INNOVATIONS IN PHARMACOLOGICAL TREATMENT OF MAJOR DEPRESSIVE DISORDER AND ASSOCIATED PATIENT OUTCOMES

by

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Dedicated to My Parents

for their love and unwavering support

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ABSTRACT

The overarching topic of this research was to study the adoption and utilization of innovative antidepressants and its associations with patient labor market participation and health outcomes. The differences in adoption across patient and physician characteristics, geographic regions, insurance status, and other related factors in the United States needed further studies. The adoption of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) is characterized by the prescription volume and reflected in physician's adherence to practice guidelines and patient's adherence to SSRI/SNRI medications. Therefore, the objective of this research was to try to understand the pattern of prescribing and use of SSRI/SNRI medications for patients with major depressive disorder (MDD) and the process of its adoption, and patients adherence to these medications. In addition, patient outcomes such as employment duration and quality of life associated with the use of SSRI/SNRI antidepressants were studied as well.

This research used the 1993-2007 National Ambulatory Medical Care Survey (NAMCS) and the 2000-2007 Medical Expenditure Panel Survey (MEPS), two national surveys, to explore these research objectives. A two-stage Heckman selection model along with multinomial logistic regression models were used to capture the two-stage nature of SSRI/SNRI prescription and use. In addition, linear regression and two-part models were used to examine MDD patient's medication adherence and associated health

care expenditures. Finally, proportional hazard duration models were implemented to explore antidepressant use and MDD patient's labor market participation, and linear regression models were used to examine associated quality of life of MDD patients.

We observed an association between sociological factors and physician's innovative antidepressant prescribing patterns. Differences in antidepressant adherence and health care spending across patient factors were revealed as well. In addition, patient health status and quality of life varied across patient factors, in which patient utilization of innovative antidepressants were found to have positive associations with patient mental health status.

Differences in antidepressant adherence and health care spending across patient factors could have important policy implications for drug formularies and reduction of health disparities. Effective policy interventions are needed for improving patient medication adherence and physician adherence to practice guidelines, and accommodating patient factors. Tailoring drug formularies and prescription drug benefit design within health insurance and adjusting patient payment schemes for antidepressants are strongly suggested based on this research.

CHAPTER 1

INTRODUCTION

1.1 Study Rationale

Prevalence and Pathogenesis of MDD

Mental health conditions are common not only in the United States but also in many developed countries. Estimation in recent research shows that 26.2 percent of Americans ages 18 and older suffer from a diagnosable mental disorder in a given year.[1] Among mental disorders, major depressive disorder (MDD) is attributed as the leading cause of disability in the U.S. for ages 15-44, and affects 6.7 percent of the U.S. population age 18 and older in a given year.[2]

MDD is regarded as both an acute and a chronic disease. Epidemiologic research shows the lifetime prevalence rate is between ten to twenty percent.[3, 4] According to the National Comorbidity Survey, the lifetime and annual prevalence of MDD are 17.1 percent and 10.3 percent, respectively.[5] In addition, the degree of relapse and reoccurrence is likely to be high for MDD patients and requires well maintenance, for example, with psychotropic drugs. MDD patients are also recommended long-term maintenance treatment to prevent recurrence or the emergency of a new episode of depression.[6-10] MDD is therefore regarded as a chronic disease to some extent,[3, 11] and antidepressant medication may be needed in a longer term. With the nature of being both

acute and chronic disease, a person with untreated or poorly treated MDD cannot function well for his/her daily, business and social activities.

Depression in general causes economic and social burden. In research conducted by Greenberg et al. in 1993; the authors found the total cost of depression in 1990 was $43.7 billion with $12.4 billion in direct costs, $23.8 billion in excess absenteeism and productivity loss, and $7.5 billion in suicide-related earning losses.[12]

Although depression is categorized as a mental disorder, there is neurological evidence that shows depression is associated with neurotransmitter imbalance in a person's brain. Neurotransmitters such as serotonin, norepinephrine, adrenaline and dopamine are all associated with depression. Among these chemicals, the principal neurotransmitter associated with depression is serotonin. Based on this neurological evidence, current antidepressant medications attempt to correct the imbalance of neurotransmitters. Such neurological findings essentially provide significant evidence to emphasize and support why pharmacotherapy plays an important role in treating depression although psychotherapy has been recognized as important as antidepressant medication in MDD treatment.

Increase of Medication Utilization to Treat Mental Disorders

Traditionally, most patients with mental disorders were treated by psychotherapy but as time has passed, the pharmaceutical industry has provided new psychotropic drugs for the patients with mental disorders. These new drugs are playing an increasing central role in the treatment of mental disorders. There are 5.5 million more Americans receiving treatment for mental health and substance abuse in 2001, than in 1996, and the percentage

using psychotropic drugs has increased.[13] As a result, the cost of these drugs is a rapidly increasing component of mental health care expenditures. The psychotropic drug utilization and spending has been enhanced, and there has been a shift of treatment from psychotherapy to pharmacotherapy for mental disorders. For example, the rate of outpatient treatment for depression increased from 0.73% in 1987 to 2.33% in 1997.[14]

Although treatment of mental disorders has shifted towards pharmacotherapy, in fact some psychotherapy can significantly reduce symptoms of mental disorders. The effectiveness of psychotherapy for depression is evidenced by randomized control trials.[14] To show the increasingly important role of pharmacotherapy, recent literature presents a number of possible reasons why psychotropic drug utilization has increased for treating mental disorders. Factors such as gains in efficacy and effectiveness of newer products, expanding prescription drug insurance coverage, incentives that promote prescriptions, direct-to-consumer advertising, and expanding public acceptance of drugs to treat mental disorders have contributed to the increased use of pharmacological interventions.[15-17] These factors are discussed in the following paragraphs.

First of all, efficiency and efficacy gains may increase medication utilization. While many new medication therapies have been introduced, treatments gain more and more efficiency and efficacy; pharmaceutical advances have kept patients from hospitalization and institutionalization. Expenditures for prescription drugs in the U.S. was $200.7 billion in 2005, which is about five times more than the $40.3 billion spent in 1990.[18] Meanwhile, prescription drug coverage in health insurance has been expanded. In particular, the Medicare Modernization Act of 2003, which covers prescription drugs for Medicare enrollees from January 2006. Theoretically, expansion of prescription drug

coverage is likely to raise patients' utilization of medications because patients with such coverage face lower out-of-pocket costs.

Second, the managed behavioral health carve-outs (MBHC), a special HMO design for mental health insurance, have increased the use of pharmacotherapy for patients with mental disorders. The rationale of carving out mental health services from HMO coverage is because of the high expenditure for treating mental disorders and substance abuse, and HMOs gain economic scale and efficiency by specializing mental services in MBHC institutions. The MBHCs usually do not cover prescription drugs for mental disorders. As a result, psychotropic drugs for the MBHC is a "free input" for the MBHCs and therefore mental health specialists are more likely to prescribe drugs than give patients referrals to psychotherapists.[16] This is a possible reason for the increased utilization of psychotropic drugs.

Third, direct-to-consumer advertising (DTCA) also accounts for part of the increase of drug utilization. Expenditure for DTCA in 2005 was over five times the amount spent in 1996.[18] DTCA enhances patients' perceptions of medications as a treatment for mental disorders and may bias patients' perceptions that medications are the only effective treatment. Patients may even actively ask for pharmacotherapy from their doctors.

In addition, demographic factors such as gender, ethnicity, age and education may affect a patient's decision on taking pharmacotherapy as well. There is a greater tendency for female patients to receive psychotropic drugs.[19-21] In particular, gender is a positive and significant predictor of use of antidepressant medications when all other factors are controlled.[21] In terms of ethnicity, there is a distinct lower rate of pharmacological

treatment (including stimulants, antidepressants, antipsychotics, benzodiazepines, and lithium) for patients with mental illness who are African-Americans,[22] which may be interlinked with patients' psychosocial factors such as socioeconomic status, health beliefs, and health disparities.

Use and Adoption of SSRI/SNRI Medication for MDD Treatment

As Prozac™ (fluoxetine Hcl), the first selective serotonin reuptake inhibitors (SSRI) antidepressant, was introduced in 1988, SSRIs have become the major and preferable medication treatment for MDD patients. SSRIs, compared to old generation antidepressants, have a unique treatment mechanism which selectively increases the level of serotonin.[23] SSRIs were soon adopted by physicians and patients because of their innovative mechanism of action and superior efficacy. The adoption of SSRIs is not only characterized by their relative prescription volume, but is also reflected in physician's adherence to practice guidelines and patient's adherence on SSRI medications. In mid-1990, serotonin-norepinephrine reuptake inhibitor (SNRI), another innovative class of antidepressants, was introduced to treat MDD. Unlike SSRIs which act more selectively upon serotonin, SNRI increases both serotonin and norepinephrine to treat MDD. SNRIs have also been widely adopted by physicians as a prescription for MDD treatment recently.

SSRIs/SNRIs have been widely adopted by physicians; however the differences and trend in adoption of innovative SSRI/SNRI antidepressants across patient's and physician's characteristics, geographic regions, insurance status, and other related factors needs more research. Although previous studies have investigated the influences of

sociological factors on patient mental healthcare utilization, there was a lack of either consideration of antidepressant medication choice or physician characteristics, or the study period was relatively short and old.[24-28] Understanding how sociological factors influence physician prescribing decision on antidepressants and patient medication utilization for MDD treatment could complement previous study results and have important implications for mental health policy especially for several specific groups whose mental disorders are undertreated. This study could help policy makers identify sources of variation in mental healthcare while reducing undertreatment. The aforementioned points motivated this research to explore the adoption of SSRIs/SNRIs for MDD treatment in terms of physician prescribing, patient antidepressant adherence, and associated patient outcomes which were three main research interests for this study.

1.2 Study Objectives and Hypotheses

As mentioned in the previous section, the differences in adoption across patient's and physician's characteristics, geographic regions, insurance status, and other related factors needs more research. Besides, the adoption of SSRIs/SNRIs is characterized by the prescription volume and reflected in physician's adherence to practice guidelines and patient's adherence to SSRI/SNRI medications. Therefore, the overarching objective of this research was to try to understand the pattern of prescribing and use of SSRI/SNRI medication for MDD patients and the process of its adoption, and patients adherence to these medications. In addition, patient outcomes such as employment duration and quality of life associated with the use of SSRI/SNRI antidepressants were studied as well. There were three interlocked specific objectives and their corresponding research

hypotheses of this research which are shown as follows. These hypotheses were formed based on previous literature which will be discussed in Chapter 2. These three study objectives and corresponding research hypotheses are:

Objective 1: To disentangle the patterns and dynamics of adoption of SSRI/SNRI medications in MDD patients over time. (Addressed in manuscript 1)

Hypothesis 1: Physician characteristics, patient characteristics, the physician's relationship with the health care system, and the physician's relationship with the patient have influences on SSRI/SNRI adoption in MDD patients over time.

Objective 2: To understand how sociological factors and antidepressant choice influence medication adherence and associated health care expenditures in patients with MDD. (Addressed in manuscript 2)

Hypothesis 2: Patient predisposing factors, enabling factors, need factors and antidepressant choices have influences on antidepressant adherence in patients with MDD.

Objective 3: To identify patient factors, and antidepressant choice and utilization which may influence MDD patient's quality of life and labor market participation. (Addressed in manuscript 3)

Hypothesis 3: Patient factors and antidepressant choice and utilization may influence MDD patient's quality of life and labor market participation such as duration of employment.

Because of their innovative drug mechanisms, the innovation specifically refers to the introduction of SSRI/SNRI antidepressants in this study.

1.3 Overview of This Study

This research applied health behavior models as conceptual frameworks. Eisenberg model of physician decision making and Anderson model of health care utilization were applied to analyze the adoption of SSRIs/SNRIs, the patterns of physician prescribing and medication choice for MDD patients, and MDD patient medication adherence and associated patient outcomes in the U.S.

This research used the National Ambulatory Medical Care Survey (NAMCS) and the Medical Expenditure Panel Survey (MEPS), two national surveys, to explore the three research objectives. Since the NAMCS and the MEPS are nationally representative datasets, the study results have good generalizability and can help formulate national policies in this area. A two-stage Heckman selection model along with multinomial logistic regression models were used to capture the two-stage nature of SSRI/SNRI prescription and use. In addition, a multiple regression and a two-part regression model were used to examine MDD patient's medication adherence and associated health care expenditures. Finally, semiparametric Cox proportional-hazard models and parametric exponential proportional-hazard models were implemented to discuss antidepressant use and MDD patient's labor market participation, and linear regression models were used to examine associated quality of life of MDD patients.

The results of this study could provide meaningful contributions for U.S. health policy. Understanding the sociological influences on patient, physician and healthcare

system behaviors that may impact the successful treatment of the MDD patient in the U.S., as well as the determinants of medication adoption and the predictors of antidepressant prescribing helps identify demographic, clinical and socioeconomic obstacles to medication adoption, prescribing and utilization, and associated healthcare spending and patient outcomes in the U.S. This study could also help policy makers identify sources of variation in mental healthcare while reducing undertreatment.

CHAPTER 2

LITERATURE REVIEW

2.1 Taxonomy And History of Antidepressants

Both psychotherapy and pharmacotherapy (and other therapies such as electroconvulsive therapy) are common for MDD treatment. However, a treatment shift occurred significantly in treating MDD patients with the introduction of a variety of antidepressant medications for treating MDD, such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) which have been introduced since 1950s, and more recently introduced selective serotonin reuptake inhibitors (SSRIs) since 1980s, and serotonin-norepinephrine reuptake inhibitors (SNRIs) since 1990s. Such antidepressant innovation has changed effectiveness, efficacy and efficiency of therapies for treating MDD. Among medications for treating MDD, Prozac™ (fluoxetine Hcl), the first product of SSRIs, was introduced in 1988 and became widely used for its better efficacy, safety in overdose, better adverse drug event profiles and simplicity of dosing schedules compared to existing antidepressants.[29-33]

The mechanisms of different types of antidepressants vary. The MAOIs eliminates the enzymes which destroy the neurotransmitters to balance the chemical itself, whereas the TCAs and SSRIs directly correct the chemical imbalance in the neurotransmitter. TCAs inhibit the reuptake of serotonin and norepinephrine into a patient's central nervous system whereas SSRIs help prevent the reuptake of serotonin by

a person's secreting cells which release the neurotransmitters. Recent innovations in antidepressant pharmacotherapy include introduction of agents such as the serotonin and norepinephrine reuptake inhibitors (SNRIs) which consist of reuptake inhibitors of other neurotransmitters and of other enzymes' antagonists.[23]

A brief history of antidepressants reveals the evolution of antidepressant innovation and recalls that the innovation of SSRIs was a cornerstone of antidepressant pharmacotherapy.[34] In the late 1950s iproniazid (an MAOI antidepressant) and imipramine (a TCA antidepressant), the first two antidepressants in the world, were introduced. MAOIs were more popular than TCAs when antidepressants were first introduced, but TCAs became more widely used afterwards when more side effects of MAOIs were recognized. Until the drug combinations of TCAs were introduced in the early 1980s, TCA antidepressants had steadily expanded their market share. In 1988, Prozac™ (marketed by Eli Lilly), the first introduced SSRI—a striking innovation of antidepressant arena—was introduced in the market and soon seized a large proportion of the market share. The appearance of Prozac caught public attention for its proclaims of being safer in overdose and less harmful in adverse drug events. The volume of SSRIs prescribed has risen since it was introduced, and thus amounts to around 80% of the $3.5 billion antidepressant market in the U.S. in 1995[35] and has been growing 25% every year.[36] The success of Prozac led to more SSRI products and innovative newer generation antidepressants such as SNRIs in 1990s, which have overwhelmed the antidepressant market ever since.

A summary of the types of antidepressants and their drug mechanisms is shown in the following Table 2.1 on the next page. There are several widely used antidepressants

including bupropion, mirtazapine, nefazodone, selegiline, and trazodone, which do not share common drug mechanisms and therefore do not belong to any of these categories.

Table 2.1 Taxonomy of antidepressants

Classification	Type of Antidepressant	Year of Introduction	Examples	Mechanism
Older Antidepressants	Tricyclic antidepressants (TCAs)	Late 1950's	Anafranil™ (clomipramine), Elavil ™ (amitriptyline)	Inhibits reuptake of serotonin and norepinephrine into central nervous system
	Monoamine oxidase inhibitors (MAOIs)	Late 1950's	Marplan ™ (isocarboxazid), Nardil ™ (phenelzine)	Eliminates enzymes which destroy the neurotransmitters to balance the chemical
Newer Innovative Antidepressants	Selective serotonin reuptake inhibitors (SSRIs)	1988	Prozac ™ (fluoxetine), Paxil ™ (paroxetine), Zoloft ™ (sertraline)	Selectively prevents reuptake of serotonin by secreting cells releasing neurotransmitters
	Serotonin and norepinephrine reuptake inhibitors (SNRIs)	1990's	Cymbalta ™ (duloxetine), Effexor ™ (venlafaxine)	Consists of reuptake inhibitors of other neurotransmitters and of antagonists of other enzymes

Source: compiled by this study

For operational purposes, the categorization of antidepressant throughout this study was according to drug mechanisms as well as years of their introduction, which was different from the categorization revealed in Table 2.1. The detailed operational categorization of antidepressants for this study will be described in the following chapter.

2.2 Use And Adoption of SSRIs/SNRIs to Treat MDD

Among all types of antidepressants, the MDD practice guidelines from the American Psychiatric Association (APA) and the Agency for Health Care Policy and Research (AHCPR, i.e. the former Agency for Healthcare Research and Quality, AHRQ) recommend using SSRIs to treat mild to severe MDD patients in several major circumstances, which implies SSRIs are widely accepted by psychiatrists and their efficacy is evidenced by rigorous clinical trials.[6-8]

SSRIs have become widely used for their better efficacy, safety in overdose, better adverse drug event profiles and simplicity of dosing schedules. However, there is one disadvantage of utilizing SSRIs to treat MDD: it is higher-priced for patients to obtain SSRI antidepressants compared to older antidepressants. However, a study done by Frank and colleagues shows that using SSRIs to treat depression may either reduce the overall health care spending or keep the total spending the same.[30]

Because SNRIs were developed recently, there is a lack of abundant systematic research studying SNRIs' efficacy and side effect profiles compared to other types antidepressants. A recent study done by Sheehan and colleagues shows SNRIs yield higher remission rates than placebos for patient with MDD; however SNRIs do not show better remission rates compared to SSRIs.[37] However, physicians have been widely adopting SNRIs to treat MDD patients for their "double-acting" mechanisms upon both serotonin and norepinephrine.[23]

As mentioned in the previous chapter, the innovation refers to the introduction of SSRI/SNRI antidepressants in this study. Although the use of SSRIs/SNRIs has been obviously increased, differences in their adoption across patient and physician

characteristics, geographic regions and insurance status needs to be further studied. Differences of SSRI/SNRI adoption could have important policy implications for drug formularies; sociological factors which may influence physician prescribing and patient use of SSRI/SNRI therefore need to be further examined and disentangled. In particular in the U.S., because of the existence of managed care, the high volume of uninsured people, and the elevating costs of pharmaceuticals, sociological factors such as patient health insurance status could impact physician prescribing behaviors. Although previous studies have investigated the influences of sociological factors on patient mental healthcare utilization, they was a lack of either consideration of antidepressant medication choice or physician characteristics, or the study period was relatively short and old.[24-28] Understanding how sociological factors influence physician prescribing decision on antidepressants for MDD treatment could complement previous study results and have important implications for mental health policy especially for several specific groups whose mental disorders are undertreated. This study could help policy makers identify sources of variation in mental healthcare while reducing undertreatment. Therefore, the first objective of this research was trying to disentangle the pattern of adoption of SSRIs/SNRIs and the patterns of medication choice for MDD treatment.

People in different research fields including economists, marketing researchers, and health services researchers are concerned about antidepressant adoption and diffusion for either marketing or policy making purposes. Previous health services research shows there are several factors influencing patient's tendency to receive antidepressants. Women, older patients and patients with white race are more likely to receive antidepressants.[21, 38, 39] In addition, people with higher education level and patients who

visit psychiatrists (rather than primary care physicians) are more likely to receive antidepressants.[20, 38] Among these studies, a study conducted by Sleath and Shih used the Heckman two-step selection model to examine people's treatment choices between SSRIs and non-SSRIs.[28] Their research results showed that patient characteristics, physicians characteristics, the physician's interaction with the health care system, and the physician's interaction with the patient all influenced antidepressant prescribing on SSRI or non-SSRI medications. Sleath and Shih's methodology was elegant but they used relatively old (1998) one-year cross-sectional data; therefore using more updated and long-term data would benefit the understanding of patient treatment choices and further as well as capture the dynamics related to prescribing.[40, 41]

Economists and marketing researchers studied antidepressant diffusion for social welfare analysis, drug pricing and cost-effectiveness from the pharmaceutical company's perspective. A study conducted by Berndt and colleagues used U.S. sales, price, quantity and marketing data taken from the IMS Health and found that total antidepressant sales were positively and significantly related to price reduction, increased marketing efforts, and the level and variety of side effect profiles involving antidepressants.[42] The authors argued that there were significant societal benefits to antidepressant innovations because there were a variety of antidepressants available on the market for patients with different depression conditions and acceptability for antidepressant medications.[42] In other words, an increase in product variety could facilitate the match between a particular patient and a specific antidepressant medication. These findings from this marketing perspective were valuable; however how physicians and patients make their treatment choices was not

disentangled in this study. Therefore, this study could provide complement perspectives to the aforementioned previous findings.

