A QUALITATIVE STUDY ON BARRIERS AND FACILITATORS AND STRATEGIES TO IMPROVE ADHERENCE TO ANTIDEPRESSANTS AMONG OUTPATIENTS WITH MAJOR DEPRESSIVE DISORDER

HO SIEW CHING

UNIVERSITI SAINS MALAYSIA

2017

A QUALITATIVE STUDY ON BARRIERS AND FACILITATORS AND STRATEGIES TO IMPROVE ADHERENCE TO ANTIDEPRESSANTS AMONG OUTPATIENTS WITH MAJOR DEPRESSIVE DISORDER

by

HO SIEW CHING

Thesis submitted in fulfilment of the requirements

for the degree of

Master of Science (Clinical Pharmacy)

January 2017

ACKNOWLEDGEMENT

First and foremost, I would like to express my heartiest appreciation and deepest gratitude to my supervisor, Dr. Balamurugan Tangiisuran for his able guidance, patience and support throughout my journey which has allowed me to realise this academic endeavour and in completing this work.

I am also extremely grateful to my co-supervisors, Dr. Sabrina Anne Jacob for her assistance and guidance during the course of this project. She has given me wonderful practical suggestions and insight along the way. My special thanks also go to my field supervisor Ms. Anusuya Krishnarajah for her help in data provision.

I'd like to express my sincere gratitude to the Ministry of Health, Malaysia for awarding me the scholarship to undertake my higher studies.

I would like to thank all my family and friends for their unconditional love and untiring support. People who deserve special mention is my spouse-Johnny Ng, who has provided constant support and encouragement at all time. He has constantly stood by me and has pulled me through against impossible odds at times. Words are inadequate to express the gratitude I owe him.

Last but not least, I would like to thank my acknowledgement to the fellow pharmacists and staff based in the Psychiatric Department, Hospital Tengku Ampuan Rahimah, Klang who have assisted me during my data collection and contributed in one way or another in the successful completion of this study.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
BDI-II	Beck Depression Inventory-II
BHT	Bed Head Ticket
BPIT	Brief Psychodynamic Interpersonal Therapy
BT	Behavioural Therapy
CBT	Cognitive Behavioural Therapy
CP	Compliance enhancing Program
CSM	Common Sense Model
DA	Disagree
DAI	Drug Attitude Inventory
DALYs	Disability Adjusted Life Years
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders IV
ED	Emergency Department
HBM	Health Belief Model
HEDIS	Health Plan employer Data and Information Set
HIV	Human Immunodeficiency Virus
HMR	Home Medication Review
HTAR	Hospital Tengku Ampuan Rahimah
ICD-10	International Classification of Diseases
IPS	Individual Placement and Support
MCO	Manage Care Organization
MDD	Major Depressive Disorder

MIDS	Mood Disorder Insight Scale
MOH	Ministry of Health
MREC	Medical Research Ethics Committee
MTAC	Medication Therapy Adherence Clinic
NGT	Nominal Group Technique
NHMS IV	National Health Morbidity Survey IV
NT	Neurotransmitter
PTSD	Post-Traumatic Stress Disorder
RCT	Randomised Controlled Trials
SDA	Strongly disagree
SMBG	Self Monitoring of Blood Glucose
SMS	Short Message Service
SPUB	Sistem Pendispensan Ubat Bersepadu
SSRIs	Selective Serotonin Reuptake Inhibitors
STD	Short Term Disability
SUMD	Scale to Assess Unawareness of Mental Disorder
TCM	Traditional and Complementary Medicine
TCA	Tricyclic Antidepressants
TEAM	Telemedicine Enhanced Antidepressant Management
TIP	Treatment Initiation and Participation
UK	United Kingdom
US	United States
USM	Universiti Sains Malaysia
WHO	World Health Organization

KAJIAN KUALITATIF TENTANG HALANGAN DAN GALAKAN DAN STRATEGI UNTUK MENINGKATKAN PEMATUHAN KEPADA ANTIDEPRESAN DALAM KALANGAN PESAKIT LUAR DENGAN KECELARUAN EPISOD KEMURUNGAN MAJOR

ABSTRAK

Kecelaruan episod kemurungan major (MDD) adalah berkaitan dengan kadar relaps dan perulangan yang tinggi. Salah satu cabaran utama dalam merawat penyakit MDD adalah pesakit tidak patuhi terhadap pengambilan ubat-ubatan. Objektif kajian adalah: (1) meneroka halangan dan galakan terhadap pematuhan kepada antidepresan dalam kalangan pesakit luar dengan penyakit MDD; (2) mengenalpasti strategi untuk meningkatkan pematuhan pengambilan antidepresan dari perspektif pelbagai pihak yang berkepentingan. Satu kajian kualitatif dengan menggunakan temubual secara individu yang mendalam dan berstruktur separa telah dijalankan dalam kajian fasa I. Tiga-puluh peserta daripada kumpulan etnik yang berlainan dipilih dan terlibat dalam kajian ini untuk mencapai variasi maksimum dalam pensampelan, dan data dikumpulkan sehingga mencapai ketepuan. Temubual telah dijalankan dengan menggunakan panduan topik yang disahkan dan direkod secara audio, disalin kata demi kata, diperiksa dan dianalisis dengan menggunakan 'grounded theory'. Dalam kajian fasa II, satu kajian Delphi yang melibatkan 20 ahli panel dari pakar-pakar perubatan, ahli farmasi, dan jururawat / pembantu perubatan dijalankan untuk mengesahkan senarai strategi untuk meningkatkan pematuhan dalam kalangan pesakit MDD. Dua pusingan soal selidik telah dilengkapkan oleh ahli panel untuk mencapai persetujuan bagi strategi yang dikenalpasti. Hasil daripada

