 2021 [6]	USA	337 (55.0)	56 (13)	HD	Number of medications	The mean number of medications was 10 ± 5.	Frailty	Patients taking >11 medications showed higher odds for frailty than the patients taking < 8 medications (OR 1.54, 95% CI 1.05– 2.26). Patients taking the highest number of medications showed significantly higher odds of having exhaustion and low physical activity over time than the patients taking < 8 medications (OR 1.62, 95% CI 1.11–2.35 and OR 1.52, 95% CI 1.09–2.02, respectively). During the 2-year of follow-up, 87 patients developed frailty	Cohort study across 14 dialysis centres

								among those who were nonfrail at baseline. Compared with the patients taking < 8 medications, the incidence of frailty was approximately 2-fold in those taking >11 medications (sub-distribution hazard ratio 2.15, 95% CI 1.32–3.48).	
Alikari et al., 2021 [7]	Greece	321 (65.0)	56.5 (10.0)	HD	Daily number of pills	The mean daily number of pills was 12.1 ± 2.4.	QoL (assessed with Greek version of Kidney Disease Questionnaire)	The daily number of pills was independently related to the QoL total score and its dimensions. There was a positive correlation between the number of pills with well-being and interpersonal dimensions.	Cross-sectional study across six HD units
							Medication adherence (assessed with the GR-SMAQ-HD)	The more pills the participants received per day, the worse their adherence to medication treatment.	
							Attendance at HD sessions	The more pills the participants received per day, the worse their attendance at HD sessions.	
Al-Mansouri et al., 2023 [8]	Qatar	280 (54.6)	59 (19)	HD (*n* = 223) and non-dialysis (stages 4 & 5 CKD) (*n* = 57)	Pill burden	The median (IQR) number of medications a patient consumed per day was 12 (5.7) oral medications	Treatment burden (assessed with TBQ)	Patients who had high pill-burden (≥112 pills/week) had significantly higher perceived treatment burden compared to low pill-burden patients (<112 pills/week) [47 (36.2) vs. 38.5 (36.7); *p* = 0.0085]. Patients who were prescribed	Single centre cross-sectional study

						and 3 (2) parenteral medications. HD patients were prescribed significantly higher number of parenteral medications relative to non-dialysis patients (median (IQR) of 3 (2) vs 1 (2), respectively (p < 0.001).		more than 12 oral medications per day perceived significantly higher treatment burden compared to the lower category [47 (37) vs. 36 (35.5); p = 0.006]. Similarly, patients who received higher parenteral medications (4–7) experienced significantly higher treatment burden compared to lower parenteral medication consumers (<4) [50.5 (38.7) vs. 36.5 (32.5); p < 0.001].	
Kosoku et al., 2022 [9]	Japan	211 (59.0)	55 (46-66)	Kidney transplant-ation	Number of medications	The mean number of medicines taken regularly was 9.4 ± 3.4 (range, 3-22) and the median number of medicines was 9 (IQR, 7-11). 43% were classified as hyper-polypharmacy (≥10	Frailty status (determined based on the Kihon Checklist (KCL))	Hyperpolypharmacy was associated with both the total KCL score (OR 1.13; p = .016) and being frail compared with being robust (OR 5.70; p = .007) after adjustments for age, sex, and BMI. The number of medications was associated with both the total KCL score (ß = 0.20; p < .001) and being frail compared with being robust (ß = 2.51; p < .001) after adjustments for age, sex, BMI, dialysis vintage, time after transplant, serum	Single centre cross-sectional study

						medications) participants.		albumin, and estimated glomerular filtration rate.	
Teles et al., 2018 [10]	Brazil	200 (60.5)	46.6 (15.4)	HD	Number of medications	Data on the mean number of medications used by patient was not reported.	Prevalence of depression (evaluated with BDI)	Patients who used > five medications had a higher prevalence of depression (38.7 vs. 24.5%, p = .039).	Single centre cross-sectional study
							QoL (assessed with SF-36)	Only 33 (25.6%) of the patients taking > five medications achieved physical functioning (PF) values greater than 50, compared to 96 (74.4%) of those taking < five medications (p < .05). Patients who used > five medications also had worse scores in the mental health domain (MH < 60 in 38.7 vs. 19.6%, p = .005). In the general health (GH) domain, it was observed that patients with a GH greater than 40 used fewer than 5 medications (p = .009).	
Alves et al., 2018 [11]	Brazil	197 (61.4)	56.5 (13.2)	HD	TCI; presence of poly-pharmacy (use of ≥ 5 medications)	65.9% of patients took > 5 medications.	QoL (assessed with SF-36)	No significant difference with SF-36 domains was noticed (p > 0.05) with regards to the presence of polypharmacy.	Single centre cross-sectional study
							Compliance to drug therapy (evaluated with MMAS-4 & BMQ)	The TCI was compared with the compliance profile and no significant difference was obtained for the MGT test (p = 0.953) and BMQ beliefs (p = 0.422). Logistic regression analysis showed association	

								between BMQ regimen versus TCI (OR = 0.856), BMQ-recall versus TCI (OR = 0.524), as well as between MGT and TCI (OR = 1.053).	
Toida et al., 2021 [12]	Japan	152 (57.9)	70.3 (10.6)	HD	Polypharmacy (≥ 6 internal medications)	The number of prescribed drugs per patient averaged 7.4 ± 3.7 at admission and 7.0 ± 3.5 at discharge for initial HD. 100 (65.8%) and 94 patients (61.8%) had polypharmacy at admission and discharge, respectively.	All-cause mortality	Polypharmacy did not correlate with all-cause mortality at admission and at discharge.	Prospective cohort study across two dialysis centres
							All-cause hospitalisation	Polypharmacy at discharge correlated with all-cause hospitalisation (adjusted HR [95% CI] 2.81 [1.46–5.41]), but not at admission.	
Adhikari et al., 2016 [13]	India	110 (65.5)	38.1 (12.8)	Renal transplant-ation	Pill burden	The mean pill burden was 18.3 ± 5.38 initially (after discharge following transplant) to 14.4 ± 4.67 pills at the end of the 12-month	Medication compliance	No association was observed between individual patients' median pill burden across the 12-month observation period and their compliance status. There was no statistically significant difference in median pill burden between compliant and noncompliant subgroups.	Prevalence study across two tertiary care hospitals