2.3 Antidepressant Medication Adherence

Adherence, to some extent has the same meaning as compliance, is defined as patients taking the correct dose during the proper time interval for the appropriate time period.[43] Although SSRIs are widely accepted and used, it is however that, medication treatment adherence in patients with mental illness is generally low as discussed more in depth in later paragraphs. Even effective medications cannot improve patients' mental health status without good medication adherence. In addition, it has been widely reported that medication non-adherence is highly associated with adverse health conditions which increases economic burden on the healthcare system.[44-46] Previous research shows major differences in medication adherence among various antidepressants, which are primarily attributed to intolerability of side effects and dosing inconvenience.[47, 48] As a result, antidepressant choice and adherence are two closely interlinked issues and dimensions of antidepressant utilization which were jointly explored in this study.

Adherence to pharmacotherapy is influenced by patients, providers and the social environment; there are several factors which may affect patient medication adherence. Specifically, patient demographics such as ethnicity, socioeconomic status and levels of education have been reported to be associated with medication adherence.[49, 50] Moreover, patient's psychological factors, such as health beliefs, perceived seriousness of illnesses, are also associated with patient's medication adherence.[51, 52] Systematic factors, such as patient's health insurance status and access to health care, affect medication adherence as

well.[44, 49] Therapy-related factors, such as the number of medications, dosing frequency, administration schedule, complexity of treatment regimen, side effects, and cost of medication, contribute substantially to patient's medication adherence.[49] These therapy-related factors are in turn associated with physician factors; different pharmacotherapies may be prescribed by different physicians with different specialties, HMO status, ownership status, and geographic regions of practice. Therefore, understanding a physician's clinical decision making in prescribing pharmacotherapy plays an important role in disentangling the complexity of patient's medication adherence behaviors.

Broadly speaking, pharmacotherapy for mental disorders can be categorized into antidepressants and antipsychotics. Research has shown poor medication adherence to both antidepressants and antipsychotics in patients with mental disorders. It has been shown that early discontinuation of antidepressants is widespread.[53] In particular, 28% to 40% of patients with depression discontinue antidepressant medication, which significantly increases health care expenditures.[54] Besides, reports reveal that rates of non-adherence to antipsychotics range from 20% to 89%, and 50% on average.[55, 56] In other words, research has shown that non-adherence to pharmacotherapy in patients with mental disorders is indeed a serious problem and needs more research. However, previous studies lack for either national representability or consideration for choice of antidepressants, which may be unable to indicate policy implications nationally or target on specific types of antidepressants. In this research, the national representative Medical Expenditure Panel Survey (MEPS) dataset was used for its national generalizability. "Proportion of days covered (PDC)" was adopted to measure medication adherence for different types of antidepressants in this study.

In addition, patient antidepressant adherence could be associated with health care spending. Previous research shows that for some chronic diseases, increased medication utilization may contribute to an economic return driven by better long-term medication adherence.[57] Gilmer and colleagues found that hospital costs were lower whereas pharmacy costs were higher for those patients who were better adherent to their antipsychotic medications than for those who were nonadherent among Medicaid beneficiaries with schizophrenia.[58] Thieda and colleagues also found a similar result that lower rates of medication adherence led to higher costs of treating schizophrenia.[59] As mentioned in previous the chapter, MDD patients are recommended taking long-term maintenance treatment to prevent reoccurrence [6-10] and therefore an economic return associated with better antidepressant adherence is expected. Although the association between antidepressant adherence and related health care spending was explored in MDD treatment, previous studies lacked for the consideration for antidepressant choice and its association with antidepressant medication and related health care expenditure.

As a number of innovative antidepressants have been introduced, the second objective of this research was trying to understand how patient factors and antidepressant choice influenced medication adherence and associated health care expenditures given patient antidepressant choice was considered. Establishing the association between antidepressant choice and antidepressant adherence, and in turn, their associations with related health care expenditures could benefit policy makers to more accurately target on effective adherence-improving strategies.

2.4 Antidepressant Medications and Labor Market Participation

Work is an important aspect of most human beings' lives. For many people, his or her identity is partly composed of their work, and the self-worth, self-perception and satisfaction from it.[60, 60-62] However, health issues, including both physical and mental disorders, interfere with people's work performance which may be likely to reduce people's satisfaction with current work status, health status and quality of life.[63-65] The role of medication is to treat patients' illnesses and in turn, raise their quality of life and work performance. To measure the influences of medications, there are several valid and useful measures developed to assess work outcomes; for example, perceived performance, absence from work, employment status, and productivity at paid work.

The influences of antidepressants on MDD patient's daily life, work performance and quality of care has been researched intensively. Work performance has been measured using psychometric scales and associated absenteeism (i.e. work loss) has been explored as well. Previous research shows significant differences between medication (either older or newer antidepressant) and placebo groups for work performance.[66-70] Studies in Europe in the 1980's show MDD patients treated by SSRIs had lower absenteeism compared to those treated by TCAs, and absenteeism was lower in patients treated by TCAs than those who were untreated.[71, 72] However, these studies are out-of-date and the generalizability is low to Americans, which could not indicate adequate information for the U.S. mental health policy. Although previous studies explored the influences of antidepressants on patient's work outcomes by examining their employment status and work performance, none of them examined patient employment duration. Examining patient's employment duration could indicate how, how likely, and in how

long a patient's job would be terminated, which could bring implications for labor market participation and mental health policy for patients with mental disorders.

Therefore, the third objective of this dissertation was trying to study the influences of innovative antidepressants on patients' employment duration and quality of life. As previous literature concluded that health issues could interfere with people's work performance which may have negative impact on people's quality of life,[63-65] this part of the study analyzed patient employment duration and quality of life as two patient outcomes with MDD treatment. This part of study was done by using the national representative MEPS dataset and analyzed by semiparametric and parametric proportional hazard duration models.

2.5 Theory and Conceptual Framework

This research applied health behavior models as conceptual frameworks to guide the study hypotheses. Eisenberg model of physician decision making was applied to analyze the adoption of SSRIs/SNRIs and patterns of physician prescribing and medication choice for MDD patients in the U.S. Anderson model of health service utilization was applied to examine MDD patient's antidepressant medication adherence and associated health care expenditures. The behavior factors involved in the treatment choice of MDD are stated in the following paragraphs followed by a brief description of these two models.

Behavior Factors Involved in the Treatment Choice of MDD

Before looking into the three models, the behavior factors involved in the treatment choice of MDD are described to address the importance of the psychological and sociological factors. The effective management of patients with mental health issues, especially the MDD patients, is complex and involves a myriad of factors in the choice of treatment. An understanding of these factors benefits healthcare providers and patients to plan and conduct effective treatment strategies. These factors may be clinical, psychological and sociological in nature. Clinical factors include issues such as severity of the patient's condition, the presence of comorbid conditions, the effective use of appropriate psychotherapy or pharmacotherapy agents and the monitoring of the patient's response to therapy as well as other patient outcomes (such as patient satisfaction and overall quality of life).[73-78]

Psychological and sociological factors are also important in the successful management of the MDD patient. Psychological factors may include patient's perception or beliefs of MDD and the treatment of MDD, patient's perception of their overall well-being and disease severity, patient's ability to adhere to therapy, clinician's ability to adopt and follow clinical practice guidelines and the clinician's beliefs and behavior regarding MDD treatment.[79-81] Sociological factors include demographic and sociodemographic variables of the patient, physician and healthcare system that may influence MDD treatment.[16, 18] These factors are under the control of society at large, the patients, the clinicians and the healthcare system. Some of these factors are biologically endowed such as race/ethnicity, gender and age, and are basically not changeable.[76]

There are three elements of MDD treatment that make these psychological and sociological factors play a more important role in MDD treatment. The first element is the fact that in the U.S. healthcare providers and the healthcare system are primarily geared to successfully manage acute medical problems in terms of identifying and aggressively treating the offending condition in the shortest time. However, as mentioned in the previous sections, most of the time MDD is recognized as a chronic disease and may affect an individual throughout their lifetime.[3, 11] Unlike most of other diseases, MDD patients have to self-monitor their disease and be prepared to handle exacerbations of MDD symptoms. In other words, MDD patients have to be geared to successfully manage their illness and interventions that can address both the psychological and sociological influences on patient behavior.[82-84]

Another element of MDD treatment that makes MDD different than other conditions is the fact, as mentioned in previous sections that, there has been a major treatment shift from psychotherapy to pharmacotherapy for patients with mental health conditions.[14] In spite of the number of studies conducted to address this controversy, researchers have not been able to establish relative superiority between these two types of therapies as both are considered effective. For example, DeRubeis and colleagues found that cognitive therapy could be as effective as medication treatment.[85, 86] In addition, a patient's knowledge, perceived risk/benefit, and belief of drugs could potentially influence a patient's attitude toward or against medication treatments. A study by Croghan and colleagues found that patients in the U.S. tend to believe in the effectiveness of psychotropic drugs; however, the preferences of a majority of patients are still against taking drugs for treatment even if they understand their effectiveness.[87] This indicates that

both patients and providers have had difficulty in making the transition totally from the psychotherapy to pharmacotherapy of MDD treatment and it has been recognized that both psychological and sociological factors are strongly implicated in this problem.

Finally, as mentioned in the previous sections, we have seen a tremendous health and economic burden of MDD even with the widespread dissemination of the depression treatment guidelines and also the advances made in the pharmacotherapy of MDD.[12] The growth in the prevalence of MDD in certain population groups may suggest that there are barriers to both the provision of care and the intensity of care provided to these populations. These barriers may be artificial constructs due to psychological and sociological beliefs and behaviors of patients, physicians and the overall healthcare system.[21, 38, 39] It is therefore important to study these factors so that interventions addressing these barriers may be indentified to improve the overall treatment of the MDD patient.

In conclusion, clinical, psychological and sociological factors are all important in the successful treatment for MDD. It is crucial that we have an understanding of the psychological and sociological influences on patient, physician and healthcare system beliefs and behaviors that may impact the adoption of effective, innovative and successful treatment for MDD patients. In this study, because of the limited psychological measures in the NAMCS and the MEPS datasets, the primary focus was on sociological determinants of physician prescribing and patient utilization.

Eisenberg Model of Physician Decision Making

Eisenberg model of physician decision making describes the sociological factors influencing a physician's decision making. This model has been widely used for characterizing a physician's decision making on prescribing treatment and the factors which influence this decision making.[88-90] This model was applied in this study for its comprehensiveness of characterizing the sociological factors which influence a physician's behavior (i.e. adopting and prescribing SSRI/SNRI medications in this study.) A physician's behavior of decision making is influenced and interplayed by four factors: (1) physician characteristics (e.g. age, gender, race, specialty); (2) patient characteristics (e.g. age, gender, race, educational level, insurance status, income); (3) physician's relationship with the health care system (e.g. practice setting, ownership); and (4) physician's relationship with the patient (e.g. patient demand, patient presentation of symptoms).[91] Other studies also emphasized that these factors had important influences on physician prescribing.[92, 93] These four factors which influence physician decision making are illustrated in Figure 2.1 on next page and described as follows.

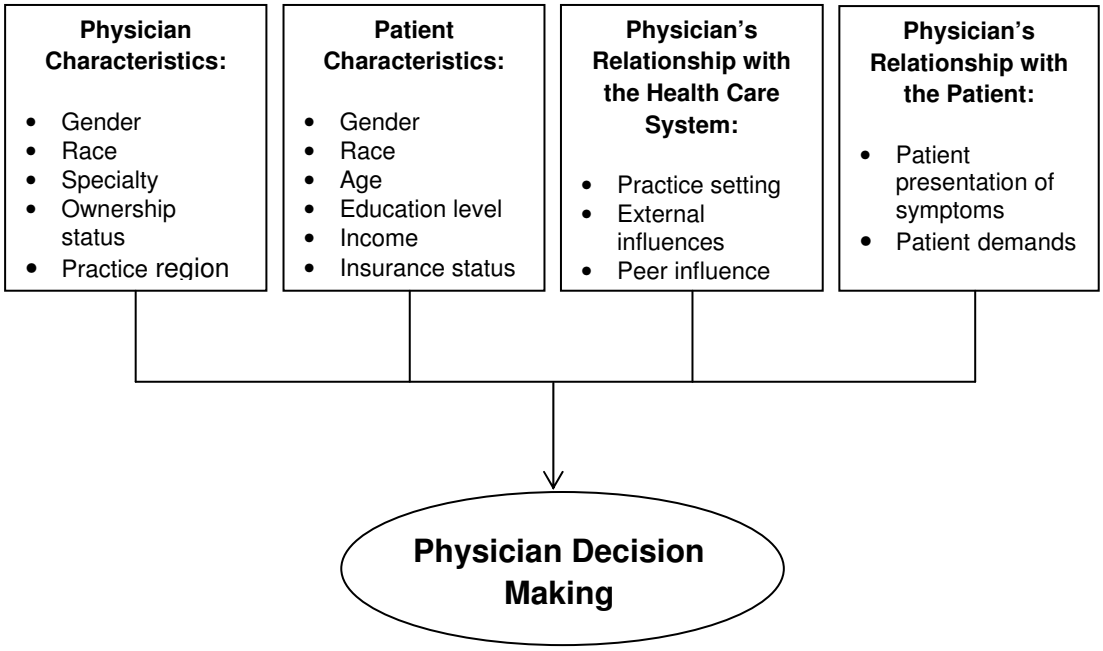

Figure 2.1. Eisenberg model of physician decision making

Physician characteristics: previous research shows that several factors such as physician specialty, age, gender and personality influence physician's prescribing decisions. For example, in a cumulative prospective study conducted by Tamblyn and colleagues with 1,842 study subjects around the U.S., physicians were found to be less likely to prescribe drugs appropriately and order laboratory tests.[88] In addition, Eisenberg pointed out that medical decisions were made relatively slowly in medicine and psychiatry whereas decisions were made more rapidly and with less reflection in surgery.[91] Eisenberg referred to physician characteristics as "physician styles" which were categorized by him as either interventionist or oriented toward health maintenance. He hypothesized that interventionist physicians were more likely to be disease oriented whereas health maintenance oriented physicians were more likely to be patient oriented.[91]

Patient characteristics: patient age, gender, educational level, insurance status and socioeconomic status are shown to influence physician's decision making on diagnosis and treatment as well. For example, patients with lower socioeconomic status are more likely to be recommended for less than optimal care compared with their peers with higher socioeconomic status. This association is revealed, for example, in the retrospective cohort study done by Nirula and colleagues who use data from the 2002-2004 National Trauma Data Bank.[94] In addition, research shows discrepancies in the provision of care as well as the quality of care provided to poor people. Similar discrepancies appear in racial minorities and females. For example, in the cross-sectional study done by Young and colleagues using 1997-1998 data, the authors conclude that appropriate treatment for depressive and anxiety disorders in the U.S. is less likely for

men who are black and less educated.[95] Besides, previous literature shows the impact of a patient's health insurance status on the level of care that the patient receives.[91]

Physician's relationship with the health care system: Eisenberg model proposes that physician practice settings as well as the physician's interaction with other professionals influence physician's decision making.[91] External factors such as advertising, pharmaceutical sales representatives, and regulation influence physician's prescribing behavior. For example, in the descriptive study done by Wilkes and colleagues using the 1989-1998 Intercontinental Medical Statistics (IMS) drug sales data, the authors find that physicians are more likely to adopt new drugs if they practice in a group practice compared to a solo practice.[89] Another study concluded by Leffler, which uses the 1976-1978 IMS data, shows similar results.[89, 90] Eisenberg and Nicklin also use the 1974-1977 Medicaid billing claim data and apply the case mix control method to show that the bureaucratic structure of the organization in which the physician practices can influence the physician's decision making.[96]

Physician's relationship with the patient: a physician's interaction with his/her patients indeed influences the physician's decision making. For example, a patient may reveal his/her demand and describe his/her symptoms using different presentations which may be different from the decision that a physician makes alone. Stewart analyzes 21 articles published from 1983 to 1993 and concludes that most of the studies reviewed demonstrate a correlation between effective physician-patient interaction and a physician's behavior and in turn, improved patient health outcomes.[97] Eisenberg model categorizes the physician-patient relationship into three categories. First, "activity-passivity" captures the relationship that the physician is the controller for the decision

making and the patient just follows the decision. Second, "guidance-cooperation" describes that the physician advices the patient on the decision making and the patient is expected to accept the advice. Finally, "mutual-participation" describes the relationship that the patient is involved in the physician's decision making and the decision is influenced by their interaction.[91]

Eisenberg model provides a good framework to categorize factors that influence a physician's decision making on prescribing SSRI/SNRI medication, and benefits the selection of independent variables for this research. Therefore it was considered a fundamental model for this study's conceptual framework.

Anderson Health Service Utilization Model

The theoretical framework of Objective 2 of this study was based on Anderson health service utilization model. The basic Anderson model consists of predisposing characteristics, enabling resources and need. The predisposing components contain demographic, social structure and health belief variables such as race, ethnicity, gender, health attitudes, values, and genetic factors. The enabling components contain resources available to the individual such as personal income, health insurance, and access to health care. The need refers to professional judgment about people's health status and their need for medical care.[98] Among the above three population components, predisposing characteristics precede enabling components which in turn, precede the need components.

Anderson model provides good insights into patient health behaviors. Although there are different phases of the model, the main message of it is to suggest that an individual's use of health services is a function of their predisposition to use services,

factors which enable or impede use, and their need for care.[98] After several revisions, the latest version of Anderson model further includes environmental and outcomes factors/measures in it, which then comprises structure, process, and outcomes measures as a complete structural model of health behavior. The major components of this complete model are illustrated in Figure 2.3 below and described as follows.

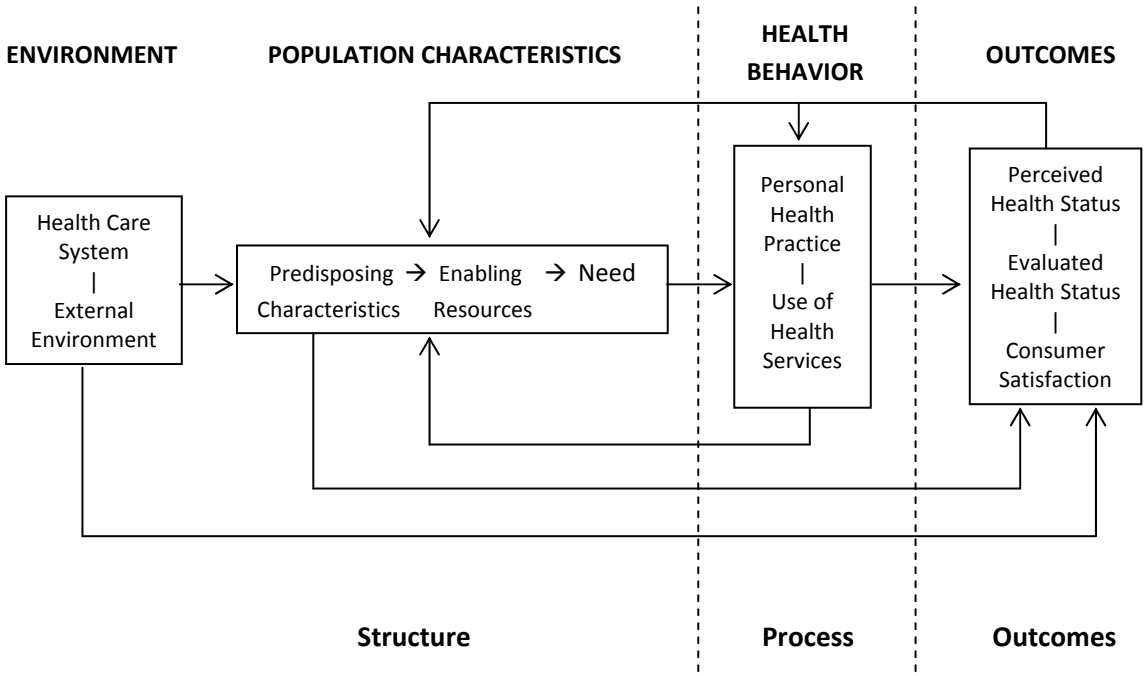

Figure 2.2. The latest version of Anderson model

Source: Anderson (1995)[98]

The "structure" measures in this model consist of population characteristics and environment factors. Population characteristics, which are preceded by health care system and external environment, comprise predisposing characteristics, enabling resources and need. The predisposing components include demographic, social structure and health belief variables such as race, ethnicity, gender, health attitudes, values, and genetic factors. The enabling components include resources available to the individual such as personal income, health insurance, and access to health care. The need refers to professional judgment about people's health status and their need for medical care.[98] Among the above three population components, predisposing characteristics precede enabling components which in turn, precede the need factors.

The structure measures precede the process outcomes. The "process" measure refers to health behavior components, which contains personal health practices and use of services. Such components measure including what type services, which site of services, for what purpose for these services and how long the time interval between services is. The process measures then precede outcomes measures. The "outcomes" measures consist with perceived health status, evaluated health status and consumer satisfaction.

All the aforementioned factors interact to each other. Besides the aforementioned relationship between structure, process and outcomes measures, the structure measures may have direct impacts on outcomes and so do process measures. In addition, outcomes and process measures may feedback on structure measures.

For this study, Anderson model served as a good framework to characterize not only the dependent and independent variables in this study but also their relationship, and thus enabled the study to characterize several important predictors on treatment and labor

market outcomes. For this study, according to Anderson model, the measures of predisposing variables included age, gender, education, and race/ethnicity. The measures of enabling factors included personal annual income and health insurance status. The main need measure was comorbidities and health status. The outcomes measure included patient antidepressant adherence and associated health care expenditure. Among these measures, Anderson model helped characterize the relationship between each and the variables that should be controlled for in this study.

