PRESCRIBING PATTERNS AND DRUG DOSAGE ADJUSTMENT IN PATIENTS UNDERGOING CHRONIC HAEMODIALYSIS AT DIALYSIS CENTERS IN WINDHOEK, NAMIBIA.

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ABSTRACT

Patients with End Stage Renal Disease (ESRD) are in chronic kidney disease stage 5 with a Glomerular Filtration Rate of <15 ml/min/1.73m^2. These patients have a high burden of co-existing diseases. Consequently, they may take as many as six or more different drugs to manage these conditions. The use of many medicines by these patients puts them at significant risk of drug-related problems. The aim of the study was to investigate prescribing patterns and explore appropriateness of drug therapy among ESRD patients undergoing regular haemodialysis at dialysis centers in Windhoek. This was a quantitative cross-sectional analytical study involving the review of clinical records of patients with ESRD on maintenance haemodialysis at two dialysis centers in Windhoek. A total of 147 patients' clinical records were reviewed and included in this study, 53.7% were males and 46.3% were females. More than half of the patients (53.1%) were state funded while 46.9% were privately funded patients. The mean age of the participants was 47.3±15.1 years. The majority of patients had between 3 to 4 comorbidities, with the most common co-morbid conditions being hypertension, anaemia, diabetes mellitus, secondary hyperparathyroidism and venous thromboembolism. A total of 163 different drugs were prescribed to all patients, with an average of 11.50 (±3.5) drugs per patient. The most common drug classes prescribed were cardiovascular drugs (38.3%) followed by alimentary tract and metabolism drugs (25.6%) as well as drugs for blood and blood forming organs (23.1%). Medications were appropriately selected in 80.3% of the patients, while the remaining 19.7% had at least one or more inappropriately selected drugs. Out of the total prescription entries, 15.6% required renal dosage adjustment, 48.7% of those that required adjustment were appropriately adjusted while 51.3% were inappropriately adjusted. For the inappropriately adjusted entries, 21 (15.6%) prescription entries were underdosed, 111 (82.2%) were overdosed, treatment duration was inappropriately long for 3 (2.2%) entries. 18.0% of the patients had all (100%) of their medications appropriately renally adjusted while 82.0% had at least one or more inappropriately renally adjusted drugs. The number of drugs prescribed was significantly associated with medication choice errors, while increasing age unexpectedly increased the likelihood of appropriate dosage adjustment. In conclusion, patients with ESRD on haemodialysis were being managed with a relatively large number of drugs and although

the drugs were appropriately selected for their indications in most cases, the dose was not appropriately adjusted.

Key words: haemodialysis, chronic kidney disease, renal dosage adjustment, drug selection.

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LIST OF ABBREVIATIONS AND ACRONYMS

ACE	Angiotensin-converting enzyme
ANM	Anaemia
ART	Antiretroviral Therapy
ATC	Anatomical Therapeutics Chemical classification
BMI	Body Mass Index
BNF	British National Formulary
CI	Confidence interval
CKD:	Chronic Kidney Disease
DM	Diabetes Mellitus
ESRD	End Stage Renal Disease
eGFR	Estimated Glomerular Filtration Rate
HPT	Hypertension
HREC	Human Research and Ethics Committee
INR	International Normalized Ratio
IQR	Interquartile range

KDIGO Kidney Disease Improving Global Outcomes

KDOQI The Kidney Disease Outcomes Quality Initiative

MOHSS Ministry of Health and Social Services

NEMLIST Namibia Essential Medicines List

OR Odds ratio

PCNE Pharmaceutical Care Network European

SAMF South African Medicines Formulary

SD Standard Deviation

SHPT Secondary Hyperparathyroidism

SPC Summary of Product Characteristics

SPSS Statistical Package for the Social Sciences

USA United States of America

VTE Venous thromboembolism

WHO World Health Organization

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DEDICATION

I dedicate this thesis to my sweet daughter baby Faith Hambereren Reginalda Kampanza, for the many sleepless nights that allowed me to spend many hours on my thesis.

DECLARATION

I, Martha Siwombe, hereby declare that this study is my work and is a true reflection of my research, and that this work, or any part thereof has not been submitted for a degree at any other institution.

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1. INTRODUCTION

1.1. Background of the study

The Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation defines Chronic Kidney Disease (CKD) as abnormal kidney function and kidney structure with a reduced Glomerular Filtration Rate (GFR) of < 60 mL/min/1.73m^2 that is present for three months or more (1). CKD is classified into 5 stages based on the estimated GFR; stage 1: GFR >90 ml/min/1.73m^2 , stage 2: GFR 60-89 ml/min/1.73m^2, stage 3: GFR 30-59 ml/min/1.73m^2 , stage 4: GFR 15-29 ml/min/1.73m^2, Those in End Stage Renal Disease (ESRD) are in stage 5 with a GFR of <15 ml/min/1.73m^2 (1). In 2017, the reported global prevalence of CKD was 9.1% and was ranked as the 12th leading cause of death globally (2). There is a higher mortality among those on dialysis compared to the general population, with more deaths among men compared to women (3–6). In many parts of the world, diabetes mellitus is known to be the leading cause of ESRD, however it is also commonly caused by many other known chronic conditions such as hypertension, systemic lupus erythematosus and immunodeficiency virus (HIV) infection (6). Apart from the premature deaths, ESRD also results in significantly reduced quality of life (6). In Namibia, CKD is reported as a major determinant of poor health outcomes for common non-communicable diseases, mainly diabetes mellitus and hypertension (7). Patients with ESRD have a high burden of co-existing diseases as well as complications due to the renal disease as well as due to the dialysis treatment (6,8). Consequently, these patients may take as many as six or more different drugs to manage these conditions. Among the reported common comorbid conditions are mineral and bone disorders, diabetes, hypertension, renal anaemia and infectious diseases which may all require

pharmacological management (9,10). The use of many medicines by these patients puts them at great risk of drug-related problems (9).

The four main processes that influence the pharmacokinetics of a drug include absorption, distribution, metabolism and excretion. These pharmacokinetic parameters are important in determining whether drugs and their active metabolites reach their sites of action as well as whether drugs or active metabolites cause a therapeutic or toxic effect (10). These pharmacokinetic parameters may be influenced by disease states such as kidney disease (10). In renal dysfunction, the most impacted are drugs that are mainly excreted renally, as the renal excretion of these drugs and their metabolites is reduced (11). However, severe kidney dysfunction may also lead to decreased plasma protein binding and alteration in the activity of drug metabolizing enzymes and drug transporters, thus significantly affecting drug pharmacokinetics (11). These changes therefore necessitate adjustment of drug doses as failure to do so may lead to drug or metabolite accumulation and predispose the patient to adverse drug reactions.

The number of patients with ESRD requiring renal replacement therapy has greatly increased over the years (1). In 2010, haemodialysis was reported to be the most common renal replacement therapy of choice worldwide (12). Haemodialysis is known to result in significant changes in the pharmacokinetics of many drugs. It has an impact on drug distribution, metabolism, and excretion (9). The extent to which haemodialysis affects a drug depends on its physicochemical properties such as molecular size, water solubility as well as pharmacokinetic properties, including, plasma protein binding, volume of distribution and renal clearance. Consequently, the haemodialysis process may effectively

clear certain drugs and/or their active metabolites from the circulation, which further warrants the need to adjust drug doses in these patients (11).

1.2. Statement of the problem

Patients with ESRD on haemodialysis usually have several pre-existing conditions as well as complications of the kidney disease which in most cases require pharmacological management (9). The multimorbid state of these patients, which calls for use of multiple drugs as well as the renal failure state which additionally puts limitation on the type of drugs that can be used as well as how they should be dosed, complicates the management of ESRD patients. Studies carried out in other countries have continuously highlighted the challenge faced by prescribers in drug selection as well as dosage adjustment for CKD patients (2,13–19). This results in either under-prescribing and under-dosing or overprescribing and overdosing. CKD patients on haemodialysis are prone to increased risk of adverse drug effects, drug interactions and other drug related problems due to the altered pharmacokinetic profile of most of their drugs, and the use of multiple drugs including polypharmacy (9,20,21). Appropriate drug selection and dosage adjustment is therefore crucial in prevention of undesirable health outcomes, mortality and morbidity in CKD patients. The major impact that CKD has on public health outcomes and the challenges in rational prescribing in these patients is well known as a global challenge (22). There is currently no data on the prescribing patterns and dosage adjustments of drugs in patients undergoing haemodialysis in Namibia. Moreover, the predictors of medication choice and dosage adjustment errors in these patients are also unknown. Therefore, a study to assess appropriateness of drug therapy and investigate for predictors

of medication choice and renal dosage adjustment errors in patients undergoing haemodialysis in this setting is necessary.

1.3. Objectives of the study

1.3.1 Overall aim

To investigate prescribing patterns and explore appropriateness of drug therapy among ESRD patients undergoing regular haemodialysis at two dialysis centers in Windhoek.

1.3.2 Specific objectives

i. To describe the prescribing patterns among ESRD patients undergoing haemodialysis
ii. To assess the appropriateness of medication choice in patients with ESRD undergoing haemodialysis
iii. To assess appropriateness of renal drug dosage adjustment in patients with ESRD undergoing haemodialysis
iv. To investigate the predictors of medication choice and dosage adjustment errors in patients with ESRD undergoing regular haemodialysis

1.4. Significance of the study

This study was aimed at investigating the prescribing patterns and dosage adjustment of drugs in patients undergoing haemodialysis. The findings of this study highlight the importance of continuously assessing prescribing in haemodialysis patients as these types of studies will inform clinical practice and potentially improve patient outcomes. The findings of this study may also encourage and inform pharmacist interventions in the pharmaceutical care of haemodialysis patients. The findings on the prescribing patterns

and drug selection has helped to identify opportunities for promoting rational drug use, reduce adverse drug reactions, reduce drug-drug interactions and improve adherence to drug therapy in ESRD patients undergoing chronic haemodialysis.

1.5. Limitations of the study

This study made use of data abstracted from patients' clinical records, as such some data may have been missing or recorded wrongly. For example, some biochemical parameters were monitored irregularly therefore some complications of ESRD could not be confirmed. Due to cost constraints, therapeutic drug monitoring and pharmacokinetic studies to evaluate the drug concentrations in blood and urine before, during and after a haemodialysis sessions were not undertaken. Although the initial plan was for the study to be conducted at all three dialysis centers in Windhoek, permission for data collection was only obtained from two of the three centers. Therefore, the findings cannot be generalized to other centers in Windhoek or in other parts of the country. Information on self-medications or any other herbal medicines patients may have been taking were not included in their records, therefore they could not be assessed. Lastly, only a few drugs had information on the prescribed time of administration, for this reason this parameter was not included when assessing dosage adjustment appropriateness.

1.6. Delimitation of the study

The proposed study was confined to highlighting prescribing patterns, assessing drug selection and renal dosage adjustment among ESRD patients on haemodialysis at two of the dialysis centers in Windhoek. The findings of this study will therefore not be generalized to the whole population. No therapeutic drug monitoring was undertaken.

2. LITERATURE REVIEW

2.1. Literature search

The following key search terms were used in the literature search: “haemodialysis OR dialysis OR renal replacement therapy”, “ hypertension OR high blood pressure in dialysis”, “anaemia in haemodialysis”, “mineral bone disease OR renal bone disease" comorbidities AND complications of haemodialysis, “haemodialysis in chronic kidney disease”, “chronic kidney disease in Namibia AND Africa”, “comorbidities in chronic kidney disease”, “prescribing patters in chronic kidney disease AND haemodialysis patients”, “dosage adjustment in chronic kidney disease AND haemodialysis.” Only relevant articles published between the years 2009-2023 recovered from Google Scholar, ScienceDirect and PubMed were included in this literature review.

2.2. Haemodialysis as a form of renal replacement therapy

Haemodialysis is the most common form of renal replacement therapy worldwide, 89% of patients requiring dialysis are reported to receive haemodialysis (23). The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines recommend that dialysis be initiated for patients with an eGFR of <15ml/minute/1.73m^2 experiencing one or more of the following; acid-base or electrolyte abnormalities, pruritus, inability to control blood pressure, deterioration in nutritional status despite adequate dietary interventions or cognitive impairment (24). The process of haemodialysis maintains homeostasis by removing nitrogenous waste products and toxins from the blood (25). These solutes move from uraemic blood, across a semipermeable membrane via diffusion and convection into the dialysate (25,26). This prevents permanent damage to other vital organs.

The frequency and duration of dialysis sessions are individualized per patient (25,26). The current recommended minimum frequency of haemodialysis is three times weekly (27). Longer dialysis sessions of 4 hours or more, at this frequency, have been reported to be superior compared to shorter daily sessions (28). However, the frequency of haemodialysis seems to vary depending on the setting. For example, a study conducted in China found that 65.1% of recruited patients received haemodialysis three times weekly, 24.0% received twice weekly and 10.9% received once a week (29). Another study conducted in India reported that the majority of the patients (70.0%) were receiving haemodialysis twice a week and only 30.5% were receiving thrice weekly (30). An international survey including participants from 182 developed and developing countries found that 77.0% of these countries reported haemodialysis sessions between 3-4 hours thrice weekly (31).

In addition to the pharmacokinetic changes caused by ESRD, continuous haemodialysis also has a significant impact on drug clearance. This should be considered when prescribing to these patients. Small molecules, including many drugs can diffuse from the patient's blood, though the semipermeable membrane, into the dialysate (20). Drug-related factors such as: water solubility, molecular weight, protein binding as well as volume of distribution, determine the extent of haemodialysis drug clearance (20,32). Haemodialysis factors such as type of filter membrane used, modality and timing of haemodialysis may also influence the extent of clearance of some drugs (25). For example, drugs with low protein binding, low volume of distribution and low nonrenal clearance may require renal dosage adjustment (32). In a clinical setting, patients on haemodialysis are at risk of both overdosage as well as underdosage. In this group of patients, it is

therefore crucial for prescribers to consider the following aspects relating to dosing in haemodialysis; use of higher single daily dosing or shorter dosing intervals, the need for supplemental dosing or avoiding use of drugs until after dialysis sessions (32).

2.3. Management of comorbidities and complications of ESRD

There are several conditions that may lead to the development and progression of CKD. The most common causes of CKD in both developed and developing countries being chronic conditions such as diabetes mellitus and hypertension (6,30). A number of studies have reported the prevalence of hypertension among patients with ESRD on haemodialysis ranging from 80-90% (33,34). Although there has been a somewhat decline in the incidence rate of ESRD resulting from diabetes over the past decade, the prevalence still remains unacceptably high (35). For example In the United States alone diabetes mellitus accounts for up to 44% of ESRD cases (35).