						observation period.			
Yılmaz et al., 2022 [14]	Turkey	52 (51.9)	53.7 (15.7)	HD	Pill burden	The mean number of daily tablets was 13.5 (4–22).	Interdialytic weight gain (IDWG)	There were significant differences in pill burden between the patients with high IDWG and normal IDWG (mean 17.2 and 11.6 respectively, p = 0.02). A significant positive correlation was observed between IDWG and pill burden (r = 0.243, p = 0.041). In univariate logistic regression analysis, pill burden (p: 0.028, OR: 1.218, CI: 1.061–1.872) was related to high IDWG. In multivariate logistic regression analysis, pill burden was an independent factor associated with high IDWG.	Single centre cross-sectional study
							Prevalence of thirst and xerostomia (evaluated using the DTI and XI, respectively)	No significant relationship was observed between pill burden and unstimulated saliva flow rate (USFR) (p > 0.05).	
Murasawa et al., 2021 [15]	Japan	188 (67.0)	68.7 (10.3)	HD	Pill burden	The mean number of daily tablets was 19.7 ± 10.0.	Interdialytic weight gain percentage	A significant positive correlation was observed between %IDWG and the number of daily tablets (r = .215, p = .003). Multiple linear regression analysis showed a regression	Multi-centre cross-sectional study

								coefficient of 0.021 (95% CI: 0.004-0.039), indicating that one additional tablet prescription increased the IDWG by 0.021%.	
							High %IDWG	The OR was 1.04 (95% CI: 1.000-1.078) when adjusted by the same covariates as in the primary analysis, indicating that one additional tablet prescription per day increased the risk of %IDWG by >3.0%.	
Chiu et al., 2009 [16]	USA	233 (58.0)	52.9 (14.7)	In-centre HD (*n* = 184), home HD (*n* = 5), and PD (*n* = 44)	Total number of medications; total pill burden; pill burden from phosphate binders	The mean number of medications was 11 ± 4 (nine oral two parenteral); the oral medications contributed to a median daily pill burden of 19 (IQR, 12). The median pill burden from phosphate binders was 9 (IQR, 6).	Serum phosphate level (SPL) (mean of all measured values over three-month period)	There was a significant direct relationship between SPLs and pill burden from phosphate binders (r = 0.16, *p* = 0.01). There was a modest but significant increase in SPLs with increasing quintiles of pill burden from phosphate binders. On multivariate, linear regression analysis, higher SPLs were independently associated with greater pill burden from phosphate binders.	Cross-sectional study across three dialysis centres
							HRQoL (assessed with SF-36)	Higher pill burden was independently associated with lower physical component summary scale scores on HRQoL on both univariate and multivariate analyses. There was no relationship between	

								pill burden and mental component scores on either univariate or multivariate analyses.	
							Adherence to phosphate binder(s) (calculated as the ratio of the actual to the expected no. of pills consumed from the time of last refill to the date of the study visit)	There was a significant inverse relationship between adherence to phosphate binders and pill burden from phosphate binders (r = -0.19, p = 0.006). There was a modest relationship between pill burden from phosphate binders and adherence and SPLs.	
Cardone et al., 2011 [17]	USA	35 (68.6)	54.2 (10.8)	Nocturnal home HD (NHHD)	Number of medications; pill burden; medication administration burden (number of administrations per day); MRCI	Compared with the baseline of 10.5 ± 4.4 home medications, the number of medications was increased at day 1 (12.0 ± 4.0) of NHHD (p < 0.05) and at 12 months (12.2 ± 4.1) (p < 0.05). The patients had a mean pill burden of 19.1	HRQoL (assessed with SF-36)	None of the measures of medication regimen complexity were correlated with the SF-36 score at baseline, 6, 12 and 24 months of NHHD.	Non-randomised experi-mental study

						± 11.4 and the beginning and 15.5 ± 9.5 at the end of the study. Shortly after starting NHHD, patients showed a sustained decrease in medication administration burden from 5.0 ± 1.5 at baseline to 3.6 ± 1.5 at 24 months on NHHD (p < 0.05). At baseline, the mean MRCI score was 22.4 ± 10.2 and increased to 28.3 ± 11.6 at 24 months (p < 0.05).			
Ghimire et al., 2016 [18]	Australia	53 (58.5)	67.9 (11.5)	HD	Number of medications; pill burden; MRCI	The average prescribed medications was 11.1 (range 4-19), with a mean daily pill	Self-reported medication adherence (assessed by the MMAS-4)	The number of medicines prescribed, daily pill burden and MRCI scores did not differ between adherent and non-adherent patients while a significant number of patients prescribed with phosphate	Single centre cross-sectional study

						burden of 16.3 (range 5-35). The mean MRCI was 27.0 ± 10.9 (range 9.5-55.0).		binders (73.3%, *n* = 22) were found to be non-adherent on self-reports. No association was found between regimen complexity and self-reported adherence.	
							Objective adherence (measured using the mid-week, pre-dialysis serum phosphate levels in the sub-group of patients who were prescribed with phosphate binder(s))	The adherent patients had a significantly higher daily pill burden ($p < 0.01$) and regimen complexity scores ($p = 0.01$). The analysis based on the objective measure identified higher regimen complexity (OR 1.14; 95% CI 1.02–1.27) as one of the significant predictors of adherence.	
Parker et al., 2019 [19]	Norway	157 (73.0)	76 (7.2)	HD (*n* = 73), PD (*n* = 19), predialytic CKD stage 5 (*n* = 65)	MRCI; pill burden	The MRCI score was 24.7 ± 7.9 in HD patients, 23.3 ± 6.4 in PD patients and 20.5 ± 7.3 in predialytic patients. The overall number of medications was 11 (range 4-19) and 16 (range 3-45)	Medication adherence (evaluated with MMAS-8)	The multivariable logistic regression analyses found no association of medication complexity, age or other variables with medication adherence.	Cross-sectional study across three hospitals