kajian fasa I menunjukkan bahawa 40 tema dan sub-tema telah dikenalpasti dan dibahagikan kepada dua kategori utama yang berkaitan dengan halangan dan galakan kepada pematuhan antidepresan. Halangan yang dikenalpasti: halangan yang khususnya berkaitan dengan pesakit (sub-dikategorikan kepada kepercayaan yang salah, pelupaan, sikap yang negative, dan kekurangan pengetahuan), halangan yang khususnya berkaitan dengan ubat-ubatan (kesan sampingan, beban pil, tempoh rawatan, dan kos), peruntukan penjagaan kesihatan dan sistem, halangan sosial-budaya (kekurangan sokongan, halangan yang berkaitan dengan agama dan kepercayaan, dan stigma), dan halangan logistik. Galakan yang dikenalpasti: mempunyai pengertian terhadapt rawatan, manfaat kesihatan yang dilihat, aktiviti yang selalu dijalankan, hubungan pesakit dengan ahli kesihatan, peringatan, dan rangkaian sokongan sosial. Untuk kajian fasa II, 33 strategi telah disenarai dan persetujuan telah dicapai bagi 26 strategi di kaji selidik Delphi pusingan 1. Pendapat ahli panel telah diambil kira untuk mengubahsuai sesetengah strategi yang tidak mencapai persetujuan. Akhirnya, persetujuan penuh dicapai pada pusingan 2 untuk membolehkan strategi dimuktamadkan. Secara kesimpulannya, penemuan kami menunjukkan bahawa halangan yang khususnya berkaitan dengan pesakit dan kesan sampingan ubat-ubatan adalah cabaran utama untuk rawatan MDD. Manfaat kesihatan yang dilihat dan mempunyai pengertian terhadap keperluan rawatan adalah galakan yang paling kerap disebut oleh pesakit. Sejumlah 30 strategi telah dimasukkan dalam kajian akhir yang memberi pengesahan pakar mengenai strategi untuk membantu menyelesaikan dan melaksanakan intervensi yang berkesan untuk meningkatkan tidak pematuhan di kalangan pesakit MDD. Pendekatan pelbagai disiplin didapati bermanfaat untuk menangani halangan utama, dan menggalakkan langkah-langkah untuk memudahkan pematuhan dalam kumpulan pesakit ini.

A QUALITATIVE STUDY ON BARRIERS AND FACILITATORS AND STRATEGIES TO IMPROVE ADHERENCE TO ANTIDEPRESSANTS AMONG OUTPATIENTS WITH MAJOR DEPRESSIVE DISORDER

ABSTRACT

Major depressive disorder (MDD) is associated with a high rate of relapse and recurrence. One of the major challenges in treating MDD is patients' non-adherence to medication. The objectives aimed: (1) to explore the barriers and facilitators of patients' adherence to antidepressants among outpatients with MDD; (2) to identify strategies that aimed to improve adherence from the perspective of various stakeholders. A qualitative study using semi-structured and individual in-depth interviews was conducted in phase I of the study. Thirty participants were purposively sampled from different ethnicities to achieve maximum variation in sampling, and data were collected until it reached thematic saturation. Interviews were conducted using a validated topic guide and responses were audio-tape recorded, transcribed verbatim, checked, and analysed using the grounded theory approach. In phase II, a Delphi survey involving 20 panellists from physicians, pharmacists, and nurses/medical assistant; was conducted to validate a list of strategies that aimed to improve patients' adherence. Panellists completed two-rounds of self-administered questionnaires to obtain a group consensus for the strategies identified. Results from phase I showed that 40 different themes and sub-themes were identified which were conceptually divided into two distinct categories related to barriers and facilitators to adherence. The barriers were: patient-specific barriers (sub-categorised into erroneous beliefs, forgetfulness, negative attitudes, and

lack of knowledge), medication-specific barriers (side effects, pill burden, treatment duration, and costs), healthcare provision and system, social-cultural barriers (lack of support, barriers related to religion and cultural beliefs, and stigma), and logistic barriers. The facilitators were: having insight, perceived health benefits, regular activities, patient-provider relationship, reminders, and social support networks. In phase II, there were a total of 33 strategies listed and consensus was achieved for 26 strategies at Round 1 survey. The panellists' opinions were taken into consideration when modifying the strategies that did not achieve consensus. Full consensus was achieved at Round 2, enabling the finalisation of the strategies. In conclusions, our findings suggest that patients' specific barriers and medication side effects were the major challenges for the treatment of MDD. Perceived health benefits and having insight on the need of treatment were the most frequently cited facilitators. A total of 30 strategies were included in the final study that provides expert confirmation on the strategies that help to solve and be used to implement effective interventions to improve non-adherence in patients with MDD. Multi-disciplinary approach was found beneficial to address the key barriers, and promote measures to facilitate adherence in this group of patients.

CHAPTER 1

INTRODUCTION

1.1 Background of the Study

Major Depressive Disorder (MDD) is a significant mental health problem that is characterised by sense of hopelessness and persistently low or depressed mood that is accompanied by a loss of interest or pleasure in normal enjoyable activities (American Psychiatric Association, 2000). The disease's burden resulting from MDD is estimated to increase both in economically developed and under-developed countries. According to World Health Organization (WHO) health report 2001, depression is a major burden for the health care system worldwide in terms of health-related quality of life, loss of working days, and increased utilisation of healthcare services (Greenberg, Fournier, Sisitsky, Pike, & Kessler, 2015; Greenberg et al., 2003; World Health Organization, 2001). MDD is found to be the most prevalent burden that it was rated as the fourth leading disabling condition and is expected to be second to ischemic heart disease by the year 2020 (Murray & Lopez, 1997; Ustun, Ayuso-Mateos, Chatterji, Mathers, & Murray, 2004). In addition, MDD is expected to be the highest disorder in developed countries by the year 2030 (World Health Organization, 2001).