2.3.1. Diabetes mellitus

The KDIGO clinical practice guideline recommends monitoring of glycaemic control in ESRD patients with diabetes using glycated haemoglobin (24). The target glycated haemoglobin in these patients is 7% (24). In ESRD hypoglycaemic agents such as biguanides and glucagon-like peptide-1 should be discontinued and avoided due to the increased risk of adverse effects such as lactic acidosis (24,36,37). The more suitable recommended hypoglycaemic drug classes in patients on chronic haemodialysis are dipeptidyl peptidase-4 inhibitors, thiazolidinediones, and insulin (24,35). Dipeptidyl peptidase-4 inhibitors such as sitagliptin require dosage adjustment in haemodialysis (35,37). Other drug classes such as second generation sulphonyl urea and alpha glucose inhibitors may also be used in patients not achieving their glycaemic control targets (24).

The *Drug Prescribing in Renal Failure Handbook* recommends that insulin be dosed according to clinical response of patients and no specific dosing adjustment strategy is provided (37). Haemodialysis may reduce insulin requirements up to 50% % by reducing peripheral insulin resistance (35,38). The majority of patients with diabetes mellitus will continue to need pharmacotherapy after haemodialysis is started. However, there are cases where some patients may experience unexpected decrease in glycated hemoglobin of <6% as well as frequent hypoglycaemic episodes and therefore pharmacotherapy may be discontinued (35). This is referred to as burn-out diabetes phenomenon (35,39).

2.3.2. Hypertension

There are currently no standardized blood pressure targets for patients on chronic haemodialysis. This is mainly due to the complexity of the relationship between clinical outcomes, such as cardiovascular events and mortality, and blood pressure control in this group of patients (40). The KDOQI recommends blood pressure targets of <140/90 mmHg pre-dialysis and 130/80 mmHg post-dialysis (41). Turner *et al.* recommend that clinical decisions on patients hypertension treatment should be based on home blood pressure readings instead of in-center readings (40). In this case, the target systolic blood pressure should be between 120-135 mmHg and a diastolic blood pressure between 60-80 mmHg (40). Nonetheless, the role of hypertension control in reducing cardiovascular events and all-cause mortality in this population has been demonstrated in a number of studies (42–46).

All classes of antihypertensives are commonly used in the management of hypertension in patients receiving dialysis and are mainly used as combination therapy. Drugs that block the renin-angiotensin-aldosterone system such as angiotensin-converting enzyme

inhibitors and angiotensin receptor blockers are the preferred first line antihypertensive drugs in most settings (41,47). The main indication for renin-angiotensin-aldosterone system is the presence of proteinuria (24). KDIGO guidelines recommend renin-angiotensin-aldosterone inhibitors for patients with diabetes, hypertension and albuminuria (24). However, the benefits obtained by haemodialysis patients from the use of this drug class has been called into question (48). This may explain why they may not be agents of choice in some settings. For example, a study conducted in Nepal including 105 haemodialysis patients did not have a single patient prescribed renin-angiotensin-aldosterone system inhibitors (49). In other settings, renin-angiotensin-aldosterone inhibitors are only preferred as third line after beta blockers and calcium channel blockers (50). β-Blockers are also largely recommended as first line antihypertensives of choice (48). β-Blockers inhibit sympathetic activity hence preventing premature death and cardiovascular events in dialysis patients (48). The study conducted in Nepal reported calcium channel blockers to be the most frequently prescribed antihypertensive class, followed by diuretics (49). This may be due to two main reasons: firstly, they appear to be more effective in controlling blood pressure in volume overload state and secondly, all calcium channel blockers do not require dosage adjustment in haemodialysis (47,51). Interestingly, a study conducted in Japan reported an equal number of patients receiving renin-angiotensin-aldosterone inhibitors and calcium channel blockers (52). Mineralocorticoid receptor antagonists, such as spironolactone, are not routinely prescribed due to potentially life-threatening hyperkalaemia associated with these drugs. However, newer clinical trials have demonstrated the cardioprotective effects of mineralocorticoid receptor antagonists (45,48,53,54).

Patients with ESRD may suffer from complications of both renal failure as well as those caused by chronic haemodialysis. Complications from ESRD include: coronary heart diseases, peripheral vascular disease, hypertension, mineral and bone disorders, hyperuricaemia, metabolic acidosis, hyperphosphatemia, anemia and erectile dysfunction (6). Complications due to haemodialysis include; bleeding, intravascular infections, electrolyte imbalances and dialysis dementia (6). Several studies have reported that mortality among patients receiving haemodialysis is commonly due to cardiovascular events and infections (55–57). Therefore, these complications require appropriate management to reduce morbidity, mortality and improve the quality of life of these patients.

2.3.3. Cardiovascular complications

Patients receiving chronic haemodialysis are twenty times more likely to suffer from cardiovascular diseases compared to the general population (58–60). This is mainly due to a combination of general risk factors such as obesity and risk factors unique to renal failure, such as anaemia, hyperparathyroidism, hyperphosphataemia and volume overload (25). The prevalence of coronary heart disease and ventricular hypertrophy are significantly high in haemodialysis patients (60). Although the use of moderate and high dose statins are recommended as primary and secondary prophylaxis for cardiovascular disease in patients with CKD, they are shown to not be beneficial in dialysis patients (61). Despite concerns of bleeding in patients with ESRD, aspirin is the recommended drug of choice for secondary prophylaxis of cardiovascular disease for patients with acute coronary syndrome (61). Dual antiplatelet therapy for at least one year may also be considered in this case (59).

2.3.4. Anaemia

The risk of anaemia increases with decline of eGFR and it is mainly due to the lack of erythropoietin, impairing red blood cell production (25,62). Active blood loss through haemodialysis is an additional risk factor for anaemia in haemodialysis patients (25,63). Treatment of anaemia in patients receiving haemodialysis does not only reduce mortality and morbidity, it also improves patient exercise capacity by improving cardiac status, improves quality of life and nutrition status (25,63). The main drugs used for management of anaemia in haemodialysis are erythropoietic stimulating agents and iron. Carbepoetin, methoxy polyethylene glycol-epoetin beta and all forms of epoetin are all appropriate in ESRD (25,62). Pharmacotherapy is recommended for dialysis patients with symptoms of anaemia or a haemoglobin of <10 g/dL (25). It is recommended that before treatment with erythropoietic stimulating agents is initiated; iron deficiency should be addressed first in those with inadequate iron stores and blood pressure should be well controlled (25,64). The absorption of oral iron is impaired in patients receiving haemodialysis, therefore intravenous iron preparations are often preferred (63). No renal dosage adjustment is needed for both oral and intravenous iron as well as epoetin products (37).

2.3.5. Mineral and bone disorders

In CKD, mineral and bone disorders include hyperphosphataemia, hypocalcaemia, low vitamin D levels and secondary hyperparathyroidism (65). All the changes in these hormones and minerals put haemodialysis patients at risk of bone fractures and cardiovascular events. The KDIGO clinical practice guidelines recommend that the results for phosphate, calcium and parathyroid hormone levels be assessed together when deciding on therapy for treatment for CKD-mineral bone disease (66). The main treatment

goals in patients on haemodialysis are: to maintain serum phosphate between 1.13 to 1.78 mmol/L, maintain calcium levels <2.37 mmol/L and maintain parathyroid hormone at less than two to nine times the upper limit (65 Picogram per milliliter) (66,67). In patients with high parathyroid hormone levels, hyperphosphatemia should be managed first. Haemodialysis, phosphate diet restrictions and phosphate binders are all effective for correcting persistent hyperphosphataemia in ESRD patients (65,66). Treatment options available for hyperparathyroidism include calcimimetics, calcitriol and synthetic vitamin D analogs (66). The decision on which of these agents or combination to prescribe for individual patients, depends on the serum calcium and phosphate levels (67). A study conducted in China reported that less than 50% of patients on haemodialysis had corrected calcium (40.4%), serum phosphate (29.7%) and parathyroid hormone (47.1%) (29).

2.4. Prescribing patterns among ESRD patients undergoing haemodialysis

The progression of CKD increases the risk for developing other coexisting conditions and increases the severity of existing conditions (68). A study carried out in Kenya reported an average of 3-7 comorbidities per CKD patient, with hypertension, electrolyte imbalance, anaemia and cardiovascular diseases as the most common comorbidities (16). Another study reported urinary tract infections as well as diabetes mellitus as one of the common co-morbidities for those on maintenance haemodialysis (69). These multiple complications require multiple therapies (22). As a result, many of the ESRD patients receive drugs belonging to one or more of the following drug classes: gastrointestinal, cardiovascular, anti-infectives, anticoagulants, lipid lowering drugs and haematopoietic drugs as reported by several studies (21,22,70,71).

The WHO core drug use indicators are recognized globally as an objective assessment tool for drug prescribing patterns (72). A number of studies have used these WHO core drug use indicators to report on the prescribing patterns among patients undergoing haemodialysis (21,69,73,74). Furthermore, several studies identified polypharmacy in haemodialysis patients (21,22,71). A cross-sectional study carried out in Saudi Arabia reported that from 41 prescriptions analyzed, there were a total of 504 drugs prescribed, with an average of 12.3 drugs per prescription (21). Similarly, another study conducted in India among haemodialysis patients found an average of 12.8 drugs per patients with antihypertensives as the most prescribed drug class (69). Marin *et al.* alluded that polypharmacy observed in haemodialysis may be due to the increase in symptom burden during dialysis as well as the lack of reassessment of therapy once it is initiated (73). The WHO recommends prescribing by generic name and use of medicines from the WHO Essential Medicines List. These indicators highlight prescribing practices conformity to local regulations (72). Tadvi *et al.* reported that 71.4% of drugs were prescribed by generic name, however another study reported that out of 3132 drugs prescribed only 4.4% were prescribed by generic name (21). Tadvi *et al.* further reported that out of the 504 drugs prescribed, 65.3% were from the WHO Essential Medicines List and only 1.2% were given as fixed dose combinations; this is much lower than the fixed dose combination rate reported from a study carried out in India of 17.6% (21,75).

2.5. Appropriateness of selection of drugs used in haemodialysis patients

Several studies report improper drug selection as one of the common drug therapy problems in chronic kidney disease patients (16,17,76–78). A cross-sectional survey carried out in Kenya in CKD patients reported a statistically significant association

between the CKD stage and improper drug selection, as patients in stage 4 were 6 times more likely to have improper drug selection (16). Srikanth *et al.*, however, reported improper drug selection to be the least prevalent drug related problem (78). Improper drug selection was reported to be mainly due to prescribing of drugs that are contraindicated in renal insufficiency, use of ineffective therapy and the use of combination drug therapies where a single drug therapy would be equally effective (16,78).

2.6. Appropriateness of dosage adjustment in haemodialysis patients

Inappropriate dosage adjustment among haemodialysis patients has been reported by a number of studies (17,71,78,79). A study carried out in India identified overdose as the second most common drug related problem in haemodialysis patients. This was linked to the occurrence of adverse drug reactions and poor treatment outcomes (78). In this study, 123 drug related problems were reported of which 19.4% were due to inappropriate dosage (78). Failure to adjust drug doses in kidney disease may be due to the lack of checking if a drug requires dosage adjustment or not, especially those drugs not commonly known to require dosage adjustment in renal impairment (77).

2.7. Predictors of medication choice and dosage adjustment errors in ESRD patients

Only a few studies have assessed possible predictors of medication choice and dosage adjustment errors in CKD patients. However, despite the fact that medication choice and dosage adjustment errors are more common in ESRD patients, unfortunately no studies of this nature have focused only on ESRD patients. A study conducted in Kenya reported a statistically significant association between both number and presence of comorbidities as well as number of medications and drug related problems in CKD patients (16). Similarly,

in another study carried out in Pakistan, the CKD stages, the presence of a comorbidity such as hypertension as well as the number of medications were associated with medication dosing adjustment errors (80). However, both studies reported no association between medication dosing adjustment errors and age and sex (16,80).

2.8. Conceptual framework

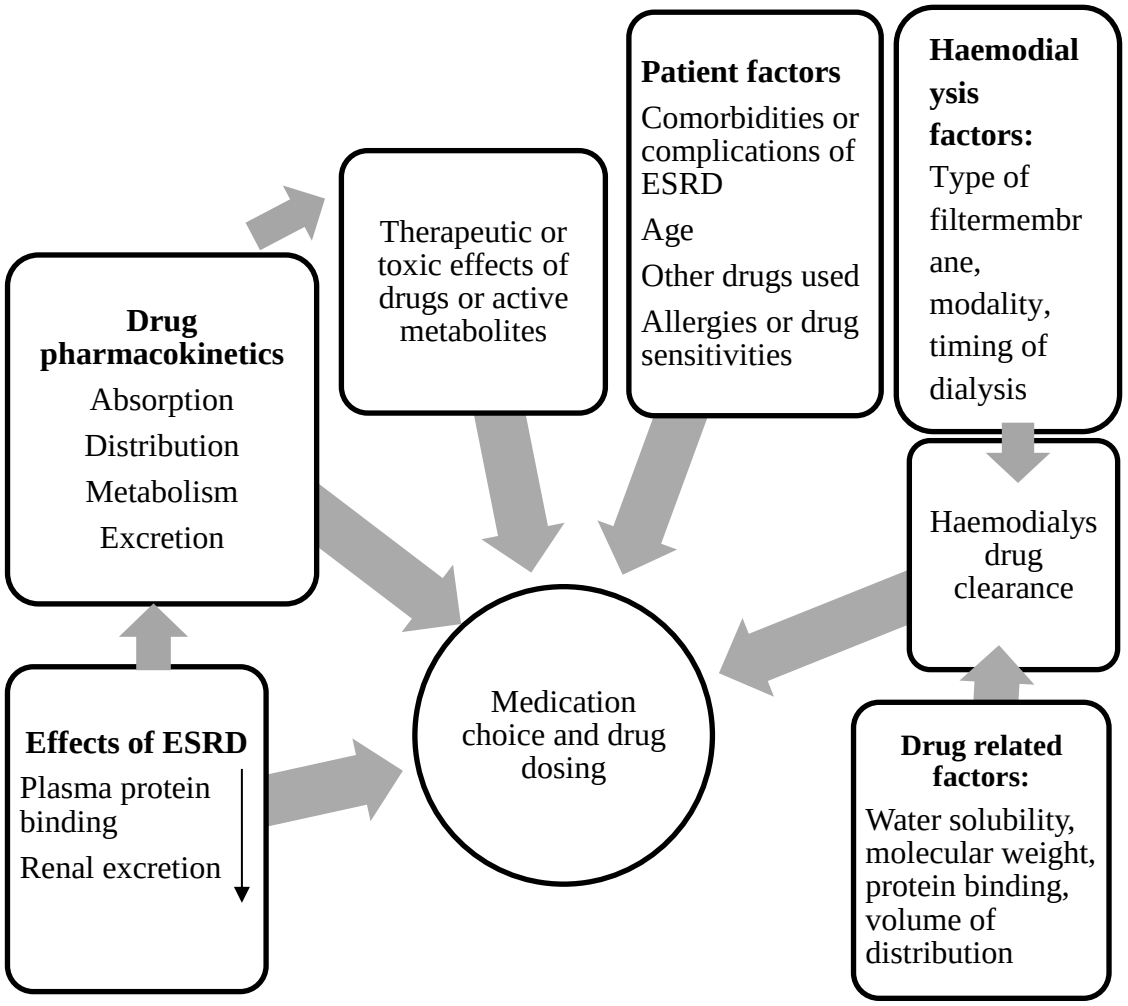


Figure 1: Conceptual framework on medication choice and drug dosage adjustment in patients with ESRD undergoing haemodialysis

Figure 1 illustrates the different factors which may affect medication choice as well as renal dosage adjustment in patients with ESRD that are undergoing chronic haemodialysis. This includes drug-related factors such as drug pharmacokinetic parameters, water solubility, molecular weight, protein binding, volume of distribution. Patient related factors such as comorbidities, age, other drugs used, allergies and haemodialysis related factors such as type of filter membrane, dialysis modality, timing

of dialysis may also affect the type of drugs prescribed to these patients as well as the dosage used (9–11,20,25,32,37).

