DRUG THERAPY PROBLEMS AND QUALITY OF LIFE IN PATIENTS WITH CHRONIC KIDNEY DISEASE

MANSOUR ADAM MAHMOUD

UNIVERSITI SAINS MALAYSIA

2008

DRUG THERAPY PROBLEMS AND QUALITY OF LIFE IN PATIENTS WITH CHRONIC KIDNEY DISEASE

By

MANSOUR ADAM MAHMOUD

Thesis submitted in fulfillment of the requirements for the degree of Master of Science

June 2008

Dedication

This work is dedicated to the people in my life that I appreciate and love more than words can say:
My mother, Fatima Idris, my father Engineer Adam Mahmoud, my brothers and sisters for their unconditional love, sacrifices, encouragements, supports and "patience".

Acknowledgments

First of all my many deepest gratitude to the Almighty Allah for His great help, blessing and spiritual guidance for making this piece of work successful.

I owe an extreme gratitude to my main supervisors Professor. Yahaya Hassan and my co-supervisor Assoc.Prof. Dr. Noorizan Abd Aziz for their invaluable encouragement and parently care and support. The clinical foundation of this work is extremely enhanced by their supervision.

I shall never, ever forget to send my warmest love and regards to my mother. She has taught me that endurance is long-suffering; however it is indeed worthwhile. Mother I would say that, at this juncture of my new life, I fully understand the value of your patience during those eight years when my father was studying abroad and away from you and me.

I would like to extend all the respect, pride and extreme appreciation to my father Engineer Adam Mahmoud. The man who has been teaching me since I was a child that, proper education is the best way to be a salutary person to the society, and success is never an easy thing. Father, you were my precious model and you will forever be.

Special thanks and gratitude goes to my field supervisor, Dr Rozina Ghazali, Consultant Nephrologist of Penang General Hospital. I would also like to thank Dr Punita, Head of the Department of Clinical Research in Penang General Hospital who provided me with the acceptance to conduct my research in the respective hospital. I am greatly indebted to the physicians and nurses in the medical ward of Penang General Hospital, especially those in C-7 (Nephrology ward).

I owe a very deep appreciation to Puan Zalila Ali, lecturer in the School of Mathematics of USM, for her continuous and valuable guidance regarding the statistical analysis.

I would never forget the kindness and friendship of the ESRD patients in C-7 (Nephrology ward). I am grateful to Mr. Ruzli, an ESRD patient with several comorbidities who is undergoing haemodialysis and yet the smile never leaves his face. He taught me that, life is beautiful and we have to enjoy it as long as we can breathe.

A special thank you is due to brother Ahmed Awaisu and brother Ahmed Ibrahim, PhD candidates of Clinical Pharmacy at the School of Pharmaceutical Science of USM, for their encouragement, guidance, support and generosity in suggesting some helpful ideas for my thesis. Last, but never the least I am grateful to all my friends, for their social and moral support. They make me feel that, there is always another home away from the origin.

"May Allah bless you"

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

DTP	Drug Therapy Problem
QoL	Quality of Life
ESRD	End Stage Renal Disease
CKD	Chronic Kidney Disease
USRDS	United States Renal Data System
ACCP	American College of Clinical Pharmacy
DI	Drug Interaction
ADR	Adverse Drug Reaction
ICU	Intensive Care Unit
PGH	Penang General Hospital
RM	Ringgit Malaysia
USD	United States Dollar
USA	United States of America
HD	Haemodialysis
DM	Diabetes Mellitus
IWD	Indication Without Drug
ASA	Acetylsalicylic Acid
ACEI	Angiotensin Converting Enzyme Inhibitor
MI	Myocardial Infraction
CHD	Chronic Heart Disease
DWI	Drug Without Indication
IDS	Improper Drug Selection
UD	Under Dose
OD	Over Dose
EPO	Erythropoietin
Cl_{Cr}	Creatinine Clearance
NSAID	Non-steroidal anti-inflammatory drug
NKF-K/DOQI	National Kidney Foundation-Kidney Disease Outcome Quality Initiative
GFR	Glomerular Filtration Rate
MDRD	Modification of Diet in Renal Disease
SCr	Serum Creatinine
BUN	Blood Urea Nitrogen
RBC	Red Blood Cell
CVD	Cerebrovascular Disease
WHO	World Health Organization
BP	Blood Pressure
NHANES III	Third National Health and Nutrition Examination Survey
CAPD	Continuous Ambulatory Peritoneal Dialysis
CCB	Calcium Channel Blocker
ARB	Angiotensin-Receptor Blocker
RAAS	Renin-Angiotensin Aldosterone System

LDL	Low-Density Lipoprotein
TG	Triglycerides
HDL	High-Density Lipoprotein
HbA1c	Glycosylated haemoglobin
TAST	Transferring Saturation
IV	Intravenous
SC	Subcutaneous
PTH	Parathyroid Hormone
HRQoL	Health Related Quality Of Life
SF-36	36-Item Short Form Health Survey
NHP	Nottingham Health Profile
SIP	Sickness Impact Profile
HUI	Health Utilities Index
AQoLQ	Asthma Quality of Life Questionnaire
KDQoL	Kidney Disease Quality of Life
DQoL	Diabetes Quality of Life
MOS-HIV	Medial Outcomes Study Human Immunodeficiency Virus Survey
PF	Physical Functioning
REP	Role Physical
GH	General Health
TV	Vitality/Energy
SF	Social Functioning
REE	Role Emotional
MH	Mental Health
CRC	Clinical Research Centre
IQoLA	International Quality Of Life Assessment
IEC	Independent Ethics Committee
SPSS	Statistical Package for Social Sciences
PD	peritoneal dialysis
GIT	Gastrointestinal disease
PVD	Peripheral Vascular Disease
COPD	Chronic Obstructive Pulmonary Disease
DJD	Degenerative Joint Disease
LVH	Left Ventricular Hypertrophy

