PHARMACOEPIDEMIOLOGY OF MEDICATION OVERSUPPLY AND ASSOCIATED FINANCIAL BURDENS IN THAILAND

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ABSTRACT

Medication oversupply is an important healthcare problem in Thailand. It causes unnecessary but avoidable healthcare cost. Although, some previous studies related to medication oversupply were conducted in Thailand, no study has been conducted to estimate national prevalence and financial burden of the problem. Moreover, there is no study determining factors associated with medication oversupply. This study was conducted 1) to estimate national prevalence of medication oversupply focusing on patients receiving medications for chronic conditions, 2) to estimate national financial burden due to medication oversupply, and 3) to determine factors associated with medication oversupply. This study was divided into four parts; **Part I: Pharmacoepidemiology of medication oversupply for chronic conditions within hospitals.** A retrospective database analysis from three public hospital databases was performed. Patients visiting outpatient departments of the hospitals in 2010 were included. Patients who have modified medication possession ratio (MPRm) >1.20 were defined as medication oversupply. The measures of interest were prevalence of medication oversupply, and its financial burden. **Part II: Pharmacoepidemiology of medication oversupply across hospitals.** A national dataset of all healthcare services collected by the National Health Security Office (NHSO) was linked to a regional hospital dataset. Patients receiving same medications across hospitals were identified. The medication supply of each patient who received same medications across hospitals

was estimated. **Part III: Estimation of the national prevalence and financial burden due to medication oversupply for chronic conditions.** A mathematical model using a decision tree framework was performed to estimate the number of oversupplied patients, prevalence of medication oversupply, and its national financial burden in national level. Prevalence and financial burden from Part I was used as key parameters. The number of patients visiting public hospitals from NHSO database was used. Probabilistic sensitivity analysis was also undertaken. **Part IV: Factors associated with medication oversupply.** The databases used in Part I was used in Part IV. Factors associated with medication oversupply were determined. Because hospitals' data structure which individual-level data (level-1) were nested in hospital-level data (level-2), two-level hierarchical regression model was performed. The individual-level variables including age group (children/adolescent, adult, and elderly), gender, health insurance, Charlson's co-morbidity index (an algorithm commonly used for assessing the comorbidity burden of patients), types of hospital (regional vs. district hospital), and number of medications patients received (<5 vs. ≥5 medications) were used as fixed-effects variables, while hospital was used as a random-effects variable.

Overall, the estimated number of oversupplied patients at national level was about 3.1 million (ranged from 2.8 to 3.5 million). The estimated national prevalence of medication oversupply was 7.84% (7.06% to 8.68%). The estimated national financial burden was $30.8 million each year ($26.9 to $35.6 million). It accounted for 0.035% of Thailand gross domestic product (0.031% to 0.041%). The problem was mainly occurred within hospital. Only 2.7% of patients received same medications across hospitals. Patients who were under civil servant medical benefit schemes (CSMBS), children, and received at least five medications were more likely to be oversupplied.

In conclusion, medication oversupply results in millions U.S. dollars in financial loss each year in Thailand. Around eight percent of patients receiving chronic medications have medication oversupply and Thai government experiences unnecessary financial loss due to such problem about three million U.S. dollars each year. Although, a total financial loss is not tremendous, it would be better for Thai government to avoid unnecessary financial loss and spend the saved money to improve their healthcare system. Policy-makers should consider to develop policies or strategies to minimize this problem.

LIST OF CONTENTS

LIST OF CONTENTS (CONT.)

Chapter **Page**

LIST OF CONTENTS (CONT.)

LIST OF TABLES

Table **Page**

LIST OF FIGURES

Figure **Page**

CHAPTER I

INTRODUCTION

Statement of Purpose

Healthcare expenditure in Thailand continues to increase during the past decades. It has been risen from 227.5 billion baht (1995) to 558.1 billion baht (2008). It has grown faster than Thailand gross domestic products (GDP). An increase in healthcare expenditure is about 7.8% per year, while an increase in GDP is about 5.8%.[1] Healthcare expenditure composes several components. Major components include hospital, physician and clinic, and medication expenditure.

Medication expenditure is an important sector of healthcare expenditure. In Thailand, medication expenditure accounts for 46.4% of healthcare expenditure. [1] Potential factors which affect medication expenditure are medication price and quantity of medication use. Medication price has been increasing overtime as well as quantity of medication use. [2] One of important causes of an increase in quantity of drug use is medication waste. [3]

Medication waste, medications which are not used by patients, is an important problem of Thailand healthcare system. The president of pharmacy council of Thailand states that patients possess amounts of medication about 3-4 times of patients needed. [4] Medication waste increases hospitalization [3] and cost of care. [3, 5, 6] Conceptually, medication waste is caused by patients' non-compliance and factors not associated with non-compliance. Non-compliance is focuses on under-use of medications, while factors not associated with non-compliance are treatment revision, patient death and medication oversupply.

Medication oversupply is focuses on the amount of medications which is over-supplied to patients. Although, medication oversupply could cause medication waste and increase medication expenditure, a few studies have been conducted to determine magnitude and impacts of medication oversupply as well as factors associated with medication oversupply.

The magnitude of medication oversupply in the United States (U.S.) is relatively substantial. Previous studies showed that prevalence of medication oversupply ranged from 30-47%. [7, 8, 9, 10] Patients who had medication oversupply had 11-18% higher medication expenditure than patients who had appropriate medication supply. [7, 8] Patients with medication oversupply had higher risk of hospitalizations than patients with appropriate supply. [7, 8, 9] Similar to medication oversupply in the U.S., magnitude of medication oversupply in Sweden was about 22-30% [11, 12, 13, 14, 15] and financial loss due to medication oversupply was 4.5% of all medication costs. [12]

A few studies were conducted in Thailand to determine the magnitude and financial burden of medication oversupply. A study by Kaojarern and colleagues, which was conducted in a university hospital, revealed that the prevalence of medication oversupply which defined by patients receiving medication more than needed for at least 30 days-supply was 2.9 - 3.5%. [16] Another study [17] by Chaiyakunapruk and colleagues was conducted in a regional hospital. Based the top five highest medication expenditure, the prevalence of medication oversupply ranged from 20 to 60%. [17] However, definition of oversupply used in the study was different from another study. [16] This study by Chaiyakunapruk and colleagues defined oversupply as those receiving medications more than needed (medication possession ratio (MPR) >1.00) using a time period of 1 year for evaluation.

According to financial loss due to medication oversupply, Kaojarern's study reported the financial burden of 2.1 – 2.7% of medication expenditure [16], while t Chaiyakunapruk's study reported the financial burden of 3.8% of the hospital medication expenditure in only five medications. [17] The differences of financial burden were likely due to differences in definitions of medication oversupply, the number of medications investigated, and drug utilization patterns at those two settings.

It was very important to note that there was no study exploring factors associated with medication oversupply. Although, there were a couple of studies evaluating prevalence and financial burden in some hospitals, there was no study estimating the overall prevalence and financial burden for Thailand as a whole. Studies estimating prevalence, financial burden and associated factors of medication oversupply are still needed.

This study aimed to determine national prevalence of medication oversupply and its financial burden in patients visiting outpatient department and receiving medications for chronic conditions. Furthermore, it also aimed to explore potential factors associated with medication oversupply in Thailand. The findings of this study are important information to inform healthcare professionals and policy makers to develop proper policies or strategies to manage medication oversupply problem in Thailand.

Research questions

1. What is the national prevalence of medication oversupply?
2. What is national financial burden due to medication oversupply in payer perspective?
3. What are factors associated with medication oversupply?

Research objectives

1. To determine national prevalence of medication oversupply in Thailand
2. To determine national financial burden due to medication oversupply
3. To determine factors associated with medication oversupply

Scope of the study

Medication waste is an important healthcare problem in Thailand. As illustrated in Figure 1, medication waste is caused by patients' non-compliance and factors not associated with non-compliance including medication oversupply. Despite a few studies determining magnitude and financial burden of medication oversupply, those studies did not provide overall estimates for Thailand as a whole. In order to healthcare professionals and policy makers to develop proper policies or strategies to minimize medication oversupply problem, there is a strong need to conduct a study determining prevalence, financial burden due to medication oversupply in national level, and factors associated medication oversupply. Based on the abovementioned justification, we therefore decided to conduct this study focusing on medication oversupply. This study aimed to determine national prevalence of medication oversupply, its financial burden in patients receiving medications for chronic conditions in outpatient departments of government hospitals and factors associated with medication oversupply in Thailand.

This study was conducted using a retrospective electronic database analysis using databases from two regional hospitals and one district hospital. Databases included demographic data, dispensing data, diagnosis data and financial data from January 1st, 2010 to June 30th, 2011. The medication supply was calculated using modified medication possession ratio (MPRm).

Prevalence of medication oversupply and its financial burden in hospital level were calculated. Only direct financial burden was estimated by the multiplication of the number of pills which were oversupplied and referent cost of each medication. Additional to prevalence of medication oversupply and its financial loss, prevalence of patients receiving same medications across hospitals was estimated because receiving same medications across hospitals might increase a likelihood of medication oversupply. National database from national health security office (NHSO) was used to determine prevalence of patients receiving same medications across hospitals. National prevalence of medication oversupply and its national financial burden were estimated using a mathematical model with a decision tree framework with probabilistic sensitivity analysis.

Factors associated with medication oversupply were determined using a hierarchical regression analysis. Dependent variable was dichotomous for having medication oversupply for each patient. A number of factors including patient characteristics, and types of hospital were used as independent variables. Hospital variable was treated as random-effects variable, while other independent variables (leve-1) were treated as fixed-effects variables which were nested to hospital variable (level-2).

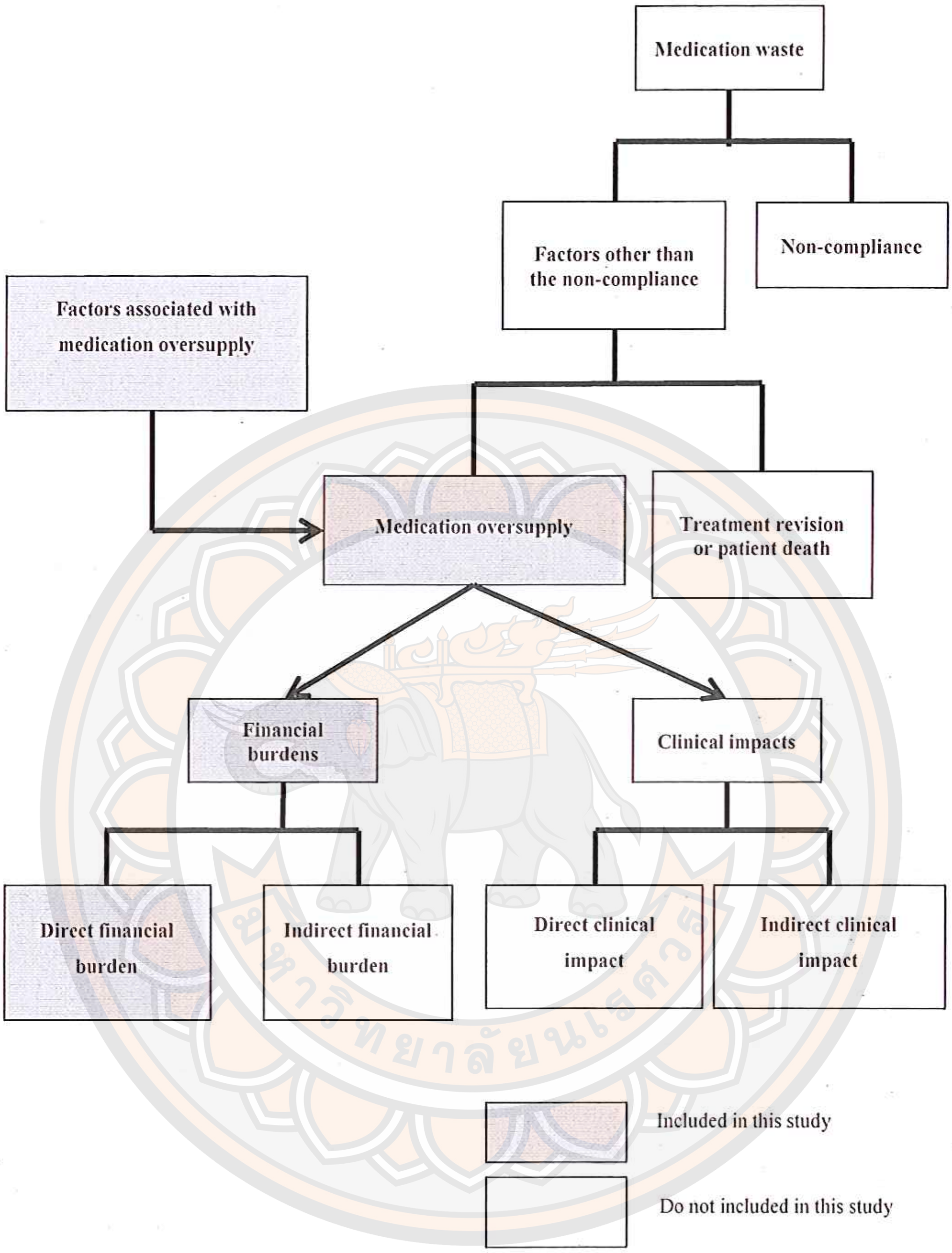

Figure 1 Scope of work

Definition of terms

Prevalence: is the frequency of existing cases in a defined population at a given point in time

Medication oversupply: is the number of medications that patients receive more than are needed

Prevalence of medication oversupply: is the proportion of patients who are oversupplied to all included patients

Medication possession ratio: is the total number of days' supply of a drug was divided by the sum of the number of days from first dispensing up to the date of last dispensation and the number of days' supply obtained at the last dispensation

Direct financial burden: is the results of the number of pills which is oversupplied are multiplied by drug costs

Probabilistic sensitivity analysis: is a method of exploring the effects of the uncertainty on results by varying all of parameters in the model simultaneously over their entire ranges

Decision tree model: is a decision support tool that uses a tree-like graph or model of decisions and their possible consequences, including chance event outcomes, and resource costs

Factors associated with medication oversupply: are factors which are associated with medication oversupply and might be causes of medication oversupply

Expected outcomes

This study is expected to provide important information of medication oversupply. It is probably used as relevant information to develop proper policies or strategies to solve medication oversupply. Moreover, it is expected to be used to raise healthcare professionals' awareness of medication oversupply problem.