2.9. Gaps in literature

There are several studies carried out in a few African countries on the prescribing patterns as well as dosage adjustment in haemodialysis patients. However, there was no data found relating to prescribing patterns and dosage adjustment in haemodialysis patients in Namibia.

3. RESEARCH METHODS

3.1. Research design

For the present study a quantitative, cross-sectional, analytic design was used involving the review of patient clinical records. Based on the information retrieved, prescribing patterns were described and appropriateness of drug selection and renal drug dosage adjustment was assessed for patients attending haemodialysis at two dialysis centers from July 2022 to December 2022. In addition, the predictors of medication choice and dosage adjustment errors in ESRD patients undergoing regular haemodialysis were investigated.

a) Population

Patients undergoing haemodialysis therapy for at least one month and regularly attending in-center dialysis sessions at two of the dialysis centers in Windhoek, Khomas region, Namibia were included in the study.

b) Study setting

This study was carried out at two outpatient dialysis centers in Windhoek, Namibia.

3.2. Sample

Based on literature data, the prevalence of inappropriate drug selection and inappropriate dosage adjustment among CKD patients ranges from 12-39% and 32-72% respectively (8,14,22,26,26–28). Using Epi Info version 7.2.4.0 (CDC, Atlanta, GA, USA) at 95% confidence interval, 80% power, assuming prevalence of inappropriate drug selection of 39% (14) and prevalence of inappropriate dosage adjustment of 72% (14) among haemodialysis patients in Windhoek, minimum sample sizes of 133 and 125, respectively, were determined for these two main outcome measures. These two haemodialysis centers in Windhoek each attend to an average of 70 patients per month. For the purpose of this

study, all haemodialysis patients that fit the inclusion criteria of this study and attended haemodialysis sessions at these centers between July 2022 and December 2022 were included. The participants included were those with comorbid conditions being managed with at least one medication or more. There were no sex and age restrictions in this study. Those being managed for acute kidney injury or receiving emergency dialysis were excluded. Patients whose clinical records did not contain complete information of prescription medications were also excluded.

3.3. Research Instruments

An eligibility form in **Appendix A** was be used to screen the patients to assess whether they meet the study inclusion criteria or not. A data collection tool in **Appendix B** was used to collect data from patient clinical records. This data collection tool was reviewed by both research supervisors prior to conducting the study. A pilot study, including the review of 10 patient clinical records at both dialysis centers, was carried out to ensure content validity. The pilot study revealed that there was no information recorded on over the counter medicines that the patients were taking, therefore this component was removed from the data collection tool.

3.4. Procedure

The principal investigator obtained the list of all patients that receive dialysis services at each of the centers from the nursing managers. The patient clinical records were obtained from the filing cabinet and each screened for eligibility to be included in the study by using a screening form in **Appendix A**. The patient demographic information such as age, sex, health cost funder, the comorbid conditions, all drugs prescribed and the necessary clinical laboratory data of all eligible patients were collected using the data collection tool

in **Appendix B**. In this study, comorbidities included both comorbid conditions and complications of CKD. Different biochemical parameters such as parathyroid hormone, haemoglobin, phosphate, calcium, vitamin D, bicarbonate, sodium, chloride and urine albumin were included in the data collection tool. This was done to ensure that all common complications of ESRD the patient may have presented with were identified by the researcher. Data collection was done for a period of 6 months, from July 2022 and concluded in December 2022. The prescribing patterns were described in terms of types of drugs prescribed, total number of drugs prescribed, average number of drugs per prescription, number of drugs prescribed by generic name and the number of drugs from the WHO Essential Medicines List. Additionally, the prescribed drugs were classified and reported according to the Anatomical Therapeutic Chemical (ATC) classification. Medications containing combinations were considered as single drugs, represented by one ATC code. Unfortunately, due to the lack of local guidelines for prescribing and drug dosing in haemodialysis, dosage adjustment appropriateness was evaluated using the *Drug Prescribing in Renal Failure Handbook* as the primary reference. For each patient, each of their prescribed drugs was assessed to determine whether or not they required dosage adjustment in haemodialysis based on the recommendations from the *Drug Prescribing in Renal Failure Handbook* (37). The *Oxford Handbook of Dialysis* was also used as a secondary source of information on renal dosage adjustment for cases were information provided by the primary reference was insufficient (25). A drug dosage was rated as 'appropriate' when the dosage prescribed was suitable for those receiving haemodialysis. A drug dosage was rated as 'inappropriate' if the dosage prescribed was not in conformity with the recommended adjustment in haemodialysis. A dosage adjustment error was defined as failure to change a dose or dosing interval to that recommended for patients on

haemodialysis or with ESRD. Each prescribed drug was also studied to determine the appropriateness of medication choice by checking several aspects; they were assessed on whether they were the correct drug to manage the comorbid condition(s), any contraindications in ESRD, use of drug without indication, presence of clinically significant major drug interactions between the drugs used, therapeutic duplications as well as any allergies to drugs the patient may have had. Drug choices that met the above criteria were rated as 'appropriate' and those that did not meet one or more of the criteria were rated as 'inappropriate'. Fixed dose combinations were rated as 'inappropriate' if any of the active pharmaceutical ingredients in the combination was inappropriately dosed or selected. The primary reference used to check for the appropriateness of medication choice was the KDIGO clinical practice guidelines (81). A medication choice error was defined as prescribing an inappropriate drug by failing to meet one or more of the criteria described above when selecting a drug. Other sources such as the British National Formulary (BNF), South African Medicines Formulary (SAMF), *Oxford Handbook of Dialysis* were all used as secondary sources in case of missing, unclear or conflicting information in the primary reference source (25,36).

3.5. Data Analysis

Data were entered in Microsoft Excel and exported to GraphPad Prism version 9.3.0 for Windows (GraphPad Software, San Diego, California USA) as well as IBM® SPSS® Statistics version 29 (IBM Corporation, Chicago, IL, USA) for analysis. The participants' demographics were analyzed using descriptive statistics in GraphPad Prism and IBM® SPSS® Statistics. Categorical variables were expressed as proportions. Differences between different groups were compared using chi-square test of association or Fischer's

exact test. A p value < 0.05 was considered statistically significant. Continuous variables were presented as mean/median, standard deviation and range. The Kolmogorov-Smirnov test was used to test normality of data distribution. Analysis of inferential statistics was performed using both univariate and binary logistic regressions to identify predictors of inappropriate drug selection and inappropriate renal dosage adjustment. Sex, age, health insurer, number of prescribed medicines, type of comorbidities, and number of comorbidities were used as independent variables. For the univariate logistic regression, a p value of 0.25 was used for the selection of variables that were included in the multivariate logistic regression. For the multivariate logistic regression, a p value < 0.05 was considered statistically significant.

4. RESEARCH ETHICS

Ethical clearance and approval were obtained from the University of Namibia Human Research and Ethics Committee (HREC), permission letter dated 16 May 2022 *Ref: SOP0001* (**Appendix D**). Since the study only involved the review of patient clinical records, a waiver for need for consent as well as permission to conduct the study was obtained from the Ministry of Health and Social Services (MOHSS), permission letter dated 13 June 2022 *Ref: 17/3/3 MS* (**Appendix E**). Permission for data collection was also obtained from the management of the dialysis centers before accessing any patient information at these centers, letter dated 20 June 2022 (**Appendix F**).

4.1. Autonomy

Informed consent from the patients was not required since the current study only involved the review of clinical records. The researcher intends to publish the results in a scientific journal subject to additional approval from MOHSS as well as the dialysis centers, and it will also be shared with other health care workers through workshops and CPD events.

4.2. Privacy and confidentiality

Each patient was given a code that serves as a patient identifier without directly linking them to any data collected for the purpose of the study. All hardcopy data collection tools are kept in a secure place and will be shredded 1 year after completion of the study. The analyzed data is stored as a password encrypted file.

4.3. Non-maleficence

No direct harm came to the patients and the dialysis centers as a result of this study.

4.4. Fairness

All patients that met the inclusion criteria were fairly included in the study, and findings will be communicated to the dialysis centers.

5. RESULTS

5.1. Patient demographics

A total of 147 patients that met the inclusion criteria were included in the study of which 53.7% were male and 46.3% were female. The mean age of ESRD patients undergoing chronic haemodialysis was 47.3±15.1 years. A total of 142 patients had a weight recorded in their clinical records. The mean weight for these patients was 67.2±17.3 kg. Only 93 patients had their height recorded, with a median height of 1.64m (IQR: 1.74-1.60). More than half of the patients (53.1%) were state funded, 46.9% were privately funded patients (Table 1).

Table 1: Demographic data of patients on chronic haemodialysis

Demographic characteristic	N (%)	Mean (SD)	Median (IQR)
N (Total number of patients)	147		
Sex			
Male	79 (53.7)		
Female	68 (46.3)		
Age (years)	147	47.3±15.1	
Weight (Kg)	142	67.2±17.3	
Height (m)	93		1.64 (1.74-1.60)
BMI (kg/m^2)	89		22.1 (26.8-18.6)
Privately funded patients	69 (46.9)		
State funded patients	78 (53.1)		

5.2. Co-morbidity profile of patients

A total of 33 (22.4%) patients had 3 comorbidities. Similarly, the number of patients who had 4 comorbidities were 33 (22.4%). While 32 (21.8%) had 2 comorbidities, 22 (15%) had 6 comorbidities and 18 (12.2%) had 5 comorbidities, 3 (2%) had 7 comorbidities, another 3 (2%) had 11 comorbidities. Only one patient (0.7%) had 1, 8 or 9 comorbidities. The most common co-morbid conditions were hypertension, anaemia, diabetes mellitus, secondary hyperparathyroidism and venous thromboembolism. Patients with hypertension and anaemia accounted for 52 (35.4%) while 37 (25.2%) patients had a combination of hypertension, anaemia and secondary hyperparathyroidism (Table 2).

Table 2: Co-morbidity profile of patients

Number of comorbidities	N (%)
1	1 (0.7)
2	32 (21.8)
3	33 (22.4)
4	33 (22.4)
5	18 (12.2)
6	22 (15.0)
7	3 (2.0)
8	1 (0.7)
9	1 (0.7)
11	3 (2.0)
Types of comorbidities	
HPT+DM+ANM+SHPT	5 (3.4)
HPT+SHPT+ANM	37 (25.2)
HPT+ANM	52 (35.4)
HPT+VTE+SHPT+ANM	9 (6.1)
HPT+DM+ANM	15 (10.2)
HPT+DM+VTE+ANM	7 (4.8)
HPT+SHPT+VTE	2 (1.4)
HPT+VTE+ANM	3 (2.0)
SHPT+ANM	2 (1.4)
HPT+VTE	2 (1.4)
HPT+DM	3 (2.0)
HPT only	1 (0.7)
HPT+SHPT	3 (2.0)
HPT+DM+VTE+SHPT+ANM	3 (2.0)
ANM only	1 (0.7)
VTE+SHPT+ANM	1 (0.7)
HPT+DM+SHPT	1 (0.7)

HPT: Hypertension, DM: Diabetic Mellitus, ANM: Anaemia, SHPT: Secondary Hyperparathyroidism, VTE: Venous Thromboembolism

5.3. Distribution of BMI values among ESRD patients receiving chronic haemodialysis

Patients with normal weight accounted for 53.9% while 15.7% were underweight, 15.7% overweight and 14.6% were obese (Figure 2).

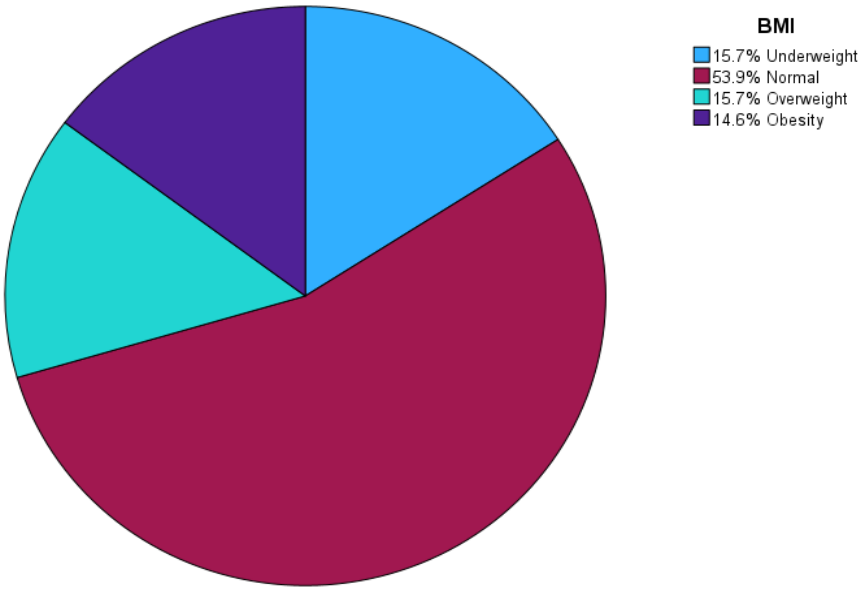


Figure 2: Distribution of BMI values among ESRD patients receiving chronic haemodialysis

5.4. Prescribing patterns among ESRD patients undergoing haemodialysis

There were 163 different drugs prescribed to the 147 participants during the study period classified based on their ATC classification. Of these different types of drugs, 98 (60.1%) were drugs that are part of the WHO Essential Medicines List. There were 1691 prescription entries (medication orders) for all participants, with an average of 11.5 (±3.5) drugs per patient. Of the total prescription entries to all participants, 811 (50.1%) were prescribed using generic names (Table 3).

