THE PREVALENCE AND ECONOMIC IMPACT OF POTENTIALLY INAPPROPRIATE MEDICATION USE IN THE U.S. ELDERLY

by

ZHUO JIANG

(Under the Direction of Matthew Perri III)

ABSTRACT

Objectives: To determine the prevalence of potentially inappropriate medication (PIM) use and estimate the extra expenditures related to PIM among the U.S. elderly. **Methods:** Patients over 65 years were taken from the Medical Expenditure Panel Survey through January 2000 to December 2001. A Retrospective cohort study was conducted. The prevalence of PIM was evaluated by the 2002 explicit criteria and the expenditures were estimated by employing multiple regression models and the propensity score method. **Results:** The prevalence of PIM among the non-institutionalized elderly in 2000, 2001 and 2-year period were 27.75%, 27.80% and 35.58%, respectively. The median expenditures attributable to PIM were $1,372 per person annually. **Conclusions:** This study found that the prevalence of PIM use among the elderly is slightly higher than the previous studies and identified significant relationship between the PIM use and higher total health care expenditures.

INDEX WORDS: Potentially inappropriate medication, The 2002 explicit criteria, Medical Expenditure Panel Survey

THE PREVALENCE AND ECONOMIC IMPACT OF POTENTIALLY INAPPROPRIATE MEDICATION USE IN THE U.S. ELDERLY

by

ZHUO JIANG

BMED. Shanghai Second Medical University School of Medicine

Shanghai China, 1995

A Thesis Submitted to the Graduate Faculty of The University of Georgia in Partial Fulfillment of the Requirements for the Degree

MASTER OF SCIENCE

ATHENS, GEORGIA

2005

THE PREVALENCE AND ECONOMIC IMPACT OF POTENTIALLY INAPPROPRIATE MEDICATION USE IN THE U.S. ELDERLY

by

ZHUO JIANG

Major Professor:	Matthew Perri III
Committee:	Jack E. Fincham Jaxk H. Reeves

Electronic Version Approved:

Maureen Grasso
Dean of the Graduate School
The University of Georgia
May 2005

TABLE OF CONTENTS

Page

LIST OF TABLES

Page

LIST OF FIGURES

Page

CHAPTER ONE

INTRODUCTION

Drug related problems (DRPs) in the elderly have been a major health care safety concern due to the increasing number of people in this population (Ferguson JA. 1990) Persons 65 years or older constitute less than 15% of the US population but consume nearly one third of all prescription medications in the United States (Arnett RH III et al 1990, Rahtore et al 1998, Soumerai et al 1999). Since older people have a greater likelihood of having more than one chronic disease, they tend to take more medications concurrently than other age groups (Hanlon JT et al 2001). Additionally, the elderly population is more likely to have a prolonged drug half-life time and reduced capability of metabolizing drug products, which can result in the potentially increased drug toxicity and adverse drug events (ADEs) (Montamat et al 1989, Mahoney et al 1991).

The report by the Institute of Medicine indicated that DRPs in inpatient care alone are responsible for about 44,000 to 98,000 deaths each year (Kohn et al 2000). A 1997 study (Bootman and Johnson) estimated that the annual cost due to drug related morbidity and mortality for patients in nursing facilities is $7.6 billion, where others estimated that $76.6 billion for ambulatory care and $5.6 billion for hospitals (Johnson and Bootman 1995, Bates et al 1997).

Previous research has suggested that inappropriate medication use in the elderly is one of the primary risk factors of DRPs (Lindley et al 1992). The most widely used approach that can be used to assess the appropriateness of drugs prescribed for the elderly was Beers criteria. It was

first developed by Beers and colleagues for nursing home residents in 1991(Beers et al 1991). Inappropriate medication use was defined as those drugs pose more risks than benefits to the elderly. In 1997, Beers updated the criteria to make them more applicable to the general elderly population (Beers 1997). In 2002, Fick and colleagues updated and revised the 1997 Beers criteria by adding new information for both existing and newer drug agents (Fick et al 2003).

Although a number of studies have been done to examine the prevalence and potential risk factors for inappropriateness of prescriptions in the elderly (Aparasu RR et al 2000, Liu GG et al 2002), no study has been done using the 2002 explicit criteria. Most of the latest published research used data before 2000 (Caterino et al 2004, Lau et al 2004, Aparasu et al 2004). Recent studies estimated the economic impact of DRPs in different settings (Bootman et al 1997, Johnson et al 1995, Bates et al 1997), but no study has been done to estimate expenditures attributable to inappropriate medication use for the non-institutionalized elderly.

This study will determine the prevalence of inappropriate medication use among the non-institutionalized elderly population with the latest Medical Expenditure Panel Survey (MEPS) from 2000 to 2001 with the updated 2002 explicit criteria (Fick et al 2003). Secondly, the current study will estimate the different health expenditures between elderly patients who use potentially inappropriate medication and those who don't.

CHAPTER TWO

BACKGROUND

The drug related problem in the U.S.

When medications are prescribed to patients for treatment of disease, optimal therapeutic outcomes are always desired by patients and healthcare providers. With the advent of modern drug therapy, pharmacotherapy has brought benefits to all ages, including the elderly population. However, if patient outcomes are not optimal, a drug related problem (DRP) has occurred.

A DRP is defined as an event or circumstance involving a patient's drug treatment that actually or potentially interferes with the achievement of an optimal outcome (ASHP statement on pharmaceutical care). Strand et al (1990) identified 8 categories of DRP: untreated indication, improper drug selection, subtherapeutic dosage, failure to receive drugs (including patients noncompliance), over dosage, adverse drug reaction, drug interaction, and drugs used without an indication. Although many DRPs are preventable with appropriate prescribing, patient compliance or outpatient monitoring, there is considerable literature demonstrating that DRPs result in adverse outcomes and contribute to high rates of morbidity and mortality.

Lazarou et al (1998) estimated that in 1994 more than 1 million Americans were hospitalized because of adverse drug events accounting for 4.7% of all admissions. Another meta-analysis reported that data retrieved from eight retrospective and four prospective trials indicated that as many as 28% of all emergency department visits were drug related, of these, as many as 24% resulted in hospital admission (Patel et al, 2002). There is also some evidence that adverse DRPs occur more frequently among inpatients. Bates et al (1995) reported that during a

6-month period, 247 adverse drug reactions and 194 potential adverse drug reactions were identified in the medical and surgical units of two hospitals. This study showed that 6.5% of hospitalized patients had an adverse drug event. In a nursing home facility, during a four year period, Cooper (1999) showed that one in seven patients experienced adverse drug reactions led to hospitalization.

DRPs not only lead to a serious negative health outcomes, but also present a serious economic problem to society. As previously noted, one report from the Institute of Medicine estimates that DRPs may cause between 44,000 and 98,000 deaths annually in hospitals in the US, and cost $8 billion annually(Kohn et al, 2000). Using a cost-of-illness model, Johnson and Bootman (1995) estimated that drug-related morbidity and mortality in the ambulatory setting in the US cost $76.6 billion per year and this cost exceeded prescription pharmaceutical use ($73 billion) while Perry and colleagues (2000) estimated that DRPs may result in 106,000 deaths and cost $85 billion annually. In their 1997 study, Bootman and colleagues estimated that the cost of drug related morbidity and mortality was $7.6 billion annually in nursing facilities, while Bates et al (1997) projected $5.6 billion for hospitals related to DRPs.

The causes of drug related problems

From the time a drug is prescribed to the time it is taken, there are many possible interrelated occurrences, which can lead to a DRP. Thus, the causes of DRPs may be multifactorial, such as inappropriate prescription, dispensing errors, patient noncompliance, idiosyncrasy of patients, and the lack of monitoring (Hepler et al 1990), among which inappropriate medication use is the principal cause attributable to DRPs (Lindley et al 1992).

The previous studies demonstrated that between 56% and 72% of DRPs could be due to prescribing errors by physician (Lindley et al 1992, Bates et al 1993, Bates et al 1995). Bates and

colleagues (1999) found many DRPs also occurred at the monitoring stage by nursing personnel. Senst and colleagues (2001) found that patient noncompliance was the cause of the 69% of the ADES causing hospital admission. Dennehy and colleagues (1996) reported that 58% of DRPs in patients visiting one hospital's emergency department were caused by noncompliance. Col and colleagues (1990) estimated that up to 17% of all elderly patients admitted to a hospital resulted from ADEs were related to noncompliance.

Drug related problems in the elderly population

Frail older people are more likely to experience multiple acute and chronic diseases. Martin (2000) showed that the use of prescription and over-the-count (OTC) medications increased with age. In the US, patients older than age 65, who comprise less than 15% of the population, receive 30% of all prescriptions. Since body compositions change substantially with age, especially decreased liver and kidney function, elderly persons do not eliminate drugs from their bodies as efficiently as younger persons. Therefore, the elderly are more likely to experience DRPs.

Criteria measured for inappropriateness of prescribing

Inappropriate prescribing is one of the primary risk factors of DRPs especially in the elderly population (Lindley et al 1992). Although many studies have been done to examine inappropriate drug use in the elderly in the past, there were no uniform criteria defining inappropriate drug use, which made it difficult to compare results across studies (Beers et al 1991). In response, Beers and colleagues (1991) developed the first set of criteria to measure the inappropriate prescription medication use in nursing home residents. This list provided an approach for researchers to quantitatively examine and compare the extent of inappropriate medication use across studies. In the Beers criteria, inappropriate medications are defined as

those drugs which pose more risks than benefits to the elderly. Based on the consensus opinions of thirteen nationally recognized experts in psychopharmacology, pharmacoepidemiology, clinical geriatric pharmacology, general clinical geriatrics and long–term care, the criteria identified two types of inappropriate medications regardless of the health condition being treated: (1) medications that should be generally avoided, and (2) doses, frequencies, or durations of medication use that should generally not be exceeded. The criteria list the following categories of inappropriate medications: sedative-hypnotics, antidepressants, antipsychotics, antihypertensives, non-steroidal anti-inflammatory agents, oral hypoglycemics, analgesics, dementia treatments, platelet inhibitors, histamine blockers, antibiotics, decongestants, iron supplements, muscle relaxants, gastrointestinal antispasmodics, and antiemetics. The detailed descriptions of the criteria are shown in Appendix A (Beers 1991).

In 1992, Hanlon and colleagues developed a Medication Appropriateness Index (MAI) for measuring drug therapy appropriateness. The MAI consists of a 10-item scale, including indication, effectives, dosage, correct directions, practical direction, drug-drug interaction, drug-disease interaction, duplication, duration, and expense. Although this index brought a reliable method to assess drug therapy appropriateness, only two studies have been identified which have used these explicit criteria (Schmader 1994, Hanlon 2004). One possible reason for this is that the MAI may be more complex to use than the Beers criteria.

Because the original Beers criteria were developed for the elderly in nursing homes, who are frailer than the noninstitutionalized elderly population, Stuck and colleagues (1994) modified the original list to study the inappropriateness of prescription use in the community-dwelling elderly. The modified criteria by Stuck et al kept most of the same drugs as the original list, with the exception of methyldopa and propranolol which were not included in the Stuck list.

In 1997, Beers (1997) updated the criteria to make them more applicable to the general elderly population. Similar to the 1991 criteria, the updated one was based on the consensus of a panel of six nationally recognized experts on the appropriate use of medications among the elderly. Compared with the original one, the updated list consists of two categories of inappropriate medications: one of drugs defined as inappropriate regardless of the disease condition and the other of drugs defined as inappropriate if the clinical information is available on certain known diagnoses. The unconditional inappropriate medication list was used in most of the studies (Liu and Christensen, 2002). Another advantage of the 1997 Beers criteria is that a severity rating to each criterion was indicated to each drug. A high severity was defined as a combination of both the likelihood that an adverse outcome would occur and the clinical significance of that outcome if it occurs. Among the inappropriate medications in the final criteria, 14 of these were considered high severity, others were low. Drugs added to the 1997 criteria included antihistamine, doxepin, meperidine, ergot mesyloids, cyclospasmol, ticlopidine, oxybutynin, chlorzoxazone, metaxalone, disopyramide, and gastrointestinal antispasmodics. Drugs dropped in the 1997 criteria were pentobarbital, secobarbital, propranolol, cyclandelate, isoxuprine, and orphenadrine because they are now seem as not being a problem when used in the elderly (See Appendix B).