CHAPTER 3

METHODS

This study was a retrospective cross-sectional study which used the NAMCS and the MEPS datasets. The first objective of this study was to disentangle physician's prescribing patterns for innovative antidepressants in MDD patients, using multinomial logistic regression as well as the Heckman two-step selection model. The second objective of this study was to examine the impact of antidepressant choices on medication adherence as well as the associated health care expenditures, using a two-part regression model. The third objective of this study was to examine antidepressant use and its impact on MDD patient's employment duration and quality of life, using the semiparametric Cox proportional-hazard duration model as well as the exponential parametric proportional-hazard model. The NAMCS and the MEPS datasets, study sample eligibility criteria, measures and the econometric models will be introduced in the following paragraphs.

3.1 Conceptual Framework

A Synthesized Conceptual Framework

To capture the physician adoption of SSRI/SNRI antidepressants and patient treatment choices, a synthesized model of Eisenberg model of physician decision making

as well as Anderson healthcare utilization model was proposed as a conceptual framework for this study, which is shown as Figure 3.1.

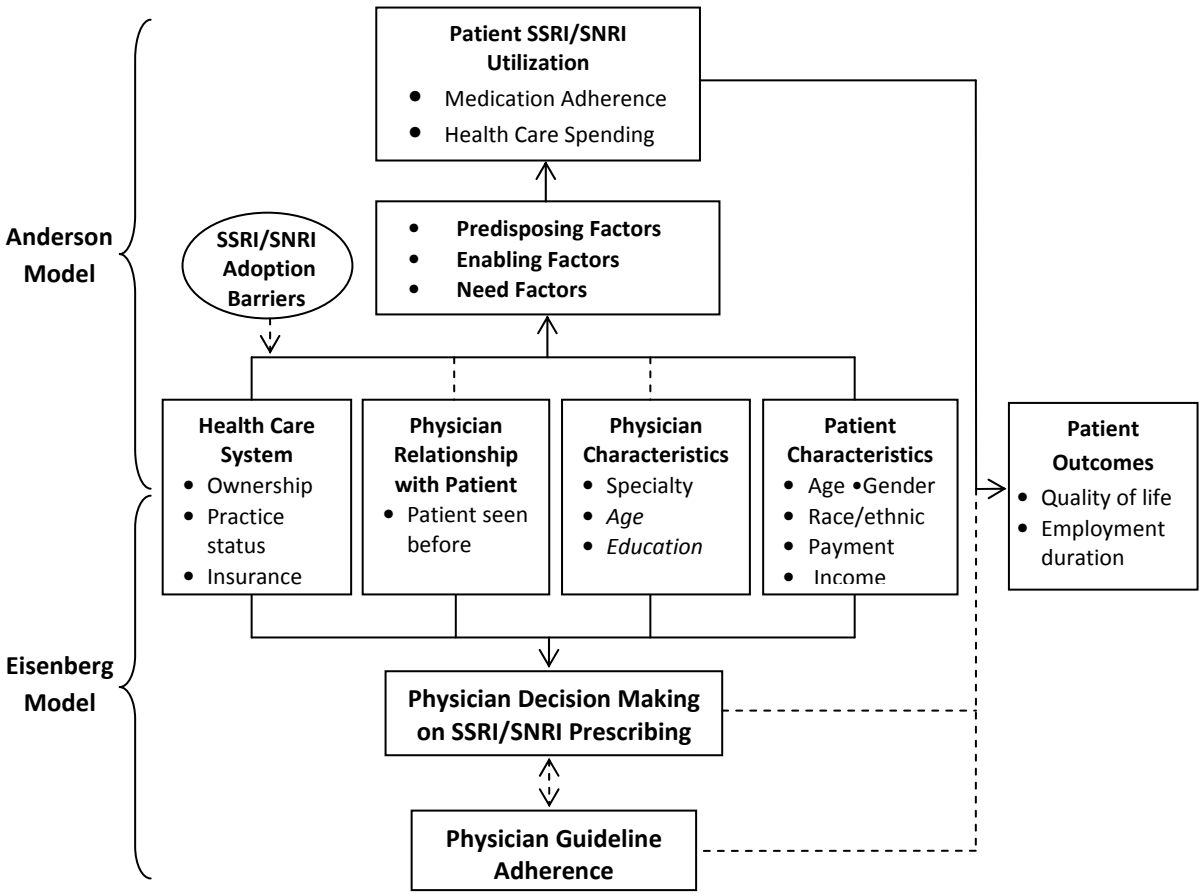

Figure 3.1. Conceptual model of this study

Note:

- The solid lines represent the associations this study attempted to address and the dashed lines imply an influencing effect that could not be directly measurable but had a strong theoretical association.
- Italics are used to connote variables that were not directly measurable due to the limitations of the NAMCS or the MEPS

Eisenberg model and Anderson model were integrated in this synthesized model. The Eisenberg and the Anderson models were applied as the main structure of the synthesized model. The bottom part of this synthesized model applied Eisenberg model where physician's decision making on SSRI/SNRI adoption and prescription was influenced by four groups of sociological factors including patient characteristics, physician characteristics, health care system, and physician relationship with patients. The top part of this synthesized model applied Anderson model where patient's SSRI/SNRI adherence was influenced by predisposing, enabling and need factors.

In Figure 3.1, the solid lines represent the associations that this study attempted to address whereas the dashed lines implied an influencing effect that could not be directly measurable but had a strong theoretical association. In addition, italics in Figure 3.1 were used to connote variables that were not directly measurable due to the limitations of the NAMCS and the MEPS datasets.

Throughout the synthesized model, the complete picture for the adoption and use of SSRIs/SNRIs and its influence on patient's medication adherence, associated healthcare expenditure as well patient outcomes could be comprehensively explored and discussed. Based on this conceptual model, the dynamics of antidepressant choice, antidepressant adherence, and associated patient outcomes which were revealed by special statistical methodologies described in later sections. The statistical results were bases to draw an overall picture capturing the patterns of the dynamic antidepressant prescribing and utilization when contextualizing these two models.

3.2 Data Sources

National Ambulatory Medical Care Survey (NAMCS)

The first manuscript of this study (Chapter 4) used the National Ambulatory Medical Care Survey (NAMCS) to analyze SSRI/SNRI adoption and medication choice for MDD patients. The NAMCS is a national probability sample survey conducted by the Division of Health Care Statistics of the National Center for Health Statistics (NCHS) and the Centers for Disease Control and Prevention (CDC).[99] The survey was conducted annually from 1973 to 1981, then in 1985, and annually again since 1989. The sampling frame for each year is composed of physician names as documented in the files maintained by the American Medical Association and the American Osteopathic Association. The survey primarily involved sample of visits to non-federally employed office-based physicians (excluding those in the specialties of anesthesiology, radiology, and pathology) who are primarily engaged in direct patient care.

The NAMCS makes use of three-stage probability sampling design. An initial probability sample is drawn from primary sampling units (112 PSUs) consisting of counties, groups of counties, county equivalents or towns and townships. At the second-stage probability sample is drawn from practicing physicians within each of these PSUs selected from master files. The third stage involved random sampling of the visits for a physician. Specially trained interviewers collect the data from physicians. Each physician is randomly assigned to a one-week reporting period. The physician or a member of the physician's staff provides information about a patient's sociodemographics, physician specialty, reasons for the visit, source of payment for the visit, patients' complaints and symptoms, diagnoses made, second time or first-time visit, medication prescribed, and

also therapeutic and preventive services recommended for each visit. The basic sampling unit for the NAMCS is the physician-patient encounter or outpatient visit. To obtain national estimates, each individual record is assigned an inflation factor called the patient visit weight, which is used to obtain the total number of office visits made in the United States. All estimates from the NAMCS are related to the number of patient visits and subject to sampling variability. An estimate is considered reliable if it has relative sampling errors of ≤ 30% of the estimate, as per NCHS standards.

Due to limitations of data availability and the consistency of survey methods, this study used data from year 1993 to year 2007 (year 2007 is the latest available data year). The annual datasets from 1993 to 2007 were compiled to ensure there was enough long yearly cross-sectional data to reflect the time trend and the SSRI/SNRI adoption process.

Medical Expenditure Panel Survey (MEPS)

Additionally, the second and the third manuscripts of this study (Chapter 5 and Chapter 6, respectively) used the Medical Expenditure Panel Survey (MEPS) to obtain a nationally representative sample of MDD patients whose health care utilization and outcomes could be studied. The MEPS is a national probability survey cosponsored by the Agency for Healthcare Research and Quality (AHRQ) and the National Center for the Health Statistics (NCHS). The MEPS survey is designed to provide nationally representative estimates of health care use, expenditures, source of payments, and insurance coverage for the U.S. civilian noninstitutionalized population. The sampling design utilized by MEPS is a stratified multi-stage area probability design in which certain groups such as ethnic minorities and low income households are oversampled.[100]

The MEPS data consist of four major components: the Household Component (HC), the Medical Provider Component (MPC), the Insurance Component (IC) and the Nursing Home Component (NHC).

The MEPS is a tremendously large dataset; researchers retrieve and merge needed components (datasets) from the MEPS according to study purposes. For research purposes, this study used the HC component of the MEPS. First, the HC collects data from families and individuals in selected communities across the U.S. and are self-reported. The HC includes demographics, health conditions, health status, income, health insurance coverage, employment, and both use and expenditure and health care services collected using computer-assisted personal interviewing technology. For instance, the latest panel (Panel 11) of the MEPS-HC was collected in years 2006 and 2007 with five rounds of interviews and can be used to analyze changes in the two-year period. This panel contains 3,286 variables and 18,014 survey samples.[100] Secondly, although the MPC component was not used directly in this study, it supplements and/or replaces information on medical care expenditures reported by the HC by contacting all hospitals and pharmacies by the household respondents. The MPC is conducted through telephone interviews and record abstraction.[100]

There were several subsets of the HC component that were used in this study. For Objective 2, in addition to the MEPS full-year consolidated data files (i.e. the pooled file of five rounds within one calendar year) from year 2000 to year 2007, three additional groups of files were also used for the purpose of this study. First, the medical condition file which is an event file that provides detailed information of each medical condition reported by the household respondents, was used to identify patients with mental

disorders (MDD and comorbid mental disorders). Second, the prescription drug files are also event files that provide data on all prescribed medicines which are self-reported by the HC respondents and supplemented by the MPC pharmacies. Specifically, counts of prescribed medicine utilization are based entirely on HC, whereas drug information such as expenditure and payment data, as well as details of medications (e.g., strength, quantity, etc.) is from the Pharmacy Component (PC) within the MEPS-MPC. Third, the longitudinal weight files were used to correct the sample weights according to the MEPS survey structure (five interview rounds in a two-year period panel) to develop cross-sectional estimates.

For Objective 3 of this study, the panel longitudinal data files from 2004-2007 (MEPS panels 9-11) were used (instead of using the full-year consolidated data files as Objective 2) in order to capture more complete employment duration information within five interview rounds in two survey years. In addition to the aforementioned prescription drug files, the job files with job-level data which contain variables pertaining to household-reported job, such as job start and end dates, wage rate, hours, industry and occupation, were also used in this study.

3.3 Eligibility Criteria

This research focused on patients with MDD, therefore only patients diagnosed with MDD were extracted from the NAMCS and the MEPS datasets and included in this study. Sample extraction was according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR, American Psychiatric Association, 2000) classification of mental disorders identified by the International

Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes contained in NAMCS and MEPS. Only subjects with ICD-9 codes 296.2x (major depressive disorder: single episode) and 296.3x (major depressive disorder: recurrent) were extracted.

Unfortunately the public-available MEPS dataset only provides the first three-digit ICD-9 codes due to patient's confidentiality concerns. That is, in this study all patients with ICD-9 code 296 were extracted from the MEPS dataset. However, ICD-9 code 296.xx includes both MDD and bipolar disorder. It is recommended that patients with bipolar disorder to be treated by mood stabilizers (for depression episodes) and antipsychotics. Antidepressants such as SSRIs are very seldom used as monotherapy to treat depression episodes of bipolar disorder; clinical research shows that several types of antidepressants may trigger patient's maniac episodes unless mood stabilizers are adjunctively used.[101] In order to exclude bipolar patients from the study sample, an extra exclusion strategy was accordingly implemented: patient who used mood stabilizers and antipsychotics were excluded from the study sample.

In order to avoid the heterogeneity of treatment between adults and children with MDD, this study excluded children from the study sample. Specifically in Objective 2, only MDD patients who took antidepressants were included in this study in order to study their antidepressant adherence. In Objective 3, in order to accurately capture the impact of antidepressants on patient's employment duration, only primary jobs were included in this study; miscellaneous jobs were excluded. Also, job termination records due to change of jobs, giving birth, and attending school were excluded in order to capture purer impact of diseases on employment duration.

3.4 Covariates and Measures

Categories of Antidepressants

The taxonomy of antidepressants was described in Chapter 2. For operational purposes, antidepressants were categorized as SSRI/SNRI antidepressants, other newer antidepressants, and older antidepressants (TCAs, MAOIs and other older antidepressants) throughout this study. For detailed antidepressant in each category, please refer to Table 3.1 below. Patients who took more than one types of antidepressants were classified as having combination therapy. The creation of the combination therapy category was to avoid double-counting of antidepressant utilization. Under this categorization, SSRIs and SNRIs were grouped for their similar pharmacological mechanisms. Other newer antidepressants, for example bupropion, and mirtazapine, were separated from SSRI/SNRI category for their different drug mechanisms. This categorization benefited to examine the net effects of SSRI/SNRI antidepressants from other newer ones.

Table 3.1 Categories of antidepressants from NAMCS and MEPS datasets

Type of Antidepressant	Coded Medications in NAMCS and MEPS
SSRI/SNRI antidepressants	citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine,
Other newer antidepressants	bupropion, mirtazapine, nefazodone, mianserin
Older antidepressants	amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, isocarboxazid, maprotiline, nortriptyline, phenelzine, protriptyline, selegiline, tranylcypromine, trazodone, trimipramine,

Measurements for Objective 1 (Manuscript 1)

Using Eisenberg physician decision making model as a framework for analyses, there were four categories of social factors in this study: (1) physician characteristics; (2) patient characteristics; (3) physician's relationship with the health care system; and (4) physician's relationship with the patient.[91] Descriptions of these four factors were mentioned in previous sections. Specific covariates are described below.

The dependent variables of this study were the decision related to prescribing antidepressant medications (yes/no), and which type(s) of antidepressants was (were) prescribed. The dependent variables were simply recoded from the NAMCS prescription data. There was an intermediate dependent variable in the first stage regression of the Heckman's two-stage model considering whether or not any antidepressants were prescribed. The rationale of including this regression will be explained in the methodology section. The NAMCS data recode up to six medications associated with each visit and a five-digit medication code is assigned to each medication. The dependent variable (i.e. different types of antidepressants prescribed by physicians) was identified by the prescribed medications listed in Table 3.1.

The main study purpose of Objective 1 was to disentangle physician's prescribing patterns of innovative antidepressants for MDD patients. The measures of the independent variables for Objective 1 are described as follows and listed in Table 3.2 on the next page.

Table 3.2 Study covariates for Objectives 1

1. Physician Characteristics
- Provider:
  - Psychiatrist
  - Non-psychiatrist

2. Patient Characteristics
- Gender: male
- Age
- Age square
- Race/ethnicity:
  - Non-Hispanic white
  - Non-Hispanic black
  - Hispanic
  - Other
- Primary source of payment:
  - Private insurance
  - Medicare
  - Medicaid
  - Self-pay
  - All others
- Capitated payment: yes
- Patient belongs to HMO: yes
- Capitated*HMO
- Comorbidity:
  - Psychotic disorders
  - Anxiety disorders
- Taking psychotherapy: yes
- Patient education: yes

3. Physician's Relationship with the Health Care System
- Ownership status:
  - Owner of solo practice
  - Owner of non-solo practice
  - Non-owner
- Geographic region of practice:
  - Northeast
  - Midwest
  - South
  - West
- Metropolitan area: yes

4. Physician's Relationship with the Patient
- Patient seen before: yes
- Depression is the primary diagnosis listed for the visit: yes

In Objective 1 of this study, the patient characteristics included age, gender, race/ethnicity, and payment structure. Age square was also included to capture the nonlinearity of age in the regression model. A patient's race/ethnicity was categorized as Hispanic and non-Hispanic. Payment structure includes source of payment (Medicare, Medicaid, self-pay, and other) and method of payment (capitated or not). Finally whether a patient belongs to an HMO, patient's comorbid mental disorders, whether a patient took psychotherapy, and whether a patient received patient education were considered. For physician characteristics, unfortunately the NAMCS provides limited physician characteristics. The only physician characteristic included was specialty which was categorized as psychiatrist and non-psychiatrist. Because a patient's HMO status was likely to correlate with whether the visit was capitated or not, an interaction term of these two covariates was included.

Physician's relationship with the health care system includes physician ownership of practice, geographic region of practice and whether a metropolitan area or not. Physician ownership of practice was categorized as owner of solo practice, owner of non-solo practice and non-owner. The practice region was categorized as Northeast, Midwest, South and West according to the original coding of the NAMCS. Physician's relationship with the patient included whether the physician had seen the patient before, and whether depression was the primary diagnosis listed for the visit.

Table 3.3 Study covariates for Objectives 2

1. Predisposing Factors
- Gender: male
- Age category:
  - 18-25
  - 26-49
  - 50-64
  - 65+
- Education years
- Race/ethnicity:
  - Non-Hispanic white
  - Non-Hispanic black
  - Hispanic
  - Other
- Region:
  - Northwest
  - Midwest
  - South
  - West
- Metropolitan area: yes

2. Enabling Factors
- Annual personal income:
  - <$20,000
  - $20,000-$40,000
  - $40,000-$60,000
  - $60,000+
- Health insurance status:
  - Private insurance
  - Public insurance only
  - Uninsured
- Patient belongs to HMO: yes
- Prescription drug insurance: yes

3. Need Factors
- Comorbidity:
  - Psychotic disorders
  - Anxiety disorders
- SF-12 PCS
- SF-12 MCS

4. Types of Antidepressants
- SSRIs/SNRIs only
- Other newer antidepressants only
- Older antidepressants only
- Combination therapy

Measures for Objective 2 (Manuscript 2)

The main goals of Objective 2 were to examine the impact of antidepressant choice on MDD patient's medication adherence and associated health care utilization expenditure. For Objective 2, Anderson model served as a good framework to characterize not only dependent and independent variables but also their relationship, and therefore enabled the study to characterize several important predictors on antidepressant medication adherence and associated health care expenditure. For this study, according to Anderson model, covariates are listed in Table 3.3. Measures of predisposing variables included age, gender, education year, race/ethnicity, geographic region, and metropolitan area. The measures of enabling factors included total annual personal income, health insurance status, patient HMO status, and prescription drug insurance status. The need factors included comorbid mental disorders and evaluated health status (SF-12 summary scores). These aforementioned factors and measures were used as independent variables in this study. Specific covariates of Objective 2 are listed in Table 3.3.

One of the research outcomes of this study was patient's antidepressant medication adherence. This study adopted the proportion of days covered (PDC) as the measure of medication adherence to capture the suggested long-term use of antidepressants and due to the data availability of MEPS. PDC is essentially a continuous, multiple-interval measure of medication availability according to Steiner and Prochazka's categorization, which is suggested to be more useful in testing cumulative drug dosage and longer-term exposure of medication.[102, 103] As discontinuation of antidepressants brings high likelihood of recurrence and serious withdrawal symptoms, antidepressants are suggested for long-term maintenance use. [6-10] Therefore, the use of PDC as a

continuous, multiple-interval measure of medication availability is an appropriate measure for antidepressant adherence. Besides, Martin and colleagues show that PDC is less likely to overstate medication adherence compared with other measures and should be considered when there is multiple medications within a class of medication which are used concurrently,[104] which supports the use of PDC as an appropriate measure for medication adherence in this study. In addition, the MEPS prescription data file provided exactly the needed drug information for PDC calculation.

In the calculation of PDC, medication adherence was defined as the proportion of "days covered" by a given drug in each time interval, based on number of days supplied and quantity of medication dispensed for each filled prescription. The PDC standardizes the time period over which adherence is examined.[48] The PDC can be calculated by the following formula according to its definition:

$$\text{PDC}(\%) = \frac{\text{Number of days with drug on hand}}{\text{Number of days in specified time interval}} \times 100.$$

The denominator for PDC is a clinically meaningful number of days that is the same for all intervals and patients. In this study, 365 days (one year) was defined as the duration of study in order to capture the suggested long-term use of antidepressants and due to data structure of MEPS. Regarding the numerator, however, the MEPS dataset did not provide information regarding "days supply" of medication. Therefore, the days of supply was calculated as "quantity of prescriptions dispensed" divided by "number of times took per day". "Quantity of prescriptions dispensed" could be obtained simply from the MEPS prescription drug files, and "number of times took per day" for every single antidepressant was obtained from the daily dosing recommendation at EPROCRATES ONLINE®, an online drug dictionary. The MEPS prescription drug files contained all

drug dispense records of every single patient within one survey year, therefore the numerator in the PDC formula was in fact the days supply aggregated from every single drug records within one year. According to the definition of PDC and all the available information, PDC in this study was calculated and defined as follows:

$$\text{PDC}(\%) = \frac{\text{Number of days with drug on hand}}{\text{Number of days in specified time interval}} \times 100$$

$$= \frac{\Sigma\,(\text{Quantity of drugs dispensed} / \#\text{ of times took per day})}{365} \times 100.$$

Note that differential dosage forms of drugs were considered in the coding of drug entries by MEPS already as well as in compiling daily dosing recommendation from EPOCRATES ONLINE. For example, the suggested "number of times took per day" from EPOCRATES ONLINE for Wellbutrin-SR™ is 2, whereas "number of times took per day" for Wellbutrin-XL™ is 1. That is, the calculation of PDC in this study implicitly considered differential dosage forms for each medication. This method of PDC calculation in this study provided a drug- and strength- specific measure which was more accurate than the measures in previous studies.

