ASSESSMENT OF KNOWLEDGE, ATTITUDES, PERCEPTION AND BARRIERS TOWARDS PHARMACOVIGILANCE ACTIVITIES AMONG COMMUNITY PHARMACISTS AND FINAL YEAR PHARMACY STUDENTS IN MALAYSIA

By

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DEDICATION

I would like to dedicate this humble dissertation with lots of love and respect to my father Mohamed Elkalmi and my mother Fatima Alamani and to my wife Najat and my children Yazeed, Arwa and Yazan

without their support, love and care, I would not have realized my dreams in life.

To the loving memory of my late brother “Almarhoum” Mohamed Massoud Elkalmi (ALBAHLOL) for his love of science.

May Allah forgive him and bring him rest in eternal peace.

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In the Name of Allah, the Most Gracious, the Most Merciful

All praise is due to Allah alone, I praise him, seek his aid and seek his forgiveness. I testify that there is no God but Allah, and that Mohammed (peace be upon him) is his slave and messenger. I thank Allah Almighty for giving me the inspiration, patience, time, and strength to finish this work. With Allah's will and mercy I have been able to achieve all of this

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reactions
ADE	Adverse Drug Events
BNF	British National Formulary
CPD	Continuous Pharmaceutical Development
CPs	Community Pharmacists
DCA	Drug Control Authority
DSAP	Discipline of Social and Administrative Pharmacy
ISoP	International Society of Pharmacovigilance
MADRAC	Malaysian Adverse Drug Reactions Advisory Committee
MIMS	Monthly Index of Medical Specialties
MPS	Malaysian Pharmaceutical Society
OTC	Over The Counter
PV	Pharmacovigilance
PVS	Pharmacovigilance System
SRS	Spontaneous Reporting System
UK	United Kingdom
UMC	Uppsala Monitoring Center
UMMC	University of Malaya Medical Center
US	United States
WHO	World Health Organization

LIST OF APPENDICES

PENILAIAN PENGETAHUAN, SIKAP, PERSEPSI DAN HALANGAN TERHADAP LAPORAN KESAN MUDARAT UBAT (ADR) DALAM KALANGAN AHLI FARMASI KOMUNITI DAN PELAJAR TAHUN AKHIR FARMASI DI MALAYSIA

ABSTRAK

Tindak Balas Ubat Berbahaya (Adverse Drug Reactions, ADR) sering kali dikaitkan dengan kadar morbiditi dan mortaliti yang tinggi di serantau dunia. Dalam usaha menangani masalah ini, banyak negara menubuhkan sistem farmakovigilans kebangsaan di negara masing-masing. Kebanyakan sistem farmakovigilans yang ada kini bergantung sepenuhnya pada Sistem Laporan Spontan (Spontaneous Reporting System, SRS) ADR yang dikemukakan oleh profesional penjagaan kesihatan seperti doktor dan ahli farmasi.

Dalam konteks ini, Malaysia menubuhkan sistem farmakovigilansnya pada tahun 1987. Jawatankuasa Penasihat Tindak Balas Ubat Berbahaya Malaysia (Malaysian Adverse Drug Reaction Advisory Committee, MADRAC) ditubuhkan di bawah naungan Pihak Berkuasa Kawalan Ubat (Drug Control Authority, DCA) Malaysia untuk mendokumenkan laporan SRS yang diperoleh daripada profesional penjagaan kesihatan. Berdasarkan kebanyakan sistem laporan ADR secara spontan di seantero dunia, laporan ADR di Malaysia juga turut terkesan, terutamanya dalam kalangan farmasi komuniti.

Data yang dikeluarkan oleh MADRAC menunjukkan bahawa kadar laporan yang dikemukakan oleh farmasi komuniti adalah rendah jika dibandingkan dengan negera lain. Tambahan pula, tiada kajian komprehensif dijalankan di Malaysia untuk mengetahui alasan di sebalik permasalahan ini.

Tesis ini bermatlamat untuk mengetahui pengetahuan, sikap dan persepsi / tanggapan yang ada pada farmasi komuniti berhubung dengan laporan ADR. Di samping itu, tesis ini juga memberi tumpuan terhadap halangan penglibatan yang mereka hadapi dalam aktiviti farmakovigilans dan pelaporan ADR. Dalam usaha mencapai objektif penyelidikan, suatu metodologi gabungan yang menggunakan pendekatan kualitatif dan kuantitatif diaplikasikan.

Untuk memahami alasan di sebalik permasalahan ini, sejumlah 16 farmasi komuniti telah ditemu bual. Hampir kesemua mereka tidak begitu biasa dengan sistem farmakovigilans yang sedia ada serta mengatakan tidak tahu-menahu tentang utilitinya. Walaupun kesemua yang ditemu bual tidak mengemukakan sebarang laporan ADR, namun mereka menunjukkan sikap yang positif terhadap laporan ADR.

Halangan tidak mengemukakan laporan ADR yang utama adalah kerana mereka tidak biasa dengan sistem ADR, tiada borang laporan ADR, tidak tahu cara untuk membuat laporan, ragu-ragu atau tidak yakin tentang kepentingan tindak balas serta tiada masa. Selain menerima maklum balas daripada pihak berkuasa berkenaan, para peserta turut mencadangkan agar mereka diberi pendedahan yang meluas tentang sistem ini.

