REPORTING OF ADVERSE DRUG EVENT BY CONSUMERS TO COMMUNITY PHARMACISTS IN THAILAND

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A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Social and Administrative Pharmacy

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การรายงานเหตุการณ์ไม่พึงประสงค์จากยาโดยผู้บริโภคต่อเภสัชกรชุมชนในประเทศไทย

น.ส.จิรัญญา อัสนี

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TABLE OF CONTENTS

Page

List of Tables

Page

List of Figures

Page

CHAPTER I
INTRODUCTION

1.1 Background and Rationale

Adverse Drug Event (ADE) is a health problem or injury occurring from medical intervention related to a medicine. It includes adverse drug reaction and overdose.(1) Adverse drug reaction (ADR) is any noxious and unintended response to a drug and occurs at doses used for prophylaxis, diagnosis, or therapy in humans, excluding failure to accomplish the intended objective.(2) ADR is one of the major causes of patient related and mortality worldwide.(3) ADRs have affected economies since they lead to emergency department visits, hospital admission and prolongation of hospital stay and have effect to public health expenditure.(4)

An epidemiological study of ADR showed 2.5-10.6% of hospital admissions in Europe, 5.7-18.8% of admissions in Australia and 4.2-30% of admissions in the USA and Canada were caused by ADRs.(4) In US, the estimated cost of ADR management was 30.1 – 130 billion US dollars per year depending on severity of case scenario.(4, 5) The estimated direct hospital costs of adverse events in Australia was 4.83 – 9.00 billion Australian dollars annually and half of them may be preventable.(6) Prevention of drug-related morbidity and mortality has been an increasingly important requirement for reducing healthcare expenditures.

Pharmacovigilance is a part of patient care and patient safety that ensures the suitable use of medicines or prevention of adverse drug reactions. It is related to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems.(2) The purpose of pharmacovigilance is to identify drug safety signals as early as possible to decrease potential clinical events and expenditure of ADRs.(7) ADR monitoring is a part of pharmacovigilance. ADR monitoring can detect adverse events before clinically manifestation occurs and acquire new knowledge of drug usage. ADR monitoring can detect signals that may show a potential hazard of medicines. The signals can trigger healthcare professionals to use medicines carefully including counselling or restrictions, or the removal of a medicine.(8)

Health care professionals such as physician, nurse, dentist and pharmacist, etcetera, are responsible persons to monitor ADRs, but ADR reporting is voluntary. It was estimated that only 6-10% of all ADRs are reported.(9) The limitation of spontaneous reporting system is under-reporting of ADR. The First International Conference on Consumer Reports on Medicines was established in 2000 and the conference concluded that consumers or patients' ADR reporting has potential benefit in pharmacovigilance. Consumer ADR reporting can provide more information and cover the situations that healthcare professionals do not report. Healthcare organisations can benefit from consumers or patients involvement.(7, 10) Consumers have unique perspectives and experiences.

Many studies comparing ADR reports between health professionals and patients showed that patients' reporting had more details than healthcare professional reporting. (7, 8, 11, 12) Reporting types of drugs and reactions by patients were different from reporting by healthcare professionals. The different information added potential value in pharmacovigilance in terms of generating new potential signals and describing suspected ADRs in enough details to provide useful information on likely causality and impact on patients' lives.(7, 8) Even though, patients lacked medical knowledge, the information from patients' reports without medical confirmation may interfere with the interpretation of ADR possibility, patient reports are still beneficial in pharmacovigilance. Patients can provide the information about daily use of medicines and tolerable adverse effects. Their reports may be different from a medical point of view, and the report may be a true signal.(11, 12)

Promoting patients to be involved in pharmacovigilance is able to increase spontaneous reporting and earlier detect important ADRs.(7) Therefore, patients have become important players in pharmacovigilance. They are the ultimate goal of the healthcare systems.(12) There were few studies about patients reporting ADRs. A study in the European Union showed that the percentages of ADR reports from patients in 2014 were around 0.02% in Bulgaria, 0.04% in Portugal, 5% in France, 20% in the Netherlands, and 21% in Sweden 34% in Denmark and in 2013 was 0.05% in Romania.(13)

In Thailand, ADE reporting is under pharmacovigilance center called 'Health Product Vigilance Center (HPVC)'. HPVC is an organisation that has responsibility to collect and evaluate the ADE reports of healthcare professionals. HPVC has collected the ADE reports since 1984. The trend of ADE reporting is increasing compared with the past. Around 89% of ADE reports come from hospitals and others come from entrepreneurs, community pharmacies and pharmaceutical companies.(14) Community pharmacies are private healthcare service places which are very close with consumers. According to the 2015 survey on health and welfare, 27.2 % of consumers decided to buy medicines to treat by themselves.(15) If consumers have non-serious healthcare problem, the community pharmacies are the first choice that consumer's access because they are comfortable and spend less time with the service. Thus, community pharmacists are important persons who have chance to receive any ADE information from consumers during counselling and report ADEs to HPVC. The ADE reporting to community pharmacists is one important pathway to detect new signals. Consumers are important stake holders to provide information of ADEs. Up until now, there have been no researches studying about ADE reporting from consumers to community pharmacists in Thailand.

LITERATURE REVIEW

Adverse drug event and adverse drug reaction

Adverse Drug Event (ADE) is a health problem or injury occurring from medical intervention related to a medicine. ADE may be associated with inappropriate use of medicine or other confounders that present during medical treatment. The cause of ADE may not come from the pharmacology of medicine. Adverse drug reaction is also included in adverse drug events**.**(1) Adverse drug reaction (ADR) is any unwanted symptom, or abnormal laboratory finding including diseases that are related to drug administration under normal conditions of use.(2) ADR is classified six types as follows:(16)

Type A reaction (augmented) is reaction that is related to a pharmacological action of the drug. The severity of symptom depends on dose of drug (dose-dependent).

A reaction has high incidence (more than 80%) and can be predictable. The reaction can be resolved by reduced dose or withhold or consider effects of concomitant therapy.

Type B Reaction (bizarre) is reaction that is not related to a pharmacological action of drug and not predictable. This is less common (less than 20%), but has high mortality. The reaction can be resolved by withdrawal and avoidance in the future.

Type C Reaction (chronic) is reaction that is related to the cumulative dose. This type can be divided into three subtypes such as adaptive changes, rebound phenomena and other effects. This reaction is uncommon and can be resolved by reduced dose or withheld or prolonged withdrawal.

Type D Reaction (delayed) is reactions that are usually dose-related. It occurs or becomes apparent sometime after use of drug. The reaction is often intractable.

Type E Reaction (end-of-use) is reaction that is associated with the withdrawal of drug. The reaction can be resolved by reintroduction and withdrawal slowly.

Type F Reaction (failure) is reaction that is related to dose of drug. It is often caused by drug interaction. The reaction can be resolved by increase or decrease in dosage or consider effects of concomitant therapy.

ADRs are the major healthcare problems causing both morbidity and mortality of patients and are associated with huge economic burden on health care systems around the word.(17, 18) The severity of ADR depends on the intensity of events which affect patients' everyday life. It can be classified into three levels; mild, moderate and severe. Seriousness of ADR is based on action criteria or outcome of patient or event. Serious adverse drug reaction is any unfavorable medical occurrence at any dose as one in which patient outcome is death, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, life-threatening or results in a congenital anomaly or birth defect.(1)

Situation of adverse drug reaction in the world

Adverse drug reactions are the significant cause of morbidity and mortality worldwide. The incidence and the cost of adverse drug reaction has been studied in many countries. In the United Statse, ADR is ranked as fourth and sixth leading causes

of death.(19, 20) Around 5-20% of all hospitalised patients had ADRs and 3-28% of all hospital admissions were related to an ADR.(21) ADRs leading to prolongation of existing hospitalisation and fatal were 8.25% and 19.18%, respectively. The treatment cost of ADR which was 19.86% of medical care, 9.15% of drugs and 2.82% of laboratory charges was increased.(20) The estimated cost of ADR management was 30.1 – 130 billion US dollars per year, depending on the severity of case scenario.(4, 5) Around 30–60% of ADRs might be preventable.(19) he number of adverse events that were reported to FDA during 2008-2017 is shown in Figure 1. (22)

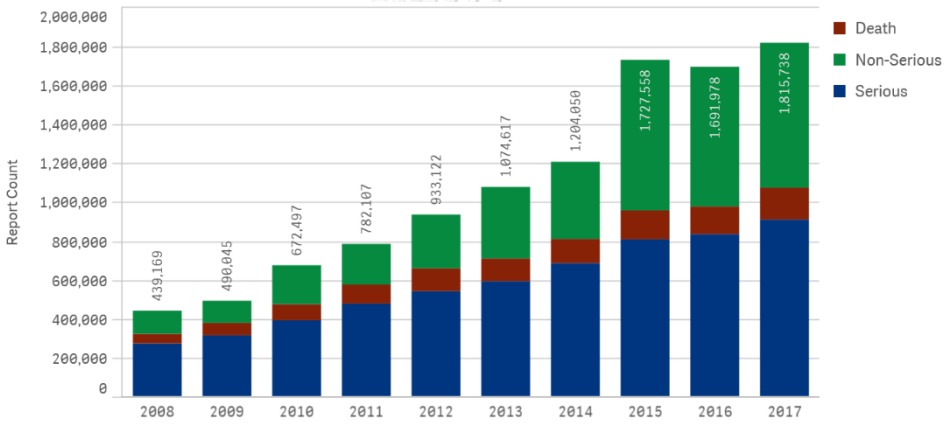

Figure 1 The number of adverse event reports divided by seriousness during 2008-2017

In Switzerland, around 11% of all hospitalisations occurred because of ADRs and approximately 3.3% of all hospital admissions were related to ADRs. ADRs caused prolonged hospitalization which were around 8.6% of hospital days. The incidence of death possibly related to ADRs was 1.4%.(23) In 2009, 4,914 ADR cases were reported; with 37% of non-serious cases, 31% of medically important conditions, 27% of hospitalisations, 3% of life threatening, 2% of disabling, 0.1% of congenital anomaly and 4% of fatal.(Figure 2)(24)

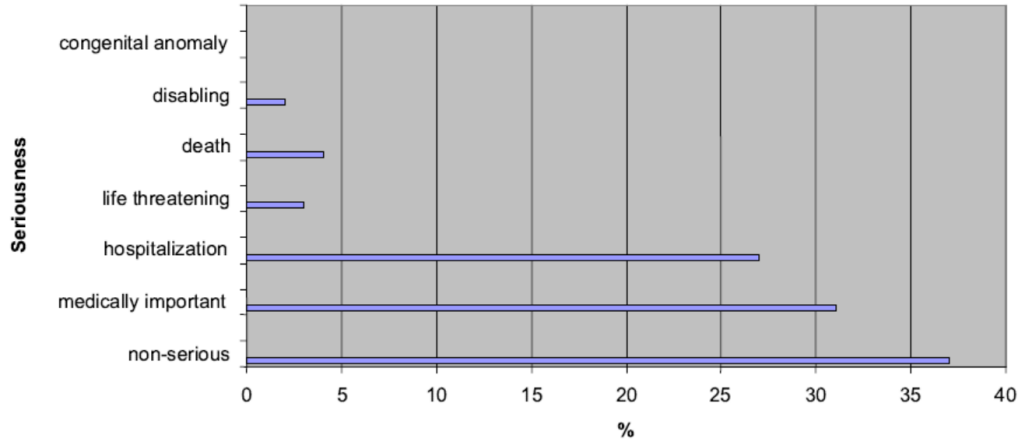

Figure 2 Distribution of ADR case reports by seriousness in 2009

In the United Kingdom (UK), the prevalence of ADR was 6.5%. Around 80% of those ADRs resulted in hospital admission and 0.15% were fatal. The median length of hospitalisation was eight days. The expected annual cost of the hospital admissions was 466 million pounds.(25)

In Australia, 6.88% of patients who were admitted at Victorian public hospitals had at least one adverse event. They stayed longer than 10 days and their life-threatening complication was more than seven times compared with those without complications. In 2003-2004, the total cost of adverse events was 460.311 million Australian dollars of which the total expenditure on direct hospital costs was 15.7% or the total inpatient hospital budget was increased 18.6%.(6)

Around 5.7% of all admitted patients in a Dutch hospital had one or more adverse events and 12.8% of those adverse events resulted in permanent disability or contributed to death.(26) The direct medical costs were increased due to adverse event and had impact on the annual healthcare budget. The total of direct medical costs was estimated as 355 million euros per year. Half of those adverse events were preventable.(27)

In Germany, the incidence of hospitalisation possibly related to serious outpatient ADRs was around 3.25%. The average hospitalisation of patients who had ADRs was around 9.3 days. The average cost of a single ADR treatment was

approximately 2,250 euros. The total costs of ADR treatments were 434 million euros per year. Around 20.1% of ADRs were able to be prevented and the cost of treatment could save 87 million euro per year.(28)

In Portugal, the incidence of adverse events in patients attending an outpatient setting was around 0.4 – 9.1 persons per month. The percentage of ADRs leading to hospital admissions was around 5%. About 55% of those ADRs were serious and 6.4% were life-threatening and/or death.(29)

In Thailand, ADRs are associated with a high prevalence of hospital admissions ranging from 15.46 % to 17.72% and prevalence of fatal ranging from 0.11% to 0.38% during 2012-2016. (Table 1)(30)

Table 1 Number of ADRs divided by severity during 2012-1016

Type of ADR	**Severity of ADR**	**2012 (%)**	**2013 (%)**	**2014 (%)**	**2015 (%)**	**2016 (%)**
Unknown	-	6.94	6.25	6.88	7.29	6.96
Not serious	-	72.58	72.87	72.68	73.53	73.88
Serious	Not identified	0.41	0.70	0.51	0.38	0.55
	Results in persistent or significant disability or incapacity	<0.01	0.03	0.04	0.05	0.03
	Requires prolonged hospitalisation	17.72	17.45	17.56	15.93	15.46
	Caused congenital abnormality	-	-	-	0.01	0.01
	Life threatening	0.95	1.33	1.06	1.21	0.90
	Death	0.11	0.20	0.16	0.12	0.38

Pharmacovigilance and reporting system

Pharmacovigilance is “the science and activities which relate to detect, assess, understand and prevent adverse effects or any other drug-related problem. The purposes of pharmacovigilance are to improve patient care and patient safety from the use of

medicines, medical and paramedical interventions, to improve public health and safety of medicines use, to support the assessment of benefit and risk of medicines, encouraging safe, rational and more effective (including cost-effective) use of medicines and to promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public.(31) The scope of pharmacovigilance covers adverse drug reactions or events, interaction between medicines, lack of efficacy of medicines, medication errors, misuse and abuse of medicines and counterfeit or substandard medicines. The monitoring applies to all healthcare products which are conventional medicines, herbal medicines, other traditional and complementary products, biological products, vaccines, blood products and medical devices.(32)

Drug safety was defined a long time ago (the 1800s to the mid-1900s)(33), but it was not given precedence until the tragedy of thalidomide occurred. Thalidomide was marketed in 1957 and its indication was to relieve morning sickness and nausea. Thalidomide was the drug of choice to use for nausea and vomiting in pregnant women and physicians widely dispensed it in Europe, Australia, Africa, Asia and the Americas. Allegedly, Thalidomide was safe and had not toxic. In the early 1960s, more than 10,000 cases in over 46 nations found birth defects in women who took Thalidomide during pregnancy. By then, all children born had amelia or phocomelia of legs, arms, feet and hands; spinal cord defects; cleft lip or palate; absent or abnormal external ears; heart, kidney, and genital abnormalities; and abnormal formation of the digestive system. This event alerted a worldwide response to prevent a recurrence and increased importance of pharmacovigilance in many countries.(34)

In 1968, the WHO established the pilot project as “the Programme for International Drug Monitoring (PIDM)”. PIDM is a systematic collection of information on serious adverse drug reactions during the development of medicines and marketing of medicines. Initially, only 10 countries from Australia, Europe and North America participated in the program. Each member country is a national center to collect and evaluate all spontaneous reports which are suspected of ADRs sent by the health professionals. Then, these national centers submit suspected adverse drug reaction reports to the WHO global database.(35, 36) PIDM now cover many countries.

As of January 2016, there were 123 countries that joined the WHO PIDM, and 28 associate member countries awaiting full membership.(37)

The interactions of the pharmacovigilance system at the local, regional, national and supranational levels are shown as Figure 3. At the local level, healthcare providers (HCPs), patients and manufacturing industries send suspected ADR reports to regional or national centers for collection. The regional or national center analyses and evaluates the report before forwarding information to the WHO individual case safety report (ICSR) database. After that, the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden (UMC) sends significant feedback to the national pharmacovigilance centers after findings are promptly communicated.(32)

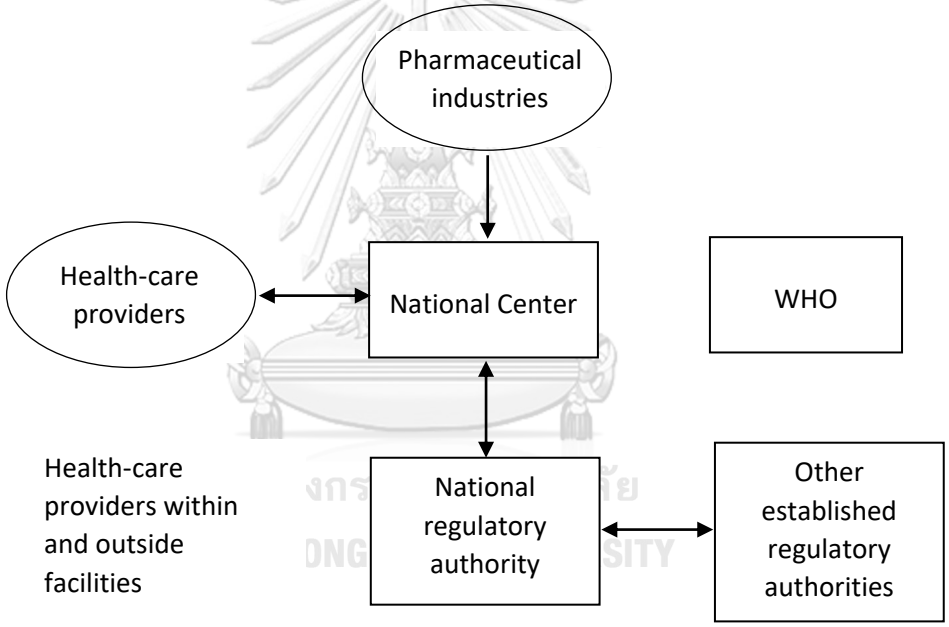

Figure 3 Diagrammatic representation of the pharmacovigilance system

There are three Pharmacovigilance Methods as follows:(38, 39)

1. Passive Surveillance consists of:
    - *Spontaneous Reports* is a voluntary communication by healthcare professionals or consumers to company, regulatory authority or organisation that reports any ADRs of a patient who receives one or more medicinal products. The communication does not derive from any studies or any organised data collection projects. The

spontaneous report is a major method to identify safety signals after a drug is authorised in markets. Since there are limitations in clinical studies which are sample size of the patient population, narrow population, narrow indication and short duration, any adverse effects of drugs or adverse drug reactions may not be detected during clinical studies. Therefore, spontaneous report can provide important information about at-risk groups, risk factors and clinical features of known serious adverse events. The weak point of this method is that reports are often incomplete information and the rate of reporting depends on many factors which are time, media attention, regulatory activity of pharmacovigilance, and the indication for use of the drug.