LIST OF PUBLICATIONS AND SEMINARS

MASALAH-MASALAH TERAPI DRUG DAN KUALITI KEHIDUPAN BAGI PESAKIT DALAM YANG MENGHIDAP PENYAKIT GINJAL KRONIK

ABSTRAK

Masalah-masalah terapi drug (DTP) merupakan suatu cabaran penting kepada pengamal penjagaan kesihatan, ianya juga mempengaruhi morbiditi, mortaliti dan kualiti kehidupan pesakit (QoL). Pesakit ginjal kronik (CKD) menerima pelbagai agen farmakoterapi yang menyebabkan mereka berisiko tinggi untuk mendapat DTP. Sehingga kini tidak terdapat kajian mengenai DTP dikalangan pesakit dalam CKD di Malaysia. Maka kajian ini bertujuan untuk menilai DTP dan kualiti kehidupan dengan menggunakan borang kaji selidik SF-36 pada pesakit CKD. Satu kajian pemerhatian prospektif telah dijalankan ke atas 308 pesakit CKD, berumur 18 tahun dan ke atas yang dimasukkan ke wad perubatan Hospital Pulau Pinang . Daripada bilangan ini,154 pesakit telah didiagnosis mengalami penyakit ginjal tahap penghujung (ESRD) (kumpulan ESRD) dan 154 lagi pesakit telah di diagnosis mengalami CKD tahap satu ke tahap empat (kumpulan bukan –ESRD). Daripada 154 pesakit ESRD yang disusuli, empat orang telah keluar dari hospital atas kehendak sendiri dan tiga pesakit telah meninggal dunia di wad perubatan. Manakala 154 pesakit bukan- ESRD pula, dua pesakit telah keluar wad tanpa pengetahuan manakala tiga lagi didiscas keluar wad atas kehendak sendiri. Maka data yang lengkap hanya didapati untuk 147 pesakit ESRD dan 149 pesakit bukan-ESRD. DTP telah dikenalpasti melalui penilaian carta pengubatan pesakit dan temubual pesakit. DTP telah dibahagikan kepada lapan kategori: Indikasi tanpa drug (IWD), drug tanpa indikasi (DWI), pemilihan drug yang tidak sesuai (IDS), pengubahsuaian dos yang tidak sesuai, tindakbalas mudarat drug (ADR), interaksi drug (DI), ketidaksesuaian pemantauan makmal dan pesakit yang tidak patuh. Manakala QoL pesakit telah dinilai dengan menjawab sendiri soalselidik tervalidasi SF-36. SPSS versi 12 telah di gunakan untuk analisis data. Ujian “Chi-square”, ujian tepat “Fisher’s”, hubungan angkatap dan analisis regresi lelurus telah di gunakan apabila sesuai dan nilai $P < 0.05$ dianggap sebagai signifikan statistik. Purata umur pesakit ESRD ialah 53±15.3 tahun dan 48.9±17.9 tahun untuk pesakit bukan-

ESRD. Pesakit ESRD mengalami lebih DTP berbanding pesakit bukan-ESRD (P<0.001). DTP yang sering terjadi dikalangan pesakit ESRD adalah IWD (20.9%), IDS (20.7%) dan DI (19.4%) sementara dikalangan pesakit bukan-ESRD pula adalah IWD (20.3%), DI (19.0%) dan IDS (18.0%). Peningkatan umur, jantina perempuan, tempoh hospitalisasi yang panjang dan tempoh CKD telah didapati ada hubungkait dengan peningkatan DTP. Selanjutanya, hipertensi, penyakit jantung koronari (CHD), peningkatan bilangan drug, drug antihipertensif dan drug anemia juga mempunyai hubungkait dengan peningkatan DTP. Penilaian kualiti kehidupan telah menunjukkan pesakit ESRD mempunyai QoL rendah yang signifikan secara statistik berbanding bukan ESRD (P<0.001). Manakala, faktor-faktor seperti peningkatan umur, bangsa India atau bangsa lain, bilangan komorbiditi yang tinggi, klearans kreatinin yang rendah, ADRs, drug-drug anti-infektif, dialisis dan tempoh CKD telah didapati menpunyai hubungkait dengan penurunan QoL (P<0.05).

DRUG THERAPY PROBLEMS AND QUALITY OF LIFE IN PATIENTS WITH CHRONIC KIDNEY DISEASE

ABSTRACT

Drug therapy problems (DTP) are a significant challenge to health care providers that are associated with morbidity, mortality and patient's quality of life (QoL). Patients with chronic kidney disease (CKD) receive a wide range of pharmacotherapeutic agents and are therefore at higher risk to experience DTP. To date, DTP in hospitalized CKD patients have not been investigated in Malaysia. Thus, this study was aimed to assess DTP and to evaluate QoL using SF-36 instrument in CKD patients. A prospective observational study was conducted among 308 patients with CKD who were aged 18 years or older and admitted to the general medical ward of Penang General Hospital (PGH). Of this, 154 patients had confirmed diagnosis of end stage renal disease (ESRD) (ESRD group) and 154 patients had the diagnosis of stage one to stage four of CKD (non-ESRD group). Out of the 154 ESRD patients initially followed in the study, four patients took discharge at their own risk and three patients died in the medical ward during the follow-up. On the other hand, of the 154 non-ESRD patients, two patients absconded from the medical ward and three patients took discharge at self risk. Hence, data with complete information were available for 147 ESRD patients and 149 non-ESRD patients. DTP were identified through review of patients' medical charts and patients interviews. DTP were categorized into eight: indication without drug (IWD), drug without indication (DWI), improper drug selection (IDS), inappropriate dosage adjustment, adverse drug reactions (ADR), drug interactions (DI), inappropriate laboratory monitoring and patient's non-adherence. While, patients' QoL was assessed using a validated and self