Dalam usaha mengitlak dapatan kajian kualitatif awal, suatu tinjauan melalui pos dijalankan dengan semua farmasi komuniti (n = 470) di empat buah negeri di Utara Semenanjung Makaysia. Dengan kadar respons total 25.2 %, dapatan tinjauan mendapati bahawa majoriti responden (n = 75, 74%) tidak sedar atau tidak tahu-menahu tentang kewujudan sistem farmakovigilans yang sedia ada di negara ini. Walaupun lebih daripada separuh (n=65, 61.5%) responden menekankan tentang kepentingan laporan

ADR, namun hanya 13 daripada mereka (12.9%) mengakui ada menghantar laporan ADR kepada MADRAC.

Halangan tidak mengemukakan laporan ADR yang biasa dihadapi oleh farmasi komuniti adalah tidak tahu di mana laporan perlu dibuat (n = 75, 54.8%) serta tidak pasti sama ada mudarat yang terjadi disebabkan ubat atau ADR (n = 46,44.2%). Oleh itu, fasa kajian ini cuba mengenal pasti jurang pengetahuan tentang laporan ADR dalam dikalangan farmasi komuniti yang akhirnya akan mengesahkan hasil kajian kualitatif. Berdasarkan hasil ini serta usaha memastikan bahawa pendidikan jangka pendek mampu meningkatkan pengetahuan mereka, maka satu kajian intervensi pendidikan diolah dan dijalankan.

Semua farmasi komuniti di negeri Pulau Pinang, Malaysia dipelawa untuk mengikuti seminar pendidikan sehari mengenai Farmakovigilans dan Laporan ADR. Seramai 42 farmasi komuniti turut mengambil bahagian dalam seminar ini. Hasil perbandingan tentang pengetahuan sebelum dan selepas seminar, secara signifikannya menunjukkan adanya perbezaan yang berkaitan dengan pengetahuan laporan ADR, dan penambahbaikan dalam skor min yang berkaitan dengan pengetahuan farmakovigiland dan laporan ADR ($z = -5458$, $N= 42$, $p<0.001$). Hampir sebahagian daripada peserta seminar (45%), begitu yakin bahawa mereka lebih berpengetahuan untuk mengesan serta melaporkan ADR ($z = -2.866$, $N=42$, $p = 0.004$).

Komponen awal penyelidikan semasa menonjolkan tentang kurangnya pengetahuan serta tanggapan yang salah di kalangan farmasi komuniti berhubung dengan laporan ADR. Dalam memastikan bakal pengamal farmasi pada masa hadapan mendapat pendedahan yang secukupnya tentang laporan ADR dalam pengajian mereka di peringkat ijazah, di samping menilai persepsi mereka terhadap laporan ADR, maka

suatu kajian telah diadakan yang melibatkan pelajar farmasi tahun akhir di semua universiti awan di Malaysia (n = 5). Dengan kadar respons total 84.0%, lebih kurang 60% (n = 240) daripada responden menyatakan bahawa dalam kurikulum farmasi sedia ada, terdapat kursus tentang konsep farmakovigilans. Min skor pengetahuan farmakovigilans bagi pelajar farmasi tahun akhir adalah 6.91±1.36. Terdapat perbezaan yang signifikan dalam min skor bagi pengetahuan konsep farmakovigilans berdasarkan universiti ($F = 5.89$; $p < 001$). Majoriti (n =343, 82.3%) responden merasakan perlunya dijelaskan perbezaan di antara kemudaratan yang disebabkan ubat dan ADR.

Sebagai kesimpulan, tesis ini mengesahkan bahawa terdapat jurang pengetahuan tentang farmakovigilans dan laporan ADR dalam kalangan farmasi komuniti serta bakal pengamal farmasi di Malaysia. Faktor faktor utama yang dikenal pasti tentang kurangnya laporan ADR menekankan betapa perlunya menentukan strategi yang bersesuaian untuk meningkatkan serta melestarikan laporan ADR di kalangan Pengamal Farmasi Komuniti di Malaysia.

ASSESSMENT OF KNOWLEDGE, ATTITUDES, PERCEPTION AND BARRIERS TOWARDS PHARMACOVIGILANCE ACTIVITIES AMONG COMMUNITY PHARMACISTS AND FINAL YEAR PHARMACY STUDENTS IN MALAYSIA

ABSTRACT

Adverse Drug Reactions (ADRs) are associated with a high rate of morbidity and mortality worldwide. In order to overcome this problem, many countries around the world have established national pharmacovigilance systems. Most of the pharmacovigilance system nowadays depends largely on ADR Spontaneous Reporting System (SRS) by healthcare professional such as physicians and pharmacists.

Within this context, Malaysia established its pharmacovigilance system in 1987. The Malaysian Adverse Drug Reaction Advisory Committee (MADRAC) was established under the umbrella of Drug Control Authority (DCA) for documenting SRS reports received from healthcare professionals. As with most of the spontaneous ADRs reporting system worldwide, the Malaysian SRS has also been affected by under-reporting of ADRs especially by the community pharmacists.