With the continuous arrival of new drugs and increasing knowledge about geriatric medicines, in 2002, Fick and colleagues (2003) updated and revised the 1997 Beers criteria by adding new information for both existing and newer drug agents. Consistent with the previous criteria, the latest updated criteria were developed through a consensus opinion from a panel of 12 nationally and/or internationally recognized experts in psychopharmacology, pharmacoepidemiology, pharmacy practice, clinical geriatric pharmacology and clinical geriatric

medicines after they completed a two rounds survey. Similar to 1997 criteria, there are two types of statement included in the updated criteria: (1) medications that should be generally avoided regardless of medical conditions. (2) medications should not be used in the elderly if certain specific medical conditions are known. There were 11 medications/medication classes in the 1997 list but not in 2002 list, most of them were related to medical conditions; four medications/medication classes were modified in the 2002 update list and 44 medications were added to the update list. (See Appendix C)

Continual updating of the previously established criteria regularly is important so that healthcare practitioners can better monitor, evaluate and select therapies for the elderly. In this manner, potentially inappropriate medication (PIM) prescribing can be reduced.

CHAPTER THREE

LITERATURE REVIEW

When the first criteria developed by Beers and colleagues in 1991, a number of empirical papers were carried out using both the 1991 and 1997 criteria. Aparasu and Mort (2000) completed a review of eight studies conducted from 1992 through 1999 to explore the prevalence and risk factors of PIM of the elderly in various settings based on the 1991 Beers criteria (See Table 1). Liu and Christensen (2002) conducted another review of nine studies published between 1997 and the end of 2001 applying 1997 criteria (See Table 2). The two studies reported that the prevalence in the elderly varied from 10.6% in an urban hospital Emergency Department to 40.3% in nursing homes.

Thus, our literature review will only focus on the studies which were published after 2001 and examined the prevalence of potentially inappropriate medication (PIM) with Beers criteria. There were ten published studies that were identified in the literature search indicating PIM use in the elderly since 2002.

Inappropriate medication prescribing for elderly in the ambulatory setting

Stuart and colleagues (2003) recently examined the trends of PIM use among U.S. community–dwelling elderly patients between 1995 and 1999 using the 1995 and 1999 Medicare Current Beneficiary Surveys (MCBS). They showed that 24.8% of patients took at least one PIM in 1995 and 21.3% in 1999, which indicated that there was a significant decrease in the PIMs use between 1995 and 1999 among the elderly.

Based on the national pharmaceutical benefit manager (PBM) outpatient pharmacy claims database, Curtis and colleagues (2004) conducted a retrospective cohort study analyzing the prevalence of PIM for the U.S. elderly. They reported that 21% of the outpatients aged over 65 received one or more PIMs. Amitriptyline and doxepin were the most commonly used offending agents.

According to 1997 National Ambulatory Medical Care Survey (NAMCS), Huang and colleagues (2002) conducted a study to analyze the pattern of PIM use among elderly ambulatory care patients at a national level. They estimated that 10% of patients in the U.S. who visited physician's office would take at least one PIM in 1997.

Recently, Goulding (2004) studied two national surveys: NAMCS and the National Hospital Ambulatory Medical Care Survey (NHAMCS) between 1995 and 2000 to analyze the trends in the prevalence of PIM usage at ambulatory care visits in the elderly. The study concluded that the prevalence of PIM in the ambulatory setting among the older patients did not change a lot in 1995 (7.62%), 1996 (7.63%), 1997 (7.63%), 1998 (7.63%), and 2000 (7.82%). In this study, the most common agents for PIM were pain relievers and central nervous system drugs.

Aparasu and Mort (2004) examined inappropriate psychotropic medication use in the elderly by the 1996 MEPS dataset. They used both types of Beers criteria to explore their study: inappropriate psychotropic drugs should be avoided with and without medical conditions and found that an estimation of 2.3 million community–dwelling elderly persons (7.14%) administrated inappropriate psychotropic medications in 1996.

Inappropriate medication prescribing for elderly in emergency departments

Base on 1992-2000 National Hospital Ambulatory Medical Care Surveys, Cateruno and colleagues (2004) found that a national level estimation of 16.1 million or 12.6% elderly in emergency department (ED) visits received at least one PIM from 1992 to 2000. The rates did not statistically significantly differ over the study period: from 1992 to 1994 the rate was 12.1%; from 1995 to 1997, the rate was 12.9%; from 1998 to 2000 the rate was 12.6%. The most frequently used medications in general were promethazine, meperidine, propoxyphene, hydroxyzine, diphenhydramine and diazepam.

Inappropriate medication prescribing for elderly in nursing homes

Lau and colleagues (2004) examined a nationally representative sample of PIM use among nursing homes residents using the 1996 Medical Expenditure Panel Survey (MEPS). They reported that 50% of all residents aged over 65 administrated at least one PIM with an NH stay for three months or longer. The most common agents used were propoxyphene, diphenhydramine, hydroxyzime, oxybutynin, amitriptyline, cyproheptadine, iron supplements and ranitidine.

A recent study conducted by Perri and colleagues (2005) analyzed the prevalence of inappropriate medication use in nursing homes in Georgia in 2002. After reviewing patient medical records in 15 Georgia nursing homes, they estimated that 46.5% of patients received at least one inappropriate medication applying the 1997 Beers criteria.

Inappropriate medication prescribing for elderly in assisted living facilities

Sloane and colleagues (2002) analyzed the medication profiles of older residents in a four-state random sample of 193 residential care/assisted living facilities (RC/AL) in Florida, New Jersey, North Carolina, and Maryland between October 1997 and November 1998.

Researchers found that 16% of the residents received at least one PIM and the most common PIMs were oxybutynin, propoxyphene, diphenhydramine, ticlopidine, doxepin, and dipyridamole.

In 2003, Gray and colleagues examined 282 elderly participants in community residential care (CRC) facilities through analysis of Washington State Medicaid pharmacy prescription claims data between April 1998 and December 1998. They reported that 22% of the residents were administrated at least one PIM and the most common agents were oxybutynin and amitriptyline.

The previous studies reported here examined the prevalence of inappropriate medication use among the elderly in various settings such as emergency departments, nursing homes, residential care facilities, via ambulatory care visits, or in community dwelling options. All of the studies reviewed applied 1997 Beers criteria, most of which used the list regardless of dosage dependence and medical condition, only two studies used the complete 1997 Beers criteria (Lau et al 2004, Huang et al 2002). In general, patients in nursing homes seem to receive a higher prevalence of PIM than those in other settings. However, only one study analyzed the prevalence after year 2000 (Perri et al 2005) and no research has been done using the updated 2002 criteria. The possible reasons could be as follows: firstly, most of the studies used a retrospective database, which is always released several years after initial data collection; secondly, since the 2002 explicit criteria list is quite recently published in 2003, it is not possible for research to be conducted prior to its release in 2003.

Evaluating the costs of potentially inappropriate medication use

Although inappropriate medication use in the elderly has been linked to serious negative health outcomes and excess health care utilization, there is only one published study addressed

the association between PIM and costs and utilization (Fick et al 2001). Another two studies demonstrated the relation between additional resource utilization and an adverse drug event (Senst et al 2001, Bates et al 1997). Using a cost of illness analysis, there are another two studies published assessing the cost of drug related morbidity and mortality in ambulatory settings and nursing facilities. Here, we only included the study that sheds light on PIMs (Fick et al 2001).

Based on a Southeastern health maintenance organization's (HMO) claim dataset, Fick and colleagues (2001) conducted a study using Beers criteria demonstrated a strong relationship between the PIM and significantly higher costs, higher numbers of inpatient, outpatient and emergency room visits in the elderly. In addition to inappropriate medication use, age, gender, medication use, self-rated health and Charlson Comorbidity Index were included in the analysis, which were assumed to affect the health costs and utilization. Although a lot of confounders had been considered in this study, since the distribution of cost data is always positively skewed it might be better to use logarithmic transformation to reduce the skewness rather than use direct cost which was assessed in the regression model (Motheral Et al 2003). Moreover, their sample was drawn from a HMO database, which constrained the generalizability to a national level population.

Table 1 Results of literature review by Aparasu and Mort(2000)

Authors	Setting	Scope	Data source	Time period	Prevalence of PIM
Beers et al. 1992	Nursing home residents	LA area	prescription orders 1990-91	1 year	40.3
Stuck et al 1994	Community elderly	Santa Monica community	interview 1989-90	1 year	14.0
Spore et al. 1997	Board and care facility elderly	10 states	interview 1993	1 year	24.1
Wilcox et al 1994	Community elderly	National	NMES 1987	1 year	23.5
GAO Report 1995	Medicare recipients	National	MCBS 1992	1 year	17.5
Aparasu et al 1997	Ambulatory elderly(in physician office)	National	NAMCS 1992	1 year	5
Aparasu et al	Ambulatory Elderly(in outpatient Dep.)	National	NHAMCS 1994	1 year	2.9

Table 2 Results of literature review by Liu and Christensen (2002)

Authors	Setting	Scope	Data source	Time period	Prevalence of PIM
Chin et al. 1999	Elderly patients admitted to ED	Chicago urban area	interview 10/95-06/96	period of admission	10.6
Fick et al. 2001	Medicare managed care elderly	National	HMO claims data from 06/97-10/98	14 month	24.2
Golden et al. 1999	Nursing home home-bound	Miami	Pharmacy profiles from Medicaid managed care plan 1997	1 year	39.7
Hanlon et al. 2000	Community elderly	North Carolina	Duke EPESE 1989-90 1992-93	1 year	27 22.6
Meredith et al. 2001	Home health care patients	New York Los Angeles	Claims data with interview	4 week	17
Mort &Aparasu 2000	Ambulatory elderly	National	NAMCS NHAMCS 1996	1 year	27.2 (psychotropic agents only)
Mott et al. 2000	Elderly at community pharmacy	One Midwestern State	interview 1994	point of pharmacy visit	14.3
Piecoro et al. 2000	Elderly with Medicaid	Kentucky	Medicaid claims pharmacy claims 1996	1 year	27
Spiker et al. 2001	Indigent and homeless elderly	Ohio	Medical profiles from 7 government Subsidized clinics 1999-2000	5 months	35.6
Zhan et al. 2001	Community-dwelling elderly	National	MEPS 1996	1 year	21.3

CHAPTER FOUR

RESEARCH OBJECTIVES AND HYPOTHESES

Although most of the previous studies have investigated the prevalence and trends of inappropriate medication use in different settings among the elderly population, there is no current study examining this issue on the national level using updated 2002 explicit criteria. Recently, several studies (Fick et al 2001, Fu et al 2004, Perri et al 2005, Lau et al 2005) have demonstrated the relationship between inappropriate medication use in the elderly and negative health outcomes. However, none of these studies have estimated health care expenditures related to inappropriate prescribing of medication use among the older population.

The main purpose of this study is to investigate the relationship between the total health expenditures and PIM use in the elderly. The objectives of this study are: (1) to determine the prevalence of inappropriate prescription use among the non-institutionalized elderly population from 2000 to 2001 using Medical Expenditure Panel Survey (MEPS) data file and 2002 explicit criteria. (2) to determine the incremental health expenditures related to potentially inappropriate prescription medication use among the non-institutionalized elderly. The specific hypotheses to be tested are:

Hypothesis 1:

There is no relationship between PIM use and higher health expenditures.

To test this relationship a multiple linear regression model will be employed so that we can control for age, gender, race, health insurance status, total number of prescriptions, self rated health condition, co morbidities and previous year total health expenditures. Each of these has

been established as important variables in predicting health outcomes in this population (Perri et al 2005, Fu et al 2004, Fick et al 2001).

We will define total health expenditures as the sum of emergency room expenditures, in-hospital expenditures, outpatient expenditures, office based visit expenditures, prescription expenditures and home care expenditures. Self rated health status was measured by the self-report versions of SF-12 physical component summary score (PSC), which has been shown to be the best approach to differentiate between patients with PIMs and those who do not (Jiang and Franic 2005). We plan to use the same adapted Charlson Co Morbidity index as was used in Fick study(2001). The original Charlson index classified certain comoribid conditions with an international Classification of Disease (ICD-9) code (Charlson ME et al 1987); the adapted Charlson index assigns a weighted index which takes into account both the number and seriousness of different co-morbid diseases, and is commonly used with administrative databases to evaluate patient comorbidities (William D.H. et al 1996).