						pills taken daily.			
Neri et al., 2011 [20]	Italy	1,238 (64.0)	median age: 67	HD	Daily tablet prescribed; burden of oral therapy (BOT)	Mean daily burden was 9.7 tablets. The mean burden of oral therapy was 2.2 ± 0.9 in adherent patients and 2.5 ± 0.9 in non-adherent patients.	Medication adherence (evaluated with MMAS-4)	Both the number of daily tablets prescribed and BOT were significantly associated to patients' adherence. In subjects reporting low levels of burden from oral therapy, each pill added to the prescription regimen was associated to a 5% increase in non-adherence risk (p = 0.01); on the contrary, the association between regimen complexity and medication adherence was not significant for patients reporting higher levels of perceived BOT.	Cross-sectional study across 54 HD centres
Hardinger et al., 2012 [21]	USA	68	54	Renal transplant-ation	Pill burden	The median pre-transplantation pill burden was 15 pills / day, which increased to 25 pills / day at 1 month after transplantation and returned to 16 pills / day by 1 year after transplantation.	Renal function (serum creatinine concentration)	Higher pre-transplantation pill burden was associated with increased serum creatinine concentration at 6 months after transplantation (r = 0.288, p = 0.017). Higher pill burdens at 1 month (r = 0.364, p = 0.002), 3 months (r = 0.332, p = 0.006), and 6 months (r = 0.374, p = 0.002) were associated with increased 3-month serum creatinine concentration.	Single centre retrospec-tive prevalence study

BDI, Beck Depression Inventory; BMQ, Brief Medication Questionnaire; CI, confidence interval; DTI, dialysis thirst inventory; GR-SMAQ-HD, GR-Simplified Medication Adherence Questionnaire-Haemodialysis; HD, haemodialysis; HR, hazard ratio; HRQoL, health-related quality of life; IQR, interquartile range; Kidney Disease Quality of Life Instrument, KDQOL-36; MMAS-4, 4-item Morisky Medication-Taking Adherence Scale; MMAS-8, 8-item Morisky Medication-Taking Adherence Scale; MRCI, Medication Regimen Complexity Index; PD, peritoneal dialysis; SF-36, 36-Item Short Form Health Survey; TBQ, Treatment Burden Questionnaire; TCI, Therapeutic Complexity Index; QoL, quality of life; XI, xerostomia inventory

[a]Antihypertensive drugs, diuretics, antidiabetics, and statins were categorised as essential medicines since these medicines reportedly exert favourable effect on the prognosis of patients on HD.

Table S3. Characteristics of interventional studies to address medication regimen complexity included in systematic review

Study, Year	Region	Patients (% Male)	Mean Age (Years)	Treatment modality	Interventions implemented to address or improve medication complexity	Description	Clinical/patient-related outcomes	Outcome results	Study design
George et al., 2021 [22]	India	150 (68.7)	60.4 (10.9)	HD	Active deprescribing program	The de-prescription tool was formulated by the nephrologist and clinical pharmacist and was tested on 25 patients before the start of the study as a pilot project.	Average number of medications and pills per patient before and 12 weeks after implementation of deprescribing program	After deprescription, there were significant reduction in the number of medications from 11 (IQR 8–13.25) to 8 (IQR 6–9) (p < .001) and reduction in the number of pills from 16 (IQR 12.75–21.25) to 11 (IQR 8–14.25) (p < .001). Pill burden accessed using LMQ-VAS score also had a significant reduction from 7 (IQR 5–8) to 4 (IQR 3–5) (p < .001).	Single centre non-randomised experi-mental study

Kim et al., 2021 [23]	Korea	95 (58.9)	74.9 (7.3)	HD (*n* = 17), pre-dialysis, CKD stage 5 (*n* = 5), CKD stages 2-4 (*n* = 73)	Geriatric medication management service (MMS)	Under the geriatric MMS, designated pharmacists provide weekly patient counselling. Pharmacists evaluated drug-related issues, including medication adherence, effectiveness of medications, current or past adverse drug reactions, drug–drug interactions, patient dependency on medications that were not indicated at the time of counselling, and the necessity for deprescribing.	Number of overall medications	The number of overall medications decreased from 13.5 ± 4.3 to 10.9 ± 3.8 ($p < 0.001$).	Single centre, retro-spective non-randomised experi-mental study
							Proportion of patients with excessive polypharmacy (concurrent use of ≥ 10 medications)	The proportion of patients with excessive polypharmacy reduced from 85.1% to 59.8% after geriatric MMS ($p < 0.001$).	
							Number of potentially inappropriate medications (PIMs)	The number of PIMs per patient decreased from 1.6 ± 1.4 to 1.0 ± 1.2 ($p < 0.001$). The proportion of patients who used at least one PIM and ≥ 3 PIMs significantly decreased from 77.0% to 59.8% and 23.0% to 10.3%, respectively ($p < 0.001$).	
							Anticholinergic burden score (determined using KABS)	The anticholinergic burden score decreased from 2.7 ± 2.6 at baseline to 1.8 ± 2.2 after providing geriatric MMS ($p < 0.001$).	
McIntyre et al., 2017 [24]	Canada	35 (40.0)	65 (16.5)	In-centre HD	Deprescribing tool	A de-prescribing tool was developed and implemented for five target medications: quinine, diuretics, α_1-blockers, proton	Proportion of target medications completely deprescribed after 4 weeks	After 4 weeks, 31 of 40 (78%) target medications were deprescribed in 35 patients.	Single centre non-randomised experi-mental study
							Proportion of target medications completely	Six months after deprescription, only 5 of 31 (16%) medications	

						pump inhibitors (PPIs), and HMG-CoA reductase inhibitors (statins).	deprescribed after 6 months	discontinued were re-prescribed.	