CHAPTER II

LITERATURE REVIEWS

This literature review was conducted to summarize previous knowledge related to medication oversupply. The first section was a review for basic knowledge of pharmacoepidemiology which is core knowledge of this study. The second section revealed a current situation on medication expenditure and factors associated with medication expenditure globally and Thailand. The third section summarized information related to medication oversupply including definition, magnitude, impacts and potential factors associated with medication oversupply. The fourth section described methodologies used to estimate medication supply. In order to comprehensively understand factors associated with medication oversupply, the last section provided fundamental of regression analysis, especially on hierarchical regression analysis, which was used in this study.

Overview of pharmacoepidemiology

Definition of pharmacoepidemiology

Pharmacoepidemiology is the study of medication use and the effects of medications in large population. [18] It applies epidemiological techniques to study medication use and its effects. Just as the term implies, **Pharmacoepidemiology** combines **clinical pharmacology** and **epidemiology. Clinical pharmacology** is the study of medications in humans [19], while **Epidemiology** is the study of factors which determine the occurrence and distribution of diseases in population. [20] Thus, pharmacoepidemiology is a field which bridges between clinical pharmacology and epidemiology. It uses the focus of inquiry from clinical pharmacology and the methods of inquiry from epidemiology. [18]

Pharmacoepidemiologic studies are studies involved with both common predictable and uncommon unpredictable adverse drug effects. [21] In addition, pharmacoepidemiologic studies quantify medication use patterns, appropriateness of medication use, real-world medication effects, medication adherence, and predictors for medication use. [21]

Benefits of pharmacoepidemiologic studies

Pharmacoepidemiology provides information on medication utilization patterns, effectiveness and safety of medications in real-world settings. This information could be used as important information to improve overall quality of medication use in population.

Due to limitations of premarketing studies, pharmacoepidemiologic studies provide supplemental information to premarketing studies and new information which could not be found in premarketing studies. [18] Pharmacoepidemiologic studies could provide better understanding in real-world medication use and effects because they are usually conducted in a large number of population. They allow studying in the vulnerable populations (eg. pregnant women, elderly population or children). They could explore how factors modify the effects of medications in real-world settings. Moreover, pharmacoepidemiologic studies provide information on uncommon benefits, adverse effects of medications and also delayed medication effects. [18]

Another type of information which can be provided by pharmacoepidemiologic studies is the patterns of medication utilization. The information could not be predicted before a particular medication is marketed. Pharmacoepidemiologic studies can be performed to determine how a medication is actually used, and factors affecting patterns of medication utilization. [22, 23, 24) For example, a study was conducted to determine a pattern of statin utilization in a teaching hospital in Thailand. [25] The study's findings indicated that branded statins are commonly prescribed in civil servant medical benefit schemes (CSMBS) but not in other health insurances. A trend of medication shift from lower priced generic medications to higher priced branded medications is common in patients under CSMBS and out-of-pocket. On the other hand, a trend of medication shift from higher to lower priced medications is common in patient under universal coverage and social security schemes. The information is important for clinicians to treat patients and policy makers to make a policy decision.

Pharmacoepidemiologic studies could also be conducted to evaluate medications adherence [26, 27, 28, 29, 30]. For example, a cohort study [28] was conducted to determine adherence of tuberculosis prevention in HIV-infected patients. The study's findings indicated that one third of patients did not adhere to the program. The findings warned clinicians and policy-makers to improve the effectiveness of tuberculosis preventive program in Thailand.

Pharmacoepidemiologic studies could also be used to estimate clinical or economic impacts of medication utilization or patterns of medication utilization. [7, 8, 9, 17, 30, 31] For example, a study was conducted to determine clinical and economic impacts of inappropriate medication supply. [31] Its findings indicated that inappropriate medication supply tend to increase risk of hospitalizations and cost. The study provided relevant information to improve physician prescribing patterns in terms of the amount of medication.

In conclusion, pharmacoepidemiologic studies could be used to determine effectiveness and safety of medications and to understand patterns of medication use and their impacts in real-world settings. Information on effectiveness, safety, patterns of medication use and impacts of medication use in real-world setting is important for clinicians to improve their treatments to more specific to their patients and also helps policy makers to develop appropriate policies to improve healthcare system.

Relationship between pharmacoepidemiology and pharmacoeconomics

Pharmacoepidemiology applies epidemiologic methods to study the use of medications in population. Nonetheless, a recent trend of modern pharmacoepidemiologic studies has incorporated economic aspects into analyses. Pharmacoepidemiologic studies could be conducted using healthcare cost as one of the study's outcomes. Healthcare cost can be the index of quality of medication use as well as economic consequences of medication use. [18, 32]

Data on total medication cost have been often used in medical and health services researches. Total medication cost is another form of medication utilization. Total medication cost is usually broken down to medication groups or therapeutic areas. For instance, an introduction of new expensive anti-cancer agents may be found to be a driver of an increase in total medication cost in a hospital. Changes in total medication cost could result from changes in the amount of medication prescription, quantity per prescription, or average cost per prescription. Pharmacoepidemiologic studies could be applied to forecast budget impact of new medications on total budget and to determine factors affecting the use of new medications. Findings from those types of study could help policy makers to manage total budget of the next fiscal year and also to develop strategies or policies to control the use of new medications.

Total medication cost may be used as an indicator of quality of a program. For instance, a refill clinic was implemented to improve patients' clinical outcomes. Several indicators should be assessed for a success of the program such as the number of patients enrolled in the clinic and satisfactions of enrolled patients. A decrease in total medication cost should be one of key performance indicators of the success because a decrease in medication cost will be important information for policy maker to consider whether the program should continue. Pharmacoepidemiologic studies could be applied to assess cost of the program.

In conclusion, pharmacoepidemiology is closely related to pharmacoeconomics, especially in the real-world medication utilization.

Current situation and factors affecting medication expenditure

A current situation & a global trend of medication expenditure

Medication expenditure is the largest components of healthcare expenditure accounted for 24.9% of global health spending in 2006. [33] A World Health Organization [33] reported a highly positive correlation of total medication expenditure and total healthcare expenditure. However, proportions of medication expenditure on healthcare expenditure varied among high-income and low-income countries. These proportions were 19.7%, 23.1%, 27.6% and 30.4% for high-income, upper-middle-income, lower-middle- income and low-income countries, respectively. On average, poorer countries spent proportionally more of their healthcare expenditure on medications than richer countries. [33]

Spending on medications is also an important component of gross domestic product (GDP). In 2006, world's spending on medications accounted for 1.5% of GDP and varied by income of each country. Wealthier countries spent less share of GPD comparing to poorer countries ranging from 1.41%-1.62% of GDP. [33] It was similar to proportions of medication spending on total healthcare expenditure.

Global medication expenditure continues to increase over past decade. Reports from Organization for Economic Co-operation and Development [34] and the 2004 World Medicines Situation [35] revealed that a rate of changes in total medication expenditure was higher than a rate of changes in both total healthcare expenditure and GDP in several countries, worldwide. Overall, per capita spending on medications has risen by approximately 50% from 1995-2006. The middle-income countries (like Thailand) mostly increased in medication spending per capita. Medication expenditure in upper-middle income countries in 2006 were 1.73 times larger than in 1995, while medication spending in lower-middle income countries in 2006 were 1.82 times larger than in 1995. In contrast, medication expenditure per capita increased by 1.54 and 1.66 times for high- and low-income countries, respectively.

Similar to per capita medication expenditure, total medication expenditure as a share of GDP has also increased since 1995. It has increased from 1.22% of GDP in 1995 to 1.52 of GDP in 2006, worldwide. The largest growth of medication spending in terms of percentages of GDP occurred in low-income countries. It has increased from 1.22% to 1.62%. Total spending on medications in high-income countries has increased for 1.19% to 1.42%. The expenditure has increased from 1.19% to1.45% and 1.31% to 1.63% for upper-middle and lower middle-income countries, respectively. [33]

A current situation & a trend of drug expenditure in Thailand

Similar to global medication expenditure, Thailand has been facing on a high proportion of medication expenditure. In overall, national healthcare expenditure was 588.2 billion baht in 2008, while spending on medications was 272.8 billion. A proportion of total spending on medications on total healthcare expenditure was 47.4% in 2008. [1] Interestingly, the proportion was larger than that of upper-middle income countries, of which Thailand is a member. Furthermore, it was also greater than that of low-income countries, which is the highest proportion of medication expenditure on healthcare spending. It might be due to a healthcare system in Thailand which has universal coverage scheme. This scheme might increase medication usage and expenditure.

A trend of medication expenditure has substantially increased over the past decade. Total medication expenditure has risen from 82.8 billion baht in 1998 to 272.8 billion in 2008. The medication expenditure in 2008 was 3.3 times larger than that in 1998. An increase in medication expenditure of Thailand was 1.73 times higher than that of a global trend. In addition, total spending on medications as a share of GDP has also substantially increased from 1.82% of GDP to 3.01% of GDP or about 1.65 times. [1]

Factors affecting medication expenditure

The majority of researches on growth of medication expenditure has focused on identifying current situations and drivers of medication expenditure. Generally, drivers of medication expenditure could be classified into three major direct determinants as changes in medication price, changes in medication utilization and changes in types of medication use. [36, 37, 38, 39] Medication price could be measured in multiple ways such as cost per unit, median price ratio, wholesales acquisition price for 30-day supply, or average medication price per prescription [38]. Utilization, also called "volume of medication use", is decomposed into propensity of medication use, intensity of medication use and number of medication recipients. While, change in types of medication use is that prescription medication spending is affected when new medications enter markets and when existing medications lose their patent protection. The latter factor is incorrect to speak of this change as "price change" because the nature of the commodity being purchased is changing overtime. New medications are not simply more costly than older medications. They may be more effective or have fewer side effects; some may treat conditions for which no treatment is available. [37]

Changes in medication price

In the US, prescription medication price measured by consumer price index has increased about 3.4% in 2009, 2.5% in 2008 and 1.4% in 2007. The average annual growth in prescription medication price from 2000 to 2009 was 3.6 percent. In addition, an average prescription drug price has risen from $38.43 in 1998 to $71.96 in 2008. [39] Several factors influenced on average medication price such as changes in unit price of medication, changes in retail and wholesale markups and professional fee, international price of medication, and inflation. [40]

Changes in medication utilization

Not only medication price has increased but medication utilization also has increased overtime. According to Express Script [41], medication utilization has increased in 9.7% from 1995 through 1999. The number of prescriptions dispensed in the US increased in 39% from 1999 through 2009. [39] Moreover, a report of nine therapeutic classes in Thailand revealed that the number of prescriptions increased ranging from 2.7%-68.4% from 2000 through 2002. [2] The number of days supplied has also increased ranging from 5.4% - 83.1% from 2000 through 2002. The number of medication recipients has also increased ranging from 5.4% - 39.8%.

Several factors affect medication utilization. They could be classified as 1) population-related, 2) system-related, 3) research and technology-related, 4) pharmaceutical industry, and 5) practice-related factors. Population-related factors include changes in population size and structure, changes in health status of population, emergence of new diseases and epidemics. [40] System-related factors include healthcare system reform, health insurance coverage, changes in policies and programs, and the extent of formulary listings. Research and technology-related factors include changes outcomes research and evidence of treatments or technology, and changes in availability of more or improved diagnostic technologies. Pharmaceutical industry-related factors include product direct-to-consumer marketing, medication promotion and medication sampling. Practice-related factors include changes in prescribing and dispensing practice, poly-physician, poly-pharmacy, consumer's expectation and behaviors, adherence to treatment [40] and medication waste. [3]

Changes in types of medication use

Changes in types of medication use is that prescription medication spending is affected when new medication enter markets and when existing medications lose their patent protection. New medication entering markets have contributed substantially to growth in average price per prescription. Price of newer medications is usually much higher than that of older medications. [37] A ratio of average price per prescription of newer medications and older medications was 2.23 in 1999. [37, 41] A report of medication price in Thailand indicated that average price per day of single-source statins was 15 times higher than that of multiple-source statins and average price per day of single-source proton pump inhibitors was 18 times higher than that of multiple-source proton pump inhibitors. [2] Those reports confirmed that newer medications affect overall medication price and medication spending.

A loss of patent protection of existing medications reduces the average medication price causing a reduction of medication spending. Data from the U.S. Food and Drug Administration revealed that generic competition was associated with lower medication prices. [42] Generally, the first generic medication price is slightly lower than branded medication price. However, for product with a large number of generics, the average medication price usually falls down to at least 20% of the branded price.

The relative contributions of price, utilization and changes in types of medication use on medication expenditure

A number of studies were conducted to identify drivers of medication expenditure. The conclusion was that important drivers of medication expenditure were utilization and changes in types of medication use. Switching to more expensive medications accounted for 28% and increasing in medication utilization accounted for 48% of the annual increase in spending on medications. [39] Express Scripts reported that a total of 23% accounted for medication utilization, while 55% accounted for changes in types of medication use. [41] Other studies [2, 43] have found similar results that major drivers of medication expenditure were medication utilization and changes in types of medication use.

In conclusion, medication expenditure is an important component of healthcare expenditure and GDP in Thailand. Medication expenditure has been currently rising overtime and is an important problem of healthcare system worldwide. Several factors affect medication expenditure including changes in price, utilization, and type of medication use, especially changes in utilization and type of medication use. Interestingly, one of important factors affecting medication utilization is, in practice-related factors, medication waste because it is inappropriate use of medication and avoidable if appropriate managements and policies are developed.

Medication oversupply

According to substantial growth in medication expenditure, one of the important factors affecting medication utilization and expenditure is medication waste. Medication waste, sometimes also called "unused medication", is medications that are dispensed but are ultimately physically discarded. [3] York health economics consortium and the school of pharmacy, University of London [3] reported that approximately £300 million per year lost due to medication waste. Several factors cause medication waste which could be classified into two groups as non-compliance and factors not associated with non-compliance. The non-compliance factors include intentional non-compliance (for example, due to beliefs or side-effects) and unintentional non-compliance (for example, due to forgetfulness). Factors not associated with non-compliance include treatment revision, patient death, or medication oversupply. Because the aims of this study are to determine the magnitude of medication oversupply, its financial burden and associated factors of medication oversupply, this section aimed to review definition, prevalence, financial burden and clinical impacts of medication oversupply.