administered SF-36 QoL questionnaire. Statistical Package for Social Science (SPSS) version 12 was used for data analysis. Chi-square test, Fisher's exact test, correlation coefficient and linear regression analysis were used wherever appropriate and *P*-value <0.05 was considered as statistically significant. The mean age of patients was 53 ± 15.3 years and 48.9 ± 17.9 years for the ESRD and the non-ESRD groups, respectively. ESRD patients had more DTP than non-ESRD patients (*P*<0.001). The most common DTP among the ESRD patients were: IWD (20.9%), IDS (20.7%) and DI (19.4%) whereas, among the non-ESRD group, the most common DTP were: IWD (20.3%), DI (19.0%), and IDS (18.0%). Increased age, female gender, duration of hospitalization and duration of CKD were found to be significantly associated with the number of DTP. In addition, hypertension, coronary heart disease (CHD), number of drugs, antihypertensive drugs and anaemia drugs were also found to be associated with number of DTP. QoL evaluation revealed that ESRD patients had significantly lower QoL than their non-ESRD counterparts (*P*<0.001). Factors such as increased age, Indian or other race, number of comorbidities, creatinine clearance, ADRs, anti-infective drugs, dialysis, duration of CKD were found to be associated with a lower QoL (*P*<0.05).

CHAPTER ONE

INTRODUCTION

1.1 Background

The intention of prescribing drugs to patients is treatment, prophylaxis or diagnosis of medical conditions; however, these drugs may have negative effects on patients if not used appropriately. Pharmacists can play an important role in identifying drug therapy problems (DTPs), resolving actual DTPs and preventing potential DTPs through careful pharmaceutical practices.

A DTP is defined as an undesirable event or risk experienced by a patient, which involves or is suspected to involve drug therapy (Strand *et al*., 1990). The occurrence of a DTP could prevent or delay patients from achieving desired therapeutic goals. An actual DTP is an event that has already occurred in a patient, whereas a potential DTP is an event that is likely to develop if pharmacists do not make any appropriate interventions (Rovert *et al.*, 2004). DTPs are significant challenge to health care providers and may affect morbidity, mortality and a patient's quality of life (QoL). Several studies have shown that patients with end stage renal disease (ESRD) are among those at high risk for DTPs (Grabe *et al*., 1997; Manley *et al.,* 2003b; Grabe *et al.*, 1997).

As of 2005, the prevalence rate of ESRD in Malaysia was estimated to be 100 per million populations (USRDS, 2005c). The increasing number of ESRD patients in Malaysia certainly raises the risk of DTPs in these patients. Therefore, identifying and

resolving DTPs and improving the QoL of ESRD patients should be of the utmost importance to health care providers.

1.2 Literature Review

A literature review was performed to evaluate clinical pharmacy, pharmaceutical care, DTP, chronic kidney disease (CKD) and co-morbidities associated with ESRD.

1.2.1 Clinical Pharmacy

Clinical pharmacy practices include all services typically provided by pharmacists practicing in hospitals, community pharmacies, nursing homes, home-based care services and clinics. The American College of Clinical Pharmacy (ACCP) has defined clinical pharmacy as a health science specialty where the pharmacist applies the scientific principles of pharmacology, toxicology, pharmacokinetics and therapeutics to the care of patients (Cipolle *et al*., 1998). In Europe, the European Society of Clinical Pharmacy has defined clinical pharmacy as "a health specialty, which describes the activities and services of the clinical pharmacist to develop and promote the rational and appropriate use of medicinal products and devices" (The European Society of Clinical Pharmacy, 2007).

Clinical pharmacy focuses on population needs with regard to medication administration, use and effects on the patient (The European Society of Clinical Pharmacy, 2007). In order for clinical pharmacists to make interventions, they must have a strong clinical background and evaluative tools to correctly judge the evidence available for various treatments (Manuel *et al*., 2007). Thus, they must have a strong

understanding of disease characteristics and their progression, in addition to the characteristics of various medications and their mechanisms of action, their formulations and the ways in which they interact with the human body. Furthermore, clinical pharmacists need to be able to evaluate the real value of a drug and analyse randomized controlled trials and epidemiological studies.

1.2.1(a) The Role of a Clinical Pharmacist

The role of a clinical pharmacist is to maximise the clinical effects of medicines by ensuring the selection of the most effective drugs for each patient, minimising adverse drug events by monitoring the drug therapy course of the patient and improving the patient's adherence with the drugs (The European Society of Clinical Pharmacy, 2007). Clinical pharmacists also contribute to minimising the costs of drug therapy and health care by providing cost effective alternatives (Cipolle *et al*., 1998).

Clinical pharmacists ensure the correct use of drugs at three levels: 1) before the drug is prescribed, 2) during the time of drug prescription, and 3) after the drug is prescribed (Scroccaro *et al*., 2000). The role of the clinical pharmacist prior to the prescription of a drug can be explained in the context of conducting clinical trials and providing drug information. During the prescription stage, the clinical pharmacist detects and prevents drug interactions (DI), adverse drug reactions (ADR) and medication errors. The clinical pharmacist also pays special attention to the dosage of drugs that require serum drug concentration monitoring. After the drug is prescribed, the clinical pharmacist must communicate with the patient. By conducting patient counselling, the clinical pharmacist can improve a patient's adherence with the drugs, monitor treatment response and improve the patient's awareness of their drugs. The

clinical pharmacist also conducts outcomes research to evaluate the effectiveness of alternative drug therapy (Scroccaro *et al*., 2000).

1.2.1(b) The Impact of Clinical Pharmacy Services

The intervention of clinical pharmacists for a period of one month in an intensive care unit (ICU) at Penang General Hospital (PGH) in Malaysia resulted in a total net cost savings of Ringgit Malaysia (RM) 15253.34 (United States Dollars (USD) $4,014); hence, clinical pharmacy services were suggested as a routine practice in the hospital (Zaidi *et al*., 2003). In a review of randomised controlled studies assessing DTP and health outcomes in the elderly, clinical pharmacy services also proved to be beneficial in reducing the occurrence of DTPs (Hanlon *et al*., 2004). Chisholm (2001) and colleagues reported that renal transplant patients who received clinical pharmacy services had a significantly higher adherence rate ($P<0.001$), longer duration of adherence ($P<0.05$) and greater achievement of target serum concentration of immunosuppressive drugs (cyclosporine and Tacrolimus) ($P<0.05$) compared to those who did not receive any clinical pharmacy services.