- *Case Series*: An evidence of an association between a drug and an adverse event was found in a series of case reports and can be used to generate hypothesis.

2. Stimulated Reporting: Many methods are used to stimulate and encourage health professionals to report ADRs in specific situations which are new products or limited time periods. For example, using on-line reporting of adverse events and systematic stimulation of adverse events reporting encourage health professionals to report ADRs, but the limitations of passive surveillance are still present, especially missing information and selective reporting. Early Post-marketing Phase Vigilance (EPPV) in Japan has been set up to stimulate adverse event reporting in the early post-marketing phase. Pharmaceutical companies are leaders to stimulate adverse event reporting by notifying healthcare professionals about new therapies and providing safety information of medicines administration in the general population. This method is a spontaneous event reporting; therefore, the information from this method is not able to provide accurate incidence rates, but rates of reporting can be estimated.
3. Active Surveillance, in contrast to passive surveillance, pursues to completely determine adverse events using a continuous pre-organised process by the follow-up of patients who participate in a risk management

program and receive a particular drug. Patients who receive the drug may be asked to complete a brief survey form and give permission to follow up. In general, the individual adverse event reports by an active surveillance system provided more complete information than the reports by a passive reporting system.

- *Sentinel Sites*: It is an active surveillance that collects ADRs by reviewing medical records or interviewing participating patients and/or physicians in sentinel sites. The data of ADR report is complete and accurate. The selected sites can provide information, which is data from specific patient subgroups, that cannot be collected from a passive spontaneous reporting system. The major disadvantages of sentinel sites are the problem of selection bias, small numbers of patients, and higher costs. Active surveillance with sentinel sites is the most efficient for drugs which are mainly used in site settings such as hospitals, hemodialysis centers, nursing homes, etcetera. Drug products are frequently used in institutional settings and they can provide evidence for dedicated reporting. Moreover, using computerized laboratory reports, which systems have automatic detection of abnormal laboratory values, in selected clinical settings can provide an efficient active surveillance system. Intensive monitoring of sentinel sites can also be helpful to identify risks among patients taking orphan drugs.
- *Drug Event Monitoring* is an active pharmacovigilance surveillance method. Electronic prescription data or automated health insurance claims are used to identify patients. After that, each prescribing physician or patient receives the follow-up questionnaire at pre-specified intervals to provide outcome information. The questionnaire includes information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical events, and reasons for discontinuation. The advantage of drug event monitoring is to obtain more detail of adverse events from a large number of physicians and/or patients.

On the other hand, the limitations of drug event monitoring may be low response rate from physicians and patients.

- *Registries*: A registry is a list of specific patient groups who have a specific disease (disease registry) or a specific exposure (drug registry). The data of drug exposure and other factors associated with a clinical condition can be collected by disease registries, such as registries for blood dyscrasias, severe cutaneous reactions, or congenital malformations etcetera. A disease registry is helpful for a case-control study. The study compares the drug exposure of cases identified from the registry and controls from either patient with another condition within the registry, or patients outside the registry. If a drug has a special impact on the group of patients, exposure (drug) registries can determine populations who were exposed to drugs of interest (e.g., registry of rheumatoid arthritis patients exposed to biological therapies). A cohort study requires prospective follow ups of patients over time using standardised questionnaires. However, a cohort study can assess incidence, but cannot prove the association without a comparison group. This registry is helpful for signal detection and investigation of the safety of drugs in a specific situation.

Pharmacovigilance in the United States

The Food and Drug Administration (FDA) and the American Medical Association (AMA) started to collect voluntary reports on adverse drug events (ADEs). The FDA set up ADE registries for the voluntary suspected ADEs reports from physicians and hospitals in 1950s. In the 1960s, the FDA began a continuous surveillance of ADEs. The Kefauver-Harris amendments to the Food, Drug and Cosmetic Act required pharmaceutical companies to report all unexpected ADEs in premarketing clinical trials of their drugs under investigations to the FDA in 1962 and established computerized Spontaneous Reporting System (SRS) in 1965. Since ADE reporting was voluntary, information on the reports that identified the relationships

between drug therapy and drug toxicity or of the incidence rates of ADEs were not adequate.(40)

In 1993, the FDA launched a safety information and adverse event reporting program called MEDWATCH. The MEDWATCH is a voluntary Medical Products Reporting Program for healthcare professionals to report suspected adverse drug reactions, adverse drug events or medication error to FDA. In November 1997, the FDA established a pharmacosurveillance tool called Adverse Event Reporting System (AERS); called FAERS in 2013. The FAERS is a database to classify and search for medically significant adverse events. Electronic ADEs submissions to FAERS helps automatic signal-generation. Thus, FAERS is the tool developed for the analysis of potential adverse event signals.(1, 40, 41)

The adverse events are evaluated by clinical reviewers in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). This evaluation may affect FDA regulatory actions which are to change drug label, communicate new safety information, restrict the use of the drug or withdraw the drug from the market. If drug use shows potential serious risks, the FDA will use a boxed warning on product information inserts and other drug literature to inform the healthcare provider about appropriate drug use, e.g. patient selection, monitoring, prohibited concomitant medication, adjunctive therapies to administer, or contraindication including evaluation of the risk and benefit of the therapy.(1)

ADR reporting is voluntary for health professionals and consumers, but it is mandatory for pharmaceutical companies including drug or biologic manufacturers or packers and medical device manufacturers, distributors and user-facilities.(42) Consumers reporting system has been available in the US since 1960s.(43) Consumers can report adverse events including serious drug side effects, medication errors or product use errors, product quality problems, and therapeutic failures through reporting by Online (MEDWATCH), consumer Reporting Form FDA 3500B or Reporting Form FDA 3500 and then fax or email to FDA and call 1-800-FDA-1088 to report by telephone (Toll free). The medical products which are reported to FDA are drugs (both prescription and over-the-counter medications), medical devices (e.g., implants, pacemakers, stents, glucose test kits, and infusion pumps), biological products (e.g.,

blood components, human cells, tissues, and cellular and tissue based products), cosmetics and foods (including beverages and ingredients added to foods, dietary supplements, infant formulas and medical foods).(44) The FDA has established a web-based learning tool called MedWatchLearn to educate students, health professionals and consumers to provide the best information reporting for reviewers to further examine a problem.(45) In 2017, the percentage of consumers reporting was around 46.5%. The trend of adverse events reporting from consumers is shown in Figure 4. (22)

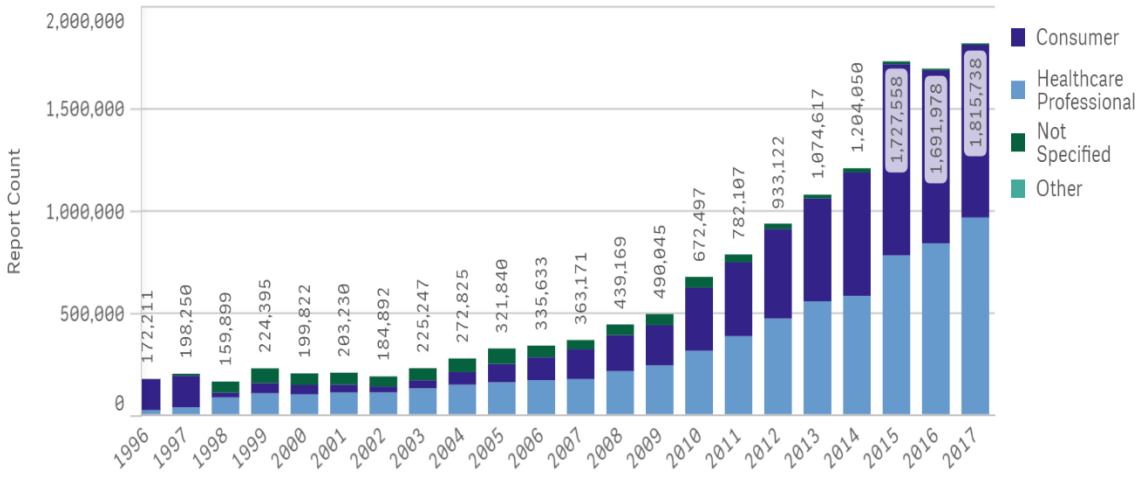

Figure 4 The number of adverse event reports by Healthcare Professional (HCP) and consumer during 1996 – 2017

Pharmacovigilance in United Kingdom

After the thalidomide disaster, the Committee on the Safety of Drugs (CSD); changed the name to the Safety of Medicines (CSM) in 1970; was established to advise about drugs on toxicity, clinical trials and therapeutic efficacy and adverse reactions in 1963. Then, the spontaneous ADR reporting scheme called “Yellow Card Scheme” was initiated in 1964. A physician or dentist can directly report suspected ADRs to the Medicines and Healthcare products Regulatory Agency (MHRA) through Yellow Card Scheme. The purpose of yellow card system is to collect spontaneous ADR reports of all licensed and unlicensed medicines including herbals irrespective of legal status. The Yellow Card Scheme can alert the MHRA and CSM about new signals or potential safety concerns about a previously unrecognized side effect or ADR which are related

to a specific drug. A signal of an ADR can be confirmed by the literature or post-marketing studies and is evaluated for comparative risks of related drugs.(7, 33, 46)

In 1967, a computer system for storing ADR reports was introduced and physicians and dentists who contributed to the Scheme received the first confidential feed-back. In the same year, the CSM was one member who participated in the World Health Organization (WHO)'s Pilot Study on the Monitoring of Adverse Reactions to Drugs. In 1971, the Yellow Card was revised by CSM. The required information of ADR on new version of Yellow card included more detail than the original version and the revised scheme encouraged ADRs reporting.(46) In the 1980s, four regional monitoring centers (RMCs) or Yellow card centers (YCCs) which are Merseyside (Liverpool), the Northern region (Newcastle), Wales (Cardiff) and the West Midlands (Birmingham) were introduced. The main purpose of the YCCs is to support education on pharmacovigilance and increase awareness of the Scheme.(33)

In 1995, electronic reporting of suspected ADRs to the MHRA were available and some pharmaceutical companies started submitting reports via the MHRA's Adverse Drug Reactions Online Information Tracking (ADROIT), and Electronically Generated Information Service (AEGIS). In the late 1990s, many healthcare professionals were working on computerized systems, because ADR reporting by paper was not convenient. Healthcare professionals were able to submit ADR reports by either the electronic submission of reports via a modem or semi-automated completion of an electronic Yellow Card which was subsequently printed out and posted to the MHRA. In 2002, the electronic Yellow Card on the MHRA website was launched and the Yellow Card website was redeveloped following the ICH E2B standard, enabling Yellow Cards submitted via the website to be automatically transferred to the MHRA's Sentinel database in 2008.(33)

The Yellow Card Scheme accepted ADR reporting by hospital pharmacists in 1997, community pharmacists in 1999, nurses in 2000 and patients in 2005.(7, 33, 41) Initially, the MHRA piloted a scheme for patients reporting in 2005 and found that patients reported significantly suspected ADRs more than healthcare professionals. Healthcare professionals focused on reporting of serious reactions that result in hospitalisation, and life threatening or death. Patient Yellow Card reporting was

formally set up in the UK in 2008. Patients can directly report ADRs to the MHRA by post, telephone or via the Internet. The MHRA created the specific ADR report form for patients.(47) The MHRA launched a six-week campaign that stimulated community pharmacists to inform patients about the Yellow Card Scheme during counselling. The MHRA increased patients' awareness of the patient reporting scheme that all pharmacists sent an information pack containing patient Yellow Card reporting forms, information leaflets and a poster to patients. In addition, copies of patient Yellow Cards were also distributed to general practice surgeries, pharmacies, hospitals, National Health Service, Primary Care Trusts and various other patient organisations. On 14 July 2015, MHRA launched the Yellow Card mobile application to report suspected reactions and receive up to date information of medicines. After the application had been launched for 2 months, there were 27 suspected adverse drug reaction reports which have contributed to signal detection activities.(48) The number of ADR reports from patients during 2008 - 2012 is shown in Figure 5.(33)

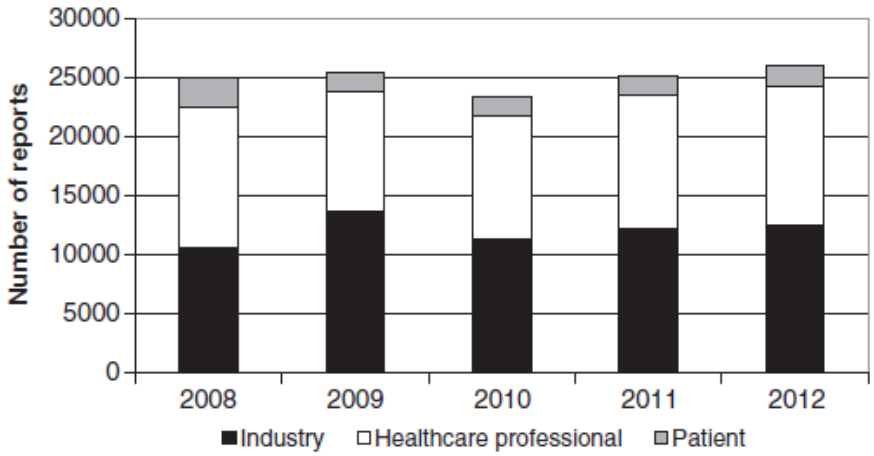

Figure 5 Spontaneous ADR reporting by source during 2008–2012

Pharmacovigilance in France(13, 33, 41, 49)

In 1979, a spontaneous reporting system with a network of 15 regional centers was established in France. The network was extended to 29 centers in 1984 and 31 centers in 1994. ADRs reporting was mandatory for prescribers and marketing authorisation holders in 1984 and pharmacists in 1995. The National Agency for the Safety of Medicines and Health Products (L'Agence nationale de sécurité du

médicament et des produits de santé or ANSM); was established as the French government agency in 1998. The ANSM functions under the Ministry of Health and has the authority to monitor and regulate health products including pharmaceuticals, biological products, medical devices, and cosmetics.

The France Pharmacovigilance system is based on a decentralized collection and validation of safety data through a network of 31 regional pharmacovigilance centers (RPVCs). A centralized evaluation and decision-making process was coordinated by the French National Agency for the Safety of Medicines and Health Products (ANSM). The RPVCs have an intervention and form a monitoring network covering the whole country. These decentralized structures are a unique system for collecting ADRs in French and this system can encourage exchanging information with healthcare professionals. RPVCs are located in departments of clinical toxicology or clinical pharmacology in the academic medical hospitals and have a scientific association included within the French Pharmacological Society.

The duty of RPVCs are to collect, record and evaluate adverse drug reactions (ADRs) reports and transfer them to a common national database after they have assessed the causality. The common national database of the Security Department of the ANSM directly connects to the RPVCs. The heads of the RPVCs have monthly meetings at the ANSM in the Technical Committee (Advisory Board). The responsibility of the Technical Committee is to coordinate the collection and evaluation of ADRs information from surveys. The Technical Committee provides recommendations to the General Director of the ANSM to prevent, reduce or eliminate drug-related accidents.

The national pharmacovigilance system is implemented by the ANSM. On May 1st, 2012, the ANSM superseded the task and duty of French Agency for the Safety of Health Products or AFSSAPS (l'Agence française de sécurité sanitaire du médicament et des produits de santé) and received a broader authority to monitor and evaluate health products. The ANSM also actively participates in standardising and harmonising regulations and practices in the European market.

The National Agency for Medicines and Health Products Safety (ANSM) has allowed patients reporting ADRs since June 2011. The reporting form can be

downloaded from the ANSM website and patients can send it by e-mail or mail to their pharmacovigilance center. The ANSM reporting form can be completed electronically. The ANSM reporting form consists of two pages and the details of the adverse reaction can be described on the second page. The requirement of essential information is instructed and indicated at the bottom of the second page in small type. A patient organisation can help patients to complete the template and patients can send the results of medical tests or other documents that relate to ADRs attached to the reporting form. The contact details of the patient's healthcare professional who has to receive feedback of ADR reporting have to be mentioned on the report form.

Some Centre Regional de Pharmacovigilance (CRPVs) send regular feedback to reporters. The social media tools such as a Twitter etcetera, are used to increase awareness about ADR reporting. The ANSM has activities to promote spontaneous reporting and to distribute informational materials to patient and consumer organisations. The consumer organisations can initiate their own activities of ADR reporting. For example, the consumer organisation, UFC Que-Choisir, increases awareness within the general public about adverse drug reactions and patient reporting using publications and website. In 2013, 46,843 ADR reports from CRPVs (initial and follow-up) were sent to the ANSM. 2,151 reports were submitted by patients. In 2014, the number of ADR reports slightly decreased to 46,497 reports (initial and follow-up). Only 1,983 reports came from patients. The percentage of patient reporting has remained stable over time. There are only 5% of all reports in the national database which came from patients.

Pharmacovigilance in the Netherlands(13, 33)

There are two main players in pharmacovigilance in the Netherlands which are the Medicines Evaluation Board (MEB) and the Netherlands Pharmacovigilance Centre Lareb. The Netherlands Pharmacovigilance Centre Lareb is the responsible organisation to maintain the spontaneous reporting system for collecting ADR reports, including reports of vaccines. Lareb, which is a regional cooperation between pharmacists and general practitioners, has started since the 1980s. The purposes of Lareb are to detect ADRs and improve pharmacotherapy.

Since conflicts of interest are possible from one organisation that is a part of decision maker in the registration and the safety monitoring of the approved drug, Lareb is the independent foundation; not a part of the regulatory authorities. Lareb became the national center for ADR reporting in 1996 and it expanded the group of reporters to general public at the beginning of the 21st century and patients in 2003. The Lareb board comprises of representatives from the large Dutch medical, pharmacists' associations and patient organisations. Lareb also is the knowledge center that provides the information of drugs; drug use during pregnancy and lactation and possible teratogenic effects of drugs, to health professionals and members of the public.

The Medicines Evaluation Board (MEB) has a responsibility to the drug registration in the Netherlands and coordinates all pharmacovigilance activities that have related regulatory implications. The MEB evaluates the continuous benefit or harm of the drug and assesses the updated safety reports. The updated safety reports are periodically submitted by the marketing authorisation holders (MAHs). The MEB is authorised to change the conditions of marketing drugs which are the relabeling of drugs insert and removing drugs from the market.

In the Netherlands, healthcare professionals and patients can report suspected ADRs of medicines and vaccines to Lareb using a paper form or the reporting forms on the Lareb website. The reporters receive feedback after submission. All submitted reports are individually coded using the MedDRA terminology and assessed. A report is uploaded in the Lareb database and an anonymous copy is uploaded in the EudraVigilance database of the EMA and the database of the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre in Sweden. While, a copy of the reports submitted to the EudraVigilance database by the MAH is also forwarded in the Lareb database. All spontaneous reports in Netherlands are filed in the Lareb database. The MAHs will get a copy of the reports on their products within 15 days after ADR data of their products were sent to Lareb.

