

**ASSOCIATION OF NONADHERENCE AND
BELIEFS ABOUT MEDICINES
AMONG HEMODIALYSIS PATIENTS
IN PENANG**

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by

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LIST OF ABBREVIATIONS

BMQ	Beliefs about medicines questionnaire
DM	Diabetes Mellitus
ESKD	End Stage Kidney Disease
HBP	Hospital Balik Pulau
MARS-5	5 Items-medication Adherence Reporting Scale
MNAD	Medication Nonadherence
MREC	Medical Research Ethics Committee
MTAC	Medication Therapy Adherence Clinic
NCF	Necessity-Concern Framework
NGO	Non-government Organization
NKF	National Kidney Foundation
NMRR	National Medical Research Registered
QOL	Quality of Life
RRT	Renal Replacement Therapy
USM	Universiti Sains Malaysia
USRDS	United State Renal Data System
WHO	World Health Organization

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**PERKAITAN DI ANTARA KETIDAKPATUHAN DAN KEPERCAYAAN
MENGENAI UBAT-UBATAN DALAM KALANGAN
PESAKIT HEMODIALISIS DI PULAU PINANG**

ABSTRAK

Ketidakpatuhan ubat dalam kalangan pesakit hemodialisis boleh disebabkan oleh kepercayaan ubat yang salah. Namun demikian, penilaian kepercayaan ubat dalam kalangan pesakit hemodialisis jarang dijalankan di Malaysia. Kajian ini bertujuan untuk menilai prevalens ketidakpatuhan ubat dalam kalangan pesakit hemodialisis dan perkaitan antara ketidakpatuhan ubat dan kepercayaan mengenai ubat-ubatan. Kajian ini merupakan kajian keratan rentas yang dijalankan di pelbagai pusat hemodialisis di Pulau Pinang dengan cara persampelan secara tujuan. Data dikumpulkan dengan menggunakan 5 item-skala laporan kepatuhan ubat-ubatan (MARS-5) dan *beliefs about medicines questionnaire* (BMQ). Regresi logistik digunakan untuk menilai perkaitan di antara ketidakpatuhan ubat dan kepercayaan ubat. Sebanyak 325 pesakit telah ditemubual. Kebanyakan pesakit adalah berusia 55 tahun ke atas (69.0%) dengan pengambilan 6-10 jenis ubat setiap hari (58.2%). Prevalensi ketidakpatuhan ubat adalah 69.5% berdasarkan skor MARS-5. Dalam aspek BMQ, median skor untuk domain *Specific-Necessity* dan *Specific-Concerns* adalah 19.00 (17.00-20.00) dan 12.00 (11.00-16.00). Manakala, median skor untuk *General-Overuse* dan *General-Harm* adalah 11.00 (10.00-12.00) dan 9.00 (8.00-10.00). Pesakit yang mempunyai kepercayaan mengenai ubat-ubatan boleh melindungi mereka daripada menjadi semakin teruk menunjukkan kurang ketidakpatuhan ubat yang signifikan (adjusted OR = 0.543, CI = 0.366, 0.903). Selain

itu, ketidakpatuhan obat adalah lebih ketara dalam kalangan pesakit yang risau pengambilan obat mereka (adjusted OR = 1.500, CI = 1.113, 2.020) tetapi kurang jelas dalam kalangan pesakit yang percaya obat akan menyebabkan ketagihan (adjusted OR = 0.637, CI = 0.450, 0.903). Sebagai kesimpulan, the prevalensi ketidakpatuhan obat dalam kalangan pesakit hemodialisis adalah sederhana tinggi. Kepercayaan mengenai obat adalah didapati mempengaruhi ketidakpatuhan obat.

ASSOCIATION OF NONADHERENCE AND BELIEFS ABOUT MEDICINES AMONG HEMODIALYSIS PATIENTS IN PENANG

ABSTRACT

Medication nonadherence (MNAD) among hemodialysis patients can be caused by erroneous medication beliefs. However, assessment on hemodialysis patients' beliefs about prescribed medicines is not routinely conducted in Malaysia. This study aimed to assess the prevalence of MNAD among hemodialysis patients and the association between patient's beliefs about medicines and MNAD. This was a cross-sectional multicentre study among hemodialysis patients conducted in Penang by purposive sampling. Data was collected by using 5 items-medication adherence report scale (MARS-5) and Beliefs about Medicine questionnaire (BMQ). Multiple logistic regression was used to assess the association of MNAD with beliefs about medicines. A total of 325 patients were interviewed. Majority patients were aged 55 years or more (69.0%) and received 6-10 prescribed medications daily (58.2%). The prevalence of MNAD was 69.5% based on MARS-5 score. Considering the BMQ score, the median score for Specific–Necessity and Specific–Concerns domain was 19.00 (17.00-20.00) and 12.00 (11.00-16.00) respectively. Whereas, the General–Overuse and General–Harm domain showed total mean score of 11.00 (10.00-12.00) and 9.00 (8.00-10.00) respectively. The patients with belief of medication will protect them from becoming worse showed significant less MNAD (adjusted OR = 0.543, CI = 0.366, 0.903). Besides, MNAD were significantly more prominent among patient who worries about taking medications (adjusted OR = 1.500, CI = 1.113, 2.020) but less prominent among patient who perceived medication are addictive to them