HD, haemodialysis; IQR, interquartile range; KABS, Korean Anticholinergic Burden Scale; LMQ-VAS, Living with Medication Questionnaire-Visual Analogue Scale

S4 Appendix – Appraisal checklist

1. Adapted appraisal checklist according to Joanna Briggs Institute (JBI) critical appraisal tool

Cross Sectional Studies		
1. Were the criteria for inclusion in the sample clearly defined?	☐	Y
	☐	N
	☐	U
	☐	NA
2. Were the study subjects and the setting described in detail?	☐	Y
	☐	N
	☐	U
	☐	NA
3. Was the exposure measured in a valid and reliable way?	☐	Y
	☐	N
	☐	U
	☐	NA
4. Were objective, standard criteria used for measurement of the condition?	☐	Y
	☐	N
	☐	U
	☐	NA
5. Were confounding factors identified?	☐	Y
	☐	N
	☐	U
	☐	NA
6. Were strategies to deal with confounding factors stated?	☐	Y
	☐	N
	☐	U
	☐	NA
7. Were the outcomes measured in a valid and reliable way?	☐	Y
	☐	N
	☐	U
	☐	NA
8. Was appropriate statistical analysis used?	☐	Y
	☐	N
	☐	U
	☐	NA

Cohort Studies		
1. Were the two groups similar and recruited from the same population?	☐	Y
	☐	N
	☐	U
	☐	NA
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	☐	Y
	☐	N
	☐	U
	☐	NA
3. Was the exposure measured in a valid and reliable way?	☐	Y
	☐	N
	☐	U
	☐	NA
4. Were confounding factors identified?	☐	Y
	☐	N
	☐	U
	☐	NA
5. Were strategies to deal with confounding factors stated?	☐	Y
	☐	N
	☐	U
	☐	NA
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☐	Y
	☐	N
	☐	U
	☐	NA
7. Were the outcomes measured in a valid and reliable way?	☐	Y
	☐	N
	☐	U
	☐	NA
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	☐	Y
	☐	N
	☐	U
	☐	NA
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	☐	Y
	☐	N
	☐	U
	☐	NA

10. Were strategies to address incomplete follow up utilized?	☐	Y
	☐	N
	☐	U
	☐	NA
11. Was appropriate statistical analysis used?	☐	Y
	☐	N
	☐	U
	☐	NA
Prevalence studies		
1. Was the sample frame appropriate to address the target population?	☐	Y
	☐	N
	☐	U
	☐	NA
2. Were study participants sampled in an appropriate way?	☐	Y
	☐	N
	☐	U
	☐	NA
3. Was the sample size adequate?	☐	Y
	☐	N
	☐	U
	☐	NA
4. Were the study subjects and the setting described in detail?	☐	Y
	☐	N
	☐	U
	☐	NA
5. Was the data analysis conducted with sufficient coverage of the identified sample?	☐	Y
	☐	N
	☐	U
	☐	NA
6. Were valid methods used for the identification of the condition?	☐	Y
	☐	N
	☐	U
	☐	NA
7. Was the condition measured in a standard, reliable way for all participants?	☐	Y
	☐	N
	☐	U
	☐	NA
8. Was there appropriate statistical analysis?	☐	Y

	☐ ☐ ☐	N U NA
9. Was the response rate adequate, and if not, was the low response rate managed appropriately?	☐ ☐ ☐ ☐	Y N U NA
Quasi-Experimental Studies		
1. Is it clear in the study what is the "cause" and what is the "effect" (i.e. there is no confusion about which variable comes first)?	☐ ☐ ☐ ☐	Y N U NA
2. Was there a control group?	☐ ☐ ☐ ☐	Y N U NA
3. Were participants included in any comparisons similar?	☐ ☐ ☐ ☐	Y N U NA
4. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	☐ ☐ ☐ ☐	Y N U NA
5. Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	☐ ☐ ☐ ☐	Y N U NA
6. Were the outcomes of participants included in any comparisons measured in the same way?	☐ ☐ ☐ ☐	Y N U NA
7. Were outcomes measured in a reliable way?	☐ ☐ ☐ ☐	Y N U NA

8. Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analysed?	☐ ☐ ☐ ☐	Y N U NA
9. Was appropriate statistical analysis used?	☐ ☐ ☐ ☐	Y N U NA

Y, Yes; N, No; U, Unclear; NA, Not Applicable

2. Quality of included studies

	Cross Sectional Studies								
	1	2	3	4	5	6	7	8	Total Quality Score (Out of 8)
Colombijn et al, 2021	Y	Y	Y	Y	Y	Y	Y	Y	8
Woźniak et al, 2018	N	N	Y	Y	Y	Y	Y	Y	6
Mansouri et al, 2021	Y	Y	Y	Y	N	N	Y	Y	6
Alikari et al., 2021	Y	Y	Y	Y	Y	Y	Y	Y	8
Al-Mansouri et al, 2023	Y	Y	Y	Y	Y	Y	Y	Y	8
Kosoku et al., 2022	Y	Y	Y	Y	Y	Y	Y	Y	8
Teles et al., 2018	Y	Y	Y	Y	Y	Y	Y	Y	8
Alves et al., 2018	U	Y	Y	Y	Y	N	Y	Y	6
Yılmaz et al., 2022	Y	Y	Y	Y	Y	Y	Y	Y	8
Murasawa et al., 2021	Y	Y	Y	Y	Y	Y	Y	Y	8
Chiu et al., 2009	Y	Y	Y	Y	Y	Y	Y	Y	8
Ghimire et al., 2016	Y	Y	Y	Y	Y	Y	Y	Y	8
Parker et al., 2019	Y	Y	Y	Y	Y	Y	Y	Y	8

Neri et al., 2011	Y		Y		Y		Y		Y		Y	8
Cohort Studies												
	1	2	3	4	5	6	7	8	9	10	11	Total Quality Score (Out of 11)
Chan et al, 2022	NA	NA	Y	Y	Y	Y	Y	Y	Y	NA	Y	8
Kitamura et al., 2021	NA	NA	Y	Y	Y	Y	Y	Y	Y	NA	Y	8
Kimura et al, 2021	NA	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
Toida et al, 2021	NA	NA	Y	Y	Y	Y	Y	Y	Y	NA	Y	8
Prevalence studies												
	1	2	3	4	5	6	7	8	9			Total Quality Score (Out of 9)
Adhikari et al, 2016	Y	Y	U	Y	Y	Y	U	Y	Y			7
Hardinger et al, 2012	Y	Y	U	Y	Y	Y	Y	Y	Y			8
Quasi-Experimental Studies												
	1	2	3	4	5	6	7	8	9			Total Quality Score (Out of 9)
Cardone et al., 2011	Y	N	Y	Y	Y	Y	Y	Y	Y			8
George et al., 2021	Y	N	Y	Y	Y	Y	Y	Y	Y			8
Kim et al., 2021	Y	N	Y	Y	Y	Y	Y	Y	Y			8
McIntyre et al., 2017	Y	N	Y	Y	Y	Y	Y	Y	N			7