PDC was the dependent variable in this study. Previous literature suggested highly medication adherent if PDC is larger than 80% in a given interval, and partially adherent if PDC is at the range of 20% to 80%. Those with PDC less than 20% were categorized as non-adherent.[105, 106]

In addition to medication adherence, the health care expenditure associated with antidepressant choice and antidepressant adherence was studied as well. There were four associated healthcare expenditures studied: outpatient (including ER) visit expenditure, inpatient visit expenditure, MDD-specific drug expenditure, and total health expenditure.

The MDD-specific drug expenditure was aggregated from all drug records in the MEPS prescription drug files by each patient, whereas the other three expenditures were directly obtained from the MEPS full-year consolidated data files.

Measurements for Objective 3 (Manuscript 3)

The main purpose of Objective 3 was to examine the impact of innovative antidepressant use on MDD patient outcomes such as labor market participation and quality of life. Detailed covariates included in this study are listed in Table 3.4 on next page. First, patient demographics such as gender, age, marital status, family size, education year, race/ethnicity, metropolitan area, and hourly wage rate were considered. Second, patient health insurance status, prescription drug insurance status, comorbid mental disorders, evaluated health status, and total annual health expenditure were controlled. Third, patient antidepressant utilization including PDC (which measured medication adherence) and antidepressant choice were considered. In Objective 3, only the patients who took antidepressant pharmacotherapy were considered their PDCs.

The dependent variables used for Objective 3, patient outcomes, were employment duration and quality of life. Employment duration was calculated from the MEPS job files in monthly spells; the year and month of each job initiation and termination (if any) was identified for the calculation. Quality of life were represented by the SF-12 summary scores PCS and MCS directly from the MEPS longitudinal data files.

Table 3.4 Study covariates for Objectives 3

1. Demographics	**4. Types of Antidepressants**
Gender: male	PDC
Age	Antidepressant used:
Age square	SSRIs/SNRIs only
Marrital status	Other newer antidepressants only
Family size	Older antidepressants only
Education years	Combination therapy
Race/ethnicity:	
Non-Hispanic white	
Non-Hispanic black	
Hispanic	
Other	
Metropolitan area: yes	
Hourly wage	
2. Health insurance & health condition	
Health insurance status:	
Private insurance	
Public insurance only	
Uninsured	
Prescription drug insurance: yes	
Comorbidity:	
Psychotic disorders	
Anxiety disorders	
SF-12 PCS*	
SF-12 MCS*	
Total Annual health expenditure	

Note: *only in employment duration models

3.5 Statistical Analyses

Statistical software Stata® version 11 was used to conduct all statistical analyses. For Objective 1, a multinomial logistic regression with the Heckman two-step selection procedure was applied to analyze medication choice and SSRI/SNRI adoption. For Objective 2, a multiple regression model was used to examine the impact of antidepressant choice on patient medication adherence, and a two-part regression model

were used to examine the impact of innovative antidepressant use on associated health care expenditures. For Objective 3, the semiparametric Cox-proportional hazard duration model and the parametric exponential proportional-hazard models were used to study the impact of antidepressant use on employment duration of MDD patients, and multiple regression models were used to study the impact of use of innovative antidepressants on MDD patient's quality of life.

Statistical analyses for Objective 1

The main purpose of Objective 1 was to disentangle physician prescribing patterns in innovative antidepressants for MDD patients, examining how sociological factors influence physician antidepressant prescribing patterns. A multinomial logistic regression with the Heckman two-step selection procedure was applied to capture the two-step nature of decision making and to analyze medication choice and SSRI/SNRI adoption. The SSRI/SNRI prescribing includes a two-step decision: first, a physician decides if an antidepressant should be prescribed; second, which type of antidepressant should be prescribed. In their research in 2003, Sleath and Shih suggested adopting the Heckman two-step selection model to capture this two-step decision.[28] The first step of the analyses examined the factors that influences if a patient was prescribed an antidepressant using a logit model. The second step of the analysis examined the factors that influenced which type of antidepressant was prescribed using the multinomial logit model.

Specifically, a term named Mill's ratio was generated in the first step logistic regression model and the inverse of this term was included as an extra independent

variable in the second-step analysis to correct the selection bias associated with physician prescribing patterns and preferences by incorporating the inverse Mill's ratio, which is essentially a transformation of the predicted individual probabilities in the first step, as an additional independent variable. The second-step equation illustrates Heckman's insight that sample selection can be viewed as a form of omitted-variable bias, as conditional on both all original independent variables as well as on the inverse Mill's ratio, as if the sample were randomly selected.[107]

Two conditions have to be considered in a selection model: the exclusion restriction condition, and the independence of irrelevant alternatives (IIA) condition. The exclusion restriction condition requires that there is at least one independent variable that influences selection. The IIA condition requires that the odds ratios between the first and the second alternatives are independent of the remaining alternatives. In their study, Sleath and Shih provides a good interpretation for the IIA condition indicating that the decision of prescribing which type of antidepressant should be based only on the clinical need of patients which is independent of the odds ratio of other alternatives.[28] These two conditions were examined in the statistical analyses.

The adoption process may be dynamic; therefore year dummies were necessarily included to conduct year fixed effects to control time-variant effects. Furthermore, a separated analysis which grouped the study years was conducted to capture the dynamics of antidepressant adoption over time. In order to obtain national estimates, all analyses were weighted. However, the three-stage weighting scheme in NAMCS was not clear. This study alternatively adopted the weighting strategy suggested by Lee et al.[108], which divided each weight by the average weight for the whole study sample. This weighting

method provided the advantage that the NAMCS weighting scheme could be retained and incorporated without inflating the sample size.

The two-step Heckman selection model with year-fixed effects can be shown in the following equations:

Step 1: Logit

$$\begin{aligned}&\Pr[Y_{it}\,[\text{Antidepresant prescribing}] = 0 \text{ or } 1]\\ &= f\,[\beta_0 + \beta_1(\text{patient factors})_{it} + \beta_2(\text{physician factors})_{it}\\ &+ \beta_3(\text{physician - health care system interaction factors})_{it}\\ &+ \beta_4(\text{physician - patient interaction factors})_{it}] + \beta_5 \text{year}_t + \varepsilon_{it}\end{aligned}$$

where Y = 0 if no antidepressant is not prescribed, Y = 1 if any antidepressant is prescribed; $f(\cdot)$ is the cumulative density function (CDF) of logistic distribution and ε is the error term.

Step 2: Multinomial Logit

$$\begin{aligned}&\Pr[Z_{it}[\text{Type of antidepressants prescribing}] = 0, 1, 2, \text{or } 3]\\ &= f\,[\beta_0 + \beta_1(\text{patient factors})_{it} + \beta_2(\text{physician factors})_{it}\\ &+ \beta_3(\text{physician - health care system interaction factors})_{it}\\ &+ \beta_4(\text{physician - patient interaction factors})_{it}] + \beta_5 \text{year}_t + \beta_6\lambda_{it} + u_{it}\end{aligned}$$

where Z = 0 if only older antidepressants is prescribed, Z = 1 if only SSRI/SNRI is prescribed, Z = 2 if only other newer antidepressants are prescribed, and Z = 3 if more than one types of antidepressants are prescribed (categorized as prescribing combination pharmacotherapy). (Detailed categorization of antidepressant in this study was described

in previous sections.) In addition, $f(\cdot)$ is the CDF of logistic distribution; λ is the inverse Mill's ratio generated from the first step logistic regression; and u is the error term.

Statistical analyses for Objective 2

The main purpose of Objective 2 was to examine the impact of antidepressant choice on MDD patient's medication adherence and associated health care expenditure. A multiple OLS regression was used to examine MDD patient's antidepressant adherence, which is shown as follows:

$$\begin{aligned}&\text{PDC}_{it}(\text{antidepressant medication adherence})\\&=\beta_0+\beta_1(\text{patient predisposing factors})_{it}+\beta_2(\text{patient enabling factors})_{it}\\&+\beta_3(\text{patient need factors})_{it}+\beta_4(\text{type of antidepressant})_{it}+\beta_5(\text{year})+\varepsilon_{it}\end{aligned}$$

where PDC stands for the proportional days covered to measure antidepressant adherence, and ε is the error term. Year-fixed effects and robust standard error estimates were incorporated in this model.

In addition, a two-part model was implemented to study the impact of MDD patient factors and antidepressant choice on associated health care expenditures. Health care expenditure data usually contain a large number of zeros as which there is a large proportion of the sample with no use of related health care in the study period. Therefore, a two-part regression model was used to capture this nature of health care expenditure data. The first part of the model was a logit model which predicted the probability of having some specific health care (e.g., outpatient visits). The second part used OLS regressions to predict the continuous amount of associated health care expenditures, given a patient had any of this specific health care. The four health care expenditures

examined in this study were (1) outpatient visit expenditure (including ER visit expenditures); (2) inpatient visit expenditure; (3) MDD specific drug expenditure; and (4) total health expenditure. The two-part model is shown in the following equations:

Part 1: Logit:

$$\Pr[Y_{it}\,[\text{health care utilization}] = 0 \text{ or } 1]$$

$$= f[\beta_0 + \beta_1(\text{patient predisposing factors})_{it} + \beta_2(\text{patient enabling factors})_{it}$$

$$+ \beta_3(\text{patient need factors})_{it} + \beta_4(\text{type of antidepressant})_{it} + \beta_5(\text{PDC}) + \beta_6(\text{year})] + \varepsilon_{it}$$

where $Y = 1$ if some specific health care is utilized and $Y = 0$ if not; $f(\cdot)$ is the cumulative density function (CDF) of logistic distribution and ε is the error term.

Part 2: Linear Regression: (given $Y = 1$)

$$\ln(\text{Health care expenditure})$$

$$= \beta_0 + \beta_1(\text{patient predisposing factors})_{it} + \beta_2(\text{patient enabling factors})_{it}$$

$$+ \beta_3(\text{patient need factors})_{it} + \beta_4(\text{type of antidepressant})_{it}$$

$$+ \beta_5(\text{PDC})_{it} + \beta_6(\text{year}) + u_{it}$$

where only observations with $Y = 1$ in Part 1 are included; health care expenditures are in logarithm formats; and u is the error term. Please refer to Table 3.3 for detailed list of independent variables in this study.

In this study, among the four studied health care expenditures, only (1) outpatient visit expenditure and (2) inpatient visit expenditure contained zeros and hence were examined using the two-part model, whereas (3) MDD specific drug expenditure and (4) total health expenditure contained no zeros and hence were examined simply using the OLS regressions (which was essentially the second part in the two-part model.)

Besides, in order to obtain national estimates, all analyses were weighted. However, the three-stage weighting scheme in the MEPS was lost because of the complicated sample extraction process in this study. This study alternatively adopted the weighting strategy suggested by Lee et al.,[108] which divided each weight by the average weight for the whole study sample. This weighting method provided the advantage that the MEPS weighting scheme could be retained and incorporated without inflating the sample size. In addition, in order to control for year effects, the year-fixed models were implemented.

Statistical analyses for Objective 3

The main purpose of Objective 3 was to examine the impact of antidepressant use on MDD patient's labor market participation and health outcomes such as employment duration and quality of life. As mentioned in previous sections, the primary dependent variables used for Objective 3 were employment duration and quality of life for MDD patients. Two separate statistical methods were implemented to conduct the statistical analyses for these two different patient outcomes. First, regarding MDD patient's labor market participation, the non-parametric Kaplan-Meier plot was drawn as a preliminary examination for the duration dependence of antidepressant choice on MDD patient's employment duration. Then the semiparametric Cox-proportional hazard duration models, which did not required specifying the probability distribution of the baseline hazard and associated covariates, were used. Finally, the parametric proportional hazard model with exponential distribution was also used to cross-compare the impact of antidepressant choice on MDD patient's employment duration with previous models.

A general form for the duration model in this study can be represented as:

Distribution Function:

$$F(t) = \int_0^t f(s)\mathrm{d}s = \Pr(T \le t) \text{ for } t > 0$$

where $f(t)$ is the density function, T is the random variable indicating duration (in monthly spells in this study), t is a realization of T, $F(\ )$ is a distribution function for the corresponding duration.

Survival Function:

$$S(t) = 1 - F(t)$$

where $S(\ )$ is the survival function, which indicates the probability that a spell lasts at least t periods.

Hazard Function:

$$\lambda(t) = \lim_{h \downarrow 0} \frac{\Pr(t \le T < t + h \mid T \ge t)}{h} = \frac{f(t)}{S(t)} = -\frac{d \ln S(t)}{dt}$$

where $\lambda(\ )$ is the hazard function, which indicates the probability of the spell ending at a given time t, given that it has lasted until at least t.

A general form for the semi-parametric Cox-proportional hazard model in this study can be represented as:

$$\lambda(t; X) = \lambda_0(t) \cdot \exp[\beta_0 + \beta_1(\text{demographics})_{it} + \beta_2(\text{insurance and health condition})_{it}$$
$$+ \beta_3(\text{antidepressant utilization and adherence})_{it}] + \varepsilon_{it}$$

where $\lambda_0(\ )$ is the baseline hazard, which will be cancelled in the likelihood function. Therefore, the assumption considering the distribution of the baseline hazard is not needed in the Cox-proportional hazard model, which illustrates its semi-parametric characteristic.

A general form for the parametric proportional hazard model in this study can be represented as:

$$\lambda(t;X) = \lambda_0(t) \cdot \kappa[\beta_0 + \beta_1(\text{demographics})_{it} + \beta_2(\text{insurance and health condition})_{it} + \beta_3(\text{antidepressant utilization and adherence})_{it}] + \varepsilon_{it}$$

where $\lambda_0(\,)$ is the baseline hazard and $\kappa(\,)$ is a particular probability distribution (i.e. exponential distribution in this study.) Please refer Table 3.4 for the detailed list of the independent variables in this study. In this study, the Akaike Information Criteria (AIC) were compared for these models' goodness-of-fit.

Secondly, regarding the impact of antidepressant utilization and patient's quality of life, the linear OLS models were implemented. The OLS model in this study is shown as follows:

$$\begin{aligned}&\text{Patient quality of life (SF-12 PCS or MCS)}\\ &= \beta_0 + \beta_1(\text{demographics})_{it} + \beta_2(\text{insurance and health condition})_{it} + \beta_3(\text{antidepressant utilization and adherence})_{it}] + \varepsilon_{it}.\end{aligned}$$

Please refer Table 3.4 for the detailed list of the independent variables in this study.

Besides, in order to obtain national estimates, all analyses were weighted. The same as Objective 2, however, the three-stage weighting scheme in MEPS was lost because of the complicated sample extraction process. This study alternatively adopted the weighting strategy suggested by Lee et al.,[108] which divided each weight by the average weight for the whole study sample. This weighting method provided the advantage that the MEPS weighting scheme could be retained and incorporated without inflating the sample size.

3.6 Conducting Overall Conclusions

As mentioned in previous chapters and sections, there were three separate but interlinked objectives in this dissertation. Although statistical analyses were conducted separately and reported in three separate dissertation chapters, this study tried to draw an overall picture of use of innovative antidepressants from both patient and physician perspectives, and associated patient outcomes. The last part of this dissertation will draw a combined picture of the use of antidepressants and associated patient outcomes, according to the results and conclusions from the three chapters. The overall conclusion was based on the proposed synthesized model shown in Figure 3.1 on page 30.

CHAPTER 4

DISSERTATION MANUSCRIPT 1

(**Title:** PHYSICIAN PRESCRIBING PATTERNS OF INNOVATIVE ANTIDEPRESSANTS IN THE UNITED STATES: THE CASE OF MDD PATIENTS 1993-2007)

Physician Prescribing Patterns of Innovative Antidepressants in the United States: The Case of MDD Patients 1993-2007

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Background: Innovative antidepressants such as SSRIs and SNRIs have been widely adopted. However, the differences in their adoption across patient's and physician's characteristics, geographic regions and insurance status needs to be further explored.

Objective: This study was trying to disentangle the pattern of physician antidepressant prescribing and patient use of SSRI/SNRI medication for MDD treatment and the dynamics of its adoption over time.

Methods: A retrospective cross-sectional study was conducted using the 1993-2007 National Ambulatory Medical Care Survey (NAMCS) database. A multinomial logistic regression with the Heckman two-step selection procedure was applied to capture the two-step nature of physician's decision making and to analyze medication choice and SSRI/SNRI adoption.

Results: Weighted logistic regression indicated that patient ethnicity and primary source of payment for services, physician ownership status, and physician's practice regions were associated with differential likelihood of patient being prescribed antidepressant. Non-Hispanic white patients were more likely to be prescribed antidepressants compared to Hispanics (OR=1.52, $p<0.01$.) Physician's choice on SSRI/SNRI antidepressant prescribing varied across with patient age and health insurance status. MDD patients whose primary source of payment for healthcare visits were private insurance were significantly more likely to be prescribed antidepressants compared to Medicare (RRR=0.69, $p<0.01$) and Medicaid (RRR=0.62, $p<0.01$) as primary payment sources. Physician's adoption patterns for SSRI/SNRI and other innovative antidepressants also varied over time.

Conclusions: We observed several strong associations between sociological factors and physician's innovative antidepressant prescribing patterns. Differences of antidepressant adoption could have important policy implications for drug formulary and health disparities. Health disparities and gaps between optimal and suboptimal health care for

patient mental health caused by systematic differences in sociological factors need to be mitigated. We need to design effective policy interventions to improve physician practice guidelines adherence to eliminate variations among physician practices.

Keywords: antidepressant; SSRI; SNRI; major depressive disorder (MDD); prescribing; sociological factor

INTRODUCTION

Mental health conditions are common not only in the United States but also in many developed countries. Estimation in recent research shows that 26.2 percent of Americans ages 18 and older suffer from a diagnosable mental illness in a given year.[1] Among mental disorders, major depressive disorder (MDD) is attributed as the leading cause of disability in the U.S. for ages 15-44, and affects 6.7 percent of the U.S. population age 18 and older in a given year.[2]

MDD is regarded as both an acute and a chronic disease. Epidemiologic research shows the lifetime prevalence rate is between ten to twenty percent.[3, 4] According to the National Comorbidity Survey, the lifetime and annual prevalence of MDD are 17.1 percent and 10.3 percent, respectively.[5] In addition, the degree of relapse and reoccurrence is likely to be high for MDD patients and requires well maintenance. MDD patients are also recommended long-term maintenance treatment to prevent recurrence or the emergency of a new episode of depression.[6-10] MDD is therefore regarded as a chronic disease to some extent,[3, 11] and antidepressant medication may be needed in a longer term. With the nature of being both acute and chronic disease, a person with untreated or poorly treated MDD cannot function well for his/her daily, business and social activities.

Depression in general causes economic and social burdens. In research conducted by Greenberg et al. in 1993; the authors found the total cost of depression in 1990 was $43.7 billion with $12.4 billion in direct costs, $23.8 billion in excess absenteeism and productivity loss, and $7.5 billion in suicide-related earning losses.[12]

Although depression is categorized as a mental disorder, there is neurological evidence that shows depression is associated with neurotransmitters in a person's brain.

Neurotransmitters such as serotonin, norepinephrine, adrenaline and dopamine are all associated with depression. Among these chemicals, the principal neurotransmitter associated with depression is serotonin. Based on this neurological evidence, current antidepressant medication attempts to correct the imbalance of neurotransmitters. Such neurological findings essentially provide significant evidence to emphasize and support why pharmacotherapy has been playing an increasing central role in the treatment of mental disorders. There are 5.5 million more Americans receiving treatment for mental health and substance abuse in 2001 than in 1996, and the percentage using psychotropic drugs has increased.[13] As a result, the cost of these drugs is a rapidly increasing component of mental health care expenditures.

As Prozac™ (fluoxetine Hcl), the first selective serotonin reuptake inhibitors (SSRI) antidepressant, was introduced in 1988, SSRIs have become the major and preferable medication treatment for MDD patients. SSRIs, compared to old generation antidepressants (i.e. tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs)), have a unique treatment mechanism which selectively increases the level of serotonin.[14] SSRIs were soon adopted by physicians and patients because of their innovative mechanism of action and superior efficacy. In mid-1990, serotonin-norepinephrine reuptake inhibitor (SNRI), another innovative class of antidepressants, was introduced to treat MDD. Unlike SSRIs which act more selectively upon serotonin, SNRI increases both serotonin and norepinephrine to treat MDD. SNRIs have also been widely adopted by physicians as a prescription for MDD treatment recently.

The volume of SSRIs prescribed has risen since they were introduced, and thus amounts to around 80% of the $3.5 billion antidepressant market in the U.S. in 1995[15]

and has been growing 25% every year.[16] The success of Prozac led to more SSRI products and innovative newer generation antidepressants such as SNRIs in 1990s, which have overwhelmed the antidepressant market ever since.

SSRIs/SNRIs have been widely adopted by physicians; however the differences and trend in adoption of innovative SSRI/SNRI antidepressants across patient's and physician's characteristics, geographic regions, insurance status, and other related factors needs more research. Although previous studies have investigated the influences of sociological factors on patient mental healthcare utilization, there was a lack of either consideration of antidepressant medication choice or physician characteristics, or the study period was relatively short and old.[17-21] A study conducted by Sleath and Shih used the Heckman two-step selection model to examine people's treatment choices between SSRIs and non-SSRIs.[21] Their research results showed that patient characteristics, physicians characteristics, the physician's interaction with the health care system, and the physician's interaction with the patient all influenced antidepressant prescribing on SSRI or non-SSRI medications.