1.2.2 Pharmaceutical Care Practice

Pharmacists with their pharmaceutical knowledge and skills are in the best position to work together with physicians and other health care providers to manage patient drug therapy and improve QoL. A concept of pharmaceutical care based on this idea was first formulated in the United States of America (USA).

Hepler and Strand (1990) defined pharmaceutical care as the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve

the patient's QoL. Pharmaceutical care can also be defined as a practice in which the pharmacist takes responsibility for a patient's drug-related needs and is held accountable for this commitment (Strand, 1997).

The four dimensions of the philosophy of pharmaceutical care in practice are social needs, a patient-centred approach to meet these needs, the development of caring through a therapeutic relationship and a description of the practitioner's specific responsibilities (Cipolle *et al*., 1998). Practitioners of pharmaceutical care can meet social needs by minimising drug-related morbidity and mortality. In order for the practitioner to meet these social needs, he or she must take a patient-centred approach. By using a patient-centred approach, then, the practitioner becomes responsible for the patient's drug-related needs such as patient concerns, expectations and understanding of illness.

Caring through a therapeutic relationship is collaboration between the patient and the pharmaceutical care practitioner in order to meet the patient's health-related needs. The practitioner in his role agrees to assess the patient's needs and follow the patient's care to ensure that effective interventions are being made. On the other hand the patient agrees to provide accurate and complete information to the practitioner so that the practitioner can make knowledgeable decisions.

The specific responsibilities of a pharmaceutical care practitioner include ensuring that the most effective and safest drugs are prescribed to patients and that a patient's drug therapies are convenient enough to be followed as indicated. It is the pharmacist's responsibility to ensure that the patient is able to adhere to medication

instructions in order to produce positive outcomes. In addition, the pharmacist is responsible for identifying, resolving and preventing DTPs.

1.2.2(a) The Impact of Pharmaceutical Care

The goal of instituting pharmaceutical care services is to reduce increasing levels of drug related morbidity and mortality associated with drug use and to prevent the high financial cost of adverse drug events (Cipolle *et al*., 1998)**.** It has been reported that pharmaceutical care in ambulatory haemodialysis (HD) units has improved medication adherence, provided drug information, raised awareness of inappropriate medication and improved biochemical and therapeutic responses to medications (Manley *et al*., 2003a; Grabe *et al*., 1997). In addition, pharmaceutical care services have also proven to be successful in effectively managing diseases such as hypertension and diabetes mellitus (DM), while improving QoL for patients (De Souza *et al*., 2007; Jaber *et al*., 1996).

1.2.2(b) Drug-Related Morbidity and Mortality

Drug-related morbidity is a failure of a drug therapy to produce the intended therapeutic outcomes, either due to treatment failure or the development of new medical indications (Hepler and Strand, 1990). It has been reported that adverse drug events are the main cause of death as well as hospital admission in ambulatory patients. The total cost of drug related morbidity and mortality in the ambulatory setting in the USA in 2000 was estimated to be USD $177 billion, which was more than double the cost estimated in 1995 (USD $76 billion) (Ernst and Grizzle, 2001). Still, other investigators have reported that 27.6% of adverse drug events are preventable (Gurwitz *et al*., 2003).

1.2.2(c) Identification of DTP

Identifying DTPs is one of the objectives of the pharmaceutical care process. Clinical pharmacists can play an important role in identifying and resolving DTPs through cooperation with patients and other health care providers (Grabe *et al*., 1997). Potential and actual DTPs can be identified thorough medication profile reviews, and these problems can be prevented by monitoring therapeutic plans (Britton and Lurvey, 1991). A number of actual DTPs can be resolved with patient counselling and recommendations to prescribers.

1.2.3 Categories of DTPs

Cipolle *et al*. (1998) broadly categorized DTPs into eight groups. These investigators ensured that all DTPs occurring in clinical practice would fall into these eight categories. Each pharmacist must be familiar with these categories and their causes in order to provide the best pharmaceutical care possible for the patient. The categories of DTPs are as follows.

1.2.3(a) Indication without Drug (IWD)

An indication without drug (IWD) occurs when there is a need to treat a previously untreated indication, to add synergistic or potentiating drug therapy or to deliver prophylactic or preventive drug therapy. For example, if a patient is being appropriately treated for peripheral vascular disease but does not receive treatment for developing anaemia, the primary condition is being treated but no drug therapy is being given to treat the new illness (Strand *et al*., 1990). Another example of IWD is using a single drug therapy instead of an appropriate combination of drugs to treat a medical condition (Cipolle *et al*., 1998).

In a prospective study conducted by Manley *et al*. (2003b), IWD was the second most common DTP among HD patients with DM, accounting for 17.5% of all DTPs identified during the study. In this study, the causes of IWD were patients with high cardiovascular risk who had no acetylsalicylic acid (ASA) prescription, patients with chronic heart failure who had no angiotensin converting enzyme (ACE) inhibitor prescription and post myocardial infraction (MI) or stroke patients who had no ASA therapy. It was also reported that more than half of DTPs identified in ESRD patients at the time of hospital admission were due to an IWD (Ong *et al*., 2006). The report revealed that most of the symptoms were not treated due to a lack of communication between patients and healthcare providers.

Several studies have reported that the need for additional drug therapy is one of the most common DTPs in patients admitted to internal medicine wards (Blix *et al*., 2006; Blix *et al*., 2004; Viktil *et al*., 2004). In addition, a report from a sample of elderly patients who received pharmaceutical care for one year at the University of Minnesota revealed that IWD was the most common DTP identified, accounting for 32% of all DTPs (Rao *et al*., 2007). Hypertension, DM, arthritis, chronic heart disease (CHD) and osteoporosis were the most common medical conditions requiring additional drug therapy.