Data from MADRAC shows that the ADRs reporting rate by community pharmacists is low compared to their counterparts in the other countries. Furthermore, there are no comprehensive studies conducted to explore the reasons behind under reporting of ADRs among community pharmacists in Malaysia.

This thesis aims to explore the knowledge, attitude and perception held by community pharmacists regarding ADR reporting. Additionally, this thesis will also focus on the perceived barrier which hinders the participation of community pharmacist

in pharmacovigilance activities and ADRs reporting. In order to achieve the research objectives, a mixed methodology using qualitative and quantitative approaches was adopted.

In order to have a deep understanding of the reasons behind the ADR under-reporting among the community pharmacists, a total of sixteen community pharmacists were interviewed. Almost all the interviewed pharmacists were unfamiliar with the existing pharmacovigilance system and expressed unawareness about its utility. However, although all the interviewed pharmacists did not submit any ADR report, they showed a positive attitude towards ADR reporting.

The major barriers hindering community pharmacists from not reporting ADRs were unfamiliarity with the ADR reporting system, unavailability of ADR reporting forms, ignorance of how to report, doubt about the importance of the reaction and time constraint. Most of the participants not only recommended receiving of feedback from the regulatory authority but also emphasized rigorous educational outreach for the community pharmacists about the ADR reporting system.

In order to generalize the initial qualitative study findings, a cross-sectional mail survey was undertaken with all community pharmacists (n = 470) practicing in 4 northern states of Malaysia. With a total response rate of 25.2 %, the survey findings revealed that the majority of respondents (n = 75, 72.1 %) were not aware of the existing pharmacovigilance system in the country. Although more than half (n = 65, 61.5%) of the respondents in this survey emphasized the importance of ADR reporting only 13 pharmacists (12.9%) claimed that they had submitted ADR reports to MADRAC.

Most common barriers reported by CPs for non-reporting were ignorance of where to report (n = 75, 54.8%) and uncertainty regarding the causal relationship between the drug and the suspected ADR (n = 46, 44.2%). Therefore, this phase of the study identified gaps in the knowledge regarding ADRs reporting among CPs which confirmed the findings of the qualitative study. Based on these findings, and in order to explore whether a short educational intervention will improve the current knowledge status among CPs on ADRs reporting, an educational intervention study was designed and conducted.

All the CPs in the state of Penang, Malaysia were invited to participate in a one-day educational seminar on pharmacovigilance and ADR reporting. A total of 42 CPs participated in the educational seminar. A comparison of CPs knowledge before and immediately after the seminar showed significant differences in relation to knowledge of ADR reporting, and an improvement in the mean scores related to knowledge of pharmacovigilance and adverse drug reactions reporting ($z = -5458$, $N= 42$, $p<0.001$). Upon completion of the education program, nearly half of the pharmacists (45%) believed that they were confident of their knowledge in detecting and performing ADR reporting ($z = -2.866$, $N=42$, $p = 0.004$).

The initial components of the current research highlight the existence of knowledge deficit and misperception towards ADR reporting held by the CPs. In order to explore whether the future pharmacy practitioners have been exposed to an adequate knowledge on ADR reporting during their undergraduate study, as well as to evaluate their perception towards ADR reporting, a nationwide survey study was undertaken with all the final year pharmacy students enrolled in Malaysian public universities (n = 5). With a total response rate of 84.0%, about 60% (n = 240) of the respondents indicated

that they had received courses on pharmacovigilance concept during their current pharmacy curriculum. The mean knowledge score for pharmacovigilance of the final year pharmacy students was 6.91±1.36. There was a significant difference in mean score for pharmacovigilance concept knowledge according to universities ($F = 5.89$; $p<001$). The majority (n =343, 82.3%) of respondents felt that it was necessary to confirm the causal relationship between the drug and the ADR.

In conclusion, this thesis confirmed the existence of knowledge gap in ADR reporting among Malaysian CPs and future pharmacy practitioners. The major identified factors for the low level of ADR reporting revealed in this research emphasized the urgent need to determine appropriate strategies to enhance and sustain ADRs reporting among CPs in Malaysia.

CHAPTER 1: GENERAL INTRODUCTION

1.1 Introduction

The global interest in the monitoring of drug safety showed a remarkable increase in the last four decades especially after the thalidomide disaster in the sixties (Meyboom et al., 1999). The thalidomide disaster opened up the issue of drug safety for the public and healthcare professionals alike and brought about an awareness of the importance of the systemic surveillance of drugs for Adverse Drug Reactions (ADRs)(Edwards & Olsson, 2002). ADRs are defined as unintended consequences suspected to be related to the use of medicinal products, including herbal medicines (WHO, 1972). ADRs are often associated with high mortality and morbidity rates. They were believed to be the 4th to the 6th largest causes of death in the United States and were responsible for 0.3% to more than 10 % hospital admission in some countries and up to 20% of healthcare budget spent on drug complication and ADRs consequences (Lazarou et al., 1998; Rabbur Reza & Emmerton, 2005). ADRs have a major impact on the public health system and impose unnecessary and unreasonable economic burdens on the society although most of these ADRs are preventable (Ayani et al., 2000; Geisslinger et al., 2000).