Across the Asia Pacific region, the top five mental health problems are depression, anxiety disorder, Post-Traumatic Stress Disorder (PTSD), suicidal behaviour, and substance abuse disorder (OECD, 2012). Of these, depression is the top mental health problems contributing to 15.2 to 21.1 Disability Adjusted Life Years (DALYs)

per year (Samy, Khalaf, & Low, 2015). A survey conducted across the Asia Pacific region found that 5% of the population has MDD and up to 15% has suffered from depression symptoms. Of this, rates of MDD are comparable to that of the Western countries (Chiu, 2004). In Malaysia, depression is the most common mental illness reported (Mukhtar & Oei, 2011). The National Health Morbidity Survey IV (NHMS IV) in 2011 has showed that the prevalence of lifetime depression is 2.4% and the current depression rate among adults is 1.8%, which is approximately 0.3 million adults in Malaysia (Institute for Public Health, 2011).

Patients with MDD often suffer from residual symptoms, which interfere with their functioning (Keller, Hirschfeld, Demyttenaere, & Baldwin, 2002). Furthermore, MDD constitutes a high economic and societal burden resulting from its high prevalence, under-diagnosed, and under-treatment (White, Vanderplas, Ory, Dezii, & Chang, 2003; Wu et al., 2012).

One of the major challenges in treating depression is patients' non-adherence to medication, which has been reported to vary from 10-60% of patients by missing their doses or by prematurely discontinuing their medication altogether (Bull et al., 2002; Demyttenaere & Haddad, 2000; Keller et al., 2002; Lingam & Scott, 2002). This subsequently results in failure in treating patients with MDD. In addition, non-adherence to antidepressants has been shown to result in significantly poorer clinical outcomes such as increased risk of relapse and recurrence, increased emergency department visits, and hospitalisations rates (K. H. Kim, Lee, Paik, & Kim, 2011; Liu, Tepper, & Able, 2011; Yau et al., 2014). This has subsequently translated to an increased in healthcare utilisation and charges in this subset of patients (Iuga &

McGuire, 2014). However, non-adherence remains a major problem in patient care, despite of the large number of studies conducted in this area over a decade (Al-Qasem, Smith, & Clifford, 2011).

Little is known about the attitudes and beliefs of MDD patients towards their antidepressants. The definitions of adherence by WHO appear to take a clinical perspective on patients' behaviour towards their treatment instead of patients' perceptions or experiences (World Health Organization, 2003). Patients may choose not to adhere to treatment because of their experiences that it is inappropriate or inaccessible. Thus, it would be desirable to explore further to obtain more information from patients on barriers and facilitators on adherence to their therapeutic regime as prescribed by the doctors.

1.2 Statement of the Problem

MDD is a disorder that can be reliably diagnosed and treated in the primary care setting (Marcus, Yasamy, van Ommeren, Chisholm, & Saxena, 2012). As outlined in the Malaysia Clinical Practice Guideline of MDD (Ministry of Health Malaysia, Malaysian Psychiatric Association, & Academy of Medicine of Malaysia, May 2007), antidepressants are found to effectively reducing depressive symptoms and that Selective Seratonin Reuptake Inhibitors (SSRIs) are drugs of first choice due to its better tolerability. Other newer antidepressants such as mirtazapine, venlafaxine, escitalopram have also been found to be efficacious. Generally, follow up should be done within 2 weeks of initial treatment for dose titration according to patients' depressive symptoms. If patient does not show any response after 4 weeks of antidepressants treatment at adequate dosage, switching of antidepressants may be

considered. Antidepressants should be continued for at least 6-9 months after remission of the depressive episode to reduce the risk of relapse. Besides pharmacological treatment, MDD can also be managed by using psychological interventions such as supportive therapy, problem-solving therapy, counselling or cognitive behavioural therapy (CBT). Of these, CBT is considering as the intervention of choice for patients with moderate or severe MDD. However, combination of both pharmacological and psychological therapy was recommended when patients present with severe MDD (Ministry of Health Malaysia et al., May 2007).

MDD is a pernicious illness associated with a high rate of relapse and recurrence, which occurs in almost 85% of depressed patients (Murata, Kanbayashi, Shimizu, & Miura, 2012). The National Institute of Mental Health Consensus Development Conference on relapse and recurrence of depression reported that 50 to 85% of depressed patients will suffer an episode of recurrence during their lifetime, of these, 50% will experience recurrence within 2 years of the initial episode (Melfi et al., 1998). Recurrence of depression, in turn, increases the likelihood that future episodes will be more frequently and more severe in term of depressive symptoms and increase in hospitalization rates; resulting in multiple medications having to be used or lifelong maintenance therapy needed (Kessing, Hansen, & Andersen, 2004; Murata et al., 2012). In addition, recurrence of depression can have significant personal and public health consequences. For example, a study over 3000 MDD patients found that 90% of those with recurrent depression reported very much impairment, limiting work productivity and social interaction, and 40% sought professional help as a result of recurrence (Wittchen, Nelson, & Lachner, 1998).

Despite the proven efficacy of antidepressants, many depressed patients still do not receive an adequate dosage and duration of treatment, which has been frequently seen in both primary care and specialised settings (Al-Jumah & Qureshi, 2012). In addition, the reported levels of non-adherence have been consistently high; which remains a serious concern. Hence, there is clearly a need for a better understanding on why non-adherence occurs in patients with MDD in the country for effective interventions to facilitate adherence (Clatworthy, Bowskill, Rank, Parham, & Horne, 2007; Delamater, 2006).