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PROSPERO Application

The impact of medication regimen complexity on patient-related and clinical outcomes in kidney failure: A Systematic Review

Jing Xin Goh, Wubshet Tesfaye, Connie Van, Kamal Sud, Surjit Tarafdar, Ronald Castelino

To enable PROSPERO to focus on COVID-19 submissions, this registration record has undergone basic automated checks for eligibility and is published exactly as submitted. PROSPERO has never provided peer review, and usual checking by the PROSPERO team does not endorse content. Therefore, automatically published records should be treated as any other PROSPERO registration. Further detail is provided here.

Citation

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Review question

What is the impact of medication regimen complexity on patient-related and clinical outcomes in kidney failure?

Searches

The following databases will be searched from inception to November 2023: PubMed, Embase, Scopus and Web of Science. Only studies published in English will be included in the review. The search strategy will be developed in consultation with a research librarian and the study investigators. A combination of controlled vocabulary search terms (i.e. Medical Subject Headings) will be used, and the PubMed search strategy will be adapted for the other databases. Reference lists of all relevant and selected publications will be searched manually to identify further studies.

Types of study to be included

Inclusion criteria

1. Studies that were conducted in patients with kidney failure ≥ 18 years of age, undergoing dialysis or transplantation, and included measure(s) of medication regimen complexity.
2. All medication regimen complexity measures such as complexity index, polypharmacy, and pill burden were considered if medication regimen complexity definition was provided, and the extent of complexity was reported.
3. Studies that related medication regimen complexity with patient-related and clinical outcomes.
4. Studies with longitudinal or cross-sectional designs were included for review.
5. No restriction on date of publication.
6. Studies published in English.

Exclusion criteria

1. Studies that included patients who opted out of dialysis and are on kidney supportive care.
2. Studies from which the medication regimen complexity cannot be determined.
3. Studies that did not relate medication regimen complexity with patient-related and clinical outcomes.
4. Review articles, editorials, letters to the editor, opinion pieces, commentaries, case-reports, case studies and images that were published without data on medication regimen complexity.

Condition or domain being studied

Patients with kidney failure

Participants/population

Patients with kidney failure ≥ 18 years of age, undergoing dialysis or transplantation. Patients who opted out of dialysis and are on kidney supportive care are excluded from the review.

Intervention(s), exposure(s)

Medication regimen complexity as defined by measures such as complexity index, polypharmacy, and pill burden.

Comparator(s)/control

Not applicable

Main outcome(s)

Patient-related and clinical outcomes

Additional outcome(s)

Treatment/Health outcomes

Quality of life

Medication adherence

Adverse drug events

Medication-related problems

Hospitalisation

Morbidity

Mortality

Data extraction (selection and coding)

After an initial literature search the resulting abstract will be screened against pre-specified eligibility criteria. Studies that met the criteria will then be included in the study by each independent reviewer. A final reconciliation list of included studies will be drawn between these two independent reviewers. Where disagreement arose regarding a particular study eligibility between the independent reviewers, this will be resolved by consensus; failing which a third reviewers adjudicates between them.

Risk of bias (quality) assessment

Loney criteria will be used to determine the risk of bias and by implication the methodological quality of the included studies.

Strategy for data synthesis

The following variables will be extracted from the studies: Last name of first author, year of publication, study design, site, country where study was carried out, population, age, gender distribution, sample size, proportion of kidney failure patients with complex medications, iteration of medication complexity definitions (where available), and duration of study.

Analysis of subgroups or subsets

Where necessary we will carry out meta-regression analysis on secondary outcome measures.

Contact details for further information

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Organisational affiliation of the review

The University of Sydney

Review team members and their organisational affiliations

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Dr Wubshet Tesfaye. The University of Queensland

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Assistant/Associate Professor Kamal Sud. The University of Sydney

Dr Surjit Tarafdar. Blacktown Hospital, Sydney; Western Sydney University

Assistant/Associate Professor Ronald Castelino. The University of Sydney

Collaborators

Ms Tess Aitken. University of Sydney Library

Anticipated or actual start date

01 December 2023

Anticipated completion date

31 May 2024

Funding sources/sponsors

No funding required.

Conflicts of interest

Language

English

Country

Australia

Stage of review [1 change]

Review Completed not published

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

MeSH headings have not been applied to this record

Date of registration in PROSPERO

17 April 2024

Date of first submission

06 April 2024

Stage of review at time of this submission [1 change]

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Revision note

Updated review progress. Review completed, currently under review for publication.

Appendix B:

Supplementary material for Chapter 3

- Methodology

Participant Information Sheet

Participant Information Sheet/Consent Form

Non-Interventional Study - *Adult providing own consent*

Blacktown Hospital, Mount Druitt

Title	**The impact of medication regimen complexity on patient-related and clinical outcomes in end stage kidney disease**
Short Title	**Medications complexity and adherence in kidney failure**
Coordinating Principal Investigator/ Principal Investigator	A/Prof Ronald Castelino
Associate investigator(s)	Dr Surjit Tarafdar, A/Prof Kamal Sud, Dr Wubshet Tesfaye; Jing Xin Goh
Location	Blacktown Hospital, WSLHD

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project named, "The impact of medication regimen complexity on patient-related and clinical outcomes in end stage kidney disease." This is because you are currently undergoing dialysis within Western Sydney Local Health District (WSLHD).

This Participant Information Sheet/Consent Form tells you about the research project. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether to take part, you might want to talk about it with a relative, friend or local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.
If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read.
- Consent to take part in the research project.
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

This main purpose of this research is to investigate medication regimen complexity in patients on dialysis and understand the association between the complexity and adherence as well as treatment outcomes. We anticipate the outcome of this research will help us develop strategies to improve medication adherence and treatment outcomes in people undergoing dialysis.