Differences of SSRI/SNRI adoption could have important policy implications for drug formularies; sociological factors which may influence physician prescribing and patient use of SSRI/SNRI therefore need to be further examined and disentangled. In particular in the U.S., because of the existence of managed care, the high volume of uninsured people, and the elevating costs of pharmaceuticals, sociological factors such as patient health insurance status could impact physician prescribing behaviors. Understanding how sociological factors influence physician prescribing decision on antidepressants for MDD treatment could complement previous study results and have

important implications for mental health policy especially for several specific groups whose mental disorders are undertreated. Although Sleath and Shih's methodology was elegant, they used relatively old (1998) single-year cross-sectional data; therefore using more updated and longer-term data and including more innovative classes of antidepressants would benefit the understanding of patient treatment choices and further as well as capture the dynamics related to antidepressant prescribing.[22, 23] Therefore, the objective of this research was trying to disentangle the pattern of physician antidepressant prescribing and patient use of SSRI/SNRI medication for MDD treatment and the process of its adoption over time. This study could help policy makers identify sources of variation in mental healthcare while reducing undertreatment.

This study used the National Ambulatory Medical Care Survey (NAMCS) along with Eisenberg model of physician prescribing as the conceptual framework, and the Heckman two-step decision model as the statistical method, to explore the adoption of SSRIs/SNRIs, the patterns of physician prescribing and medication choice for MDD patients in the U.S.

METHODS

Conceptual framework and research hypothesis

This was a retrospective cross-sectional study. This research applied a health behavior model as a conceptual framework to guide study hypothesis. Eisenberg model of physician decision making was applied to analyze the adoption of SSRIs/SNRIs and the pattern of a physician prescribing and medication choices for MDD patients in the U.S.

Eisenberg model of physician decision making describes the sociological factors influencing a physician's decision making. This model has been widely used for characterizing a physician's decision making on prescribing treatment and the factors which influence this decision making.[24-26] This model was applied in this study because of its comprehensiveness of characterizing the sociological factors which influence a physician's behavior (i.e. adopting and prescribing SSRI/SNRI medications in this study.) A physician's behavior of decision making is influenced and interplayed by four factors: (1) physician characteristics (e.g. age, gender, race, specialty); (2) patient characteristics (e.g. age, gender, race, educational level, insurance status, income); (3) physician's relationship with the health care system (e.g. practice setting, ownership); and (4) physician's relationship with the patient (e.g. patient demand, patient presentation of symptoms).[27]

According to Eisenberg model and previous studies, the study hypothesized that physician characteristics, patient characteristics, physician's relationship with the health care system, and physician's relationship with the patient had influences on SSRI/SNRI adoption.

Study sample

This study used the National Ambulatory Medical Care Survey (NAMCS) to analyze SSRI/SNRI adoption and medication choice for MDD patients. The NAMCS is a national probability sample survey conducted by the Division of Health Care Statistics of the National Center for Health Statistics (NCHS) and the Centers for Disease Control and Prevention (CDC).[28] The survey was conducted annually from 1973 to 1981, then in 1985,

and annually again since 1989. The sampling frame for each year is composed of physician names as documented in the files maintained by the American Medical Association and the American Osteopathic Association. The survey primarily involved sample of visits to non-federally employed office-based physicians (excluding those in the specialties of anesthesiology, radiology, and pathology) who are primarily engaged in direct patient care. Due to limitations of data availability and the consistency of survey methods, this study used data from year 1993 to year 2007 (year 2007 is the latest available data year). The annual datasets from 1993 to 2007 were compiled to ensure there was enough long yearly cross-sectional data to reflect the time trend and the SSRI/SNRI adoption process.

This research focused on patients with MDD, therefore only patients diagnosed with MDD were extracted from the NAMCS datasets and included in this study. Sample extraction was according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR, American Psychiatric Association, 2000) classification of mental disorders identified by the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes contained in NAMCS. Only subjects with ICD-9 codes 296.2x (major depressive disorder: single episode) and 296.3x (major depressive disorder: recurrent) were extracted. In addition, this study excluded children from the study sample in order to avoid the heterogeneity of treatment between adults and children with MDD.

Categories of antidepressants

In this study, antidepressants were categorized as SSRI/SNRI antidepressants, other newer antidepressants, and older antidepressants (TCAs, MAOIs and other older antidepressants.) The detailed list of antidepressants for each category in the NAMCS dataset is shown in Table 4.1.

Table 4.1. Categories of Antidepressants from NAMCS Dataset

Type of Antidepressant	Coded Medications in NAMCS
SSRI/SNRI antidepressants	citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine,
Other newer antidepressants	bupropion, mirtazapine, nefazodone, mianserin
Older antidepressants	amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, isocarboxazid, maprotiline, nortriptyline, phenelzine, protriptyline, selegiline, tranylcypromine, trazodone, trimipramine,

Patients who took more than one types of antidepressants were classified as having combination therapy. The creation of the combination therapy category was to avoid double-counting of antidepressant utilization. Under this categorization, SSRIs and SNRIs were grouped for their similar pharmacological mechanisms. Other newer antidepressants, for example bupropion and mirtazapine, were separated from SSRI/SNRI category for their different drug mechanisms. This categorization benefited to examine the net effects of SSRI/SNRI antidepressants from other newer ones.

Measurements

Using Eisenberg physician decision making model as a framework for analyses, there were four categories of social factors in this study: (1) physician characteristics; (2) patient characteristics; (3) physician's relationship with the health care system; and (4) physician's relationship with the patient.[27] Specific covariates are described below.

The dependent variables of this study were the decision related to prescribing antidepressant medications (yes/no), and which type(s) of antidepressants was (were) prescribed. The dependent variables were simply recoded from the NAMCS prescription data. There was an intermediate dependent variable in the first stage regression of the Heckman's two-stage model considering whether or not any antidepressants were prescribed. The NAMCS data recode up to six medications associated with each visit and a five-digit medication code is assigned to each medication. The dependent variable (i.e. different types of antidepressants prescribed by physicians) was identified by the prescribed medications listed in Table 4.1.

In this study, the patient characteristics included age, gender, race/ethnicity, and payment structure. Age square was also included to capture the nonlinearity of age in the regression model. A patient's ethnicity was categorized as Hispanic and non-Hispanic. Payment structure includes source of payment (Medicare, Medicaid, self-pay, and other) and method of payment (capitated or not). Finally whether a patient belongs to an HMO, patient's comorbid mental disorders, whether a patient took psychotherapy, and whether a patient received patient education were considered. For physician characteristics, unfortunately the NAMCS provides limited physician characteristics. The only physician characteristic included was specialty which was categorized as psychiatrist and non-

psychiatrist. Because a patient's HMO status was likely to correlate with whether the visit was capitated or not, an interaction term of these two covariates was included.

Physician's relationship with the health care system includes physician ownership of practice, geographic region of practice and whether a metropolitan area or not. Physician ownership of practice was categorized as owner of solo practice, owner of non-solo practice and non-owner. The practice region was categorized as Northeast, Midwest, South and West according to the original coding of the NAMCS. Physician's relationship with the patient included whether the physician had seen the patient before, and whether depression was the primary diagnosis listed for the visit.

Statistical Analyses

A multinomial logistic regression with the Heckman two-step selection procedure was applied to capture the two-step nature of decision making and to analyze medication choice and SSRI/SNRI adoption. The SSRI/SNRI prescribing includes a two-step decision: first, a physician decides if an antidepressant should be prescribed; second, which type of antidepressant should be prescribed. In their research in 2003, Sleath and Shih suggested adopting the Heckman two-step selection model to capture this two-step decision.[21] The first step of the analyses examined the factors that influences if a patient was prescribed an antidepressant using a logit model. The second step of the analysis examined the factors that influenced which type of antidepressant was prescribed using the multinomial logit model.

Specifically, a term named Mill's ratio was generated in the first step logistic regression model and the inverse of this term was included as an extra independent

variable in the second-step analysis to correct the selection bias associated with physician prescribing patterns and preferences by incorporating the inverse Mill's ratio, which is essentially a transformation of the predicted individual probabilities in the first step, as an additional independent variable. The second-step equation illustrates Heckman's insight that sample selection can be viewed as a form of omitted-variable bias, as conditional on both all original independent variables as well as on the inverse Mill's ratio, as if the sample were randomly selected.[29]

Two conditions have to be considered in a selection model: they are the exclusion restriction condition, and the independence of irrelevant alternatives (IIA) condition. The exclusion restriction condition requires that there is at least one independent variable that influences selection. The IIA condition requires that the odds ratios between the first and the second alternatives are independent of the remaining alternatives. In their study, Sleath and Shih provides a good interpretation for the IIA condition indicating that the decision of prescribing which type of antidepressant should be based only on the clinical need of patients which is independent of the odds ratio of other alternatives.[21] These two conditions were examined in the statistical analyses.

The adoption process may be dynamic; therefore year dummies were necessarily included to conduct year fixed effects to control time-variant effects. Furthermore, a separated analysis which grouped the study years was conducted to capture the dynamics of antidepressant adoption over time. In order to obtain national estimates, all analyses were weighted. However, the three-stage weighting scheme in NAMCS was not clear. This study alternatively adopted the weighting strategy suggested by Lee et al.,[30] which divided each weight by the average weight for the whole study sample. This weighting

method provided the advantage that the NAMCS weighting scheme could be retained and incorporated without inflating the sample size.

The two-step Heckman selection model with year-fixed effects can be shown in the following equations:

Step 1: Logit

$$\begin{aligned}&\Pr[Y_{it}\,[\text{Antidepresant prescribing}] = 0 \text{ or } 1]\\ &= f\,[\beta_0 + \beta_1(\text{patient factors})_{it} + \beta_2(\text{physician factors})_{it}\\ &+ \beta_3(\text{physician - health care system interaction factors})_{it}\\ &+ \beta_4(\text{physician - patient interaction factors})_{it}] + \beta_5 \text{year}_t + \varepsilon_{it}\end{aligned}$$

where Y = 0 if no antidepressant is not prescribed, Y = 1 if any antidepressant is prescribed; $f(\cdot)$ is the cumulative density function (CDF) of logistic distribution and ε is the error term.

Step 2: Multinomial Logit

$$\begin{aligned}&\Pr[Z_{it}[\text{Type of antidepressants prescribing}] = 0, 1, 2, \text{or } 3]\\ &= f\,[\beta_0 + \beta_1(\text{patient factors})_{it} + \beta_2(\text{physician factors})_{it}\\ &+ \beta_3(\text{physician - health care system interaction factors})_{it}\\ &+ \beta_4(\text{physician - patient interaction factors})_{it}] + \beta_5 \text{year}_t + \beta_6\lambda_{it} + u_{it}\end{aligned}$$

where Z = 0 if only older antidepressants is prescribed, Z = 1 if only SSRI/SNRI is prescribed, Z = 2 if only other newer antidepressants are prescribed, and Z = 3 if more than one types of antidepressants are prescribed (categorized as prescribing combination pharmacotherapy). In addition, $f(\cdot)$ is the CDF of logistic distribution; λ is the inverse

Mill's ratio generated from the first step logistic regression; and *u* is the error term. Statistical software Stata® version 11 was used to conduct all statistical analyses.

RESULTS

[Insert Table 4.2.]

A total weighted number of 125,605,444 subjects were studied. Table 4.1 outlines the descriptive statistics of the study sample. First regarding the provider characteristics, more than ninety percent patients (91.63%) were provided healthcare visits by psychiatrists. A majority of the study subjects was female (66.80%) and non-Hispanic white (84.24%) MDD patients. The average age of study subjects was 46 years old. More than half of the study subjects (52.10%) were covered by private insurance for their MDD-related healthcare, whereas a relatively small percentage of them were covered by Medicare (14.01%) and Medicaid (11.16%). There were around one-third patients (33.46%) whose MDD related visits were capitated.

Third, regarding the physician's relationship with health care system, more than half of the patients whose visits (53.20%) were provided by physicians who were owners of solo practice settings, and around one-fourth (26.93%) of them were provided by physicians who were not owners of practice settings. A majority of physicians (89.93%) practiced in metropolitan areas. Regarding the physician's relationship with patients, a majority of patients were seen by surveyed physicians before, and had MDD as the primary diagnosis.

Among all study subjects, a very high proportion of patients (71.22%) were prescribed at least one antidepressant, among which 40.17% were treated by SSRI/SNRI

antidepressants, 10.54% were treated by other types of new antidepressants, and only 8.72% were treated by older generation antidepressants. Besides, 40.57% patients were treated by combined pharmacotherapy which included more than one types of aforementioned antidepressants.

[Insert Table 4.3.]

The exclusion restriction condition and the independence of irrelevant condition (IIA) of the two-step selection model were tested and indicated that there was at least one independent variable that influences selection, and the decision of prescribing which type of antidepressant was based only on the clinical need of patients which was independent of the odds ratios of other alternatives (all $p<0.05$).

The results of the Heckman two-step model with year-fixed effects are reported in two parts. The results of the first-step fixed-year logistic regression are shown in Table 4.3 and the results of the fixed-year second-step multinomial logit model are shown in Table 4.4. These results are reported as follows. Table 4.3 shows the results from the weighted logistic regression predicting the probability of physician prescribing at least one antidepressant to MDD patients (i.e. the probability that a patient was prescribed any antidepressant or not.) The weighted odds ratios (ORs) and the 95% confidence intervals are reported in Table 4.3, and percentages (or means) of covariates are reported separately for antidepressant users and nonusers in Table 4.3 as well. The weighted odd ratios revealed that non-Hispanic white patients were more likely to be prescribed antidepressants compared to Hispanics ($p<0.01$). MDD patients whose primary source of payment for healthcare visits were private insurance were significantly more like to be prescribed antidepressants compared to Medicare ($p<0.01$) and Medicaid ($p<0.01$) as

primary payment sources. In addition, physicians who were owners of solo practice settings, compared to non-owners, were less likely to prescribe antidepressants for MDD patients ($p<0.01$). Physicians who practiced in non-metropolitan areas and had seen the patients before were more likely to prescribe antidepressants to MDD patients ($p<0.05$).

[Insert Table 4.4.]

Table 4.4 reports the second stage of the Heckman selection model which examined which type(s) of antidepressants a physician prescribed for MDD patients (conditional on the patients who were prescribed at least one antidepressant), using the multinomial logit model. The weighted relative risk ratios (RRRs) of covariates as well as the 95% confidence intervals of the RRRs are reported in Table 4.4. The base case of the multinomial logistic regression was "older antidepressants only" in this study; all RRRs were reported and compared to the base case.

Table 4.4 reveals that among the study samples who were prescribed antidepressants, an increase in patient age was associated with a decreased likelihood of being prescribed only innovative SSRI/SNRI antidepressants compared to older antidepressants ($p<0.05$). Compared to Medicare, patients who were primarily covered by private insurance were more likely to be prescribed innovative SSRI/SNRI or only other newer antidepressants ($p<0.05$). In addition, MDD patients who belonged to HMOs possessed a higher likelihood of being prescribed only other newer antidepressants; patients who were enrollees of capitated HMOs possessed a higher likelihood of being prescribed combined pharmacotherapy to treat their MDD. Compared to West regions, physicians who practiced in Northeast regions tended to prescribe less other newer antidepressants and less combined therapy for MDD patients ($p<0.05$).

[Insert Table 4.5.]

Table 4.5 reports the statistical results of the multinomial logit in the second-stage Heckman selection model with grouped study years. Significant covariates associated with time trends or across different year periods are reported as follows. Table 4.5 shows that psychiatrists possessed an extremely high likelihood of prescribing other newer antidepressants for MDD treatment compared to non-psychiatrists or primary care physicians in years 1993-1997 ($p<0.05$).

Regarding patient characteristics, male patients were more likely to be prescribed SSRI/SNRI and other newer antidepressants both in years 1993-1997 and 2002-2004 ($p<0.05$). Regarding patient's primary source of payment for healthcare, in years 2002-2004 patients who paid by self were associated with a higher likelihood of being prescribed other newer antidepressants compared to those covered by private insurance ($p<0.05$).

DISCUSSION

While innovative antidepressants such as SSRIs and SNRIs have been widely adopted, this study noticed physician's antidepressant prescribing patterns varied with several sociological factors as some of them were associated with physician's prescribing antidepressants for MDD treatment or not, and others were associated with physician's choice of antidepressants. Many of these factors varied across different time periods as innovative new antidepressants were introduced and adopted more broadly.

There were three strong associations that are of great interest. First, patient's race/ethnicity and health insurance status were indeed associated with physician's

adoption of antidepressant pharmacotherapy for MDD treatment. From the study results, Hispanic patients were unproportionally less likely to be prescribed antidepressant pharmacotherapy for MDD treatment. The study results complemented previous study findings for racial/ethnic disparities in antidepressant use and depression treatment.[17-20] Also patients with private insurance coverage were unproportionally more likely to be prescribed antidepressant pharmacotherapy for MDD treatment. Health disparities then came across as a possible issue regarding physician prescribing and patient utilization of antidepressants. Health insurance in turn, may play a more important role regarding MDD patient's access to pharmacotherapy. Racial/ethnic health disparities may come from discrimination, differential insurance benefits, lower rates of participation in health care decision making, and differential attitudes toward use of antidepressant therapy.[31] However, the sources of racial/ethnic health disparities in MDD treatment were not identified in this study; further research is needed to disentangle it.

In addition, physician's relationship with patients and the healthcare system were revealed to be associated with physician's prescribing decision as well. Physician's ownership status complicated physician's decision making on antidepressant prescribing, and therefore physician's adherence to MDD practice guidelines were more an issue given the findings of this study; in particular, previous studies showed a poor physician adherence to MDD guidelines.[32-34] Although pharmacotherapy for MDD treatment has both advantages and disadvantages compared to psychotherapy, whether physician factors overrode MDD guidelines adherence for both therapies is an important and urgent issue to be researched.

The second association that was of great interest was physician's prescribing choice for innovative antidepressants. In this study, patient's health insurance coverage had a strong association with physician's adoption of innovative antidepressants. Compared to public health insurance or uninsurance, private insurance did associate with an increased likelihood of antidepressant prescribing, which was likely to be attributed by higher costs of SSRIs/SNRIs compared to older generation antidepressants. However, from a societal stand point, a physician should provide appropriate and effective choice health care to patients if it is needed regardless a patient is covered by either private or public health insurance or even uninsured.

The third association that was of great interest was the dynamics of adoption of innovative antidepressants. Compared to non-psychiatrists or primary care physicians, psychiatrists were extremely more likely to adopt innovative newer antidepressants while they were newly introduced (in years 1993-1997). This finding echoed the study by Green and colleagues which indicated that primary care physicians as "pragmatists" who were less concerned about new knowledge than about practicalities of getting patients seen,[35] which implied psychiatrists were comparatively keener in adopting newer antidepressants.

As a few of other newer antidepressants were not introduced until 1990's, these newer medications were more likely to be adopted by patients who were afford to pay by self. As many of these innovative medications were not included in health insurance's drug formularies while being newly introduced on market, only patient who were afford to pay by self would be prescribed such innovative medications. As more cost-effectiveness evidence were revealed over time, such new medications would be more

widely adopted and considered first-line treatment, and thus being included in drug formularies, which was also shown in this study.

Patient gender difference was consistently shown across different time periods in this study. Although the general finding was that male patients were consistently more likely to be prescribed innovative antidepressants over time, the source of gender difference was not clear in this study. Further research can help explore such difference and its impacts. Further, patient capitated health insurance status helped physician adopting innovative SSRI/SNRI antidepressants in middle 1990's; however it in turn attributed to the lesser use of them. A possible explanation was related to the exponential growth in managed care in 1990's and the backlash of it starting from the beginning of the 21st century, and the special design of carve-outs for mental health services of managed care. In one hand, capitated payment scheme in managed care plans might address patient's general health status more, but in the other hand its gatekeeper strategy and carve-out design might also impede patients to access to appropriate or newer treatment for MDD patients.

The above three associations brought strong implications with respect to mental health policies. First, as the existence of managed care, the high volume of uninsured people, and the elevating costs of pharmaceuticals in the U.S., this study confirmed previous study findings that sociological factors, such as race/ethnicity and patient health insurance status, imposed substantial influences on physician prescribing behaviors, in particular in MDD treatment. As the health care reform committing in reducing the number of U.S. uninsured people being proposed by President Obama, health insurance is hoped to increase people's accessibility to optimal health care especially for those whose

health care need is unmet. While enhancing the accessibility to health insurance and in turn health care services, policy makers have to make sure optimal health care for people's mental health could be appropriately provided and delivered. Specifically, gaps between optimal and suboptimal health care for patient mental health caused by systematic differences in sociological factors, for example patient's gender and race/ethnicity, need to be well mitigated. Policy makers should take into account the sources of heterogeneity in MDD treatment indicated by this study.

The second implication for mental health policy came from the study results indicating the influences of physician characteristics, for example physician specialty, on antidepressant prescribing. In order to eliminate variations among physician practices and to obtain optimal health care for patients, we need policy makers to design effective policy interventions to improve physician practice guidelines adherence. The MDD practice guidelines were compiled and published by both the American Psychiatric Association (APA) and the Agency for Health Care Policy and Research (AHCPR, i.e. the former Agency for Healthcare Research and Quality, AHRQ), which incorporated clinical study results from rigorous clinical trials recommending effective treatment for MDD.[6-8] Previous studies also indicated associations between better depression guideline adherence and improved patient outcomes.[32-34] All of this calls for policy makers to try to improve physician's guideline adherence and enhance appropriate treatment for MDD to eliminate treatment heterogeneity due to systematic sociological factors.

CONCLUSION

The main objective of this research was trying to disentangle the pattern of physician antidepressant prescribing and patient use of SSRI/SNRI medication for MDD

treatment and the process of its adoption over time. The results provided further evidence that physician antidepressant prescribing was associated with sociological factors such as patient race/ethnicity and health insurance status. Differences of SSRI/SNRI adoption could have important policy implications for drug formularies and health disparities.