Definitions of medication oversupply

General definitions of medication oversupply

Medication oversupply has been defined by a number of researchers. For example, Troupe and colleagues [10] define medication oversupply as "Refilling medications more frequently than required for adherence". Medication oversupply defined by Yang and colleagues [44] is that "patients receive more medications than are needed." Another one is "a divergence from prescribed treatment time above +20% of perfectly refill adherence means drug stockpiling or oversupply" which is defined by Anderson colleagues [11] (Table 1). Generally, medication oversupply is defined as patients received medications for their treatment more than medications they needed to be used in hospital perspective. For example, a patient continuously receives medications for a chronic condition for one year or 365 day-supply but the patient actually receives medications for 450 day-supply. Therefore, the patient receives medications more than he needs or he has oversupplied medication.

Table 1 General definitions of medication oversupply

Authors (Year)	Definition of medication oversupply
Andersson K (2005)	"Another one is that a divergence from prescribed treatment time above +20% of perfectly refill adherence means drug stockpiling or oversupply"
Yang M (2007)	"Patients receive more medications than are needed."
Troupe CT (2009)	"Refilling medications more frequently than required for adherence"

Operational definitions of medication oversupply

Although, medication oversupply conceptually is that patients receive more medications than they are needed but acceptable cut-off point for defining medication oversupply is still debatable. Operational definitions of medication oversupply varies from > 20%, >10% and >0% excessive of a perfect medication supply.

A number of studies define that the 20% of excessive medication is defined as medication oversupply.[8, 10, 11, 12, 13, 14, 15, 17, 31] Theoretically, if a patient receives a medication for 1-year period (52 weeks), a patient who has medication oversupply have to possess a medication for 62.5 weeks.

Other studies define that the 10% of excessive medication are the acceptable level for medication oversupply. [7, 45, 46, 47, 48] Again, a patient is classified as medication oversupply when the patient possesses a medication for 57.2 weeks of one year. However, a few studies define that a patient possesses at least one pill more than needed as the medication oversupply. [17, 46] In addition, a study conducted in a teaching hospital in Thailand defines medication oversupply as when the quantity of medication leftover from the preceding visit is more than 30 days. [16]

Because there is no gold standard operational definition of medication oversupply, a definition of medication oversupply which will be used in further studies should be discussed by all stakeholders for appropriateness in local context. Sensitivity analysis of various operational definitions should be conducted to explore the effects of definition's uncertainty on outcomes.

Magnitude of medication oversupply

A number of studies were conducted to estimate magnitude of medication oversupply using several techniques. [3, 6, 7, 8, 10, 12, 17] Some studies were conducted using survey techniques, [3, 6] while some studies were undertaken using electronic medical records. [7, 8, 10, 12, 17]

Two previous survey studies were conducted to estimate volume of medication waste including medication oversupply. [3, 6] Their findings indicated that medication oversupply was accounted for 0.7-1.7% of medicine waste. Common oversupplied medications were nutrition and endocrine medications. Those studies were conducted under patient perspective (demand-side).

A number of studies were conducted using electronic database analyses under hospital perspective (supply-side). The studies showed that 4.8% - 47% of patients had medication oversupply. [7, 8, 9, 10, 48, 49] In patients with hypertension, prevalence of medication oversupply ranged from 30% through 40%, [8, 10] while such prevalence in patients with chronic heart failure was 37%. [9] Medication groups which were commonly oversupplied were oral hypoglycemic medications, digoxin and angiotensin converting enzyme inhibitors. [7] Prevalence of medication oversupply in Canada was about 3% in patients with diabetes. [46] Studies in Sweden indicated that prevalence of medication oversupply was 22% - 30%. [11, 14, 15] Medication groups which were commonly oversupplied in Sweden were anti-dementia (60%), coxibs (36%) and inhaled adrenergic anti-asthmatic medications. [11]

Those studies abovementioned were conducted in western countries. Their findings might not be applicable for Asian countries because of differences in healthcare system. Studies in Thailand [16, 17, 31] showed that prevalence of medication oversupply ranged from 1.6% through 42.7%. Medication groups which were commonly oversupplied were ear, mouth and throat (15.4%), nutrition (3.0%) and cardiovascular drugs (2.7%). [16]

However, those studies in Thailand have limitations such as limited to only top five highest expenditure drugs [17], limited to only a teaching hospital where health services system might be different from other types of hospitals. [16] Therefore, further studies which are conducted to determine magnitude of medication oversupply in various types of hospitals are still needed.

Impacts of medication oversupply

Financial burden of medication oversupply

Medication oversupply causes inappropriate healthcare resource utilization. Excessive medication cost which is lost due to medication oversupply accounted for 2.6%-4.5% of total out-patient medication cost. [7, 12, 16, 17] For example, a study [7] conducted in the U.S. showed that a total outpatient medication cost was approximately $7 million, while excessive medication cost due to medication oversupply was $280,000 during three-year period or 4% of a total outpatient medication cost.

Inpatient and outpatient healthcare costs of patients with medication oversupply are higher than those of patients with appropriate supply. Overall, inpatient healthcare cost of oversupplied patients is 1.36 – 1.89 times higher than that of patients with appropriate supply, while outpatient healthcare cost of oversupplied patients was 1.12-1.31 times greater than that of patients with appropriate supply.[7, 8, 9] For example, a study which was conducted in patients with chronic heart failure in the U.S. [9] showed that average inpatient cost of oversupplied and appropriate-supply patients were $6,129 and $3,242, respectively. Inpatients cost of those patients with oversupply was 1.89 times higher than that of patients with appropriate-supply.

Clinical impacts of medication oversupply

Medication oversupply affects not only healthcare cost but also clinical outcomes. A number of studies reported that patients with medication oversupply had 1.11 to 3.19 time higher risk of hospitalizations than patients with appropriate-supply. [7, 8, 9, 31] For example, a study which was conducted in patients with uncomplicated and complicated hypertension showed that adjusted odds ratios for hospitalizations in patients with medication oversupply compared to patients with appropriate supply were 1.11 and 1.16, respectively. [8] Another study which was conducted in chronic heart failure patients in Thailand indicated that adjusted hazard ratio for hospitalization in patients with medication oversupply compared to those with appropriate supply was 3.19. [31] A study which was conducted in patients with diabetes indicated that patients with medication oversupply were less likely to achieve goal A1C. [45] The adjusted risk ratio of oversupplied patients compared to patients with appropriate supply to achieve A1C goal (<7.0%) was 0.95 with statistical significance ($P<0.01$). The same was true when determining the outcomes of A1C improvement. Patients with medication oversupply were less likely to improve A1C [risk ratio 0.98; 95% confidence interval (CI) 0.98 – 0.99] compared to patients with appropriate supply. [45]

These indicated that medication oversupply could cause inappropriate healthcare resource utilization and clinical inefficiencies. In addition, it may lead poor clinical outcomes.

Factors associated with medication oversupply

Several factors are associated with medication oversupply. They include 1) medication related factors, 2) patient related factors, 3) prescriber related factors, and 4) hospital system related factors.

Magnitude of medication oversupply is associated with types of medications. A number of studies indicated that medication class was one of the important factors affecting medication oversupply. [7, 11, 45] Proportion of medication oversupply for respiratory medications ranged from 27.6% through 35.5%, while proportion of medication oversupply for cardiovascular medications such as angiotensin converting enzyme inhibitors, beta-adrenergic antagonists, calcium-channel antagonists, and digoxin ranged from 43.9% through 52.9%. [7] It could infer that cardiovascular medications were more likely to be oversupplied than respiratory medications. A study from Sweden showed that anti-dementia medications were more likely to be oversupplied than others. [11] In summary, medication class was an important factor associated with medication oversupply. Moreover, type of medications in the same class is also another factor related to medication oversupply. [44, 46] The second generation of antipsychotics was more likely to be oversupplied than the first generation (odds ratio ranged from 1.6 through 2.5). [44] There are other medication related factors which are related to medication oversupply such as taking at least one medication at least three times per day, new scheduled medications at discharge [50], and the number of medication supply per prescription. [45]

Medication oversupply is associated with patient demographics such as education, working status, and marital status. Low education has higher risk of medication oversupply than high education. [50] For example, patients with education lower than 9^{th} grade had 2.67 time higher risk of medication oversupply than patients with education higher than 9^{th} grade. [50] Married individuals had also increased a likelihood of medication oversupply (relative risk reduction 1.99; 95%CI 1.24 to 3.20), while full-time working was associated with decreased likelihood of medication oversupply compared to part-time working (RRR 0.47; 95%CI 0.28 to 0.81). [10] Clinical factors can also attribute to medication supply. Patients with 1-point greater in Charlson comorbidity index had an increased likelihood of medication oversupply for 24% (RRR 1.24; 95%CI 1.08-1.42) compared with appropriate supply. [10]

The number and types of prescribers also relate to medication oversupply. Multiple prescribers may increase a likelihood of excessive medication supply. Fifty-one percent of patients with four or more prescribers are excessive supply compared to 29% of patients with one prescriber. Moreover, having two, three or four prescribers increased a probability of medication oversupply by 7%, 8%, and 23%, respectively. [51] Medication oversupply is also affected by types of prescribers. Patients with medications prescribed by nurses and midwifes have the lowest medication oversupply (3%), while the highest medication oversupply is observed among those who have medications prescribed by company-based physicians (29%). Patients with prescriptions from general practitioners (GPs) have lower rate of medication oversupply (20%) than those with medications prescribed by chief physicians (25%). [11]

A number of hospital system factors is associated with medication oversupply. Medication oversupply is directly affected by hospital service systems including prescribing, dispensing, appointment, and medication reconciliation systems. [52] For example, a patient received a medication for four weeks but his next appointment was the day after three weeks of current medical visit, therefore the patient received medication oversupply because of inappropriate appointment system. Another theoretical example is that a patient with chronic conditions was hospitalized before his next outpatient appointment and he was discharged from the hospital without an appropriate medication reconciliation system. The patient received the same medication that he has had, so the patient had medication oversupply because of inappropriate medication reconciliation and dispensing systems. [52] Evidence indicates that an appropriate medication reconciliation system could reduce approximately 64% of the prevalence of medication oversupply. [53]

Methodologies used to measure medication oversupply using administrative datasets

Based on our knowledge, there is no method which has been developed to specifically measure magnitude of medication oversupply using electronic database. However, there are many methods which is developed to measure medication adherence. The methods could be adapted to assess magnitude of medication oversupply. They include Medication Possession Ratio (MPR), Medication Possession Ratio, modified (MPRm), Continuous Measure of Medication Acquisition (CMA), Continuous Multiple Interval Measure of Oversupply (CMOS), Medication Refill Adherence (MRA), Continuous, Single Interval Measure of Medication Acquisition (CSA), Refill Compliance Rate (RCR), Dates Between Fills Adherence Rate (DBR), and Compliance Rate (CR). The summary of those formulas and values for each measure are presented in Table 2.

Table 2 Formulas for calculating medication oversupply

Measurements	Formula
Measures based on medication availability using pre-specified observational period as denominator	
MPR	$\frac{\text{Days supplied}}{\text{Days in evaluation period}}$
MRA	$\frac{\text{Total days supplied}}{\text{Total number of days evaluated}} \text{ x } 100$
CMA	$\frac{\text{Cumulative days supplied of medication obtained}}{\text{Total days to end of observation period}}$
Measures based on medication availability using refill interval as denominator	
RCR	$\frac{\frac{\text{Sum of quatity dispensed over interval}}{\text{quantity to be taken per day}} \text{ x } 100}{\text{number of days in interval between first and last refill}}$
MPRm	$\frac{\text{Total days supplied}}{(\text{last cliam date} - \text{first claim date}) + \text{last days' supply}} \text{ x } 100$
DBR	$\{1 - \frac{[(\text{last claim date} - \text{fisrt claim date}) - \text{total days' supply})]}{(\text{last claim date} - \text{fisrt claim date})}\} \text{ x } 100$
CR	$\frac{\text{Total days supplied} - \text{last days supplied}}{(\text{last claim date} - \text{fisrt claim date})} \text{ x } 100$

Table 2 (cont.)

Measurements	Formula
Measures based on gaps of medication refill	
CMOS	$\frac{\text{Total days of treatment gaps or surplus}}{\text{Total days in observation period}}$
Measures based on independent refill episode	
CSA	$\frac{\text{Days supplied obtained at beginning of interval}}{\text{Days in interval}}$

Note: CMA: Continuous Measure of Medication Acquisition, CMOS: Continuous Multiple Interval Measure of Oversupply, CR: Compliance Rate, CSA: Continuous, Single Interval Measure of Medication Acquisition, DBR: Dates Between Fills Adherence Rate, MPR: Medication possession ratio, MPRm: Medication Possession Ratio, modified, MRA: Medication Refill Adherence, RCR Refill Compliance Rate

There are many formulas which are used to calculate medication adherence and medication supply. However, measurement options may vary depended on patterns of utilization in dataset and objectives of studies. [54] It should not be assumed that all formulas are equivalent. [55, 56, 57] These measures are classified into 4 groups as

1. Measures based on medication availability using pre-specified observational period as denominator: MPR, CMA and MRA
2. Measures based on medication availability using refill interval as denominator: RCR, MPRm, DBR, and CR
3. Measures based on gaps of medication refill: CMOS
4. Measures based on independent refill episode: CSA

Measures based on medication availability using pre-specified observational period as denominator: MPR, CMA, and MRA

These formulas including MPR, CMA and MRA are similar for calculating medication adherence. These measures are based on medication availability using a pre-specified observational period as denominator. However, there are some differences among these formulas.