The tragedy of the thalidomide disaster in 1960s has led many countries to set their observational systems for early detection of potential adverse drug reactions associated with pharmacotherapy (Meyboom et al., 1999). These systems became known as the pharmacovigilance systems. Pharmacovigilance has been defined by the World Health Organization (WHO) as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems" (WHO, 2002a). In a few literature, it was defined as the process of

identifying and responding to safety issues related to marketed drugs under the practical conditions of clinical usage in large communities (Mann & Andrews, 2002; Rawlins, 1995). Pharmacovigilance plays a crucial role in the study of medication safety (Herdeiro et al., 2006), and now it is regarded as the quality control system of the society (Arnaiz et al., 2001). The WHO program for monitoring of drug safety was established in 1968 as the pilot project with the participation of ten countries initially and as of May 2010, 98 countries have joined the WHO Drug Monitoring Program, and in addition, 32 associate members are awaiting compatibility between the national and international reporting formats. The WHO Drug Monitoring Program database has grown from over 600,000 to over 5 million reports (Uppsala Monitoring Centre, 2010). Malaysia was accepted as the 34th full member of the WHO Drug Monitoring Program in 1990.

In fact, most of the pharmacovigilance systems around the world depend on spontaneous reporting systems to collect information about ADRs, where the reports are submitted on a voluntary basis from the (reporters) health care professionals and then the information is entered onto a data base which is assessed regularly for signal generating (Waller, 2009b). Spontaneous reporting is considered the main mechanism in the pharmacovigilance system by which the ADRs are identified after the drug is released onto the market and it is the foundation of the WHO data base (Edwards & Olsson, 2002). Unfortunately, the spontaneous ADR reporting system is affected by a number of weaknesses, the most noticeable of these being the phenomena of ADRs underreporting from healthcare professionals. The reasons behind underreporting were not well documented in the developing countries although it had been proposed early in the developed countries, there were numerous obstacles preventing health care professionals

from ADRs reporting as noted in the literature (Bateman et al., 1992; Inman, 1976; Vallano et al., 2005; Belton et al., 1995).

In Malaysia, the Malaysian pharmacovigilance system is a spontaneous voluntary ADR reporting system. MADRAC is responsible for collecting ADR reports in the country. Physicians, dentists, pharmacists and recently patients are encouraged to report suspected ADRs to MADRAC. The Malaysian Spontaneous Reporting System like other SRSs around the world suffers from ADR under-reporting from healthcare providers and it was reported that the number of reports received by MADRAC was lower than the recommendations of The WHO Program for International Drug Monitoring. At the time of establishing this study, little information was known about the Malaysian community pharmacist's knowledge, attitude and reporting behavior towards ADRs reporting system.

Thus the aim of the present study was to gain insight into the knowledge, attitude and perception and to explore the reasons behind under-reporting of ADRs among of community pharmacists in Malaysia and also among future pharmacy practitioners.

1.2 Problem Statement

One of the pivotal objectives of the spontaneous reporting of ADRs is to generate signals about new possible ADRs (Backstrom et al., 2004). SRS basically relies on the voluntary reporting of suspected ADRs from health-care professionals and in some countries from the patients themselves. Under-reporting of ADRs is the major problem that weakens the efficiency of the SRS. In the beginning, Inman et al. (1976) proposed the most common obstacles leading to the non-reporting of ADRs and then it has been reported in many different studies which were carried out amongst all health care professionals including the community pharmacists (Belton et al., 1995; Bateman et al., 1992; Milstien et al., 1986; Inman, 1976). However, these factors vary from one country to another (Lopez-Gonzalez et al., 2009; Aziz et al., 2006). It was estimated that only around 6-10% of all ADRs are reported (Feely et al., 1990; Smith et al., 1996; Lumley et al., 1986). It was documented that knowledge has a major effect on the attitude and perception of the community pharmacists towards adverse drug reactions reporting. Previous studies indicated that educational interventions which aimed at improving the level of knowledge of ADR reporting among the community pharmacists had a positive effect (Granas et al., 2007).

The literatures reported that community pharmacists can play a vital and supportive role in ADR reporting because they are considered as the first point of contact within the health care system and daily contact with patients makes them ideally placed to learn of possible ADRs (Van Grootheest et al., 2002b; Green et al., 1999). In some developed countries, it was estimated that the rate of ADR reporting among community pharmacists accounted for approximately 40% of the reports received by their

pharmacovigilance centers (Rabbur Reza & Emmerton, 2005). Although the community pharmacists had a positive attitude towards pharmacovigilance activities, they suffered from insufficient knowledge and virtually no experience with regard to the reporting of ADRs (Sears & Generali, 2005).

Malaysia, like other countries, depends on the spontaneous reporting system to collect information about ADRs. Malaysia became a member of the World Health Organization (WHO) program for international drug monitoring in 1990. The amount of ADR reports received by MADRAC (the body responsible for running the pharmacovigilance system) reached about 4826 reports in 2009 (MADRAC., 2009). However, this amount is considered low according to the WHO recommendation (Uppsala Monitoring Centre, 2010).