(adjusted OR = 0.637 CI = 0.45, 0.903). As conclusion, the prevalence of MNAD among hemodialysis patients was moderately high. Medication beliefs were found to influence the MNAD.

CHAPTER 1

INTRODUCTION

1.1 Background

End stage kidney disease (ESKD) is defined as chronic kidney disease stage five with irreversible and permanent loss of renal function when estimated glomerular filtration rate $< 15\text{ml/min per } 1.73 \text{ m}^2$ (Levin et al., 2013). ESKD is one of the chronic disorders that increasing rapidly worldwide due to the high prevalence of chronic disorder such as hypertension and diabetes mellitus (DM) (Hamer and El Nahas, 2006, Bujang et al., 2017). Globally, the annual growth rate of ESKD was 7% (Lysaght, 2002). This brings a high global mortality rate with over one million patients passed away secondary to ESKD annually (Hamer and El Nahas, 2006).

Forecast of worldwide ESKD cases indicated that the population of ESKD will reach more than 2 million by the year 2030 (Szczech and Lazar, 2004). The United State Renal Data System (USRDS) 2019 reported that the number of ESKD cases has continued increased about 20,000 cases per year in United State Population ((USRDS), 2019). In Malaysia, the National Renal Registry (NRR) data showed that the prevalence of ESKD cases was increased about 96 % over 10 years, which is 4076 cases in 2010 and increased to 7996 cases in 2017 (National Renal Registry, 2017).

The only medically recognized therapy for ESKD is renal replacement therapy (RRT), either by kidney transplantation or through renal dialysis which are peritoneal dialysis or in-centre hemodialysis. Although kidney transplantation is the best choice of therapy for ESKD, resource constraints of kidney donation remain an issue (Naalweh et al., 2017). According to NRR 2017, majority of Malaysian patients

received RRT as the treatment of hemodialysis which usually performed at a hospital or clinic on an outpatient basis (National Renal Registry, 2017). The number of patients commencing dialysis in Malaysia is predicted to be more than tripled, from 32026 cases in year 2013 to 106249 cases in year 2040 (Bujang et al., 2017). In worldwide statistic, there is an estimated two-fold increase of patients received RRT for ESKD by year 2030, with the most growth in Asia (Liyana 2015).

Hemodialysis is a life-saving procedure which can replaces only about 10% of the normal renal function (Levin et al., 2013). Compliance to hemodialysis session 3 times per week, the prescribed medication in addition to many dietary restrictions make the therapeutic regimens more complex (Alkatheri et al., 2014). This subsequently could place a significant burden on the patients and make them become more depression. This also usually makes patients dependent on their family member and health-care providers for many aspects of their treatment such as serving medications, guiding to the dialysis session and medical visit. Besides, the patients also require the help of providing suitable meals, giving the patients with physical, emotional, and social support all the times.

ESKD patients is having mortality risk with eight times higher than general population because of the cardiovascular or non-cardiovascular risk. Besides, the risk of clinical complication such as hypocalcemia, hyperphosphatemia, hyperkalaemia, metabolic acidosis, anemia, hyperuricemia, hyperlipidemia, hypertension and uncontrol DM is very high among the ESKD patients (De Jager et al., 2009). The goal of the ESKD treatment usually includes prevention and treatment of complication of decreased renal function. Thus, hemodialysis patients often required average of 10-12

regular medications which some must take several times daily (Manley et al., 2004). Indeed, hemodialysis patient found to have consumed an average (median) of nineteen pills per day in a previous study (Chiu et al., 2009). This large pill burden including calcimimetic agent, vitamin D supplements, phosphate binders, iron supplements, antihyperlipidemia agent, antidiabetics agent, antihypertensives agent and erythropoiesis stimulating agents (Manley et al., 2004). The resulting high pill load, polypharmacy, and regimen complexity could predispose the hemodialysis patients to high risk of adverse drug reactions and leads to medication nonadherence (MNAD) (Mason, 2011, Neri et al., 2011).