A substantial literature has documented that there are several factors of being the cause of non-adherence such as patients' social and demographic factors, education levels, poor patient-clinician interaction, negative attitudes, and culture–influenced beliefs (Aikens, Nease, & Klinkman, 2008; Aikens, Nease, Nau, Klinkman, & Schwenk, 2005; Chakraborty, Avasthi, Kumar, & Grover, 2009; A. Gabriel & C. Violato, 2010; Holma, Holma, Melartin, & Isometsä, 2010; Jin, Sklar, Oh, & Shu, 2008; Anthony F. Jorm, Christensen, & Griffiths, 2005; K.-U. Lee et al., 2010). Of all these factors, patients' attitudes and personal beliefs on MDD and its treatment are thought to differ significantly between different cultures.

In contrary to the Western population, Malaysia consists of a multiracial society with a diversity of cultural beliefs that exists among the three main ethnic groups, namely the Malays, Chinese and Indians (Razali, Khan, & Hasanah, 1996). A study conducted at Sabah (East Malaysia) found that the Malays population tend to believe that mental illness behaviour is sinful and should be punished and it is usually caused by social stresses, that it could be treated by changing societal responsibilities

(Swami, Loo, & Furnham, 2010). However, the study finding might not be generalised to the Malays population living in Peninsular Malaysia, which has larger populations of Malays with more developed socio-economic status. Other studies showed that the Malays found mental illness is an illness of the soul that caused by spiritual and religious factors or as a social punishment (Haque, 2005; Parameshvara Deva, 2004). Among the Chinese, mental illnesses are stigmatised and are often attributed to 'bad genes' and the concept of 'losing face', if the patients receive treatment at psychiatric clinics. Thus, it is usually dealt with by folk healers such as the Chinese Mediums (Ariff & Beng, 2006). Among the Indians, most patients hold the belief that mental illnesses are the effects of ill spirits and this erroneous belief has directly influenced the medication adherence behaviour in Indian patients (Chakraborty et al., 2009). All these evidences have shown that perceptions towards the disease vary in different cultures. Therefore, cultural backgrounds should be taken into consideration when providing treatment to MDD patients. For this reason, it is especially important to carry out studies to explore patients' adherence behaviours in our country where cultural health beliefs within that patient or treatment group might be a one of the contributing factor of patients' non-adherence to medication.

There have been studies exploring patients' experiences in relation to other health problems such as hypertension and antiretroviral drug therapy, but there are limited studies in neurotic disorder such as depression (Ogedegbe, Harrison, Robbins, Mancuso, & Allegrante, 2003; Wasti, Simkhada, Randall, Freeman, & van Teijlingen, 2012). More recently, there is a similar study conducted in Malaysia, but the study is aimed to explore the self-monitoring of blood glucose (SMBG) in patients with type

2 diabetes using insulin instead of study in psychiatric illnesses (Ong, Chua, & Ng, 2014). Hence, the present study is needed to explore the barriers and facilitators of patients' adherence to medication in mental illness.

There are several studies conducted in Malaysia that have been quantitative in nature (Jacob, Ab Rahman, & Hassali, 2015; Tahir M. Khan, Sulaiman, & Hassali, 2010; T. M. Khan, Sulaiman, Hassali, & Tahir, 2009; Tahir Mehmood Khan, Sulaiman, & Hassali, 2009). However, using a structured set of close-ended interview instruments has not allowed the patients to fully express themselves and to give responses outside the options given on the questionnaires. The patients are unable to express in their own words, of their experiences of treatment, and more qualitative study in this area has been called for (Ariff & Beng, 2006; Razali et al., 1996).

Grounded theory is defined as the discovery of a theory from data systematically obtained in the view of participants (Strauss & Corbin, 1998). It is a qualitative research design in which the researcher generates a general explanation (a theory) of a process, an action, or an interaction shaped by the views of the participants (Creswell & Creswell, 2013). In an exploratory study, only by using qualitative grounded theory that allowed researchers to understand the underlying reasons and to uncover prevalent trends in thought as well as opinions of patients from their 'native' point of view through their experiences (Al-Busaidi, 2008; Christine Brown & Lloyd, 2001; Sbaraini, Carter, Evans, & Blinkhorn, 2011; Whitley & Crawford, 2005). This is particularly important in Malaysia, as there is a need for further qualitative research to account for the culture, religion, and socioeconomic factors that influence peoples' decision in health-seeking behaviours (Tahir Mehmood Khan et al., 2009;

Swami et al., 2010). Therefore, we choose to conduct a qualitative study using the grounded theory method to explore the patients' experiences and their adherence behaviours on antidepressants in Malaysian population.

Qualitative studies that have been conducted thus far have either focused on general public or healthcare providers, as opposed to the people who are actually affected by the disease (W. W. Chong, Aslani, & Chen, 2013; Hanafiah & Van Bortel, 2015; Jang, Chiriboga, & Okazaki, 2009; Tahir M. Khan et al., 2010; T. M. Khan et al., 2009; Tahir Mehmood Khan et al., 2009; Yeap & Low, 2009). The results of these studies, however, would not be generalisable to the majority of the patients' population in MDD. In addition, a number of qualitative studies conducted are on focus group instead of individual interviews (Interian, Martinez, Guarnaccia, Vega, & Escobar, 2007; Uebelacker et al., 2012). This approach has a setback, as some patients may not be comfortable to share their experiences openly in the presence of other patients. Moreover, as many of the previously-published studies were conducted in the West that specially focused on the Latino community, the findings obtained might not be applicable to the Asian population (Interian et al., 2007; Uebelacker et al., 2012; Yeap & Low, 2009). Hence, it is crucial for a local study to be conducted.