The Malaysian pharmacovigilance system, like most of the pharmacovigilance systems around the world, suffers from the under-reporting of ADRs by health care professionals (Aziz et al., 2006; Nichols et al., 2009). There is a lack of information about the reasons behind under reporting amongst health care professionals in general and community pharmacists in particular.

This study is meant to gain insight into the knowledge, attitudes and perceptions held by Malaysian community pharmacists towards pharmacovigilance concept and adverse drug reactions process, as well as to investigate the barriers preventing community pharmacists from reporting the adverse drug reactions.

1.3 Rational of the Study

Malaysia, like many other countries, uses the pharmacovigilance system (PV) as the main way to collect information about ADR occurrences in both the hospital and community settings. In Malaysia, the pharmacovigilance system was established in 1987.

The effectiveness and success of any pharmacovigilance system depends highly on the participation of all health care professionals, including community pharmacists, and also relies upon the degree of co-operation and communication between these professions.

As in most of the pharmacovigilance system around the world, Malaysian pharmacovigilance also suffers from the problem of ADR under-reporting (Haq, 2003). It has been documented that the knowledge, attitude, and perception of the community pharmacists have a major impact on the participation and contribution of this profession to the pharmacovigilance system (Sweis & Wong, 2000; Herdeiro et al., 2006; Bawazir, 2006).

The study of the knowledge, attitudes and perception of the community pharmacists towards the pharmacovigilance system and ADR reporting has already been researched in the developed countries but there is a lack of studies carried out and recorded in this country.

Involvement of the community pharmacists in pharmacovigilance activities can improve the rate and the quality of the ADR reporting, as this profession has the competence and is suitably equipped to perform this task (Van Grootheest et al., 2002a; Herdeiro et al., 2008).

In Malaysia , although the ADR reporting system has been in place for more than 30 years , very few studies have been conducted to gain insight into the barriers and factors which can facilitate the participation of the community pharmacists in the pharmacovigilance activities in general and ADR reporting in particular.

In a country like Malaysia, with multiethnic groups and a high rate of use of herbal and complementary medicine, community pharmacists can play a major role in detecting and reporting ADRs associated with the use of such products. Based on the abovementioned justifications, it is obvious that there is an urgent need to conduct comprehensive studies to explore and evaluate the actual role and contributions made by the community pharmacists in the pharmacovigilance system activities. Due to the lack of information about the magnitude of ADRs under-reporting associated with the Malaysian pharmacovigilance system, it is necessary to carry out evaluation studies prior to any intervention aiming to improve the pharmacovigilance system.

1.4 Aims

This study in its entirety has two main parts; of which the first part (Qualitative method) is to explore and gather baseline information about the knowledge, attitude and perception of the Community Pharmacists towards Pharmacovigilance activities and ADR reporting. Furthermore, the study has been conducted to gain insight into the reasons and the perceived barriers for under-reporting amongst community pharmacists.

The second part of the study (Quantitative methods) is mainly aimed at evaluating and assessing the knowledge, attitude and barriers towards ADR reporting amongst Malaysian community pharmacists and the final year pharmacy students (future pharmacy practitioners). Information about knowledge, attitude and barriers of the

community pharmacists have to be assessed and the needs associated with these factors have to be identified. This would provide valuable knowledge on the issue of ADR reporting and which can contribute to the development and evaluation of the pharmacovigilance system.

The specific objectives of this study are:

(1) To explore the knowledge, attitude and perception of the community pharmacists towards ADR reporting.

(2) To evaluate the knowledge, attitude and perception towards ADR reporting system amongst community pharmacists.

(3) To determine barriers faced by community pharmacists towards ADR reporting

(4) To evaluate the impact of educational intervention on the knowledge and perception of the Malaysian community pharmacists towards pharmacovigilance and ADR reporting

(5) To explore the factors that affect knowledge ,perception and practice towards performing ADR reporting

(6) To assess the knowledge and perception of the final year pharmacy students towards pharmacovigilance and ADR reporting in some Malaysian public universities.

1.5 Significance of the Study

1) This study has many important implications that can provide health care policy makers and planners with useful data to explore the current ADR reporting status among the community pharmacists.
2) It will provide a base line data that can be used in the future evaluation or reconstruction plans for the current PV system.
3) The study is the first of its kind in Malaysia that will evaluate the factors that could possibly affect ADRs reporting among healthcare professionals and community pharmacists in particular.
4) It is also to evaluate the overall conditions of ADRs reporting by observing the present system in place so that suggestions to improve reporting amongst health professionals can be offered.
5) The result of the study will help in improving the ADR reporting procedure by highlighting the drawbacks in the system.
6) To provide to the policy makers and planners proper suggestions and a mechanisms that can be used to improve the ADRs reporting among community pharmacists in particular and the other health professionals in general.

The study provides policy makers in MADRAC management with knowledge about the current situation of ADRs reporting and thus enabling them to discuss the suitable methodology to improve reporting process.