Undeniable, lifetime commitment towards medication is one of the important aspects for a successful hemodialysis treatment despite adherence to dietary guideline, fluid restriction and dialysis. A systematic review showed that the MNAD prevalence among hemodialysis patients was ranged from 12.5% to 98.6% (Ghimire et al., 2015). This is a motive of worry because MNAD can lead to poor treatment outcome, increased financial burden for society, and further increase the burden of healthcare system (Sabaté, 2003, Svarstad et al., 2001, Vermeire et al., 2001). In other words, it can reduce patient's nutritional status, clinical outcome and quality of life (QOL) followed by increase the mortality, hospitalization rate and healthcare cost (Saran et al., 2003, Ibrahim et al., 2015).

Medical intervention and counselling of self-monitoring play an important role in enhancing the clinical outcome of ESKD (Chen et al., 2014, Curtin et al., 2005, O'Connor et al., 2008). However, despite the advanced medical intervention and wide selection of treatment, many hemodialysis patients still do not achieve the desired

therapeutic outcome. One of the important determinants is psychological factor (Ghimire et al., 2015). The psychosocial factors cannot be exempted, although there are several other factors which cause MNAD. These factors includes socioeconomic, therapy-related, health-care system and disease-related factors (Jin et al., 2008, Horne and Weinman, 1999). Researchers found that patient's beliefs and negative attitude towards their chronic medicine and treatment are strongly related to medication taking behaviour especially in hemodialysis patients (Cummings et al., 1982, Wileman et al., 2015, Jin et al., 2008). Based on their personal beliefs and experiences, the ESKD patients create their own implicit on the consumption of prescribed medicines. The patients' wrong perception may cause intentional MNAD (Horne and Weinman, 1999, O'Connor et al., 2008). Undeniable, patients always weight the risk and benefit of their prescribed medication. Subsequently, they make their own decision by considering the effectiveness, safety profile and clinical health outcome which could resulting from the used of their prescribed medicines (Horne et al., 1999).

Many healthcare providers would agree that hemodialysis patient has the right to stop taking their prescribed medication. Nevertheless, this is problematic if their decision is not guided by a realistic appraisal of the ESKD and the relative benefits and risks of the prescribed medication (Horne et al., 2001). Hence, targeted individualized education needs to be facilitated after any transitioning of medication treatment. The MNAD issues can be addressed by capitalizing in the necessity and importance of taking medication (Clifford et al., 2006). Currently, assessment of hemodialysis patients' beliefs about medicines is not being incorporated in Malaysia healthcare setting. Therefore, there is a need to gain insight on whether the use of Beliefs about Medicines questionnaire (BMQ) tool in medication counselling would be a promising approach to solve the issues of MNAD among hemodialysis patients.

1.2 Problem statements

The prevalence of ESKD is growing in Malaysia. As a result, it raises total national health expenditures, which include the cost of RRT and medication. ESKD patients require many complex regimens to avoid multiple problems such as fluid overload, hyperphosphatemia, anaemia, hyperkalemia, hypocalcemia, metabolic acidosis, and uncontrolled blood pressure. The complicated regimen results in a variety of adverse medication reactions, including gastrointestinal upset, hypotension, and constipation. Thus, despite nonadherence to thrice weekly dialysis sessions, hydration restriction, and dietary restriction, hemodialysis patients are predisposed to MNAD. Thus, it is critical to determine the current prevalence of MNAD among hemodialysis patients in order to address the problem of poor medication adherence.

Sociodemographic factors were shown to influence MNAD levels in hemodialysis patients in the local population. A local study discovered that patients who were younger in age and had been on hemodialysis for a longer period of time had a considerably higher likelihood of nonadherence to their medication (Chan et al., 2012). However, limited study was conducted to determine the effect of medication beliefs on hemodialysis patients' attitudes toward MNAD in a local hemodialysis community. Thus, this study was done to determine the relationship between beliefs about medications and MNAD.

1.3 Justification for the study

Currently, pharmacist-led medication therapy adherence clinics (MTACs) are widely established in government hospitals and health clinics throughout Malaysia. The major goal of a nephrology medication adherence treatment clinic in Malaysia is to educate patients about their medications through systematic medication counselling. It is critical, however, to have an understanding of hemodialysis patients' views, anxieties, and attitudes regarding the risks and advantages of their given medication. Their implicit attitudes toward medication must be adequately understood and handled. A previous study demonstrated that patient attitudes regarding medications can influence MNAD, consequently affecting the morbidity and mortality of patients undergoing hemodialysis (Drangsholt et al., 2019). Thus, comprehensive treatment must involve an awareness of patients' attitudes toward medications in order to avoid MNAD difficulties in hemodialysis patients.

This was a pioneering study in Malaysia, analysing hemodialysis patients' medication beliefs in connection to MNAD. This study may aid in understanding the pharmaceutical beliefs elements that contribute to MNAD in Malaysian hemodialysis patients. The findings of this study will aid in the development of an improved nephrology MTAC procedure. In the future, physicians and pharmacists may consider conducting medication beliefs assessments during medication reviews for hemodialysis patients in Malaysian healthcare institutions. By including medication beliefs into medication counselling, we can have a better understanding of the perceived barrier associated with MNAD. This will result in more effective communication and, as a result, increased patient knowledge of the critical nature of their medication for ESKD control.