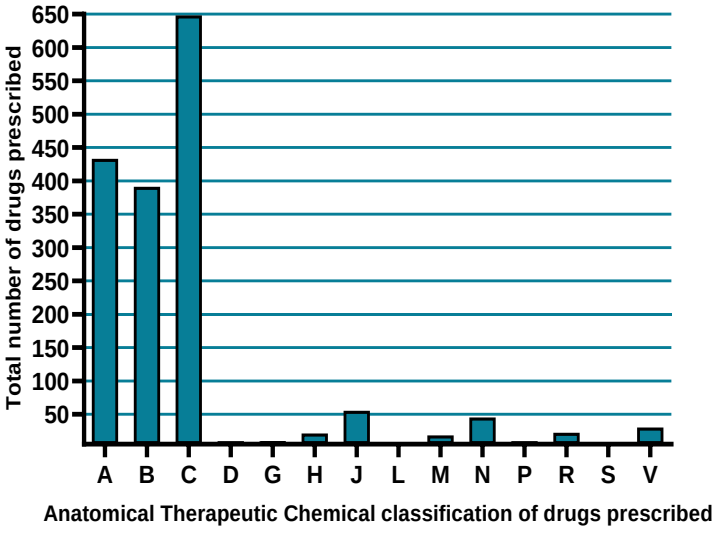
Table 3: Prescribing patterns among ESRD patients undergoing haemodialysis

Variable	N (%)
Number of different drugs prescribed	163
Number of drugs from WHO Essential Medicines List	98 (60.1)
Total prescription entries	1691
Average number of drugs per patient	11.50 (±3.5)
Number of drugs prescribed by generic name	811 (50.1)

5.5. Drugs prescribed amongst ESRD patients undergoing chronic haemodialysis

Figure 3 shows the drug classes prescribed to the patients according to the ATC classification. The most common drug classes prescribed were cardiovascular drugs followed by alimentary tract and metabolism drugs as well as drugs for blood and blood forming organs. Cardiovascular drugs accounted for 648 (38.3%) of the total prescription entries for the study participants. Alimentary tract and metabolism drugs accounted for 433 (25.6%) whereas drugs for blood and blood forming organs accounted for 391 (23.1%) of the total prescription entries. The least prescribed drug classes included

antineoplastic and immunomodulating agents (0.8%) and drugs that work on sensory organs (0.2%). **Appendix G** shows the specific drugs prescribed to the study participants under each class. The ten most prescribed drugs in the study were epoetin beta (89.1%), alfacalcidol (83.0%), furosemide (79.6%), iron sucrose (70.7%), carvedilol (60.5%), amlodipine (53.7%), doxazosin (53.7%), calcium gluconate (47.6%), perindopril (40.1%) and ergocalciferol (32.0%).



KEY:

A	Alimentary tract and metabolism
B	Blood and blood forming organs
C	Cardiovascular system
D	Dermatologicals
G	Genito urinary system & sex hormones
H	Systemic hormonal preparations (excl. sex hormones and insulins)
J	Antiinfectives for systemic use
L	Antineoplastic & immunomodulating agents
M	Musculo-skeletal system
N	Nervous system
P	Antiparasitic products, insecticides & repellents
R	Respiratory system
S	Sensory organs
V	Various

Figure 3: Prescribed drug classes according to the ATC classification

5.6. Appropriateness of medication choice in ESRD patients undergoing haemodialysis

Figure 4 shows the results for the assessment of appropriateness of medication choice in the study participants. Among the 147 patients included in the current study, 80.3% had all their drugs appropriately selected while the remaining 19.7% o had at least one or more inappropriately selected drugs.

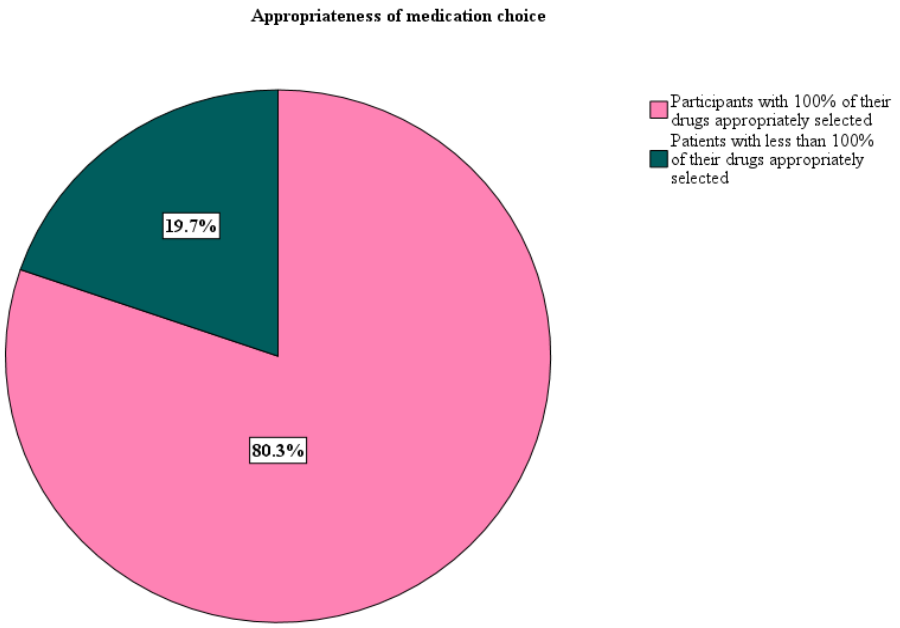


Figure 4: Medication choice appropriateness in ESRD patients undergoing haemodialysis

5.7. Appropriateness of renal drug dosage adjustment in ESRD patients undergoing haemodialysis

In total, 163 different drugs corresponding to 1691 prescription entries were prescribed to the 147 patients during the study period. Some of the different drugs were prescribed on multiple occasions to more than one patient. Only 41 (25.2%) of the different drugs had recommendations for dosage adjustment in CKD based on the estimated GFR. Additionally, only 263 (15.6%) of the prescription entries required renal dosage adjustments. Of these, 128 (48.7%) were appropriately adjusted whilst 135 (51.3%) were inappropriately adjusted. For the inappropriately adjusted prescription entries, 21 (14.6%) were underdosed, 111 (82.3%) were overdosed and treatment duration was inappropriately long for 3 (2.2%). Table 4 provides a summary of this data.

Table 4: Renal drug adjustment in ESRD patients undergoing haemodialysis

Variable	N (%)
Number of different drugs prescribed	163
Drugs with guidelines for dosage adjustment	41 (25.2%)
Total number of prescription entries	1691
Prescription entries requiring dosage adjustment	263 (15.6)
Prescription entries appropriately adjusted	128 (48.7)
Prescription entries inappropriately adjusted	135 (51.3)
Underdosage	21 (15.6)
Overdosage	111 (82.2)
Treatment duration too long	3 (2.2)

Figure 5 shows the results for the assessment of appropriateness of renal dosage adjustment in the study participants. In 18.0% of the patients, all (100%) of the medications prescribed to them were appropriately renally adjusted while 82% of the patients had at least one inappropriately renally adjusted drugs.

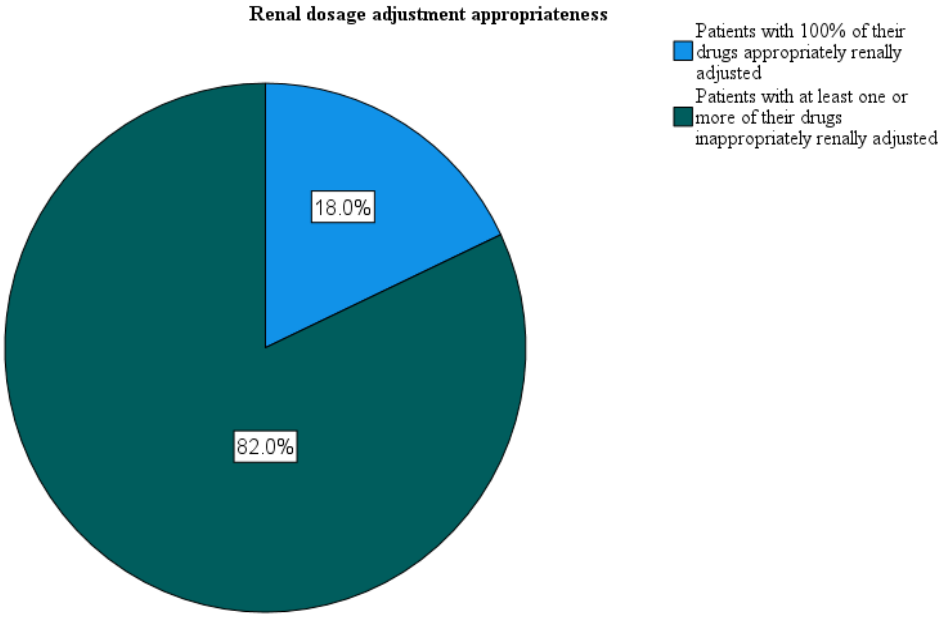


Figure 5: Appropriateness of renal dosage adjustment in ESRD patients undergoing haemodialysis

5.8. Most frequently prescribed drugs, medication selection and drug dosage adjustment

Appendix H shows the top 5 most prescribed drugs per ATC classification as well as the number of patients in which each drug was prescribed. The table also highlights whether or not the drug was appropriately selected and renally adjusted. Among the ten most prescribed drugs in the study, epoetin beta, alfacalcidol, furosemide, iron sucrose, carvedilol, amlodipine, doxazosin, calcium gluconate, perindopril and ergocalciferol. Epoetin beta, alfacalcidol, furosemide, iron sucrose, carvedilol, amlodipine, doxazosin, calcium gluconate were all appropriately selected and did not require renal dosage adjustment in all patients they were prescribed. Perindopril was appropriately selected in all patients (n=57), however, its renal dosage adjustment was not appropriate in 55 patients. Ergocalciferol, which does not require renal dosage adjustment in patients with ESRD, was prescribed for 46 patients. It was an appropriate medication choice in 44 patients but was inappropriately selected in 2 patients. Other drugs such as warfarin, calcitonin and amitriptyline were improperly selected. Folic acid, warfarin, sildenafil, solifenacin, colchicine as well as anti-infectives such as meropenem, cloxacillin were among drugs that were inappropriately dosage adjusted. Although warfarin is dosed based on the international normalized ratio (INR) and not renal function, 5 of the 31 patients were assessed as inappropriate dosage adjustment because their INR had not been checked for several months. Although these patients were still coming for dialysis every week, they still remained all the same dose throughout, which is not appropriate. **Appendix I** shows the different kinds of medication choice and drug dosage adjustment errors for each of the most frequently prescribed drugs.

5.9. Predictors of inappropriate choice of medication in ESRD patients undergoing haemodialysis

Table 5 shows that a higher percentage of male patients (79.7%) had appropriately selected drugs compared to female patients (54.6%). State referred patients also had a higher percentage (83.3%) of appropriate drug selection compared to private patients (76.8%). A chi-square test for association was conducted between appropriateness of medication choice and patients' sex and health insurer, respectively. All the expected cell frequencies were greater than five. There was no statistically significant association between the variables, sex (χ^2 =0.03, p= 0.863) and health insurer (χ^2 =0.983, p= 0.321), and appropriateness of medication choice.

Table 5: Association between appropriateness of medication choice and, patients' sex and type of health insurer

Predictor	Category	Medication choice					
		Appropriate drug choice		Inappropriate drug choice			
		n	%	n	%	χ^2	*p*
Sex	Male	63	79.7	16	20.3	0.03	0.863
	Female	55	54.6	13	19.1		
Health insurer	State	65	83.3	13	16.7	0.983	0.321
	Private	53	76.8	16	23.2		

In the current study, types of comorbidities were classified into two categories: cardiovascular and non-cardiovascular related comorbidities. Out of the 147 patients included in this study, 42 had cardiovascular related comorbidities while 105 had non-cardiovascular comorbidities. Of those with cardiovascular comorbidities, 37 (88.1%) had their drugs appropriately selected and 5 (11.9%) had their drugs inappropriately selected. Of those with non-cardiovascular comorbidities, 81 (77.1%) had their drugs appropriately selected while 24 (22.9%) had their drugs inappropriately selected. A Fisher's exact test revealed no statistically significant association between type of comorbidities (cardiovascular vs non-cardiovascular) and appropriateness of medication choice (p= 0.170) as shown in Table 6.

Table 6: Association between type of comorbidities and appropriateness of medication choice

Predictor	Category	Medication choice				
		Appropriate drug choice		Inappropriate drug choice		
		n	%	n	%	*p*
Type of comorbidities	Non-cardiovascular	81	77.1	24	22.9	0.170
	Cardiovascular	37	88.1	5	11.9	

*Level of statistical significance, $p < 0.05$

Univariate binary logistic regression was performed to determine the effects of each of the variables, i.e. age, sex, health insurer, total number of drugs, type of comorbidities (cardiovascular/non-cardiovascular) and number of comorbidities, on the likelihood of inappropriate choice of medication among the participants. Linearity of the continuous variable (age) with respect to the logit of the dependent variable, appropriateness of medication choice, was assessed via the Box-Tidwell procedure. Based on this assessment, the continuous variable age was found to be linearly related to the logit of the dependent variable, therefore included as a possible predictor in the binary logistic regression models (82). Each of these variables were added to the models separately. Table 7 shows the results of the univariate logistic regression models for the different predictor variables. Of the six predictor variables, only one namely total number of drugs was statistically significant. An increase in the total number of drugs was associated with a 19.6% reduction in the likelihood of having appropriately selected drugs with a 95% CI of 0.706 to 0.915 (OR: 0.804, $p<0.001$).

Table 7: Univariate logistic regression models predicting likelihood of inappropriate choice of medication

							95% CI	
	B	S.E.	Wald	*df*	*p*	OR	Lower	Upper
Age	-.022	0.014	2.369	1	0.124	0.978	0.952	1.006
Total number of drugs	-0.219	0.066	10.97	1	<0.001	0.804	0.706	0.915
Number of comorbidities	-0.154	0.095	2.659	1	0.103	0.857	0.712	1.032
Sex	0.072	0.417	0.030	1	0.863	1.074	0.475	2.431
Health insurer	0.412	0.417	0.976	1	0.323	1.509	0.667	3.416
Types of comorbidities	0.785	0.530	2.193	1	0.139	2.193	0.776	6.197

A multivariate binary logistic regression was performed including only variables that had a *p* value of <0.25 from the univariate analysis. Taking into consideration the Event Per Variable (EPV) of 10, a maximum of three variables could be added to the model. Predictor variables that made sense clinically; number of comorbidities, total number of drugs and types of comorbidities (cardiovascular/ non-cardiovascular) were included in this model. The logistic regression model was statistically significant, χ^2 =17.082, p<0.001. The model explained 17.4% (Nagelkerke R^2) of the variance in appropriateness of medication choice and correctly classified 81.6% of cases. The model sensitivity was 98.3% and specificity was 13.8%, positive predictive value was 82.2% and negative predictive value was 66.7%. Of the three predictor variables, only the total number of drugs was statistically significant as shown in table 9. An increase in the total number of drugs was associated with a 22.2% reduction in the likelihood of having appropriately selected drugs, 95% CI of 0.677 to 0.926 (OR: 0.792, p= 0.001) as shown in table 8.