1.2.3(b) Drug without Indication (DWI)

A drug without indication (DWI) occurs when a patient takes an unnecessary drug therapy for which the clinical indication is not present at that time (Cipolle *et al*., 1998). There are several causes for DWI. First, the medical condition could be more appropriately treated with non-drug therapy such as diet, exercise or surgery. Second,

the patient might be on a drug therapy to treat an avoidable ADR of another drug. Third, narcotics abuse, tobacco and alcohol consumption might all be causing the problem. Finally, multiple drug therapies might be used to treat a condition that requires only a single drug therapy. For example, some patients receive more than one laxative for the treatment of constipation; some patients receive more than one anti-diarrhoeal for the treatment of diarrhoea; and some patients receive more than one analgesic for pain treatment.

DWIs were reported to be a major DTP among HD patients, accounting for 29.8% of all DTPs (Manley et *al*., 2003b). In addition, a prospective study conducted to compare DTPs in patients admitted to cardiology, geriatric, respiratory and rheumatology departments found that DWI was more common in geriatric patients compared to the other three groups ($P<0.01$) (Viktil *et al*., 2004). In a study conducted in the ICU of PGH, Malaysia, unnecessary drug therapy was the most common DTP identified, and among these DWIs, 39% were accepted by the physicians (Zaidi *et al*., 2003).

1.2.3(c) Improper Drug Selection (IDS)

An IDS is a situation in which the patient has been prescribed the wrong drug. Examples of this type of DTP include the following (Strand *et al*., 1990 and Cipolle *et al*., 1998).

i. The drug therapy used to treat the patient's medical condition is ineffective.
ii. A much more effective drug exists but was not prescribed to the patient.
iii. A contraindicated or an allergic drug was prescribed to the patient.

iv. The patient received combination drug therapy instead of an equally effective single drug therapy.
v. The patient received an expensive drug instead of a cheaper and equally effective drug.

Kaplan *et al*. (1994b) reported that 40% of HD patients had potentially suboptimal or ineffective drug therapy and needed an alternative drug selection. Soendergaard *et al*. (2006) reported that 18.4% of DTPs in general practice were due to inappropriate selection of drugs. It has also been reported that IDS is very common (36.8%) in type 2 DM patients (e.g. prescribing insulin instead of oral anti-diabetic agents and contraindications due to prescribing metformin for patients over the age of 70 years) (Haugbølle *et al* 2006).

1.2.3(d) Inappropriate Dosage Adjustments

Inappropriate dosage adjustment can be classified into two sub-categories under dose (UD) and over dose (OD).

i. Under Dose (UD)

It is often challenging for health care providers to ensure appropriate medication dosing for patients who are on dialysis due to the potential increase in co-morbidities over time and changing laboratory parameters, pharmacokinetic and pharmacodynamic parameters and dialysis treatments. Careful and continual monitoring of patient progress in addition to drug dosage adjustments by a clinical pharmacist that take into account all appropriate drug, disease, and patient specific information may decrease the number of dosing problems in ESRD patients (Pillans *et al*., 2003). In addition,

parameters such as age and body weight can often be useful to assist in determining the optimal drug dose for a patient (Cipolle *et al*., 1998).

The causes of UD are inappropriate dosing frequency, short duration of therapy, inappropriate drug storage (e.g., storing drugs in an excessively hot or humid place, leading to degradation of the dosage form and sub-therapeutic dosing), inappropriate drug administration and DI (Rover *et al*., 2004).

An example of UD in dialysis patients is decreased erythropoietin (EPO) dosing with regard to recent haemoglobin values (John and Marc, 2004). Other reasons such as dosage calculation errors and incorrect conversion of different formulations of drug therapy could also lead to suboptimal treatment (Cipolle *et al*., 1998).

Ong *et al*. (2006) reported that drug UD was the second most common DTP in ESRD patients (13.6%) that took place at the time of hospital admission. The investigators reported that more than half of drug UD problems were due to inadequate communication between patients and healthcare providers regarding the medication. Manley *et al*. (2003a) reported that contradictions between information provided by HD patients during a drug interview and information from electronic medical records were found to be predominantly associated with dosing errors (34.5%). Half of these dosing errors resulted in drug UD. It has also been reported that drug UD is one of the most common DTPs in elderly patients (Rao *et al*., 2007).

- **Over Dose (OD)**

As stated by Cipolle *et al*. (1998), when a patient receives a dose of an agent that is too high and experiences a dose-dependent or concentration-dependent toxic effect, he or she is experiencing a DTP. In patients with decreased renal function, the ability of the kidney to eliminate drugs and their metabolites is decreased, which in turn leads to the accumulation of drugs and toxic products in the kidney. For instance, if the dose of procainamide is not adjusted for patients with compromised renal function, N-acetylprocainamide can accumulate in the kidney (Cipolle et al., 1998).

Pillans *et al*. (2003) reported that the doses of 44.8% of drugs with a narrow therapeutic index were inappropriately high in patients with creatinine clearance (Cl_{Cr}) ≤ 40 ml/min at the time of hospital admission. Drug OD in ESRD patients could also result from contradictions between information provided by patients and information obtained from electronic medical records (Ong *et al*., 2006).

1.2.3(e) Adverse Drug Reactions (ADRs)

As stated by Cipolle *et al*. (1998), "ADRs can be defined as undesirable negative effects caused by the medication that were not predictable based on its dosage concentration or pharmacological action." According to the WHO, ADR is described as "A response to a drug which is noxious and unintended, and which occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function" (WHO, 1972). A patient may experience an ADR due to the administration of an unsafe drug, an allergic reaction, incorrect drug administration, DI, rapid dosage increment or decrement or undesirable effects of the

drug that could not be predicted. For example, bleeding due to a higher dose of anticoagulant drugs such as warfarin or heparin is an ADR (Lacy *et al*., 2004-2005).

A prospective study conducted to compare the incidence of hospital admissions due to ADRs in the general medical ward of two hospitals revealed that 4.1% out of 2,499 medical admissions and 5.7% out of 2,933 medical admissions were due to ADRs (Levy *et al*., 2004). In addition, Suh *et al*. (2000) reported that both length and cost of hospital stay were significantly higher ($P<0.01$) for patients who experienced ADRs than for those who did not.