1.4 Objectives of study

1.4.1 Primary objective

To assess the association of beliefs about medicines and MNAD among hemodialysis patients.

1.4.2 Secondary objectives

1. To assess the prevalence of MNAD among hemodialysis patients.
2. To assess the beliefs about medicines among hemodialysis patients.
3. To evaluate the demographic factors associated with the MNAD among hemodialysis patients.
4. To evaluate the demographic factors associated with the beliefs about medicines among hemodialysis patients.

CHAPTER 2

LITERATURE REVIEW

2.1 Definition of medication nonadherence

According to Oxford Advanced Learner's Dictionary, adherence means the fact of following a particular set of a fixed way of doing something (Press, 2020). According to World Health Organization (WHO), adherence is "the degree to which a patient's behavior in consuming prescribed medicines, following a diet, and/or doing lifestyles modification, in accordance with agreed advices from a prescriber" (Sabaté, 2001). According to American Society on Aging and the American Society of Consultant Pharmacists Foundation joint Adult Meducation, MNAD was documented as the following acts: either intentionally or unintentionally not filling or not refilling a prescription, missing dose(s), overconsumption of prescribed medication, stop a medication, administering medication at wrong time, consuming medication of other(s), taking a dose concurrently with the wrong foods or medications, taking expired /or damaged medications, taking improperly stored medications and lastly improperly using medicated devices (Aging and Meducation, 2006).

2.2 Type of medication nonadherence

Generally, MNAD can be categorized into intentional or unintentional.

2.2.1 Intentional medication nonadherence

Intentional nonadherence is defined as the determination to act in a certain way and is an element of behavior of every human being including health behavior (Burks, 2001). There is an underlying assumption of influencing patients undertake a reasoned decision-making process in relation to disregard professional advice (Lehane and McCarthy, 2007). The perceptual or motivational barriers including patient's beliefs

about their medicines are closely related to intentional lapses (Griva et al., 2018). Normally, intentional lapses happened when patients decide to ignore regimen recommended by prescriber. In this context, patients often decide to delay, modify, skip the dose as prescribed or take medication holidays (Lehane and McCarthy, 2007). This can be noticed when patients do not refill their medication and stop follow the current medication treatment without the advices from prescriber (Lowry et al., 2005). Although patients understand medication can prolong their survival rate, a study demonstrated that intentional nonadherence always occurred among patient who perceive enjoy a good quality of life was more essential as compared to have longer life (Lehane and McCarthy, 2007). A study mentioned that patients who engaged in intentional MNAD are more linked to higher medication concerns beliefs, lesser self-efficacy, lesser empowerment meaningfulness scores and lower acceptance towards their clinician's treatment recommendations (Náfrádi et al., 2016).

A study mentioned that intentional MNAD can be influenced by co-morbid condition and patients' perception towards the adverse effects of prescribed medication (Griva et al., 2018). In particular, it is hypothesized that intentional MNAD is strongly associated with individual's beliefs and cognition (Wroe, 2002). In the context of medication beliefs, perceive medication necessity and concerns about adverse effect of prescribed medication are important determinants of intentional MNAD. Among these two perceptions, concern about the adverse effects of prescribed medication was more likely to cause intentional MNAD than necessity beliefs (Horne et al., 2013). A study suggested that a good health communication between prescriber and patient is important to eliminate the worry of the long-term side effects of their chronic medication (Griva et al., 2018). Interventional therapy involved cognitive behavioral aspect can help to

alleviate negative beliefs and the misunderstanding about their medications (Butler et al., 2004).

2.2.2 Unintentional medication nonadherence

Unintentional nonadherence is a passive process for which patients do not adhere to prescribing instructions because of forgetfulness, negligence or conditions out of their control (e.g., health literacy) (Lowry et al., 2005). It is less strongly associated with individual's beliefs and cognition than factors related to intentional nonadherence (Wroe, 2002). A study mentioned that patient's lack of knowledge of their medication, misplacing medications and miscommunication with prescribers are also the contributors to unintentional MNAD (Griva et al., 2014). Besides, unintentional lapses also indicate that patient has limited resources to assess the information of their prescribed medication (Lehane and McCarthy, 2007).

Several factors in relation to unintentional MNAD have been proposed which consist of the essential elements of misunderstanding the regimen, language barriers, inaccessible to medications, patient routines, and patient memory (Lehane and McCarthy, 2007). A study showed that unintentional MNAD can be associated with other factors, such as disease and treatment condition, employment status and primary renal disease diagnosis (Griva et al., 2018). A study mentioned that teaching patients in practicing of stable routine, couple with cues to actions can help to prevent unintentional nonadherence (Zygmunt et al., 2002).