The study will determine the actual intervention required in improving ADRs reporting through verifying the possible factors leading to underreporting. Information about ADRs reporting such as community pharmacists' basic knowledge, attitude, perceptions

and barriers have to be assessed and the needs associated with these factors have to be identified. This will provide valuable data on the issues of pharmacovigilance and ADRs reporting can be utilized to improve and further evolutions of the pharmacovigilance system.

The study highlights the awareness and attitudes of community pharmacists to ADR reporting guidelines and how their behavior could affect the rate of ADR reporting.

1.6 Thesis Overview

This study is constructed in two parts; part A consolidates the qualitative section and part B consolidates the quantitative section.

This thesis is composed of 7 chapters, including this chapter, and each chapter stands as a separate chapter.

CHAPTER 1:

This chapter is the introductory chapter and each topic of the study has been designated as a separate chapter.

This chapter provides a general overview of the research problem statement. It also presents the general flow of the whole research project and organization of the thesis.

CHAPTER 2:

This chapter provides the background and overview of the subject area (ADRs definition, pharmacovigilance concept, impact of ADRs on public health care system and the role of the community pharmacists in ADR reporting). As a general literature review, the chapter highlights some of the major studies related to the research area.

CHAPTER 3:

This chapter represents the qualitative approach of the study, which details the methodology and findings from qualitative interviews with conveniently sampled community pharmacists in Penang Island, Malaysia.

Findings from interviews conducted with community pharmacists about their attitudes and perceptions of towards the Malaysian pharmacovigilance system activities and the ADRs reporting process were outlined.

This chapter also discusses the issues related to the barriers which hinder the community pharmacists from reporting of adverse drug reactions and what logistic steps can be taken to overcome this problem.

The conclusions made in this chapter serve as the basis for further research, which is described in the subsequent chapters (quantitative section).

CHAPTER 4:

This chapter describes the methodology and findings from quantitative survey involving all the community pharmacists practicing in the northern states of Malaysia. The survey aimed to assess their knowledge attitude, perceptions towards Malaysian pharmacovigilance system and ADRs reporting process.

CHAPTER 5:

The goal of this chapter is to study the effectiveness and the impact of an educational program on the knowledge of and perceptions of Malaysian community pharmacists towards pharmacovigilance activities and ADR reporting.

CHAPTER 6:

Describes a comparative analysis of the knowledge and perceptions held by senior pharmacy students towards pharmacovigilance concept and ADRs reporting in 5 public universities in Malaysia

CHAPTER7:

By integrating the findings of each of the individual chapters, this chapter provides a conclusion about the study findings which is highlighted along with some further recommendations.

CHAPTER 2: LITERATURE REVIEW

2.1 Background

2.1.1 Introduction

The safe use of medicine is an important aspect that affects each and every member of society. Nowadays, reducing the incidence and consequences associated with ADRs is a crucial challenge in drug use. Despite the importance of medicine in the prevention and curing of diseases, its usage is usually associated with undesirable adverse reactions and sometimes fatal reactions (Edwards & Aronson, 2000). It has been reported that adverse drug reactions is associated with significant morbidity and mortality with huge unnecessary economic burden (White et al., 1999).

Pre-marketing studies conducted with the aim of studying effectiveness and safety of medicines often fail to detect rare and serious adverse reactions that can occur after the drug approval for use in human beings. The reasons for this are the purposive and the selective criteria which eliminate some population with specific conditions from being included in these studies. Moreover, most of these studies have a short period of follow up which eliminates the capability to detect the ADRs associated with the long term use of drugs (Stricker & Psaty, 2004; Psaty & Burke, 2006; Stephens, 1998b).

It has been reported that there is an absence of a total figure of the incidence as well as the economic burden of ADRs. This absence is attributed to several factors including the difference in drug policy between the communities, methods used to detect ADR, and the terminology used to describe the adverse event. Previous studies indicated that the terminology had a significant impact on the rate and quality of ADRs reporting (Stephens, 1998a; Morimoto et al., 2004). A commentary by Ackroyed et al.(2006) concluded that the inconsistencies in the definitions of commonly used terms have an

adverse impact on the establishment of medication safety priorities which could distress the accuracy and the quality of event rates (Ackroyd-Stolarz et al., 2006).

2.2 Definitions and Concept of ADR

Despite the tremendous development in both the fields of pharmaceutical industry and pharmacotherapy, there is no drug that is absolutely safe. All drugs can produce biological or therapeutic effects with a high probability of producing undesirable or harmful effects. The greatest problem of these harmful effects is their capability to mimic a wide range of disease symptoms. This makes it difficult for detection and reporting of adverse reactions. These effects should be taken into account in the differential diagnosis of a wide range of medical conditions.

The huge costs associated with ADRs often adversely impact the heath care directions (Oberg, 1999). For these reasons, ADRs are considered as the negative consequences of drug use (Gholami & Shalviri, 1999). Although there is a remarkable increase in concern about the issues related to drug safety among health care providers, health care institutions and the patients themselves, there is a great confusion and lack of knowledge regarding the terminology used to describe adverse drug reactions. It has been reported that one of the reasons behind the under estimation of the ADRs incidence rate is the difference in the terms used to describe ADRs (Stephens, 1998a; Waller, 2009b). Lack of consistency in ADRs definitions makes systematic reviews of ADR data extremely difficult and also deters comparisons of ADR rates between trials (Loke & Derry, 2001; Freemantle et al., 1999).