Hypothesis 2:

There is no relationship between higher expenditures for emergency room, in-patient, outpatient and office based visits, prescription and home care and utilization of PIMs.

Again, a multiple linear regression model will be used to control for age, gender, race, health insurance status, total number of prescriptions, the previous year self rated health condition, co morbidity conditions and the health services expenditures of previous year.

Hypothesis 3:

Expenditures incurred from health services such as emergency room visits, in-patient, outpatient, and home care are not related to PIM use or prior use of these services.

Because there will be many patients without emergency room visits and other expenditures, a logistic regression will be employed to predict the relationship between PIM use and no expenses in 2000 and 2001 after controlling age, gender, race, health insurance status, total number of prescriptions, the previous year self rated health condition, and co morbidity conditions.

Hypothesis 4:

PIM use is not related to gender, race and insurance type. A Chi-square test will be used to assess the relationship between these discrete variables and PIM use.

Hypothesis 5:

PIM use is not related to patient continuous demographic or descriptive variables.

These variables are age, Charlson comorbidity index, self reported health condition, total number of prescriptions, total expenditures in 2000, 2001 and their subcategories.

We will investigate if there is any relationship between the variables of age, total number of prescriptions, self rated health condition, comorbidity conditions, total expenditures, and it's subcategories between patients with and without PIM medications using independent *t*-tests.

CHAPTER FIVE

METHODS

5.1Data Sources:

Our data were drawn from the 2000 and 2001 Medical Expenditure Panel Survey (MEPS). The primary purpose of the MEPS database is to provide national estimates of health care utilization, expenditures, sources of payment, and insurance coverage for the U.S. non-institutionalized.

MEPS is a nationally representative survey and comprises three component surveys: the Household Component (HC), the Medical Provider Component (MPC), and the Insurance Component (IC). Among these segments, the HC is the core survey. The MEPS is co-sponsored by the Agency for Healthcare Research and Quality (AHRQ) and the National Center for Health Statistics. The MEPS is the most recent available survey conducted by AHRQ on the financing and use of medical care in U.S., following by the National Medical Expenditure Survey (NMCES or NMES-1, 1977) and the National Medical Expenditure Survey (NMES-2, 1987). The sampling frame for the MEPS HC is drawn from respondents of the National Health Interview Survey (NHIS) and MEPS HC collected additional data on their health care expenditures. Additionally, MEPS links these data with additional information collected from the respondents' medical providers, employers, and insurance providers.

Using computer-assisted personal interviewing technology, The MEPS data were collected on demographic characteristics, health conditions, health status, use of medical care services, charges and payments, access to care, satisfaction with care, health insurance coverage,

income and employment. The MEPS conducts a 5- round interview per household for each panel and it uses an overlapping panel design for each year, which means that there are two group participants interviewed each year, one group is from a new cohort panel started interviews from round one to round three and the other is from the previous panel round three to five (see Figure 1).

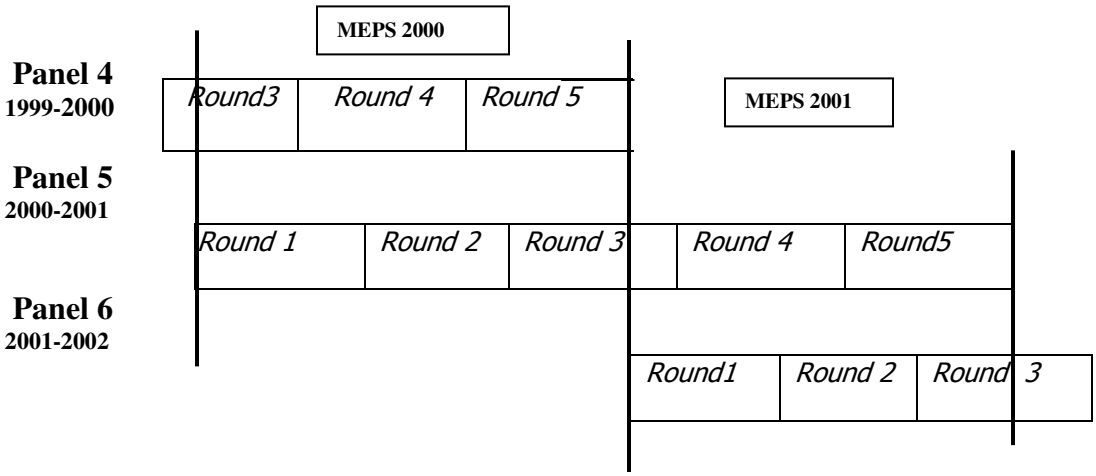

Figure1 MEPS Time Frame Year 2000 and 2001

This current study used the HC component of MEPS 2000, MEPS 2001. Involved files are as follows:

HC065: MEPS Panel 5 Longitudinal Weight file (updated on October 2004)

HC050: 2000 Full Year Consolidated Data File (updated on June 2003)

HC051a:2000 Prescribed Medicines (updated on April 2003)

HC052: 2000 Medical Conditions File (updated on June 2003)

HC060: 2001 Full Year Consolidated Data File (updated on April 2004)

HC059a:2001 Prescribed Medicines (updated on February 2004)

For each participant in the present study, there were two person-level weight variables assigned: one was a longitudinal weight designed for each panel across the two-year period and stored in the HC065 data file; the other was a cross-sectional weight for each specific year and stored in the HC050 and HC060 files, respectively. The weighting process included an adjustment for non-responses and poststratification. For example, a respondent who participated in the survey at first but died or left the country during the study period would be assigned a zero weight. Therefore, attrition from the sample is controlled for in the personal weight variable. Variables used in the established poststratification control figures included: census region; MSA status; race/ethnicity; sex and age. For instance, in order to improve the precision of estimates for subgroups of a population, investigator might select samples from those subgroups say Hispanic at higher rates than the remainder of the population. Then the sample weights for oversampled groups will be smaller than for the population not oversampled for adjustment.

The prescription information for each participant was generated for each round from the interviews and a pharmacy follow back survey and then coded in the HC051a and HC059a data file. The details of each medication included National Drug Code (NDC), medication name, strength of medicine (amount and unit), quantity (package size/amount dispended), total charge, and payment by source.

The medical conditions of the respondents were assessed by several sections of the MEPS self reported questionnaire, including the Condition Enumeration section, Health Status section, etc. The medical conditions and procedures were then recorded by the interviewer and coded by the professional coders to International Classification of Disease version Nine Clinical Modification codes (ICD-9-CM). Due to preserve respondent confidentiality, all of the condition codes in HC052 were collapsed from fully-specified codes to 3-digit ICD-9 codes. The data file

mentioned above can be used alone or in conjunction with other files by using merging procedure.

5.2 Exclusion and Inclusion Criteria:

This was a cross-sectional, longitudinal, retrospective cohort study. We used MEPS 2000, 2001 databases to estimate the one-year prevalence of inappropriate medication prescribing among a sample of non-institutionalized elderly, respectively; and used MEPS panel 5 data to estimate the two-year prevalence of PIM use. Participants drawn only from MEPS panel 5 data were utilized to estimate the different expenditures attributable to the inappropriate medication use among the non institutional elderly. The present study population is restricted to participants who were age 65 years and older.

For the one-year prevalence study, we chose the participants from MEPS 2000 and MEPS 2001 data, who were at least age 65 at that specific year; those who have zero sample weight were deleted. In the two-year prevalence and expenditure estimation study, we chose the participants from longitudinal MEPS panel 5 data set, who were at least 65 years old in 2000 and completed the five-round interviews during the two-year period.

In the expenditure study, participants were those who only had appropriate medication use in round one and round two, which was defined as our wash out period and was used to minimize the carry over effect from previous inappropriate medication exposure. After followed up for another two rounds, patients who were taking inappropriate medications in round three and/or four were our case group, while the rest were defined as our control group (See Figure 2). We didn't include patients having a PIM in round 5 to ensure that all individuals in the case group would have sufficient time in the study to incur expenditures.

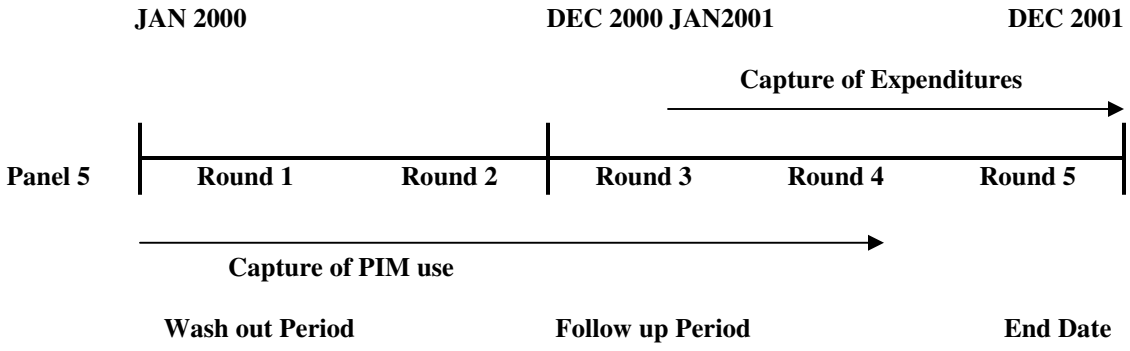

Figure 2 The composition of expenditure study

5.3 Potentially Inappropriate Medication Prescriptions Measures

For this study we adopted the updated 2002 explicit unconditional medication criteria created by Fick (2003). Among that, there are 4 classes or agents which are dosage dependent (See Table 3). Although MEPS does not provide information on daily dosage or frequency of use for every prescription, we used strength instead of dosage in our analysis. If the strength was above the dosage, we assumed that prescription was inappropriate.

Table 3 Dosage dependent PIM in the analysis

Prescription Classes or Agents	Severity
Benzodiazepines	
Lorazepam(if exceed 3 mg daily)	**Low**
Oxazepam(if exceed 60 mg daily)	**Low**
Alprazolam(if exceed 2 mg daily)	**Low**
Temazepam(if exceed 5 mg daily)	**Low**
Zolpidem(if exceed 0.25 mg daily)	**Low**
Triazolam(if exceed 0.25 mg daily)	**Low**
Digoxin (if exceed 0.125 mg daily)	**High**
Ferrous Sulfate (if exceed 325 mg daily)	**Low**
Reserpine (if exceed 0.25 mg daily)	**High**

The National Drug Code (NDC) was primarily used to identify the inappropriate prescription classes based on the 2002 criteria in the MEPS prescribed medicine files. The NDC is a nationally recognized identifier for every unique drug product marketed in the US. The U.S. Food and Drug Adminstration (FDA) designs the NDC Directory data. The NDC Directory data

can be downloaded from the FDA Center for Drug Evaluation and Research (FDA, 2001). Under Section 510 of the Federal Food, Drug, and Cosmetic Act, each drug product listed is assigned a unique 10-digit, 3-segment number. This number, known as the National Drug Code, identifies the labeler/vendor, product, and trade package size. The FDA assigns the first segment, the labeler code. A labeler is any firm that manufactures repacks or distributes a drug product. The second segment, the product code, identifies a specific strength, dosage form, and formulation for a particular product. The third segment, the package code identifies package sizes. Both the product and package codes are assigned by the firm. The NDC will be in one of the following configurations: 4-4-2, 5-3-2, or 5-4-1. In the MEPS data set, all valid NDCs are coded 11 digits.

5.4 Expenditure Measures

Expenditures in this study referred to what was paid for health care services, including out-of pocket payments and payments by private insurance, Medicaid, Medicare and other sources. Payments for over the counter drugs and for alternative care services were not included here.

5.5Data Analysis

The current study used weighted analysis to examine the prevalence of PIM use and explore the association between PIM use and higher health care expenditures among the U.S. elderly. We employed a non-weighted propensity score method to estimate the expenditures associated with the utilization of a PIM.

5.5.1 Prevalence Examination

Frequency counts of the number of participants who were dispensed at least one PIM were used to calculate the prevalence of PIM for elderly patients in the observational period. We

not only calculated the prevalence yearly, but also the prevalence for each round in MEPS panel 5 data as well.