However, a study revealed that unintentional MNAD can be an important potential prognostic for future intentional MNAD (Gadkari and McHorney, 2012). For this, the study suggest that prescribers may need periodically monitoring on patients

unintentional MNAD. This action will proactively solve patient's incorrect medication beliefs before they decided to stop taking their medication (Gadkari and McHomey, 2012).

2.3 Methods in evaluating medication nonadherence

According to WHO, measurements of MNAD are categorized into two methods which are subjective and objective measurement. Objective measurements generally have advantages as compared to subjective measurement. Nevertheless, multiple subjective measurements might have better sensitivity than a single objective measurement according to a previous meta-analysis on MNAD outcomes (Ghimire et al., 2015).

2.3.1 Subjective measurement

Patient medication consumption behavior evaluation is involved in subjective measurements (Lam and Fresco, 2015). In this measurement, MNAD is assessed based on validated questionnaires which defined nonadherence according to adherence rating scales (Ghimire et al., 2015). The advantages of this method include synchronal response, inexpensive and easy to conduct (Nguyen et al., 2014). Due to the practicality and flexibility, the self-report questionnaire can help to determine how patient's concern about their treatment and thus customized intervention can be given to patient (Svarstad et al., 1999).

However, the drawback of this measurement is that patients prone to less reported nonadherence to prevent disagreement from their prescriber (Lam and Fresco, 2015). Besides, the nonadherence response can also be affected by patient's

psychological problem at that moment (Svarstad et al., 1999). Besides that, the poor communication skills by interviewer during survey in addition to poor design of questionnaire can also cause bias in the result. Sometimes, the false data given by patients intentionally or unintentionally can lead to unreliable response (Lam and Fresco, 2015).

An example of validated questionnaire widely used to define MNAD among hemodialysis patients are Medication Adherence Report Scale (MARS) (Theofilou, 2013, Horne and Weinman, 1999), Brief Medication Questionnaire (Svarstad et al., 1999), Medication Adherence Questionnaire (Wileman et al., 2011), Simplified Medication Adherence Questionnaire (Arenas et al., 2013), Morisky 8-item Medication Adherence Scale (Alkatheri et al., 2014) and Drug Intake Percentage Questionnaire (Ossareh et al., 2014). For the study using non-validated questionnaire, the method to assess the MNAD included divergencies in the self-reported adherence, self-reported missed or skipped doses, cost-related MNAD, or direct record from patient's prescription (Ghimire et al., 2015).

2.3.2 Objective measurement

Objective measurement methods of MNAD involved the biochemical measurement, pill counting, electronic monitoring and secondary data analysis (Lam and Fresco, 2015). Objective measures act as physical evidence to ensure patient has taken their medication. These methods are considered to be more accurate compared to subjective measurement (Lam and Fresco, 2015). However, limitation of this measurement is the intrusiveness which cause stress and fear in patients (Farmer, 1999). Comparing to subjective measure, objective measurement is more costly because the

health care providers are needed to carry out the steps of measurement test. This method is more suitable for hospitalized patients or those without complicated therapy (Vermeire et al., 2001).

Considering hemodialysis patients, the objective MNAD was usually measured by using pill counting (consuming less than eighty percent of medication in a prescription), refill rate of prescription, occurrences of bottle opening which can be detected by using devices specially designed for medication event monitoring. The most common biochemical measurement used to estimate the MNAD among hemodialysis patients involved the pre-dialysis serum phosphate level at the maximum value of 5.50 mg/dl. A clinical proxy measure like pre-dialysis serum phosphate level is usually affected by the clinical or dietary factors. Hence, this could bring less specificity result of the correlation between serum phosphate with the MNAD (Ghimire et al., 2015).

2.4 Prevalence of medication nonadherence among hemodialysis patient

Based on a systematic review in year 2015, MNAD in hemodialysis patients was ranged from the prevalence of 12.5% to 98.6% (Ghimire et al., 2015). The variation of the prevalence rate was due to different measurement method in assessing the MNAD prevalence. The rate of adherence was lower when assesses using objective measure-pre-dialysis serum phosphate level (13.9% to 45.1%), whereas higher report rates of MNAD were noticed when using patient self-report measures (40.0% -60.0%) (Ghimire et al., 2015). A local study by Chan et al. showed that the MNAD rate for hemodialysis patient was 33.5% by using predialysis serum phosphate level and 49.5% by using

Modified dialysis diet and fluid non-adherence questionnaire which is a self-report questionnaire.