The results of this research will be used by student researcher Jing Xin Goh to obtain a Master of Philosophy degree.

The study has been initiated by researchers, A/Prof Ronald Castelino, Dr Surjit Tarafdar, A/Prof Kamal Sud, Dr Wubshet Tesfaye and Jing Xin Goh.

3 What does participation in this research involve?

You will be provided an explanation of the study, and any inquires you may have will be addressed. If you agree to participate in this study, you will be asked to sign the participant consent form. The researchers will conduct and complete the data collection during the dialysis sessions or when you visit your doctor, in which you will be asked to fill out questionnaires asking you about your:

- Understanding and beliefs about taking the prescribed medications
- Satisfaction with dialysis treatment
- Quality of life.

This information will be collected using 3 short questionnaires and one grading scale. The entire process will take approximately 15 minutes of your time.

A review of your electronic medical records will also be conducted to acquire relevant data. There are no costs associated with participating in this research project, nor will you be paid.

4 What do I have to do?

The only requirement we have is complete the questions provided in the questionnaires and surveys to the best of your ability. You do not have to make any changes to your diet, medications, or your lifestyle. There will be no changes to your current dialysis treatment.

5 Other relevant information about the research project

The research project is being carried out at the Blacktown Regional Dialysis Centre and the University of Sydney. All the patients undergoing dialysis at the centre are being invited to participate in the study.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with the Blacktown Regional Dialysis Centre or the University of Sydney.

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital. Your decision to participate or not participate will not affect your routine treatment.

8 What are the possible benefits of taking part?

There are no direct benefits from this research. The information will help the research team in developing strategies to improve medication taking behaviour in people with kidney disease including yourself in the future.

9 What are the possible risks and disadvantages of taking part?

This research does not involve any interventional treatment, hence there is no foreseeable risk regarding your participation in the study.

10 What will happen to my test samples?

This research project does not involve collection of any test samples.

11 What if new information arises during this research project?
This research project does not involve initiation or change of your treatment. The research team is only collecting data on your existing medication regimen. If any new information regarding your medications becomes available, your regular health care team will inform you about it.

12 Can I have other treatments during this research project?
Participation in this research project does not affect your regular/additional treatments at the hospital.

13 What if I withdraw from this research project?
You have the option to withdraw for this study at any point in time.
If you decide to withdraw from this research project, please notify a member of the research team regarding your withdrawal. If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You will not be identifiable in any of the data stored during the research.

14 Could this research project be stopped unexpectedly?
This research project is an observational study, and the participants data will be collected at only one point for analysis.

15 What happens when the research project ends?
You can be provided a summary of the results when the research is completed, and results have been compiled.

Part 2 How is the research project being conducted?

16 What will happen to information about me?
By signing the consent form, you consent to the study research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. The data supplied will be kept separately from and without any identifying information in password-protected files on a shared drive of the Pharmacy Department at Blacktown Hospital.

Your information will only be used for the purpose of this research project, and it will only be disclosed with your permission, except as required by law. Information about you may be obtained from your health records held in the electronic medical record (eMR) for the purpose of this research. By signing the consent form, you agree to the research team accessing the eMR to collect relevant health information for the research project.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified. All data related to the study will be retained for five years and then discarded.

17 Complaints and compensation
This study has been approved by the Human Research Ethics Committee (HREC) at Western Sydney Local Health District (WSLHD). If you have any concerns about the conduct of the study, please contact the HREC at the WSLHD using the details listed below.

18 Who is organising and funding the research?
This research project is being conducted by the Pharmacy department, Blacktown hospital and the University of Sydney. The results from this study will form part of Master of Philosophy student's thesis (Ms Jing Xin Goh).

19 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent committee: HREC. The ethical aspects of this research project have been approved by the HREC of WSLHD.

This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007). This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project you can contact the principal study investigator A/Prof Ronald Castelino, on 02 9351 0609 or email on Ronald.Castelino@health.nsw.gov.au.

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Patients of Blacktown Mount Druitt Hospitals:
Office of the General Manager, Blacktown-Mt Druitt Hospitals
Email: wslhd-bmdhexec@health.nsw.gov.au
Telephone: 98818000 (Blacktown Hospital switchboard) and ask to be connected to the Office of the General Manager.

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	*WSLHD Human Research Ethics Committee*
Executive Officer	*Kellie Hansen*
Telephone	*02 8890 9007*
Email	*Wslhd-researchoffice@health.nsw.gov.au*

Consent Form - *Adult providing own consent*

Title	**The impact of medication regimen complexity on patient-related and clinical outcomes in end stage kidney disease**
Short Title	**Medications complexity and adherence in kidney failure**
Coordinating Principal Investigator/ Principal Investigator	A/Prof Ronald Castelino
Associate investigator(s)	Dr Surjit Tarafdar, A/Prof Kamal Sud, Dr Wubshet Tesfaye; Jing Xin Goh
Location	Blacktown Hospital, Mount Druitt

Declaration by Participant

I have read the Participant Information Sheet, or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the project without affecting my future health care.

I acknowledge that the pharmaceutical company and any regulatory authorities may have access to my medical records **specifically related** to this project to monitor the research in which I am agreeing to participate. However, I understand my identity will not be disclosed to anyone else or in publications or presentations.

I understand that I will be given a signed copy of this document to keep.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to *the University of Sydney* concerning my condition and treatment for the purposes of this project. I understand that such information will remain confidential.

Name of Participant (please print) _____

Signature _____ Date _____

Under certain circumstances if a witness is required to provide informed consent.*

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project; its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

Form for Withdrawal of Participation - *Adult providing own consent*

Title	**The impact of medication regimen complexity on patient-related and clinical outcomes in end stage kidney disease**
Short Title	**Medications complexity and adherence in kidney failure**
Coordinating Principal Investigator/ Principal Investigator	A/Prof Ronald Castelino
Associate investigator(s)	Dr Surjit Tarafdar, A/Prof Kamal Sud, Dr Wubshet Tesfaye; Jing Xin Goh
Location	Blacktown Hospital, Mount Druitt

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with Blacktown Hospital or the University of Sydney.