Manley *et al* (2003c) reported that ADRs were the second most common DTP identified in HD patients. ADRs are also very common in elderly patients (Hajjar *et al*., 2003; Williamson and Chopin 1980). Patients who are on polypharmacy, those with multiple chronic medical conditions, those with a history of ADRs and those with dementia are at a greater risk for ADRs (Hajjar *et al*., 2003). Furthermore, non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics and antihypertensive agents were among drugs commonly associated with ADRs, accounting for 26.5%, 23.6%, and 17.7% of hospital admission cases, respectively (Capuano *et al*., 2004).

1.2.3 (f) Drug Interactions (DIs)

DIs result from a drug-drug, drug-food and drug-laboratory interactions (Cipolle *et al*., 1998). They can occur in patients receiving drugs from different pharmacological classes as well as within the same pharmacological class. Calculates can displace first generation hypoglycaemic agents from protein binding sites and may potentate hypoglycaemia in DM patients.

A DI between calcium salts and iron products is one of the most common seen in ESRD patients (Grabe *et al.,* 1997). Milk can inhibit the absorption of oral iron preparations (Lacy et al., 2004-2005). Drugs such as ascorbic acids, beta-lactam antibiotics (e.g., cephalosporins and penicillins), levodopa and salicylates have all been well-documented to interfere with urine glucose testing (Rotbblatt and Koda-Kimble, 1987).

Grabe *et al*. (1997) reported that DIs were common (27.5%) in outpatient HD patients. Another study performed to compare the frequency of DTPs among patients admitted to cardiology, geriatrics, respiratory and rheumatology wards revealed that DI was most common (12.2%) in patients admitted to the cardiology ward compared to the other three wards (Viktil *et al*., 2004).

1.2.3(g) Inappropriate Laboratory Monitoring

Laboratory tests should be used to monitor a patient's drug therapy and ensure that co-morbid conditions are adequately identified and treated (Manley *et al*., 2003b). If the laboratory monitoring needs of a patient's therapy are not being considered, then the patient might be experiencing a DTP.

Examples of inappropriate laboratory monitoring are seen in patients with high cardiovascular risk without monitoring of their fasting lipid profile, blood pressure (BP) or blood sugar. Other examples of inappropriate laboratory monitoring include patients who have been prescribed long-term aluminium-binding drugs without measuring aluminium levels (normal serum aluminium concentration = 1-30 ng/ml)

and patients who have been prescribed amiodarone therapy or have a history of thyroid disease without getting a thyroxine level monitoring (Manley *et al*., 2003b).

Inappropriate laboratory monitoring is very common among ambulatory HD patients (Manley *et al*., 2005; Manley *et al*., 2003b). The need for laboratory tests was found to be one of the most frequent DTPs in inpatients and was also found to be associated with a number of clinical and pharmacological risk factors ($P<0.01$) such as reduced renal function ($Cl_{Cr} \leq 50$ ml/minute), reduced liver function and increased number of drugs (≥ 5 drugs on admission) (Blix *et al*., 2004). In addition, patients admitted to the cardiology department were reported to be more likely to experience inappropriate laboratory monitoring (25.2%) compared to patients admitted to geriatric, respiratory and rheumatology departments (Viktil *et al*., 2004).

1.2.3(h) Patient Non-adherence

The term "adherence" is preferred over "compliance" in medical practice (Tilson, 2004). Compliance suggests that the patient acquiesce or obey the physician's instructions, while adherence defines the patient as an intelligent and independent people who is able to make medical treatment decisions based on the recommendations of the prescriber. The main difference between adherence and compliance is that adherence requires the patient's agreement to the prescriber's recommendations.

A patient's non-adherence to a drug regimen can be defined as the patient's inability or unwillingness to follow a drug regimen that has been prescribed by the practitioner and judged to be clinically appropriate, effective and able to produce the desired outcome without harmful effects (Cipolle *et al*., 2004). Non-adherence can be

due to a number of reasons: some are within the patient's control and some are beyond it (Strand *et al*., 1990). A patient's non-adherence to a drug regimen can occur for reasons that fall into both of these categories depending on the nature of the cause. Financial problems can prevent patients from buying the appropriate drug, and failures in the drug distribution or administration system can also contribute to a patient's non-adherence (Cipolle *et al*., 1988). Factors such as vision, hearing, health literacy, disability and social and financial resources may further complicate matters in older patients' adherence to pharmacological prescriptions (Murray *et al*., 2003).

Measuring a patient's adherence to a drug regimen is often difficult. One of the most useful methods to measure patient adherence is a patient interview (Fletcher et al., 1979). Pill counting is another method but suffers from the major drawback that patients rarely bring all of their medications to the ward. Another established method is therapeutic drug monitoring using blood and urine tests (Joyce and Bert, 1991). The four major strategies to enhance patient adherence to a drug regimen include patient education, planning a dosing schedule that fits into the patient's life-style, clinic scheduling for patient follow-up and communication between the patient and physician (Joyce and Bert *et al*, 1991).

A study of HD patient adherence to a drug regimen showed that 50.2% of them were non-adherent to a drug regimen, and 49.5% were non-adherent to fluid restrictions (Bame et al., 1993). Other investigators reported that 67% of HD patients missed an average of 3.4 medication doses (Kaplan *et al*., 1994b). In a sample of elderly patients who received pharmaceutical care in their homes for one year, non-adherence to drug therapy was the most common DTP identified, comprising 32% of all DTPs (Rao *et al*.,

2007). The reasons for patients' non-adherence to drug therapy were poor understanding of the disease and/or treatment, lifestyle issues and treatment anxiety.

1.2.4 Chronic Kidney Disease (CKD)

CKD is increasingly becoming a chronic medical condition of public health concern. In 2002, the National Kidney Foundation-Kidney Disease Outcome Quality Initiative (NKF-K/DOQI) developed a clinical practice guideline in the USA. The guideline introduced the terminology of chronic kidney disease (CKD) and a classification scheme to promote early disease detection, delay disease progression and prevent related complications.