Over the past years, the number of ADR reports has gradually increased in the Netherlands. Most of the ADR reports have come from healthcare professionals. (Figure 6).(33) In 2011, 11,420 reports which included 4,968 by healthcare professionals and 2,089 by patients were submitted to Lareb. Around 1,421 reports were

associated with vaccinations. Lareb has improved the mechanisms of ADRs reporting since 2012. The number of ADR reports has dramatically increased. Lareb received 17,057 reports in 2013; with 3,961 reports by patients or consumer, and 21,713 reports in 2014; with 4,393 reports by patients or consumer. Approximately 95% of reports were electronically submitted.

Many strategies are used to improve patients' reporting such as electronic reporting for patients and campaigns, etcetera. The patients' reporting e-form is promoted on the main page of Lareb's website (Dutch version). Patients, their relatives or caretakers can complete the ADR report with only five steps. A help function icon that instructs patients to accurately complete the template is available and is next to the questions. In addition, there are the tips provided how to improve the reporting form in the last section of the e-form. Individualised feedback is provided by Lareb in the case of serious reports. The response is to specificy a question, and/or to provide a recommendation for the patient, and in relation to reports that may have legal implications. Moreover, statistical summaries of all ADR submission reports are available and information with brand name or international non-proprietary name is listed on online.

Lareb's Board consists of 10 members which have two patient representatives. The Foundation works with patient and consumer organisations to promote the direct patient reporting. Lareb launched campaigns and cooperated with the Central Bureau for Drugstores to promote the reporting of over-the-counter (OTC) medicines. Information leaflets explaining how to report have been provided to all consumers who buy OTC drugs. This campaign could increase the number of reports on OTC medicines by 170%.

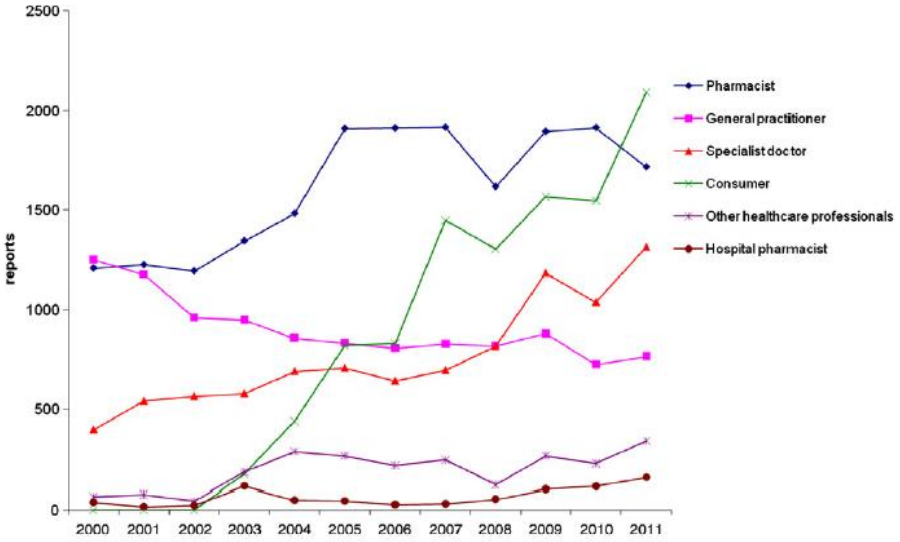

Figure 6 Number of reports stratified by source since 2000

Pharmacovigilance in India(33, 50-52)

ADR monitoring program consisting of 12 regional centers was set up in 1986, but it was not successful. India became a member in the World Health Organization (WHO) Adverse Drug Reaction Monitoring Program in 1997. National Pharmacovigilance Centre consists of three centers for ADR monitoring. The main responsibility of these centers was to monitor ADRs of the marketed medicines in India, but these centers were not functional. This was because prescribers had never accessed the required information of ADR reporting and function of centers. Moreover, there was no funding from government. Thus, this program failed.

In Jan 2005, National Pharmacovigilance Program (NPVP) was established by the supporting of WHO and World Bank. The NPVP was supervised by the National Pharmacovigilance Advisory Committee based at the Central Drugs Standard Control Organisation (CDSCO) as the national regulatory body in India. The NPVP had two zonal centres which were the south-west zonal centre (Mumbai) and the north-east zonal centre (New Delhi). Both centers collected information from the whole country and send it to the committee and the Uppsala Monitoring Centre in Sweden. However, the program was not successful.

In late 2009, the Department of Pharmacology, India Institute of Medical Sciences (AIIMS) and CDSCO brainstormed to restart NPVP. The NPVP was changed name to "the Pharmacovigilance Programme for India (PvPI)". The PvPI became functional in mid July 2010. New Delhi was set up as the National Coordination Centre (NCC) to monitor ADRs in the country for safe-guarding public health. In 2010, twenty-two Adverse Drug Reaction Monitoring Centres (AMCs) including AIIMS, New Delhi was established under this program.

In mid of April 2015, the NCC (New Delhi) was moved from the AIIMS to the Indian Pharmacopoeia Commission (IPC), Ghaziabad, Uttar Pradesh to ensure the implementation of this program was more effective. Indian Pharmacopoeia Commission (IPC) is an autonomous body under the Ministry of Health and Family Welfare in India. It functions as a National Coordination Centre (NCC) for PvPI. The main purpose of the NCC at IPC is to generate independent data on the safety of medicines and become the global drug safety monitoring standard. The main responsibility of NCC is to monitor all ADRs of medicines which occur in Indian population and to develop and maintain its own pharmacovigilance database for patient safety which focuses on usage of medicine in India.

ADR reporting is voluntary in India. All healthcare professionals can report ADRs using Suspected Adverse Drug Reaction Reporting Form that can be downloaded from the official website of IPC (www.ipc.gov.in) or CDSCO (www.cdsco.nic.in). NCC-PvPI has allowed patients to report ADRs and launched "Medicines Side Effect Reporting form for Consumer on 1st August 2014. Patients can download the Medicines Side Effect Reporting form for consumers from the official website of IPC (www.ipc.gov.in). Healthcare professionals and patients or consumers can report ADRs to the nearest Adverse Drug Reaction Monitoring Centre (AMC), directly reporting to the National Coordination Centre (NCC), send email to pvpi@ipcindia.net or call on Helpline (Toll Free) at 1800 180 3024. In addition, PvPI established the ADR reporting application as a smart phone application for android users on 22nd May, 2015. Physician, pharmacists and other healthcare professionals can instantly report ADRs from across the country using this application. During Apr 2015 – Mar 2016, the NCC-PvPI received a total of 63,970 reports which were 56% by the physicians, 19% by

other healthcare professionals, 13% by pharmacists and 12% by consumers or other non-healthcare professionals. (Figure 7)(53)

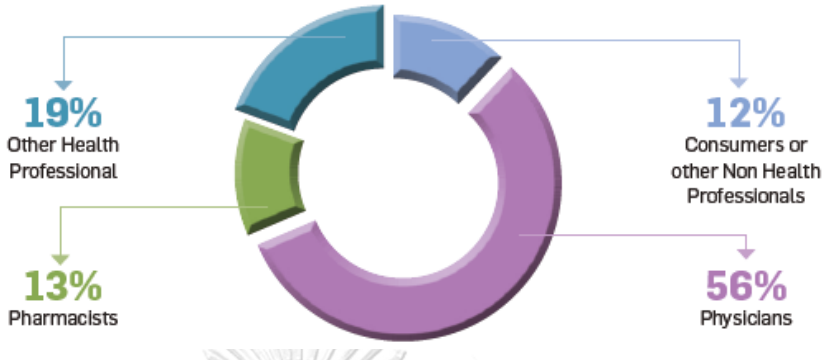

Figure 7 Reporter wise Distribution of ICSRs received at NCC-PvPI (2015-2016)

Pharmacovigilance in Thailand(30, 54, 55)

The Ministry of Public Health (MOPH) and two faculties of medicine cooperated and developed the pilot ADR monitoring program which was officially processed in hospitals under MOPH in 1980. In 1983, adverse drug reaction monitoring center (ADRMC) under the Food and drug administration (FDA) was established. The responsibility of ADRMC was to collect, analyse and evaluate adverse drug reactions reported from hospitals. ADRs were evaluated for the severity, scope and cause using data of epidemiology and statistics. The summary report of ADRs was submitted to FDA. Then, FDA resolved the problem and sent the result to related persons. In 1984, Thailand joined in WHO International Drug Monitoring Program and has been the 26th member since then.

Adverse drug reaction monitoring center changed its name to “Adverse Product Reaction Center” in 1997. Adverse Product Reaction Monitoring Center has expanded to monitor all products under the responsibility of FDA which are medicines, drugs, food, cosmetics, medical devices and health hazard products. In addition, the Adverse Product Reaction Monitoring Center has expanded the ADR monitoring to other healthcare services; drug stores and public health centers. Finally, Adverse Product

Reaction Monitoring Center was changed to be named as “Health Product Vigilance Center (HPVC)” to be consistent with the responsibility of the organisation in 2008.

In 2010, HPVC had developed the area of surveillance by dividing into regions following the inspecting zones of MOPH (18 regions) and developed the adverse event report in online system. Then, HPVC revised the area of surveillance to be 12 regions following the region of healthcare service of MOPH and Health insurance office. The HPVC has supported entrepreneurs to safely report information and has generated the guideline of safety reporting of medicines and biosimilar products. They have expanded the type of report that covers all problems of products such as medical error, product defect, pregnancy exposure, lack of efficacy, off label use, etcetera. In 2017, the HPVC expanded the surveillance and risk management to medical devices.

The operation of HPVC is a network model in which over 800 public and private hospitals have participated in the ADR monitoring program. The responsibilities of HPVC are surveillance and report of adverse events of health care products to FDA. The types of surveillance are spontaneous reporting of ADR, safety drug monitoring program, intensive drug monitoring (drug event monitoring) and registry. The roles of HPVC are as follows:

1. To research, develop and stimulate the safety monitoring system of sustainable healthcare products.
2. To be international pharmacovigilance to conduct management database of ADR from Thai healthcare products and cooperate with network safety monitoring of in-country and aboard.
3. To evaluate signal detection and assess the use of healthcare products and their benefit and risk according to evidenced based research including establishment of risk management.
4. To investigate epidemiology and risk management of healthcare products.
5. To exchange information between other domestic and international healthcare organisations to improve the effectiveness of pharmacovigilance network.

6. To distribute information of healthcare products to healthcare professionals through media.

Vigilance Network(55)

The vigilance network consists of public and private hospitals covering primary, secondary and tertiary levels of the whole country which are more than 1,000 centers. This network includes entrepreneurs and drug stores to monitor adverse events and to send reports to the HPVC. The network operations are divided to 3 levels which are as follows:

Level 1: Hospital

Hospitals, clinics and health service units are the most important sources of ADR report in surveillance system. The surveillance system is the collaboration between physicians, pharmacists, nurses and other medical personnel and there is at least one pharmacist who is assigned to be a main coordinator. The main coordinator's responsibility is to develop the protection system from harm of drug use through dispensing process and pharmaceutical care; counseling, preventing the preventable ADR, preventing recurrent drug allergy including evaluation of the relationship between adverse event and drugs, collecting ADR reports and sending them to HPVC and feedback related information to related reporters.

Level 2: Province

There are many public and private hospitals and healthcare service centers in each province. The regional vigilance network is established by pharmacists in several provinces who have responsibility for surveillance. The provincial network may consist of hospitals, healthcare service centers, provincial public health offices, faculties of pharmacy and drug stores. The purpose of the network is to support surveillance system, develop human resource and resolve any problem of hospitals and healthcare service centers in the provinces such as conference or using social media to exchange information and experience etcetera. If a problem occurs at regional level, provincial public health offices will be responsible to resolve it or send it to other related provinces. If a problem occurs in country level, the problem will be sent to MOPH. However, the provincial network has not yet covered every province.

Level 3: District of health service

The regional network is similar to the provincial network, but the regional network has a wider scope than provincial network, covering the provinces in the district. In addition, the regional network focuses on the development of reporting system and human resource. The limitation of this regional network is the same as the provincial-level that it does not yet cover all districts.

In addition, there is also a network of vaccine products which need surveillance and investigation of adverse event investigation after stimulating the immune system (AEFI network). The office of epidemiology, department of disease control is the main responsible department to control and manage AEFI network under HPVC. Risk management of all drugs including vaccines is under the MOPH responsibility.

Vigilance method

Vigilance system of health product consists of surveillance, collection of adverse event or adverse drug reaction, surveillance of information and related researches regarding safety problem of health products.

1. Pharmacovigilance method
    - ***Spontaneous reporting*** is a main surveillance system worldwide including Thailand. Healthcare professionals and entrepreneurs send adverse event reports to HPVC. The detection of new signals depends on a great number of reports and good-quality reports. The advantage of this method is to provide the highest volume of information at lower cost than other methods.(56) Underreporting of adverse reactions is the main problem in spontaneous reporting.(2)
    - ***Intensified (stimulated) reporting*** is a spontaneous reporting, but adds on some campaigns or activities to encourage the reporting such as Safety Monitoring Program (SMP) etcetera.(55) FDA announced the amended guideline of safety monitoring program on 6 July 2012 that there are two periods for the registration of new drugs. First period, FDA approves the registration of new drug with condition. New drugs can be used in public and private health care centers which have physicians to

closely follow up and monitor for 2 years. Pharmaceutical companies have to submit safety monitoring plan of a new drug to FDA. After FDA committee review and approve the safety monitoring plan, pharmaceutical companies will receive a number of the new drug registration.

Second period, if there is enough safety information of the drug, FDA will approve new drug registration without condition and new drug can be distributed in market. Pharmaceutical companies have safety unit departments that collect, evaluate and report ADR to HPVC. The pharmaceutical companies apply safety monitoring program for all drugs in their companies. Therefore, ADR reporting of drugs is mandatory for pharmaceutical companies.(57)

- ***Targeted spontaneous reporting*** is a spontaneous reporting that specifies the target group (patients or drugs) and/or interested risk. The data from this method can be used to evaluate the incidence or rate of the event. This method is applied in surveillance of patients in risk group in special clinics such as HIV clinic, and tuberculosis clinic etcetera.(55)
- ***Cohort event monitoring*** is a proactive surveillance by epidemiological studies using observations of the suspected adverse events related to one drug or more in a specific duration of time. All patients in a targeted group are interviewed before and after treatment to collect the related information and adverse events. This method is called "Follow up Closely Intensive Monitoring Program (IMP)" which includes the surveillance of influenza vaccine (H1N1), and monitoring adverse drug reactions of herbal medicines in the 1999 national drug list.(55)
- ***Registry***: In Thailand, there are registered patients to surveil drug safety. In 2008, the project “Prospective, Immunogenicity Surveillance Registry of ESA with Subcutaneous Exposure in Thailand” was set up since the number of patients with chronic kidney disease who received erythropoiesis stimulating agents (ESAs) and had severe anemia type pure red cell aplasia (PRCA) increased.(55)

2. Surveillance of other health products

   HPVC has expanded the surveillance covering other healthcare products which are food, cosmetics, medical devices and health hazard products. Spontaneous reporting is used to surveil the safety.(55)

3. Surveillance of safety information

   Surveillance of information consists of information related to change of risk management in foreign countries including new safety issues which are drug withdrawal, drug recall, safety information alert in leaflet and related research that indicated the risks of products.(55)

Situation of Adverse event reporting

HPVC has collected the AE report since 1984. The trend of AE reporting is increasing compared with the past. (Figure 8)(58) HPVC has cooperated with over 800 public and private hospitals to surveil and report adverse events of health care products. Therefore, most AE reports come from health professionals in healthcare centers.(14) No AE reports from consumers have been submitted to HPVC before.

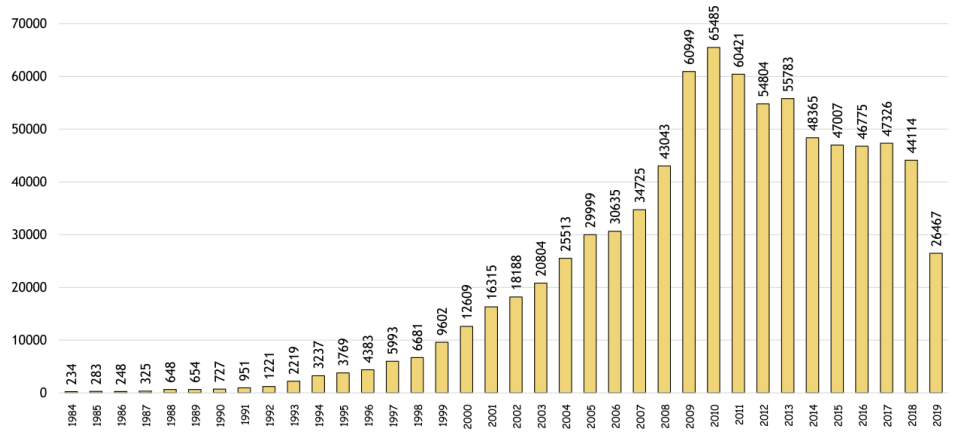

Figure 8 The number of adverse events reported by hospitals and entrepreneurs during 1984 to Sep 2019

ADR reporting is voluntary by healthcare professionals such as physician, pharmacist, nurse, etcetera and entrepreneurs. They can report ADR by four methods which are report through AE online-reporting at http://www.fda.moph.go.th/vigilance, send ARD report by e-mail at adr@fda.moph.go.th, fax ADR report at 02-5907253 or

02-5918457 and send ADR report to HPVC by mail. Health professionals and entrepreneurs should request username and password form HPVC for online reporting. The ARD report form is available at http://www.fda.moph.go.th/vigilance.(59)

The information of ADR; patient information, suspected drug information, healthcare problem, reporter information, captured symptom or disease of patient, duration of ADR, and severity and causality assessment of ADR, should be provided to HPVC. Severity of ADR is classified into two types (non-serious and serious). Serious ADR is any unfavorable medical occurrence that at any dose results in patient death, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, life-threatening or results in a congenital anomaly or birth defect.(59)

Causality assessment is the evaluation of the possible relationship between a medicine and an observed adverse reaction. Causality assessment is usually made according to established algorithms. It is classified to five levels; certain, probable, possible, unlikely and unclassified. The assessment criteria of each level are as follows:

- Certain is adverse event or abnormal laboratory test which occurs with plausible time relationship to suspected drug intake and cannot be explained by disease or other drugs. Adverse event or abnormal laboratory test can be improved after drug withdrawal. The adverse event or abnormal laboratory test recurs after drug re-administration.
- Probable is adverse event or abnormal laboratory test which occurs with reasonable time relationship to suspected drug intake and is not related to disease or other drugs. Adverse event or abnormal laboratory test can be improved or resolved after drug withdrawal, but the adverse event or abnormal laboratory test does not recur after drug re-administration.
- Possible is adverse event or abnormal laboratory test which occurs with reasonable time relationship to suspected drug intake and cannot be explained by disease or other drugs. There is no information or incomplete information after drug withdrawal.