Name of Participant (please print) _____

Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project, and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

Ethics Approval Letter

Health
Western Sydney
Local Health District

HREC Committee Secretariat:

A/Prof Clement Loy
Medical Graduate – Neurologist

Mrs Patricia Fa
Clinical Trials Pharmacist

HREC Committee Members:

Ms Narelle Bell
Lawyer

Dr Grahame Ctercteko
Medical Graduate – Colorectal Surgeon

Prof Angus Dawson
Professor of Bioethics

Mr John Fisher
Lawyer

Mr John McLeod
Layman

Mr Sean Mungovan
Physiotherapist

Mrs Janette Parry
Laywoman

Dr Christopher Ryan
Medical Graduate - Psychiatrist

Mrs Katherine Schaffarczyk
Nurse Educator

Prof Ramon Shaban
Nursing – Community Health

Dr Tony Skapetis
Dental Graduate

Dr Howard Smith
Medical Graduate – Endocrinologist

Ms Jennifer Sullivan
Laywoman

Ms Shane Waterton
Laywoman

Dr Christine Wearne
Clinical Psychologist

Mrs Christina Whitehead
Research Co-Ordinator - RN

Research Office File No: (5810)
HREC Ref: AU RED LNR/18/WMEAD/330
SSA Ref: AU RED

3 October 2018

Dr Ronald Castelino
Department of Pharmacy
Blacktown Hospital

Dear Dr Castelino

LNR Research Project: Medication regimen complexity and adherence to prescribed medications in pre-dialysis patients

Your request to undertake the above protocol as a Low and Negligible Risk (LNR) research project was reviewed by a subcommittee of members of the Scientific Advisory Committee (SAC) and the Human Research Ethics Committee (HREC). We are satisfied that your protocol meets the criteria for an LNR research project and does not require review by the full HREC.

The WSLHD HREC has been accredited by the NSW Ministry of Health as a lead HREC to provide the single ethical and scientific review of proposals to conduct research within the NSW public health system. This lead HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and the *CPMP/ICH Note for Guidance on Good Clinical Practice.*

This proposal meets the requirements of the National Statement and
I am pleased to advise that the HREC has granted ethical approval of this LNR research project to be conducted by you at:

- Blacktown Hospital

The following documentation has been reviewed and approved by the HREC:

- LNR Application Form submission code AU/6/9CD736
- Protocol version 2, dated 4 September 2018
- Participant Information and Consent Form version 4, dated 3 October 2018
- Questionnaire Version 2, dated 4 September 2018
- Data Collection Form version 2 dated 3 October 2018

Please note the following conditions of approval:

- The chief investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project.

HUMAN RESEARCH ETHICS COMMITTEE

Research Office, Level 2, REN Building
Westmead Hospital, Hawkesbury & Darcy Roads, Westmead NSW 2145
Telephone 02 8890 9007 Facsimile 02 9845 9636
Email: WSLHD-ResearchOffice@health.nsw.gov.au

WESTERN SYDNEY LOCAL HEALTH DISTRICT
ABN 48 702 394 764
WSLHD Office, Westmead Hospital Campus
Institute Road, Westmead NSW 2145
PO Box 533, Wentworthville NSW 2145
Telephone 02 8890 5555

- The chief investigator will immediately report any protocol deviation / violation, together with details of the procedure put in place to ensure the deviation / violation does not recur.
- Proposed amendments to the protocol or conduct of the research which may affect the ethical acceptability of the project, must be provided to the HREC to review in the specific format. Copies of all proposed changes must also be provided to the research governance officer.
- The HREC must be notified, giving reasons, if the project is discontinued at a site before the expected date of completion.
- The Coordinating Chief Investigator must provide an annual report to the HREC and a final report at completion of the study, in the specified format. HREC approval is granted for a period of 12 months and ongoing approval is contingent upon annual submission. Annual Reports for all studies should be submitted in November, they will be processed and presented to the HREC at their January meeting. A copy of the Annual / Final Research Report Form can be obtained electronically from the Research Office on request.
- It should be noted that compliance with the ethical guidelines is entirely the responsibility of the investigators.

You are reminded that this letter constitutes *ethical approval only*. You must not commence this research project until separate authorisation from the Chief Executive or delegate has been obtained. Copies of this letter, together with any approved documents as enumerated above, must be forwarded to the Research Governance Officer as part of the Site Specific Assessment (SSA) application.

In all future correspondence concerning this study, please quote Research Office File number *(5810).* The HREC wishes you every success in your research.

Yours sincerely

Mrs Patricia Fa
Secretary
WSLHD Human Research Ethics Committee

cc: Research Governance Officer

Medication Regimen Complexity Index

Patient ID: _____

Total no. of medications (including prn/sos medications): _____

Instructions

1. *MRCI applies only to prescribed medications. All entries are to be made only based on information on the label or drug chart (at the time of dispensing or discharge). No assumptions are to be made based on clinical judgement.*
2. *There are three sections in the scale. Complete each section before proceeding to the nest. At the end, add the scores for the three sections to give the MRCI.*
3. *If the same medication (same brand and same dosage form) is present more than once in different strengths in a regimen (e.g. Marevan 5mg, 3mg and 1mg mdu), it is still considered as one medication.*
4. *In cases where the dosage is optional, choose the dosing instruction with the smallest dose/frequency. (e.g. Ventolin MDI 1-2 puffs, 2-3 times daily will get weightings for 'metered dose inhalers', 'variable dose' and ;twice daily'; but not for 'multiple units at one time').*
5. *In certain cases the dosing frequency needs to be calculated (e.g. Ranitiine 1mane and 1nocte is 1twice daily).*
6. *It is possible that with certain 'use as directed' instructions, the regimen will not get a score under dosing frequency (e.g. Prednisolone 5mg mdu).*
7. *If there is more than one dosing frequency direction, they should be scored for all the dosing frequency directions (e.g. Ventolin MDI 2 puffs bd and prn, will get scores for 'metered dose inhalers', 'multiple units at one time', 'twice daily' as well as 'prn').*
8. *Instances where two or more medications are mutually exclusive, they need to be scored twice or more as prn with the recommended dosing frequency (e.g. Ventolin MDI or*

Ventolin nebuliser twice daily will get scores for both 'metered dose inhalers' and 'nebuliser' under dosage forms, but needs to be scored two times for 'twice daily prn').