Medication Possession Ratio (MPR) is generally defined as a proportion of days' supply obtained during a specified time period. [58] It is calculated by a total days supplied divided by the number of days in observation period. The measure which is estimated by MPR is presented in ratio form such as 1.5:1. [59]

Continuous Measure of Medication Acquisition (CMA) is days supplied of medication obtained throughout a study period and divided by the number of days from the first dispensation until the participant's study completion date. The measure from CMA is presented in proportion such as 1.5 or 2.5. [49]

Percentage of total days' supply during a specific time period is defined by Medication Refill Adherence (MRA). It is calculated by a total days supplied divided by the number of days of study participation and multiplied by 100. [60] The measure from MRA is presented as percentage such as 150% or 200%. The average value of each participant's MPR/CMA/MRA provides an overall study adherence value. [55]

Measures based on medication availability using refill interval as denominator: RCR, MPRm, DBR, and CR

Similar to MPR, measures from these formulas including MPRm, RCR, DBR, and CR are based also on medication availability. However, they do not use a pre-specified observational period as denominator but they use a period of refill interval as denominator. An advantage of such measures is that it could reduce underestimation of adherence value. For example, when a patient died or lost to follow up during study period, formulas using pre-specified observational period as denominator include time period after a patient died to denominator which contributes underestimate of the value but these measures do not include such time period. Therefore, the measures do not underestimate. However, the measures using refill interval as denominator may contribute overestimate in some situations.

A total days supplied was multiplied by 100 and divided by the number of days from index date to last medication dispensation date with use of the Refill Compliance Rate (RCR). [61] Cases with only one dispensation were excluded because it cannot be calculated as denominator. [55]

Modified Medication possession ratio (MPRm) is developed from a concept of RCR. It also uses refill interval as denominator but it incorporates the number of days supplied of last dispensation into denominator to overcome a limitation of RCR denominator. Using MPRm [62], a total days supplied of medication was divided by the number of days from first to last dispensation and the number of days supplied in last dispensation. An important assumption of MPRm is that each participant being 100% adherent during last dispensation period. This assumption might result in higher adherence value than other measures. However, it might not affect value in perspective of oversupply.

A total days supplied is subtracted from the number of days between dispensations. Then, it is divided by the number of days between dispensations. The dividend is subtracted from 1. The result is multiplied by 100 to provide an adherence percentage for each participant for the overall study period. It is a formula of the Days Between Fills Adherence Rate (DBR).

A concept of Compliance Rate (CR) is that to reduce the overestimate of adherence value, the total days supplied is subtracted by the number of days supplied in last dispensation and dividing by the number of days from first to last dispensation.

Measures based on gaps of medication refill: CMOS

The Continuous Multiple Interval Measure of Oversupply (CMOS) is adapted from the Continuous Measure of Medication Gaps (CMG), a measure using for estimating only adherence value. [63] It is used to estimate non-adherence value by incorporating medication surplus. A concept of CMOS is that a patient could accumulate a deficit or a surplus by either coming to pick up too early or too late. Future deficits and surpluses are accumulated based on existing deficits or surpluses. An old surplus could cancel out a new deficit. At the end of the accumulated surplus and deficit are divided by the total days between the first and last prescription to get CMG and CMOS value. [46]

Measures based on independent refill episode: CSA

Continuous Single-interval Medication Availability (CSA) is calculated by the days supplied of a drug divided by the number of days in the interval from the index dispensation date up to the next dispensation date. This provides an adherence value for each participant between dispensations. An average of all dispensation adherence value of each participant provides an overall patient adherence value. [49]

Hypothetical examples of adherence calculation using each measurement

To illustrate a calculation of each measurement, hypothetical data are provided in Table 3. Adherence value is 109.6% using three measures: CMA, MPR and MRA. The value estimated by MPRm and CR are slightly lower (105.3%), while the value estimated by DBR and RCR are slightly higher (114.3%). Using CMOS, the result is -0.10 or approximately 10% surplus. The value estimated by CSA is the highest value (138.0%) compared to the others (Table 3).

Three measures including MPR, CMA, and MRA provide same adherence value because those three measures are calculated using similar formulas. A few differences among those formulas are the way of presenting formulas and value but a theoretical concept are closely similar. Although, the MRA is recommended to assess adherence value using electronic datasets, it may contribute an underestimate of medication supply. In case of a patient died or loss to follow-up during study period, MRA and MRA-related formulas do not adjust denominator. They still use pre-specified observational period. Medication surplus of the patient before loss to follow-up are counted as a follow-up period. That causes underestimate of medication supply.

Adherence value which are calculated by MPRm and CR are slightly lower than the value calculated by MPR, CMA, and MRA because they use time period from the first and last dispensation. Moreover, they take into account days supplied of last refill in those formulas. The MPRm adds the number of days supplied of the last dispensation as a part of denominator, while CR subtracts the number of days supplied of the last dispensation for nominator. They could decrease underestimate of medication supply. In a situation of a patient died or loss to follow-up during the study period, these formulas do not take into account time period after a patient died or loss to follow-up into denominator. That can prevent underestimate of medication supply.

Adherence value calculated by RCR and DBR are slightly higher than the value calculated by MRA and MPRm. The RCR and DBR also use refill interval as denominator but they do not take into account the number of days supplied of the last dispensation in those formulas. The number of days supplied of the last dispensation is counted in nominator of both formulas, but it is not counted in denominator which can cause overestimate of medication supply.

The gaps measure (CMOS) produces a similar adherence value compared to MRA. Medication surplus calculated by CMOS is -0.1 which is equivalent to 110.0% of MRA. A disadvantage of CMOS is also similar to MRA. It could underestimate the medication supply because it uses denominator as similar as MRA.

Adherence value which is calculated by CSA is the highest value compared to value calculated by other formulas and might lead to overestimation. It might be affected by a concept of its calculation which is an average of each proportion of days in interval and the number of days supplied. Overall value calculated by CSA may be affected by a proportion which is extremely high. In the opposite way, CSA might lead the underestimate of medication supply, if there is a proportion which is extremely low.

Table 3 Hypothetical data to illustrate the calculation of each measure

Dispensed date	**The number of days' supply (A)**	**Days in interval (B)**	**Gaps(+)/surplus (-)(C)**	**CSA (A/B)**
Jan 1st	70	59	-11	1.19
Mar 1st	60	45	-15	1.33
Apr 15th	30	16	-14	1.88
May 1st	90	111	+21	0.81
Aug 20th	30	25	-5	1.20
Sep 15th	60	76	+16	0.79
Nov 30th	30	15	-15	2.00
Dec 15th	30	16	-14	1.88

Study period: Jan 1st to Dec 31st(365 days[D])

First date – Last dispensation date: 350 days[E]

Results:

MPR: 400:365 = 1.096:1 ΣA:D

MRA: 109.6% [(ΣA)/D] x 100

Table 3 (cont.)

Dispensed date	The number of days' supply (A)	Days in interval (B)	Gaps(+)/surplus (-)(C)	CSA (A/B)
CMA:1.096	[(ΣA)/D]			
RCR: 114.3%;	[(ΣA)/E] x 100			
MPRm:105.3%;	[(ΣA)/(E+30)] x 100			
DBR:114.3%;	{1-[E-(ΣA)/E]}x 100			
CR:105.7%;	{[(ΣA)-30]/E} x 100			
CMOS: -0.10;	[(ΣC)/D]Mean CSA: 1.38			

Note: CMA: Continuous Measure of Medication Acquisition, CMOS: Continuous Multiple Interval Measure of Oversupply, CR: Compliance Rate, .CSA: Continuous, Single Interval Measure of Medication Acquisition, DBR: Dates Between Fills Adherence Rate, MPR: Medication possession ratio, MPRm: Medication Possession Ratio, modified, MRA: Medication Refill Adherence, RCR Refill Compliance Rate

It is important to note that the terms 'MPR' is widely used to measure adherence value with different formulas. The use of different formulas with the same term leads to confusion in comparing adherence value across studies. When evaluating what is described as MPR, one should be clear as to what the value represent. [55]

In conclusion, measurements for calculating medication supply can be adapted from measurements for assessing medication adherence. Different measurements produce different adherence value. Researchers should select appropriate measurements based on a purpose of their studies. MPRm or CR might be appropriate measurements to estimate magnitude of medication supply under a payer perspective.

Fundamentals of regression analysis

Regression analysis

Regression analysis is a statistical tool to determine an association of an outcome variable (also called **dependent variable**) and one or more risk factors (also called **independent variables or predictors**). [64, 65, 66] It is a very general and widely applied technique. Regression analysis is often used in a survey or an observational study including pharmacoepidemiologic studies. [64] Nonetheless, it is also applicable to experimental studies.

Regression analysis could be applied for many situations as follow [64]

1. Characterizing a relationship between dependent (Y) and independent variables (X_1, X_2 ...X_k)

2. Seeking a quantitative equation to predict a dependent variable (Y) as a function of independent variables (X_1, X_2,...X_k)

3. Controlling for the effects of confounding factors

4. Determining independent variables (X_1, X_2,...X_k) whether or not they are important to describe a dependent variable (Y)

5. Determining the best mathematical model to describe a relationship between dependent (Y) and independent variables (X_1, X_2,...X_k)

6. Comparing several derived regression relationships

7. Assessing interactive effects of two or more independent variables

8. Obtaining a valid and precise estimate of one or more regression coefficients

How to select a type of regression analysis

Regression analysis is a family of methods to associate predictor(s) to an outcome. Basically, there are various types of variables such as dichotomous, ordinal and continuous variables. [64, 65] Generally, for example, cost outcome is a numerical measure and can be classified as a continuous variable. This outcome should be analyzed using **linear regression model** (also called **Gaussian regression**). A dichotomous variable, death or alive as an example, should be analyzed as **logistic regression model**, while ordinal variable should be analyzed using an extent of logistic regression (such as **ordinal or polytomous logistic regression model**).

Another potential outcome is time-to-event variable. This variable is also continuous, but it would only be known to the end of a follow-up period. This type of outcome can be analyzed using survival analysis (such as **Cox proportional hazard model**).

Count data (for example, the number of oversupplied items per patient, the number of medical visits) is a type of outcomes which are often used in medical researches. **Poisson regression model** could be used to analyze count data. An empirical guidance for basic family of regression analysis is shown in Table 4.

Table 4 An empirical guidance to regression analysis

Regression model	**Classification of variables**	
	Dependent	**Independent**
Linear regression model	Continuous	Various types
Logistic regression model	Dichotomous	Various types
Ordinal or polytomous regression model	Ordinal	Various types
Survival analysis (such as Cox-proportional hazard model)	Time-to-event	Various types
Poisson regression model	Count data	Various types

Source: Adapted from Kleinbaum [64]

Not only a type of outcome variables have to be considered for a type of regression model, a type of data also have to be considered. Some features of data, such as correlated observations are noteworthy and contributes to an appropriate selection of statistical analysis.

In repeated measure data or hierarchical data, observations are correlated. There is a strong need to choose statistical analysis that takes into account the correlation. Two main methods which are often used to accommodate correlated data are **generalized estimating equation** (GEE) and **hierarchical model** (also called **mixed-effects model,** or **multilevel model**).

According to the analyses of this dissertation, hierarchical data structure was used. We decided to use hierarchical model to determine determinants of medication oversupply. Therefore, we reviewed hierarchical model as follow.

Hierarchical model

Hierarchical model is a statistical model of parameters which vary at more than one level. [67] The model corresponds to a hierarchy of levels with a repeated, correlated measurement. Parameters of the lower level unit (level-1) are nested to each particular higher level unit (level-2). It provides a general, flexible approach for correlated data analysis. The model is the extension of linear model but also used as a non-linear model. [68]

The hierarchical model could be applied in healthcare research. Data in healthcare research is usually available in hierarchical fashion [69, 70] with correlated data. For example, patients are managed by physicians who practice within hospitals. Patients within hospitals may share characteristics of physicians or hospitals and outcomes are likely to be dependent with one another because of the differences in physician practice and hospital systems. The hierarchical model is more suitable for healthcare data than conventional regression. Conventional regression tend to increase statistical significance and might lead to erroneous conclusion but the hierarchical model can prevent the problem. [71]

The hierarchical model is developed using a concept of fixed and random-effects variables. [66, 69, 70, 72] Thus, it is important to have an understanding of fixed and random-effects variables. In ideal experimental study, researcher is interested in whether or not one factor affects outcomes. The factor is a fixed-effects variable. Researcher is only interested in exact categories of the factor. The typical model for one factor is:

$$y_{ij} = \mu + \alpha_i + \varepsilon_{ij} \qquad \text{Equation (1)}$$

where the score on a dependent variable for individual *i* is equal to the grand mean (μ) of the sample (α_i), the effect of receiving drug *j*, and an individual error term (ε_{ij})

However, a particular factor may not be fixed in some situations. Different nurses, for example, may administer an experimental drug to subject. The effect of different nurses is not of interest but it should be controlled for possibilities that an independent care-giver effect is present beyond the fixed medication effect being investigated. In such case, researchers may add a term (different nurse) to be controlled as a random-effects variable. The general of two-level hierarchical model is equation (2), equation (3), and equation (4). In this case, the level-1 is an experimental drug, while the level-2 is nurses-effect. In another word, the effect of an experimental drug is nested within nurse-effect.

$$Y_{ij} = \beta_{0j} + \beta_{1j}X_{ij} + r_{ij} \qquad \text{Equation (2)}$$

$$\beta_{0j} = \gamma_{00} + \gamma_{01}G_j + U_{0j} \qquad \text{Equation (3)}$$

$$\beta_{1j} = \gamma_{10} + \gamma_{11}G_j + U_{1j} \qquad \text{Equation (4)}$$

where:

Y_{ij} = dependent variable measured for *i*th level-1 nested within the *j*th level-2

β_{0j} = intercept for the *j*th level-2

β_{1j} = regression coefficient associated with for the *j*th level-2 (slope)

X_{ij} = value on the level-1 predictor

r_{ij} = random error associated with the *i*th level-1 nested within the *j*th level-2

γ_{00} = overall mean intercept adjusted for *G*

γ_{10} = overall mean intercept adjusted for *G*

γ_{01} = regression coefficient associated with *G* relative to level-1 intercept

γ_{11} = regression coefficient associated with *G* relative to level-1 intercept

G_j = value on the level-2 predictor;

U_{0j} = random effects of the *j*th level-2 unit adjusted for *G* on the intercept

U_{1j} = random effects of the *j*th level-2 unit adjusted for *G* on the slope

CHAPTER III

RESEARCH METHODOLOGY

This chapter presented methodology of this dissertation including overall study description, data sources, patients and study period, measurement of medication supply, outcomes of interest, and data analysis.