The formula for determine the prevalence is as follows:

$$\frac{\text{The number of patients received PIMs}}{\text{The total number of the studied population}} * 100\%$$

5.5.2 Expenditure Estimation

In the expenditure study, the total expenditures and subcategories of expenditure (emergency expenditures, in-hospital expenditures, outpatient expenditures, office based expenditures, prescription expenditures and homecare expenditures) in 2001 were our dependent variables.

The variable of interest in terms of prescription utilization was whether or not a dispensed medication was appropriate for use in the elderly, as defined by the Fick criteria described above. PIM was coded (=1) if inappropriate and (=0) if not inappropriate within round three and or round four from the MEPS Panel 5 data file.

Age, race, gender, total number of prescription, type of health insurance, comorbidity, self rated health status and previous year health expenditures were included as independent variables and used to control for differences in utilization when comparing health care expenditures between patients who used a PIM and those who did not.

Participant age was defined as their age in year 2000 and was treated as a continuous variable. Race was categorized into white coded as '1' and non-white coded as '0'. Gender was also treated as a dichotomous variable, '1'for male and '0' for female. We classified insurance type into private insurance (person had any private insurance coverage any time during 2000), public insurance (person had only public insurance coverage during 2000), uninsured (no insured

during all of the period in 2000). Comorbidity condition was measured by the adapted Charlson index (see Table 4). Self rated health condition was measured by SF-12 PCS.

Table 4 Adapted Charlson Comorbidity Index

Weights	Conditions	ICD-9 codes
1	Myocardial infarct	410, 411
	Congestive heart failure	398, 402, 428
	Peripheral vascular disease	440-447
	Dementia	290, 291, 294
	Cerebrovascular disease	430-433, 435
	Chronic pulmonary disease	491-493
	Connective tissue disease	710, 714, 725
	Ulcer disease	53 l-534
	Mild liver disease	571, 573
2	Hemiplegia	342, 434, 436, 437
	Moderate or severe renal disease	403, 404, 580-586
	Diabetes	250
	Any tumor	140-195
	Leukemia	204-208
	Lymphoma	200, 202, 203
3	Moderate or severe liver disease	070, 570, 572
6	Metastatic solid tumor	196-199

Reference: William DH et al 1996

5.5.2.1 Descriptive Analysis of Expenditure Estimation Study

We performed Chi-squared tests to analyze the association of categorical variables between the patients who were prescribed PIM and those were not, such as gender, race, and insurance type. *t*-tests were used to examine the relationship of continuous variables between case and control group, including age, Charlson comorbidity index, self reported health condition, total number of prescription, total expenditures in 2000, 2001 and their subcategories.

Although a temporal relationship between PIM use and these descriptive and demographic variables may be present, a simple bivariate analysis cannot be used to infer a reliable relationship between the case and control group. In the next section, the explanatory multiple regression analysis will be used to establish a better design.

5.5.2.2 Explanatory Analysis of Expenditure Study

After controlling for demographic and clinical differences such as age, race, gender, insurance type, total number of prescription, and previous total expenditure and health conditions, a multiple regression analysis was applied to examine our main hypothesis whether expenditures were different between those prescribed PIM and those who did not.

Because the distribution of expenditures was highly skewed, we transformed the expenditure variables into natural LOG term. The multiple regression models were as below:

$$LN(TOTEXP01) = \beta_0 + \beta_1 LN(TOTEXP00) + \beta_2\ Age + \beta_3 Race + \beta_4 Gender + \beta_5\ Insurance\ Type + \beta_6\ Comorbidity\ Index + \beta_7\ SF\text{-}12PCS00\ Status + \beta_8\ Number\ of\ Prescription + \beta_9 Index.$$

We also performed the multiple and logistic regression models on subcatogories of total expenditures such as prescription drug expenses, emergency room expenses, inpatient visit expense, outpatient visit expenses, office based visit expenses and home care visit expenses, the detailed modeling was described as below.

Since there were a lot of zero expenses for both years in emergency room visits (n=527), inpatient visits (n=497), out patient visits (n=389) and home care visits (n=638) we developed a logistic regression model for these cases to predict the factors affecting the zero expenditure in the following year. The subcategory expenditures in 2001 were still used as dependent variables in the logistic regression models, but we treated the dependent variable as a dummy variable. If patients had no expenditure in 2001 then the variable is 0, otherwise it was coded as 1. We classified the variables of subcategorical expenditure in 2000 as dummy variables applying the same criteria. Secondly, we used multiple regression to estimate the relationship between inappropriate medication use and each subcategory expenditure after deleting those participants

who had no subcategory expenses within 2 years. A detailed description of variables was presented in table 5 and 6.

The multiple linear and logistic regression models for subcategories were as below:

LN (Expenditure in subcategories in 2001)= β0+ β1PIM exposure or not +β2 LN(Expenditure in subcategories in 2000)+β3Age+β4Gender+β5Racer+β6Insurance Type+β7Comorbidity+β8Self-rated Status+ β9Rxs

Pr (No Expenditure incurred for ER, Inpatient, outpatient,homecare in 2001)= β0+β1(No Expenditure incurred for Inpatient, outpatient, ER, homecare in 2000)+β2(No PIM exposure)+ β3Age+β4Gender+β5Racer+β6InsuranceType+β7Comorbidity+β8Self-rated Status+ β9Rxs.

A propensity score (simple matching with caliper) was used to estimate the expenditure difference between case group and controls. The propensity score is defined as the conditional probability of being treated given the covariates (D'Agostime RB 1998). Patients in case and control groups with nearly equal propensity score will tend to have same distributions on their background covariates so that to remove the bias in the background covariates. With the same propensity scores, we could imagine that paired case and control subjects are 'randomly' assigned to each group and receive treatment and control. As we know that in many observational studies, investigators have no control over the treatment assignment, so propensity score method is a good example to reduce bias and increase precision especially in observational studies (Lavori PW et al 1988, Cook EF et al 1988, Fiebach NH et al 1990).

The function for calculating caliper is as follows (Martin BC and Ganguly R):

Caliper=0.20*sqrt[(VARcase+VARcontrol)/2]

The non parametric Sign test was performed to evaluate the paired samples of the difference in expenditures between case and control groups for 2001.

The median difference expenditures in 2001 between the case and control group was the estimate of expenditure attributable to PIM among the elderly.

5.6 Statistical

All data analyses were accomplished with the SAS (Release 8.1. SAS Institute Inc., Cary, NC) statistical software. The level of significance was set at .05 levels.

Table 5 Variables in the Multiple Regression Models

Variables	Description	Character
Dependent Variables		
TOTEXP01	Total health Expenditures in 2001	Continuous
RXEXP01	Expenditure of prescription drugs in2001	Continuous
EMGEXP01	Expenditure of emergency visits in2001	Continuous
INHEXP01	Expenditure of inpatient visits in 2001	Continuous
OBVEXP01	Expenditure of office based visits in 2001	Continuous
OUTHEXP01	Expenditure of outpatient visits in 2001	Continuous
HHCEXP001	Expenditure of home care in 2001	Continuous
Independent Variables		
Age	Age in years	Continuous
Gender	Gender	DV=1 for female, 0 for male
Race	Race	DV=1 for whites, 0 for non-whites
Insurance Type		
	Private	DV=1 for private insurance, 0 for others
	Public	DV= 1 for public insurance, 0 for others
	Uninsured	DV=1 for people have no insurance, 0 for otherwise
Charlson Comorbidity Index	Adapted Chalson Comorbidity Index	Continuous
TOTEXP00	Total Expenditures in 2000	Continuous
Index	Had PIM or not	DV=1 for had PIM, 0 for appropriate
SF-12 PCS 00	SF-12 physical condition summary score interviewed in 2000	Continuous
RXEXP00	Expenditure of prescription drugs in 2000	Continuous
EMGEXP00	Expenditure of emergency visits in 2000	Continuous
INHEXP00	Expenditure of inpatient visits in 2000	Continuous
OBVEXP00	Expenditure of office based visits in 2000	Continuous
OUTHEXP00	Expenditure of outpatient visits in 2000	Continuous
HHCEXP00	Expenditure of home care in 2000	Continuous

Table 6 Variables in Logistic Regression Model

Variables	Description	Character
Dependent Variables		
EMGEXP01	Expenditure of emergency visits in2001	DV=1 for expenditure>0 0 for expenditure=0
INHEXP01	Expenditure of inpatient visits in 2001	DV=1 for expenditure>0 0 for expenditure=0
OUTHEXP01	Expenditure of outpatient visits in 2001	DV=1 for expenditure>0 0 for expenditure=0
HHCEXP001	Expenditure of home care in 2001	DV=1 for expenditure>0 0 for expenditure=0s
Independent Variables		
Age	Age in years	Continuous
Gender	Gender	DV=1 for male, 0 for female
Race	Race	DV=1 for whites, 0 for non-whites
Insurance Type		
	Private	DV=1 for private insurance, 0 for others
	Public	DV= for public insurance, 0 for others
	Uninsured	DV=1 for people have no insurance, 0 for otherwise
Charlson Comorbidity Index	Adapted Chalson Comorbidity Index	Continuous
TOTEXP00	Total Expenditures in 2000	Continuous
Index	Had PIM or not	DV=1 for had PIM, 0 for appropriate
SF-12 PCS 00	SF-12 physical condition summary score interviewed in 2000	Continuous
EMGEXP00	Expenditure of emergency visits in 2000	DV=1 for expentidure>0 0 for expenditure=0
INHEXP00	Expenditure of inpatient visits in 2000	DV=1 for expentidure>0 0 for expenditure=0
OUTHEXP00	Expenditure of outpatient visits in 2000	DV=1 for expentidure>0 0 for expenditure=0
HHCEXP00	Expenditure of home care in 2000	DV=1 for expentidure>0 0 for expenditure=0

CHAPTER SIX
RESULTS

6.1 Results of prevalence analysis

Tables 7-9 list the numbers and national estimates of potentially inappropriate medications use by the non-institutionalized elderly from MEPS 2000, MEPS 2001 and MEPS Panel 5 data sets.

In MEPS 2000 file, the original study sample contained 2,834 elderly aged over 65. After deleting 50 patients who had zero weight, which means they either expired or moved out of the country, our final study sample comprised 2,734 elderly patients, which represented an estimation of 33,247,684 community dwelling elderly in the U.S. in the calendar year 2000. There were 757 patients (an estimate of 9,226,379 elderly) used at least one potentially inappropriate medication (PIM) identified by the 2002 explicit criteria regardless of medical diagnosis, yielding a 27.75% prevalence of PIM use in 2000.

In the 2001 dataset, our final sample consisted of 3,704 elderly patients with valid personal weights, which represented an estimated 34,490,045 non institutionalized U.S. elderly population, in which 1,017 persons (an estimate of 9,590,937 elderly) took at least one PIM. The prevalence of PIM for the year 2001 was approximately 27.80% from MEPS 2001 data set.

The MEPS Panel 5 file data contained 1,161 elderly participants with personal longitudinal weights in our study sample, we estimated 32,653,181 nationally non-institutionalized U.S. elderly in year 2000 and 2001. There were 407 patients (an estimate of 11,618,744 elderly) receiving one PIM during 2 years which was equivalent to a prevalence of 35.58%. We also calculated the prevalence for each round in MEPS panel 5. The average duration of each round was 3.5, 5.0, 6.0, 6.0, and 3.5 months from round one to five. There were

179 participants (15.84%) out of 1,161 received at least one inappropriate medication in round 1, 198 participants (17.43%) in round two, 210 (18.06%) in round three, 224 (19.78%) in round four, and 179 (16.74%) in round five, respectively.

Since some patients could have several different inappropriate prescriptions at the same time, the sample size and estimated population statistics listed on tables 7-9 are not the sum of all the statistics on the above column.

The results showed that the prevalence in 2000 and 2001 did not shift dramatically; neither did the round-specific period. But the prevalence of 2-year period is not the simply sum of each year or each round, which implied that certain proportion of patients repeatedly took the inappropriate medications each year or every round.

The most frequently prescribed inappropriate medications for the years 2000, 2001 and for the two year period were, respectively: propoxyphene, digoxin, naproxen, doxazosin, and amitriptyline; propoxyphene, digoxin, doxazosin, amitriptyline, naproxen; and propoxyphene, digoxin, amitriptyline, naproxen and doxazosin. Propoxyphene is found to be the top PIM in our study where naproxen and doxazosin are new agents added to the list by Fick in 2002 explicit criteria.