9. *In cases where there is no matching option, choose the closest option (e.g. six times daily could be considered as 'q4h').*

A) Circle the weighting corresponding to each dosage form (ONCE ONLY) present in the regimen.

Dosage Forms		Weighting
ORAL	Capsules/Tablets	1
	Gargles/Mouthwashes	2
	Gums/Lozenges	2
	Liquids	2
	Powders/Granules	2
	Sublingual sprays/tabs	2
TOPICAL	Creams/Gels/Ointments	2
	Dressings	3
	Paints/Solutions	2
	Pastes	3
	Patches	2
	Sprays	1
EAR, EYE & NOSE	Ear drops/creams/ointments	3
	Eye drops	3
	Eye gels/ointments	3
	Nasal drops/cream/ointment	3
	Nasal spray	2
INHALATION	Accuhalers	3
	Aerolizers	3
	Metered dose inhalers	4
	Nebuliser	5

	Oxygen/Concentrator	3
	Turbuhalers	3
	Other DPIs	3
OTHERS	Dialysate	5
	Enemas	2
	Injections: Prefilled Ampoules/Vials	3 4
	Pessaries	3
	Patient controlled analgesia	2
	Suppositories	2
	Vaginal creams	2
	Total for Section A	

DPI = dry-powder inhaler; MDI = metered-dose inhaler.

B) For each medication in the regimen tick a box [/] corresponding to the dosing frequency. Then, add the no. of [/] in each category and multiply by the assigned weighting. In cases where there is no exact option, choose the best option.

Dosing frequency	**Medications**														**Total**	**Weighting**	**Weighting × No. of medications**
Once daily																1	
Once daily prn																0.5	
Twice daily																2	
Twice daily prn																1	
Three times daily																3	
Three times daily prn																1.5	
Four times daily																4	

Four times daily prn															2	
q 12h															2.5	
q 12h prn															1.5	
q 8h															3.5	
q 8h prn															2	
q 6h															4.5	
q 6h prn															2.5	
q 4h															6.5	
q 4h prn															3.5	
q 2h															12.5	
q 2h prn															6.5	
prn/sos															0.5	
On alternate days or less frequently															2	
Oxygen prn															1	
Oxygen <15hrs															2	
Oxygen >15hrs															3	
														Total for Section B		

C) Tick a box [/] corresponding to the additional directions, if present in the regimen. Then, add the no. of [/] in each category and multiply by the assigned weighting.

Additional Directions	**Medications**								**Total**	**Weighting**	**Weighting × No. of medications**
Break or crush tablet										1	

Dissolve tablet/powder										1	
Multiple units at one time (e.g. 2 tabs, 2 puffs)										1	
Variable dose (e.g. 1-2 caps, 2-3 puffs)										1	
Take/use at specified time/s (e.g. mane, nocte, 8 AM)										1	
Relation to food (e.g. pc, ac, with food)										1	
Take with specific fluid										1	
Take/use as directed										2	
Tapering/increasing dose										2	
Alternating dose (e.g. one mane & two nocte, one/two on alternate days)										2	
										Total for Section C	

Medication Regimen Complexity = Total (A) + Total (B) + Total (C) =

EuroQol 5-dimension 5-level (EQ-5D-5L) questionnaire

THE UNIVERSITY OF SYDNEY

NSW GOVERNMENT Health Western Sydney Local Health District

Adherence to medications in adults with kidney failure

Health Questionnaire (EQ-5D-5L)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

☐ I have no problems in walking about
☐ I have slight problems in walking about
☐ I have moderate problems in walking about
☐ I have severe problems in walking about
☐ I am unable to walk about

SELF-CARE

☐ I have no problems washing or dressing myself
☐ I have slight problems washing or dressing myself
☐ I have moderate problems washing or dressing myself
☐ I have severe problems washing or dressing myself
☐ I am unable to wash or dress myself

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

☐ I have no problems doing my usual activities
☐ I have slight problems doing my usual activities
☐ I have moderate problems doing my usual activities
☐ I have severe problems doing my usual activities
☐ I am unable to do my usual activities

PAIN / DISCOMFORT

☐ I have no pain or discomfort
☐ I have slight pain or discomfort
☐ I have moderate pain or discomfort
☐ I have severe pain or discomfort
☐ I have extreme pain or discomfort

ANXIETY / DEPRESSION

☐ I am not anxious or depressed
☐ I am slightly anxious or depressed
☐ I am moderately anxious or depressed
☐ I am severely anxious or depressed
☐ I am extremely anxious or depressed

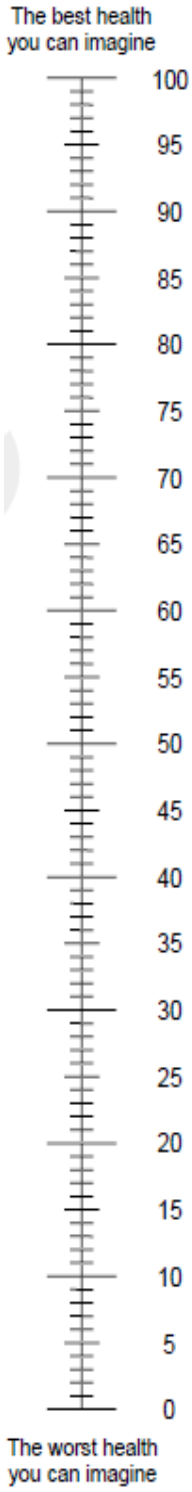
THE UNIVERSITY OF SYDNEY

NSW GOVERNMENT Health Western Sydney Local Health District

Adherence to medications in adults with kidney failure

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
- 0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is **TODAY**
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Quality of Life Questionnaire (EQ-5D-5L), V1 21_9_22