Overall study description

This dissertation aimed to understand pharmacoepidemiology of medication oversupply for chronic conditions in Thailand including prevalence, its determinants and its financial burden. A retrospective database analysis using hospital datasets was used to estimate prevalence and financial burden due to medication oversupply within and across hospitals. In combination with national datasets from National Health Security Office (NHSO) in Thailand, the national prevalence and financial burden of medication oversupply under a payer perspective were estimated using a mathematical model. Factors associated with medication oversupply were also determined using an exploratory hierarchical regression analysis based on hospital datasets. According to associated factor analysis, we have known that database analysis could not capture all potential factors such as patients' collaboration factors, physicians, practice factors, or health service factors, however, we would like to use anticipated findings to aid health policy makers for preliminary consideration and emphasize the usefulness of existing databases which are available in Thailand. Thus, the analysis is useful and appropriate to be conducted within electronic hospital datasets.

This dissertation were separated into four parts including I) pharmacoepidemiology of medication oversupply for chronic conditions within hospitals, II) pharmacoepidemiology of medication oversupply across hospitals, III) estimation of national prevalence and financial burden due to medication oversupply for chronic conditions, and IV) factors associated with medication oversupply. The details of methods used in each section are described below.

Part I: Pharmacoepidemiology of medication oversupply for chronic conditions within hospitals

Data sources

A retrospective database analysis was undertaken under a payer perspective. Electronic databases obtained from three hospitals were used. Two hospitals were regional hospitals located in northern part and north-eastern part of Thailand. Another one hospital was a district hospital located in northern part of Thailand. The electronic databases included demographic databases, outpatient diagnostic databases, and pharmacy databases. They contained information on age, sex, health insurance, date of birth, International Statistical Classification of Disease, 10th Revision (ICD-10), visit date, drug name, drug code, drug regimen, and amount of medication per prescription.

Patient and study period

All patients visiting outpatient departments (OPD) of the three hospitals in 2010 were identified. The inclusion criteria were the following: 1) patients visiting the OPD of the hospitals from Jan 1st – Dec 31st, 2010; 2) patients receiving at least two prescriptions within six months for the same specific generic name of medications for chronic conditions. A medication for chronic conditions was defined as a medication which was used to treat patients for least six months for at least one indication. Patients were tracked from the first date to the last date of medication dispensation or Jun 30th, 2011.

Medication supply measurements

Medication supply was measured by modified medication possession ratio (MPRm) for each medication. Medications which patients received for only one time were excluded. The MPRm was calculated by dividing a total days supplied of a specific generic name of medications for a patient by the number of days from the first to the last date of dispensation, plus the number of days supplied in the last dispensation. We defined our operational definition of medication oversupply as MPRm>1.20 based on two reasons. First, we selected 120% of perfect supply to represent a potentially clinically significant medication oversupply. Several studies indicated that a cut-off point of non-adherence should be 80% of perfect adherence (20% difference from perfect adherence) which affects morbidity and mortality in several diseases. (73-75) We felt that a 20% difference from perfect adherence (100%) may also be meaningful for an insight of medication oversupply. While there are no studies that have evaluated a clinical significance of this value, we felt that the absolute difference of 20% was a reasonable estimate to identify patient with a medication oversupply. Second, we considered an issue of medication supply management. It is reasonable that patients are allowed some excessive medications for medication loss or delayed refill. In the U.S., insurance companies allow for a 7-day overlap of a refill for a medication with a 30-day supply. The 7-day overlap allowance is about a 23% of the amount of medication overlapped. Based on these two reasons, we considered that the MPR>1.20 was the reasonable cut-off value to determine medication oversupply. Patients were identified as having an appropriate supply when they had an MPRm between 0.80 - 1.20 in all of medications patients received. Since patients usually received more than one medication, we classified patients as medication oversupply if at least one of the MPRms was >1.20.

The MPRm was slightly modified from medication possession ratio (MPR) by changing denominator of the formula from a pre-specified time period (such as one year follow-up period) to the number of days from first to last dispensation, plus the number of days' supply in the last dispensation. [16, 55, 62]

$$MPRm = \frac{Total\ days\ supplied}{(last\ dispensation\ date - first\ dispensation\ date) + number\ of\ days'supply\ in\ last\ dispensation}$$

Each patient was tracked to determine their medication supply. The index date of each medication was determined as the first dispensation date of each specific medication. Each patient was followed from the index date to the last dispensation date of each specific medication (Figure 2). For instance, patient A received three medications. The 1st medication was dispensed from January 1st to October 31st, 2010. The 2nd medication was dispensed from February 1st to November 30th, 2010. The last medication was dispensed from November 15th, 2010 to June 30th, 2011. The patient was tracked from January 1st, 2010 to June 30th, 2011 and the medication supplies of the patient were calculated for each specific generic name of medication.

The MPRm for each specific generic, except for transdermal medications and eye, ear, and nasal drops, was calculated. We excluded transdermal medications, eye, ear, and nasal drop out of our study because they have no exact dose of administration and the MPRm could not be calculated. Medications prescribed for use as needed (PRN) and immediate use (STAT) were also excluded because they could not be used to calculate the MPRm.

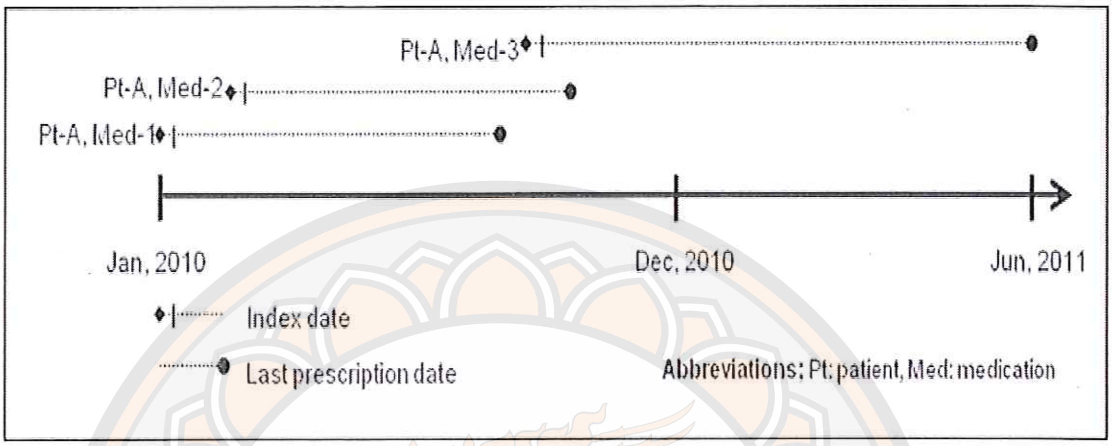

Figure 2 Index date, patient tracing, and study period

Legends: This figure illustrates how the patients in this study were followed up. For example, patient A received in total 3 medications (Med-1, Med-2, and Med-3). We followed patient A from Jan 2010 to Jun 2011 but we tracked data for medication 1 of patient A until the last dispensation date. We also tracked the data for each medication that patient A received. We calculated the modified medication possession ratio (MPRm) for each medication that patient A received based on the first and last date of dispensation. Thus, patient A had 3 MPRms. We classified patient A as oversupplied if any MPRm of patient A >1.20.

Outcome measures of interest

The primary outcome measure of interest was prevalence of patients having a medication oversupply. Secondary outcome measures were the number of oversupplied pills, and financial loss due to medication oversupply. Prevalence of patients having a medication oversupply was defined as a proportion of patients that had an MPRm>1.20 over the total number of patients. Patients that had an MPRm 0.8-1.2 were classified as having an appropriate supply and patients that had an MPRm<0.8 were classified as having an undersupply. The number of oversupplied pills was presented as the total number of oversupplied pills and the average number of oversupplied pills per patient.

Financial loss due to medication oversupply was determined by the number of oversupplied pills multiplied by the reference costs of each medication purchased during the year 2012. [76] Financial loss was converted to US$ using an exchange rate of 29.42 baht/US$. [77] The cost was annualized.

Data analysis

Descriptive statistics were used to describe baseline characteristics and outcome measures. Sensitivity analysis was also performed by changing a definition of medication oversupply from MPRm 1.20 to 1.10. Subgroup analysis was performed by types of hospitals (regional vs. district), and health insurance [universal health coverage schemes (UCS), social security schemes (SSS), and civil servant medical benefit schemes (CSMBS)]. We used types of hospitals for subgroup analysis because different hospitals have different outpatient medication management systems. It may modify our findings. In our study, we used two types of hospital as regional and district hospitals. We also used health insurance for another subgroup analysis. In Thailand, there are three main health insurances, including the UCS, SSS, and CSMBS. Conceptually, the UCS and SSS employ capitation payment, while the CSMBS is fee-for-service payment. That might affect prescribing patterns and medication supply. Chi-square statistic was used to examine differences in the number of oversupplied patients among subgroups. The Mann-Whitney U-test or the Kruskal-Wallis test was used to examine differences in financial loss among subgroups.

Part II: Pharmacoepidemiology of medication oversupply across hospitals Data sources

An electronic national dataset of all healthcare services collected by National Health Security Office (NHSO) were linked with a regional hospital dataset (Buddhachinaraj hospital). The national dataset contained information on personal data (patient ID, age, sex, hospital code, address and marital status), services data (date of services, service types), diagnosis data (patient diagnosis codes (icd-10) and pharmacy data (drug name, drug code, dispensing date).

Patient and study period

Patients visiting outpatient departments (OPD) of the regional hospital (Buddhachinaraj hospital) in 2010 were identified. The inclusion criteria were 1) patients visiting OPD of the hospital from Jan 1st – Dec 31st, 2010, 2) patients receiving at least two prescriptions within six months for the same specific generics for chronic conditions. Included patients were linked to the national dataset (in person data) by patient identification code. The matched patients were linked to others national sub-dataset including service, diagnosis, and pharmacy datasets. A flow of linking process was shown in Figure 3 below.

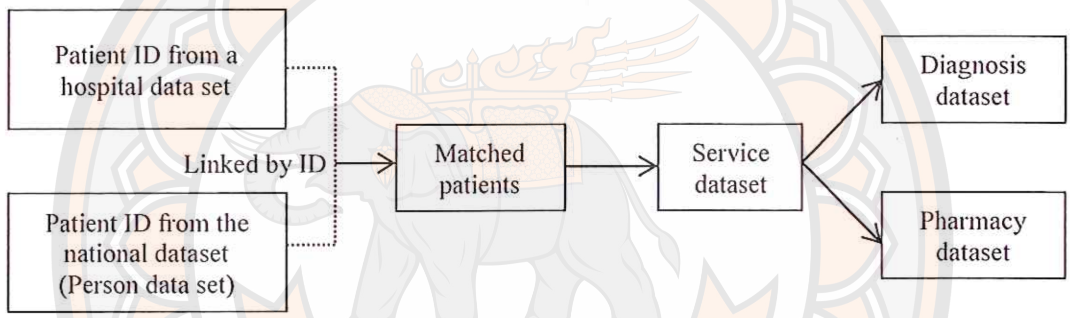

Figure 3 A linking process of Buddhachinaraj hospital and national datasets collected by the National Health Security Office

Note: ID; identification number

Outcome measures of interest

Outcomes of interest were prevalence of patients receiving same medications across hospitals, prevalence of medication oversupply, and financial loss due to medication oversupply classified by patients receiving same medication across hospitals. Prevalence of patients receiving same medication across hospitals was determined by a proportion of patients who received same medications across hospitals over a total number of patients. Prevalence of medication oversupply was defined as the proportion of patients who had medication possession ratio (MPRm) >1.20 over a total number of patients. Financial burden was determined by the number of oversupplied pills multiplied by reference cost of each medication.

Data analysis

Descriptive analysis was used to describe baseline characteristics, and outcomes of interest. Sensitivity analysis by changing the definition of medication oversupply was also used to explore the effects of the definition of medication oversupply. The definition was varied from MPRm>1.20 to MPRm>1.10.

Part III: Estimation of the national prevalence and financial burden due to medication oversupply

In this part, findings from part I and II were used as key inputs to estimate national prevalence of medication oversupply and its financial loss using a mathematical model with a decision tree framework.

Outcome measures of interest

The outcomes of interest were estimated national prevalence of medication oversupply, its financial loss due to medication oversupply, and the estimated number of patients who had medication oversupply as a whole country.

The mathematical model

To estimate national prevalence and financial burden due to medication oversupply, a concept of expected value, which is a product of probabilities and payoffs, was used. A mathematical model with decision tree framework was constructed (Figure 4). The decision tree model, originally, is used as a supportive tool of decision making, but it was used in this study to estimate outcomes of interest according to a concept of expected value.