- Unlikely is adverse event or abnormal laboratory test which occurs without reasonable time relationship to suspected drug intake and can be explained by disease or other drugs.
- Unclassified is no information related to drug and adverse event or abnormal laboratory test.(59)

The time frame of ADR reporting is divided by severity of ADR as follows:

- If patient died from drug, vaccine or unexpected or unlabeled ADRs, the initial report of ADR should be submitted to HPVC with 24 hours after awareness and the full report should sent to HPVC within 7 days.
- If the cause of patient death comes from other, the initial report should be submitted to HPVC within 7 days and the full report should sent to HPVC within 7 days. When health professional receives additional information of ADR, the follow up report should be sent to HPVC within 15 days.
- If ADR is serious, the initial report and follow up report should be submitted to HPVC within 15 days and 30 days, respectively.
- If ADR is non-serious, the initial report and follow up report should be submitted to HPVC within 60 days.(59)

HPVC established patient reporting in 2010. The reporting system was posted in the first page of the HPVC website; http://thaihpvc.fda.moph.go.th/thaihvc/index.jsf. Patients can report any problems which have occurred from medicines, drugs, food, cosmetics, and medical devices to HPVC. Since HPVC has not effectively promoted the patient reporting system, the system is not well known and not successful.(60, 61)

Adverse event reporting from patients or consumers in other countries

The First International Conference on Consumer Reports on Medicines in 2000 was set up. The conclusion of the conference was that consumer reporting can provide valuable information in pharmacovigilance. Since consumers have actual experience in adverse events, their report can provide informative, clear and more complete data of adverse event.(10) Patient reports can contribute significantly to signal detection.(62)

Many countries, such as the US, Canada, Australia, New Zealand, Denmark, Sweden and the Netherlands, have allowed patients to report ADRs directly.(7, 63) Adverse drug reactions reporting from patients or consumers have benefit and add value in pharmacovigilance. Consumers can provide primary information about their experience with drugs and their adverse effect affecting people's lives. Patients ADR reporting provided more detail than healthcare professional and it could contribute to understanding of certain ADRs.(7, 8, 64) Normally, patients have no medical knowledge. Patients might provide different information from a medical point of view. Even though, reporting ADRs from patients without medical confirmation might interfere with the evaluation of the ADRs, but getting more data from patients or consumers might detect a true signal.(8)

Many researches studied the comparison of adverse drug reaction reporting between patients or consumers and healthcare professionals.(65-67) In Australia, healthcare professionals usually reported hospitalisation and life-threatening events and medicine-related side effects. While, patients or consumers always reported adverse events that affected their daily activities, and those ADRs were related to medication risk, new adverse reactions of prescription and complementary medicines, identified serious reactions and drug-induced hospitalisations, and mentioned to severity of their symptoms and stress including emotional and social impacts on their lives.(65)

Another study about comparison of suspected ADR reports by patients and health professionals in UK in 2011, found that patients reported ADRs of different group of drugs from health professionals. Therefore, patients reporting could generate new signals and provided the sufficient detail of suspected adverse reaction to evaluate the causal relationship and impact of ADRs on the everyday life of the patient. Patient reports had more detail and more accuracy than health professionals. (66) These results were the same as an India study. The ADR reports form patients provided more detail of ADR narrative while the reports from healthcare professional had no or insufficient narrative. Patients were more likely to emphasize emotional, occupational and social impact of ADRs that affected them. However, the study showed patients usually report mild ADRs while healthcare professional reported moderate ADR.(67)

The advantage of spontaneous ADR reporting by patients or consumers were to stimulate patients or consumers to become involved in their treatment, increase adherence of drug therapy, increase communicate with health professionals and assess the impact of the severity of ADRs on patients or consumers' life. Reporting about severity of ADRs was generally missed in physician's reports.(66, 68) Promoting patients or consumers to become involved in pharmacovigilance would increase spontaneous reporting and early detection of important adverse drug reactions.(7, 68) Thus, patients or consumers are important players in pharmacovigilance who we should not ignore.

Role of community pharmacist

The responsibilities of community pharmacists in healthcare system are as follows:

1. Processing of prescriptions

Community pharmacist reviews the legality, safety and appropriateness of prescription order. If patients' medical records are available, community pharmacist will check them before dispensing medicines to patients. The community pharmacist ensures that the quantities of medicines dispensed to patients is accurate, decides that medicines should be dispensed to patients and provides the counselling of medication handling and administration to patients.(69) Reviewing and dispensing prescription are the main role of community pharmacists in many countries especially Western countries and North America. In Thailand, only 0-1.8% of community pharmacists review and dispenses prescription.(70)

2. Monitoring of drug utilisation and pharmacovigilance

Community pharmacist can compile and maintain information on all medicines and particularly on newly introduced medicines. Community pharmacist can educate patients' about diseases, instruct drug administration, monitor over-the-counter products, reduce the prevalence of adverse drug reaction and drug-drug interaction and suggest alternative therapies. Therefore, community pharmacist is a consultant of drug therapy for patients.(71) Community pharmacist is one channel that patients inform their abnormal symptoms from related medicines. Community pharmacist can detect

adverse drug reactions through reviewing prescription and counselling with patients. ADR reporting is a significant role of community pharmacist.

3. Responding to symptoms minor ailment

Drug store is a primary healthcare service place where patients easily access and buy any medicines for self-administered treatment. Community pharmacist dispenses appropriate medicines to treat patient's illness and provides counselling which includes information of illness, disease and medicine to patient. If community pharmacist decides that patient' illness should be diagnosed by physician or evaluated by physical exam and/or laboratory test, the community pharmacist will refer the patient to clinic or hospital.(69, 70)

4. Refills prescription in chronic disease

Patients with chronic disease such as diabetes, hypertension, hyperlipidemia, etcetera, have to continually treat by taking medicines and physicians usually follow up their diseases. The frequency of follow up depends on the controlling of patients' diseases. Hospital is a primary healthcare service place that patients go to find physicians, to follow up their diseases and to receive medications for treatment. Many patients come to receive healthcare service at hospital, so patients spend a long time waiting for service. Patients may be boring to go to hospital and be lost to follow up. Finally, patients cannot control their diseases. Drug store is an optional healthcare service place that patients can refill their medicines regarding to prescription. Community pharmacist take care of drug administration of the patients, counsel drug administration and follow up their diseases such as blood sugar, blood pressure, etcetera. Community pharmacists contribute to increase compliance of patients and follow up their diseases. If patients' diseases are worsening or not under control, community pharmacist will refer patients to hospital.(70)

5. Diseases screening

Community pharmacies are easily accessible in rural and urban locations. Patients do not make an appointment to visit the pharmacist. Visiting community pharmacist is an alternative channel that patients seek help to manage minor illnesses. Minor illness and some symptoms of patients resemble early signs of non-

communicable diseases, so community pharmacist is primary service to identify the risk factors of diseases, screen diseases and refer patients to hospital for treatment.(70, 72)

6. Health promotion

Community pharmacist can be a part in both local and national health promotion campaigns.(69) Community pharmacist is located in the community, they assist in promoting patient or consumer behaviour and contribute to delay the advance of chronic state and stop the progression of infectious to virulent disease conditions.(73) Community pharmacist provides information about healthcare to patients, encourage patients to modify their lifestyle and protects any diseases in provinces such as smoking cessation counselling, contraceptive counselling, HIV infection counselling etcetera.(69, 70)

7. The service of home visit-based medication therapy management (MTM)

Providing medication therapy management (MTM) service is a model of patient care that uses patient information to continually care for patient. MTM service model consists of medication therapy review (MTR), personal medication record (PMR), medication-related action plan (MAP), intervention and/or referral and documentation with follow-up.(74) The purposes of MTM service by pharmacists are reducing drug related problems, improving the understanding of patients about their state of diseases and drug therapy, helping patients to self-monitor, and collaborate with health care team to optimise drug therapy.(75)

An integrated behavioural model

An integrated behavioural model (IBM) is a model in which constructs come from Theory of Reasoned Action (TRA), the Theory of Planned Behaviour and other influential theories. (Figure 9)(76) The IBM is used to explain and predict behaviour. The model consists of seven main components. Four components directly affect behaviour. First, a person who has knowledge and skills to perform the behaviour has a strong behavioural intention. Second, no or few environmental constraints are barriers to perform behaviour. Third, behaviour should be salient to the person. Finally,

a person has experience to perform the behaviour and the doing is habitual, so the intention is less important in determining individual behavioural performance.

In addition, three components which are attitude, perceptive norm and personal agency influence the behaviour through the impact on behavioural intention. Each component consists of two constructs. Behavioural intention is determined by the three constructs which are attitude, perceived norm, and personal agency in the theory. Their influences on behavioural intention will vary in different behaviours and different populations. Before designing an effective intervention to influence behavioural intentions, it is necessary to investigate the extent to which that behavioural intention is influenced by experiential and instrumental attitude (attitude), injunctive and descriptive norms (perceived norm), and self-efficacy and perceived control (personal agency).(76)

Attitude toward the behaviour is determined by the individual's feeling, belief, or opinion about performing the behaviour. Attitude in the IBM is divided into two constructs such as experimental attitude and instrumental attitude. Experiential attitude is the individual's feeling to behaviour performance. If person has a positive emotional response to perform the behaviour, she or he is likely to perform the behaviour. Instrumental attitude is the individual's beliefs about outcomes of doing a behaviour, as in the TRA or TPB. If a person believes performing a behaviour provides benefit, she or he has intention to perform the behaviour.(76)

Previous studies showed patients or consumers' attitude influenced to self ADR reporting. The main motivation of spontaneous ADR reporting was altruism.(62, 77) Consumers or patients expected that ADR report could help prevent other people from suffering and could be used to improve drug development.(56) Consumers or patients voluntarily informed regulators, pharmacy manufacturers, healthcare professionals and the public about ADRs because they wanted to raise their awareness about ADRs.(78) Consumers or patients expected to get more drug information or get treatment benefit from ADR reporting in the future after ADR reporting. For example, patients got improvement of treatment or practice from healthcare professionals after they informed healthcare professionals about unknown ADRs.(56, 62, 78)

These results were same as researches in Thailand that attitude was a influencing factor of ADR reporting in out-patients.(79, 80) Most patients who had taken statin at least one month had good and very good attitude of ADR reporting.(80) Patients who had experienced an ADR thought that ADR reporting to healthcare professionals would influence their treatment. One-third of them (68%) focused on monitoring ADRs since the ADRs affected their quality of life and thought that ADR reporting was their responsibility.(80) In addition, a qualitative study supported that most patients had positive attitude to report ADRs to regulatory authorities by themselves, because they knew their health status more than healthcare professionals. They also would like to reduce medical staff workload.(81)

More than 50% of patients had expectation that they get more information after they report ADRs to health authorities, healthcare professionals and manufacturers. Some patients expected the authorities confirmed safety and quality of marketed medicines and prescribed medicines after reporting. Most patients expected that their ADR reporting was able to improve medicines, that leaflets might be widely available and the ADRs should be mentioned in leaflets. Healthcare professionals might monitor and manage their abnormal symptoms after they reported ADRs. Moreover, their ADR reporting could help others to be aware of ADRs. While, others stated that no patients know that they could directly report ADR to HPVC. They need the authorities to promote the patient reporting system.(81)

Conversely, few patients did not agree to directly report ADR to regulatory authorities because these patients thought that ADR reporting was not important, they might report incorrect information and ADR reporting process was difficult.(81) Sometimes, occurrence of adverse drug reaction is expected and known, but not serious and suffering. Consumers or patients could resolve the ADR by themselves, so they were more likely to not report ADRs.(56, 82) A study showed that majority of customers or patients had experienced a suspected adverse drug reaction, but they did not inform their healthcare professional. If the adverse drug reaction was not severe, they would decide to self-manage their event by stop taking the medicine or seeking information from the internet or asking the suggestion from family members or friends.(82, 83) In addition, patients understood that ADR reporting were the

responsibilities of physicians, pharmacists and other healthcare professionals, so they did not report ADRs.(3, 63, 84)

Perceived norm reflects the social acceptance to perform a behaviour. Perceived norm consists of injunctive norm and descriptive norm. Injunctive norm; is defined as subject norm in TRA or TPB, and is individual's belief about others' expectations of certain behaviours. A person's subjective norm influences with his or her normative beliefs. Important referent individuals influence to individual's decision to do the behaviour. Descriptive norm is perceptions about what others in one's social or personal networks are doing. The stronger one's beliefs that referents think a person should perform the behaviour or that referents are performing the behaviour, the stronger one's perception of social pressure to do the behaviour.(76) The results of researches from the Netherlands and United Kingdom were consistent with the theory. The results showed that healthcare professions such as pharmacists can motivate consumers or patients to self-report ADR.(62, 78)

Personal agency consists of perceived control and self-efficacy. Perceived control is the perception of the difficulty or ease in performing a behaviour under different situations. It is measured by an individual belief about their ability to perform a specific behaviour under various obstacles.(76) Affecting motivations and barriers of patients' or consumers' reporting were researched.(3, 56, 78) The researches found that patients' or consumers' knowledge and awareness of ADR and ADR reporting process were barriers to self ADR reporting. Most consumers or patients had no knowledge about adverse drug reaction, side effect of over-the-counter medicines (OTC) and prescription drugs, reporting method and process.(9, 63, 65) The consumers or patients understood that over-the-counter medicines and prescription drugs were safe, so they were not aware about side effect of drugs.(56, 82) Most of them had never heard about pharmacovigilance and had never known about available organisations of monitoring and adverse drug reaction prevention (pharmacovigilance center).(8, 63, 83) These might make patients or consumers not report ADRs.

Furthermore, difficulties with ADR reporting procedures and forms, no feedback on previous ADRs submitted and cost of mailing were barriers of

reporting.(78) Conversely, facilities such as specific ADR reporting form for patients, access to ADR form and available center to receive ADR report can motivate consumers or patients to report ADR.(3) These results were not different from a qualitative study in Thailand. The out-patients stated that the convenient methods of ADR reporting were internet, email, Facebook, telephone, call canter and post. They needed feedback, so they could discuss their ADRs with healthcare professionals after they reported ADRs.(81)

Personal, confidential and illiteracy were factors affecting adverse drug reaction reporting of consumers or patients.(8, 84) Sometimes patients had difficultly to discuss about ADRs with physician or pharmacist. Then they report ADR to Pharmacovigilance center by themselves.(56) Conversely, consumers or patients who had low literacy and poor writing were not interested to report adverse drug reaction, so the education level had negative effect on ADR reporting.(56, 84)

Self-efficacy is an individual's confidence of their ability to perform challenging behaviour.(76) Patients who had more diseases' conditions and abnormal symptoms experienced difficulty to identify the association of their ADRs and medicines. This might be a barrier to report ADRs.(80) Several researches in Thailand studied the patients' confidence to evaluate and report ADRs.(79, 80) Around 65% of patients were confident to report ADRs and 50.7% were able to report ADRs correctly.(80) Almost 89.2% of patients always monitored ADRs by themselves and they could evaluate ADRs by themselves.(79) In contrast, another study showed that 51.9% of patients could not identify whether their abnormal symptom was related to medicines. This study also reported that 59.9% of patients thought that ADR reporting was difficult.(80)

In addition, other factors affected to ADR reporting of consumers or patients such as severity of adverse drug reaction, gender, age and education level.(56, 62, 83, 84) Severity of adverse drug reaction has either positively or negatively affected ADR reporting. If consumers or patients were suffering from ADR or angry about their adverse situation or ADR influenced consumers' or patients' daily activities, the consumers or patients would have intention to report ADRs.(56, 77, 83) In contrast,

another research showed patients with serious and even life-threatening of ADRs were less interested to report ADR, because they thought that they did not directly get health or financial benefit.(84)

A couple of studies showed that gender, age and education level had effect to ADR reporting in consumers or patients. Older consumers with lower educational level had less knowledge of pharmacovigilance and ADR reporting.(56) There were different levels of ADR reporting motive between male and female. Men felt more important about the potential future personal benefits from ADR reporting than women felt.(62)

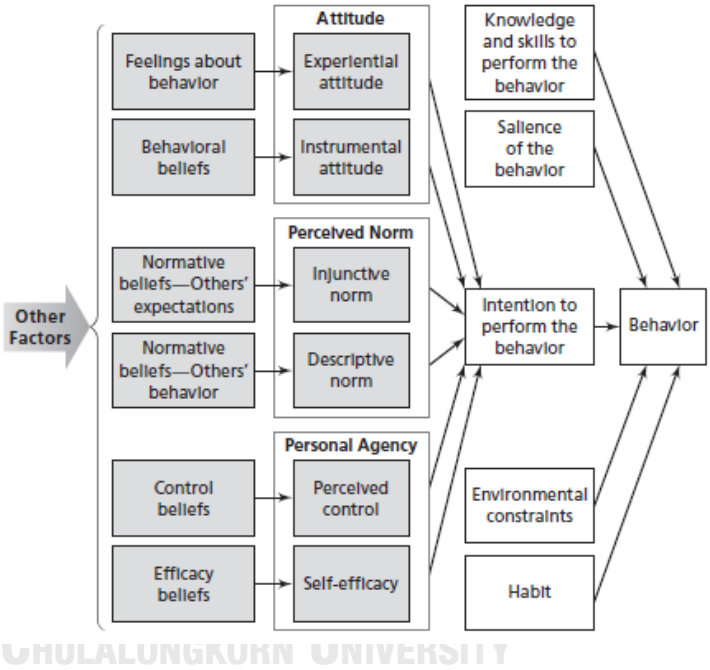

Figure 9 Integrated Behavioural Model

1.2 Objectives

1. To explore problems and possibility of consumers directly reporting adverse drug events to Pharmacovigilance center and indirectly reporting via community pharmacists from community pharmacists and Thai FDA's points of view
2. To explore consumers' attitude, problems and limitations of adverse drug event reporting to community pharmacists in Thai consumers' viewpoint

3. To investigate factors that affect consumers' intention to report adverse drug event to community pharmacists

METHODOLOGY

According to literature review, several research in many countries studied the factors affecting adverse drug event reporting in consumers but there is currently no study in Thai consumers. Factors from literature review may not be applicable to adverse drug event reporting in Thai consumers. Therefore, this study was conducted 2 parts. First part, qualitative study was conducted to explore problems and possibility of consumers directly reporting adverse drug events to Pharmacovigilance center and indirectly reporting via community pharmacists from consumers, Thai FDA's points of view and to explore community pharmacists and consumers' attitude, problem and limitation of adverse drug event reporting in community pharmacists and consumers' viewpoint. Second part, quantitative study was conducted to investigate factors that affect consumers' intention to report adverse drug event to community pharmacists.

Part I: Qualitative study

Study design

In-depth interview was used to collect the data.

Data collection and sampling method

Three parties who were involved in the ADE reporting system were purposively and conveniently recruited. These three parties were consumers, community pharmacists, and employees of a pharmacovigilance center (HPVC). The HPVC participants included the former director, the present director, and the operational staff of the HPVC. They were asked about the situation and problems of adverse drug event reporting and their opinion about direct adverse drug event reporting by consumers. Community pharmacists who participated the meeting of Thai pharmacies association on 28 Oct 2018 were interviewed. Community pharmacists were individuals who currently worked at either accredited or non-accredited pharmacies. The pharmacy accreditation, a tool to create standards that drive quality of care, is granted by the Pharmacy Council. It is used to motivate good pharmacy practices on community

pharmacies. A previous report conducted by the Thai FDA 20 years ago addressing the problems and barriers to report ADEs was used to guide the open-end questions for the present interview.(85) People in the shopping malls located in Bangkok and 4 big cities in 4 regions of Thailand, such as Udonthani province, Songkhla province, Chiang Mai province and Chonburi province, were targeted for the interviews. The sites were purposively selected as they serve different consumer populations. Convenience sampling of consumers was those who willing to be interviewed. Two constructs in the theory of planned behaviour, attitude toward reporting and perceived behaviour control, were also used to guide the open-end questions for the interview. Both community pharmacists and consumers were asked about the experience of ADE reporting. Experience about direct ADE reporting by consumers was asked in community pharmacists. Both community pharmacists and consumers were interviewed until data saturation.(86)

Data analysis

The interviews were recorded with the consent of the participants. An audio recording was transcribed verbatim and a verification process was performed to reconcile the content of the transcription. The verification was done by a different person than the one who did the interview and transcribe the audio recording. The analysis of qualitative interview data from community pharmacists and consumers was focused on the experiences, inducers and barriers of ADE reporting. Thematic analysis was used to analyze the content. The data were analyzed word by word to display significant themes. The sentences from each participant that are used in the study were highlighted and then were broken into smaller segments.(87, 88) All differences and similarities in coded segments of both community pharmacists and consumers were categorized. Each category created a new code that captured the meaning of the group. The codes analyzed from an in-depth interview were used to build the theme. The reliability on theme, coding, and categorization consisted of coding spot checking to see if they were consistent and agreeable to another experts.