Table 8: Multivariate binary logistic regression predicting likelihood of inappropriate choice of medication

							95% C.I.	
	B	S.E.	Wald	df	*p*	OR	Lower	Upper
Type of comorbidities	-1.049	0.589	3.172	1	0.075	0.350	0.110	1.111
Total number of drugs	-0.251	0.079	10.112	1	0.001	0.792	0.677	0.926
Number of comorbidities	0.048	0.119	0.163	1	0.687	1.049	0.830	1.326

5.10. Predictors of inappropriate renal drug dosage adjustment in ESRD patients undergoing haemodialysis

Table 9 shows that a slightly higher percentage of female patients (87.0%) had their drugs inappropriately renally adjusted compared to male patients (78.4%). Both privately insured and state referred patients had a similar percentage of inappropriately renally adjusted drugs (83.1 % and 81.0%, respectively). A chi-square test for association was conducted between each variable (sex and health insurer) and appropriateness of renal drug dosage adjustment as all expected cell frequencies were greater than five. There was no statistically significant association between appropriateness of drug dosage adjustment and these variables, sex (χ^2 =1.588, p=0.208) and health insurer (χ^2 =0.098, p=0.754).

Table 9: Association between appropriateness of renal drug dosage adjustment and patients' sex and type of health insurer

Predictor	Category	Renal drug dosage adjustment					
		Appropriate drug dosage adjustment		Inappropriate drug dosage adjustment			
		n	%	n	%	χ^2	*p*
Sex	Male	16	21.6	58	78.4	1.588	0.208
	Female	7	13.0	47	87.0		
Health insurer	State	12	19.0	51	81.0	0.098	0.754
	Private	11	16.9	54	83.1		

*Level of statistical significance, $p < 0.05$

Table 10 shows that of those patients with cardiovascular comorbidities, 32 (80%) had their drugs inappropriately adjusted and only 8 (20%) had their drugs appropriately adjusted. Of` those with non-cardiovascular comorbidities, 73 (83%) had their drugs inappropriately adjusted while 15 (17%) had their drugs appropriately adjusted. A Fisher's exact test revealed no statistically significant association between type of comorbidities (cardiovascular/ non-cardiovascular) and appropriateness of renal drug dosage adjustment (p=0.804).

Table 10: Association between type of comorbidities and appropriateness of renal drug dosage adjustment

Predictor	Category	Renal drug dosage adjustment				
		Appropriate drug dosage adjustment		Inappropriate drug dosage adjustment		
		n	%	n	%	*p*
Type of comorbidities	Non-cardiovascular	15	17	73	83	0.804
	Cardiovascular	8	20	32	80	

*Level of statistical significance, *p <0.05*

Univariate binary logistic regression was performed to determine the effect of each of the predictor variables, i.e. age, sex, health insurer, total number of drugs, type of comorbidities (cardiovascular/non-cardiovascular) and number of comorbidities, on the likelihood of inappropriately renally dosage adjusted drugs among the participants. Linearity of the continuous variable (age) with respect to the logit of the dependent variable, appropriateness of renal drug dosage adjustment, was assessed via the Box-Tidwell procedure. Based on this assessment, the continuous variable age was found to be linearly related to the logit of the dependent variable, therefore included as a possible predictor in the binary logistic regression models (82). Each of these variables were added to the models separately. Table 11 shows the results of the univariate binary logistic regression models for the different predictor variables. Of the six predictor variables, only age was statistically significant. An increase in a patients' age by one year was associated with a 3.5% increase in the likelihood of having appropriately dosed drugs, at 95% CI of 1.002 to 1.068 (OR: 1.035, p=0.035) as shown in Table 11.

Table 11: Univariate binary logistic regression models predicting likelihood of inappropriate renal drug dosage adjustment

							95% CI	
	B	S.E.	Wald	*df*	*p*	OR	Lower	Upper
Age	0.034	0.16	4.434	1	0.035	1.035	1.002	1.068
Total number of drugs	-0.031	0.068	0.212	1	0.645	0.969	0.849	1.107
Number of comorbidities	0.35	0.105	0.110	1	0.740	1.035	0.843	1.272
Sex	-0.616	0.494	1.558	1	0.212	0.540	0.205	1.421
Health insurer	0.144	0.461	0.098	1	0.754	1.155	0.468	2.850
Types of comorbidities	-0.196	0.486	0.163	1	0.687	0.822	0.317	2.132

A multivariate binary logistic regression was performed including only variables that had a *p* value of <0.25 from the univariate analysis. Taking into consideration the Event per variable (EPV) of 10, a maximum of three variables could be added to the model. However, only two predictor variables had a *p* value <0.25 in the univariate binary logistic model; age and sex. These were the only ones included in the multivariate binary logistic regression model. The logistic regression model was statistically nonsignificant, χ^2 =5.458, *p*=0.065, however, the Hosmer and Lemeshow goodness of fit test shows that the model is not a poor fit, *p*=0.617. The model explained 6.8% (Nagelkerke R^2) of the variance in appropriateness of drug dosage adjustment and correctly classified 82% of cases. The model sensitivity was 0% and specificity was 100%, positive predictive value was 0% and negative predictive value was 82%. None of the two variables, age and sex, were statistically significant predictors of the appropriateness of dosage adjustment, although the *p* value for age (*p* =0.057) approaches statistical significance as shown in table 12.

Table 12: Multivariate binary logistic regression predicting likelihood of inappropriate renal drug dosage adjustment

							95% C.I.	
	B	S.E.	Wald	df	*p*	OR	Lower	Upper
Age	0.032	0.017	3.621	1	0.057	1.032	0.999	1.066
Sex	-0.424	0.509	0.693	1	0.405	0.655	0.242	1.775

The univariate logistic regression models showed that an increase in the patient's age was significantly associated with an increase in the likelihood of having appropriately dosed drugs. Since these findings were not consistent with literature, an additional analysis was performed to assess the relationship between age and total number of drugs. A linear regression was run to understand the effect of the age of patients on total number of drugs. The linear regression established that age of a patient could statistically significantly predict total number of drugs, F (1,145) = 18.960, $p < 0.0005$ and age accounted for 11.6% of the explained variability in total number of drugs with adjusted R^2 = 11.0%, a medium size effect according to Cohen (1988) (83). There is a predicted increase in total number of drugs of 0.079 (95% CI, 0.043 to 0.115) drugs for every one year increase in age of the patient. The regression equation was: predicted total number of drugs = 7.77 + 0.079 x (age).

6. DISCUSSION

This study aimed to investigate the prescribing patterns and explore appropriateness of drug therapy amongst ESRD patients undergoing regular haemodialysis at dialysis centers in Windhoek. Thus far, this is the first study in Namibia to investigate prescribing patterns and drug use appropriateness in this study population.

6.1. Patient demographics

In this study, there were more male (53.7%) patients compared to female patients (46.3%) undergoing chronic haemodialysis. A similar sex distribution was observed in a study done in India (21) and other studies have reported a higher frequency of male patients (71,73). Male patients undergoing haemodialysis are consistently reported to be more than female patients. Although the prevalence of CKD is more in women due to increased risk from recurrent urinary tract infections and eclampsia during pregnancy, men tend to develop ESRD and consequently end up on haemodialysis earlier compared to women (84,85). The mean age (SD) of the study participants was 47.3±15.1 years, this is consistent with findings of a number of studies (13,16,73). Another study reported a higher mean age of 72.3 ± 7.6 (17). The median (IQR) BMI of the patients that had both their weight and height recorded in their clinical records was 22.1 (26.8-18.6) kg/m^2. Majority (53.9%) of the patients had normal weight while 14.6% were obese. Another study on drug related problems in haemodialysis reported similar findings on BMI with a median (IQR) of 23.9 (28.3–21.5) kg/m^2 (86) . The current study also found that a slightly higher percentage of the patients on haemodialysis were those referred from public hospitals (53.1%). This may be due to the fact that although Namibia is an upper-middle-income country, with a dual health care system of both public and private health care providers,

majority (82%) of the population does not have access to medical aid and therefore mainly receive health care from the public health system (87). However, individual patient economic standing or whether they could afford to pay for the dialysis services without medical aid was not investigated and was beyond the scope of the study. Each study participant had at least one co-morbidity or complication of ESRD. Majority of the participants (44.8%) had either 3 or 4 comorbidities. This observation was expected as the current study only included patients with ESRD. Patients with ESRD are known to have multimorbidity as a consequence of their poor renal function. The most common comorbidities were hypertension with anaemia (35.4%) followed by a combination of hypertension, anaemia and secondary hyperparathyroidism (25.2%). Hypertension and anaemia were also reported to be the top 2 associated comorbid conditions in two similar studies by Tadvi *et al.* and Abhisek *et al.* (21,69). Other studies have reported diabetes mellitus to be one of the most common comorbidity after hypertension (13,17,73,88,89).

6.2. Prescribing patterns among ESRD patients undergoing haemodialysis

In this study, 'WHO prescribing indicators' such as the total number of drugs prescribed, average number of drugs per patient, number of drugs prescribed by generic name, number of drugs from WHO Essential Medicines List were used to describe the prescribing patterns (72). The current study revealed a mean of 11.5 drugs per patient. According to the WHO standard, which recommends a cutoff point of 5 drugs, this is considered polypharmacy (11). This finding is consistent with the findings of other studies that observed similar high average number of drugs prescribed per patient on maintenance haemodialysis varying from 5 to 13 drugs (8,16,21,22,71,73,88). In the current study, 28.6% of the patients had cardiovascular comorbidities, this may explain the high numbers

of drugs used per patient since these conditions are generally associated with the need for prescribing several drug classes (86). Cardiovascular diseases are actually known to be one of the major causes of mortality and morbidity in dialysis patients. As evidenced by the current study as well as other studies done in different settings, polypharmacy remains a challenge in this group of patients as the use of multiple drugs is somewhat unavoidable due to multimorbidity. Due to the complexity of managing these patients, there may be instances where the use of multiple drugs may be clinically appropriate, hence in recent years some studies have suggested redefining polypharmacy from merely counting number of drugs prescribed to adopting terms such as 'appropriate or inappropriate polypharmacy' (90–92). However, ensuring medication safety while still meeting all patient clinical needs remains priority (92). In this study, 50.1% of the drugs prescribed were prescribed by their generic names; this is lower than what was reported by another study by Tadvi *et al.* (21). Other previous studies have reported an even much lower result, ranging from 0%-40.96% (69,88,89,93). The WHO recommends that 100% of all medicines prescribed should be by generic name in order to promote rational use of medicines. Locally, the MOHSS Namibia recommends that acceptable cut of point of 80% of all medicines prescribed should be prescribed using generic names (94). The results of these studies show that despite the recommendations in place, prescribing using brand names has become normal practice both in the public and private health sector as only 50.1% of the drugs were prescribed using generic names. From a total of 163 different drugs prescribed to all study participants, 60.1% were from the WHO Essential Medicines List. This finding is higher than that reported by Bajait *et al.* (41.5%) and lower than that reported by Tadvi *et al.* (65.3%) (21,88). The difference may be due to the fact that in the current study, 53.1 % of patients were referred from state-run health facilities. Drugs that

are available and prescribed in public sector health facilities are mainly those that are included in the Namibia Essential Medicines List (NEMLIST). The NEMLIST is based on the WHO Model Essential Medicines List. This is to ensure that affordable medicines that adequately manage majority of public health conditions prevailing in Namibia are available (95).

According to the ATC classification system, cardiovascular system drugs were the most prescribed (38.3%), followed by alimentary tract and metabolism drugs (25.6%) and blood and blood forming organs (23.1%). Other studies have reported similar drug utilization patterns with varying frequencies (88,89,93). In the current study, among the cardiovascular drugs, furosemide was the most prescribed drug. It was prescribed to 80% of the patients. Other studies by Abhisek *et al.*, Ahlawat *et al.*, and Devi *et al.* also found that diuretics, mainly loop diuretics, were the most prescribed drugs (69,89,93). In the cited studies, loop diuretics were prescribed to 53.9%, 54% and 50% of the patients respectively. The use of furosemide in the current study was relatively higher accounting for 79.6%. This difference in the extent of use of furosemide could be explained by the fact that the current study only included ESRD patients while the other studies also included patients with CKD stage 4. This difference in the frequency of furosemide prescribing between the current study and previous studies shows the previously reported inconsistent practice in diuretic use in haemodialysis (96). Some studies have even reported as low as only 13% of haemodialysis patients receiving diuretics and have suggested changes in drug pharmacokinetics in ESRD and haemodialysis as well as dosing uncertainty to be the possible reasons for such inconsistent practice (96). The use of loop diuretics in haemodialysis patients has been shown to lower interdialytic weight

gain, intradialytic hypertension and hospitalization therefore improving quality of life of these patients (97–100).

Carvedilol was the second most prescribed cardiovascular drug followed by amlodipine and doxazosin. β-Blockers are also reported to be the most commonly prescribed antihypertensive agents by Sonawane *et al.*(101). A study by Al-Mirza *et al.* including patients with all CKD stages, with majority of patients (49.7%) in CKD stage 3, found that β-blockers were the second most prescribed antihypertensive drug class after diuretics (102). Other studies, involving majority of the patients in ESRD, reported calcium channel blockers to be the most commonly utilized antihypertensive drugs in patients with CKD after diuretics (22,88,89). Angiotensin-converting enzyme (ACE) inhibitors as well as angiotensin receptor blockers (ARB) were one of the least prescribed drugs in the current study as well as in the study by Sonawane *et al.*, (101). This may largely be due to their side effect of worsening hyperkalemia. Some studies have suggested that it is safe to put patients on maintenance dialysis on ACE inhibitors or ARBs as dialysis plays the major role in potassium homeostasis (101,103,104). In contrast to the findings of the current study, a study by Liu *et al.* reported that renin angiotensin system inhibitors were the most frequently prescribed hypertensive agents in those with CKD (105).

Among the alimentary tract and metabolism drugs, alfacalcidol was the most commonly prescribed drug, followed by calcium gluconate and then ergocalciferol accounting for 83.0%, 47.6% and 32.0%, respectively. This finding is contrary to reports by previous studies that found phosphate binders to be the most prescribed drugs under this drug class (22,69,88,89). Interestingly, in the current study, calcium carbonate, a phosphate binder was only prescribed to 14.3% of the participants. The main reason for the under-

prescription of phosphate binders may be due to the fact that more than half (53.1%) of the patients in the current study were those referred from state hospitals. Phosphate binders, due to their high cost, are not part of the NEMLIST and are therefore not readily available in state hospitals. A study by Tadvi *et al.* found proton pump inhibitors and H_2 antagonists to be the most prescribed drugs among the gastrointestinal system drugs, prescribed to 65.8% and 14.6% of patients respectively (21). Interestingly, these drugs were one of the least prescribed in the current study. The use of vitamin D analogues was found to be higher (83.0% for alfacalcidol and 32.0% for ergocalciferol) than in other studies by Ahlawat *et al.* and Bajait *et al.* (88,89). This difference may be explained by the high prevalence of secondary hyperparathyroidism in the current study. Some studies have suggested an association between vitamin D supplementation and decreased all-cause mortality amongst ESRD patients requiring dialysis (106).