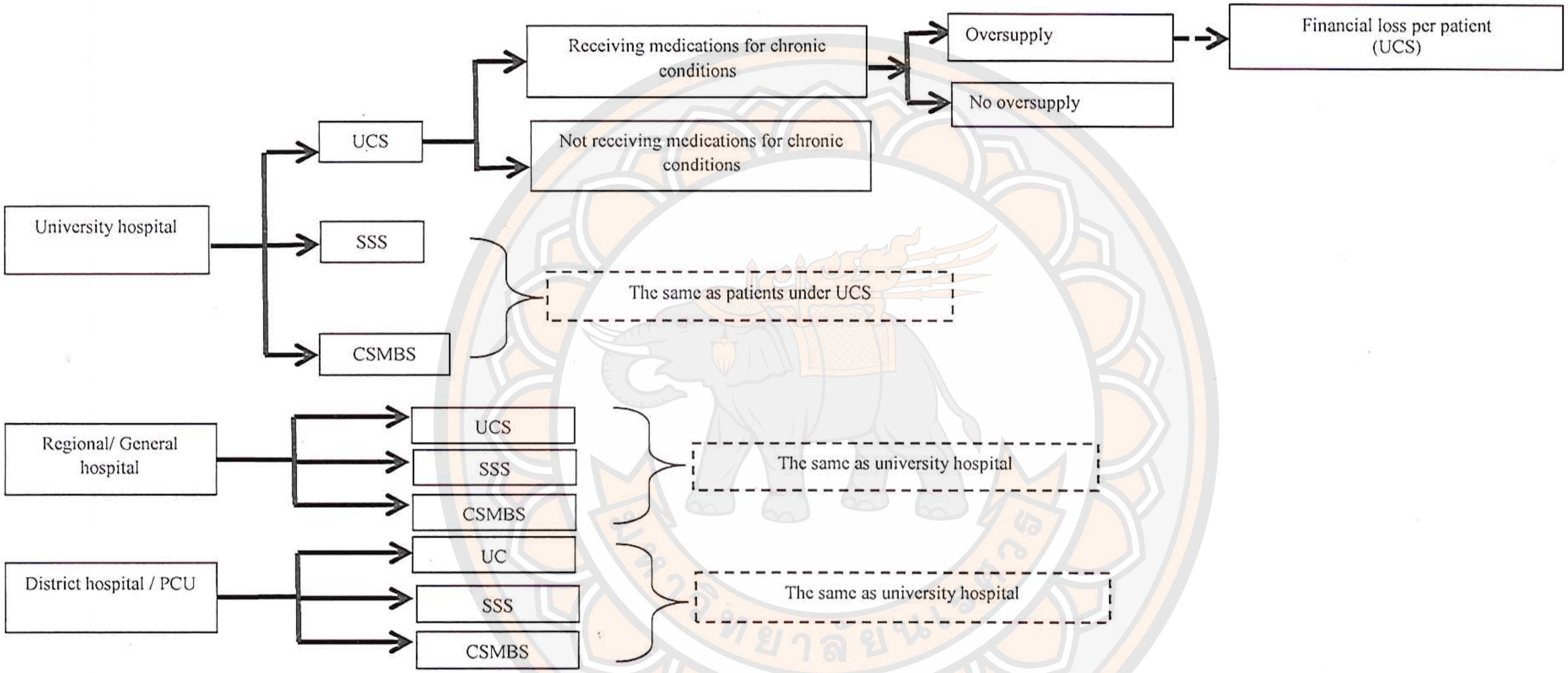

Figure 4 A decision tree model for estimating financial loss due to medication oversupply

Note: CSMBS: civil servant medical benefit schemes, PCU: primary care unit, SSS: social security schemes, UCS; universal coverage schemes

The model was constructed based on two major policy-relevant factors associated with prevalence of medication oversupply and its financial loss. They included types of hospitals and health insurance. These factors were selected based on our preliminary analysis of factors associated with medication oversupply which indicated that these two factors were associated with prevalence of medication oversupply and its financial loss.

Inputs for the model included the number of patients visiting outpatient departments in Thailand, a proportion of patients receiving medication for chronic conditions, a proportion of medication oversupply in each type of hospital and health insurance, and financial loss due to medication oversupply per patient. The number of patients was retrieved from NHSO, while a proportion of patients receiving medication for chronic conditions, prevalence and financial loss due to medication oversupply per patient was the findings of Part I. In fact, we supposed to use findings of Part II as other inputs. However, the magnitude of patients receiving same medications across hospitals was very small (3%). We decided not to use the information because using the information as another input might lead to have a very sophisticate model with small advantage.

The number of patients, prevalence and financial loss were classified by type of hospitals and health insurance. The type of hospital was classified as three types including university hospital, regional and general hospital, and district hospital and primary care unit, while health insurance was classified as universal coverage schemes (UCS), social security schemes (SSS), and civil servant medical benefit schemes (CSMBS).

The number of patients was adjusted for each health insurance by a systematic approach **(process of adjustment were described in the input parameter section)** because the number of patients visiting outpatient departments retrieved from NHSO was probably overestimated. The database does not take into account an issue of patients visiting more than one hospital. That might cause a problem of double counting.

The adjusted number of patients was multiplied by prevalence of patients with medication oversupply. The result was the estimated national number of patients with medication oversupply by type of hospital and health insurance.

The national financial loss was calculated by the summation of the number of patients who had medication oversupply multiplied by financial loss due to medication oversupply per patient in each type of hospital and health insurance.

Input parameters

Inputs for the model could be classified into five groups as follows;

1. The number of patients visiting out-patient departments in Thailand

   The data was retrieved from NHSO.

2. The proportion to adjust for double counting

   2.1 The proportion was calculated using NHSO data.

   2.2 The proportion was calculated by an analysis of patients visiting hospitals across different types of hospitals. For example, a total of 10% of all OPD patients had a history of visiting regional hospital and district hospital. The proportion of 0.1 was used to adjust the number of patients. The process of adjustment was as following;

   2.2.1 In UCS and SSS patients, the number of patients was subtracted from higher level of hospitals (Figure 5), because patients with UCS and SSS have to register for a main hospital which usually was the lower level of hospital. Patients visiting more than one hospital were likely due to referral system which was usually referring patients from lower to higher level of hospitals. Patients usually visited lower level of hospitals more frequent than higher level of hospitals.

   2.2.2 In CSMBS patients, the number of patients was subtracted from lower level of hospital (Figure 5), because patients with CSMBS do not have to register for a main hospital. Patients visiting more than one hospital were likely due to the decision of each patient which was usually select higher level of hospitals.

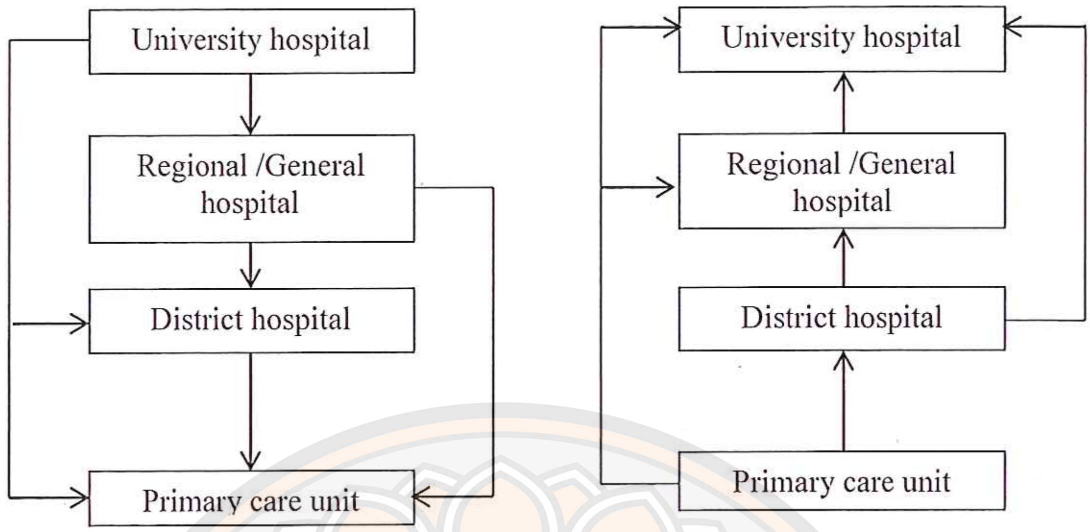

Figure 5 (left) the adjustment for double counting in UCS and SSS patients, (right) the adjustment for double counting in CSMBS patients

2.3 Proportion of patients receiving medications for chronic conditions

The proportion came from hospital database analysis used in Part I. It was calculated by the number of patients included in the final analysis (99,734 patients) divided by the number of patients who met inclusion criteria before excluded because they did not receive medications for chronic conditions (138,254 patients). Thus, a proportion of patients receiving medications for chronic conditions was 0.721 (99,734/138,254) with standard error of 0.0012.

2.4 Prevalence of medication oversupply

2.4.1 Prevalence of medication oversupply in regional/general and district hospital came from hospital database analysis.

2.4.2 Prevalence of medication oversupply in university hospital came from a contact of authors who studied medication oversupply in a university hospital in Thailand. The authors were requested to conduct a study using a university hospital database with the same method used in Part I.

2.5 Financial loss due to medication oversupply per patient

2.5.1 Financial loss due to medication oversupply per patient in regional/general and district hospital came from hospital database analyses.

2.5.2 Financial loss due to medication oversupply per patient in university hospital came from a contact of authors who studied the medication oversupply in a university hospital in Thailand. Again, the authors were requested to conduct a study using a university hospital database with the same method used in Part I.

The detailed input parameters were shown in Table 5.

Table 5 Input parameters for estimating national prevalence and financial burden due to medication oversupply

Parameters	UC	SSS	CSMBS
1. The number of patients receiving cares in hospitals in Thailand$ (number)			
UH	328,338	76,834	252,704
RH/GH	5,529,147	1,245,502	1,673,112
DH /PCU	35,197,299	3,609,599	2,748,206
2. The proportion to adjust for double counting of the number of patients$ [probability, (SE)]			
From UH to RH/GH	0.1259 (0.00859)	0.1259 (0.00859)	NA
From UH to DH	0.0248 (0.00402)	0.0248 (0.00402)	NA
From UH to PCU	0.1936 (0.01023)	0.1936 (0.01023)	NA
From RH/GH to DH	0.0726 (0.00165)	0.0726 (0.00165)	NA
From RH/GH to PCU	0.2620 (0.00279)	0.2620 (0.00279)	NA
From PCU to UH	NA	NA	0.0259 (0.00164)
From PCU to RH/GH	NA	NA	0.2465 (0.00446)
From DH to UH	NA	NA	0.0211 (0.00176)
From DH to RH/GH	NA	NA	0.2240 (0.00510)
From RH/GH to UH	NA	NA	0.0240 (0.00097)

Table 5 (cont.)

Parameters	UC	SSS	CSMBS
3. Proportion of patients receiving medications for chronic conditions			
	0.721 (0.0012)	0.721 (0.0012)	0.721 (0.0012)
4. Prevalence of medication oversupply (p, SE)			
MPRm>1.20			
UH*	0.310 (0.0019)	0.240 (0.0021)	0.34 (0.0009)
RH/GH#	0.141 (0.0015)	0.117 (0.0037)	0.138 (0.0021)
DH /PCU#	0.083 (0.0033)	0.068 (0.0183)	0.074 (0.0086)
MPRm>1.10			
UH*	0.380 (0.0020)	0.300 (0.0023)	0.440 (0.0010)
RH/GH#	0.239 (0.0019)	0.196 (0.0046)	0.239 (0.0025)
DH /PCU#	0.131 (0.0040)	0.090 (0.0208)	0.120 (0.0107)
5. Financial loss due to medication oversupply# *(Thai baht)*			
MPRm>1.20			
UH*	3,066 (119.88)	2,480 (132.55)	2,855 (98.72)
RH/GH#	387 (16.83)	287 (24.85)	569 (28.60)
DH /PCU#	132 (17.92)	64 (27.53)	137 (24.34)
MPRm>1.10			
UH*	2,550 (98.83)	2,064 (109.06)	2,331 (76.77)
RH/GH#	355 (12.08)	267 (20.86)	571 (21.43)
DH /PCU#	121 (12.83)	70 (26.87)	177 (19.66)

Note: CSMBS; civil servant medical benefit schemes, DH; district hospital, GH; general hospital, NA; not applicable, PCU; primary care unit, RH; regional hospital, SE; standard error, SSS; social security schemes, UC; universal coverage, UH; university hospital

Source: $Data from National Health Security Office database

*Data from Ramathibodi hospital

#Data from Part I of this dissertation

Data analysis

Base case analysis was conducted using average value of each input. The MPRm>1.20 was used as a definition of medication oversupply in primary analysis. The secondary analysis was conducted by changing the definition from MPRm>1.20 to MPRm>1.10.

A probabilistic sensitivity analysis (PSA) was also performed to examine the effects of all parameter uncertainty simultaneously using a Monte Carlo simulation performed by Microsoft Excel 2003 (Microsoft Corp., Redmond, WA). The distribution of each parameter were assigned following:

a. Proportion to adjust double counting, proportion of patients receiving medications for chronic conditions, and prevalence of medication oversupply, in which their values ranged between zero and one, were specified to beta distribution.

b. Financial loss due to medication oversupply per patient value was commonly positively skewed. The value was always above zero. Thus it was assigned to be gamma distribution.

A Monte Carlo simulation was run for 1,000 simulations to give a range of value of national financial burden and the number of patients with medication oversupply.

Part IV: Factors associated with medication oversupply

In this part, data from Part I was used to explore factors associated with medication oversupply using a two-level hierarchical model. Data sources, patients and study period, and a measurement of medication supply were the same as described in Part I. The outcomes of interest and data analysis were described below.

Outcome measures of interest

The outcomes of interest were factors associated with medication oversupply.

Data analysis

Two-level hierarchical logistic regression was used. The structure of data fits to hierarchical model because the individual level data (level-1) were nested in the hospital level variable (level-2). The dependent variable was having a medication oversupply (MPRm>1.20) for each patient. Patients with medication oversupply were compared to patients with appropriate supply. Patients with undersupply were not considered to be included in our analysis. The primary reason was that we were only interested in investigating factors predicting medication oversupply. Having an appropriate supply as a comparator would help us understand the differences between these two groups.

We used hospital as a random-effects variable and used age group (children/adolescent, adult, and elderly), gender, health insurance, Charlson's co-morbidity index (an algorithm commonly used for assessing the comorbidity burden of patients), types of hospital (regional vs. district hospital), and number of medications patients received (<5 vs. ≥ 5 medications) as fixed-effects variables. All fixed-effects variables were included in the model as these were identified as important factors in our literature review. A generalized chi-square was used to assess goodness of fit of the model (A generalized chi-square per degree of freedom <2.0 indicates no lack of fit).

CHAPTER IV

RESULTS

The study's findings were separately presented into four parts belongs to research methodology reported in chapter III.

Part I: Pharmacoepidemiology of medication oversupply for chronic conditions within hospitals

A total of 276,756 patients visited OPD in 2010. Among those, 99,743 patients met our inclusion criteria (Figure 6). Patients were on average 49.7 ± 21.2 years of age with 42.8% being male. Most of them were adults (53.7%). Among those patients, 60.2% were under a Universal Coverage Schemes (UCS). Detailed baseline characteristics were shown in Table 6. A pattern of medication supply was shown in Table 7. Percentage of patients with medication oversupply was 13.4%, while 47.7% of the patients had an appropriate supply. On average, the number of days' supply was 354.7 ± 247.3 days for patients with medication oversupply and 371.1 ± 185.1 for patients with appropriate supply. Average numbers of items patients received were 6.2 ± 4.4 and 3.9 ± 2.7 for patients with medication oversupply and patients with appropriate supply, respectively.