Till date, there are relatively few studies conducted in Malaysia that neither concentrate on the patients' experience on the use of their antidepressants nor to explore the underlying reason for medication adherence behaviour. Therefore, this study aims to explore the barriers and facilitators of adherence to antidepressants in MDD patients. Understanding the attitudes and reasons underlying their behaviours

can provide valuable insights into the rationale for identifying adherence problems in patients with MDD. Apart from that, results obtained from the study will be of significance for any future attempts to develop strategies or interventions that can help to solve the identified adherence problems and to design a better adherence program that is going to cater for our Malaysian setting and culture.

1.3 Objectives of the Study

1.3.1 The General Objective:

The general aim of this study is to explore the barriers and facilitators of patients' adherence to antidepressants and to identify strategies that aimed to improve adherence among outpatients with MDD.

1.3.2 The Specific Objectives:

a) To explore the barriers to adherence with antidepressants among outpatients with MDD.
b) To explore the facilitators to adherence with antidepressants among outpatients with MDD.
c) To identify strategies that aimed to improve adherence from the perspective of various stakeholders.

1.4 Conceptual Framework of the Study

Many conceptual models have been used to help understanding the barriers to medication adherence, including the health belief model (G. R. Kelly, Mamon, & Scott, 1987) and Necessity-Concerns framework (Cameron & Leventhal, 2003). The health belief model (HBM) has been used to study the relationships between

patients' health belief behaviour and medication adherence. The core component of this model includes perceived susceptibility, perceived severity, barriers, benefits, and a 'cue to action' which affect patients' adherence to their medication (G. R. Kelly et al., 1987). In HBM, patients who are aware of and perceived the severity of their illness are more prone to adhere to their medication. In addition, patients who perceived the effectiveness and are satisfied with their current therapy would promote medication adherence. In contrary, the experience of adverse effects acts as a barrier to adherence (DiMatteo, Haskard, & Williams, 2007).

The Necessity-Concerns framework is conceptualised as the patients' perceptions of the necessity and need of treatment to maintain their health condition, and their concerns about the actual and potential adverse effects of treatment (Cameron & Leventhal, 2003; Rob Horne et al., 2013; Robert Horne & Weinman, 1999). The utility of this framework has been identified in study conducted by Aikens et al. (2005), which explained the adherence to maintenance-phase antidepressants as a function of patient beliefs about medication.

While perceptions are acknowledged to be a major factor in patients who were non-adherent to medication, however, none of these models dominates the other or fully explains the barriers and facilitators to medication adherence in MDD patients. Thus, a qualitative study using grounded theory approach is conducted to explore the barriers and facilitators of adherence to antidepressants in patients with MDD. Based on the identified barriers and also from the literature review, a list of strategies to improve antidepressants' adherence will be listed using the Delphi technique to overcome the barriers of adherence in MDD.

1.5 Significance

In brief, the results and findings from this study could be used in the following manner:

Table 1.1
Potential Application and Impact of the Study

Government (MOH, Malaysia)	To review and alter healthcare practices which might affect patients' adherence behaviour
	To develop mental health programs that facilitate antidepressants medication adherence by taking into account the different cultural, religion and socioeconomic barriers
Mental health care provider (psychiatrists, medical officer at psychiatric department, psychologists, counsellors)	To modify interventions that facilitate adherence
	To focus more on the facilitators of adherence that are identified from the study and apply in the practice when treating MDD patients
Pharmacists (MTAC or clinical pharmacist at psychiatric department)	To develop specific counselling protocols that are patient-centered by taking into account the different beliefs and attitudes that affect the health-seeking behaviour of MDD patients
	The identified adherence problem can be used as a guide to deal with depressed patients to ensure patients' adherence
Patients (who taking antidepressants medication)	To obtain utmost benefit from the strategies or interventions that are implemented by the government, mental health care provider and the pharmacist, based on the result obtained from the study

1.6 Chapter Outline

A brief outline of the chapter for this thesis is as follows:

Chapter 2 – This chapter reviews the existing literature relating to the study objectives. This chapter is organised into four sections: Firstly, the literature on factors associated with antidepressants non-adherence among patients with MDD is presented in which it is sub-organised into patient-specific factors, medication-specific factors, socio-cultural related factors, healthcare provision and system related factors, and disease related factors. Secondly, literature on impacts of non-adherence to antidepressants among patients with MDD is presented, which focuses on clinical, economic, and humanistic impacts. Thirdly, strategies/intervention to improve adherence to antidepressants among patients with MDD is reviewed. Lastly, the overviews of consensus methods are presented relating to the objectives for the phase II of the study.

Chapter 3 – This chapter presents and justifies the methodology used in the study. This chapter is divided into two parts: (1) Phase I: Exploring the barriers and facilitators of patients' adherence to antidepressants among outpatient with MDD; (2) Phase II: Identifying list of strategies that aimed to improve patients' adherence to antidepressants among outpatient with MDD. Each phase begins with the study design and a description of the setting in which the study took place. It is followed by discussion on the study population which has included the sample size and sampling method used. Finally, the study procedure is presented in the form that includes the manner in which the data was collected and a short discussion on the data analyses.