1.2.4(a) Definition

CKD is defined as a glomerular filtration rate (GFR) $\leq$ 60 ml/minute/1.73m^2 or a GFR $\geq$ 60 ml/minute/1.73m^2 in the presence of kidney damage for more than three months (National Kidney Foundation, 2002).

1.2.4(b) Assessment of Kidney Function

Estimation of GFR is very important in the clinical management of patients with CKD. GFR is used to assess the presence and degree of renal function and helps in performing dosage adjustments of renally excreted drugs. The NKF-KDOQI guidelines recommend the modification of diet in renal disease (MDRD) and the Cockcroft-Gault equation as a useful measurement to estimate GFR (National Kidney Foundation, 2002). Therefore, serum creatinine (SCr) cannot be used alone to assess the level of kidney function due to the nonlinear correlation between SCr and kidney function (Shemesh *et al*., 1985).

(i) Cockcroft-Gault Equation

The Cockcroft-Gault equation was derived from 249 inpatients (96% male, age range 18-92 years) with mild renal dysfunction at the Queens Mary Veterans Hospital in Canada based on a single measurement of 24-hour Cl_{Cr} (Cockcroft and Gault 1976). The Cockcroft-Gault equation provides a quantitative estimation of Cl_{Cr} from SCr.

Cockcroft-Gault equation:

$$\text{Men: } Cl_{Cr} \text{ (ml/min)} = \frac{[(140\text{-age}) \times \text{weight (kg)}]}{\text{SCr (mg/dl)} \times 72}$$

$$\text{Women: } Cl_{Cr} \text{ (ml/min)} = \frac{[(140\text{-age}) \times \text{weight (kg)}]}{(\text{SCr (mg/dl)} \times 72)} \times 0.85$$

Body surface area (BSA)-adjusted Cockcroft-Gault equation

$$\text{Men: } Cl_{Cr} \text{ (ml/min)} = \frac{[(140\text{-age}) \times \text{weight (kg)}]}{(\text{SCr (mg/dl)} \times 72)} \times 1.73\ m^2 / \text{BSA}$$

$$\text{Women: } Cl_{Cr} \text{ (ml/min)} = \frac{[(140\text{-age}) \times \text{weight (kg)}]}{(\text{SCr (mg/dl)} \times 72)} \times 1.73\ m^2 / \text{BSA} \times 0.85$$

(a) Limitations of Cockcroft-Gault Equation

The Cockcroft-Gault equation depends on SCr, which is associated with the tubular secretion of creatinine. This could lead to overestimation of GFR by 10 to 40% in individuals with normal renal function (National Kidney Foundation, 2002). In addition, SCr can be influenced by many non-renal factors such as diet (e.g., vegetarian diet and creatinine supplements), body mass (e.g., amputation, malnutrition and emaciation) and drug therapy (e.g., cimetidine and trimethoprim) (Larsson *et al*., 1980; Myre *et al*., 1987). Despite these limitations, the Cockroft-Gault equation has been

widely used to determine drug dose individualization based on kidney function in the clinical setting (Patel, 2004; Pillans *et al*., 2003; Chertow *et al*., 2001).

(ii) MDRD Equation

The MDRD equation was introduced in 1999 to overcome the limitations of Cl_{Cr}-based estimation of GFR. In 1999, the 6-variable MDRD equation was derived from an MDRD population of 1,628 patients with non-diabetic CKD (mean GFR 40 ml/minute/1.73m^2) who concomitantly had GFR measurements using an iothalamate (Levey *et al*., 1999). This equation was developed using patient variables including age, SCr, blood urea nitrogen (BUN), albumin, race and gender. Later in 2000, an abbreviated 4-variable version of the MDRD equation based on only age, gender, race and SCr level was introduced and has become the most accepted and used equation in outpatient clinical settings, superseding the 6-variable MDRD equation and the Cockcroft-Gault equation.

Estimated GFR (6-variable MDRD equation)

$$eGFR = 170 \times (SCr)^{-0.999} \times (Age)^{-0.176} \times (0.762 \text{ if female}) \times (1.180 \text{ if African American}) \times (BUN)^{-0.170} \times (Alb)^{+0.318}$$

Estimated GFR (4-variable MDRD equation)

$$eGFR = 186 \times (SCr)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$$

(b) Limitations of MDRD

Estimation of GFR using MDRD resulted in underestimation of true GFR in healthy individuals, kidney donors and patients with type 1 DM (Lin *et al*., 2003; Ibrahim *et al*., 2005). In addition, the 125I-iothalamate (iGFR) was reported to be more reliable in measuring the actual level of GFR compared to MDRD equations in hospitalized patients with advanced renal disease (Poggio *et al*., 2005). The MDRD equations have not been validated in children, pregnant women, the elderly (older than 70 years) or ethnic subgroups other than Caucasians and African Americans.

1.2.4(c) Classification of CKD

The NKF-KDOQI has classified CKD into five stages, irrespective of the underlying cause and based on GFR.

Stage 1: Kidney damage with normal or increased GFR (GFR ≥ 90 ml/minute/ $1.73m^2$)

Stage 2: Kidney damage with a mild decrease in GFR (GFR 60-89 ml/minute/$1.73m^2$)

Stage 3: Moderate decrease in GFR (GFR 30-59 ml/minute/$1.73m^2$)

Stage 4: Severe decrease in GFR (GFR 15-29 ml/minute/$1.73m^2$)

Stage 5: Kidney failure (GFR < 15ml/minute/$1.73m^2$) (ESRD).

1.2.4(d) Risk Factors for CKD

Risk factors for CKD include DM, high BP, proteinurea, family history of renal disease, increasing age, hyperlipidaemia and tobacco usage (DiPiro *et al*., 2002). As recommended by the NKF-KDOQI (2002), individuals at risk for CKD should undergo testing for markers of kidney damage such as proteinurea, urine sediment, dipstick for red blood cells (RBC) and white blood cells and imaging tests of the kidneys.