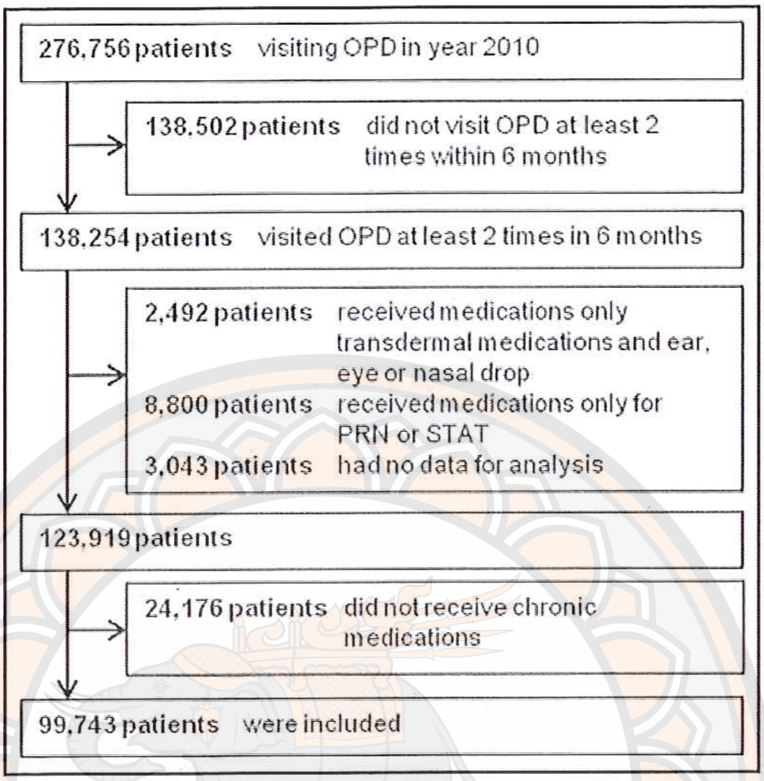

Figure 6 A flow of patient selection

Table 6 Patient characteristics (For medication oversupply for chronic conditions within hospitals)

Patient characteristics	Number of patients (%) (N= 99,743)
Type of hospital	
Regional hospital	91,614 (91.9)
District hospital	8,129 (8.2)
Age (Mean ± SD)	49.7±21.2
Children/adolescent (<18 years old)	10,799 (10.8)
Adult (18-59 years old)	53,564 (53.7)
Elderly (≥60 years old)	35,380 (35.5)

Table 6 (cont.)

Patient characteristics	Number of patients (%) (N= 99,743)
Gender	
Male	42,651 (42.8)
Female	56,860 (57.0)
Missing data	232 (0.2)
Health insurance	
Universal health coverage schemes	60,026 (60.2)
Social security schemes	7,760 (7.8)
Civil servant medical benefit schemes	29,203 (29.3)
Others	2,522 (2.5)
Missing data	232 (0.2)
Charlson's co-morbidity index	
Mean ± SD	1.1 ± 1.7
0	51,073 (51.2)
1-2	36,107 (36.2)
>3	12,312 (12.3)
Missing data	251 (0.3)

Note: SD; standard deviation

Table 7 A pattern of medication supply

Variables	Undersupply (<0.8)	Appropriate supply (0.8-1.2)	Oversupply (>1.2)
Number of patients (%)	38,881 (39.0)	47,527 (47.7)	13,324 (13.4)
Average day supply (days)	260.7 ± 185.1	371.1 ± 185.1	354.7 ± 247.3
Average follow-up time (days)	334.4 ± 169.3	365.9 ± 180.1	331.0 ± 18.6
Average MPRm	0.6 ± 0.3	1.0 ± 0.7	1.2 ± 0.6
Average number of medication receipts	5.2 ± 3.4	3.9 ± 2.7	6.2 ± 4.4
Average oversupplied items per patient	N/A	N/A	0.3 ± 0.5

Note: MPRm; modified medication possession ratio, N/A; not applicable

Prevalence of medication oversupply for chronic conditions

There were 13.4% of patients with medication oversupply (13,330/99,743 patients). A total oversupplied pills were 785,223 pills or 7.9 ± 68.6 pills per patient. Prevalence of medication oversupply was 22.7% when the definition of medication oversupply was changed to MPRm >1.10 (Table 8).

Prevalence of medication oversupply in regional hospital was higher than that in district hospital (13.8% VS 8.2%; $p<0.001$). Medication oversupply was slightly different among health insurance schemes. Among patients under UCS, 8,061 patients out of 60,026 patients (13.4%) had medication oversupply, while patients under SSS and CSMBS were at 11.6% and 13.6%, respectively ($p<0.001$) (Table 8).

Table 8 Magnitudes and financial loss due to medication oversupply

Variables	Prevalence of oversupplied patients (%)	Total oversupplied pills or units	Average oversupplied pills or units/patients	Total financial loss per year (US$)	Average financial loss (US$/patient/year)
MPRm >1.20	13.4	785,223	7.9 ± 68.6	189,024	1.89 ± 19.04
MPRm >1.10	22.7	1,584,955	15.9 ± 91.8	307,552	5.24 ± 31.61
By type of hospital (MPRm>1.20)					
Regional hospital	13.8	771,727	8.4 ± 71.1	93,030*	2.03 ± 19.82
District hospital	8.2	13,496	1.7 ± 28.4	2,963	0.36 ± 4.14
By health insurance (MPRm>1.20)					
UCS	13.4	470,620	7.8 ± 66.7	101,280	1.7 ± 18.1
SSS	11.6	34,976	4.5 ± 37.7	8,669	1.1 ± 9.0
CSMBS	13.6	249,456	8.5 ± 60.5	76,030	2.6 ± 23.2
Others	13.3	28,719	11.4 ± 181.6	2,810	1.1 ± 8.1
Missing	23.7	1,452	6.7 ± 23.1	234	1.0 ± 5.5

Note: CSMBS; civil servant medical benefit schemes, MPRm; modified medication possession ratio, SSS; social security schemes, UCS; universal coverage schemes

*Financial loss per hospital

Financial loss due to medication oversupply

The total financial loss due to medication oversupply was $189,024 per year or $1.9 ± 19.0 per patient per year. A total outpatient medication expenditure of the entire cohort was $16,533,401. A total financial loss due to medication oversupply accounted for 1.1% of the total outpatient medication expenditure. When the definition of medication oversupply was changed to MPRm>1.10, the financial loss was increased to $307,552 (1.9% of the total outpatient medication expenditure). The average financial loss was 5.2 ± 31.6 $/patient/year for MPRm >1.10 (Table 8).

Financial loss due to medication oversupply in regional hospital was higher than that in district hospital. A total financial loss in regional hospital was 93,030 $/hospital, while a total financial loss in district hospital was 2,963 $/hospital. An average financial loss was 2.0 ± 19.8 $/patient/year in regional hospital, while an average financial loss was 0.4 ± 4.1 $/patient/year in district hospital ($p<0.001$) (Table 8). An average financial loss for patients under CSMBS (2.6 ± 23.2 $/patient/year) was higher than that in patients under UCS (1.7 ± 18.1 $/patient/year) and SSS (1.1 ± 9.0 $/patient/year) ($p=0.004$).

Among patients with medication oversupply, an average financial loss was $14.17 ± 50.37. An average financial loss in patients visiting regional hospital was $14.63 ± 51.53, while an average financial loss in patients visiting district hospital was $4.45 ± 13.83. The detailed financial loss due to medication oversupply among oversupplied patients by health insurance was shown in Table 9.

Table 9 Financial loss due to medication oversupply among oversupplied patients

Financial loss ($)	Total	UC	SSS	CSMBS
MPRm>1.20 [mean ,(sd)]				
Number of patients	13,330	8,061	896	3,982
Overall	14.17 (50.37)	12.54 (47.89)	9.65 (24.92)	19.07 (60.33)
Regional hospital	14.63 (51.53)	13.15 (49.46)	9.76 (29.42)	19.34 (60.81)
District hospital	4.45 (13.83)	4.48 (14.62)	2.18 (3.37)	4.66 (6.80)

Table 9 (cont.)

Financial loss ($)	Total	UC	SSS	CSMBS
MPRm>1.10 [mean ,(sd)]				
Number of patients	22,588	13,612	1,500	6,870
Overall	13.60 (48.67)	11.52 (44.83)	9.00 (27.16)	19.17 (59.41)
Regional hospital	14.07 (49.73)	12.07 (46.26)	9.08 (27.29)	19.41 (59.86)
District hospital	4.04 (12.51)	4.11 (13.15)	2.38 (3.74)	3.98 (7.04)

Note: CSMBS; civil servant medical benefit schemes, MPRm; modified medication possession ratio, sd; standard deviation, SSS; social security schemes, UCS; universal coverage schemes

Part II: Pharmacoepidemiology of medication oversupply across hospitals

A total of 26,763 patients visiting OPD at Buddhachinaraj hospital was matched to a national dataset from NHSO. Of those, 8,490 patients were excluded because of data availability and completeness. Thus, 18,237 patients were included. A flow of patient selection was showed in Figure 7. Patients were on average 60.5 ± 17.3 years of age with 45.2% being male. Among those patients, 48.3% of the patients were under the UCS and 44.5% were under the CSMBS. The detailed baseline characteristics were shown in Table 10.

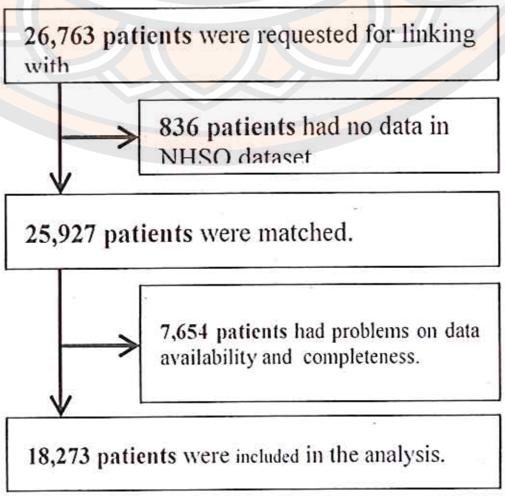

Figure 7 A flow of patient selection for pharmacoepidemiology of medication oversupply across hospitals

Table 10 Patient characteristics (For medication oversupply across hospitals)

Patient characteristics	Number of patients (%) (N= 18,273)
Age (mean ± SD)	60.5 ± 17.3
Gender	
Male	8,222 (45.1)
Female	9,980 (54.7)
No data	35 (0.2)
Health insurance	
UCS	8,802 (48.3)
SSS	1,094 (6.0)
CSMBS	8,107 (44.4)
Others	199 (1.1)
No data	35 (0.2)

Note: CSMBS; civil servant medical benefit schemes, MPRm; modified medication possession ratio, SSS; social security schemes, UCS; universal coverage schemes

Prevalence of patient receiving same medications across hospitals and medication oversupply

Only 500 patients (2.7%) received same medications across hospitals. Of those, 285 patients (57.0%) had medication oversupply (MPRm >1.20), while 6.3% (1,222 patients out of 17,737 patients) of patients who did not receive same medications across hospitals had medication oversupply (Figure 8).

A sensitivity analysis, which the definition of medication oversupply was changed from MPRm>1.20 to 1.10, indicated that 342 of 500 patients (68.4%) who received the same medication across hospitals had medication oversupply, while 13.1% (2,331 patients out of 17,773 patients) of patients who did not receive same medication across hospitals had medication oversupply (Figure 8).

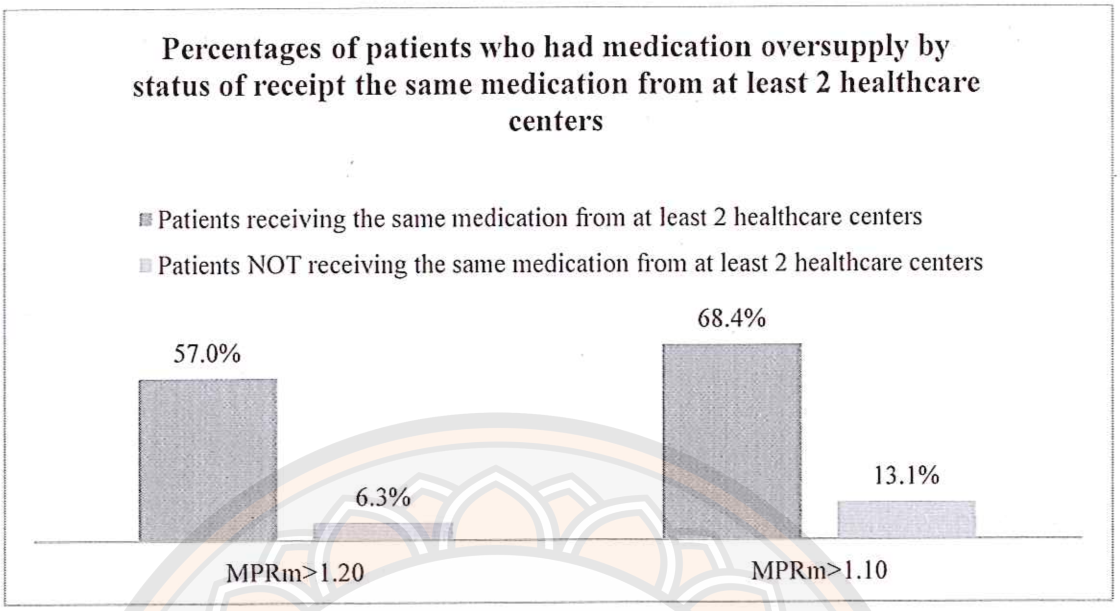

Figure 8 Percentages of patients who had medication oversupply by status of receipt the same medications from at least two healthcare centers

Financial burden due to medication oversupply

A total financial loss due to medication oversupply of these patients was $23,521 per year or $1.29 per patient per year. A total financial loss in patients who received the same medication across hospitals was $1,189 per year (accounted for 5.1% of total burden) or $2.38 per patient per year, while a total financial loss in patients who did not received same medications across hospitals was $22,332 per year or $1.26 per patient per year (Table 11).

A sensitivity analysis indicated that a total financial loss due to medication oversupply was $41,128 per year or $2.25 per patient per year. Of those, $1,427 was for patients who received the same medications across hospitals (3.3% of a total financial loss) (Table 11).