Part II: Quantitative research

Study design

A cross-sectional survey was conducted to evaluate the factors that influence patient's intention to report adverse drug reactions to community pharmacists in Thailand.

Study sample and sample size

A snowball sampling was used in the study. The study samples were people who lived in all regions of Thailand. The inclusion criteria for participants in the study were who were 1) ≥ 18 years old, 2) not physicians, pharmacists, dentists, and nurses, and 3) able read and write the Thai language. The duration of data collection was 3 months. With the anticipated effect size 0.25, desired statistical power level 0.8, probability level 0.05, number of latent variables 7, number of observed variables 30, and number of distinct parameters to be estimated, 79; the maximum sample size to detect effect was 790.(89)

Measurement

The questionnaire was developed based on the integrated behavioral model (IBM). In-depth interviewing of patients was also conducted to fine tune the questionnaire. The questionnaire consisted of nine sections: (a) experience of ADR reporting; (b) intention of ADR reporting; (c) experimental attitude to ADR reporting; (d) instrumental attitude to ADR reporting; (e) injunctive norm of ADR reporting; (f) descriptive norm of ADR reporting; (g) self-efficacy to ADR reporting; (h) perceived behavior control to ADR reporting and (i) characteristics of patients (gender, age, living location, education level, type of education and career).

The questionnaire was examined the validity of content and language by three experts in the area of social and administrative pharmacy, education, and nursing administration. The index-objective congruence (IOC) was used to evaluate the content of each item. Each expert evaluated each item by giving the item a rating of 1 for clearly measuring, 0 for degree to which it measures the content area is unclear or -1 for not clearly measuring. IOC of each item was calculated following formulation.(90)

$$IOC = \frac{\sum R}{N}$$

R is the rating of each item of each expert and N is the number of experts who evaluate the content of questionnaire.

The questionnaire comprised of 32 questions was sent to experts to evaluate if the content really measured the construct of instrumental attitude to ADR reporting, injunctive norm of ADR reporting, descriptive norm of ADR reporting, self-efficacy to ADR reporting and perceived behavior control to ADR reporting. The questions with IOC scores less than 0.67 were deleted from the measurement.

Questionnaire pretesting was conducted three times prior to widespread distribution. This resulted in two unreliable items being deleted and wording changes to better reflect patient perceptions. One notable change was redefining “adverse drug reactions” to “abnormal symptoms or healthcare problems from medicines”.

Study Process

The survey was generated using a Google form questionnaire. The purpose of the study and the definition of an adverse drug reaction were mentioned at the beginning of the Google form questionnaires. All questions were set so that the answers were required, and mandatory, so missing data was not found. The Google form questionnaires were distributed to people living in all regions of Thailand and respondents were asked to distribute the questionnaire web link to their friends and relatives.

Data Analysis

SPSS version 22 was used to analyze descriptive statistics and correlation analysis. Internal consistency of the components of the scales of all constructs was assessed by Cronbach’s alpha. A reliability coefficient of ≥ 0.7 was considered acceptable.(91) A confirmatory analysis and a structural equation model were performed by IBM SPSS Statistics AMOS version 22 licensed by Chulalongkorn University, Thailand.

The dependent variable of this model was patients’ intention to report adverse drug events defined as the perceived likelihood of reporting ADRs to community

pharmacists in the various situations. The independent variables associated with the IBM theoretical model consisted of

1. Patients' attitude toward ADR reporting to community pharmacists: It consisted of experimental attitude which were measured by 4 items and instrumental attitude was measured by 6 items.
2. Perceptive norm toward ADR reporting to community pharmacists: It consisted of injunctive norm and descriptive norm. Injunctive norm was measured by 4 items and descriptive norm was measured by 3 items.
3. Personal agency toward ADR reporting to community pharmacists: It consisted of two constructs such as self-efficacy and perceived behavior control. Self-efficacy was measured by 4 items and perceived behavior control was measured by 5 items.

All constructs in the model were measured by 5-point Likert scales (strongly disagree to strongly agree). IBM constructs were created by averaging the individual items representing the construct. The data set was tested with normal probability plots to check normal distribution of all variables prior to the analysis. The Model fit was evaluated using four indices. 1) Goodness-of Fit Index (GFI): Adequate model fit is obtained when GFI > 0.9; 2) Normal Fit Index (NFI Delta 1): Adequate model fit is obtained when NFI Delta 1 > 0.9; 3) Comparative Fit Index (CFI): Adequate model fit is obtained when CFI > 0.9; and 4) Root Mean-Square Error of Approximation (RMSEA): Values closer to 0 represent a good fit. Acceptable model fit is obtained when RMSEA <0.08. (92, 93) Standardized Residual Covariance was used to evaluate the items of each construct. If most of the standardized residuals are less than two in absolute value, the model is correctly specified.(94)

1.3 Significance of the study

The results from this study can contribute to academic knowledge in pharmacovigilance area as follows:

1. The study can help Thai FDA to understand the situation of reporting adverse drug event in Thai consumers to community pharmacists including

understanding factors affecting the intention of Thai consumers to adverse drug event reporting.

2. The study will be beneficial for Thai FDA to be a guideline to setup adverse drug event reporting in consumers in the future.
3. The study will be applied to improve social and behavioral sciences.

CHAPTER II

Consumers' Adverse drug event reporting via community pharmacists: Three stakeholder perception

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Abstract

Background: Adverse drug event (ADE) reporting is a significant process to increase consumer care and consumer safety associated with the use of medicines. An in-depth investigation into low ADE reporting by consumers and community pharmacists was undertaken to uncover interventions to improve reporting.

Method: In-depth interviewing of the three parties; consumers, pharmacists and employees of the Pharmacovigilance Center in Thailand, was used to collect the data. They were interviewed about ADE reporting experiences and contributing factors and problems of ADE reporting. Thematic analysis was used to interpret the results.

Result: The HPVC received few ADE reports from consumers. Most community pharmacists received ADE reports from consumers, however the Pharmacovigilance

Center received few ADE reports from community pharmacists. ADE reporting of community pharmacists and consumers were influenced by many factors which were categorized into four themes which were 1) “Cognition” (awareness, attitude and responsibility); 2) “Reporting process” (complication, competency, deficiency, feedback, and resource); 3) “Inducer” (service orientation, acquaintanceship, motivation, severity level, regulatory and reward); and 4) “Obstacle” (doubt, belief and prosecution).

Conclusion: Health professionals should motivate consumers to report ADEs. Building social responsibility and benefits and increasing knowledge of reporting process, channels, and system to both community pharmacists and consumers were recommended. Providing rewards and making community pharmacists feel comfortable to report ADEs by simplifying the ADE form and providing training, guidelines, and an ADR assessment tool can drive them to report ADEs. Feedback to consumers by confirming whether it was ADE and feedback to pharmacists that the Pharmacovigilance Center received their reports and their reports were utilized were also important. Consumer confidentiality and erasing the fear of being sued should also not ignore.

Keyword: Adverse drug event reporting, stakeholder perception, consumers, community pharmacists and pharmacovigilance center

Introduction

Adverse Drug Events (ADEs) is a health problem or injury occurring from medical intervention related to a medicine. It includes adverse drug reactions and overdose.(1) Adverse drug reaction monitoring is a part of Pharmacovigilance. Pharmacovigilance is "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem."(2) The purposes of medication monitoring systems are to increase consumer safety, improve public health, and support medication evaluation, effectiveness and understanding.(3-5) The Pharmacovigilance Center has the responsibility to collect, analyse and evaluate adverse drug reactions.(3)

The Pharmacovigilance Center has established an adverse event reporting system. The system relies on consumers recognizing abnormal symptoms and linking these symptoms to medicines. The number of reports for similar medication situations are very important for signal detection. To get an accurate association between medicines and an ADE, the data must be large enough for signal detection.(6)

Healthcare professionals are responsible to monitor and report ADEs to the Pharmacovigilance Center. Pharmacists can be and should be essential health care professionals who report ADEs because they are experts in medicines. Community pharmacists can be an important source of ADE information from people because they are primary care healthcare professionals who people easily access and consult for their health problems. When consumers report their suspected ADEs to community pharmacists, community pharmacists can screen the suspected ADEs before sending the ADE reports to reporting systems of the Pharmacovigilance Center. However, there was Adverse Drug Reaction (ADR) underreporting from community pharmacists in many countries; 4% reported in UK during 2013-2014, 5% reported in Australia in 2016 and 10.7% reported in Korea in the second quarter of 2014.(7-9) In Thailand, less than 0.2% of ADE reports came from community pharmacists.(10)

The ADE reporting system usually is a spontaneous reporting, therefore, underreporting is frequent. The systematic review research showed that only 6 -10% of all ADRs are reported.(11) People rarely report ADEs to Pharmacovigilance center. The situation, problems, obstacles, and facilitators of ADE reports from community pharmacists and consumers were unknown. This study aimed to explore the basic foundation of ADE reporting and the perceptions and problems with low ADE reporting by community pharmacists and consumers. Consumer viewpoints of ADE reporting to community pharmacists were also explored.

Methodology

A descriptive, qualitative study was conducted to understand factors related to ADE reporting. Semi-structured face to face interviews were used to collect the data. Open-ended questions were used to initiate an in-depth interview. Three parties who were involved in the ADE reporting system were purposively and conveniently recruited. These three parties were consumers, community pharmacists, and employees

of a pharmacovigilance center. The Pharmacovigilance Center in Thailand is named the Health Product Vigilance Center (HPVC). It is under the Thai Food and Drug Administration, Ministry of Public Health. Three of eight HPVC employees were interviewed. The HPVC participants included the former director, the present director, and the operational staff of the HPVC. They were asked about the situation and problems of adverse drug event reporting and their opinion about direct adverse drug event reporting by consumers. Community pharmacists who participated the meeting of Thai pharmacies association on 28 Oct 2018 were interviewed. Community pharmacists were individuals who currently worked at either accredited or non-accredited pharmacies. The pharmacy accreditation, a tool to create standards that drive quality of care, is granted by the Pharmacy Council. It is used to motivate good pharmacy practices on community pharmacies. A previous report conducted by the Thai FDA 20 years ago addressing the problems and barriers to report ADEs was used to guide the open-end questions for the present interview.(12) People in the shopping malls located in Bangkok and 4 big cities in 4 regions of Thailand, such as Udonthani province, Songkhla province, Chiang Mai province and Chonburi province, were targeted for the interviews. The sites were purposively selected as they serve different consumer populations. Convenience sampling of consumers was those who willing to be interviewed. Two constructs in the theory of planned behaviour, attitude toward reporting and perceived behaviour control, were also used to guide the open-end questions for the interview. Both community pharmacists and consumers were asked about the experience of ADE reporting. Experience about direct ADE reporting by consumers was asked in community pharmacists. Both community pharmacists and consumers were interviewed until data saturation.(13)

The interviews were recorded with the consent of the participants. An audio recording was transcribed verbatim and a verification process was performed to reconcile the content of the transcription. The verification was done by a different person than the one who did the interview and transcribe the audio recording. The analysis of qualitative interview data from community pharmacists and consumers was focused on the experiences, inducers and barriers of ADE reporting. Thematic analysis was used to analyze the content. The data were analyzed word by word to display

significant themes. The sentences from each participant that are used in the study were highlighted and then were broken into smaller segments. All differences and similarities in coded segments of both community pharmacists and consumers were categorized. Each category created a new code that captured the meaning of the group. The codes analyzed from an in-depth interview were used to build the theme. The reliability on theme, coding, and categorization consisted of coding spot checking to see if they were consistent and agreeable to another experts. This study was approved by the Office of the Research Ethics Review Committee for Research Involving Human Subjects of Chulalongkorn University (COA number 274/2018).

Results

Demographic data

Three pharmacists at the HPVC and thirty-one community pharmacists participated in the in-depth interview. The community pharmacists average age was 35.6 years old (range 26-61 years old) and 55% of them were female. The average years of community pharmacist's experience was 7.06 years (range 0.3-29 years) and twenty participants were full-time community pharmacists and twenty of them were working in the Bangkok metropolitan area.

Thirty-five consumers were interviewed. The average age was 41.3 years (range 20-71 years old) and 25 participants (71%) were female. Fourteen of the participants (40%) had a Bachelor's degree, eight of them (23%) had a Master's degree and the rest (37%) had education below a Bachelor's degree.

Experience in adverse drug event reporting

Community pharmacists

Twenty-five pharmacist participants (81%) had received ADE information from consumers but only one of them had reported the ADEs to the Thai FDA. She reported ADEs by using ADE forms and sent them to the HPVC by email.

All community pharmacists were asked about their ability to evaluate whether reported symptoms could be related to medicines. Eighteen participants (58%) were

confident to investigate ADEs, ten of them (32%) thought they could probably evaluate ADEs, Three-participants (10%) were not able to evaluate ADEs.

Twenty-three participants (74%) believed that ADE reporting is important because the information from the reports could improve knowledge about the medication and increase consumers' safety from medicines' use. The rest thought that the Thai FDA did not do anything with these ADE data. Besides, they thought that few ADEs occurred from medicines used by consumers in community pharmacies and those ADEs were well known and already mentioned in the leaflets. Therefore, ADE reporting was not necessary. The finding was similar to the studies in Saudi Arabia, Japan, and UAE.(14-16)

Twenty-nine community pharmacists (93%) thought that ADE reporting was the healthcare providers' responsibility. Fourteen of them (45%) agreed that it was the pharmacists' responsibility to report ADEs. Only two of 31 persons (7%) said that pharmaceutical companies and the Thai FDA were responsible to report ADEs. Asking about the intention to report, twenty-eight community pharmacists (90%) had the intention to report ADEs and nine pharmacists said that they would report ADEs each time consumers reported them.

Consumers

Half of the participants (17) had an ADE at least once. No one reported ADEs to community pharmacists. Ten of them reported their ADEs to their physicians, 4 of them reported to their relatives and 3 persons did not report ADEs to anybody. Only one who had ADEs knew that she could report her abnormal symptoms to community pharmacists but she reported her ADEs to her physician.

All interviewed consumers did not know that there was an adverse event reporting system available in Thailand. Only 4 consumers were aware that they could report ADEs to community pharmacists. Five consumers knew that they could report their abnormal symptoms to the Thai FDA but did not know how to report. The participants were asked about their willingness to report ADEs. Only 23 of 35 participants were willing to report their ADEs to community pharmacists (48%), the Thai FDA (35%), and physicians (17%).

Pharmacovigilance experts' perspective

The Health Product Vigilance Center (HPVC) officer stated that underreporting of adverse drug events by consumers was a problem in Thailand and similar to other countries (17-19). The amount of adverse drug event reports from consumers are fewer than 10 cases per year. The two main reasons that consumers did not report ADEs were consumer perception of ADE reporting and the HPVC intervention. The HPVC reported that most people feel it is time-consuming to report and did not see direct benefits of ADE reporting.

"[1]I think consumers feel that reporting to the HPVC is useless. They were better to report to their physicians or pharmacists. They can get direct benefits from their physicians or pharmacists such as the treatment and advice about the abnormal symptom." "They think that reporting to the HPVC is a waste of time and take a quite long time for the reporting process."

The HPVC did not promote or encourage consumers to report ADEs directly to the HPVC. They mainly focused on encouraging ADE reporting from hospitals because of the manpower issues. The Food and Drug Administration (FDA), however, had established consumer hotline call center ("1556") for reporting health product-related problems. All health problems were reported to the hotline call center. Hotline employees had always focused on quality issues and far less interested in ADE issues. Therefore, the HPVC had rarely received suspected ADE reports from consumers via this hotline call center.

"Actually, consumers can report any health problems through 1556 including ADEs, but hotline employees are concerned only with product quality. Most of them have never thought that the problems may come from adverse events by those health products."

The HPVC mentioned that ADE reports from consumers were very useful for new signal detection. Physicians and pharmacists reported only known ADEs to the HPVC. In addition, they would report only severe abnormal symptoms.

[1] Quotations in this manuscript are English translations of comments made in the Thai language.

"Consumers tell their physicians that the abnormal symptom comes from their medicine. Physicians don't believe that it comes from medicine because it does not be mentioned in the leaflets or they have never learned before."

The HPVC was still insisted that pharmacists were the appropriate persons to detect and report ADEs.

"It was the pharmacist's responsibility in ADE monitoring and reporting. Pharmacists should ask information from consumers, be able to evaluate the relationship between abnormal symptoms and medicine, and report ADEs to HPVC."

However, Thailand is still faced with the problem of underreporting of ADEs from community pharmacists. From the HPVC database, it was found that the HPVC received a total of 1,562 ADE reports from community pharmacists since 1984. This was considered to be very few. The HPVC commented about the causes of very low ADE reporting from the community pharmacists in various ways.

The HPVC stated that most consumers came to buy medicines only and had no intention of reporting any abnormal symptoms from their medicines. A private, comfortable area was believed to make consumers like to talk with community pharmacists. Experience and counseling skills allowed community pharmacists to detect ADEs from consumers. Community pharmacists had to get adequate information from consumers to evaluate the relationship between abnormal symptoms and medicines. They should have analytical and communication skills to ask and detect ADEs from the consumers.

"Consumers normally do not talk with pharmacists when they have mild abnormal symptoms. They will talk if they have severe symptoms. Community pharmacies should have enough private space that consumers are comfortable to talk."

"There are few ADE cases found at community pharmacies. For example, there is a case that pharmacists can trigger ADEs during counselling. In this case, a consumer comes to buy an antihistamine, the pharmacists had asked for more information from the consumer and figure out that it was an allergic symptom from her health product. If the community pharmacists did not have enough experience, knowledge, and

communication skill to probe consumers' problems, they would be unable to detect ADEs."

Asking for information about and reporting ADEs were time-consuming. Spending time on ADEs does not generate profit; community pharmacists had no motivation to report ADEs.

"Pharmacists have many tasks at community pharmacies such as marketing, financing, and managing. Evaluating ADEs and completing ADE reports take a lot of time. If many consumers are waiting at community pharmacies, community pharmacists have not enough time to ask for information from consumers."

"The goal of community pharmacies is to increase sales and profits. ADE reporting is a Corporate Social Responsibility (CSR) and does not provide any profit to pharmacy businesses."

The HPVC had planned to promote ADEs reporting by consumers and community pharmacists. They planned to publicize the significance and benefits of ADE reporting through many channels. The current ADE reporting form is for healthcare professionals and it is quite difficult for consumers to use. Currently, there is no specific form for consumers to report ADEs; therefore, the HPVC has encouraged consumers to report their ADEs via community pharmacists.