Erythropoietin was the most commonly prescribed drug among the blood and blood products ATC class; it was prescribed to 89.1% of the patients, followed by iron sucrose (70.7%) and aspirin (28.6%). Similarly, a study by Tadvi *et al.* observed that erythropoietin stimulating agents (ESA), specifically erythropoietin and darbepoetin, were prescribed in 92% of the patients (21). The use of erythropoietin in the study undertaken by Tadvi *et al.,* and the current study was higher than reported by previous studies where the use of ESA ranged from 20% to 60% (22,69,107). The underutilization of these agents was attributed to the high cost of these agents as well as the low economic status of the study participants (88). However, this may not have been the case in the current study as the patients with medical aid had a large part of the cost covered by health insurance while patients referred from state-run health facilities received these drugs at no

cost as all costs were covered by the government. However, determining the economic status of the study participants was beyond the scope of this study. Iron sucrose was expectedly also one of the most prescribed drugs, alongside erythropoietin, due to the high prevalence of anaemia among these patients. Previous studies reported that both erythropoietin and iron were under-prescribed in anemic patients as only 20% and 32% of anemic patients received treatment at baseline (22,88,107). Aspirin was the most prescribed antithrombotic agent in this study as well as other similar studies (107,108). However, the frequency of use of aspirin in this study (28.6%) is much lower than previous studies. Bailie *et al.* reported that aspirin was prescribed to 37% of patients included in the study, additionally, 65% of patients with coronary artery disease received aspirin (107). Low dose aspirin in haemodialysis patients is used as a secondary prevention of atherosclerotic disease as well as a routine treatment to prevent ischemic events after percutaneous interventions (41,109). Nevertheless, the use of antiplatelet agents in haemodialysis has remained controversial due to the additional risk of bleeding in haemodialysis patients compared to the general population; this may explain the lower prescribing rate of aspirin in this study compared to previous studies (107,108). Additionally, the results of a meta-analysis findings suggested that the risk of bleeding in haemodialysis patients receiving antiplatelet agents is associated with the use of two antiplatelet agents as opposed to using a single agent (109).

6.3. Appropriateness of medication choice in ESRD patients undergoing haemodialysis

Among the 147 patients included in the current study, 80.3% had all their drugs appropriately selected while the remaining 19.7% had at least one or more of an inappropriately selected drug. Inappropriate drug selection entailed inappropriate drug for indication(s) according to guidelines or formulary, contraindication in ESRD, drug use without indication, presence of clinically significant drug interactions, therapeutic duplication as well as allergies to drugs. In the current study, an example of inappropriate drug for indication was failure to prescribe an appropriate antiretroviral therapy (ART) regimen to a patient in accordance with recommendations of the national guidelines. The use of drugs contraindicated in ESRD commonly involved use of co-trimoxazole for prophylaxis of opportunistic infections in HIV positive patients with ESRD. An example of drugs used without indication included the use of analgesics such as combination of tramadol and paracetamol without any clinical evidence suggestive of pain or fever. Several drug interactions were identified in this study, ranging from minor to serious drug interaction. An example of a common minor drug interaction was an interaction between calcium-based phosphate binders such as calcium acetate and oral ferrous fumarate preparations. Serious drug interactions between omeprazole and drugs such as clopidogrel and atazanavir were noted. The case of therapeutic duplication was seen in the use of vitamin supplements that contained similar active pharmaceutical ingredients. For instance, the use of pyridoxine in addition to vitamin B complex that contained vitamins B1, B6 and B12. The use of a drug to which a patient was allergic was not detected in the current study. In the current study, some of the frequently prescribed drugs that were inappropriately chosen for some of the patients included co-trimoxazole, thiamine,

warfarin, tramadol and paracetamol combination, and amitriptyline. A number of studies have suggested that majority of the medication choice problems were related to the misuse of antibiotics and cardiovascular agents (110–113). However, other studies suggested that erythropoietin and iron supplements were associated with drug therapy problems (114). The difference with these findings may be due to differences in study population and study setting. Drug therapy problems such as inappropriate drug selection are common in patients with ESRD requiring haemodialysis, due to the high number of drugs as well as the complexity of managing this group of patients (114). Njeri *et al.,* reported a lower frequency of improper drug selection (12.2%); making it the fourth most prevalent drug therapy problem identified in that study after drug interactions, indication without drug and failure to receive drug (16). The study by Njeri *et al.* included patients in CKD stages 3 and 4. The number of associated comorbidities as well as the number of drugs needed to manage a patient with CKD increases as their renal function worsens, making patients on haemodialysis to be more prone to drug errors than those who are not (16).This may explain the lower frequency of medication choice errors in the study conducted by Njeri *et al.*.

In contrast to findings of the current study, Ramadaniati *et al.,* found drug selection to be the most prevalent cause of drug related problems that pharmacists identified in CKD patients in an Indonesian hospital (13). It constituted 37.7% of all identified drug related problems (13). Similarly, a number of studies by Adibe *et al.*, Pehlivanli *et al.* and Zhang *et al.* also reported inappropriate drug selection amongst chronic kidney patients as the commonest drug therapy problem in this group of patients contributing 27.7%, 38.5%, 46.9% and 60.3% of the identified drug therapy problems, respectively (17,110,115).

Unlike the current study that specifically investigated the appropriateness of drug selection in haemodialysis patients, the other cited studies explored for all drug therapy problems in addition to drug selection in patients in different CKD stages and used the Pharmaceutical Care Network European (PCNE) criteria to classify drug related problems. This may explain the heterogeneity in the findings of these studies and the current study with regard to drug selection related medication errors. Additionally, in the current study, the patients were normally seen by one prescriber who was responsible for initiating therapy as well changing dialysis regimens; this has been shown to be a factor that may lead to less medication choice errors (116). Nonetheless, all these studies including the current study, highlight the challenge experienced by prescribers in selecting the safest and most appropriate drug choices for patients with CKD more so those with ESRD maintained on haemodialysis.

6.4. Appropriateness of renal drug dosage adjustment in ESRD patients undergoing haemodialysis

The pharmacokinetics of a lot of drugs change significantly in patients with ESRD, for this reason, drug dosage adjustment of drugs is crucial to maximize therapeutic efficacy and prevent toxicity (11). In the current study, 163 different drugs were prescribed to the patients of which 41 (25.2%) required dosage adjustment. The main factors that determine the need for dosage adjustment in haemodialysis are: drug renal clearance, therapeutic index, clearance by haemodialysis , plasma protein binding and volume of distribution (20).

The prevalence of dosage adjustment errors among CKD patients varies across different parts of the world. In the current study, out of the 1691 total prescription entries for the

patients, 263 (15.6%) entries required dosage adjustment. With respect to drugs that required dosage adjustment, 128 (48.7%) were appropriately adjusted while the remaining 135 (51.3%) were inappropriately or not adjusted at all. These findings are similar to those reported by studies undertaken in other developing countries such as Pakistan, Palestine and South Africa. These countries have reported that dosage adjustment errors are one of the most prevalent drug related errors in CKD patients (15,18,77,80). Two studies conducted in Pakistan by Hassan *et al.* and Saleem *et al.* reported that a total of 1549 and 1534 drugs, respectively, were prescribed (18,80). A total of 480 and 522 drugs required dosage adjustment and only 194 (40.4%) and 218 (41.8%) were appropriately adjusted while the remaining 59.58% and 58.2% were unadjusted, respectively. Although both the two studies conducted in Pakistan included patients in different CKD stages, majority of the participants in both studies, 90.5% and 75.6% respectively, were in CKD stage 5. Another study carried out in a government hospital in Palestine, including patients with CKD stages 3 to 5, reported a higher frequency of inappropriately adjusted drugs (73.6%) (15). In the Palestine study, majority of the patients (two-thirds) had cardiovascular diseases, such as hypertension, congestive heart failure and ischemic heart disease. This may explain the high prevalence of inappropriate dosage adjustment as the study further reported that cardiovascular drugs were amongst one of the most commonly inappropriately dosed drugs (15). A study conducted in South Africa by Decloedt *et al.* reported that only 37% of the prescription entries that required dose adjustment were correctly adjusted (77). The high prevalence of dosage adjustment errors in developing Asian and African countries are not too surprising as dose adjustment in patients with renal impairment is rarely done due to prescribers underestimating the potential adverse consequences of lack of dose adjustment (15,18,77,80,117).

In the study by Sweileh *et al.*, 81% of patients had at least one inappropriately adjusted drug, with those in stage 5 having a higher average number of inappropriately dosed medications compared to those in stage 3 and 4 (2.6 inappropriate medications per patient) (15). Similarly, the study by Decloedt and colleagues also reported that only 29% of the patients had all their drugs correctly, none of the patients receiving dialysis had all their prescription items adjusted correctly (77). These findings are similar to the current study. In the current study, only 18% of the 147 patients had all their drugs appropriately adjusted while the remaining 82% had at least one inappropriately adjusted drug. These findings show that there is a relatively large number of drugs that require dosage adjustment that are being used to manage ESRD patients, however, appropriate renal dosage adjustment is not carried out. A study carried out in New Zealand, a developed country, reported a lower prevalence of dosage adjustment errors in haemodialysis patients (118). In the New Zealand study, only 13.6% of the haemodialysis patients had dosage adjustment errors (118). A difference between developing and developed countries is also noted among studies that investigated the prevalence of drug related problems amongst CKD patients. Studies conducted in African countries have reported a high prevalence of drug related problems ranging from 78.6% to 100% with average ranging from 1.6 to 4.5 medication related problems per patient (16,119,120). However, a study conducted in China reported a much lower prevalence of 46% , with an average of 0.5 drug related problems per patient (110). Similarly, a study conducted in North America by Manley *et al.* among ambulatory haemodialysis patients, reported a low rate of 0.5 lower drug related problem per patient per month (19). For all these studies, dose related problems such as dose too low or too high, were among the common drug related problems reported. The main reason for these differences is probably due to the varied levels in development

of health care systems. For instance, CKD patients in developed countries are more likely to be attended to by a multidisciplinary health care team consisting of both doctors and clinical pharmacists. Although the practice of pharmacy has transformed in most parts of the world to become more patient-oriented, in some developing countries, the pharmacists still carry out a traditional role which focuses on pharmaceutical products and dispensing (121).

Several past studies have evaluated the impact of clinical pharmacists in managing drug related problems in haemodialysis patients (122–124). These studies report a significant improvement in patient drug therapies as clinical pharmacists were able to identify drug therapy problems and resolve them. The collaboration between clinical pharmacists and medical personnel is also reported to have a positive impact on patient clinical outcomes and reduces health care costs. In a systematic review by Pai *et al.* they found that recommendations made by pharmacists on patient therapy were accepted and implemented by the medical team up to 96% of the time (125). Currently, there are no clinical pharmacists involved in the direct care of patients at the dialysis centers. This may explain the high number of patients (82.0%) in whom dosage adjustment was not appropriately done in the current study.

The most common category of drug dosage adjustment errors in the current study was overdosage (82.2%), followed by underdosage (15.6%) and lastly, too long treatment duration (2.2%). Similar studies conducted in other developing countries, such as India and Saudi Arabia, have reported drug dosing problems as one of the common drug related problems in haemodialysis patients (78,86). A prospective study conducted in dialysis units in India found overdosage (19.4%) to be the second most common drug related

problem amongst haemodialysis patients after drug interactions (78). While the study conducted in Saudi Arabia, on drug related errors among haemodialysis patients, identified dosage adjustment errors as one of the major identified drug related problems, with subtherapeutic dosing and overdosing being the main sources of dosage adjustment errors (with a frequency of 23% and 15% of the identified drug related problems respectively) (86). However, the drug dosage problems in haemodialysis patients are reported to be relatively lower in a study conducted in the United States (dose too high made up of only 4.6% and dose too low 13.1% of the identified drug related problems (123). Unlike those with normal kidney function, in patients with ESRD the risk for adverse drug reactions is increased when doses are not reduced or renally adjusted (18). Ineffective therapies still increase treatment cost and add extra burden on both patients and the healthcare system (18). The discrepancies in the percentage of inappropriate dosing could be explained by the differences in study settings and differences in prescribing patterns; as dosing is dependent on the types of drugs prescribed. These studies and their findings of different rates of drug related problems, demonstrate that ESRD patients are among those at high risk of drug related problems such as inappropriate dosage adjustment and there is a need for regular review of drugs as well as dosages prescribed to haemodialysis patients (14,86).

In the current study, the most commonly used drugs that were inappropriately adjusted were perindopril (inappropriately adjusted in 96% of cases), folic acid (inappropriately adjusted in 16% of cases), warfarin (inappropriately adjusted in 16% of cases), colchicine (inappropriately adjusted in 75% of cases) as well as antibiotics meropenem, ciprofloxacin and cloxacillin. In contrast to the findings of the current study, Sweileh *et al.* reported that

ranitidine was the most inappropriately dosed drug, followed by antibiotics (amikacin, trimethoprim/sulfamethoxazole, ciprofloxacin and cefuroxime), digoxin, cardiovascular medications and metoclopramide (15). A study in CKD patients, by Ossman *et al.* found that erythropoietin was the most inappropriately dosed drug, followed by iron supplements, alfacalcidol, calcium tablets and antihypertensive drugs (14). Additionally, the study by Hassan *et al.* found meropenem, cefepime, ciprofloxacin, rosuvastatin, cefoperazone/sulbactam, ranitidine, and piperacillin/tazobactam to be the most frequently unadjusted drugs (18). There is some variation on the types of drugs that were commonly inappropriately adjusted in the different studies in literature, however most agree on the fact that antibiotics were one of the most inappropriately adjusted drugs (15,18,111). In the current study, there were not a lot of patients on antibiotics. This may be due to the fact that the study sites are outpatient centers and patients may be seen at other hospitals or clinics in case of acute infections.

6.5. Predictors of medication choice and renal dosage adjustment errors in ESRD patients undergoing haemodialysis

In the current study, univariate as well as multivariate binary logistic regression models were used to ascertain whether factors such as the age, sex, number of prescribed drugs, number of co-morbidities, type of co-morbidities as well as type of health insurer were predictors of drug selection as well as renal dosage adjustment errors. Several of these variables, i.e. number of co-morbidities, types of comorbidities as well as type of health insurer were not found to be statistically significantly associated with either medication choice or renal dosage adjustment errors in the present study. This is consistent with studies conducted in Japan and Pakistan that found no significant association between

number and type of comorbidities, sex and the prescribing of inappropriate medication and dosage adjustment errors in CKD patients (18,80,116).

Another study conducted in Pakistan reported that the presence of HPT and DM were statistically significant predictors of patient having a dosage too high whereas the presence of other cardiovascular diseases was associated with the use of too low dosages (126). This is in contrast to the findings of the current study, as this variable i.e. type of comorbidities was not found to be statistically significant.