Chapter 4 – The results for phase I and phase II of the study are presented in this chapter. In phase I, the socio-demographic characteristics of patients are presented. The themes for barriers and facilitators are organised into two distinct categories. For the barriers to antidepressants adherence, they are sub-categorised into five categories: (1) patient-specific barriers, (2) medication-specific barriers, (3) healthcare provision and system, (4) socio-cultural barriers, and (5) logistic barriers. For facilitators to antidepressants adherence, they are sub-categorised into six categories: (1) illness-related factors, (2) perceived health benefits, (3) regular activities, (4) Patient-provider relationship, (5) reminders, and (6) social support networks. In phase II, the Delphi results will be presented in two sections: (1) Round 1, and (2) Round 2; at which demographic characteristics of panellists and consensus agreement of the strategies are included in each of the section.

Chapter 5 – The discussion for phase I and phase II of the study is presented in this chapter. In phase I, the findings for barriers and facilitators of adherence to antidepressants are discussed in comparing with various studies in the field. It is followed by discussion on the strategies that achieved consensus of disagreement and agreement in phase II of the study.

Chapter 6 – This final chapter presents a summary of the study. It is followed by the discussion on strengths and limitations of the study. The implications of the findings in the context of current Malaysia mental health policy and recommendation for future research are also presented in this chapter.

CHAPTER 2

LITERATURE REVIEW

This chapter reviews some of the literature relating to the various factors associated with non-adherence to antidepressants in patients with MDD in an outpatient setting. The impacts of non-adherence to antidepressants are also discussed in this chapter. By having knowledge on the dire consequences of patients' non-adherence, it is of utmost importance to understand the barriers of treatment non-adherence in patients with depression. Furthermore, knowing the reasons of non-adherence to antidepressants in patients with MDD would provide directions for designing effective intervention program that aims to tackle the non-adherence problems. Therefore, the strategies or interventions that aim to tackle the issue of patients' non-adherence in the treatment of MDD have also been reviewed. Lastly, the overviews of consensus methods are reviewed to support the importance of Delphi method used in answering the research question for phase II of the current study.

2.1 Factors Associated with Antidepressants Non-adherence among Patients with MDD

Non-adherence to antidepressants is perceived to be a complex problem in patients with MDD, due to multiple contributing factors. It is crucial to understand the reasons why MDD patients may or may not take their medication. Thus, several studies have been conducted to assess which specific factors influence adherence to antidepressants amongst patients with MDD. According to the American College of Preventive Medicine (2011) and WHO (2003), the factors associated with non-

adherence in patients with depression are classified into five domains: patient-specific factors, medication-specific factors, socio-cultural related factors, healthcare provision and system related factors, and disease related factors.

2.1.1 Patient-specific Factors

Patients with MDD tend to believe that regular usage of antidepressants could result in long-term adverse effects, so antidepressants are needed only when their depressive symptoms get worse, and that antidepressants are addictive and may cause dependence. This misconception tends to negatively affect patients' acceptance of their treatment (Chakraborty et al., 2009; Jacob et al., 2015; Tamburrino, Nagel, Chahal, & Lynch, 2009).

Jacob et al. (2015) conducted a 6-month study to determine the attitudes and beliefs of 104 patients with depression toward their illness and its treatment in an out-patient setting of a government-run hospital in Malaysia. Of the 104 patients, 40% of the participants believe that antidepressants are addictive and 59% believe that it would be difficult to discontinue the treatment if they are taking their antidepressants for a long term. This is mainly due to the misconception with regard to treatment of MDD, as most patients tend to confuse antidepressants with tranquilizers. Tranquilizers also known as 'sleeping pills', which have the same drowsy effect like antidepressants, but tranquilizers have the potential for addiction (Angermeyer & Matschinger, 1996). In addition, certain antidepressants, such as Mirtazepine, are needed to be tapered off slowly over several days to weeks instead of to be stopped abruptly. Therefore, many patients tend to misunderstand that it is difficult to discontinue the treatment if they have taken it for a long period of time.

In India, Chakraborty et al. (2009) conducted a study on 50 patients with depression and who were taking antidepressants to assess their attitudes and beliefs on treatment adherence. In the study, antidepressants compliance questionnaire (consisted of four components) was used as a scale together with a treatment adherence questionnaire to measure patients' attitudes and beliefs towards antidepressants and treatment adherence. The results have shown that 88% of patients believed that antidepressants can alter their personality, whereas 72% of patients felt that fewer tablets could be taken on days when they felt their depressive symptom has improved (Chakraborty et al., 2009). It is very common that when patients are asymptomatic, they waiver in their adherence to treatment and vice versa; which has also been proven by the study conducted by Tamburrino et al. (2009). Hence, patients' attitudes and beliefs play an important role in determining the adherence pattern in MDD. Further exploration in this area should be acknowledged as an important issue in the treatment of MDD.

A cross-sectional study that was conducted among 239 patients at the psychiatric out-patient department of a tertiary hospital in Kolkata, India showed that simply forgetting to take the prescribed medication is the most common reported factor of non-adherence to antidepressants; which has been mentioned by more than half of the patients (56.5%) in the study (Banerjee & Varma, 2013). This scenario is the same throughout the world where there are studies conducted in the non-Asian countries which reported that forgetfulness has been acknowledged as the factor that makes it difficult for patients adhering to antidepressants, which was seen in 75% of patients in a study conducted in Canada, 43% in a study conducted in United States (US), and 35% of the patients in a study conducted in Spain (Ashton, Jamerson, W,

& Wagoner, 2005; Bulloch & Patten, 2010; M. J. Martin et al., 2009; Tamburrino et al., 2009).