Hemodialysis patient often need multiple regimens to control their chronic illness such as phosphate binders, antihypertensive agent, antidiabetic agent and antihyperlipidemia agent. The rate of MNAD towards phosphate binder is the highest due to the high frequency of daily dose compare to other medication (Neri et al., 2011). A systematic review showed that the mean percentage of MNAD to phosphate binders by using subjective measure was 47.9% whereas the objective measure was 78.4%. For antihypertensive agent, the prevalence of MNAD in hemodialysis patients by using subjective measure was 24.3% whereas the objective measure was 38.5%. The estimated MNAD to antidiabetic medication was 61.2% whereas for antidyslipidemia agent was 46.0% (Ghimire et al., 2015).

2.5 Factors associated with medication nonadherence

According to WHO, the five major factors associated with MNAD in hemodialysis patients are patient-related, therapy-related, disease-related, social/economic and health system-related factor (Sabaté, 2003, Ghimire et al., 2015). The most influencing factors in hemodialysis patients' medication-taking behavior is demographic factor, psychosocial factor and patient knowledge (Ghimire et al., 2015).

2.5.1 Patient-related factor

There are several factors categorized in patient-related factor. One of those is demographic factors which included the age, gender, race, level of education and marital status. Besides that, patient-related factors also involved psychosocial factors which is related to patient's beliefs, attitude, and motivation. Other than that, the

patient's level of knowledge, patient-clinician relationship and health literacy perception also been considered as part of the patient-related factors. Lastly, patient's physical difficulties, forgetfulness, alcohol taking and cigarette smoking also cannot be ruled out in patient-related factors which can affect the adherence outcome (Jin et al., 2008).

2.5.1 (a) Demographic factors

In term of demographic data, age was the most frequently found to be significantly associated with MNAD among hemodialysis patients. Four studies found that MNAD is more prevalent in older population (Leggat et al., 1998, Chiu et al., 2009, Theofilou, 2013, Cukor et al., 2009). Elderly patients may have hearing, eyesight, memory and physical strength problems which lead to difficulties in following therapy instructions (Jin et al., 2008). Other factors significantly associated with MNAD in hemodialysis patients include non-Caucasian ethnicity, smoker, living single and illness interfering family life (Ghimire et al., 2013). Some studies revealed that male patients, higher education, and employed were significantly associated with medication adherence. Besides, support from prescribers and family members was found to improve medication adherence among hemodialysis patients (Sajadi et al., 2017).

2.5.1 (b) Psychosocial factors

The psychosocial factors that were found to affect MNAD were lack of motivation, poor medication beliefs, health locus of control, and emotional representation (Ghimire et al., 2015).

A meta-analysis found that depression individuals with comorbidities were about triple times having MNAD problem compared to general population (DiMatteo et al., 2000). A study results indicated that hemodialysis patient's reported high depressive symptoms. The MNAD was significantly affected by the dimension of health locus of control which defined as the patient's beliefs according to their previous experience in the health issues (Theofilou, 2013). Better adherence was found among those patients with internal locus of control as they confident that renal disease progression can be personally controlled via a proper action (Marks, 1998).

Patient's fault beliefs or misunderstanding about the medication would attribute to MNAD. The worry becoming too dependent on long term medication also can lead to MNAD (Jin et al., 2008). Besides, medication beliefs are also an important factor which could affect MNAD behavior. The lack of understanding about medication can triggered uncertainty of the medication necessity and worry with the possible side effects (Ghimire et al., 2017). This can be solved by educating them by incorporating the psychological aspects. On top of that, intervention with giving comprehensive information about their prescribed medication can help to increase the knowledge of their medications (Ghimire et al., 2017).

2.5.1 (c) Patient knowledge

In hemodialysis treatment, patient's understanding towards their illness is always been neglected. Besides, some patients have strong ignorance of their treatment role. Some of them beliefs that their medication is temporarily needed and thus they try to stop the medication and observe whether those medication was still need (Jin et al., 2008). For those reason, disease education and medication counselling are crucial.

Study had found that both interventions would improve patient's active involvement in their therapy (Rubin, 2005). Improving patient's understanding on their own drug regimen definitely can combat the MNAD issues (Jin et al., 2008).

2.5.2 Therapy-related factor

The issues to be considered in the therapy related factors were administration route, treatment duration, complexity of regimen, adverse drug reactions, extend of required behavioral changed, medication taste and medication storage (Jin et al., 2008). The most common perceived barriers given by hemodialysis patients to explain MNAD was total daily pill burden. A study found that majority of the hemodialysis patient were prescribed over 20 pills daily. The high daily pill burden was majority contributed by the phosphate binder which usually need to be taken in multiple doses per day (Chiu et al., 2009). Besides, the dosage schedule with more frequency can caused the MNAD especially the phosphate binder which needs to be taken with each meal (Chiu et al., 2009). The poor tolerance with the side effects of prescribed medication and the large tablet size were also the contributing factor of MNAD (Ghimire et al., 2017).