In the current study out of the six studied variables only one variable, total number of drugs, was found to be significantly associated with inappropriate choice of medication. The univariate as well as the multivariate binary logistic regression models showed that an increase in the total number of drugs was associated with a reduction in the likelihood of having appropriately selected drugs. Similarly, the study in Japan reported that an increase in the number of prescribed medications was significantly associated with prescription of potentially inappropriate medications (116). A systematic review looking into inappropriate prescribing in CKD also identified polypharmacy, presence of comorbidities and age as predictors of inappropriate prescribing (127). In the current study, there was a high prevalence of polypharmacy as each patient was on an average of 11.50 (±3.5) drugs, therefore this may explain the prevalence of inappropriate drug selection of 19.7%.

The univariate binary logistic regression model showed that age was significantly associated with the likelihood of having appropriately dosed drugs. An increase in a patients' age by one year was associated with an increase in the likelihood of having

appropriately dosed drugs. This finding was not consistent with literature and was unexpected. Older CKD patients are known to be at higher risk for drug related problems such as inappropriate dosage due to the prescribing of a higher number of drugs (17). A study by Hayat *et* al. found that age >40 years was significantly associated with prescribing of higher doses (126). A secondary linear regression analysis further showed that there was a predicted increase in total number of drugs of 0.079 drugs with each one year increase in the patient's age. It is therefore not very clear why an increase in age was significantly associated with an increased likelihood of having appropriately dosed drugs. Sweileh *et al.* attributed the high prevalence of inappropriate dosage adjustment in haemodialysis patients to prescribers underestimating potential adverse consequences to unadjusted drug doses (15). Perhaps it may be that in the current study, prescribers are more cautious with dosage adjustment when prescribing to elderly patients compared to younger patients, due to a higher risk of consequences such as adverse drug reactions in elderly with ESRD (128). Hayat *et* al. also found that the likelihood of adverse drug reactions significantly increased with age > 60 years in patients with CKD (126). Similarly, a study by Njeri *et al* also reported a statistically significant association between age and adverse drug reactions in CKD patients (16). Other studies conducted in non-dialysis CKD patients that looked into age, as an independent predictor of drug related problems reported that age was not a statistically significant predictor of drug dosing problems (16,110,113). The difference may also be due to the fact that the aforementioned studies included patients with different CKD stages, unlike the current study that only included those with ESRD.

There were several limitations in our study. Firstly, this study made use of data from patient clinical records, for this reason some data may have been recorded wrongly. Since

the study involved the review of medical records only, information on other drugs that the patients may have been taking such as self-medications or herbal medicines was not available. Interviewing patients may have also revealed other issues such as poor adherence, inappropriate timing of drug administration and may have helped identify drugs that may no longer be necessary for the patient. The sample size was calculated using literature data on the prevalence of inappropriate drug selection and inappropriate dosage among CKD patients in other countries as there was no local data on the prevalence of these two main outcome measures. For this reason, the sample size may have not been sufficient enough to investigate all independent variables as possible predictors for drug selection and dosage adjustment errors.

7. CONCLUSIONS

This is the first study in Namibia to assess prescribing in ESRD patients on maintenance haemodialysis, which proves that there is still much work that needs to be done to ensure safe management of these patients. A wide variety of drugs were prescribed to the patients with ESRD, cardiovascular system drugs were the most prescribed drug class. The current study found that patients with ESRD on haemodialysis are being managed with a relatively large number of drugs and although the drugs are appropriately selected for their indications in most cases, the renal dosage adjustment is still poorly done. Clinical pharmacy services would therefore be of great value in the care of ESRD patients as they could optimize drug therapy as well as improve patient outcomes. The number of drugs prescribed was significantly associated with medication choice errors, while increasing age unexpectedly increased the likelihood of appropriate dosage adjustment.

8. RECOMMENDATIONS

Based on the findings of this study, there are a number of recommendations proposed by the principal investigator to the dialysis centers as well as the University of Namibia, School of Pharmacy.

Renal dosage adjustment errors were highly prevalent in the current study, therefore there is a need for dosage adjustment charts of commonly prescribed drugs to be availed to the prescribers at the dialysis centers. Although ESRD patients present with several comorbidities as well as complications of ESRD, the prescribers should stick to prescribing essential medicines only, to reduce polypharmacy.

The dialysis management can conduct trainings of prescribers on appropriate management of common comorbid conditions in ESRD patients. The University of Namibia, School of Pharmacy could take up this opportunity by designing continuous development short courses in the area of prescribing and dosing in ESRD that could be offered to both pharmacists and doctors.

There may be different kinds of references resources available, especially online, with different recommendations on prescribing and dosing in CKD. This may result in non-evidence based and ineffective clinical practices. The growing prevalence of CKD in Namibia calls for a need to develop local renal prescribing guidelines that will include recommendations on drug dosing as well as management of common CKD complications or comorbid conditions. This can be achieved with the collaboration between the private health sector and the Ministry of Health and Social Services.

Currently there is no clinical pharmacist involved in the direct care of patients at the dialysis centers, it would be suitable for the center to employ a clinical pharmacist that will be an integral member of the dialysis health care team as they are specially trained to detect medication choice errors or renal dosage adjustment errors and properly intervene. The two centers can employ one clinical pharmacist that can rotate between the two centers. Clinical pharmacists are able to carry out activities such as medication reconciliation and other therapy management services that will reduce drug therapy problems as well as reduce health care costs for both patients and health insurers.

Although this research already looked into medication choice and dosage adjustment errors in ESRD patients, more research is needed to look into other types of therapy related problems such as adverse drug reactions. Future studies should also look into the impact of a clinical pharmacist on improving treatment outcomes for ESRD patients at these dialysis centers.

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10. APPENDICES

10.1. APPENDIX A: Eligibility screening form

All patients should meet the inclusion criteria on screening before they are enrolled in this study

I. Study Information

Study Title: Prescribing patterns and drug dosage adjustment in patients undergoing chronic haemodialysis at two dialysis centers in Windhoek, Namibia.

Principal Investigator: Martha Siwombe
Date of screening……..

II. Patient information

Patient code: ……

Sex: Male ☐ Female ☐ Other ☐

Age……..

Body weight…….

III. **Inclusion Criteria**	**Yes**	**No**
ESRD diagnosis		
Patient receiving haemodialysis at any of the dialysis centers in Windhoek, Namibia		
Has at least one co-morbid conditions / Taking at least one drug or more		

10.2. APPENDIX B: Data collection tool

PRESCRIBING PATTERNS AND DRUG DOSAGE ADJUSTMENT IN PATIENTS UNDERGOING CHRONIC HAEMODIALYSIS AT TWO DIALYSIS CENTERS IN WINDHOEK, NAMIBIA.

Patient Code: …….

I. **PATIENT DEMOGRAPHICS**	
Sex 1. □ Male 2. □ Female 3. □ Other	Age……. State patient □ Private patient □ Body weight: ……. Height: …….....

II. **COMPLICATIONS OF CKD & COMORBID CONDITIONS**

Biochemical parameters	**Result**	**Date**
Parathyroid hormone		
Hemoglobin		
Phosphate		
Calcium		
Vitamin D		
Bicarbonate		
Sodium		
Chloride		
Urine albumin		

Hypertension □ Diabetes mellites Type 1□ Type 2 □ HIV □	Complications of CKD: Anaemia □ Renal bone disease □ Hyperkalemia □	

Others:…… …… ……	Others:…… ……

III. **CURRENT eGFR**

……

……

……

IV. **CURRENT DRUG THERAPY**

(acute and chronic)

Medicine/Dose	Indication	Duration (start and stop dates)	Route of admin,
Current medication: acute and chronic medicines			
Total number of prescribed medicines			
Allergies			

10.3. APPENDIX C: Dialysis center information sheet

Study Title: Prescribing patterns and drug dosage adjustment in patients undergoing chronic haemodialysis at two dialysis centers in Windhoek, Namibia.

Institution: University of Namibia

Primary investigator: Ms. Siwombe Martha, postgraduate student (Master of clinical pharmacy)

Supervisors: Prof. Roger Verbeeck, Professor, University of Namibia.

Mr. Mubita Mwangana, Senior Lecturer, University of Namibia

I am Martha Siwombe, a 3rd year postgraduate student, conducting the above study to partly fulfil requirements for a Master Degree in Clinical Pharmacy of the University of Namibia.

PURPOSE OF STUDY

This study aims to investigate prescribing patterns and explore appropriateness of drug therapy among ESRD patients undergoing regular haemodialysis at dialysis centers in Windhoek.

STUDY PROCEDURE

This study will involve a review of patient clinical records. The data collected will be handled professionally, kept confidential and will only be used to fulfil the aims and objectives of this study. Patient codes will be used instead of patient names, and data will be saved in a password protected electronic file during data analysis which will only be accessible to the researcher and supervisors. At the end of the study, the

researcher intends to publish the results in a scientific journal, and shared with other health care workers through workshops and CPD events.

BENEFITS

This study will generate data on the prescribing patterns and dosage adjustment of drugs in patients undergoing haemodialysis. This data will inform clinical practice and potentially improve patient outcomes. The findings on the prescribing patterns and drug selection will help identify opportunities for promoting rational drug use, reduce adverse drug reactions, reduce drug-drug interactions and improve adherence to drug therapy in ESRD patients undergoing chronic haemodialysis.

In case of any concerns or questions regarding this study, contact me on Email: Siwombe.martha@gmail.com Cell: +264 817734553

10.4. APPENDIX D: University of Namibia ethical clearance certificate

UNAM
UNIVERSITY OF NAMIBIA

ETHICAL CLEARANCE CERTIFICATE

Ethical Clearance Reference Number: SOP0001 **Date: 16 May 2022**

This Ethical Clearance Certificate is issued by the University of Namibia Ethics Committee (REC) in accordance with the University of Namibia's Research Ethics Policy and Guidelines. Ethical approval is given in respect of undertakings contained in the Research Project outlined below. This Certificate is issued on the recommendations of the ethical evaluation done by the ethics committee.

Title of Project: Prescribing patterns and drug dosage adjustment in patients undergoing chronic haemodialysis at three dialysis centres in Windhoek, Namibia

Principal researchers: Ms. Martha SIWOMBE

Staff Number/ Student number: 201307308

Remarks: This research meets the requirements for Ethical Clearance.

Centre for Research Services

Take note of the following:

1. Any significant changes in the conditions or undertakings outlined in the approved Proposal must be communicated to the ethics committee. An application to make amendments may be necessary.
2. Any breaches of ethical undertakings or practices that have an impact on ethical conduct of the research must be reported to the ethics committee
3. The Principal Researcher must report issues of ethical compliance to the ethics committee (through the Chairperson) at the end of the Project or as may be requested by the ethics committee
4. The ethics committee retains the right to:

i) Withdraw or amend this Ethical Clearance if any unethical practices (as outlined in the Research Ethics Policy) have been detected or suspected,

ii) Request for an ethical compliance report at any point during the course of the research.

The ethics committee wishes you the best in your research.

Francis KALEMEERA

(Chairperson Decentralized Ethics Committee)

Prof. Davis Mumbengegwi (Head, Multidisciplinary Research)

10.5. APPENDIX E: Ministry of health and social services permission letter

REPUBLIC OF NAMIBIA

MINISTRY OF HEALTH AND SOCIAL SERVICES

Ministerial Building
Harvey Street
Private Bag 13198, Windhoek

OFFICE OF THE EXECUTIVE DIRECTOR

Tel: No: 061 -203 2507
Fax No: 061-222 558
Andreas.Shipanga@mhss.gov.na

Ref: 17/3/3/ MS
Enquiries: Mr. A. Shipanga

Date: 13 June 2022

Ms. Martha Siwombe
PO Box 2312
Rundu
Namibia

Dear Ms. Siwombe

Re: *Prescribing patterns and drug dosage adjustment in patients undergoing Chronic Haemodialysis at three Dialysis Centers in Windhoek, Namibia.*

1. Reference is made to your application to conduct the above-mentioned study.
2. The proposal has been evaluated and found to have merit.
3. **Kindly be informed that permission to conduct the study has been granted under the following conditions:**
   - 3.1 The data to be collected must only be used for academic purpose;
   - 3.2 No other data should be collected other than the data stated in the proposal;
   - 3.3 Stipulated ethical considerations in the protocol related to the protection of Human Subjects should be observed and adhered to, any violation thereof will lead to termination of the study at any stage;
   - 3.4 A quarterly report to be submitted to the Ministry's Research Unit;
   - 3.5 Preliminary findings to be submitted upon completion of the study;
   - 3.6 Final report to be submitted upon completion of the study;
   - 3.7 Separate permission should be sought from the Ministry for the publication of the findings.
4. All the cost implications that will result from this study will be the responsibility of the applicant and **not** of the MoHSS.

Yours sincerely,

EXECUTIVE DIRECTOR
MINISTRY OF HEALTH AND SOCIAL SERVICES

BEN NANGOMBE
EXECUTIVE DIRECTOR

10.6. APPENDIX F: Dialysis center permission letter from management

Fresenius Medical Care Approval letter.

Protocol

PRESCRIBING PATTERNS AND DRUG DOSAGE ADJUSTMENT IN PATIENTS UNDERGOING CHRONIC HAEMODIALYSIS AT THREE DIALYSIS CENTERS IN WINDHOEK, NAMIBIA.

BY

MARTHA SIWOMBE

Dear Ms Siwombe

Thank you for sending the protocol of your proposed study (a research proposal submitted in partial fulfilment of the requirement for the degree of Master of Pharmacy of the University of Namibia) for us to approve.

I support your doing the study.

Be aware that eGFR results obtained from patients on dialysis are very inaccurate. You may wish to include residual renal function as a parameter in your dissertation?

Please ensure that the unit managers in the dialysis centres are informed and kept up to date with your activities.

Confidentiality of the patient data obtained during your study, must be maintained. Any breach in this confidentiality clause will result in cancellation of this approval and notification of the relevant authorities.

Please give us a report back on the conclusions from the study.