2.2.1 Definition of Adverse Drug Reactions (ADRs)

According to WHO's definition which has been used more than 30 years, ADRs has been defined as "a response to a drug that is noxious and un-intended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function"(WHO, 2002a). For this reason, adverse drug reactions are considered as adverse events with a causal link to a drug (Nebeker et al., 2004).

Grootheest et al. (2003) indicated that the WHO definition fails to define the term ADRs adequately (Van Grootheest et al., 2003b). Other critics have concluded the WHO definition as being vague because it includes all adverse reactions, despite how trivial it is (Edwards & Aronson, 2000). There have been other definitions raised to overcome this point and have focused on making the WHO definition much more precise by excluding the minor unwanted reactions. Laurence et al defined ADRs as "A harmful or significantly unpleasant effect caused by a drug at doses intended for therapeutic effect which warrants reduction of dose or withdrawal of the drug and /or predicts hazard from future administration" (Laurence & Carpenter, 1998).

Edwards and Aronson (2000) described the WHO definition for ADRs as having an unlimited scope, and proposed the following definition referring to ADRs: "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment or alteration of the dosage regiment, or withdrawal of the product" (Edwards & Aronson, 2000).

2.2.2 Adverse Drug Events (AE)/Adverse Drug Experience (ADE)

An adverse drug event is defined as "Any untoward medical occurrence that may appear during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with the treatment"(WHO, 2002a; Asscher et al., 1995). This implies an adverse drug reaction characterized by the suspicion of a causal relationship between the drug and the event, contrary to an adverse drug event (Farcas & Bojita, 2009).

However, an adverse drug experience has been defined as " any adverse event associated with the use of a drug in humans, whether or not considered drug related including the following: an adverse event occurring in the course of the use of drug in professional practice, an adverse event occurring from overdose whether accidental or intentional, an adverse event occurring from drug abuse, an adverse event occurring from drug withdrawal and any significant failure of expected pharmacological action"(Nelson,1988). In Malaysia, the Malaysian Adverse Drug Reaction Advisory Committee (MADRAC) define adverse drug experience as "any untoward medical occurrence that at any dose results in death, leading to a life-threatening condition, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect"(MADRAC, 2002). It has been reported that adverse drug events and adverse drug experience used are synonymous (Ahmad et al., 1996). Furthermore, although the distinction between the adverse reactions and adverse event is vital, still these terms are widely misused (Waller, 2009a).

2.3 Epidemiology of Adverse Drug Reactions

Numerous studies have been carried out to study the incidence of ADRs in the hospital and community settings. There was considerable variation in the incidence estimations of ADRs in these studies (Lazarou et al., 1998). This variation was attributed to the difference in the methodologies used to identify ADRs as well as the difference in definitions applied to define an ADRs and the obvious development in the diagnostic methods (Beard & Lee, 2006; Tai-Yin et al., 2010). The Thalidomide tragedy the in 1960s triggered the interest in the monitoring of drug safety and stimulates the heightened interest in ADRs reporting (D'Arcy & Griffin, 1994).

Many studies adopting both retrospective and prospective designs have been conducted aiming at estimating ADRs incidence in different settings. These studies started in the 60s were the epidemiological data basis of ADRs that has been established (Beard & Lee, 2006). Despite the proposed detailed analysis and criticism for the studies which has been published at that time (Karch & Lasagna, 1975),the large early studies concerned with the epidemiology of ADRs estimated that the incidence of ADRs ranged from 10 to 20 per cent in general practicing setting (Seidl et al., 1966; Smith et al., 1966; Ogilvie & Ruedy, 1967; Hurwitz, 1969). The justification of the disparity in the rate figures was the difference in the methods used to detect and report ADRs and whether the researcher depended on himself or relied on other people in identifying ADRs (Davies, 1985).

It was reported that most studies only just give rough indicators about the incidence of ADRs due to the under-reporting phenomena associated with ADRs spontaneous reporting systems and also due to the poor communication, poor training

and education about drug safety among healthcare professionals (Davies, 1985; Lawton & Parker, 2002; Davies et al., 2007).

A study conducted in UK in the early 70s suggested that in general practice, 1 in 40 consultations were for ADRs (Mulroy, 1973). Another study conducted at the same period of time revealed that 25% of the practice population may have had an ADR (Martys, 1979). It was estimated that the incidence of ADRs in the community setting ranged from 2.6% to 41% of patients (Beard & Lee, 2006).

In US, a telephone survey study carried out by Gandhi et al (2003) reported that 25% of the study population experienced ADRs, with a total of 181 events. The authors also concluded that the ADRs which occurred in the primary care setting were common and most of them were preventable (Gandhi et al., 2003). It was reported in anther cohort study that 421(27.6%) of 1523 of ADRs events were preventable (Gurwitz et al., 2003)

2.3.1 Adverse Drug Reactions as Cause for Hospital Admission

Most of the studies conducted in the early 80s, reported that ADRs were responsible for large numbers of hospital admissions, with narrow ADRs reporting rates ranging from 2.9- 6.2 per cent. In addition, the rate of ADRs incidents among the patients admitted to the general medical wards were higher than that related to the total admission to hospitals (Black & Somers, 1984).