There were limitations that can be drawn from this study. First, we discuss the SSRI/SNRI innovation and adoption from a patient's and a physician's perspectives but not from a pharmaceutical firm's standpoint since pharmaceutical firms may have marketing strategies targeting on physician prescribing behaviors. Dataset such as IMS provides pharmaceutical sales data which may provide another view of SSRI/SNRI adoption process. Second, the NAMCS contains only ambulatory care data; emergency department visits and inpatient care data are not included which might not include the very severe cases in this study. Third, the episodes and severities of MDD were not taken into account in this study. Severities may contribute to physician's prescribing of pharmacotherapies. Fourth, the NAMCS dataset contains self-reported information which may be inaccurate due to recall bias, respondent bias, or interview bias. However, we believe these limitations did not outweigh the relative contribution of this study.

The findings of this study could benefit the understanding of how innovative medications were adopted by physicians and patients over time, and what might be the accelerator or decelerator for adoption and diffusion. This study revealed important implications for mental health policy especially for several specific groups whose mental disorders were undertreated, and could also help policy makers identify sources of variation in mental healthcare while reducing undertreatment. This study was the first one which analyzed a large nationally representative survey dataset, the National Ambulatory

Medical Care Survey (NAMCS), to examine physician, patient and healthcare system factors associated with SSRI/SNRI prescribing for MDD patients. This study provided the first investigation for SSRI/SNRI adoption using such large dataset with long-term cross-sectional data. As patients themselves are getting more and more involved in their own health care decisions, this study was helpful for health care providers to better understand how to assist patients to make decisions on antidepressant medications, and for policy makers to revisit and tailor current policies which may distort a patient's or a physician's decision making on antidepressant medications.

Table 4.2. Descriptive statistics of study subjects

Variable	% or mean (std. dev.)
Provider Characteristics	
Psychiatrist	91.63
Patient Characteristics	
Gender: male	33.20
Age	46.00 (15.95)
Race/ethnicity:	
Non-Hispanic white	84.24
Non-Hispanic black	5.83
Hispanic	7.59
Other	2.33
Primary source of payment:	
Private insurance	52.10
Medicare	14.01
Medicaid	11.16
Self-pay	16.44
All others	6.28
Capitated visits: yes	33.46
Patient belong to HMO: yes	10.69
Capitated HMO	2.96
Comorbidity:	
Psychotic disorders	0.78
Anxiety disorders	21.62
Taking psychotherapy: yes	53.57
Patient education: yes	74.85
Physician's Relationship with Health Care System	
Ownership status:	
Owner of solo practice	53.20
Owner of non-solo practice	19.87
Non-owner	26.93
Region of practice:	
Northeast	27.16
Midwest	17.99
South	30.44
West	24.42
Metropolitan area	89.93
Physician's Relationship with Patient	
Patient seen before	91.91
MDD is primary diagnose	88.37
Antidepressant use:	71.22
SSRI/SNRI antidepressants	40.17
Other newer antidepressants	10.54
Older antidepressants	8.72
Combination pharmacotherapy	40.57
N (total weighted counts)	125,605,444

Table 4.3. Weighted odds ratios of antidepressant use by sample characteristics by logistic regression

Variable	Antidepressant users (%)	Non antidepressant users (%)	Weighted OR	95% Confidence Interval
Provider Characteristics				
Psychiatrist	92.31	89.96	1.2084	(0.8790, 1.6611)
Patient Characteristics				
Gender: male	33.22	33.16	1.018	(0.8611, 1.2034)
Age	45.76#	46.58#	1.006	(0.9853, 1.0272)
Age square	2344.85#	2432.68#	1	(0.9998, 1.0002)
Race/ethnicity:				
Non-Hispanic white	80.18	71.6	1.5217**	(1.2407, 1.8665)
Non-Hispanic black	5.41	5.3	1.4876	(0.9771, 2.2649)
Hispanic	6.24	8.9	---	--- ---
Other	2.13	2.2	1.1941	(0.7166, 1.9898)
Primary source of payment:				
Private insurance	52.27	46.49	---	--- ---
Medicare	13.57	15.07	0.6853**	(0.5242, 0.8957)
Medicaid	9.51	12.78	0.6227**	(0.4752, 0.8160)
Self-pay	15.63	14.97	0.8136	(0.6427, 1.0301)
All others	6.23	5.06	0.7582	(0.5339, 1.0766)
Capitated visits: yes	31.97	36.91	0.9302	(0.7690, 1.1252)
Patient belong to HMO: yes	12.29	6.71	1.3219	(0.9230, 1.8933)
Capitated HMO	3.77	1.09	1.4108	(0.6943, 2.8668)
Comorbidity:				
Psychotic disorders	0.75	0.84	1.3159	(0.3248, 5.3319)
Anxiety disorders	21.50	21.91	1.0938	(0.9043, 1.3230)
Taking psychotherapy: yes	54.44	51.4	0.9412	(0.7909, 1.1200)
Patient education: yes	80.05	61.56	1.0486	(0.8608, 1.2773)
Physician's Relationship with Health Care System				
Ownership status:				
Owner of solo practice	39.65	47.83	0.7473**	(0.6084, 0.9179)
Owner of non-solo practice	16.07	14.76	0.9549	(0.7498, 1.2162)
Non-owner	28.38	23.51	---	--- ---
Region of practice:				
Northeast	26.87	27.86	1.2112	(0.9580, 1.5313)
Midwest	18.37	17.05	1.1442	(0.8874, 1.4752)
South	30.73	29.71	1.0154	(0.8124, 1.2691)
West	24.03	25.38	---	--- ---
Metropolitan area	89.04	92.13	0.7335*	(0.5558, 0.9681)
Physician's Relationship with Patient				
Patient seen before	92.26	91.04	1.3957*	(1.0466, 1.8612)
MDD is primary diagnose	89.17	86.39	1.1365	(0.8833, 1.4625)
N (total weighted counts)	89,453,386 (71.22%)	36,152,058 (28.78%)		

Notes:
1. *p <0.05; **p <0.01
2. Data source: NAMCS 1993-2007
3. #: mean

Table 4.4. Relative risk-ratios of antidepressant use by multinomial logistic regression

Base case: older antidepressants only

Variable	SSRI/SNRI only			Other newer antidepressants only			Combination therapy		
	Weighted RRR	95% CI		Weighted RRR	95% CI		Weighted RRR	95% CI	
Provider Characteristics									
Psychiatrist	0.6439	(0.1891,	2.1923)	1.0501	(0.2755,	4.0022)	3.7906	(0.7643,	18.7998)
Patient Characteristics									
Gender: male	1.0034	(0.6842,	1.4714)	1.3663	(0.8979,	2.0790)	0.9039	(0.5931,	1.3776)
Age	0.9304*	(0.8807,	0.9830)	0.9451	(0.8872,	1.0068)	0.9878	(0.9293,	1.0500)
Age sqruare	1.0006*	(1.0000,	1.0011)	1.0005	(0.9999,	1.0012)	1.0001	(0.9994,	1.0007)
Race/ethnicity:									
Non-Hispanic white	1.3557	(0.6788,	2.7076)	1.0538	(0.4935,	2.2502)	1.6305	(0.7541,	3.5253)
Non-Hispanic black	1.6502	(0.5855,	4.6506)	1.3673	(0.4318,	4.3295)	2.4406	(0.8060,	7.3901)
Hispanic	---	---	---	---	---	---	---	---	---
Other	0.6303	(0.2305,	1.7239)	0.3615	(0.1012,	1.2915)	1.0002	(0.3150,	3.1762)
Primary source of payment:									
Private insurance	---	---	---	---	---	---	---	---	---
Medicare	0.4201*	(0.2124,	0.8307)	0.3894*	(0.1809,	0.8383)	0.6956	(0.3335,	1.4508)
Medicaid	0.4936	(0.2083,	1.1698)	0.4163	(0.1594,	1.0870)	0.7133	(0.2888,	1.7618)
Self-pay	0.9422	(0.5574,	1.5924)	1.4237	(0.7882,	2.5715)	1.0949	(0.5970,	2.0080)
All others	0.6488	(0.3194,	1.3181)	0.7588	(0.3434,	1.6766)	1.3568	(0.6316,	2.9148)
Capitated visits: yes	0.9679	(0.5598,	1.6737)	1.1739	(0.6480,	2.1267)	1.1411	(0.6438,	2.0224)
Patient belong to HMO: yes	1.4008	(0.7020,	2.7954)	2.1902*	(1.0378,	4.6226)	2.1497	(1.0182,	4.5385)
Capitated HMO	1.1414	(0.3524,	3.6964)	0.608	(0.1606,	2.3016)	1.0545*	(0.3054,	3.6402)
Comorbidity:									
Psychotic disorders	0.7199	(0.1442,	3.5947)	1.2619	(0.1797,	8.8628)	0.4039	(0.0478,	3.4150)
Anxiety disorders	1.3517	(0.8447,	2.1631)	1.1379	(0.6657,	1.9452)	1.226	(0.7290,	2.0619)
Taking psychotherapy: yes	0.7504	(0.5021,	1.1214)	0.7876	(0.5055,	1.2270)	0.7759	(0.4968,	1.2119)
Patient education: yes	1.3811	(0.7784,	2.4504)	1.1215	(0.5953,	2.1127)	1.3011	(0.6844,	2.4735)
Physician's Relationship with Health Care System									
Ownership status:									
Owner of solo practice	0.8629	(0.5349,	1.3919)	0.6716	(0.3916,	1.1517)	0.7999	(0.4760,	1.3442)
Owner of non-solo practice	1.2702	(0.7350,	2.1953)	1.2249	(0.6677,	2.2471)	1.1026	(0.6022,	2.0191)
Non-owner	---	---	---	---	---	---	---	---	---
Region of practice:									
Northeast	0.8412	(0.5199,	1.3611)	0.5701*	(0.3317,	0.9797)	0.571*	(0.3349,	0.9736)
Midwest	0.8715	(0.5028,	1.5104)	0.8264	(0.4487,	1.5218)	0.717	(0.3926,	1.3096)
South	1.0095	(0.6146,	1.6584)	0.7053	(0.4039,	1.2317)	0.6729	(0.3897,	1.1618)
West	---	---	---	---	---	---	---	---	---
Metropolitan area	0.6046	(0.3404,	1.0736)	0.5729	(0.3019,	1.0872)	1.013	(0.5327,	1.9263)
Physician's Relationship with Patient									
Patient seen before	0.8271	(0.3970,	1.7229)	0.7431	(0.3232,	1.7083)	0.8865	(0.3862,	2.0348)
MDD is primary diagnose	1.4698	(0.7999,	2.7006)	1.6021	(0.8016,	3.2020)	1.0404	(0.5380,	2.0122)
Inverse Mill's ratio	11.7713	(0.5793,	239.20)	5.7721	(0.2103,	158.40)	3.2922	(0.1222,	88.70)

Notes:
1. *p <0.05; **p <0.01
2. N (total weighted) = 70,383,022
3. Data source: NAMCS 1993-2007

Table 4.5.Relative risk-ratios of antidepressant use by multinomial logistic regression in different time periods

Base case: older antidepressants only

	Weighted RRR: SSRI/SNRI only				Weighted RRR: other newers only				Weighted RRR: combination therapy			
Variable	1993-1997	1998-2001	2002-2004	2005-2007	1993-1997	1998-2001	2002-2004	2005-2007	1993-1997	1998-2001	2002-2004	2005-2007
Physician Characteristics												
Psychiatrist	3.7667	0.3514	0.5424	---#	71.8913*	0.5105	11.6044	---#	---#	3.5241	1.8803	---#
Patient Characteristics												
Gender: male	3.4811*	0.6142	3.3594	0.7990	7.4685**	0.7801	4.4853*	1.1209	1.9170	0.3165**	4.7405*	0.8226
Age	0.9070	0.9749	0.8986	0.8545**	0.9194	1.0989	0.8877	0.8474**	0.8997	1.0872	0.9217	0.8921
Age square	1.0007	1.0002	1.0006	1.0013*	1.0006	0.9990	1.0008	1.0016*	1.0009	0.9991	1.0005	1.0011
Race/ethnicity												
Non-Hispanic white	0.5835	4.9613**	1.1751	0.3390	0.6367	4.2274*	2.2047	0.2768	1.0197	4.3661*	2.6708	0.5019
Non-Hispanic black	0.3383	2.1593	---#	1.2268	1.8866	1.2672	---#	0.9823	0.5465	3.1025	---#	0.9338
Hispanic	---	---	---	---	---	---	---	---	---	---	---	---
Other	0.2752	1.0504	---#	0.6561	0.9195	0.3447	---#	0.2646	---#	1.7576	---#	0.8225
Primary source of payment												
Private insurance	---	---	---	---	---	---	---	---	---	---	---	---
Medicare	1.5498	0.1301**	1.6195	0.4932	1.1707	0.2367*	2.1864	0.3087	1.0073	0.5313	1.0944	0.5689
Medicaid	0.5818	0.2715*	0.5482	0.8560	0.3081	0.2978	0.4470	0.4623	1.5394	0.3586	0.4925	1.0657
Self-pay	1.6541	0.3707*	2.3902	1.1366	4.7838	0.4343	6.2138*	0.6839	5.9009*	0.2334**	2.5154	1.7166
All others	1.8717	0.3763	2.9136	---#	0.2731	0.3857	10.0210	---#	5.2309	0.5357	7.3055	---#
Capitated visits: yes	0.2416	2.2345	2.0085	0.6767	0.0046**	1.6443	2.7331	1.3532	0.2297	0.6215	2.4874	1.0452
Patient belong to HMO: yes	4.7141	0.8795	---#	0.0444	3.2810	1.5826	---#	0.1074	4.9615	1.6024	---#	0.1466
Capitated HMO	0.8100	0.6495	---#	1.4590	46.3174	0.3016	---#	1.2002	0.5530	2.3114	---#	1.1565
Comorbidity												
Psychotic disorders	---#	---#	---#	---#	---#	---#	0.7039	---#	1.0215	---#	0.2456	---#
Anxiety disorders	1.0188	0.7753	2.0205	1.5247	0.3017	0.7883	0.8924	1.1679	2.0723	0.4060	1.9649	1.8845
Taking psychotherapy: yes	0.5123	0.5687	2.1638	0.4878	0.7366	0.6525	1.7071	0.4679	0.4001	0.9704	1.6199	0.4777
Patient education: yes	---#	2.2694	0.5226	1.5771	---#	1.5948	0.5312	1.1806	---#	0.8207	0.3802	1.9667
Physician's Relationship with Health Care System												
Ownership status												
Owner of solo practice	4.3025*	0.9932	0.7763	0.6445	0.3134	0.6892	1.7395	0.7472	5.4979	0.8606	0.7451	0.5477
Owner of non-solo practice	2.9286	1.8630	0.8454	0.6800	3.5714	1.8168	2.6050	0.5193	13.7945*	1.0593	0.6540	0.8105
Non-owner	---	---	---	---	---	---	---	---	---	---	---	---
Region of practice												
Northeast	1.0233	0.8320	0.8830	0.4641	0.9166	0.6342	0.7802	0.1834*	0.9211	0.4007*	1.3336	0.3668
Midwest	0.4436	0.4903	0.7252	1.1306	6.5628*	0.6197	1.1233	0.2967	0.1278	0.5957	1.0526	0.9031
South	0.7034	0.4872	3.2554	0.8337	0.5440	0.5274	3.1893	0.2663	0.1737	0.7939	3.4721	0.3418
West	---	---	---	---	---	---	---	---	---	---	---	---
Metropolitan area	2.1049	0.5799	1.3489	0.3110	0.3498	0.7113	0.6903	0.2353	9.7442	0.6241	1.6883	0.5528
Physician's Relationship with Patient												
Patient seen before	1.5804	0.5595	0.2881	1.1471	3.3498	0.2924	0.2598	0.8254	2.6856	0.2661	0.5041	4.4047
MDD is primary diagnose	1.6895	2.1191	4.0956	0.4396	3.3158	2.3187	2.0685	1.2038	1.6480	1.0067	3.7239	0.4214
Inverse Mill's ratio	1.5292	12.7798	0.0646	0.4593	17.1332	13.3945	0.0003	0.3233	7.8174	3.3451	0.1734	2.2496
N (weighted)	5,683,644	15,375,216	11,098,842	16,894,115	5,683,644	15,375,216	11,098,842	16,894,115	5,683,644	15,375,216	11,098,842	16,894,115

Notes:

1. *p <0.05; **p <0.01
2. Data source: NAMCS 1993-2007
3. #: dropped due to extreme values in dataset

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CHAPTER 5

DISSERTATION MANUSCRIPT 2

(**Title:** ANTIDEPRESSANT UTILIZATION, ADHERENCE AND HEALTH CARE SPENDING IN THE UNITED STATES: THE CASE OF MDD PATIENTS 2000-2007)

Antidepressant Utilization, Adherence and Health Care Spending in the United States: The Case of MDD Patients 2000-2007

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Background: Innovative antidepressants such as SSRIs and SNRIs have been widely adopted. However, the differences in patient antidepressant adherence and associated health care spending across patient factors and antidepressant choice needed further research.

Objective: This study was trying to understand how patient factors and antidepressant choice influenced medication adherence and associated health care expenditure.

Methods: A retrospective cross-sectional study was conducted using the 2000-2007 Medical Expenditure Panel Survey (MEPS) database. A multiple OLS regression was used to examine MDD patient's antidepressant adherence measured by proportional days covered (PDC). A two-part model was implemented to study the impact of MDD patient factors and antidepressant choice on associated health care expenditure.

Results: Linear regression models indicated that patient gender, ethnicity and health insurance status were associated with differential levels of antidepressant adherence and associated health expenditure. Hispanic ethnicity was associated with decreased antidepressant adherence compared to non-Hispanic white (β=12.53, p<0.05) and other ethnicities (β=28.27, p<0.01). Patient who were covered by public insurance had better PDC compared to uninsured patients (β=16.23, p<0.05). Patient who were covered by private insurance spent more on MDD-specific drug compared to uninsured patients (β=0.36, p<0.05). Higher antidepressant adherence (PDC) was associated with higher MDD-specific drug expenditure (β=0.03, p<0.01). Use of innovative antidepressants such as SSRIs and SNRIs was associated with an increase in MDD-specific drug expenditure, whereas its associations with adherence were not significantly revealed.

Conclusions: Differences in antidepressant adherence and health care spending across patient factors could have important policy implications for drug formularies and health disparities; there are certain patient populations that may be at higher risk for inadequate health care. Solutions for gaps between optimal and suboptimal health care for patient mental health caused by systematic differences in sociological factors need to be well tailored. We need policy makers to be engaged in designing effective policy interventions

to improve patient medication adherence, and to fund cost-effectiveness studies to improve patient outcomes and in turn, reduce associated health expenditure.

Keywords: health expenditure; drug expenditure; adherence; antidepressant; SSRI; SNRI; major depressive disorder (MDD); patient factor

INTRODUCTION

Mental health conditions are common not only in the United States but also in many developed countries. Estimation in recent research shows that 26.2 percent of Americans ages 18 and older suffer from a diagnosable mental disorder in a given year.[1] Among mental disorders, major depressive disorder (MDD) is attributed as the leading cause of disability in the U.S. for ages 15-44, and affects 6.7 percent of the U.S. population age 18 and older in a given year.[2]

MDD is regarded as both an acute and a chronic disease. Epidemiologic research shows the lifetime prevalence rate is between ten to twenty percent.[3, 4] According to the National Comorbidity Survey, the lifetime and annual prevalence of MDD are 17.1 percent and 10.3 percent, respectively.[5] In addition, the degree of relapse and reoccurrence is likely to be high for MDD patients and requires well maintenance. MDD patients are also recommended long-term maintenance treatment to prevent recurrence or the emergency of a new episode of depression.[6-10] MDD is therefore regarded as a chronic disease to some extent,[3, 11] and antidepressant medication may be needed in a longer term. With the nature of being both acute and chronic disease, a person with untreated or poorly treated MDD cannot function well for his/her daily, business and social activities.

Depression in general causes economic and social burdens. In research conducted by Greenberg et al. in 1993; the authors found the total cost of depression in 1990 was $43.7 billion with $12.4 billion in direct costs, $23.8 billion in excess absenteeism and productivity loss, and $7.5 billion in suicide-related earning losses.[12]

Although depression is categorized as a mental disorder, there is neurological evidence that shows depression is associated with neurotransmitters in a person's brain.

Neurotransmitters such as serotonin, norepinephrine, adrenaline and dopamine are all associated with depression. Among these chemicals, the principal neurotransmitter associated with depression is serotonin. Based on this neurological evidence, current antidepressant medication attempts to correct the imbalance of neurotransmitters. Such neurological findings essentially provide significant evidence to emphasize and support why pharmacotherapy has been playing an increasing central role in the treatment of mental disorders. There are 5.5 million more Americans receiving treatment for mental health and substance abuse in 2001 than in 1996, and the percentage using psychotropic drugs has increased.[13] As a result, the cost of these drugs is a rapidly increasing component of mental health care expenditures.

As Prozac™ (fluoxetine Hcl), the first selective serotonin reuptake inhibitors (SSRI) antidepressant, was introduced in 1988, SSRIs have become the major and preferable medication treatment for MDD patients. SSRIs, compared to old generation antidepressants (i.e. tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs)), have a unique treatment mechanism which selectively increases the level of serotonin.[14] SSRIs were soon adopted by physicians and patients because of their innovative mechanism of action and superior efficacy. In mid-1990, serotonin-norepinephrine reuptake inhibitor (SNRI), another innovative class of antidepressants, was introduced to treat MDD. Unlike SSRIs which act more selectively upon serotonin, SNRI increases both serotonin and norepinephrine to treat MDD. SNRIs have also been widely adopted by physicians and patients as a prescription for MDD treatment recently.