Other than digoxin, the strength of all other three classes or individual agents is no greater than the amount listed in the criteria.

6.2 Results of Expenditure Analysis

The original sample contained 1,161 participants in MEPS panel 5, after the wash out period, the final sample consisted of 720 patients who had appropriate drug use in round 1 and round 2, after another 2 rounds of follow up, there were 115 patients who had inappropriate

medication use in round 3 and /or 4. The balance of patients in the group (605 patients) was our comparators.

TABLE 7Distrubution of PIM use in 2000

Prescription classes or individual agents	Sample size	Estimated PIM use in thepopulation
Analgesics		
propoxyphene and combination products	145	1,683,856
pentazocine	N/A	
meperidine	2	18,282
NSAIDs		
indomethacin	29	305,154
naproxen,	75	961,155
oxaprozin,	8	98,319
piroxicam	2	26,397
ketotolac	1	20,873
Dementia treatment		
ergot mesyloids,	1	3,177
cyclospasmol	N/A	
Sedative or hypnotic agents		
All barbituates except phenobarbital	1	26139
meprobamate	3	36,793
Antipsychotics		
thioridazine	2	12,490
mesoridazine	N/A	
Antiemetics		
trimethobenzamide	2	31,035
Benzodiazepine hypnotics		
flurazepam	5	47,277
chlordiazepoxide	15	159,913
diazepam	25	342,834
chlorazepate	12	124,500
Hypoglycemic agents		
chlorpropamide	1	20,191
Antiarrhythmic drugs		
disopyramide	5	51,603
amiodarone	23	385,288
Antidepressants		
doxepin	11	130,913
amitriptyline	64	758,643
fluoxetine	35	494,868
Antihypertensives		
methyldopa	12	131,300
guanethidine	N/A	
clonidine	42	485,680
ethacrynic acid	N/A	
guanadrel	N/A	
doxazosin	79	803,480
Antihistamine		
diphenhydramine	15	181,221

chlorpheniramine,	30	263,626
hydroxyzine,	29	264,209
cyproheptadine,	8	74,037
promethazine,	30	384,782
tripelennamine,dexchlorpheniramine	N/A	
orphenadrine	6	56,745
cimetidine	39	367,187
Platelet inhibitors		
ticlopidine	17	264,843
Short acting dipyridamole(Persantine®)	8	96,584
Gastrointestinal antispasmodic drugs		
dicyclomine,	17	169,967
hyoscyamine,	23	360,061
propantheline,	N/A	
belladonna alkaloids	4	64,914
Muscle relaxants and antispasmodic drugs		
methocarbamol,	8	85,754
carisoprodol,	16	274,893
oxybutynin (excluding Ditropan XL®),	20	212,803
metaxalone,	6	56,295
cyclobenzaprine,	20	224,683
chlorzoxazone	1	10,624
Antibiotics		
nitrofurantoin	26	389,938
Amphetamines and anorexic agents	1	10,010
Stimulant laxatives		
bisacodyl,	4	44,752
cascara sagrada,	N/A	
castor oil (Neoloid®)	N/A	
hormone		
estrogens only(oral)	8	72,147
methyltestosterone	1	12,200
isoxsuprine	N/A	
Short acting nifedipine(Procardia® and Adalat®)	6	103,794
mineral oil	N/A	
desiccated thyroid	22	326,012
Benzodiazepines		
Lorazepam(if exceed 3 mg daily)	N/A	
Oxazepam(if exceed 60 mg daily)	N/A	
Alprazolam(if exceed 2 mg daily)	N/A	
Temazepam(if exceed 5 mg daily)	N/A	
Zolpidem(if exceed 0.25 mg daily)	N/A	
Triazolam(if exceed 0.25 mg daily)	N/A	
Digoxin (if exceed 0.125 mg daily)	119	1,508,008
Ferrous Sulfate (if exceed 325 mg daily)	N/A	
Reserpine (if exceed 0.25 mg daily)	N/A	
TOTAL	**757**	**9,226,379**

Table 8 DISTRUBUTION OF PIM USE IN 2001

Prescription classes or individual agents	Sample size	Estimated PIM use in the population
Analgesics		
propoxyphene and combination products	207	1,989,807
pentazocine	1	6,969
meperidine	3	31,026
NSAIDs		
indomethacin	33	313,709
naproxen,	95	810,473
oxaprozin,	10	73,898
piroxicam	10	74,747
ketotolac	5	41,103
Dementia treatment		
ergot mesyloids,	N/A	
cyclospasmol	N/A	
Sedative or hypnotic agents		
All barbituates except phenobarbital	N/A	
meprobamate	4	49,045
Antipsychotics		
thioridazine	2	11,320
mesoridazine	N/A	
Antiemetics		
trimethobenzamide	4	23,351
Benzodiazepine hypnotics		
flurazepam	5	42,280
chlordiazepoxide	14	143,751
diazepam	45	429,088
chlorazepate	10	81,064
Hypoglycemic agents		
chlorpropamide	5	53,345
Antiarrhythmic drugs		
disopyramide	3	28,678
amiodarone	48	378,039
Antidepressants		
doxepin	18	150,195
amitriptyline	87	801,667
fluoxetine	42	464,608
Antihypertensives		
methyldopa	23	167,156
guanethidine	N/A	
clonidine	42	485,680
ethacrynic acid	N/A	
guanadrel	N/A	
Antihistamines		
diphenhydramine	22	234,208
chlorpheniramine,	30	269,485
hydroxyzine,	41	332,176
cyproheptadine,	6	32,614
promethazine,	63	527,221
tripelennamine,dexchlorpheniramine	N/A	

orphenadrine	4	25,678
cimetidine	34	283,565
Platelet inhibitors		
ticlopidine	11	144,987
Short acting dipyridamole(Persantine®)	8	59,922
Gastrointestinal antispasmodic drugs		
dicyclomine,	20	233,607
hyoscyamine,	13	151,499
propantheline,	1	18,201
belladonna alkaloids	8	82,571
Muscle relaxants and antispasmodic drugs		
methocarbamol,	17	142,520
carisoprodol,	17	203,913
oxybutynin (excluding Ditropan XL®),	34	339,551
metaxalone,	14	128,026
cyclobenzaprine,	8	59,083
chlorzoxazone	4	42,328
Antibiotics		
nitrofurantoin	25	253,996
Amphetamines and anorexic agents	3	23,569
Stimulant laxatives		
bisacodyl,	4	55,741
cascara sagrada,	N/A	
castor oil (Neoloid®)	N/A	
Hormone		
estrogens only(oral)	9	83,443
methyltestosterone	N/A	
isoxsurpine	N/A	
doxazosin	101	913,578
Short acting nifedipine	5	30,279
mineral oil	N/A	
desiccated thyroid	24	234,384
Benzodiazepines		
Lorazepam(if exceed 3 mg daily)	N/A	
Oxazepam(if exceed 60 mg daily)	N/A	
Alprazolam(if exceed 2 mg daily)	N/A	
Temazepam(if exceed 5 mg daily)	N/A	
Zolpidem(if exceed 0.25 mg daily)	N/A	
Triazolam(if exceed 0.25 mg daily)	N/A	
Digoxin (if exceed 0.125 mg daily)	155	1,606,918
Ferrous Sulfate (if exceed 325 mg daily)	N/A	
Reserpine (if exceed 0.25 mg daily)	N/A	
TOTAL	**1,017**	**9,590,937**

Table 9 DISTRUBUTION OF PIM USE IN MEPS Panel 5

Prescription classes or individual agents	Sample size	Estimated PIM use in the population
Analgesics		
propoxyphene and combination products	110	3,040,596
pentazocine	1	15,482
meperidine	1	26,437
NSAIDs		
indomethacin	13	375,054
naproxen,	37	939,058
oxaprozin,	10	73,898
piroxicam	3	83,292
ketorolac	4	49,959
Dementia treatment		
ergot mesyloids,	1	6,856
cyclospasmol	N/A	
Sedative or hypnotic agents		
All barbituates except phenobarbital	N/A	
meprobamate	2	99,339
Antipsychotics		
thioridazine	1	10,920
mesoridazine	N/A	
Antiemetics		
trimethobenzamide	1	40,183
Benzodiazepine hypnotics		
flurazepam	2	43,116
chlordiazepoxide	9	203,080
diazepam	14	405,588
chlorazepate	4	123,768
Hypoglycemic agents		
chlorpropamide	5	53,345
Antiarrhythmic drugs		
disopyramide	4	64,499
amiodarone	21	617,769
Antidepressants		
doxepin	3	79,775
amitriptyline	39	1,198,818
fluoxetine	24	552,899
Antihypertensives		
methyldopa	9	48,582
guanethidine	N/A	
clonidine	20	612,320
ethacrynic acid	N/A	
guanadrel	N/A	
Antihistamines		
diphenhydramine	7	222,661
chlorpheniramine,	28	858,091
hydroxyzine,	20	509,559
cyproheptadine,	5	79,370
promethazine,	29	759,024
tripelennamine,dexchlorpheniramine	N/A	
orphenadrine	3	70,092

cimetidine	21	478,7515
Platelet inhibitors		
ticlopidine	9	328,090
Short acting dipyridamole(Persantine®)	5	145,452
Gastrointestinal antispasmodic drugs		
dicyclomine,	11	388,012
hyoscyamine,	15	593,071
propantheline,	1	18,201
belladonna alkaloids	2	81,722
Muscle relaxants and antispasmodic drugs		
methocarbamol,	9	190,730
carisoprodol,	16	614,545
oxybutynin (excluding Ditropan XL®),	16	459,193
metaxalone,	8	216,340
cyclobenzaprine,	19	578,702
chlorzoxazone	4	42,328
Antibiotics		
nitrofurantoin	19	569,343
Amphetamines and anorexic agents	3	23,569
Stimulant laxatives		
bisacodyl,	3	101,230
cascara sagrada,	N/A	
castor oil (Neoloid®)	N/A	
Hormone		
estrogens only(oral)	9	83,443
methyltestosterone	N/A	
isoxsurpine	N/A	
doxazosin	37	922,495
Short acting nifedipine(Procardia® and Adalat®)	5	207,412
mineral oil	N/A	
desiccated thyroid	13	447,451
Benzodiazepines		
Lorazepam(if exceed 3 mg daily)	N/A	
Oxazepam(if exceed 60 mg daily)	N/A	
Alprazolam(if exceed 2 mg daily)	N/A	
Temazepam(if exceed 5 mg daily)	N/A	
Zolpidem(if exceed 0.25 mg daily)	N/A	
Triazolam(if exceed 0.25 mg daily)	N/A	
Digoxin (if exceed 0.125 mg daily)	54	11,618,744
Ferrous Sulfate (if exceed 325 mg daily)	N/A	
Reserpine (if exceed 0.25 mg daily)	N/A	
TOTAL	**407**	**2,093,341**

6.2.1 Results of Descriptive Analysis:

The results of bivariate comparisons between the patients prescribed and not prescribed inappropriate medications were shown in Tables 10 and 11. The descriptive analyses showed significant differences in total expenditures, office based visit expenditures and outpatient expenditures between patients who used inappropriate medications and who did not in 2001 (See Table 10). On the other hand, people who took inappropriate prescriptions were more likely to receive prescriptions and consume more in health services utilizations in the previous year than their comparators (See Table 11*).*

A multiple regression model was conducted to access the effect of inappropriate medication use on expenditures by controlling the previous year health expenditures, total number of prescriptions, comorbidity conditions, self perceived health status in the prior year, and social demographic characteristics. Since the distribution of expenditures is highly skewed, the variable of expenditure in dollars is transformed into natural log in our study. Such a model will provide us with more reliable information on how patients' health expenditures will differ based on the use of PIMs.