Community pharmacists and consumers' perspective

What makes you report or not report ADEs?

ADE reporting by community pharmacists and consumers were influenced by the four themes from the analysis; cognition, reporting process, inducer and obstacle. Each theme consisted with several factors. (Figure 10) "Cognition" consisted of three factors: awareness, attitude and responsibility. These three factors influenced both community pharmacists and consumers to report ADEs. "Reporting process" consist of 5 factors: complication, competency, deficiency, feedback, and resource. Complication, feedback, and resource influenced ADE reporting in community pharmacists and consumers. Competency, and deficiency were mentioned in community pharmacists. Six factors were categorized into "inducer" which were

service orientation, acquaintanceship, motivation, severity level, regulatory and reward. The first 4 factors could induce consumers to report and the last 2 factors could induce community pharmacists to report ADEs. Three factors were grouped into “Obstacle” which were doubt, belief and prosecution. Doubt and belief were the barriers of ADE reporting in consumers and prosecution was the obstacle of reporting in community pharmacists.

Theme: Cognition

Awareness

Results from in-depth interviews found that majority of consumers did not know that they can report ADEs to any accessible healthcare providers, including community pharmacists. Community pharmacists, thus, were not able to report ADEs to the FDA because they did not get information from consumers. Community pharmacists suggested publicizing the need for people to report ADEs to community pharmacists. Both groups also did not know reporting channels.

Community pharmacist (female, 28 years old)	*Consumer (female, 48 years old)*
“*Thai FDA should notify people to report any abnormal symptoms or ADEs to community pharmacists. Consumers are willing to report their abnormal symptoms and provide more information to community pharmacists.”*	*"Most people do not know that they can report ADEs. Thai FDA should promote that consumers can report ADEs and how to report ADEs.”*
Community pharmacist (male, 61 years old)	*Consumer (female, 32 years old)*
“Even though, I am a pharmacist. I don’t know how to report ADRs.”	*“I have never known before that I can report my abnormal symptoms, I don’t know whom I should report with and don’t know how to report.”*

Attitude

Both groups thought about the benefits of reporting. They had good attitude that the reporting would be a benefit to society. The information would be a benefit for drug development and warn other consumers. However, some did not believe that their information would be utilized, so they did not report ADEs. Consumers were more likely to report their abnormal symptoms to pharmacists if it made them used medication correctly.

<u>Community pharmacist</u> (male, 32 years old)	*<u>Consumer</u> (male, 39 years old)*
"I am not sure that Thai FDA will use my report. Thai FDA should inform people how they use these data. Knowing that the information was used will encourage me to report ADEs."	*"If I tell Thai FDA about my abnormal symptoms from my medication, are they going to use my information? Are there any evidences showing the use of this information? If I know that my information benefit for the development of medicine, I will report my abnormal symptoms."*
	<u>Consumer</u> (male, 58 years old)
	"I report ADEs to pharmacists because I would like to ensure that I take medicines accurately and safely."

Responsibility

ADE reporting is opened for anyone who had or detected suspected ADEs to report. Currently, ADE reporting is voluntary, so it is a moral obligation. Social responsibility is a motivation for reporting ADEs.

<u>Community pharmacist</u> (female, 38 years old)	*<u>Consumer</u> (male, 65 years old)*
"I think ADE reporting is my responsibility. Every pharmacist should	*"ADE reporting is what I have to do. My information will be evidence of ADEs. It*

have this responsibility. Thai FDA should raise moral awareness in pharmacists to report ADEs."	*helps people know medication precaution."*

Theme: Reporting process

Complication

Both community pharmacists and consumers concurred that an ADE reporting process was complicated and difficult.

Community pharmacist (female ,43 years old)	*Consumer (male, 34 years old)*
"ADE reporting form is not user friendly. There is too much information to fill out. I think some points are not important."	*"I feel that reporting ADEs requires much information and many steps. I may report to Thai FDA If I have just made a call to Thai FDA and not provided too much information."*

Competency

Knowledge about ADEs and ADRs, and signal detection skill were very important. Some pharmacists did not know ADE reporting requirements and processes. Training and guidelines were reported as needed for many pharmacists. About half of pharmacist participants were not confident to investigate the relationship between abnormal symptoms and medicines. Providing an ADR assessment tool to evaluate the relationship would encourage them to report ADEs.

"I cannot evaluate ADEs of all medicines. If they are the medicines that I am familiar with, I can evaluate the ADEs. If they were the medication I rarely dispense such as medication for chronic disease from physician's prescriptions I cannot assess their ADEs." (Male, 38 years old)

*"How severe of ADEs do I have to report? I don't know how to report. Thai FDA should provide the training of ADE reporting." (Community pharmacist, fem*ale, 38 years old)

*"How often should I report ADEs to FDA, monthly or quarterly? I don't know how to report ADEs. Thai FDA should provide the guideline". (Community pharmacist, m*ale, 37 years old)

"Thai FDA should create screening tools for evaluating ADRs and distribute them to all community pharmacists. The tools will help me assess ADRs accurately." (Community pharmacist, male, 27 years old)

Feedback

Some community pharmacists and consumers used to report ADEs. They said that they had never gotten any responses or feedback from the Thai FDA.

<u>Community pharmacist</u> (female, 40 years old)	*<u>Consumer</u> (female, 50 years old)*
"I did not receive any feedback from Thai FDA about my ADE reporting. I don't know whether Thai FDA received my report or not. I also want to confirm whether those abnormal symptoms were ADEs but Thai FDA had never responded."	*"I would like to get confirmation of whether my abnormal symptom is ADEs from my medication. I am more likely to report if I can get these confirmations. I also would like to know whether other people have the same abnormal symptoms as me after taking this medicine. Are there any precautions from this medicine?"*

Deficiency

Some consumers were not willing to provide their health information because of the confidentiality issue. Concern about prescriber reputations was also another issue that made consumers not willing to provide more information.

*"It is difficult to evaluate whether the abnormal symptom related to their diseases or medicines. My consumers are not willing to give me more information, I cannot evaluate whether it is an ADR or not." (Community pharmacist, fem*ale, *38 years old*)

"My consumers are afraid that their physicians will be blamed if they report their abnormal symptoms from the prescribed medication." (Community pharmacist, female, 35 years old)

"My consumers report to me some information. They don't want to tell me more information. I think they might be concerned with their confidentiality." (Community pharmacist, female, 38 years old)

Resource

Both groups commented that assessing ADEs was time-consuming. Pharmacists did not have time to detect and report ADEs and consumers did not have time to provide information. Manpower need was also mentioned by community pharmacists.

<u>Community pharmacist</u> (male, 40 years old) *"There is only me working in the community pharmacy. I have to spend time to ask information from consumers to get enough information on ADR detection. During rush hours, I cannot do that because other consumers are waiting for my service. If I was compulsory to report ADRs, I have to hire more pharmacists."*	*<u>Consumer</u> (female, 43 years old)* *"Where can I report my abnormal symptom from my medication? Why do I have to report it? How far do I have to go? Is it worth to spend my time and travel to report what you call ADE?"*
<u>Community pharmacist</u> (female, 30 years old) *"My community pharmacy is very busy. I have no time for asking for information from consumers so it is impossible to collect data and report ADEs."*	

Theme: Inducer

Service orientation and Acquaintanceship

Community pharmacist service orientation and good relationships with consumers made consumers more comfortable to provide their information and report their abnormal symptoms. If consumers felt that community pharmacists were willing to listen to their problems and provide suggestions to them, they were willing to report ADEs.

"*If I report ADEs to pharmacists who do not dispense my medicine, I am afraid that they will not pay attention to my problems or ADEs. They may not do anything after I report them." (Consumer, female, 59 years old)*

"Some pharmacists did not pay attention or listen to my problems. Some were not willing to provide information or answer my health questions. I am not comfortable to report my ADEs to them." (Consumer, female, 32 years old)

Motivation

Significant individuals in a person's life, such as physicians, pharmacists, families, and relatives, were able to influence consumers to report ADEs.

"When I have abnormal symptoms from medicines, I will tell my son. If he tells me to report ADEs, I will do it." (Consumer, female, 53 years old)

"My pharmacist dispenses medicines for me. If she tells me to report abnormal symptom from medicine to her, I will do it." (Consumer, female, 52 years old)

Severity level

The severity of abnormal symptoms affected consumers' decisions related to reporting their ADEs. Some participants reported their ADEs only if they felt they were harmed by abnormal symptoms.

"I have sever abnormal symptoms from medicines and I have to spend money for treatment. I will report ADEs." (Consumer, female, 43 years old)

Regulation

Underreporting is the primary problem because ADE reporting is spontaneous. Lack of mandatory reporting regulations and chain community pharmacies policies were other issues that obstructed community pharmacists to direct reports ADEs to the Thai FDA since they must report to the head of departments.

*"If ADR reporting is mandatory, I will report it to FDA." (Community pharmacist, f*emale, 38 years old)

"I cannot directly report ADEs to FDA due to my company policy. If I detect ADEs from my consumers, I have to send the information to my company, not to FDA." (Community pharmacist, male, 27 years old)

Rewards

Community pharmacists stated that financial incentives or professional incentives such as Continuing Pharmaceutical Education (CPE) credits might motivate them to report ADEs to the Thai FDA.

"I have to spend more time asking for information and fill out an ADE report form. I do not receive any income from ADE reporting. If I have to do this task, I have to pay money to hire more employees. I would report ADEs if I get some incentives." (Community pharmacist, female, 26 years old)

"I don't get any benefit for ADE reporting. If I get the CPE credits from ADE reporting, I will report ADEs to Thai FDA." (Community pharmacist, male, 29 years old)

Theme: Obstacle

Doubt

Some consumers did not report ADEs if they could not identify the relation between their abnormal symptoms and medicines. They doubted that healthcare professionals would believe their data.

"I do not report ADEs because I am not sure that my abnormal symptoms are related with my medicines." (Consumer, female, 32 years old)

“I cannot prove that my abnormal symptoms related to medicines. I am afraid that pharmacists do not believe my information." (Consumer, female, 27 years old)

Belief

Pharmacists recognized that some consumers did not report the ADEs to them because consumers knew their medication and disease information well. Furthermore, they were more likely to search information from the internet than consult with pharmacists. Most consumers came to pharmacy with the intention to buy medications only.

“I feel consumers know their medicines and diseases well. They can search and believe information from internet. They do not need my helps. They come to seek medication only, not information.” (Community pharmacist, male, 28 years old)

Prosecution

Reporting ADEs required consumer personal and medical information. Some pharmacists did not report ADEs to the HPVC because they were afraid of being prosecuted by both consumers and drug companies. They perceived that reporting ADEs would destroy the drug company reputation. Being prosecuted would ruin their community pharmacy reputation.

"I am afraid of being prosecuted by consumers because I have to disclose their personal information to the FDA. I am also afraid of being sued by drug companies. I feel like I blame their products. Finally, these will destroy my pharmacy reputation.” (Community pharmacist, male, 28 years old)

Figure 10 Themes related to ADE reporting in the perspectives of community pharmacists and consumers

*** Bold** words in the circles refer to themes. Normal letter words in the squares refer to the factors influencing to report ADEs of community pharmacists, *italicized words* in the squares report ADEs of consumers, and **italic and bold words** in the squares refer to the factors influencing to report ADEs of both community pharmacists and consumers

Discussion

The basic foundation and problems of ADE reporting were explored. The factors influencing community pharmacists and consumers to report ADEs were identified. The finding could guide interventions to improve ADE reporting by community pharmacists and consumers. The results of this study found that underreporting of ADEs was still considered a major problem in Thailand similar to other countries.(17-19)

No consumers knew that there is a specific adverse event reporting system for consumers. Consumer perception that ADE reporting process is complicated and time consuming was the significant factor to influence consumers to not report ADEs. Moreover, no feedback to consumers on whether it was ADE or not made them hesitant to report ADEs. Consumers would report ADEs only if the symptoms were severe. Healthcare professionals and other influential persons were found to be effective

channels to encourage consumers to report ADEs. While some consumers knew they could report their abnormal symptoms to healthcare professionals, most consumers did not know that they could report their ADEs to community pharmacists. Some consumers much believed information from the internet so they would not seek information from healthcare provider. This would obstruct consumers go to the pharmacies for reporting ADEs. Most consumers were comfortable to report ADEs to community pharmacists who were familiar with or had good service orientation. Similar to previous research from other countries, the perceived benefit of ADE reporting was another contributing factor to stimulate consumers to report ADEs.(20-22)

Publicizing the ADE reporting process, channels, and system and consumers were recommended because it could increase the number of ADE reports from consumers. Not only publicizing the report system but also interventions to increase numbers of reports in consumers. Establishing campaigns emphasizing consumers' social responsibility and perception on benefits of ADE reporting can drive them to report ADEs. Convincing consumers to report any suspected ADEs no matter how serious it is and confirming whether it was ADE would motivate them to report ADEs. Emphasizing healthcare professionals to tell consumers to report their ADEs could be also increase the number of reporting from consumers. Since almost half of the interviewed consumers preferred to report their abnormal symptoms to community pharmacists. Another effective channel is reporting ADEs to community pharmacists. Encouraging consumers to report and community pharmacists to accept ADE reports from any consumers even though they are not their regular customers were recommended. The campaign should also emphasize confidentiality concerns.

In implementing joint FIP/WHO guidelines on Good Pharmacy Practice (GPP); standards for quality of pharmacy service, pharmaceutical care, the responsibilities of pharmacists are to improve medicine use. Monitoring treatment to evaluate adverse medicine events is an important part of the process of the use of medicines.(23)

ADE reporting process was the significant factor to influence community pharmacists to report ADEs. Some community pharmacists did not know how to report ADEs. These results aligned with many studies that community pharmacists are

unaware of the method of ADR reporting.(7, 14, 17, 18) The current ADE reporting form is complicated, required a lot of information and a lot of time to complete it. Most community pharmacists did not receive information or receive inadequate information from the consumers because some consumers were protective of their confidentiality. Therefore, pharmacists were not able to report ADEs. No feedback to community pharmacists on whether it was received or not made hesitant to report ADEs. Competency about ADE assessing and reporting affected ADE reporting of community pharmacists. The problems were ADE and ADR knowledge and signal detection skills. This result was similar to the research from Spain that pharmacists' knowledge was an important factor influenced by ADE reporting.(19)

Resource and time constraints influenced ADE reporting by community pharmacists. Many community pharmacists did not keep consumers' health records since they did not have sufficient time. This result was similar to previous researches from many countries that the workload and lack of time were the barriers to ADE reporting from community pharmacists.(7, 8, 14, 17, 19, 24) Moreover, ADE reporting is voluntary and it does not provide profit to pharmacy business. These made there were less ADE reports from community pharmacists. The perceived benefit of ADE reporting was the significant factors to motivate community pharmacists to report ADEs.

Community pharmacists were aware that ADE reporting was their social responsibility. This result was same as the Mahmoud MA, et al's study that ADR reporting was the duty of physicians and hospital pharmacists.(14, 19) However, some community pharmacists were afraid of being sued by drug companies. They also were afraid of being sued by consumers because of the confidentiality issues. Community pharmacists working in some chain pharmacies must report ADEs to their headquarters instead of directly to the HPVC because of the company's policy.

In conclusion, establishing the intervention about knowledge of the ADE reporting process, channels, and system to in community pharmacists can increase the number of ADE reports. Simplifying the ADE form and providing training, guidelines, and an ADR assessment tool can drive community pharmacists to report ADEs. Providing feedback after receiving the ADE reports from community pharmacists

would make them ensure that the Pharmacovigilance center received their reports and their reports were utilized. Making community pharmacists feel comfortable to report ADEs could encourage them to report ADEs. Moreover, asking for cooperation from chain companies to transfer these reports to the Pharmacovigilance center can augment number of ADE reporting. Information on benefit of ADE reporting either for pharmacists or society and drug developments should also added in the intervention. Providing rewards for ADE reporting can drive community pharmacists to report ADEs. Emphasizing community pharmacists' duty and social responsibility could drive them to report ADEs. If ADE reporting is compulsory, underreporting problems would be lessened.

Community pharmacists are medicine experts thus they should be suitable to receive reports of abnormal symptoms from consumers, screen the consumers' information, and evaluate the association between abnormal symptoms and the specified healthcare products. In addition, HPVC manpower and time limitations were always mentioned. Therefore, consumers reporting ADEs via community pharmacists should be the effective channels and could assist reducing HPVC problems.

Conclusion

Unawareness of the ADE reporting process was a significant problem in Thailand and the official nonuser-friendly ADE reporting form was the barrier to reporting. Taking into account a consumer's accessibility and knowing community pharmacists are qualified gatekeepers to screen ADEs for the Pharmacovigilance Center, community pharmacists should be receiving ADEs information from consumers and reporting them to the Pharmacovigilance Center. Publicizing the ADE reporting process, channels, and system to both community pharmacists and consumers and establish user-friendly ADE reporting forms for community pharmacists can increase number of ADE reports. In the digital era, an application for a mobile phone might be the recommended channel of ADE reporting. In addition, providing training about ADE reporting and offering ADE signal detection tools can encourage community pharmacists to report ADEs.

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Factors influencing patient intention to report adverse drug reaction to community pharmacists: A structural equation modeling approach

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Abstract

Background: Under-reporting of adverse drug reactions (ADRs) is the main problem of spontaneous ADR reporting systems, especially reporting from community pharmacists. However, community pharmacists cannot report ADRs, if patients do not report them. *Objective:* To investigate factors that can influence patients' intention to report ADRs to community pharmacists and to develop a structural model of influencing factors to report ADRs from patients. *Method:* Self-administered questionnaire via a Google form was used. The study samples were people living in all regions of Thailand. Structural equation modeling (SEM) was used to determine the influencing factors to intention to report ADRs to community pharmacists. *Results:* A total of 2,774 responses were collected. The structural equation model was an adequate fit for the data; Goodness-of Fit Index (GFI) = 0.903, Normal Fit Index (NFI Delta 1)

= 0.908, Comparative Fit Index (CFI) = 0.913 and Root Mean-Square Error of Approximation (RMSEA) = 0.077. Intention to report ADRs to community pharmacists was significantly influenced by instrumental attitude, injunctive norm, descriptive norm and self-efficacy. *Conclusion:* Positive attitude of ADR reporting, self-efficacy and their reference person such as physicians, community pharmacists, their families and friends could encourage and motivate their intention to report ADRs to community pharmacists.

Keywords: ADR reporting, community pharmacists, patient intention and an integrated behavioral model

Introduction

An adverse drug reaction (ADR) is any noxious and unintended response to a drug and occurs at doses used for prophylaxis, diagnosis, or therapy in humans, excluding failure to accomplish the intended objective.(1) ADRs are one of the major causes of patient related morbidity and mortality worldwide.(2) ADRs cause emergency department visits, hospital admission and also prolongation of hospital stay. A epidemiological study of ADRs showed that 4.2-30% of hospital admissions in the USA and Canada, 5.7-18.8% of admissions in Australia, and 2.5-10.6% of admissions in Europe were caused by ADRs.(3) Consequently, ADRs effect public health expenditures.(3) In the US, the estimated cost of ADR management was 30.1 – 130 billion US dollars per year depending on severity of case scenario.(3, 4) The estimated direct hospital costs of adverse events in Australia was 4.83 – 9.00 billion Australian dollars annually and half of them may be preventable.(5) Prevention of drug-related morbidity and mortality has become an increasingly important requirement for reducing healthcare expenditures.