The volume of SSRIs prescribed has risen since it was introduced, and thus amounts to around 80% of the $3.5 billion antidepressant market in the U.S. in 1995[15]

and has been growing 25% every year.[16] However, the adoption of innovative SSRIs/SNRIs is not only characterized by the physician prescription volume but is also reflected in patient's adherence to medications.

Adherence, to some extent has the same meaning as compliance, is defined as patients taking the correct dose during the proper time interval for the appropriate time period.[17] Although SSRIs are widely accepted and used, it is however that, medication treatment adherence in patients with mental disorders is low in general. Even effective medications cannot improve patients' mental health status without good medication adherence. In addition, it has been widely reported that medication non-adherence is highly associated with adverse health conditions which increases economic burden on the healthcare system.[18-20] Previous research shows major differences in medication adherence among various antidepressants, which are primarily attributed to intolerability of side effects and dosing inconvenience.[21, 22] As a result, antidepressant choice and adherence are two closely interlinked issues and dimensions of antidepressant utilization which were jointly explored in this study.

Adherence to pharmacotherapy is influenced by patients, providers and the social environment; there are several factors which may affect patient medication adherence. Specifically, patient demographics such as ethnicity, socioeconomic status and levels of education have been reported to be associated with medication adherence.[23, 24] Moreover, patient's psychological factors, such as health beliefs, perceived seriousness of illnesses, are also associated with patient's medication adherence.[25, 26] In addition, systematic factors, such as patient's health insurance status and access to health care, affect medication adherence as well.[18, 23] Finally, therapy-related factors, such as the number of

medications, dosing frequency, administration schedule, complexity of treatment regimen, side effects, and cost of medication, contribute substantially to patient's medication adherence.[23]

Research has shown poor medication adherence to both antidepressants and antipsychotics in patients with mental disorders. It has been shown that early discontinuation of antidepressants is widespread.[27] In particular, 28% to 40% of patients with depression discontinue antidepressant medication, which significantly increases health care expenditures.[28] Besides, reports reveal that rates of non-adherence to antipsychotics range from 20% to 89%, and 50% on average.[29, 30] In other words, research has shown that non-adherence to pharmacotherapy in mentally ill patients is indeed a serious problem and needs more research. However, previous studies lack for either national representability or consideration for choice of antidepressants, which may be unable to indicate policy implications nationally or target on specific types of antidepressants. In this research, the national representative Medical Expenditure Panel Survey (MEPS) dataset was used for its national generalizability. "Proportion of days covered (PDC)" was adopted to measure medication adherence for different types of antidepressants in this study.

In addition, patient antidepressant adherence could be associated with health care spending. Previous research showed that for some chronic diseases, increased medication utilization might contribute to an economic return driven by better long-term medication adherence.[31] Gilmer and colleagues found that hospital costs were lower whereas pharmacy costs were higher for those patients who were better adherent to their antipsychotic medications among Medicaid beneficiaries with schizophrenia.[32] Thieda

and colleagues also found a similar result that lower rates of medication adherence led to higher costs of treating schizophrenia.[33] As mentioned in previous the chapter, MDD patients are recommended taking long-term maintenance treatment to prevent reoccurrence [6-10] and therefore an economic return associated with better antidepressant adherence is expected. Although the association between antidepressant adherence and related health care spending was explored in MDD treatment, previous studies lacked for the consideration for antidepressant choice and its association with antidepressant medication and related health care expenditure.

In particular in the U.S., because of the existence of managed care, the high volume of uninsured people, and the elevating costs of pharmaceuticals, sociological factors such as patient health insurance status could have impact on patient medication utilization. As a number of innovative antidepressants have been introduced and the aforementioned concerns about associated patient outcomes and health care costs, the objective of this research was trying to understand how patient factors and antidepressant choice influenced medication adherence and associated health care expenditures given patient antidepressant choice was considered. Establishing the association between antidepressant choice and antidepressant adherence, and in turn, their associations with related health care expenditures could benefit policy makers to more accurately target on effective adherence-improving strategies. This study used the MEPS dataset along with Anderson's model of health care utilization as the conceptual framework, and the two-part linear regression model as the statistical method, to explore how patient factors and antidepressant choice influenced medication adherence and associated health care expenditures in MDD treatment in the U.S.

METHODS

Conceptual framework and research hypothesis

This was a retrospective cross-sectional study. This research applied a health behavior model as a conceptual framework to guide study hypotheses. Anderson model of health care utilization was applied to analyze how patient factors and antidepressant choice influenced medication adherence and associated health care expenditure for MDD patients in the U.S.

The basic Anderson model consists of predisposing characteristics, enabling resources and need. The predisposing components contain demographic, social structure and health belief variables such as race, ethnicity, gender, health attitudes, values, and genetic factors. The enabling components contain resources available to the individual such as personal income, health insurance, and access to health care. The need refers to professional judgment about people's health status and their need for medical care.[34] Among the above three population components, predisposing characteristics precede enabling components which in turn, precede the need components. For this study, Anderson model served as a good framework to characterize not only dependent and independent variables but their relationship, and thus enabled the study to characterize several important predictors on patient medication adherence and associated health care expenditures.

Study sample

This study used the 2000-2007 Medical Expenditure Panel Survey (MEPS) to obtain a nationally representative sample of MDD patients whose antidepressant

medication adherence and associated health care expenditures could be studied. The MEPS is a national probability survey cosponsored by the Agency for Healthcare Research and Quality (AHRQ) and the National Center for the Health Statistics (NCHS). The MEPS survey is designed to provide nationally representative estimates of health care use, expenditures, source of payments, and insurance coverage for the U.S. civilian noninstitutionalized population. The MEPS dataset consists of four major components: the Household Component (HC), the Medical Provider Component (MPC), the Insurance Component (IC) and the Nursing Home Component (NHC).

For research purposes, this study used the HC component of the MEPS. First, the HC collects data from families and individuals in selected communities across the U.S. and are self-reported. The HC includes demographics, health conditions, health status, income, health insurance coverage, employment, and both use and expenditure and health care services collected using computer-assisted personal interviewing technology. For instance, the latest panel (Panel 11) of the MEPS-HC was collected in years 2006 and 2007 with five rounds of interviews and can be used to analyze changes in the two-year period. Secondly, Secondly, although the MPC component was not used directly in this study, it supplements and/or replaces information on medical care expenditures reported by the HC by contacting all hospitals and pharmacies by the household respondents. The MPC is conducted through telephone interviews and record abstraction.[35]

There were several subsets of the HC component that were used in this study. In addition to the MEPS full-year consolidated data files (i.e. the pooled file of five rounds within one calendar year) from year 2000 to year 2007, three additional groups of files were also used for the purpose of this study. First, the medical condition file which is an

event file that provides detailed information of each medical condition reported by the household respondents, was used to identify patients with mental disorders (MDD and comorbid mental disorders). Second, the prescription drug files are also event files that provide data on all prescribed medicines which are self-reported by the HC respondents and supplemented by the MPC pharmacies. Specifically, counts of prescribed medicine utilization are based entirely on HC, whereas drug information such as expenditure and payment data, as well as details of medications (e.g., strength, quantity, etc.) is from the Pharmacy Component (PC) within the MEPS-MPC. Third, the longitudinal weight files were used to correct the sample weights according to the MEPS survey structure (five interview rounds in a two-year period panel) to develop cross-sectional estimates.

This study focused on patients with MDD, therefore only patients diagnosed with MDD were extracted from the MEPS datasets and included in this study. Sample extraction was according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR, American Psychiatric Association, 2000) classification of mental disorders identified by the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes contained in MEPS. Only subjects with ICD-9 codes 296.2x (major depressive disorder: single episode) and 296.3x (major depressive disorder: recurrent) were MDD patients to be extracted. In addition, this study excluded children from the study sample in order to avoid the heterogeneity of treatment between adults and children with MDD.

Unfortunately the public-available MEPS dataset only provides the first three-digit ICD-9 codes due to patient's confidentiality concerns. That is, in this study all patients with ICD-9 code 296 were extracted from the MEPS dataset. However, ICD-9

code 296.xx includes both MDD and bipolar disorder. It is recommended that usually patients with bipolar disorder to be treated by mood stabilizers (for depression episodes) and antipsychotics. Antidepressants such as SSRIs are very seldom used singly to treat depression episodes of bipolar disorder; clinical research shows that several types of antidepressants may trigger patient's maniac episodes unless mood stabilizers are adjunctively used.[36] In order to exclude bipolar patients from the study sample, an extra exclusion strategy was accordingly implemented: patient who used mood stabilizers and antipsychotics were excluded from the study sample.

In order to avoid the heterogeneity of treatment between adults and children with MDD, this study excluded children from the study sample. Also in order to study their antidepressant adherence, only MDD patients who received at least one antidepressant were included in this study.

Categories of antidepressants

In this study, antidepressants were categorized as SSRI/SNRI antidepressants, other newer antidepressants, and older antidepressants (TCAs, MAOIs and other older antidepressants.) The detailed list of antidepressants for each category in the MEPS dataset is shown in Table 5.1. Patients who took more than one types of antidepressants were classified as having combination therapy. The creation of combination therapy was to avoid double-counting of antidepressant utilization. Under this categorization, SSRIs and SNRIs were grouped for their similar pharmacological mechanisms. Other newer antidepressants, for example bupropion and mirazapine, were separated from SSRI/SNRI

category for their different drug mechanisms; this categorization benefited to examine the net effects of SSRI/SNRI antidepressants from other newer ones.

Table 5.1. Categories of Antidepressants

Type of Antidepressant	Medications
SSRI/SNRI antidepressants	citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine,
Other newer antidepressants	bupropion, mirtazapine, nefazodone, mianserin
Older antidepressants	amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, isocarboxazid, maprotiline, nortriptyline, phenelzine, protriptyline, selegiline, tranylcypromine, trazodone, trimipramine,

Measurements

Using Anderson health care utilization model as a framework for analysis, there were three groups of social factors in this study: (1) predisposing factors; (2) enabling factors; and (3) need factors. Specific covariates are described below.

Measures of predisposing variables included age, gender, education year, race/ ethnicity, geographic region, and metropolitan area. The measures of enabling factors included total annual personal income, health insurance status, patient HMO status, and prescription drug insurance status. The need factors included comorbid mental disorders and evaluated health status (SF-12 summary scores). These aforementioned factors and measures were used as independent variables in this study. Specific covariates of this study are listed in Table 5.3 and Table 5.4.

One of the research outcomes of this study was patient's antidepressant medication adherence. This study adopted the proportion of days covered (PDC) as the measure of medication adherence to capture the suggested long-term use of antidepressants and due to the data availability of MEPS. PDC is essentially a continuous, multiple-interval measure of medication availability according to Steiner and Prochazka's categorization, which is suggested to be more useful in testing cumulative drug dosage and longer-term exposure of medication.[37, 38] As discontinuation of antidepressants brings high likelihood of recurrence and serious withdrawal symptoms, antidepressants are suggested for long-term maintenance use. [6-10] Therefore, the use of PDC as a continuous, multiple-interval measure of medication availability is an appropriate measure for antidepressant adherence. Besides, Martin and colleagues show that PDC is less likely to overstate medication adherence compared with other measures and should be considered when there is multiple medications within a class of medication which are used concurrently,[39] which supports the use of PDC as an appropriate measure for the purpose of this study. In addition, the MEPS prescription data file provided exactly the needed drug information for PDC calculation.

In the calculation of PDC, medication adherence was defined as the proportion of "days covered" by a given drug in each time interval, based on number of days supplied and quantity of medication dispensed for each filled prescription. The PDC standardizes the time period over which adherence is examined.[48] The PDC can be calculated by the following formula according to its definition:

$$\text{PDC}(\%) = \frac{\text{Number of days with drug on hand}}{\text{Number of days in specified time interval}} \times 100.$$

The denominator for PDC is a clinically meaningful number of days that is the same for all intervals and patients. In this study, 365 days (one year) was defined as the duration of study in order to capture the suggested long-term use of antidepressants and due to the data structure of MEPS. Regarding the numerator, however, the MEPS dataset did not provide information regarding "days supply" of medication. Therefore, the days of supply was calculated as "quantity of prescriptions dispensed" divided by "number of times took per day". "Quantity of prescriptions dispensed" could be obtained simply from the MEPS prescription drug files, and "number of times took per day" for every single antidepressant was obtained from the daily dosing recommendation at EPROCRATES ONLINE®, an online drug dictionary. The MEPS prescription drug files contained all drug dispense records of every single patient within one survey year, therefore the numerator in the PDC formula was in fact the days supply aggregated from every single drug records within one year. According to the definition of PDC and all the available information, PDC in this study was calculated and defined as follows:

$$\text{PDC}(\%) = \frac{\text{Number of days with drug on hand}}{\text{Number of days in specified time interval}} \times 100$$

$$= \frac{\Sigma\,(\text{Quantity of drugs dispensed} / \#\text{ of times took per day})}{365} \times 100.$$

Note that differential dosage forms of drugs were considered in the coding of drug entries by MEPS already as well as in compiling daily dosing recommendation from EPOCRATES ONLINE. For example, the suggested "number of times took per day" from EPOCRATES ONLINE for Wellbutrin-SR™ is 2, whereas "number of times took per day" for Wellbutrin-XL™ is 1. That is, the calculation of PDC in this study implicitly considered differential dosage forms for each medication. This method of PDC

calculation in this study provided a drug- and strength- specific measure which was more accurate than the measures in previous studies.

The PDC was the dependent variable in this study. Previous literature suggested highly medication adherent if PDC is larger than 80% in a given interval, and partially adherent if PDC is at the range of 20% to 80%. Those with PDC less than 20% were categorized as non-adherent.[40, 41]

The health care expenditure associated with antidepressants and their adherence was studied as well. There were four associated healthcare expenditures studied: outpatient (including ER) visit expenditure, inpatient visit expenditure, MDD-specific drug expenditure, and total health expenditure. The MDD-specific drug expenditure was aggregated from all drug records in the MEPS prescription drug files by each patient, where as the other three expenditures were directly obtained from the MEPS full-year consolidated data files.

Statistical Analyses

A multiple OLS regression was used to examine MDD patient's antidepressant adherence, which is shown as follows:

$$\begin{aligned}&\text{PDC}_{it}(\text{antidepressant medication adherence})\\&=\beta_0+\beta_1(\text{patient predisposing factors})_{it}+\beta_2(\text{patient enabling factors})_{it}\\&+\beta_3(\text{patient need factors})_{it}+\beta_4(\text{type of antidepressant})_{it}+\beta_5(\text{year})+\varepsilon_{it}\end{aligned}$$

where PDC stands for the proportional days covered to measure antidepressant adherence, and ε is the error term. Year-fixed effects and robust standard error estimates were incorporated in this model.

In addition, a two-part model was implemented to study the impact of MDD patient factors and antidepressant choice on associated health care expenditure. Health care expenditure data usually contain a large number of zeros as which there is a large proportion of the sample with no use of related health care in the study period. Therefore, a two-part regression model was used to capture this nature of health care expenditure data. The first part of the model was a logit model which predicted the probability of having some specific health care (e.g., outpatient visits). The second part used OLS regressions to predict the continuous amount of associated health care expenditures, given a patient had any of this specific health care. The four health care expenditures examined in this study were (1) outpatient visit expenditure (including ER visit expenditure); (2) inpatient visit expenditure; (3) MDD specific drug expenditure; and (4) total health expenditure. The two-part model is shown in the following equations:

Part 1: Logit:

$$\begin{aligned}&\Pr[Y_{it}[\text{health care utilization}] = 0 \text{ or } 1] \\ &= f[\beta_0 + \beta_1(\text{patient predisposing factors})_{it} + \beta_2(\text{patient enabling factors})_{it} \\ &+ \beta_3(\text{patient need factors})_{it} + \beta_4(\text{type of antidepressant})_{it} + \beta_5(\text{PDC}) + \beta_6(\text{year})] + \varepsilon_{it}\end{aligned}$$

where $Y = 1$ if some specific health care is utilized and $Y = 0$ if not; $f(\cdot)$ is the cumulative density function (CDF) of logistic distribution and ε is the error term.

Part 2: Linear Regression: (given $Y = 1$)

$$\begin{aligned}&\ln(\text{Health care expenditure}) \\ &= \beta_0 + \beta_1(\text{patient predisposing factors})_{it} + \beta_2(\text{patient enabling factors})_{it} \\ &+ \beta_3(\text{patient need factors})_{it} + \beta_4(\text{type of antidepressant})_{it}\end{aligned}$$

$$+ \beta_5(\text{PDC})_{it} + \beta_6(\text{year}) + u_{it}$$

where only observations with $Y = 1$ in Part 1 are included; health care expenditures are in logarithm formats; and u is the error term. Please refer to Table 5.3 for detailed list of independent variables in this study.

In this study, among the four studied health care expenditures, only (1) outpatient visit expenditure and (2) inpatient visit expenditure contained zeros and thus were examined using the two-part model, whereas (3) MDD specific drug expenditure and (4) total health expenditure contained no zeros and hence were examined simply using the OLS regressions (which is essentially the second part in the two-part model.)

Besides, in order to obtain national estimates, all analyses were weighted. However, the three-stage weighting scheme in the MEPS was lost because of the complicated sample extraction process in this study. This study alternatively adopted the weighting strategy suggested by Lee et al.,[42] which divided each weight by the average weight for the whole study sample. This weighting method provided the advantage that the MEPS weighting scheme could be retained and incorporated without inflating the sample size. In addition, in order to control for year effects, the year-fixed models were implemented. Statistical software Stata® version 11 was used to conduct all statistical analyses.

RESULTS

[Insert Table 5.2.]

A total weighted number of 2,111,615 subjects, who were diagnosed as MDD and prescribed antidepressants, were studied. Table 5.2 outlines the descriptive statistics of

the study sample. First regarding patient predisposing factors, a majority of study subjects were female (69.76%), aged between 26 and 49 years old (50.11%), and non-Hispanic white (85.63%) MDD patients. A large proportion of the study subjects resided in metropolitan areas (79.56%). Regarding patient enabling factors, a majority of study subjects had annual personal income less than $20,000 (52.97%). More than half of the study subjects were covered by private health insurance (61.64%) and prescription drug insurance (54.69%); less than one-third of the study samples belonged to HMOs (29.02%). Regarding patient need factors, only a small proportion of patients had comorbid psychotic disorders (3.71%), whereas around one-fourth patients were diagnosed comorbid anxiety disorders (23.43%). The study subjects had relatively poor SF-12 PCS and MCS scores (46.62 and 40.85 out of 100, respectively).

A majority of patients were prescribed SSRI/SNRI antidepressants (71.45%) whereas only a very small proportion of patients were prescribed older generation antidepressants (2.67%). Patients on average only partially adhered antidepressants (PDC=43.24 out of 100) in which only less than one-fourth patients highly adhered to medications (23.45%). Regarding associated health care expenditure, the study subjects on average spent $8,747 on all health care annually and $447 on MDD-specific medications.

[Insert Table 5.3.]

The results of the year fixed-effect linear regression examining the impacts of patient factors and medication choice on antidepressant adherence are reported in Table 5.3. Hispanic ethnicity was associated with decreased antidepressant adherence compared to non-Hispanic white and other ethnicities ($p<0.05$ and $p<0.01$, respectively). Patient

who were covered by public insurance had better PDC compared to uninsured patients (p<0.05). The results did not reveal any significant associations between types of antidepressants used and patient's medication adherence (p<0.05).

Table 5.4 and Table 5.5 report the statistical results examining the impact of patient factors and antidepressant utilization on associated health care expenditure. As mentioned in the previous section, among the four examined health care expenditures, only outpatient and inpatient expenditures had a large fraction of zeros and hence analyzed by a two-part model (models (1) and (2) in this study), whereas MDD-specific drug expenditure and total health expenditure contained no zeros in the study sample and therefore were analyzed simply using the OLS regression models (models (3) and (4) in this study). Therefore, only models (1) and (2) are reported in Table 5.4 whereas all models (1)-(4) were reported in Table 5.5.

[Insert Table 5.4.]

Table 5.4 shows the weighted odds ratios (ORs) of the year-fixed effect logistic regression predicting the probability of having outpatient and inpatient visits of the study samples. Patients who were covered by public health insurance were more likely to attend outpatient visits (p<0.05). It was statistically significant that the choice of types of antidepressants had no impact on the probability of attending outpatient visits (p<0.01). Table 5.4 also reveals that patient HMO status (p<0.05), higher annual personal income (p<0.05), and having comorbid psychotic disorders (p<0.01) had positive associations with an increased use of inpatient visits.

[Insert Table 5.5.]

Table 5.5 reports the year-fixed linear regression models examining the impacts of patient factors and antidepressant utilization on associated health care expenditures. All study samples were included in models (3) and (4) whereas only patient who had non-zero outpatient or inpatient expenditures were included in models (1) and (2).

Regarding model (1), Table 5.5 shows that having prescription drug insurance was associated with an increase in outpatient expenditure in MDD patients ($p<0.05$). Higher patient needs attributed to higher outpatient expenditure. MDD patients with comorbid anxiety disorders had higher outpatient expenditure ($p<0.05$), whereas MDD patients with better physical health status spent less on outpatient visits ($p<0.01$). Regarding model (2), Table 5.5 shows that MDD patients who had relatively higher personal income ($40,000 to $60,000) spent less on inpatient visits ($p<0.05$).

The results of model (3) in Table 5.5 show a negative association between patient being older than 65 years old and MDD-specific drug expenditure compared to patient who were aged between 18 to 25 ($p<0.05$). MDD patient who were covered by private insurance spent more on MDD-specific drug compared to uninsured patients ($p<0.05$). Besides, Table 5.5 consistently shows a positive association between the use of SSRIs/SNRIs, other newer antidepressants and combination therapy, and increases in MDD-specific drug expenditure comparatively to the use of older generation antidepressants (all $p<0.01$). In addition, higher antidepressant adherence (PDC) was associated with higher MDD-specific drug expenditure ($p<0.01$).