6.2.2 Results of Explanatory Analysis

The results of the multiple regression analyses are presented in Table 12. These results indicate statistically significant differences between elderly patients who were prescribed inappropriate medications and those who were not after controlling for age, gender, insurance type, Charlson Comorbidity Index, self perceived health status, total number of prescriptions, and previous year health expenditures. The case group had significantly higher total and outpatient expenditures than comparisons, relatively higher inpatient expenditures because the p-value is just above 0.05, but not statistically increasing expenditures on prescriptions,

Table 10 Bivariate comparisons of dependent variables between the patients prescribed (Cases) and not prescribed (controls) inappropriate medications

Variables	**Case** (115)	**Control**(605)	**P-Value**
TOTEXP01($)	9,292	6,643	0.0221**
EMGEXP01($)	178	174	0.9659
INHEXP01($)	3,889	2,904	0.2942
OBVEXP01($)	2,253	1,051	<0.0001* *
OUTHEXP01($)	935	386	<0.0011* *
RXEXP01($)	1,743	1,385	0.1560
HHCEXP01($)	263	520	0.3665

*0.05>p>0.01 **p<0.01

Table 11 Bivariate comparisons of independent variables between the patients prescribed (Cases) and not prescribed (controls) inappropriate medications

Variables		**Case** (109)	**Control**(633)	**P-Value**
Gender	Female	74.83%	60.45%	0.0023**
	Male	25.17%	39.55%	
Race	Non-White	15.58%	8.75%	0.1186
	White	84.42%	91.25%	
Insurance	Private	53%	58.67%	0.6925
	Public	47%	41.24%	
	Uninsured	0	0.09%	
Mean Age		75.62	75.18	0.5349
Mean No. of Rxs		55.41	42.79	0.0008**
Comorbidity Index		0.9804	0.8427	0.3217
SF-12 PCS 00		35.48	35.06	0.9372
TOTEXP00($)		6,588	4,821	0.0221**
EMGEXP00($)		154	100	0.3432
INHEXP00($)		2,190	1,814	0.5524
OBVEXP00($)		1,500	791	<0.0001**
OUTHEXP00($)		846	422	0.0220*
HHCEXP00($)		257	263	0.8633

*0.01<P<0.05
**P<0.01

emergency visits, office based visits and homecare facilities after controlling for those confounders.

Previous year health expenditures in each health utilization services and the total number of prescriptions used were highly correlated with the increases in following year health expenditures. The only exception to this was in home care facilities where there were no significant differences between total number of prescriptions and home care expenditures. Some of the coefficients of pervious year expenditures were negative because of the transformation of natural LOG, which still implied that the higher the expenditure in the previous year the more the expenditure the following year would be.

Based on the results of the model, both the Charlson Comorbidity Index and SF-12 PCS in the previous year significantly influenced the total health expenditure of the next year. Persons who had greater Charlson Comorbidity index, indicating that persons had various and severe disease conditions, and lower SF-12 PCS scores, which implied the worse self-assessment physical health status of persons in the previous year, tended to consume more health expenditures in the next year. Another finding is that persons who had the higher SF-12 PCS score in the previous year were likely to spend more on prescriptions and office based visits but less on emergency room, inpatient and home care settings.

Increasing age was only correlated with the higher expenditure in home care facility. Females (they are all >65 in this sample) spent more money on office based visits than males. Compared with the non-white elderly, the white elderly had higher expenditures of outpatients' visits. Patients with insurance incurred more health expenditures than those uninsured.

The results of logistic regression model in Table 13 demonstrated that patients without inappropriate medication in the previous year significantly decreased the likelihood of paying emergency visits, inpatient visits and out patient visits in the following year.

Combining the results of multiple regression model and logistic regression model, we found that in the emergency department setting, patients who had no emergency visit, no PIM use, used less prescriptions, remained in better medical conditions, or were younger were more likely to have no emergency expenditures in the next year; while patients spent more on emergency visit in the previous year or took more prescriptions in general were likely to spend more on emergency visits in the next year.

For in-patient visits, patients who had no PIM use, better preexisting health conditions or non-white elderly tended to have no in-patient cost in the next year. If patients visited the hospital more often in the previous year and had PIM use and took more prescriptions, they would more likely to receive in-patient visits in the next year.

In the outpatient visit setting, patients who had no PIM use, no outpatient cost in the previous year, or non white elderly were less likely to incur outpatient expenditures in the following year. Patients who had PIM use, spent more on outpatient visits or received more prescriptions in general were likely to incur more expenditure on outpatient visits the next year.

In homecare facilities, patients who had no home care visits in the previous year or perceived better health status by themselves in the previous year or were relatively younger, tended to spend nothing on home care visits the next year. Patients who experienced home care visits in the previous year, felt worse about their health status or were relatively old, would spend more on home care the next year.

Table 12 The results of the multiple regression models

Variable	Model R^2	Coefficient	S.E.	T	P-Value
Total Expenditures (LN) #	**0.3377**				
Prescription use					
Inappropriate		0.238	0.108	2.21	0.027*
Appropriate (Reference)					
Previous year total expenditure (LN)		0.278	0.037	7.55	<0.001**
Total numbers of prescriptions		0.009	0.001	7.31	<0.001**
Charlson's Comorbidity Index		0.077	0.030	2.53	0.010*
SF-12 PCS		-0.009	0.002	-4.13	<0.001**
Age		-0.0003	0.006	-0.06	0.9558
Gender					
Female		0.115	0.082	1.40	0.163
Male (Reference)					
Race					
White		0.249	0.134	1.87	0.060
Non-White (Reference)					
Insurance					
Private		4.868	1.069	4.56	<0.001**
Public		4.602	1.069	4.30	<0.001**
Not Insured (Reference)					
Prescription Expenditures (LN)	**0.3698**				
Prescription use					
Inappropriate		0.090	0.146	0.62	0.537
Appropriate (Reference)					
Previous year prescription expenditure (LN)		0.379	0.058	6.59	<0.001**
Total numbers of prescriptions		0.018	0.002	8.60	<0.001**
Charlson Comorbidity Index		0.028	0.040	0.70	0.484
SF-12 PCS		0.007	0.003	2.19	0.029*
Age		0.003	0.007	0.45	0.650
Gender					
Female		0.015	0.007	0.58	0.561
Male(Reference)					
Race					
White		-0.096	0.179	-0.53	0.593
Non-White (Reference)					
Insurance					
Private		3.509	1.442	2.43	0.015*
Public		3.338	1.442	2.31	0.021*
Not Insured (Reference)					
Emergency Visits Expenditures (LN)	**0.4391**				
Prescription use					
Inappropriate		1.035	0.670	1.54	0.124
Appropriate (Reference)					
Previous year emergency visits expenditure (LN)		-0.607	0.053	-11.48	<0.001**
Total numbers of prescriptions		0.0176	0.007	2.61	0.0097*
Charlson Comorbidity Index		-0.032	0.185	-0.12	0.901
SF-12 PCS		-0.030	0.016	-1.95	0.053
Age		0.067	0.038	1.74	0.084
Gender					
Female		-0.305	0.599	-0.51	0.612

Male (Reference)					
Race					
White		0.122	0.961	0.13	0.899
Non-White (Reference)					
Insurance					
Private		2.196	6.40	0.34	0.732
Public		1.879	6.40	0.29	0.770
Not Insured(Reference)					
Inpatient visit Expenditures (LN)	**0.4907**				
Prescription use					
Inappropriate		1.480	0.791	1.87	0.062
Appropriate (Reference)					
Previous year inpatient visit expenditure (LN)		-0.652	0.047	-13.73	<0.001**
Total numbers of prescriptions		0.014	0.008	1.67	0.096*
Charlson Comorbidity Index		0.083	0.197	0.42	0.673
SF-12 PCS		-0.065	0.019	-3.28	0.001**
Age		-0.059	0.045	-1.32	0.188
Gender					
Female		-0.539	0.683	-0.79	0.431
Male (Reference)					
Race					
White		2.055	1.191	1.72	0.086
Non-White (Reference)					
Insurance					
Private		2.751	8.152	0.34	0.736
Public		1.822	8.158	0.22	0.824
Not Insured(Reference)					
Outpatient visit Expenditures (LN)	**0.2384**				
Prescription use					
Inappropriate		1.949	0.629	3.10	0.002**
Appropriate(Reference)					
Previous year outpatient visit expenditure (LN)		-0.437	0.048	-9.13	<0.001**
Total numbers of prescriptions		0.017	0.006	2.65	0.008**
Charlson Comorbidity Index		-0.190	0.179	-1.06	0.292
SF-12 PCS		-0.010	0.015	-0.71	0.477
Age		-0.032	0.038	-0.81	0.416
Gender					
Female		0.101	0.554	0.18	0.856
Male (Reference)					
Race					
White		2.330	0.968	2.41	0.017**
Non-White (Reference)					
Insurance					
Private		1.916	7.752	0.25	0.805
Public		0.877	7.756	0.11	0.910
Not Insured(Reference)					
Home Care Expenditures (LN)	**0.3014**				
Prescription use					
Inappropriate		0.388	1.385	0.28	0.780
Appropriate (Reference)					
Previous year home care expenditure (LN)		-0.404	0.080	-5.03	<0.001**
Total numbers of prescriptions		0.0138	0.010	1.28	0.205
Charlson Comorbidity Index		-0.665	0.343	-1.94	0.056

SF-12 PCS	-0.081	0.027	-2.97	0.004**
Age	0.1302	0.063	2.07	0.041*
Gender				
Female	-0.164	1.012	-0.16	0.872
Male (Reference)				
Race				
White	-0.022	1.516	-0.01	0.988
Non-White (Reference)				
Insurance				
Private	-2.329	0.962	-2.42	0.017*
Public (Reference)				
Not Insured				
Office based visit Expenditures(LN) 0.1285				
Prescription use				
Inappropriate	0.251	0.270	0.93	0.3526
Appropriate (Reference)				
Previous year office based visit expenditure (LN)	0.261	0.046	5.71	<0.001**
Total numbers of prescriptions	0.012	0.003	4.32	<0.001**
Charlson Comorbidity Index	0.099	0.076	1.30	0.195
SF-12 PCS	0.015	0.005	2.72	0.007**
Age	-0.012	0.014	-0.86	0.391
Gender				
Female	0.521	0.206	2.53	0.012*
Male (Reference)				
Race				
White	0.053	0.333	0.16	0.873
Non-White (Reference)				
Insurance				
Private	4.674	2.671	1.75	0.081
Public	4.183	2.672	1.57	0.118
Not Insured (Reference)				

*0.01<p<0.05
**p<0.01
#Bolded variables are dependent variables

Table 13 Results of logistic Regression

Dependent Variable: Emergency Visits Expenditures=0	**OR**	**95% CI**	**Wald Statistics**	**P value**
Inappropriate Prescription use	0.535	0.329-0.870	6.3605	0.0117*
Previous year emergency visits expenditure=0	0.390	0.244-0.623	15.556	<0.0001**
Total numbers of prescriptions	0.994	0.989-0.999	5.5508	0.0185*
Charlson Comorbidity Index	0.768	0.672-0.877	15.0955	<0.0001**
SF-12 PCS	1.003	0.992-1.014	0.3584	0.5494
Age	0.969	0.942-0.997	4.6905	0.0303*
Gender	1.069	0.705-1.623	0.0995	0.7524
Race	1.089	0.617-1.922	0.0871	0.7679
Insurance	1.238	0.832-1.840	1.1093	0.2922
Dependent Variable: Inpatient Visits Expenditures=0	**OR**	**95% CI**	**Wald Statistics**	**P value**
Inappropriate Prescription use	0.535	0.333-0.858	6.7345	0.0095*
Previous year inpatient visit expenditure =0	0.724	0.454-1.156	1.8297	0.1762
Total numbers of prescriptions	0.996	0.991-1.001	2.8448	0.0917
Charlson Comorbidity Index	0.830	0.727-0.947	7.6327	0.0057**
SF-12 PCS	1.012	1.002-1.022	5.2717	0.0217*
Age	1.005	0.977-1.033	0.1053	0.7456
Gender	0.897	0.600-1.342	0.2797	0.5969
Race	0.521	0.274-0.989	3.9711	0.0463*
Insurance	1.324	0.903-1.941	2.0693	0.1503
Dependent Variable: Outpatient visit Expenditures=0	**OR**	**95% CI**	**Wald Statistics**	**P value**
Inappropriate Prescription use	0.586	0.377-0.912	5.6182	0.0178*
Previous year outpatient visit expenditure =0	0.326	0.230-0.463	39.1962	<0.0001**
Total numbers of prescriptions	0.997	0.992-1.002	1.7170	0.1901
Charlson Comorbidity Index	0.938	0.828-1.063	1.0049	0.3161
SF-12 PCS	1.001	0.991-1.010	0.0163	0.8983
Age	1.023	0.998-1.049	3.1349	0.0766
Gender	0.714	0.499-1.022	3.3885	0.0657
Race	0.372	0.207-0.667	10.9847	0.0009**
Insurance	1.217	0.873-1.696	1.345	0.2462
Dependent Variable: Home Care Expenditures =0	**OR**	**95% CI**	**Wald Statistics**	**P value**
Inappropriate Prescription use	0.976	0.464-2.053	0.0040	0.9495
Previous year home care expenditure=0	0.082	0.043-0.158	55.8671	<0.0001**
Total numbers of prescriptions	0.994	0.987-1.000	3.4413	0.0636
Charlson Comorbidity Index	0.973	0.799-1.185	0.0746	0.7848
SF-12 PCS	1.018	1.004-1.033	5.9940	0.0144*
Age	0.928	0.893-0.965	13.9122	0.0002**
Gender	0.955	0.531-1.718	0.0238	0.8773
Race	0.847	0.375-1.914	0.1593	0.6898
Insurance	1.042	0.606-1.793	0.0223	0.8813

*0.01<p<0.05
**p<0.01

6.2.3 Projecting the Expenditure Attributable to PIM

In the previous multiple regression models, although a significant relationship between expenditure and inappropriate medication use was established, as we used the natural LOG of expenditure instead of expenditure itself, the coefficient of the estimate is not easy to interpret.