Pharmacovigilance assists patient safety and helps to ensure the suitable use of medicines. It covers the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems.(1) The purpose of pharmacovigilance is to identify drug safety signals as early as possible to decrease potential clinical symptoms and expenditure from ADRs.(6) ADR monitoring is a part of pharmacovigilance. ADR monitoring is useful because the detection of ADRs provides new knowledge of drug

usage and prevents risk of medication use before clinically manifestations from an adverse drug reaction occurs. Health care professionals such as a physician, nurse, dentist and pharmacist, are responsible persons to monitor and report ADRs. ADR monitoring can detect signals that may show a potential hazard of medicines. The signals can trigger healthcare professionals to use medicines carefully including counselling, medication adjustments, or the removal of a medicine.(7)

A reported ADR from a patient is a valuable source of information to improve patients' safety.(8) It is not possible to detect signals if there is no ADR reporting. The reporting is voluntary. It was estimated that only 6-10% of all ADRs were reported.(9) The limitation of a spontaneous reporting system is the under-reporting of ADRs. The First International Conference on Consumer Reports on Medicines was established in 2000 and the conference concluded that consumers or patients' ADR reporting has potential benefit in pharmacovigilance. Reporting ADRs from consumers can provide more information and cover the situations that healthcare professionals do not report. Many studies comparing ADR reports between healthcare professionals and patients showed that patient reporting had more details than healthcare professional reporting.(6, 7, 10, 11) Moreover, reporting types of drugs and reactions by patients were different from reporting by healthcare professionals. The different information added potential value in pharmacovigilance in terms of generating new potential signals and describing suspected ADRs in enough detail to provide useful information on likely causality and impact on patients' lives.(6, 7)

Promoting patients to become involved in pharmacovigilance can increase spontaneous reporting and earlier detection of important ADRs.(6) Therefore, patients have become important players in pharmacovigilance.(11) There were few studies about consumers reporting ADRs. A study in the European Union showed that the percentages of ADR reports from patients in 2014 were around 0.02% in Bulgaria, 0.04% in Portugal, 5% in France, 20% in the Netherlands, and 21% in Sweden 34% in Denmark and in 2013 was 0.05% in Romania.(12)

In Thailand, ADR reporting is under a pharmacovigilance center called 'Health Product Vigilance Center (HPVC)'. HPVC is an organization under Thai Food and

Drug Administration, Ministry of Public Health that has responsibility to collect and evaluate the ADR reports of healthcare professionals. HPVC has collected the ADR reporting since 1984. Even though the trend of ADR reporting is increasing compared with the past, most of the ADR reporting (89%) comes from hospitals. The report of ADRs from community pharmacies were much less than those which came from pharmaceutical companies.(13) Improving the ADR reporting system in community pharmacies by reporting systems such as the HPVC will be the effective channel to receive ADR reports from patients.

Community pharmacies are private healthcare service places that patients can easily access. Community pharmacists are also the primary healthcare professionals whom patients are familiar, find more convenient to have conversations about medicines and are the competent healthcare personal to receive the ADR reports from patients. According to the 2015 survey on health and welfare, 27.2 % of patients decided to buy medicines to treat themselves.(14) Thus, community pharmacists were gatekeepers who have a chance to receive ADR information from patients. Patients' ADRs reports may be different from a medical point of view, and the report may or may not be a true signal.(10, 11) Since patients lack medical knowledge, the information from patients' reports without medical confirmation may interfere with the interpretation of a possible ADR. An important healthcare provider who has direct knowledge of medication is the pharmacist. Community pharmacists are the optimum persons to report ADRs to systems such as the HPVC because they are good at checking and confirming pharmaceutical information. However, if patients do not report ADRs to pharmacists, a pharmacist will not have ADR data to submit to HPVC-type databases. To encourage patients to report ADRs, an intervention needs to be implemented. Finding factors that influence patient reporting of ADRs is critical to create interventions. Increasing the numbers of ADR reports will lead to more accurate signal detection. Up until now, there has been no studies about ADR reporting from patients to community pharmacists in Thailand. Therefore, the purposes of this study were to:

1) explore patients' experience attitude, perceptive norm and personal agency to ADR reporting to community pharmacists

2) investigate factors that can influence patients' intention to report adverse drug reaction to community pharmacists.
3) develop a structural model of influencing factors to report ADRs from patients

An integrated behavioural model (IBM) was used as a theoretical framework in this study. IBM is a model that is used to explain and predict behaviour through the impact on behavioural intention. There are three components that influence on behavioural intention, attitude, perceptive norm and personal agency. Each component consists of two constructs. Attitude consists of experimental attitude, the feeling to perform behaviour, and instrumental attitude, the beliefs about outcomes of doing a behavior. Perceptive norm consists of injunctive norm, the belief about others' expectations of certain behaviours, and descriptive norm, perceptions about what others in their social or personal networks are doing. Personal agency consists of two constructs such as self-efficacy, degree of confidence to be able to perform the behaviour given the various obstacles or challenges, and perceived behavior control, the perceived ease or difficultly of performing a behaviour under different situations.(15) The study conceptual framework is shown in figure 11.

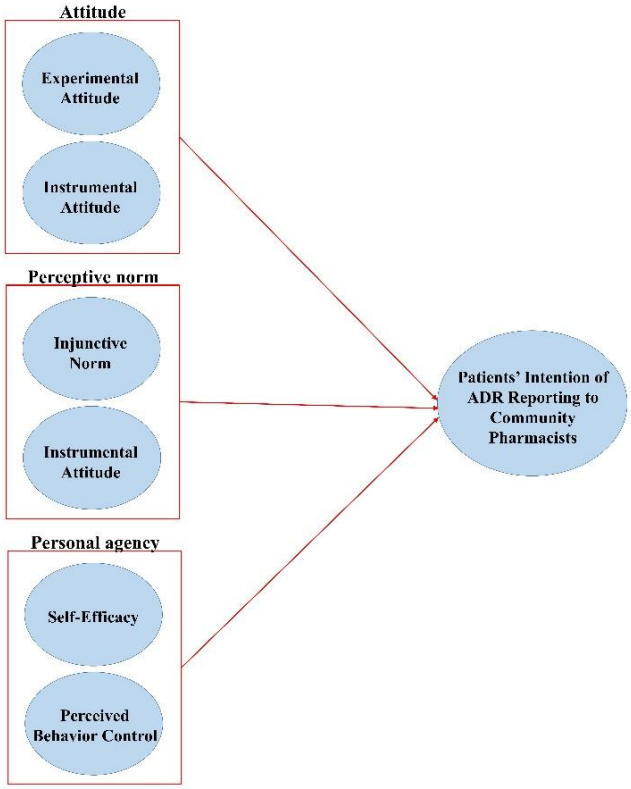

Figure 11 The study conceptual framework

Method

A cross-sectional survey was conducted to evaluate the factors that influence patient's intention to report adverse drug reactions to community pharmacists in Thailand. This study was approved by Office of the Research Ethics Review Committee for Research Involving Human Subjects of Chulalongkorn University (COA number 274/2018).

Measurement

A self-administered questionnaire was used to collect the data. The questionnaire was developed based on the integrated behavioral model (IBM). In-depth interviewing of patients was also conducted to fine tune the questionnaire. The questionnaire consisted of nine sections: (a) experience of ADR reporting; (b) intention of ADR reporting; (c) experimental attitude to ADR reporting; (d) instrumental attitude to ADR reporting; (e) injunctive norm of ADR reporting; (f) descriptive norm of ADR

reporting; (g) self-efficacy to ADR reporting; (h) perceived behavior control to ADR reporting and (i) characteristics of patients (gender, age, living location, education level, type of education and career). Content validity of the measurement was performed using itemised objective congruence (IOC) by three experts in the area of social and administrative pharmacy, education, and nursing administration. The questionnaire comprised of 32 questions was sent to experts to evaluate if the content really measured the construct of instrumental attitude to ADR reporting, injunctive norm of ADR reporting, descriptive norm of ADR reporting, self-efficacy to ADR reporting and perceived behavior control to ADR reporting. The questions with IOC scores less than 0.67 were deleted from the measurement.

Study sample and sample size

Snowball sampling was used in the study. The study samples were people who lived in all regions of Thailand. The inclusion criteria for participants in the study were 1) who were ≥ 18 years old, 2) who were not physicians, pharmacists, dentists and nurses, and 3) who were able read and write the Thai language. The duration of data collection was 3 months. With the anticipated effect size 0.25, desired statistical power level 0.8, probability level 0.05, number of latent variables 7, number of observed variables 30, and number of distinct parameters to be estimated, 79; the maximum sample size to detect effect was 790.(16)

Study Process

The survey was generated using a Google form questionnaire. The purpose of the study and the definition of an adverse drug reaction were mentioned at the beginning of the Google form questionnaires. All questions were set so that the answers were required and mandatory, so missing data was not found. Questionnaire pretesting was conducted three times prior to widespread distribution. This resulted in two unreliable items being deleted and wording changes to better reflect patient perceptions. One notable change was redefining “adverse drug reactions” to “abnormal symptoms or healthcare problems from medicines”. The Google form questionnaires were distributed to people living in all regions of Thailand and respondents were asked to distribute the questionnaire web link to their friends and relatives.

Data Analysis

SPSS version 22 was used to analyze descriptive statistics and correlation analysis. Internal consistency of the components of the scales of all constructs was assessed by Cronbach's alpha. A reliability coefficient of ≥ 0.7 was considered acceptable.(17) A confirmatory analysis and a structural equation model were performed by IBM SPSS Statistics AMOS version 22 licensed by Chulalongkorn University, Thailand.

The dependent variable of this model was patients' intention to report adverse drug events defined as the perceived likelihood of reporting ADRs to community pharmacists in the various situations. The independent variables associated with the IBM theoretical model consisted of

1. Patients' attitude toward ADR reporting to community pharmacists: It consisted of experimental attitude which were measured by 4 items and instrumental attitude was measured by 6 items.
2. Perceptive norm toward ADR reporting to community pharmacists: It consisted of injunctive norm and descriptive norm. Injunctive norm was measured by 4 items and descriptive norm was measured by 3 items.
3. Personal agency toward ADR reporting to community pharmacists: It consisted of two constructs such as self-efficacy and perceived behavior control. Self-efficacy was measured by 4 items and perceived behavior control was measured by 5 items.

All constructs in the model were measured by 5-point Likert scales (strongly disagree to strongly agree). IBM constructs were created by averaging the individual items representing the construct. The data set was tested with normal probability plots to check normal distribution of all variables prior to the analysis. The Model fit was evaluated using four indices. 1) Goodness-of Fit Index (GFI): Adequate model fit is obtained when GFI > 0.9; 2) Normal Fit Index (NFI Delta 1): Adequate model fit is obtained when NFI Delta 1 > 0.9; 3) Comparative Fit Index (CFI): Adequate model fit is obtained when CFI > 0.9; and 4) Root Mean-Square Error of Approximation (RMSEA): Values closer to 0 represent a good fit. Acceptable model fit is obtained when RMSEA <0.08. (18, 19) Standardized Residual Covariance was used to evaluate

the items of each construct. If most of the standardized residuals are less than two in absolute value, the model is correctly specified.(20)

Results

Demographic characteristics

There were 2,774 patients who completed the questionnaires. Those were from all 77 provinces in Thailand. About 38% of the respondents were living in Bangkok, the capital city of Thailand. Around 56% of respondents were female and the mean age of patients was 34.94 years. (SD = 10.19) Most of them (70.7%) had a bachelor's degree. There were 15.07% of all respondent who graduated in healthcare science and/or had careers related to healthcare.

ADR Experiences and Coping

Almost half of the respondents (44.3%) had experienced of abnormal symptoms from their medication use. Those abnormal symptoms were rash (35.3%), palpitation (35.2%), vomiting (33.8%), nausea (30.7%), abdomen pain (29.5%), dyspnea (28.6%), angioedema (17.7%) and other symptom (5.1%) such as dizziness, dry month, and abdominal pain. For the person who had past experiences with abnormal symptoms from taking the medication, 75.2% reported that they stopped taking medication, and 58.5% went to see the doctors. About 54% consulted with community pharmacists; 42.4% asked others for resolutions for the symptom; 30.2% searched for causal relationship between their medicines and their abnormal symptom; 13.4% bought other medicines to treat the symptoms; 3% did nothing and 0.7% drank a lot of water and took a rest. When asked about illness behaviour, 86.4% went to see doctors, 62.3% consulted with community pharmacists, 35.4% bought/sought for medicines to treat their illness by themselves and 0.8% informed their family and asked other persons, etcetera.

Willingness to report ADRs

Most of respondents (92.1%) were willing to report ADRs if they had abnormal symptoms from their medication use. About two-thirds of them were comfortable reporting ADRs to physicians (66.6%) and community pharmacists (65.4%). There were 57.1% and 31% who were comfortable reporting ADRs to hospital pharmacists

and Thai FDA, respectively. The convenient channels to report ADRs were telephone (50.1%), Line®, a free messaging application, (49.3%), Facebook (45.7%), website (40.0%), email (33.9%), mobile application (32.1%), face to face reporting (5.7%), post mail (4.4%) and fax (0.5%). One-third of them (35.8%) had never known that they could report ADRs to community pharmacists. When asking for the suitable channels to inform the public how to report ADRs to community pharmacists, they rated that informing via community pharmacists (30.2%), Thai FDA website/line/Facebook (23.8%), advertisement at community pharmacies (22.6%), television (14.4%), medical journal (6.2%) and radio (1.8%).

Intention of ADR reporting to community pharmacists

The respondents agreed that they would report community pharmacists if they, their family, and friends had abnormal symptom from their medicines. However, they were more likely to focus on their family and themselves than their friends. Less than 7% of respondents strongly disagreed or disagreed they would report ADRs if their ADRs were not sever or resolved. (Table 2)

Attitude toward ADR reporting to community pharmacists

The mean score of instrumental attitude was significantly higher than mean scores of experimental attitude. (Table 3) Therefore, they believed that ADR reporting to community pharmacists was associated with certain attributes or outcomes than positive or negative feelings. For the experimental attitude, they agreed that there was a benefit to report ADRs. They also agreed that reporting ADRs to community pharmacists did not waste their time but it was a complicated process. However, they were not sure about their responsibility to report ADRs.

For the instrumental attitude, they agreed that reporting ADRs to community pharmacists would make them able to use medication safely, avoid harm, know the cause of ADRs and get more information about medicine. In addition, they agreed that the ADR reporting would benefit by helping to improve drug information leaflet and medication development.

Perceived norm of ADR reporting to community pharmacists

The average score for injunctive norm, the beliefs that their referents approved reporting ADRs to community pharmacists had significantly higher than the average score of descriptive norm, the beliefs that most people report ADRs to community pharmacists. (Table 3) They perceived that their family, friends and most people reported ADRs to community pharmacists. They also perceived that physicians, community pharmacists and their family or relatives and friends encouraged them to report ADRs to community pharmacists.

Personal agency toward ADR reporting to community pharmacists

The average score of self-efficacy was significantly higher than perceived behavior control. (Table 3) They agreed more about traveling to report ADRs to community pharmacists and disclose their personal information for ADR reporting. Although they were very busy and not familiar with community pharmacists, they could report ADRs to community pharmacists. For perceived behaviour control, they did not feel confident to report ADRs to community pharmacists, if they did not worry and did not know whether the ADR was related with their medication or not. The difficulty of explanation about their ADRs, travel expense, and time cost made them unsure to report ADRs to community pharmacists. If community pharmacists were not willing to listen and consult, they were not sure to report ADRs.

Structural Model for intention to ADR reporting

The results showed that the highest mean among the six constructs was the instrumental attitude score (4.10; SD = 0.60). The lowest mean was the perceived behavior control score (3.30; SD = 0.90). All Pearson correlations among variables were statistically significant. The correlation between intention to report ADR and instrumental attitude was highest. Perceived behavior control had the lowest correlation with intention to report ADRs. The correlation between descriptive norm and injunctive norm was high (correlation coefficient = 0.666). The result suggested referent persons could also motivate them to report ADRs. (Table 3)

All variables showed normal distribution. Confirmatory factor analysis was performed for all six constructs. (Tables 4, 5 and 6) Reliability tests were done with

internal consistency. The internal consistency of experimental attitude was slightly low (0.667), so EA3 was removed from the analysis. The internal consistency of all constructs was high (Cronbach's Alpha 0.794 – 0.866). The absolute Standardized Residual Covariance of all items of each construct was checked. IA6 for instrumental attitude, IN4 for injunctive norm and PC5 for perceived behavior control were dropped from the analysis since they were more than two in absolute value.

The structural model of factors significantly influencing patents' intention to report ADRs to community pharmacists is shown in Figure 12. The parameter estimates and the goodness of fix indices indicated that the structural equation model was an adequate fit for the data; GFI = 0.903, NFI Delta = 0.908, CFI = 0.913 and RMSEA = 0.077, 90% CI [0.075-0.080]. It was found that instrumental attitude had the strongest association with the intention to report ADRs to community pharmacists (ß = 0.327 and P < 0.001). Experimental attitude had significant correlation (r=0.332) with intention to report ADRs to community pharmacists, but was not significant in the model. Both injunctive norm (ß = 0.18) and descriptive norm (ß = 0.089) had significantly relationships with intention to report ADRs to community pharmacists. Among personal agency, only self-efficacy was significantly associated with intention to report ADRs to community pharmacists (ß = 0.268). Even though, perceived behavior control had no association with intention to report ADRs to community pharmacists in the model, it had significant point biserial (r = 0.298) correlation with intention to report ADRs to community pharmacists.