The hemodialysis patients' various medical conditions usually warrant the use of multiple medication. Due to the multiple comorbidities and complication from hemodialysis, the high pill burden, polypharmacy and regimen complexity were always the consequences. Multiple complex regimens can sometimes lead to various medication-related problems in patients with hemodialysis, such as drug-drug interaction, adverse drug reaction, and overdose if patient do not properly understand the medication (Mason, 2011). For example, multiple type of antihypertensive agent may lead to hypotension side effect in certain circumstances such as during dialysis session. Moreover, the use of the nonprescribed medication such as herbal supplement

may affect the pharmacokinetic and pharmacodynamic profile of prescribed medication. Subsequently, it led to several medical problems due to the occurrence of the undesired drug-drug interaction (Mason, 2011).

As the hemodialysis patients are prescribed with multiple drug treatments, there is a need to evaluate how would the multiple therapies affect the medication adherence. Thus, healthcare providers may periodically communicate with patients so that patient can voluntarily give personal view regarding their ongoing medications and willingness to initiate new therapy. Furthermore, healthcare provider should also provide information regarding their dosage adjustment and requirement as well as the possible sides effect, they might experience when taking the treatment (Ghimire et al., 2017).

2.5.3 Disease-related factor

Severity of disease or disease complication symptoms can lead to MNAD among hemodialysis patient. The personal view of taking the long-term medication for this chronic disease make them worried the side effects of prescribed medication (Ghimire et al., 2017). Three previous studies found that the longevity of hemodialysis (5 or more years of dialysis) found to have significantly associated with MNAD (Neri et al., 2011, Chan et al., 2012, O'Connor et al., 2008). Besides, concomitant illness such as DM, hypertension, and recurrent hospitalization were among the other clinical variables which affecting MNAD (Ghimire et al., 2015).

2.5.4 Social and economic related factor

Social and economic factors related to MNAD were time commitment, social support, cost of therapy and income (Jin et al., 2008). Regarding hemodialysis patients, the most affecting factors for nonadherence are accessibility to medicines and

affordability. In term of accessibility, some of the patients were lives in countryside area and need to travel long journey for getting hemodialysis treatment, medical help, or refill prescribed medication (Ghimire et al., 2017). Besides that, the financial burden predisposed by paying the transportation, medication and treatment cost annulled the cost benefit in hemodialysis patients (Ghimire et al., 2017). Thus, social support from health care providers, family members or friends are required to motivate patients and combat their poor attitudes towards their treatment.

2.5.5 Healthcare system related factor

The main factors identified relating to healthcare systems were less accessibility to medical help, difficulty to refill prescribed medication, long waiting time and unsatisfied with treatment visits (Jin et al., 2008). A qualitative study on hemodialysis patients showed that those patients expressed poor interaction with prescribers were more likely to be MNAD. The issues raised by the patients included: less two-way communication from their prescriber, less patient's involvement during clinic visit, and less time for medication counselling (Ghimire et al., 2017). The poor interaction between patient and prescriber makes the patient loss confidence on prescriber's recommendation and advices. Patients also less informed their concerns and worries about treatment to prescriber as to impress prescriber that they are good patient (Rifkin et al., 2010). Consequently, patient may make several arrangements for their prescribed medication to express a defect sense of control over their regimen (Ghimire et al., 2017).

2.6 Consequences of medication nonadherence

2.6.1 Adverse clinical consequences

MNAD is associated with a range of clinical complication among hemodialysis patients. Deterioration of kidney function can cause patient developing edema, uremic

symptoms, anemia, electrolyte imbalance, increase in blood pressure and uncontrolled glucose level. Besides, the diabetic complication, hyperlipidemia complication and cardiovascular risk will be increased. Thus, patient require the multiple regimens to prevent the adverse complication of ESKD. Study showed that majority of patients were not adherent to phosphate binder due to the higher dosage frequency. Elevate serum phosphate indicates hyperphosphatemia which was associated with the development of myocardial hypertrophy and poor bone health (Neves et al., 2004). The nonadherence to antihyperlipidemic agent and antihypertensive agent will increase patient's triglyceride levels and blood pressure which has been strongly correlated with the development of cardiovascular risk (Lou et al., 2007). For DM patient on hemodialysis, nonadherence to antidiabetic medication will increase the risk of microvascular and macrovascular complications which included cardiovascular problems, cerebrovascular events, and peripheral vascular disease (Sørensen et al., 2007). Additionally, patient nonadherence to medication can lead to a false impression to the physician about the effectiveness of the medication regimen that was prescribed. The physician might conclude that the current regimen was not effective. Consequently, the physician might prescribe a new regimen that might result in aggravation of the patients' ESKD (Christensen et al., 1992).