In order to estimate the incremental increase in health expenditure associated with PIM, a matching method was used. The simple Mahalanobis metric matching within calipers defined by the propensity score method was used in this study. In the current study, the previous year total expenditure, prescription expenditure, emergency room visit expenditure, inpatient visit expenditure, outpatient visit expenditure, office based visit expenditure, homecare expenditure, total number of prescriptions, Charlson comorbidity index score, SF-12 PCS score, age, gender, race, insurance type were included to calculate propensity score. The caliper in the study was used as 0.14 (see the methods section for detail). We also excluded those outliers which were identified by examining the Cook's distance and Studentized residual before using the matching method.

There were 23 subjects removed due to Cook's distance greater than 0.10 and Studentized residual of -2 or lower or 2 or greater. The final sample contained 104 cases and the matched 104 controls. As we can see from Table 14, the covariances between the case and control group are much more balanced after applying matching method than that prior to matching (Tables 10, 11). Among these 104 pairs, 60.58% of cases increased the expenditure in the following year comparing to their controls from $12 to $35,460, 39.42% cases decreased the expenditure in the next year from $103 to $33,340.

Since the distribution of the expenditures in the next year did not pass the test for normality, we used the Sign test to assess the difference between the paired case and control

group. The 2-tailed p value for the Sign test was 0.0390, which means there was a significant increase in health expenditures if patients took inappropriate medication use. The median difference between the two groups was $1,372. The 95% confidence interval for the estimate is from $118 to $ 2,115.

Table 14 Comparisons for covariances after simple matching method

Variable	**Cases** (n=100)	**Controls** (n=100)	**T Test** p-value
Mean Age	76.10	75.68	0.67
Total No. of prescriptions	55.04	56.58	0.78
Charlson's Index	0.9231	0.9326	0.96
SF-12 PCS score	34.59	33.76	0.75
Total Expenditure 2000($)	6229	6345	0.93
Emergency Exp. 2000($)	206	236	0.82
Inpatient Exp. 2000($)	2559	2958	0.73
Office based Exp. 2000($)	986	1034	0.82
Outpatient Exp.2000($)	482	284	0.14
Prescription Exp. 2000($)	1215	1160	0.73
Home care Exp. 2000($)	413	380	0.91
			F Test p-Value
Female No. (%)	78(75.00)	75(72.12)	0.64
White No. (%)	87(83.65))	89(85.58)	0.72
Private Insurance No. (%)	46(44.23)	50(48.08)	0.89

*P-value<0.05

CHAPTER 7

DISCUSSION AND CONCLUSION

7.1 Potential Inappropriate Medication Use in the Elderly

Inappropriate medication use in the elderly population is a primary patient safety concern. According to our literature review, the prevalence of PIM in community-dwelling elderly is about 17.5%, 23.5% and 21.3% in 1987, 1992 and 1996, respectively, using Beer's explicit criteria. In our study, we found that the prevalence of PIM use among the elderly population in 2000 (27.75%) and 2001 (27.80%) is slightly higher than the previous studies. As we learn more about drugs and their effect on the elderly and the list of PIM in 2002 explicit criteria expands, we expect to see great prevalence of PIM use in the elderly. This put our elderly population at risk of negative health outcome. Additionally, we found more than 5% population in our study were exposed to 3 or 4 PIMs, which may result in even worse health outcomes and more health service utilizations (Perri et al 2005, Fu et al 2004, Fick et al 2001).

The most frequently prescribed medications included in our study were propoxyphene, amitriptyline, naproxen, doxazosin. There is no doubt that propoxyphene is the top inappropriately prescribed agent, which is consistent with many other studies (Perri et al 2005, Sloane et al 2002, Lau et al 2004). Although there is consensus on the inappropriateness of propoxyphene according to studies, we can still find the continuing evidence of its being prescribed among the elderly. The finding in this study suggests that the need to influence physicians to correct their prescribing behavior based on the evidence based practice.

In the descriptive analysis, we found that patients on PIM incurred significantly higher expenditures for office based visits and outpatient visits. But, we can not simply conclude that the difference between patients who had a PIM and those who didn't is due to the PIM. As we can see in Table 10, patients who had a PIM tended to take more prescriptions and consume more for health service utilization in the prior year. So, it is possible that the elderly on PIMs already had poorer health conditions, which may also explain the difference in expenditures between these two groups. To control for these confounding variables, a multiple regression model was used.

After controlling for the pre-existing health status and other covariates, our study demonstrated that inappropriate prescription medication use was significantly associated with increased health care expenditures. Patients having PIM incurred more expenses on inpatient visits and outpatient visits than those who didn't. In the logistic regression model, we found that patients having less expenditures tended to be healthier, and had no PIM use. One reason that PIM use can influence total health care expenditures might be due to drug-related morbidity among the elderly. This implies a need to improve physicians' prescribing behaviors and increase the use of other medications to treat the same condition.

As we know, in retrospective studies, the subjects are not randomly allocated and selection bias is inevitable. In our study, even though we introduced a wash out period, covariates such as gender, prescription numbers, expenditure for total health care utilization, outpatient visits, office based visits of two groups were still significantly different before matching, which means these two group were quite different other than exposure to PIM or not. So it's hard to detect the real economic outcomes attributable to PIM use. Thus, in order to better estimate the extra expenditures due to PIM use, we applied a propensity score method with

simple matching. As we can see from Table 14, the covariates between case and control group after matching are very similar. The difference average expenditures in the following year between the two groups are most likely due to PIM use itself. We are 95% confident to conclude that the real incremental expenditures due to PIMs are between $118 and $2,115 per elderly annually.

This study appears to be the first to access the relationship between inappropriate medication use and increased health care expenditures measured by 2002 explicit criteria in a non institutionalized elderly population. The present study also appears to be the first estimating the incremental expenditures due to inappropriate prescription medication use among the elderly after controlling other confounding factors.

7.2 Strength of the Study

Due to the design of the MEPS, the strength of the study is that the results of prevalence and expenditure estimation are generalizable to the whole non institutionalized U.S. elderly population. Additionally, no studies of inappropriate medication use had been done using 2002 explicit criteria. So the results in the current study would provide more information than the previous research.

7.3 Limitations of the Study

Since MEPS data is independent of indication and does not provide information on daily dosage, medications regarded as inappropriate under certain medical condition or exceeding certain amount from the explicit criteria are excluded in our study, as a result, the prevalence of our study is more likely to be underestimated. But the association between the inappropriate medication use and higher health care expenditures may not be easily violated by such limitation according to the analysis we did using strength to estimate the dosage in the criteria.

In the retrospective cohort study, we could not control all the patient characteristics of the two groups (case and control). Even though a regression model was used to control as many variables as could be included in the model, it was not possible for us to include all possible characteristics of the two groups. For example we were not able to control for possible drug-drug interactions because of the limitation of the data. If this unobserved characteristic is positively correlated with inappropriate medication use and additional expenditures, then the impact of high expenditures on PIM is probably confounded by drug-drug interactions.

In order to reduce the selection bias, we introduced a wash out period and matching method to estimate the expenditures attributable to patients on PIM, on the other hand, we also decrease the generalizablity to interpret our result. We should interpret the result with great caution. Holding all other conditions equal, we estimate that the median annual expenditures attributable to inappropriate medication use among the non institutional elderly population in the U.S. are $1,372 per person, with a 95% confidence interval of $118 to $2,115.

7.4 Conclusion

This study used 2002 explicit criteria to explore the prevalence of inappropriate medication use and examining the association between inappropriate prescriptions use and health care expenditures among the elderly population at a national level. The study identified statistically significant relationship from the use of inappropriate medication to higher total health expenditures, inpatient visit expenditures, outpatient visit expenditures by multiple regression models. The alarming amount of incremental expenditure estimation per year on inappropriate medication use suggests more interventions be done to prevent the use of inappropriate prescriptions in the elderly.

References

Aparasu RR, Mort JR. Prevalence, correlates, and associated outcomes of potentially inappropriate psychotropic use in the community-dwelling elderly. Am J Geriatr Pharmacother 2004; 2:102-111.

Aparasu RR, Mort JR et al. Inappropriate prescribing for the elderly: beers-based review. Ann Pharmacother. 2000; 34 (3): 338-346.

Arnett RH III, Blank LA, Brown AP et al. National health expenditures, 1988:office of National Cost Estimates. Health Care Financ Rev 1990; 11:1-41.

ASHP statement on pharmaceutical care. Am J Hosp Pharm 1993; 50:1720-3

Bates DW, Spell N, Cullen DJ et al. The Costs of Adverse Drug Events in Hospitalized Patients. JAMA 1997; 277:307-311.

Bates DW, Cullen D, Laired N et al. Incidence of Adverse Drug Events and Potential Adverse Drug Events: Implications for Prevention. JAMA 1995; 274:29-34.

Bates DW, Leape LL, Petrycki S. Incidence and Preventability of Adverse Drug Events in Hospitalized Adults. J Gen Intern Med. 1993; 8:289-294

Bates DW. Frequency, consequences and Prevention of Adverse Drug Events. J Qual Clin Prac 1999; 19:13-17.

Beers MH, Ouslander JG et al. Explicit criteria for determining inappropriate medication use in nursing home residents. Arch Intern Med 1991; 151:1825-1832.

Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly: an update. Arch intern Med 1997; 157: 1531-1536.

Bootman JL, Harrison DL, Cox E. The Health Care Cost of Drug-Related Morbidity and Mortality in Nursing Facilities. Arch Intern Med 1997; 157:2089-2096

Cateruno JM, Emond JA, Camargo CA. Inappropriate Medication Administration to the Acutely Ill Elderly: A Nationwide Emergency Department Study, 1992-2000. JAGS 2004; 52:1847-1855.

Col N, Fanale JE, Kronholm P. The Role of Medication Noncompliance and Adverse Drug Reactions in Hospitalizations of the Elderly. Arch Intern Med 1990; 150:841-845.

Cook EF, Goldman L. 'Asymmetric stratification: An outline for an efficient method for controlling confounding in cohort studies', American Journal of Epidemiology,1988;127:626-639.

Cooper JW. Probable adverse drug reactions in a rural geriatric nursing home population: A four-year study. J Am Geriatr Soc. 1996; 44:194-197.

Curtis LH, Ostbye T, Sendersky V et al. Inappropriate Prescribing for Elderly Americans in a Large Outpatient Population. Arch Intern Med 2004; 164:1621-1625.

D'Agostino RB Tutorial in biostatistics propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Statist Med 1998; 17:2265-81.

Dennehy CE, Kishi DT et al. Drug Related Illness in Emergency Department Patients. Am J Health Syst Pharm 1996; 53:1422-1426.

Ferguson JA. Patient age as a factor in drug prescribing practices. Can J Ageing 1990; 9:278-95.

FDA Center for Drug Evaluation and Research, http://www.fda.gov/cder/.

Fick DM, Waller JL, Maclean JR et al. Potentially Inappropriate Mediation Use in a Medicare Managed care Population: Association with higher Costs and utilizations. JMCP 2001; 7:407-413.