2.1.2 Medication-specific Factors

There are substantial researches that demonstrated medication side effects are the predominant factor associated with antidepressants non-adherence in patients with MDD (Alekhya, Sriharsha, Priya Darsini, Reddy, & Venkata Ramudu, 2015; C. Anderson & Roy, 2013; Ashton et al., 2005; W. W. Chong et al., 2013; De las Cuevas, Penate, & Sanz, 2014; Feetam, 2009a; van Servellen, Heise, & Ellis, 2011), which are discussed as follows.

Alekhya et al. (2015) conducted a cross-sectional study among 103 patients aimed to determine the factors that influenced patients' adherence to the treatment of depression. Drug attitude inventory (DAI) scores were used as adherence rating scales to measure patients' adherence in the study (Hogan, Awad, & Eastwood, 1983). The results have revealed that the overall non-adherence rate is high (70%) and that medication side effects significantly influence the mean DAI ($p=0.007$, t-test) where more patients become non-adherent due to this reason.

De las Cuevas et al. (2014) conducted a study among 145 patients to identify the determinants of non-adherence in patients with mood disorders and who were taking antidepressants. It was found that all patients in the study experienced drug-induced side effects (e.g.: drowsiness, dry mouth, insomnia, constipation, and weight gain) which were clearly related to the pharmacological action of antidepressants (Ministry of Health Malaysia et al., May 2007). However, patients who were non-adherent

claimed that they experienced more frequent and more intense adverse effects as compared to patients who were adherent, which subsequently contributed to premature discontinuation of antidepressants therapy in this group of patients.

In Australia, Chong et al. (2013) conducted a qualitative study to explore healthcare providers' views and perspectives on issues of antidepressants non-adherence in clinical practice. It was found that majority of the participants acknowledged antidepressants adverse reaction, such as sexual dysfunction, sleep disturbance, and weight gain, was the main contributor for non-adherence to treatment. Although the data collected was only based on participants' self-reports and was not verified against their actual clinical behaviours or in real patients, the findings are somehow useful in designing future intervention programs to improve adherence in patients with MDD.

Similarly, a survey was conducted with 350 patients with depression in New York, US where 42-specific questions were asked to assess reasons for non-adherence to antidepressants treatment (Ashton et al., 2005). The result obtained has shown that adverse effects, such as lost of sexual desire (23%), tiredness (18%), and weight gain (16%), were accounted for the second most common factor associated with patients' non-adherence to their antidepressants. The patients also mentioned that the adverse effects that they experienced were intolerable, as it did not resolve with time and had significantly compromised their quality of life. Hence, they decided to discontinue their antidepressants prematurely due to this reason.

Anderson and Roy (2013) performed a secondary qualitative analysis on 80 interviews from Healthtalkonline to further explored patients' experiences of using antidepressants for depression. It was found that patients who were non-adherent to antidepressants were most likely driven by the experience of adverse effects such as sexual dysfunction, dry mouth, dizziness, weight gain, sleep disturbance and inability to concentrate to routine work.

A systematic literature review study on factors associated with antidepressants non-adherence also showed that one in four patients discontinued their antidepressants medication due to specific side effects that were examined in a descriptive study (van Servellen et al., 2011). Similarly, a review on medicine taking behaviour in depression reported side effects such as sexual dysfunction (40%), weight gain (27%) and daytime drowsiness (21%) were the most common reasons for antidepressants non-adherence in a patient survey (Feetam, 2009a).

In conclusion, antidepressants side effects such as weight gain, sexual dysfunction, and drowsiness are the most common medication-specific factor that contributed to patients' non-adherent to their treatment; which was reported in almost all of the study discussed in this section. In fact, healthcare provider should inform and counsel patients on the expected side effects of antidepressants prior to starting treatment, as having information about side effects supports patients' confidence in treatment and subsequently prevent early discontinuation of treatment in MDD (C. Anderson & Roy, 2013). Collaborative care from both physician and pharmacist to perform pharmaceutical care and individualizing antidepressants therapy according to patients' needs by prescribing the lowest effective dose which might have lower

risk of adverse effects, which in turn, enhance patients' adherence to treatment of MDD is needed (K. Kelly, Posternak, & Jonathan, 2008).

2.1.3 Socio-cultural Related Factors

Stigma associated with both having depression and taking antidepressants was found by most of the studies as one of the significant factors that affects patients' acceptance of their diagnosis and subsequently resulted in non-adherence to treatment (W. W. Chong et al., 2013; Interian et al., 2007; Jang et al., 2009; Uebelacker et al., 2012). Stigma has been prominently seen as a barrier to treatment of depression in the Latino community as compared to non-Hispanic whites in the US. A qualitative analyses of six focus groups interviews on Latino outpatients receiving antidepressants (N=30) showed that Latinos have greater stigma concerns than whites that they tend to discontinue their antidepressants, before seeking employment, as they are afraid of being negatively evaluated, as a result of antidepressants treatment (Interian et al., 2007). Similarly, stigma from the community was found to be the first theme cited as a barrier to treatment in depressed Latinos in study conducted by Uebelacker et al. (2012). Apart from that, stigma was also observed in other populations such as in Australian and Korean American adults (W. W. Chong et al., 2013; Jang et al., 2009).

The lack of support networks particularly the family members was also noted as one of the contributing factors for antidepressants non-adherence in patients with MDD (Banerjee & Varma, 2013; Interian et al., 2007; van Grieken et al., 2014). This is supported by a study conducted in Latino outpatients in the US where patients mentioned that taking antidepressants seemed to be disapproved by their family and

social support system, which directly influenced them on whether to continue their antidepressants (Interian et al., 2007). In addition, the lack of social support such as reminders to take medications and nobody there to accompany patients to the hospital for clinic visits were among the reasons for antidepressants discontinuation (Banerjee & Varma, 2013). An in-depth interviews conducted by van Grieken et al. (2014) found that most participants revealed that insufficient support and information from their treating physicians would hinder them to adhere to their treatment.