2.6.2 Quality of life

In general, MNAD among hemodialysis patients will lead to hyperphosphatemia, hyperkalemia, anemia and uncontrolled blood pressure, uncontrolled blood glucose. These can deteriorate patient's ESKD complication. Subsequently, their QOL will be affected. A study showed that high prevalent of nonadherence to hemodialysis regimen is associated with poor QOL, depression and

malnutrition (Ibrahim et al., 2015). The mental and physical health dimensions of QOL is significantly associated with the morbidity and mortality (Yusop et al., 2013).

2.6.3 Burden on the healthcare system and society

MNAD among hemodialysis patients can seriously cause treatment failure. Subsequently, it might lead to alteration in the treatment plan, changes in dose and medication, unnecessary biochemical tests, and hospitalization (Alkatheri et al., 2014). Hence, the cost of treatment might increase and burden the healthcare system.

In 2003, the WHO announced that MNAD as a public health issue among patient underlying chronic disease. MNAD can result in many undesired clinical consequences and increase financial burden (Sabaté, 2003). In US, approximately \$289 billion per year was spent to overcome the consequences of the MNAD (Cutler and Everett, 2010). Compare to other countries, the ESKD expenditure in our nation was relatively high. It has increased more drastically than the national health expenses (Ismail et al., 2019). Thus, the expenditure can be even higher if included the cost of treating the complication of MNAD among hemodialysis patients.

2.7 The role of Necessity-Concern framework (NCF) towards medication nonadherence

Necessity-Concerns Framework (NCF) can be a tool for cost-benefit assessment. It was proposed for evaluating the patients' opinion on their prescribed medication (Horne and Weinman, 1999, Horne et al., 2013). This framework denotes the extent of belief to which the prescribed medication can improve health and concerns about the medication cost or adverse side effects (Horne et al., 2013). Drawing from this framework, the greater necessity beliefs represent stronger adherence. Meanwhile,

higher medication concerns represent lesser adherence. Study have showed that the MNAD are affected by a cost-benefit assessment. This can be explained by personal beliefs about necessity of the medication for maintaining or improving health are balanced against concerns about the potential adverse effects of taking it (Horne and Weinman, 1999).

In term of NCF, a study found that MNAD happened when respondents expressed concern about the side's effects greater than medication necessity beliefs. This study also recommended that beliefs about medicines (BMQ) questionnaire is useful for the identification of MNAD in clinical setting. Identifying the concerns aspect can create the basis of patient's medication counselling (Neame and Hammond, 2005).

A cross sectional study with subjects of hemodialysis patients found that self-report intentional nonadherence towards phosphate binder was significantly associated with beliefs that phosphate binder was not important for the ESKD (Wileman et al., 2015). The is consistent with another finding which mentioned that patient who has lower necessity beliefs and greater concerns about potential adverse effects of medication were higher tendency to be MNAD (Horne and Weinman, 1999).

2.8 Conclusion

MNAD is always a hidden problem among hemodialysis patients. The underlying cause of MNAD can be related to patient factor, therapy factor, disease factor, social and economic factor and healthcare system factor. In the perspective of medication beliefs, patient may always reluctant to express doubts about their prescribed medication. In Malaysia, there is limit data exploring the belief about

medicines perspective among hemodialysis patient. This perspective is explored in this study to enable development of psychological intervention when giving medication education in order to optimize medication adherence in ESKD patients undergoing hemodialysis.

CHAPTER 3

METHODOLOGY

3.1 Study design

Cross sectional study design was applied in this study. The data was collected from September 2019 to January 2020.

3.2 Study settings

This study was carried out on patient with ESKD under the RRT of in-centre hemodialysis treatment in Penang, Malaysia. A total of thirteen hemodialysis centres (government and NGO hemodialysis centres) were conveniently approached and eight centres gave permission for collecting data. They were government hospital (Hospital Balik Pulau, HBP) and seven non-government organization (NGO) hemodialysis centres (Buddhist Tzu Chi hemodialysis centre, Zakat Balik Pulau hemodialysis centre, Zakat Bayan Lepas hemodialysis centre, Zakat Georgetown hemodialysis centre, Amal NKF-Fo Yi hemodialysis centre unit I, NKF-Fo Yi hemodialysis centre unit II, and CAT Balik Pulau hemodialysis centre).

3.3 Study procedure

Prior to the visit to the hemodialysis centre, permission was obtained from the manager of respective centre. A pre-announcement of the study was performed by the manager before the data collection. The patients were visited one time within the study period to carry out the one-to-one interview by using a validated questionnaire. The interview was performed by the principal investigator of the present study who is the pharmacist from HBP. The interview was focus on the patient's understanding of indication, dose, frequency and time administration of their own medication. Besides,