Sincerely

A/Prof C R Swanepoel,
Medical Director: Fresenius Medical Care. 20/06/22

1

10.7. APPENDIX G: List of commonly prescribed drugs per ATC class

Drug class	ATC Code	N (%)
A=Alimentary tract and metabolism		433 (25.6)
Alfacalcidol	A11CC03	122 (83.0)
Calcium gluconate	A12AA03	70 (47.6)
Ergocalciferol	A11CC01	47 (32.0)
Omeprazole	A02BC01	26 (17.7)
Calcium carbonate	A12AA04	21 (14.3)
Multivitamin	A11AA04	20 (13.6)
Calcium+vitamin D+Magnesium	A12AX	19 (12.9)
Esomeprazole	A02BC05	15 (10.2)
Insulin glargine	A10AE04	9 (6.1)
Immune boosters	A11JA	8 (5.4)
Vitamin C	A11GA01	8 (5.4)
Other alimentary & metabolism drugs	-	68 (46.3)
B=Blood and blood forming organs		391 (23.1)
Epoetin beta	B03XA03	131 (89.1)
Iron sucrose	B03AC	104 (70.7)
Aspirin	B01AC06	42 (28.6)
Folic acid	B03BB01	32 (21.8)
Warfarin	B01AA03	30 (20.4)
Ferrous fumarate + folic acid	B03AD02	14 (9.5)
Enoxaparin	B01AB05	12 (8.2)
Clopidogrel+aspirin	B01AC30	8 (4.8)
Clopidogrel	B01AC04	7 (4.8)
Apixaban	B01AF02	7 (4.8)
Others	-	4 (2.7)
C=Cardiovascular system		648 (38.3)
Furosemide	C03CA01	117 (79.6)
Carvedilol	C07AG02	89 (60.5)
Amlodipine	C08CA01	79 (53.7)
Doxazosin	C02CA04	79 (53.7)
Perindopril	C09AA04	59 (40.1)
Spironolactone	C03DA01	38 (25.9)
Minoxidil	C02DC01	34 (23.1)
Atorvastatin	C10AA05	25 (17.0)
Telmisatan/Amlodipine	C09DB04	21 (14.3)
Telmisatan	C09CA07	13 (8.8)
Others	-	94 (63.9)
D=Dermatologicals		5 (0.30)

Chlorhexidine in water	D08AC02	2 (1.4)
Fusidin ointment	D06AX01	1 (0.7)
Emulsifying ointment	D02AC	1 (0.7)
Benzoyl peroxide gel	D10AE01	1 (0.7)
G=Genito urinary system and sex hormones		9 (0.5)
Sodium bicarbonate+sodium citrate + citric acid	G04BD	4 (2.7)
Sildenafil	G04BE03	2 (1.4)
Tamsulosin	G04CA02	1 (0.7)
Mirabegron	G04BD12	1 (0.7)
Solifenacin	G04BD08	1 (0.7)
H= Systemic hormonal preparations (excl. sex hormones and insulins)		21 (1.24)
Prednisolone	H02AB06	9 (6.1)
Calcitonin	H05BA03	7 (4.8)
Levothyroxine	H03AA01	4 (2.7)
Somatropin	H01AC01	1 (0.7)
J=Anti-infectives for systemic use		55 (3.3)
lamivudine, abacavir and dolutegravir	J05AR13	13 (8.8)
Tenofovir deproxil	J05AF07	5 (3.4)
Atazanavir/ritonavir	J05AR23	4 (2.7)
Cotrimoxazole	J01EE01	3 (2.0)
lamivudine and abacavir	J05AR02	3 (2.0)
Amoxycillin/Clavulanic acid	J01CR02	3 (2.0)
Lopinavir/ritonavir	J05AR10	3 (2.0)
Dolutegravir	J05AJ03	2 (1.4)
Phenoxymethyl penicillin	J01CE02	2 (1.4)
Vancomycin	J01XA01	2 (1.4)
Others	-	15 (10.2)
L=Antineoplastic and immunomodulating agents		3 (0.8)
Azathioprine	L04AX01	1 (0.7)
Cyclosporin	L04AD01	1 (0.7)
Mycophenolate	L04AA06	1 (0.7)
M=Musculo-skeletal system		18 (1.1)
Allopurinol	M04AA01	13 (8.8)
Colchicine	M04AC01	4 (2.7)
Alendronic acid	M05BA04	1 (0.7)
N=Nervous system		45 (2.7)
Tramadol+paracetamol	N02AJ13	6 (4.1)
Amitryptiline	N06AA09	6 (4.1)
Pregabalin	N02BF02	5 (3.4)
Paracetamol+codein	N02AJ06	5 (3.4)

Sodium valproate	N03AG01	4 (2.7)
Paracetamol	N02BE01	3 (2.0)
Citalopram	N06AB04	2 (1.4)
Lorazepam	N05BA06	2 (1.4)
Pramipexole	N04BC05	1 (0.7)
Zolpidem	N05BA06	1 (0.7)
Others	-	10 (6.8)
P=Antiparasitic products, insecticides and repellents		7 (0.4)
Hydroxychloroquine	P01BA02	3 (2.0)
Chloroquine	P01BA01	2 (1.4)
Primaquine	P01BA03	1 (0.7)
Quinine	P01BC01	1 (0.7)
R=Respiratory system		22 (1.3)
Cetirizine	R06AE07	6 (4.1)
Beclomethasone nasal spray	R01AD01	3 (2.0)
Salmeterol/fluticasone inhaler	R03AK06	3 (2.0)
Salbutamol	R03AC02	2 (1.4)
Tiotropium	R03BB04	1 (0.7)
Formoterol	R03AC13	1 (0.7)
Propranolol	R06AD02	1 (0.7)
Bromhixidine cough syrup	R05CB02	2 (1.4)
Flu & cold remedies combinations	R05X	1 (0.7)
Budesonide & Formoterol	R03AK07	1 (0.7)
Beclomethasone inhaler	R03BA01	1 (0.7)
S=Sensory organs		4 (0.2)
Brimonidine	S01EA05	1 (0.7)
Lubricating eye drops	S01XA	1 (0.7)
Dexamethasone eye drops	S01BA01	1 (0.7)
Oxymetazoline eye drop	S01GA04	1 (0.7)
V=Various		30 (1.8)
Calcium acetate	V03AE07	29 (20)
Polystyrene sulfonate	V03AE01	1 (0.7)

10.8. APPENDIX H: Most frequently prescribed drugs medication selection and renal drug dosage adjustment appropriateness

Medication name	N	Appropriate drug choice		Dosage adjustment required		Adjustment appropriateness	
		Yes	No	Yes	No	Yes	No
Alimentary tract and metabolism							
Alfacalcidol	122	122	0	0	122	N/A	N/A
Calcium gluconate	69	69	0	0	69	N/A	N/A
Omeprazole	27	27	0	0	27	N/A	N/A
Ergocalciferol	46	44	2	0	46	N/A	N/A
Calcium carbonate	23	23	0	0	23	N/A	N/A
Blood and blood forming organs							
Aspirin	42	42	0	0	42	N/A	N/A
Folic acid	31	31	0	31	0	26	5
Epoetin beta	132	132	0	0	132	N/A	N/A
Iron sucrose	118	118	0	0	118	N/A	N/A
Warfarin	31	26	5	31	0	26	5
Cardiovascular system							
Amlodipine	78	78	0	0	78	N/A	N/A
Carvedilol	90	90	0	0	90	N/A	N/A
Furosemide	117	117	0	0	117	N/A	N/A
Perindopril	57	57	0	57	0	2	55
Doxazosin	77	77	0	0	77	N/A	N/A
Dermatologicals							
Chlorhexidine in water	2	2	0	0	2	N/A	N/A
Fusidin ointment	1	1	0	0	1	N/A	N/A
Emulsifying ointment	1	1	0	0	1	N/A	N/A
Benzoyl peroxide gel	1	1	0	0	1	N/A	N/A
Genito urinary system and sex hormones							
Sildenafil	2	2	0	2	0	1	1
Sodium bicarbonate+sodium citrate+citric acid	4	4	0	0	4	N/A	N/A
Tamsulosin	1	1	0	0	1	N/A	N/A
Mirabegron	1	1	0	0	1	N/A	N/A
Solifenacin	1	1	0	1	0	0	1
Systemic hormonal preparations, excl. sex hormones and insulins							
Levothyroxine	4	4	0	0	4	N/A	N/A
Prednisolone	10	10	0	0	10	N/A	N/A
Calcitonin	7	5	2	0	7	N/A	N/A
Somatropin	1	1	0	0	1	N/A	N/A

Antiinfectives for systemic use							
Lopinavir/ritonavir	3	3	0	0	3	N/A	N/A
Meropenem	2	2	0	2	0	1	1
Atazanavir/ritonavir	4	4	0	0	4	N/A	N/A
Ciprofloxacin	2	2	0	2	0	1	1
Cloxacillin	1	1	0	1	0	0	1
Antineoplastic & immunomodulating							
Azathioprine	1	1	0	1	0	1	0
Cyclosporin	1	1	0	0	1	N/A	N/A
Mycophenolate	1	1	0	1	0	0	1
Musculo-skeletal system							
Alendronic acid	1	1	0	1	0	0	1
Allopurinol	13	13	0	13	0	12	1
Colchicine	4	4	0	4	0	1	3
Nervous system							
Pregabalin	5	5	0	5	0	4	1
Paracetamol+codein	4	4	0	0	4	N/A	N/A
Tramadol+paracetamol	7	6	1	6	1	6	0
Sodium valproate	4	4	0	0	4	N/A	N/A
Amitryptiline	4	2	2	0	4	N/A	N/A
Antiparasitic products, insecticides							
Hydroxychloroquine	3	3	0	2	1	2	0
Chloroquine	2	1	1	2	0	1	1
Primaquine	1	0	1	1	0	0	1
Quinine	1	0	1	1	0	1	0
Respiratory system							
Cetirizine	6	6	0	6	0	0	6
Flu & cold remedies combinations	2	2	0	0	2	N/A	N/A
Salbutamol	2	2	0	0	2	N/A	N/A
Beclomethasone nasal spray	3	3	0	0	3	N/A	N/A
Salmeterol/fluticasone inhaler	3	3	0	0	3	N/A	N/A
Sensory organs							
Brimonidine	1	1	0	0	1	N/A	N/A
Lubricating eye drops	1	1	0	0	1	N/A	N/A
Dexamethasone eye drops	1	1	0	0	1	N/A	N/A
Oxymetazoline eye drop	1	1	0	0	1	N/A	N/A
Various							
Calcium acetate	29	29	0	0	29	N/A	N/A
Polystyrene sulfonate	1	0	1	0	1	N/A	N/A

10.9. APPENDIX I: Most frequently inappropriately selected and dosage adjusted drugs in ESRD patients undergoing haemodialysis

Medication name	N	Appropriate medication choice ?		Dosage adjustment required?	Dosage adjustment appropriate?	
		No	Reason/Comments	Yes	No	Type of dosage adjustment error / comment
Alimentary tract and metabolism						
Alfacalcidol	122	0	N/A	0	N/A	N/A
Calcium gluconate	69	0	N/A	0	N/A	N/A
Omeprazole	27	0	N/A	0	N/A	N/A
Ergocalciferol	46	2	Ergocalciferol was inappropriate because the hyperphosphatemia and hypercalcaemia were not corrected first	0	N/A	N/A
Calcium carbonate	23	0	N/A	0	N/A	N/A
Blood and blood forming organs						
Aspirin	42	0	N/A	0	N/A	N/A
Folic acid	31	0	N/A	31	5	Over-dosage in all 5 cases
Epoetin beta	132	0	N/A	0	N/A	N/A
Iron sucrose	118	0	N/A	0	N/A	N/A
Warfarin	31	5	For 5 of the 31 patients that were prescribed	31	5	For 5 of the 31 patients that

			warfarin, their INR had not been checked for several months and they remined on the same dose			were prescribed warfarin, their INR had not been checked for a number of months and they remined on the same dose
Cardiovascular system						
Amlodipine	78	0	N/A	0	N/A	N/A
Carvedilol	90	0	N/A	0	N/A	N/A
Furosemide	117	0	N/A	0	N/A	N/A
Perindopril	57	0	N/A	57	55	Over-dosage in all patients
Doxazosin	77	0	N/A	0	N/A	N/A
Dermatologicals						
Chlorhexidine in water	2	0	N/A	0	N/A	N/A
Fusidin ointment	1	0	N/A	0	N/A	N/A
Emulsifying ointment	1	0	N/A	0	N/A	N/A
Benzoyl peroxide gel	1	0	N/A	0	N/A	N/A
Genito urinary system and sex hormones						
Sildenafil	2	0	N/A	2	1	Under-dosage
Sodium bicarbonate+sodium citrate+citric acid	4	0	N/A	0	N/A	N/A
Tamsulosin	1	0	N/A	0	N/A	N/A
Mirabegron	1	0	N/A	0	N/A	N/A
Solifenacin	1	0	N/A	1	1	Over-dosage

Systemic hormonal preparations, excl. sex hormones and insulins						
Levothyroxine	4	0	N/A	0	N/A	N/A
Prednisolone	10	0	N/A	0	N/A	N/A
Calcitonin	7	2	Drug without indication	0	N/A	N/A
Somatropin	1	0	N/A	0	N/A	N/A
Antiinfectives for systemic use						
Lopinavir/ritonavir	3	0	N/A	0	N/A	N/A
Meropenem	2	0	N/A	2	1	Over-dosage
Atazanavir/ritonavir	4	0	N/A	0	N/A	N/A
Ciprofloxacin	2	0	N/A	2	1	Over-dosage
Cloxacillin	1	0	N/A	1	1	Over-dosage
Antineoplastic & immunomodulating						
Azathioprine	1	0	N/A	1	0	N/A
Cyclosporin	1	0	N/A	0	N/A	N/A
Mycophenolate	1	0	N/A	1	1	Over-dosage
Musculo-skeletal system						
Alendronic acid	1	0	N/A	1	1	Under-dosage
Allopurinol	13	0	N/A	13	1	Over-dosage
Colchicine	4	0	N/A	4	3	Under-dosage in all 3 cases
Nervous system						
Pregabalin	5	0	N/A	5	1	Under-dosage
Paracetamol+codein	4	0	N/A	0	N/A	N/A
Tramadol+paracetamol	7	1	Drug without indication	6	0	N/A
Sodium valproate	4	0	N/A	0	N/A	N/A
Amitryptiline	4	2	Both cases were recent depression diagnosis-	0	N/A	N/A

			selective serotonin reuptake inhibitors would have been a preferred choice			
Antiparasitic products, insecticides						
Hydroxychloroquine	3	0	N/A	2	0	N/A
Chloroquine	2	1	Drug without indication-It was prescribed for malaria prophylaxis a couple of months earlier due to recorded plans to travel and it was continued for longer than needed	2	1	Over-dosage
Primaquine	1	1	Drug without indication- patient was receiving it after travel history, it was prescribed for more than 14 days	1	1	Duration too long -patient was receiving it after travel history, it was prescribed for more than 14 days
Quinine	1	1	Unnecessary drug therapy-Patient had not complained about dialysis associated leg cramps in a long time	1	0	N/A
Respiratory system						
Cetirizine	6	0	N/A	6	6	Over-dosage in all 6 patients

Flu & cold remedies combinations	2	0	N/A	0	N/A	
Salbutamol	2	0	N/A	0	N/A	
Beclomethasone nasal spray	3	0	N/A	0	N/A	
Salmeterol/fluticasone inhaler	3	0	N/A	0	N/A	N/A
Sensory organs						
Brimonidine	1	0	N/A	0	N/A	N/A
Lubricating eye drops	1	0	N/A	0	N/A	N/A
Dexamethasone eye drops	1	0	N/A	0	N/A	N/A
Oxymetazoline eye drop	1	0	N/A	0	N/A	N/A
Various						
Calcium acetate	29	0	N/A	0	N/A	N/A
Polystyrene sulfonate	1	1	Unnecessary drug therapy-Patient had sustained normal potassium levels.	0	N/A	N/A