Treatment of CKD includes specific therapy based on the diagnosis, evaluation and management of co-morbidities. The goals of these strategies also include slowing the loss of kidney function, prevention and treatment of cardiovascular disease and complications of decreased kidney function. If signs and symptoms of uraemia are present, there should also be preparation for kidney failure, dialysis or transplantation.

1.2.5 End Stage Renal Disease (ESRD)

1.2.5.1 Epidemiology of ESRD

The number of ESRD patients worldwide reported by the United States Renal Data System (USRDS) in 2005 has risen from 888,000 in 1999 to 1,129,000 in 2003 (USRDS, 2005c). The prevalence of ESRD in the USA, Taiwan and Japan was 1,509, 1,631, and 1,797 per million people, respectively. As of 2005, the lowest prevalence was found in the Philippines, Bangladesh and Russia. As reported by the USRDS in 2005, Malaysia was ranked the fifth highest nation in terms of ESRD incidence rate for patients between 45 and 64 years old, after Taiwan, Japan, the USA and Spain (USRDS, 2005c). It was reported that DM was the most common cause of ESRD in Malaysia; however, the number of dialysis patients with DM showed a decline in 2005 compared to the number in the past 10 years (Lim *et al*., 2005). The second most common cause of ESRD was hypertension, while the underlying cause remained unknown in 20% of cases. Glomerulonephritis and systemic lupus erythematosus accounted for 4% and 1% of ESRD cases, respectively.

1.2.5.2 Co-morbidities of ESRD

Co-morbidities of ESRD include cardiovascular diseases, hypertension and diabetes.

1.2.5.2 (a) Cardiovascular Diseases

(i) Definition

Cardiovascular diseases are those that affect the cardiovascular system such as heart failure, arrhythmia, CHD, MI, hyperlipidaemia, hypertension, stroke and venous thromboembolism. Heart failure, also known as congestive cardiac failure, is a condition in which the heart is unable to pump a sufficient amount of blood through the body to meet its metabolic needs. Arrhythmia is the loss of cardiac rhythm, especially irregularity of the heartbeat. CHD is often the result of a lack of oxygen and decreased or absent blood flow to the myocardium, resulting from the narrowing or obstruction of coronary arteries. MI is the rapid development of myocardial necrosis caused by a critical imbalance between oxygen supply and demand of the myocardium. Stroke is a rapid loss of brain function due to an interruption in the blood supply to all or parts of the brain. Venous thromboembolism is the formation of a clot or thrombus within the venous circulation, obstructing the flow of blood through the circulatory system.

(ii) Signs and Symptoms

The general and non-specific signs and symptoms of cardiovascular diseases are chest discomfort such as pressure, fullness or chest pain that lasts more than a few minutes or is intermittent, in addition to shortness of breath with or without chest pain, oedema, increased heart rate, fatigue, lack of appetite and nausea.

(iii) Risk Factors

Risk factors for cardiovascular diseases include age, family history of cardiovascular diseases, DM, hypertension, hyperlipidaemia, smoking, obesity and psychological factors such as depression and anxiety. Other risk factors specific to

ESRD patients include anaemia, hyperhomocysteinaemia, hyperparathyroidism, oxidative stress, hypoalbuminaemia, chronic inflammation and prothrombotic factors (National Kidney Foundation, 2005).

(iv) Epidemiology

A study conducted in collaboration with the Ministry of Health, Malaysia and the World Health Organization (WHO) revealed that CHD and stroke were among the five most common diseases in Malaysia. Another study conducted on 21,708 Malaysians aged 30 years and above revealed that at least 61% had cardiovascular diseases risk, while 27% had two or more risk factors (Lim *et al*, 2000).

(v) Management

The initial management of cardiovascular diseases involves lifestyle modifications such as smoking cessation, regular exercise and healthy diet. Patients with CKD and cardiovascular diseases require regular assessment and treatment of the traditional risk factors (e.g., DM, hypertension, hyperlipidaemia, anaemia and mineral metabolism abnormalities) as recommended by the NKF-KDOQI guidelines (National Kidney Foundation, 2005).

(vi) Complications

It has been reported that cardiovascular diseases are the primary cause of death among ESRD patients (Wong *et al*., 2005; Go *et al*., 2004).

1.2.5.2 (b) Hypertension

(i) Definition:

Hypertension is defined as a persistent systolic BP of 140 mmHg or higher and/or a persistent diastolic BP of 90 mmHg or higher. For patients with CKD, a systolic BP of < 130 mmHg and a diastolic BP of < 80 mmHg is recommended as a target to reduce the risk of cardiovascular disease (National Kidney Foundation, 2004).

(ii) Causes

Hypertenion results from either a specific cause (e.g. secondary hypertension) or an underlying pathophysiologic mechanism (e.g. primary or essential hypertension). Specific causes of secondary hypertension are polycystic kidney disease, renovascular hypertension, hydronephrosis, Cushing's syndrome, aldosteronism, pheochromocytoma, hypothyroidism, hyperthyroidism, sleep apnea and obesity (Ooi *et al*., 1970; Chapman and Schrier 1991; Calhoun, 2006; Saito *et al*., 1983; Nieto *et al*., 2000). Underlying pathophysiologic mechanisms that cause primary or essential hypertension include atherosclerosis, increased vascular reactivity due to excess sodium intake and increased intracellular calcium concentration (Campese *et al*., 1996).

(iii) Epidemiology

The Third National Health and Nutrition Examination Survey (NHANES III) reported that hypertension was present in 24% of American population (Burt *et al*., 1995). In 2004, the prevalence of hypertension in Malaysian adults was estimated to be 33% (Lim and Morad, 2004). The prevalence of hypertension is similarly high in Singapore (27.3%), Korea (22.9%) and India (25% urban and 10% rural subjects) (Ministry of Health, Singapore, 2001; Choi *et al*., 2006; Gupta, 2004).