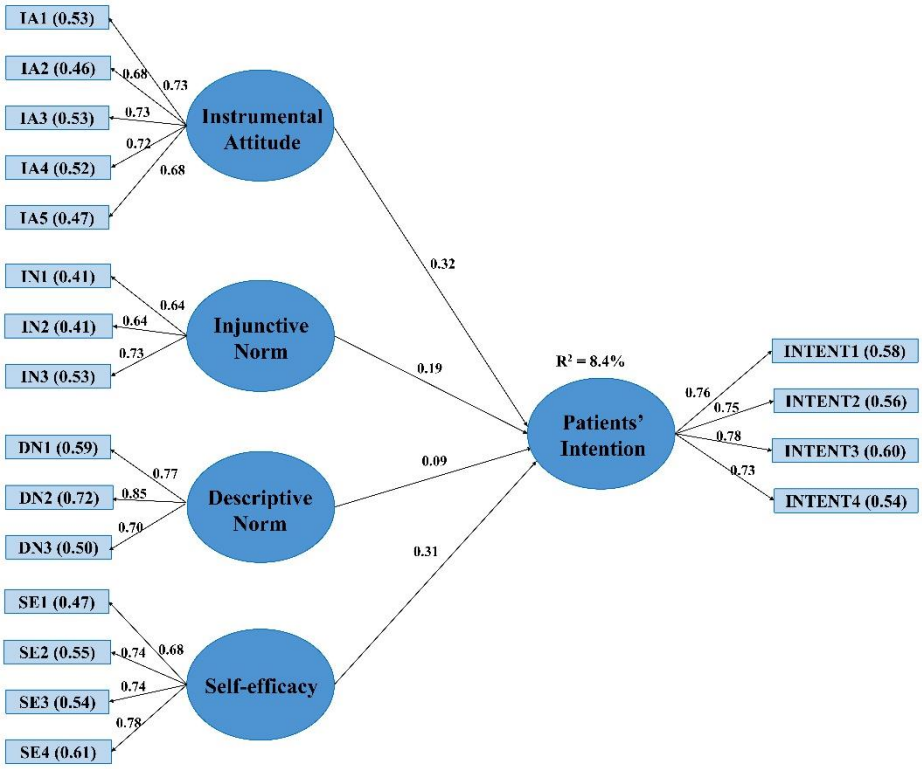

Figure 12 Results of structural equation modelling showing factors influencing intention of ADR reporting to community pharmacists (N = 2774)

Discussion

In Thailand, community pharmacies are private healthcare service locations that patients can easily access. According to the 2015 survey on health and welfare, 27.2 % of patients decided to buy medicines for self-care.(14) If patients have non-serious healthcare problem, the community pharmacists are the first choice for patients because of the convenience and time saving. Thus, when patients had any abnormal symptoms from their medication, community pharmacist should also be the first choice to consult with. Our results supported this hypothesis. The current study showed that 1,230 of 2,700 persons have had abnormal symptoms due to their medication and 54 % of those who had abnormal symptoms from their medication had consulted with community pharmacists. Thus, community pharmacists were important gatekeepers who have the opportunity to receive any ADR information from patients. Our study found that patients preferred to report their ADRs to community pharmacists (65.8%) more than directly report to the Thai FDA (31.0%). The benefits of reporting ADRs via

community pharmacists is that the information is professionally screened and investigated for the possibility of the relationship between their abnormal symptom and medication before reporting ADRs to the HPVC. Community pharmacies were more accessible for patients but one-third of patients (35.8%) did not recognize that they can report ADRs to community pharmacists. Therefore, Thai FDA should announce the roles of community pharmacists in pharmacies as the new source of ADR reports from patients. This would decrease HPVC's workload for evaluating causal relationship with the medication.

Interestingly, 92.1% of respondents were willing to report if they had abnormal symptoms from their medication use and 65.4% of them were comfortable to report to community pharmacists. Data from the HPVC showed that there were 830,502 adverse event reports since 1984 until September 2019 and up until March of 2019 there were only 1,562 adverse event reports from community pharmacies. This might be because patients were willing to report, but they did not actually report or they reported, but community pharmacists did not further report to HPVC. These two propositions should be investigated for a more complete explanation in future research.

This study found that only 5.7 % of respondents were comfortable reporting ADRs via face to face. About half of them were comfortable reporting ADRs by phone or internet such as using Line, Facebook, website, email and mobile application. The results suggested that community pharmacy should develop a new communication channel with patients via the internet.

Our results showed that although respondents were very busy and not familiar with community pharmacists, they could report ADRs to community pharmacists. Actually, there was a sign informing patients to consult with community pharmacists, whenever they have problems from medication in every pharmacy. However, one-third of respondents did not know that they could report ADRs to community pharmacists. This might be because they had never noticed the sign or did not perceive that they can report ADRs to every community pharmacist, although the pharmacist did not dispense medicine for them. Establishing communication between pharmacists and patients via internet will increase number of ADR reports. Furthermore, respondents rated the best

communication channel to inform patients about ADR reporting to community pharmacy was the pharmacist themselves.

Our study reported that 87.8% had intentions to report their abnormal symptoms due to their medication, but there were currently few ADR reports from community pharmacies. However, point biserial correlation showed a significant relationship between intention and past behaviour of ADR reporting (ß = 0.111). Future studies should follow further longitudinal data to find the magnitude of relationship between intention and future behaviour and also find out more influencing factors of ADR reporting.

Instrumental attitude was the strongest influencing factor for intention to report ADRs to community pharmacists. Not only the perception of direct personal benefit of ADR reporting to themselves, but also altruistic perception of ADR reporting benefits to others such as improving drug information leaflets and medical development could influence their intention to report ADRs to community pharmacists. Results from the study of Van Hunsel F et al.,(21, 22) also aligned with our study. The patients were concerned about the importance of drug information leaflets, this issue should be used to convince patients to report ADRs.

Injunctive norm and descriptive norm also influenced the intention to report ADRs to community pharmacists. This result was similar with the results from the Netherlands and United Kingdom that healthcare professionals including pharmacists can motivate patients to self-report ADR.(23, 24) Their reference person such as physicians, community pharmacists, their families and friends could motivate their intention to report ADRs to community pharmacists. In addition, norms based on observations of people around them reporting ADRs could inspire them to report ADRs to community pharmacists. These results suggested that systems such as the HPVC should encourage physicians and community pharmacists to encourage patients to report community pharmacists when they have abnormal symptom which they perceive occur from their medicines.

Self-efficacy and perceived behaviour control were influencing factors for intention to report ADRs to community pharmacist. Perceived behaviour control was

the least influencing factor for intention to report ADRs to community pharmacists. Intention to report ADRs to community pharmacists was influenced by their own perception of the ability to report ADRs more than perceived likelihood of a constraining or facilitating condition in making reporting ADRs difficult or easy. Results from the study showed that self-efficacy was the second important factor influencing intention to report ADRs to community pharmacists. Self-efficacy theory showed that the perception of efficacy can be built by four factors: 1) mastery experience, 2) vicarious experience, 3) verbal persuasion and 4) somatic and emotional state.(25) Therefore, the strategy to convince patients to consult with community pharmacists about their health problem would increase their mastery experience and finally make them confident to report ADRs to community pharmacists. The current study also supported significance of mastery experience since the results showed significant relationship between intention and past behaviour of ADR reporting. To build vicarious experience, the more people who report ADRs to community pharmacists is associated with the patients being watched, and the greater the influence on their belief that they can also accomplish reporting of ADRs. Verbal persuasion strategy to encourage reporting ADRs to community pharmacists was also recommended to increasing self-efficacy. Theoretically, somatic and emotional states can affect self-efficacy. In order to increase self-efficacy, reducing stress, anxiety, fears and physical obstacles would increase patients' self–efficacy and finally increase intention to report ADRs to community pharmacists.

Limitation

Theoretically, intention has an association with behavior. However, with time as a limitation, we did not follow actual ADR reporting after they formed the intention to report ADRs to community pharmacists. Most of respondents had a bachelor or higher degree (86.4%). The results of this study may not be generalized to people who have a lower education level. In addition, the questionnaires were distributed via a Google form, so the respondents of this study were only patients who could access the internet. Therefore, the results of this study may not be generalised to patients who cannot access internet. Now globalization is entering a digital era. The internet has

involved with economic, financial, and social connections, so the results of this study may be applied to the current and future situations.

Conclusion

Results from structural equation modeling showed all variables had no direct relationship with a patients' intention of ADR reporting to community pharmacists. Instrumental attitude had a strong association with patients' intention. It can be concluded that a positive attitude for ADR reporting can encourage patients to report ADRs to community pharmacists. However, current data from HPVC showed low ADR reports from community pharmacies.(13) In order to get more ADR reports from community pharmacies, patients must report their abnormal symptoms from their medication to community pharmacies. This study provides information for strategies to motivate patients' intention to report ADRs to community pharmacists which finally help create a stronger, more accurate description of ADRs.

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Table 2 Intention of ADR reporting to community pharmacists

Observation variables (English translation of items)	Mean±SD	Strongly agree and agree	Not sure	Strongly disagree and disagree
Q: If I have abnormal symptoms from my medicines, I will report community pharmacists.	4.24±0.792	87.7%	8.9%	3.4%
Q2: I intend to report community pharmacists, if my family has abnormal symptoms from their medicines.	4.11±0.798	84.3%	11.6%	4.1%
Q3: If my friends have abnormal symptoms from their medicines, I will help them to report community pharmacists.	3.95±0.782	73.8%	20.8%	5.4%
Q4: No matter whether my abnormal symptoms are not severe or resolved, I try to report to community pharmacists.	3.87±0.811	69.8%	23.5%	6.7%

Table 3 Mean, standard deviation (SD) and correlation among the constructs (N=2,774)

Constructs	Mean (SD)	Independent T-test	Correlation						
			INTENT	EA	IA	IN	DN	SE	PC
Intention (INTENT)	4.04 (0.69)		1						
Experimental Attitude (EA)	3.56 (0.77)		0.332**	1					
Instrumental attitude (IA)	4.10 (0.60)	$p < 0.0001$	0.613**	0.352**	1				
Injunctive norm (IN)	4.03 (0.66)		0.577**	0.291**	0.566**	1			
Descriptive norm (DN)	3.85 (0.69)	$p < 0.0001$	0.536**	0.249**	0.515**	0.666**	1		
Self-efficacy (SE)	3.93 (0.70)		0.608**	0.412**	0.574**	0.592**	0.531**	1	
Perceived behaviour control (PC)	3.30 (0.90)	$p < 0.0001$	0.298**	0.138**	0.248**	0.338**	0.322**	0.366**	1

** Correlation is significant at the 0.01 level (2-tailed)

Table 4 Attitude toward ADR reporting to community pharmacists

Observed variables (English translation of items)	**Strongly agree and agree**	**Not sure**	**Strongly disagree and disagree**	**Mean±SD**	**CFA Factor loading**
Component 1: Experimental attitude (Cronbach's Alpha = 0.823*)					
EA1: There is a benefit to report abnormal symptoms or health problems to community pharmacists.	75.8%	10.5%	13.7%	3.98±1.103	0.644
EA2: It does not waste my time to report abnormal symptoms or health problems to community pharmacists.	63.6%	20.0%	16.4%	3.76±1.113	0.940
EA3: It is my responsibility to report abnormal symptoms or health problems to community pharmacists.	43.7%	19.7%	36.6%	3.03±1.296	0.020
EA4: Reporting abnormal symptoms or health problems to community pharmacists is not complicated.	22.3%	23.6%	54.1%	3.49±1.159	0.780
Component 2: Instrumental attitude (Cronbach's Alpha = 0.861)					
IA1: Reporting abnormal symptoms or health problems from medicines to community pharmacists can safely use medicines.	88.5%	9.5%	2.0%	4.25±0.721	0.699
IA2: Reporting abnormal symptoms or health problems from medicines to community pharmacists help avoiding harm from using medicines.	80.3%	17.3%	2.4%	4.07±0.764	0.680
IA3: Reporting abnormal symptoms or health problems from medicines to community pharmacists can know the cause of abnormal symptoms or health problems.	80.1%	16.2%	3.7%	4.07±0.804	0.715
IA4: Reporting abnormal symptoms or health problems from medicines to community pharmacists can get more information of medicines.	83.2%	14.8%	2.0%	4.16±0.755	0.711
IA5: Reporting abnormal symptoms or health problems to community pharmacist is the benefit to improve leaflet of medicines.	80.7%	15.7%	3.6%	4.07±0.790	0.728
IA6: Reporting abnormal symptoms or health problems to community pharmacist is the benefit to develop medicines.	73.9%	20.9%	5.2%	3.96±0.855	0.743

* Cronbach's Alpha after removing EA3

Table 5 Perceived norm of ADR reporting to community pharmacists

Observed variables (English translation of items)	**Strongly agree and agree**	**Not sure**	**Strongly disagree and disagree**	**Mean±SD**	**CFA Factor loading**
Component 1: Injunctive norm (Cronbach's Alpha = 0.794)					
IN1: Physician encourages me to report abnormal symptoms or health problems to community pharmacists.	84.6%	11.4%	4.0%	4.20±0.826	0.667
IN2: Community pharmacists encourage me to report abnormal symptoms or health problems to community pharmacists.	85.5%	11.8%	2.7%	4.20±0.776	0.656
IN3: My family or relative encourages me to report abnormal symptoms or health problems to community pharmacists.	75.4%	18.3%	6.3%	3.96±0.874	0.756
IN4: My friends encourage me to report abnormal symptoms or health problems to community pharmacists.	64.4%	28.4%	7.2%	3.75±0.884	0.717
Component 2: Descriptive norm (Cronbach's Alpha = 0.807)					
DN1: I perceive my family reports abnormal symptoms or health problems to community pharmacists.	82.1%	14.6%	3.4%	4.13±0.809	0.749
DN2: I perceive my friends report abnormal symptoms or health problems to community pharmacists.	70.1%	25.3%	4.7%	3.81±0.782	0.855
DN3: I perceive most people report abnormal symptoms or health problems to community pharmacists.	54.1%	38.5%	7.4%	3.60±0.856	0.709

Table 6 Personal agency toward ADR reporting to community pharmacists

Observation variables (English translation of items)	**Strongly agree and agree**	**Not sure**	**Strongly disagree and disagree**	**Mean±SD**	**CFA Factor loading**
Component 1: Self-efficacy (Cronbach's Alpha = 0.825)					
SE1: I can disclose my personal information to community pharmacists, if it is necessary to report abnormal symptoms and health problems from medicines.	86.6%	9.6%	3.8%	4.18±0.777	0.668
SE2: I can travel to community pharmacists to report abnormal symptoms and health problems from medicines.	71.5%	21.6%	6.9%	3.87±0.866	0.753
SE3: I can report abnormal symptoms and health problems from medicines to community pharmacists, although I am very busy.	65.5%	23.9%	10.6%	3.75±0.936	0.755
SE4: I can report abnormal symptoms and health problems from medicines to community pharmacists, although I am not familiar with community pharmacists.	72.6%	21.8%	5.6%	3.91±0.858	0.776
Component 2: Perceived behavior control (Cronbach's Alpha = 0.866)					
PC1: I report abnormal symptoms and health problems from medicines to community pharmacists, although community pharmacists are not willing to listen and consult.	39.7%	19.3%	41.0%	2.92±1.321	0.698
PC2: I report abnormal symptoms and health problems from medicines to community pharmacists, although I don't know whether the abnormal symptoms are related with medicines.	54.2%	26.9%	18.9%	3.42±1.013	0.769
PC3: I report abnormal symptoms and health problems from medicines to community pharmacists, although I don't worry about them.	49.4%	27.9%	22.7%	3.33±1.112	0.779
PC4: I report abnormal symptoms and health problems from medicines to community pharmacists, although I wastes my time or travelling cost.	49.6%	25.5%	24.9%	3.31±1.123	0.702
PC5: I report abnormal symptoms and health problems from medicines to community pharmacists, although it is difficult to explain my abnormal symptoms.	59.9%	24.2%	15.9%	3.52±1.041	0.801

CHAPTER III

Benefit of the study

The study can increase more scientific knowledge of ADE reporting in the area of social, pharmacovigilance, community pharmacy and behavior. There were several practical benefits obtains form the study. Firstly, the results from this study show the basic foundation of ADR reporting and the perceptions and problems with low ADE reporting by community pharmacists and consumers. Secondly, the results described current situations and problems of ADEs reporting in Thailand. Thirdly, the stimulation and obstacle of ADE reporting on community pharmacists and consumers can be identified. Lastly, the results of this study can identify the contributing factors influencing to the consumers' intention on ADE reporting. For improving the ADE reporting system, the results can guide HPVC to establish interventions to stimulate consumers to report ADEs to community pharmacists.

Limitation

Theoretically, intention has an association with behavior. However, with time as a limitation, we did not follow actual ADE reporting after they formed the intention to report ADEs to community pharmacists. Most of respondents had a bachelor or higher degree (86.4%). The results of this study may not be generalized to people who have a lower education level. In addition, the questionnaires were distributed via a Google form, so the respondents of this study were only consumers who could access the internet. Therefore, the results of this study may not be generalised to consumers who cannot access internet. Now globalization is entering a digital era. The internet has involved with economic, financial, and social connections, so the results of this study may be applied to the current and future situations. All healthcare professional can report ADEs to HPVC but only community pharmacists was focused in this study. Therefore, the identified factors on the study may not apply all stimulations and barriers on ADE reporting system in other sectors of pharmacy such as hospital pharmacy and pharmaceutical company.

Recommendation

Due to limitation of HPVC manpower, community pharmacists should be the suitable persons for receiving ADE information from consumers and report them to HPVC. Since almost half of the interviewed consumers preferred to report their abnormal symptoms to community pharmacists, directly ADE reporting to community pharmacists is a suitable channel to increase reporting from consumers.

Unawareness of ADE reporting process was the main problem in Thailand. Publicizing the ADE reporting process, channels, and system were recommended because it could increase the number of ADE reports from consumers. The perceived benefit of ADE reporting was another important contributing factor to stimulate consumers to report ADEs. Healthcare professionals and other influential persons were found to be effective channels to encourage consumers to report ADEs. These results were consistency with the results from quantitative study. Instrumental attitude was the strongest influencing factor for intention to report ADRs to community pharmacists. Thus, in encouraging consumers, not only the perception of direct personal benefit of ADR reporting to themselves, but also altruistic perception of ADR reporting benefits to others such as improving drug information leaflets and medical development could influence their intention to report ADRs to community pharmacists. Establishing campaigns emphasizing consumers' social responsibility and perception on benefits of ADE reporting can drive them to report ADEs.

Injunctive norm and descriptive norm also influenced the intention to report ADRs to community pharmacists. Their reference person such as physicians, community pharmacists, their families and friends could motivate their intention to report ADRs to community pharmacists. Emphasizing healthcare professionals to tell consumers to report their ADEs could be also increase the number of reporting from consumers.

Intention to report ADRs to community pharmacists was significantly influenced by self-efficacy, their own perception of the ability to report ADRs. Theoretically, self-efficacy theory can be built by four factors: 1) mastery experience, 2) vicarious experience, 3) verbal persuasion and 4) somatic and emotional state. Therefore, the strategy to convince consumers to consult with community pharmacists

about their health problem would increase their mastery experience and finally make them confident to report ADRs to community pharmacists. The current study also supported significance of mastery experience since the results showed significant relationship between intention and past behaviour of ADR reporting. To build vicarious experience, the more people who report ADRs to community pharmacists is associated with the consumers being watched, and the greater the influence on their belief that they can also accomplish reporting of ADRs. Verbal persuasion strategy to encourage reporting ADRs to community pharmacists was also recommended to increasing self-efficacy. Somatic and emotional states can affect self-efficacy. In order to increase self-efficacy, reducing stress, anxiety, fears and physical obstacles would increase consumers' self–efficacy and finally increase consumer intention to report ADRs to community pharmacists.

Convincing consumers to report any suspected ADEs no matter how serious it is and confirming whether it was ADE would motivate them to report ADEs. Encouraging consumers to report and community pharmacists to accept ADE reports from any consumers even though they are not their regular customers were recommended.

The campaign should also emphasize confidentiality concerns. Simplifying the ADE form and providing training, guidelines, and an ADR assessment tool can drive community pharmacists to report ADEs. An application in mobile phone for community pharmacists were highly recommended in the digital era.

Providing feedback after receiving the ADE reports from community pharmacists would make them ensure that the Pharmacovigilance center received their reports and their reports were utilized. Making community pharmacists feel comfortable to report ADEs could encourage them to report ADEs. Moreover, asking for cooperation from chain companies to transfer these reports to the Pharmacovigilance center can augment number of ADE reporting. Perception on benefit of ADE reporting either for pharmacists or society and drug developments should also added in the intervention. Providing rewards for ADE reporting can drive community pharmacists to report ADEs. Emphasizing community pharmacists' duty

and social responsibility could drive them to report ADEs. If ADE reporting is compulsory, underreporting problems would be lessened.

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