Table 11 A financial loss due to medication oversupply by the status of receiving same medications across hospitals

Financial burden	Medication oversupply	
	MPRm> 1.20	MPRm>1.10
Financial burden ($/year)		
- A total financial loss	23,521	41,128
- The number of patients who received the same medications across hospitals	1,189 (5.1%)	1,427 (3.3%)
- The number of patients who did NOT received same medications across hospitals	22,332 (94.9%)	39,701 (96.7%)

Part III: Estimation of the national prevalence and financial burden due to medication oversupply for chronic conditions

According to our mathematical model, the estimated number of patients with medication oversupply was about 3,119,220 patients with range of 2,802,336 to 3,461,427 patients. The estimated national prevalence of medication oversupply was 7.84% (ranged from 7.06% – 8.68%). The estimated national financial burden was $30,866,773 (ranged from $26,941,487 to $35,759,680). Compared to Thai medication consumption in 2010, [78] the financial loss due to medication oversupply accounted for 0.68%, while it accounted for 0.035% when compared to Thai GDP in 2010 [79] (Table 12).

A sensitivity analysis indicated higher number of oversupplied patients (4,920,681 patients). The estimated prevalence of medication oversupply when the definition was MPRm>1.10 was 12.22% (ranged from 11.36% to 13.18%). The estimated national financial loss due to medication oversupply was $41,360,807 (ranged from $36,219,176 to $46,761,642). Compared to Thai medication consumption, [78] the financial loss accounted to 0.91%, while it accounted for 0.047% when compared to Thai GDP in 2010 (79) (Table 12).

Table 12 The national estimated number of patients; prevalence of medication oversupply, and its financial loss

Parameters	Medication oversupply	
	MPRm> 1.20	MPRm>1.10
The estimated number of patients [number, (range)]	3,119,220 [2,802,336 to 3,461,427]	4,920,681 [4,576,834 to 5,134,633]
The estimated prevalence of medication oversupply [%, (range)]	7.84% [7.06% to 8.68%]	12.22% [11.36% to 13.18%]
The estimated financial loss [$US, (range)]	$30,866,773 [$26,941,487 to $35,759,680]	$41,360,807 [$36,219,176 to $46,761,642]
The percentage of financial loss compared to Thai medication consumption in 2010 [%, (range)]	0.68% [0.59% to 0.79%]	0.91% [0.80% to 1.03%]
The percentage of financial loss compared to Thai GDP in 2010 [%, (range)]	0.035% [0.031% to 0.041]	0.047% [0.041% to 0.053%]

Note: MPRm; modified medication possession ratio, GDP; gross domestic product

Part IV: Factors associated with medication oversupply

A hierarchical logistic regression model was used to explore factors associated with medication oversupply. The generalized chi-square per degree of freedom for the final model was 1.01, which indicated no lack of fit.

Based on our multivariate hierarchical logistic regression model, children and adolescents had a higher risk of medication oversupply than adults [adjusted odds ratio (AOR) 3.303; 95% confidence interval (CI), 3.095 – 3.525)], while elderly patients tended to have a higher risk than adults but not statistically significant [AOR 1.039 (95%CI; 0.992 - 1.088)]. Females had a higher risk of medication oversupply than males [AOR 1.177 (95%CI; 1.131-1.226]. Patients under SSS were at higher risk than patients under UCS [AOR 1.200 (95%CI; 1.106 – 1.302] but patients under CSMBS had a similar risk of medication oversupply compared to patients under UCS [AOR 1.030 (95%CI; 0.982-1.079)]. Patients receiving at least five medications (also called poly-pharmacy) were at higher risk of medication oversupply than patients receiving less than five medications [AOR 2.625 (95%CI; 2.507-2.748)]. Patients visiting regional hospital tended to receive more oversupplied medication than patients visiting district hospital, but not statistically significant [AOR 1.235 (95%CI; 0.056 – 27.027)] (Table 13).

Table 13 Factors associated with medication oversupply (MPR >1.20)

Factors	Adjusted odds ratio (95% CI)	P-value
Age group		
Adult (18-59 years old)	*Reference*	
Children/Adolescent (<18 years old)	3.303 (3.095 - 3.525)	<0.001
Elderly (≥ 60 years old)	1.039 (0.992 – 1.088)	0.102
Gender		
Male	*Reference*	
Female	1.177 (1.131 – 1.226)	<0.001
Health insurance		
UCS	*Reference*	
SSS	1.200 (1.106 – 1.302)	<0.001
CSMBS	1.030 (0.982 – 1.079)	0.224
Others	1.075 (0.946 – 1.221)	0.266
Charlson's co-morbidity index	1.067 (1.055 – 1.079)	<0.001
Number of medication patients received		
<5 medications	*Reference*	
≥5 medications	2.625 (2.507 – 2.748)	<0.001
Types of hospitals		
District hospital	*Reference*	
Regional hospital	1.235 (0.056 – 27.027)	0.545

Note: CSMBS; civil servant medical benefit schemes, SSS; social security schemes, UCS; universal coverage schemes

CHAPTER IV

DISCUSSIONS AND CONCLUSION

Discussions

Medication oversupply results in millions U.S. dollars in financial loss each year in Thailand. Approximately, eight percent of patients receiving medications for chronic conditions have experienced medication oversupply. Medication oversupply is usually occurred within hospital. The problem of receiving same medications across hospitals had minimal effect on medication oversupply. Several factors are associated with the problem, however, strong factors are age group and polypharmacy (patients received at least five medications).

Our findings are different from a previous Thai study. [16] In hospital level analysis, prevalence observed in our study is around 2.3 times higher than what prevalence observed in the previous study. [16] The difference might be due to a difference in definition of medication oversupply. A definition of medication oversupply used in our study is based on MPRm>1.20, while what used in the previous study is an excessive amount of medications more than 30 days. Because of that difference, we requested authors of the previous study to perform an analysis using our methods. Prevalence of medication oversupply in the university hospital provided by the authors is 24.1% which is higher than what we observe in our study (13.8% for regional hospital, and 8.2% for district hospital). The analysis confirms that the difference in findings between our study and the previous study is likely due to the difference in definition. In contrast, an average financial loss due to medication oversupply in our study is lower than that in the previous study. [16] The financial loss accounted for 1.1% of total OP expenditure, while the financial loss in the previous study accounted for 2.6% of total OP drug expenditure. It is likely due to a difference in a list of medications in hospital formulary. Usually, university hospital are likely to have a formulary which contained more pricy medications than that of district or regional hospitals.

Subgroup analysis indicates that regional hospital has a higher prevalence of medication oversupply than district hospital. University hospital has highest prevalence of medication oversupply (24.1% for university hospital based on a request to previous study's authors, (16) 13.8% for regional hospital, and 8.2% for district hospital). This difference is likely due to the larger number of patients visiting the university hospital, which leads to a higher workload. Because of the workload, healthcare providers might not pay attention to review the amounts of medications previously dispensed. Moreover, patients with more complex diseases and more sophisticated healthcare service systems in the university hospital might also affect quality of care in the university hospitals and leads to higher prevalence of medication oversupply.

Another subgroup analysis reveals that there is no significant difference in prevalence of medication oversupply across types of health insurance schemes. However, an average financial loss occurred in patients under CSMBS is about two times higher than patients under UCS and SSS. This finding is not related to out-of-pocket money of patients because all patients under those three schemes do not need to pay any out-of-pocket money for any medications. They usually receives medications with free of charge. The difference of the average financial loss across health insurance schemes is likely due to a mechanism of reimbursement. Hospitals can fully reimburse cost of medications for patients under CSMBS using a direct billing financial mechanism to the comptroller general's department, which is a third party payer for patients under CSMBS. Since providers do not have any concerns for financial loss to their hospital, they may prescribe higher cost medications to patients under CSMBS.

An analysis of patients receiving same medications across hospitals indicates that only 3% of patients receive same medications across hospitals. Most patients who need to continuously receive medications are likely to receive same chronic medications at the same hospital. Thus, solving the medication oversupply problem should be focused on within hospital level rather than across hospitals level. However, this finding should be interpreted with caution because the finding is derived from only a linkage of a hospital database with NHSO database. That might not be a representative of the whole country.

The estimated national prevalence of medication oversupply and financial loss due to such problem are not tremendous. Less than 10% of patients receiving chronic medications has medication oversupply with financial loss of less than 0.05% of GDP.

However, we estimate only direct financial loss. Indirect financial loss of medication oversupply due to an increased risk of hospitalization in patients with medication oversupply is not taken into account. Several studies indicate that patients with medication oversupply have the higher risk of hospitalization than patients with appropriate supply. [11, 13, 17, 31] An increase of hospitalization requires an increase of the usage of healthcare resource which is the indirect financial loss to Thai government.

There are two strong factors associated with medication oversupply. They include age and the number of medications patient receives. Children have approximately three-fold higher risk of medication oversupply than adults. The number of visit of children is likely to be higher than adults. Patients visiting hospitals more often are likely to receive same medications as they receive previously than patients visiting hospitals less often. That might increase a risk of medication oversupply. The second strong factor associated with medication oversupply is poly-pharmacy (patient receiving at least five medications). Patients receiving at least five medications had about two-fold higher risk of medication oversupply than patients receiving less than five medications. It is possible that patients receiving more medications had more chronic conditions and potentially more severe conditions. They therefore might need to visit hospitals more often than less severe patients. Again, patients visiting hospitals more often are likely to receive same medications that they receive previously than patients visiting the hospital less often. It increases a risk of medication oversupply.

There are other factors which are associated with medication oversupply but could not be observed in this study. Based on a previous study [80], other factors include poor medication management system, lack of appropriate communication system, over workload of healthcare providers and staffs, lack of concern from healthcare providers, a package of medication which is not easy to be dispensed without any excessive amount, patients and caregiver collaboration, and marketing of pharmaceutical industries.

Because our findings are mostly based on only three hospital databases, Representativeness of healthcare system as a whole county should be discussed. We use hospital databases instead of national database (NHSO) because the national database do not contain administrative data such as dosage and frequency of medication use which are needed for medication supply calculation. Therefore, we need to use hospital databases instead. We have tried to access a number of hospital databases across Thailand, but unfortunately only three hospital databases could be accessed. We realize that only small number of databases might be our important limitation to estimate national financial burden because there are a lot of variation of healthcare services across the country. The healthcare system of different NHSO regions could be different. We could access the data from two hospitals located in NHSO region 2 and one hospital located in NHSO region 10. However, we have tried to select hospitals by varying type of hospitals as district hospital and regional hospital. We assume that data from the hospitals are a representative of the type of hospitals. We use data from two regional hospitals from different region (NHSO region 2 and NHSO region 10) and one district hospital located in NHSO region 2. We also request authors of a previous study [16] to re-analyze data from a university hospital located in NHSO region 13 using our methodology and we use information provided by the authors to estimate national prevalence and financial burden. Moreover, we use the number of patients, which is one of important input parameters from NHSO databases. To our knowledge, the NHSO database and hospital databases we have accessed are the best available data sources which could be used to estimate the national prevalence and its financial burden. Thus, we believe our findings are acceptable as a national estimate of effects of medication oversupply.

Our study is conducted within patients who visit outpatient department and receive medications for chronic conditions. Any interpretation of our findings should be in a scope of a treatment of chronic diseases in outpatient setting. The findings should not be generalized to other population such as patients with acute conditions, inpatient setting or patients visiting emergency department.

Several medication management strategies or policies could be considered to be implemented. An effective outpatient medication reconciliation and medication refill system should be considered because they are not costly strategies but are likely to be effective. A previous study [80] was conducted to determine potential strategies to prevent unnecessary loss due to medication oversupply in Thailand. Its findings suggest that an effective outpatient medication reconciliation and medication refill system should be the first priority to be considered as medication management strategies for solving medication oversupply problem. Those strategies may also be useful for other purposes such as preventing inappropriate medication use or increasing continuity of medication use. Based on our findings, these strategies should be implemented especially in university or regional hospital because those types of hospitals have a higher prevalence of medication oversupply and also higher financial burden. Moreover, the strategies should be firstly implemented for children or patients with poly-pharmacy.

Although, we recommend some medication management strategies for solving the medication oversupply problem, we also have a concern of getting unintended effects of the strategies. For example, a hospital implements an outpatient medication reconciliation system with too restrictive criteria. Patients might get only small excessive amount of medications and it might lead to under-adherence if patients lost their medications for a few pills or patients need to postpone their appointments. Thus, hospitals might need to develop a monitoring system belongs with a medication management strategy for solving medication oversupply to determine the unintended effects of the strategies.

Policy makers who would like to develop medication management strategies to solve medication oversupply problem might need to consider conducting a return on investment study to confirm that the strategies are worth implementing because medication management strategies have their own costs such as pharmacists' cost, nurses' cost, material cost, or other costs. Return of investment study will help policy makers to better understand cost of the strategies and saved cost due to medication oversupply related to their own context.

To our knowledge, there are a few studies related to medication oversupply have been conducted in low and middle income counties (LMIC). This study's findings raises the LMICs' government and policy makers' awareness about medication oversupply problem. This study also provides an example of methodology for national estimation, an empirical evidence of financial burden due to medication oversupply and its associated factors for other LMIC countries, especially for countries which do not have appropriate medication management system.

Study limitations

This study's limitations should be discussed. First, these findings are based on three electronic databases. Data misclassification could have occurred. However, these hospitals have used the data for claiming purposes and we believe that the data used in this study were credible. Moreover, database from the district hospital was previously assessed for quality of data, resulting in high specificity and sensitivity.

Second, a definition of medication oversupply is MPRm>1.20 for any medication. The result would likely have been different if we use a different definition. However, we decide to use the current definition because we think that any oversupplied medication reflects the fact that there are some problems in the hospital system that leads to a lack of ability to detect an excessive amount of medication patients received.

Third, findings of patients receiving same medications across hospitals are based on a linkage of one hospital database with NHSO database. That might not be a representative for Thailand as a whole. Interpretation of the findings should be done with caution.

Last, again this dissertation were conducted based on electronic databases, other factors which are associated with medication oversupply such as physician factors, and healthcare system factors could not be captured. This warrants further researches to investigate other factors associated with medication oversupply which could not be captured in electronic databases.

Conclusions

In conclusion, this dissertation reveals that medication oversupply results in millions U.S. dollars in financial loss each year in Thailand. Around eight percent of patients receiving medications for chronic conditions have medication oversupply. Thai government experiences unnecessary financial loss due to medication oversupply around three million U.S. dollars each year. Although, a total financial loss due to medication oversupply is not tremendous, it would be better for the government to avoid unnecessary financial loss and spend the saved money to improve their healthcare system. Policy-makers should consider to develop policies or strategies to minimize this problem.

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