Similarly, stigmatising attitudes and discriminatory behaviours towards people with mental illness have been shown to hinder patients from seeking helps or treatment for their illness in Asian population, which particularly seen in Malaysian society (Hanafiah & Van Bortel, 2015; T. M. Khan, Hassali, Tahir, & Khan, 2011; Minas, Zamzam, Midin, & Cohen, 2011; Yeap & Low, 2009). For example, a cross-sectional study conducted by Khan et al. (2011) to evaluate the public perception towards the causes of mental illness has revealed that regardless of ethnicity, Malaysian believe in supernatural reasons ,such as possession by spirits, are regarded as the cause of mental illness ($p=0.05$). The respondents also mentioned that people with mental illness are unfriendly, moody, dangerous, and unpredictable, hence, people are fearful of those who are perceived as mentally ill patients.

Till to date, most of the studies that reported on stigma as the barrier to medication adherence are associated with mental problems such as schizophrenia and there is little evidence found that specifically focuses on depression (Hudson et al., 2004; Sajatovic & Jenkins, 2007). If any, majority of the studies focused on the Latino population (Interian et al., 2007; Uebelacker et al., 2012); which may limit its

generalisability to Asian multi-racial population. This highlights the need for more studies to be conducted in the Asian population.

2.1.4 Healthcare Provision and System Related Factors

There has been a broad acceptance that the nature of the patient-provider relationship has an important impact upon the outcomes of treatment and it served as a predictor of treatment adherence in patients with MDD (C. Anderson & Roy, 2013; W. W. Chong et al., 2013; van Grieken et al., 2014). Van Grieken et al. (2014) conducted an in-depth interviews in a purposive sample with 27 patients with MDD and found that the lack of trust in the treating physician, and insufficient information about treatment and support from the physician were cited by majority of the patients and that resulted in a hesitation to begin treatment and to continue with it. Correspondingly, a secondary qualitative analysis of patients' experiences of using antidepressants for depression was carried out and the results showed that patients who discontinued their antidepressants were likely to have unsatisfactory rapport with their treating physician (C. Anderson & Roy, 2013). Furthermore, poor patient-provider relationship was also described by a few participants as the factor for antidepressants non-adherence in study conducted by Chong et al. (2013). Thus, the patient-doctor partnership has been shown to be essential for patients to adhere to their treatment in MDD.

Apart from patient-physician partnership, the lack of accessibility and availability of healthcare facility and system may also cause difficulties in adherence to treatment. In India, Banerjee and Varma (2013) developed a semi-structured interview schedule to further explore the factors hindering adherence in 193 patients who reported

having difficulty in adhering with the prescribed antidepressants from a cross-sectional study. The authors found that health-facility related factors such as long distance from home to hospital (47.7%) and long waiting time in the hospital (31.6%) were the reasons for therapy discontinuation.

Despite of a comprehensive search on the literature, it is found that there is limited study that focused on healthcare system and facilities related factor associated with treatment adherence in depression. There was a review study conducted to explore and evaluate factors affecting therapeutic compliance which reported that lack of accessibility to healthcare, long waiting time for clinic visits, and difficulty in getting a refill have all contributed to patients' non-adherence to treatment; but that study was not specifically conducted on patients with depression who were taking antidepressants (Jin et al., 2008). Hence, there is a need for more studies to be conducted that focus in this area for patients with MDD.

2.1.5 Disease Related Factors

Indeed, depression itself has been shown to be a contributing factor for non-adherence (DiMatteo, Lepper, & Croghan, 2000). This is because patients with depression often have impaired cognitive focus, energy and motivation that might be expected to affect their willingness and ability to follow through the treatment (Bull et al., 2002; W. W. Chong et al., 2013; M. J. Martin et al., 2009). This is further supported by a meta-analysis of 12 published studies, which concluded that depressed patients were three times more likely to be non-adherence to treatment as compared to non-depressed patients (DiMatteo et al., 2000). Similarly, a qualitative analyses of four focus groups of patients (N=30) found that sense of isolation as

being nature of depression itself; which may have contributed to patients' refusal to adhere to their antidepressants (Uebelacker et al., 2012).

A study conducted by De las Cuevas et al. (2014) found that severity of depression was related to patients' poor adherence. Beck Depression Inventory-II (BDI-II) was used to measure the severity of patients' depression in the study. The study findings showed that patients who were adherence were those who had less severe depression (BDI-II score: 18, mild) than that of patients who were non-adherence (BDI-II score: 22, moderate). Apart from that, patients with co-morbid diseases especially diabetes and hypertension often suffer from some form of depression due to their disease state (Grenard et al., 2011; Habtewold, Alemu, & Haile, 2016; Katon, 2008). It was found that the presence of depression lead to treatment non-adherence to patients' co-morbid diseases. For example, presences of depressive symptoms are associated with poor blood pressure control and complications of hypertension due to poor antihypertensive medication adherence (Krousel-Wood & Frohlich, 2010). On the other hand, patients with diabetes who are depression are less likely to adhere to diabetes sell-care regimens than non-depressed patients, which result in increase of disease burden (Markowitz, Gonzalez, Wilkinson, & Safren, 2011).

In conclusion, all of the studies found that patient-specific factors (antidepressants are addictive, forgetfulness, and patients' attitudes and beliefs), medication-specific factors (adverse effects of antidepressants), socio-cultural related factors (stigma, and lack of support network), healthcare provision and system related factors (poor patient-provider relationship, long distance from home to hospital, and long waiting time at the clinic), and disease related factors (depression severity and disease co-