Findings from literature indicated that the hospitalization rates as a result of ADRs in the other developed countries did not differ from those reported in Britain and the United States. For example, in a prospective study conducted in France, it was reported that out of 3,137 admissions, 100 (3.19%) admissions were due to ADRs (Pouyanne et al., 2000), while the data from Hong Kong in the mid 90s reported that ADRs were responsible for 6.2% of overall hospital admissions (Chan & Critchley, 2006). Similarly, in Denmark, Hallas et al (2009) reported that drug related problems accounted for 10.8% of all hospital admissions among which 8.1% were ADRs (Hallas et al., 2009).The findings of a multi-center epidemiological study conducted in Italy between 1988 and 1997 reported that ADRs were responsible for 3.4% hospital admissions (Onder et al., 2008) while in the Netherlands, it was documented that ADRs were responsible for about 12% of hospital admissions (Mannesse et al., 2000).

In the developing countries, there is paucity of data in the estimation of the rates of hospitals admissions due to ADRs. It may be due to the scarcity of studies aimed to estimate the incidence of ADRs or that most of these studies have been performed with a local nature in terms of objectives or the setting. However, data from India suggested that 0.7% of hospital admissions were due to ADRs (Ramesh et al., 2003). It has been reported in a cross-sectional study conducted in Nigeria that ADRs were responsible for about 0.5% of the patient admissions to the Lagos State University Teaching Hospital (Oshikoya et al., 2007). In a Zimbabwean study, Taylor et al (1988) suggested that around 6% of the hospital admissions in Zimbabwe were attributed to ADRs (Taylor et al., 1988).

2.3.2 Incidence of Adverse Drug Reactions during Hospital Admission

Previous studies suggested that the incidence of ADRs during hospital admission was about 5% with a range from1.5% to over 20% (Baker et al., 2004; Lazarou et al., 1998). The Harvard medical practice study reported that about 3.7% of the admitted patients experienced ADR and the incidence of ADRs during hospitalization was 6% (Brennan et al., 2004; Leape et al., 1991). It was reported that the ADRs incidence rate during the hospital admission increased remarkably (Hajjar et al., 2007). A prospective study carried out in 1990-1993 suggested that the ADRs incidence rate had increased to 2.43 per 100 admissions (Classen et al., 1997). Bates et al. (1995) reported that there were 6.5 ADRs per 100 admissions during the hospital stay (Bates et al., 1995). In US, a follow up study of more than 35, 000 patients admitted to the Salt Lake hospital between 1998- 1990 showed that about 1.67% of the patients experienced ADRs (Classen et al., 1997).

2.3.3 Mortality Associated With Adverse Drug Reactions

In the developed countries, ADRs remain as the one of the main causes of morbidity and mortality in the health care setting (Alexopoulou et al., 2008). Karch and Lasagna (1975) reported that prevalence of fatal ADRs ranges between 0.1%-0.3% among admitted patients (Karch & Lasagna, 1975). In a meta-analysis undertaken by Lazarou et al (1998), it was reported that ADRs accounted for over 100,000 deaths, making ADRs one of the leading causes of death in the United States (Lazarou et al., 1998). Data from Scandinavian countries reported that ADRs were the most common cause of death in general practice which accounted for about 3% - 5% of mortality in these countries (Juntti-Patinen & Neuvonen, 2002; Wester et al., 2008).

Pirmohamed et al (2004) in their prospective observational study suggested that the rate of incidence of fatal ADRs in UK was about 0.15% (Pirmohamed et al., 2004). The extrapolation of the results of the previous study to the rest of UK indicated that ADRs-induced hospital admissions would be responsible for 5,700 deaths every year (Beard & Lee, 2006). In the developing countries, there is a lack of data on mortality rates associated with ADRs. In addition, the WHO reported that data related to drug safety in the developing countries are limited and expect to find worse conditions than developed countries (WHO, 2002b). However, data from developed countries related to ADRs cannot necessarily be generalized to developing countries, where the incidence, pattern, and severity of adverse reactions may differ markedly because of local environmental and genetic influences (Eliasson, 2006). The main reasons for the scarcity of data on mortality rates associated with ADRs in the developing countries are lack of resources, infrastructure and experience in the drug safety monitoring programs in the most of these countries (Pirmohamed et al., 2007). The problem is also attributed to the lack of legislation and proper drug regulations, including ADR reporting, a large number of substandard and counterfeit products circulating in their markets, a lack of independent information and the irrational use of drugs (WHO, 2002b). However, reports show that the mortality rate associated with ADRs in provincial hospitals in Saudi Arabia was found to be 3.8% from the overall deaths in the general practice (Ahmed, 2008). In India, it has been reported that the overall mortality rate due to ADRs was found to be 1.8% (Ramesh et al., 2003).