Fick DM, Cooper JW, Wade WE, et al Updating the Beers Criteria for Potentially inappropriate Medication Use in older Adults: Results of a US consensus Panel of Experts. Arch Intern Med 2003; 163:2716-2724.

Fiebach NH, Cook EF, Lee TH et al. Outcomes in patients with myocardial infarction who are initially admitted to stepdown units:data from the multicenter chest pain study. American Journal of Medicine 1990;89:15-20.

FU AZ, Liu GG, Christensen DB. Inappropriate Medication Use and Health Outcomes in the Elderly. JAGS 2004; 52:1934-1939.

Goulding MR. Inappropriate Medication Prescribing for Elderly Ambulatory Care Patients.Arch Intern Med 2004; 164:305-312.

Gray SL, Hedrick SC et al. Potentially Inappropriate Medication Use in Community Residential Care Facilities. Ann Pharmacother 2003; 37:988-993.

Hanlon JT, Schmader KE, Koronkowski MJ, and et al. Adverse drug events in high-risk older outpatients. J Am Geriatr Soc 1997; 45: 945-948.

Hanlon JT, Schmader KE, Ruby CM et al. Suboptimal prescribing in older inpatients and outpatients. J AM Geriatr Soc. 2001; 49:200-209.

Hanlon JT, Artz MB, Pieper CF et al. Inappropriate Medication Use Among Frail Elderly Inpatients. Ann Pharmacother 2004; 38:9-14.

Helper CD, Strand LM. Opportunities and Responsibilities in Pharmaceutical Care. Am J Hosp Pharm 1990; 47:533-543.

Huang B, Bachmann KA, He X et al. Inappropriate Prescriptions for the Aging Population of the United States: an Analysis of the National Ambulatory Medical Care Survey, 1997. Pharmacoepidemiology and Drug Safety 2002; 11:127-134.

Jiang JZ, Franic D. Relationship between Quality of Life and Inappropriate Drug Use: A Retrospective Analysis in an Elderly Population, poster will be presented at ISPOR 10th Annual International Meeting, Washington DC, May 15-18, 2005.

Johnson JA, Bootman L. Drug-Related Morbidity and Mortality A Cost-of-Illness Model. Arch Intern Med. 1995; 155:1949-1956.

Kohn L, Corrigan K, Donaldson M. To Err is Human: Building a Safer Heath System. Wahsington, DC: Institute of Medicine, Naitonal Academy Press; 2000

Lau DT, Kasper JD, Potter DE et al. Potentially Inappropriate Medication Prescriptions Among Elderly Nursing Home Residents: Their Scope and Associated Resident and Facility Characteristics. Health Serv Res 2004; 39:1257-1276.

Lau DT, Kasper JD, Potter DE et al. Hospitalization and Death Associated with Potentiallly Inappropriate Medication Prescriptions Among Elderly Nursing Home Residents. Arch Intern Med 2005; 165:68-74.

Lavori PW, Keller MB. Improving the aggregate performance of psychiatric diagnostic methods when not all subjects receive the standard test. Statist Med 1988; 7:723-737

Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 1998; 279:1200-1205.

Lindley CM, Tulley MP et al. Inappropriate medication use is a major cause of adverse drug reactions in the elderly. Age ageing 1992; 21:294-300.

Liu GG, Christensen DB. The Continuing Challenge of Inappropriate Prescribing in the Elderly: An Update of the Evidence. J Am Pharm Assoc 2002; 42:847-857.

Mahoney JM, Miller SW, Phillipa CR. Impact of an adverse drug reaction reporting system in a geriatric health care center. Consultant Pharm 1991; 6:907-14.

Martin BC, Ganguly R. http://www.rx.uga.edu/main/home/cas/faculty/propensity.pdf

Martin U and George CF. Adverse drug reactions in the elderly: Drug therapy in old age. George CF (ed.) JON WILEY& SONS: NY, 2000, 73-86.

Montamat SC, Cusack BJ, Vestal RE. Management of drug therapy in the elderly. N Engl J Med 1989; 321:303-309.

Motheral B, Brook J, Clark MA et al. A checklist for retrospective database studies-report of the ISPOR task force on retrospective databases. Value In Health 2003; 6:90-97.

Patel P, Zed PJ. Drug-Related visits to Emergency Department: How Big is the Problem? Pharmacotherapy 2002; 22:915-923.

Perri M, Menon AM, Deshpande AD et al. Adverse Outcomes Associated with Inappropriate Drug Use in Nursing Homes. Ann Pharmacother 2005; 39:405-11

Perry DP. When Medicine Hurts Instead of Helps. Consultant Pharmacist 1999; 14:1326-30.

Rathore SS, Mehhta SS et al. Prescription medication use in older Americans: a national report card on prescribing. Family Medicine 30(10):733-9.

Schmader K, Hanlon JT, Weinberger M, and et al. Appropriateness of medication prescribing in ambulatory elderly patients. J Am Geriatr Soc 1994; 42:1241-1247.

Senst BL, Achusim LE, Genest RP, et al. Practical Approach to Determining costs and frequency of Adverse Drug Events in a Health Care Network. Am J Health Syst Pharm.2001; 58:1126-1132.

Sloane PD, Zimmerman S, Brown L et al. Inappropriate Medication Prescribing in Residential Care/Assisted Living Facilities. JAGS 2002; 50:1001-1011.

Soumerai SB, Ross-Degnan D. Inadequate prescription-drug coverage for Medicare enrollees—a call to action. [erratum appears in N Engl J Med 1999 Mar 25;340(12):976]. New Engl J Med 340(9):722-8.

Strand LM, Morley PC, Cipolle RJ, et al. Drug-related problems:their structure and function. DICP 1990; 24:1073-7.

Stuart B, Kamal-Bahl S, Briesacher B et al. Trends in the prescription of inappropriate Drugs for the Elderly between 1995 and 1999. Am J Geriatr Pharmacother 2003; 1:61-74.

Stuck AE, Beer MH. Steiner A, and et al. Inappropriate medication use in community-residing older persons. Arch intern Med 1994; 154:2195-2200.

APPENDICES

AppendixA: Inappropriate Medications for Nursing Home Elderly (Beers, 1991)

Drugs should be avoided	Drugs with specific dose and duration
Sedative-hypnotics	
Long-acting benzodiazepines	Short-acting benzodiazepines nightly >4wk
Chlordiazepoxide	Alprazolam
Diazepam	Oxazepam single dose>30mg
Flurazepam	Triazolam single dose>0.25mg
Meprobamate	
Short-duration barbiturates	Antipsychotics
Pentobarbital	Haloperidol >3mg/d
Secobarbital	Thioridazine >30mg/d
Antidepressants	
Amitriptyline	
Antihypertensives	Antihypertensives
Methyldopa	Hydrochlorothiazide >50mg/d
Propranolol	
Reserpine	
NSAIDs and analgesics	Histamine2 blockers
Indomethacin	Cimetidine >900mg & >12wk
Phenylbutazone	Ranitidine >300mg & >12wk
Propoxyphene	
Pentazocine	
Oral Hypoglycemics	Antibiotics
Chlorpropamide	Oral antibiotics >4wk
Dementia treatments	
Cyclandelate	
Isoxsuprine	Decongestants Daily >2 wk
Platelet inhibitors	Oxymetazoline
Dipyridamole	Phenylephrine
Muscle relaxants-antispasmodics	Pseudoephedrine
Cyclobenzaprine	
Orphenidrate	
Methocarbamol	Iron >325mg/d
Carisoprodol	
Antiemetics	
Trimethobenzamide	GI antispasmodics Long-term

Appendix B: Beers Criteria Drug List: Independent of Diagnosis (Beers, 1997)

Prescription classes or individual agents	Reasons of concern for elderly	Severity
Analgesics		
NSAIDs		
Phenylbutazone	May produce serious hematological side effects.	Low
Indomethacin	Produce the most central nervous system side effects.	Low
Narcotics		
Propoxyphene and combination products	Cause central nervous system side effects.	Low
Pentazocine	Cause more central nervous system side effects.	High
Meperidine	Have many disadvantages to other narcotics.	High
Dementia treatment		
Ergot mesyloids, cyclospasmol	Not effective in the doses studied.	Low
Sedative or hypnotic agents		
All barbituates except Phenobarbital	Cause more side effects than other drugs and addictive.	High
Meprobamate	Highly addictive and sedating anxiolytic.	High
Antiemetics		
Trimethobenzamide	Least effective and cause extrapyramidal side effects.	Low
Benzodiazepine hypnotics		
Flurazepam	Extremely long half-life in the elderly, producing prolonged sedation and increasing the incidence of falls and fractures.	High
Chlordiazepoxide and Diazepam		High
Hypoglycemic agents		
Chlorpropamide	Cause SIADH. Its prolonged half-life can cause prolonged and serious hypoglycemia.	High
Antiarrhythmic drugs		
Disopyramide	Strongly anticholinergic. Most potent negative inotrope and may induce heart failure in the elderly.	High
Antidepressants		
Doxepin	Strong anticholinergic and sedating.	High
Amitriptyline	Strong anticholinergic and sedating.	High
Antihypertensives		
Methyldopa	May cause bradycardia and exacerbate depression.	High
Reserpine	Induce depression, impotence, sedation, orthostatic hypotension.	Low
Antihistamines		
Diphenhydramine	Potently anticholinergic properties.	Low
Chlorpheniramine, diphenhydramine, hydroxyzine, cyproheptadine, promethazine, tripelennamine, dexchlorpheniramine	Potently anticholinergic properties.	Low
Platelet inhibitors		
Ticlopidine	Considerably more toxic. Aspirin is better alternative.	High
Dipyridamole	Cause orthostatic hypotension in the elderly.	Low

Appendix B: (Continued)

Prescription classes or individual agents	Reasons of concern for elderly	Severity
Gastrointestinal antispasmodic drugs Dicyclomine, hyoscyamine, propantheline, belladonna alkaloids	Highly anticholinergic and produce substantial toxic effects. Effective doses tolerated by the elderly is questionable.	High
Muscle relaxants and antispasmodic drugs Methocarbamol, carisoprodol, oxybutynin, chlorzoxazone, metaxalone, cyclobenzaprine	Poorly tolerated, leading to anticholinergic side effects, sedation, weakness. Effective doses tolerated by the elderly is questionable.	Low
Benzodiazepines Lorazepam (if exceed 3 mg daily) Oxazepam (if exceed 60 mg daily) Alprazolam (if exceed 2 mg daily) Temazepam (if exceed 15 mg daily) Zolpidem (if exceed 5 mg daily) Triazolam (if exceed 0.25 mg daily)	Because of increased sensitivity to benzodiazepines in the elderly, smaller doses may be effective as well as safer. Total daily doses should rarely exceed the following suggested maximums.	Low
Digoxin (if exceed 0.125 mg daily)	Because of decreased renal clearance, doses should rarely the suggested maximum daily.	High
Iron supplements (if exceed 325 mg daily)	When doses are higher, total absorption is not substantially increased, but constipation is more likely to occur.	Low

Note: NSAID = Nonsteroidal anti-inflammatory drugs. SIADH = Syndrome of inappropriate antidiuretic hormone.

Appendix C:
Summary of Changes in 2002 Explicit Criteria List from 1997 Beers Criteria: Independent of Diagnosis (Fick et al, 2003)

Medicines Modified from 1997 Beers Criteria	
1.Reserpine	3. Iron supplements>325 mg
2.Extended-release oxybutynin	4. Short-acting dipyridamole
Medicines Dropped from 1997 Beers Criteria	
Phenylbutazone	
Medicines Added in 2002 Criteria	
1.Ketorolac tromethamine	15.Desiccated thyroid
2.Orphenadrine	16.Ferrous sulfate>325mg
3.Guanethidine	17.Amphetamines
4.Guanadrel	18.Thioridazine
5.Cyclandelate	19.Short-acting nifedipine
6.Isoxsuprine	20.Daily fluoxetine
7.Nitrofurantoin	21.Stimulant laxatives may exacerbate bowel dysfunction
8.Doxazosin	22.Amiodarone
9.Methyltestosterone	23.Non-COX-selective NSAIDs
10.Mesoridazine	24.Reserpine doses >0.25
11.Clonidine	25.Estrogens in older women
12.Mineral oil	
13.Cimetidine	
14.Ethacrynic acid	