Table 5.5 also shows the results of model (4) examining the association between total health expenditure and patient factors as well as antidepressant utilization. Non-

Hispanic patients with MDD had higher total health expenditure than Hispanic patients (p<0.01). Patients who had annual personal income ranged $20,000 to $40,000 spent more on total health care (p<0.05). Also it was significant that patients covered by either private or public health insurance had higher total health expenditure than uninsured patients (p<0.01 and p<0.05). It was intuitive and significant that higher physical health status was associated with a decrease of total health expenditure (p<0.01). Finally, although choice of antidepressants was not revealed significant positive or negative associations with total health expenditure, better antidepressant adherence (PDC) was significantly associated with an increase in total health expenditure (p<0.05).

DISCUSSION

While innovative antidepressants such as SSRIs and SNRIs have been widely adopted for MDD treatment, this study noticed that patient antidepressant adherence and associated health care expenditure varied with several patient factors. Furthermore, patient antidepressant adherence was revealed to positively associated with MDD-specific drug expenditure and patient total health expenditures. However, patient choice of antidepressants did not show significant associations with patient medication adherence.

There were several strong associations that are of great interest. The first association that was of great interest was the substantial racial/ethnic differences in patient antidepressant adherence and health care utilization. The findings of this study indicated that Hispanic patients had lowest level of antidepressant adherence and were associated with lower likelihood of attending outpatient visits and lower total health care

spending among all other races/ethnicities. This finding echoed several previous studies which concluded racial/ethnic health disparities in depression treatment; Hispanic patients had less access to appropriate health care and were undertreated for mental disorders.[43-46] Racial/ethnic health disparities may come from discrimination, differential insurance benefits, lower rates of participation in health care decision making, and differential attitudes toward use of antidepressant therapy.[47] However, the sources of racial/ethnic health disparities in MDD treatment were not identified in this study; further research is needed to disentangle it. Although racial/ethnic health disparities have been researched substantially, effective policy interventions are still urgently needed to solve the issue.

The second association that was of great interest was the impact of health insurance on both patient antidepressant adherence and health care utilization. The findings of this study significantly showed substantially higher medication adherence in patient with health insurance compared to those who were uninsured. Uninsured MDD patients were more likely to suffer from under-treatment of MDD, implied by the significantly lower total heath care expenditure and MDD-specific drug expenditure. Uninsured patients were inevitably unable to initiate and follow up MDD treatment compared to patients with private or public health insurance.

Third, it was intuitive and evidenced by this study that better patient health status was associated with lower heath care spending. Patients who had better physical health status were associated with decreases in both outpatient expenditure and total health expenditure. This finding implied that an improvement in health status from effective MDD treatment might in turn result in lower future total health care costs. Therefore, we

still need effective policy interventions to efficiently improve patient medication adherence.

Fourth, this study revealed that patient choice of antidepressant was significantly associated with MDD-specific drug expenditure. Use of innovative antidepressants such as SSRI/SNRI and other newer antidepressants was associated with higher drug expenditures; this elevated drug expenditure was possibly due to higher-priced innovative antidepressants. However, a previous study by Frank and colleagues show that using SSRIs to treatment depression may either reduce the overall health care spending or keep the total spending the same,[48] which implies the use of innovative antidepressants may cost more money but may in turn, result in better cost-effectiveness in MDD treatment. This study found the similar results that innovative antidepressants were associated with lower total health expenditures; however these results were not statistical significant.

Finally, the association with great interest was the positive association with better antidepressant adherence and drug expenditure. While better antidepressant adherence required better compliance on drug refills, which obviously would raise total MDD drug expenditure. As a saving in total health expenditure from better antidepressant adherence was expected, this study showed an opposite result that better antidepressant adherence was associated with slightly increased total health expenditure. It was very likely that the expected economic return in MDD treatment from better medication adherence could not be revealed as a consequence that the one-year study period for each patient was too short for the return to be generated and revealed.

The above five associations brought strong implications with respect to the U.S. mental health policies. First, as the high volume of uninsured people and the elevating

costs of pharmaceuticals in the U.S., the study results indicated that sociological factors, such as race/ethnicity and patient health insurance status, imposed substantial influences on patient health care utilization, in particular in MDD antidepressant medication. As the health care reform committing in reducing the number of U.S. uninsured people being proposed by President Obama, health insurance is hoped to increase people's accessibility to optimal health care especially for those whose health care need is unmet. While enhancing the accessibility to health insurance and in turn, health care services, policy makers have to make sure optimal health care for people's mental health could be appropriately provided and delivered. Specifically, gaps between optimal and suboptimal health care for patient mental health caused by systematic differences in sociological factors, for example patient's race/ethnicity, need to be well tailored. Policy makers should take into account the sources of heterogeneity in antidepressant utilization indicated by this study.

Second, although the study results indicated that total MDD drug expenditures was raised while better antidepressant adherence required better compliance on drug refills, a long-term economic return in MDD treatment was still expected. This requires policy makers to fund more comparative cost-effectiveness studies identifying better cost-effective MDD treatments to improve patient outcomes and at the same time, reduce associated health expenditure.

The third implication for mental health policy came from the study results indicating the influences of sociological factors, for example patient race/ethnicity, on antidepressant adherence. As previous studies indicate that medication treatment adherence in patients with mental disorders is generally low,[28-30] it is inevitable that even

effective medications cannot improve patients' mental health status without good medication adherence. In order to enhance patient adherence to antidepressants given their substantial side effects, we need policy makers to be engaged in designing effective policy interventions to improve patient medication adherence. Example interventions include patient education regarding the knowledge of taking antidepressants, related drug side effects, and possible drug-drug interactions; financial incentives for health care providers to follow up patient medication utilization; implementing monitoring devices for medication use, and so on. While a number of possible interventions are discussed, we need further research to study the costs and effectiveness for each intervention; all of these call for policy makers' efforts to ameliorate patient health care utilization and in turn, to improve patient mental health status.

CONCLUSION

The main objective of this research was trying to understand how patient factors and antidepressant choice influenced medication adherence and associated health care expenditure. The results provide further evidence that patient antidepressant adherence and related health care expenditure are associated with sociological factors such as patient race/ethnicity and health insurance status. Differences in antidepressant adherence and health care spending across patient factors could have important policy implications for drug formularies and health disparities; there are certain patient populations that may be at higher risk for inadequate health care.

There were limitations that can be drawn from this study. First, the MEPS dataset contains only three-digit ICD-9 codes which limited the accuracy for sample extraction.

Second, the episodes and severities of MDD were not taken into account in this study. Severities may contribute to patient use of pharmacotherapies. Third, the MEPS dataset contains self-reported information which may be inaccurate due to recall bias, respondent bias, or interview bias. Fourth, PDC as the measure for antidepressant adherence is based on a strong assumption that all refilled drugs on hand are taken truly and timely by patients, which is not likely to be held in real life. Finally, this study used a simplified Anderson model which did not consider the preceding of predisposing factors to enabling factors to need factors proposed in the original Anderson model. A hierarchical model may be used to model these relationships. However, we believe these limitations did not outweigh the relative contribution of this study.

While effective policy intervention are needed for improving medication adherence, the design of prescription drug benefit within health insurance should be tailored considering its associations with patient factors according to the findings of this study. This study revealed important implications for mental health policy especially for several specific groups whose mental disorders were undertreated, and could also help policy makers identify sources of variation in mental healthcare while reducing undertreatment. This study was the first one which analyzed a large nationally representative survey dataset, the Medical Expenditure Panel Survey (MEPS), to examine patient factors associated with SSRI/SNRI antidepressant adherence for MDD patients. This study provided the first investigation for SSRI/SNRI adherence and its association with health care expenditure using such large dataset with long-term cross-sectional data. Besides, this study considered choice of antidepressants when examining antidepressant adherence and associated outcomes, alone with an innovative way to calculate medication

adherence, which could bring alternative insights in utilizing public dataset (such as MEPS) to study medication adherence. Finally, this study accommodated the issue of limited ICD-9 codes in MEPS and successfully excluded subjects with bipolar disorder, which could reveal more accurate estimates of antidepressant utilization in MDD patients; this was never done in previous studies using MEPS.

As patients themselves are getting more and more involved in their own health care decisions, this study was helpful for health care providers to better understand how to assist patients to adhere to antidepressant medications, and for policy makers to revisit and tailor current policies and insurance benefit design which may fail to improve patient antidepressant adherence.

Table 5.2. Descriptive statistics of adult patients prescribed antidepressants

Variable	% or mean (std. dev.)
Predisposing Factors	
Gender: male	30.63
Age category:	
18-25	10.24
26-49	50.11
50-64	31.43
65+	8.22
Education year	12.91 (3.36)
Race/ethnicity:	
Non-Hispanic white	85.63
Non-Hispanic black	6.20
Hispanic	5.31
Other	2.86
Region:	
Northeast	16.34
Midwest	25.98
South	39.75
West	17.94
Metropolitan area	79.56
Enabling Factors	
Annual personal income:	
<$20,000	52.97
$20,000-$40,000	26.60
$40,000-$60,000	9.78
$60,000+	10.65
Health insurance status:	
Private insurance	61.64
Public insurance only	27.18
Uninsured	11.19
Patient belong to HMO: yes	29.02
Prescription drug insurance	54.69
Need Factors	
Comorbidity:	
Psychotic disorders	3.71
Anxiety disorders	23.43
SF-12 PCS	46.62 (12.17)
SF-12 MCS	40.85 (13.33)
Antidepressant Used	
SSRI/SNRI antidepressants	71.45
Other newer antidepressants	12.82
Older antidepressants	2.67
Combination therapy	13.06
PDC	43.24 (33.61)
0<PDC≤20	35.79
20<PDC≤80	40.76
PDC>80	23.45
Attended outpatient visits	95.77
Attended inpatient visits	17.01
Health Expenditures	
Total health expenditure	8,746.83 (15,453.77)
MDD specific Rx expenditure	447.06 (479.38)
Outpatient health expenditure	2,875.53 (5,441.69)
Inpatient health expenditure	3,320.55 (13,263.05)

Notes:
1. *N* (total weighted) = 2,111,615
2. Data source: MEPS 2000-2007
3. Yearly expenditure data are adjusted by CPIs from the Bureau of Labor Statistics

Table 5.3. Year-fixed effect regression: proportional days covered (PDC)

R^2=26.28%

Variable	beta coeff.	(std. err.)
Predisposing Factors		
Gender: male	9.1281	(4.7970)
Age category:		
18-25	---	---
26-49	7.3835	(7.3765)
50-64	14.2232	(8.2915)
65+	15.0849	(10.5243)
Education year	0.7007	(0.5211)
Race/ethnicity:		
Non-Hispanic white	12.5268*	(6.0616)
Non-Hispanic black	2.9007	(8.4869)
Hispanic	---	---
Other	28.2723**	(9.6699)
Region:		
Northeast	9.7207	(7.8293)
Midwest	-1.9584	(6.5718)
South	8.8545	(6.4057)
West	---	---
Metropolitan area	-1.4485	(4.7153)
Enabling Factors		
Annual personal income:		
<$20,000	---	---
$20,000-$40,000	-6.1215	(5.2524)
$40,000-$60,000	-6.0396	(7.3089)
$60,000+	-11.6849	(9.9813)
Health insurance status:		
Private insurance	3.2207	(7.5916)
Public insurance only	16.2346*	(6.5731)
Uninsured	---	---
Patient belong to HMO: yes	4.2465	(5.2566)
Prescription drug insurance	4.5545	(6.4200)
Need Factors		
Comorbidity:		
Psychotic disorders	-6.4956	(7.2399)
Anxiety disorders	-1.4291	(4.3825)
SF-12 PCS	-0.0570	(0.2097)
SF-12 MCS	0.2185	(0.1761)
Antidepressant Used		
SSRI/SNRI antidepressants only	-12.4862	(14.0029)
Other newer antidepressants only	-18.7742	(15.1644)
Older antidepressants only	---	---
Combination therapy	17.9918	(14.3082)
Intercept	9.4075	(21.9746)

Notes:
1. *p <0.05; **p <0.01
2. N (total weighted) = 1,956,613
3. Data source: MEPS 2000-2007

Table 5.4. Year-fixed effect logistic regression models: use of outpatient and inpatient visits

Dependent variable	(1) Outpatient visits (yes/no)		(2) Inpatient visits (yes/no)	
Statistical model→	logit of two-part model (R^2=35.43%)		logit of two-part model (R^2=23.42%)	
Independent variables↓	weighted OR	(confidence interval)	weighted OR	(confidence interval)
Predisposing Factors				
Gender: male	0.6950	(0.1484, 3.2541)	2.1336	(0.9103, 5.0010)
Age category:				
18-25	---	--- ---	---	--- ---
26-49	0.1248	(0.0107, 1.4623)	1.1233	(0.1761, 7.1652)
50-64	0.2417	(0.0154, 3.7880)	1.8717	(0.2918, 12.0057)
65+	---#	--- ---	2.3246	(0.2768, 19.5229)
Education year	0.9252	(0.7193, 1.1902)	0.9707	(0.8377, 1.1248)
Race/ethnicity:				
Non-Hispanic white	12.3274	(1.1630, 130.6656)	1.0024	(0.2009, 5.0011)
Non-Hispanic black	22.2817	(0.1972, 2517.3960)	3.5689	(0.3908, 32.5954)
Hispanic	---	--- ---	---	--- ---
Other	---#	--- ---	1.7094	(0.1420, 20.5817)
Region:				
Northeast	0.3574	(0.0066, 19.2119)	0.7090	(0.1801, 2.7918)
Midwest	0.0422*	(0.0026, 0.6895)	0.8256	(0.2429, 2.8057)
South	0.0646*	(0.0055, 0.7592)	0.7864	(0.2417, 2.5582)
West	---	--- ---	---	--- ---
Metropolitan area	0.9904	(0.2406, 4.0774)	0.9993	(0.3843, 2.5986)
Enabling Factors				
Annual personal income:				
<$20,000	---	--- ---	---	--- ---
$20,000-$40,000	1.8267	(0.2908, 11.4743)	0.8509	(0.3453, 2.0969)
$40,000-$60,000	---#	--- ---	4.7855*	(1.4025, 16.3285)
$60,000+	---#	--- ---	0.2563	(0.0222, 2.9567)
Health insurance status:				
Private insurance	3.1541	(0.1562, 63.7050)	0.3934	(0.0674, 2.2955)
Public insurance only	275.5501**	(5.6820, 13,362.80)	0.6200	(0.1502, 2.5600)
Uninsured	---	--- ---	---	--- ---
Patient belong to HMO: yes	0.5435	(0.0494, 5.9842)	2.7509*	(1.1791, 6.4179)
Prescription drug insurance	1.2329	(0.0207, 73.5377)	1.9268	(0.5328, 6.9681)
Need Factors				
Comorbidity:				
Psychotic disorders	---#	--- ---	6.2599**	(1.5745, 24.8879)
Anxiety disorders	0.8592	(0.2032, 3.6330)	1.3461	(0.6174, 2.9348)
SF-12 PCS	0.9715	(0.9049, 1.0430)	0.9386**	(0.9067, 0.9716)
SF-12 MCS	1.0348	(0.9710, 1.1028)	0.9795	(0.9475, 1.0125)
Antidepressant Used				
SSRI/SNRI antidepressants only	0.0000**	(0.0000, 0.0000)	0.2828	(0.0362, 2.2107)
Other newer antidepressants only	0.0000**	(0.0000, 0.0001)	0.2832	(0.0314, 2.5516)
Older antidepressants only	---	--- ---	---	--- ---
Combination therapy	0.0000**	(0.0000, 0.0000)	0.5394	(0.0621, 4.6853)
Medication Adherence				
PDC	1.0161	(0.9929, 1.0398)	0.9866*	(0.9752, 0.9981)

Notes:
1. *p <0.05; **p <0.01
2. N (total weighted) = 1,956,613
3. #: dropped due to perfect predicts
4. Data source: MEPS 2000-2007
5. The results of the second parts of models (1) and (2) are reported in Table 5.5.

Table 5.5. Year-fixed effect regression models: related health expenditures (in logarithms)

Dependent variable	(1) Outpatient expenditure		(2) Inpatient expenditure		(3) MDD Rx expenditure		(4) Total health expenditure	
Statistical model→	OLS of two-part model (R^2=31.90%)		OLS of two-part model (R^2=69.92%)		OLS (R^2=74.71%)		OLS (R^2=37.44%)	
Independent variables↓	beta coeff.	(std. err.)	beta coeff.	(std. err.)	beta coeff.	(std. err.)	beta coeff.	(std. err.)
Predisposing Factors								
Gender: male	-0.0336	(0.2014)	0.1505	(0.4977)	-0.0718	(0.0890)	0.1445	(0.1687)
Age category:								
18-25	---	---	---	---	---	---	---	---
26-49	-0.2952	(0.3261)	-0.0608	(1.3214)	-0.0300	(0.2012)	0.2086	(0.3027)
50-64	-0.1933	(0.3479)	0.4017	(1.5043)	-0.0566	(0.2113)	0.5750	(0.3175)
65+	-0.3547	(0.4330)	-0.2622	(1.6385)	-0.5669*	(0.2715)	0.6836	(0.3551)
Education year	0.0424	(0.0248)	-0.0050	(0.0381)	-0.0171	(0.0106)	-0.0127	(0.0172)
Race/ethnicity:								
Non-Hispanic white	0.1528	(0.3573)	0.5333	(1.1127)	0.2074	(0.2673)	0.1369	(0.2219)
Non-Hispanic black	0.6470	(0.4493)	1.2877	(0.8551)	0.0726	(0.3161)	0.8805**	(0.2970)
Hispanic	---	---	---	---	---	---	---	---
Other	-0.1146	(0.5740)	1.2141	(1.7977)	0.2375	(0.2574)	-0.1562	(0.4956)
Region:								
Northeast	-0.0296	(0.2954)	0.5784	(0.8490)	-0.0982	(0.1529)	-0.0251	(0.2236)
Midwest	-0.2174	(0.2792)	0.0987	(0.7851)	-0.0708	(0.1475)	-0.2272	(0.2203)
South	-0.3650	(0.2789)	0.1639	(0.7746)	0.0292	(0.1315)	-0.3308	(0.2014)
West	---	---	---	---	---	---	---	---
Metropolitan area	0.0823	(0.1841)	0.0654	(0.6311)	0.0031	(0.1029)	0.3062	(0.1620)
Enabling Factors								
Annual personal income:								
<$20,000	---	---	---	---	---	---	---	---
$20,000-$40,000	0.3421	(0.2248)	-0.1037	(0.5343)	0.1104	(0.1156)	0.3596*	(0.1643)
$40,000-$60,000	0.4093	(0.3066)	-1.5135*	(0.6134)	0.0292	(0.1631)	0.1102	(0.1985)
$60,000+	0.6718	(0.4187)	-1.6624	(1.7692)	0.2095	(0.1915)	0.1942	(0.2329)
Health insurance status:								
Private insurance	0.3852	(0.3819)	1.5314	(1.0461)	0.3574*	(0.1561)	0.8532**	(0.3267)
Public insurance only	0.4769	(0.3024)	-0.0414	(0.9617)	0.2306	(0.1441)	0.6289*	(0.3116)
Uninsured	---	---	---	---	---	---	---	---
Patient belong to HMO: yes	-0.1117	(0.2009)	0.1241	(0.5143)	0.0286	(0.1053)	0.0918	(0.1481)
Prescription drug insurance	0.6982*	(0.3373)	-0.7803	(0.9797)	-0.0096	(0.1371)	0.0547	(0.2129)
Need Factors								
Comorbidity:								
Psychotic disorders	0.1432	(0.3224)	-0.4897	(0.6406)	-0.2603	(0.1607)	0.4934	(0.3086)
Anxiety disorders	0.4283*	(0.1940)	-0.3492	(0.5126)	0.1738	(0.1065)	0.2653	(0.1671)
SF-12 PCS	-0.0424**	(0.0078)	-0.0111	(0.0222)	0.0052	(0.0038)	-0.0289**	(0.0071)
SF-12 MCS	-0.0143	(0.0075)	0.0060	(0.0175)	-0.0045	(0.0041)	-0.0088	(0.0057)
Antidepressant Used								
SSRI/SNRI antidepressants only	-0.5247	(0.3802)	0.3853	(0.6495)	1.4440**	(0.3181)	-0.4416	(0.3205)
Other newer antidepressants only	-0.2800	(0.4395)	-0.1969	(0.9034)	1.5814**	(0.3285)	-0.4137	(0.3524)
Older antidepressants only	---	---	---	---	---	---	---	---
Combination therapy	0.0167	(0.4114)	1.4642	(0.7563)	1.4080**	(0.3276)	-0.1273	(0.3420)
Medication Adherence								
PDC	0.0032	(0.0028)	-0.0031	(0.0072)	0.0290**	(0.0013)	0.0040*	(0.0019)
Intercept	8.3610**	(0.9556)	8.1924**	(2.0744)	2.7130**	(0.4801)	9.2683**	(0.8503)
Number of weighted samples	1,891,180		330,110		1,956,613		1,956,613	

Notes:
1. *p <0.05; **p <0.01
2. Data source: MEPS 2000-2007
3. All expenditure are in logarithm format
4. Yearly expenditure data are adjusted by CPIs from the Bureau of Labor Statistics
5. The results of the first parts of models (1) and (2) are reported in Table 5.4.

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CHAPTER 6

DISSERTATION MANUSCRIPT 3

(**Title:** TRENDS IN ANTIDEPRESSANT UTILIZATION, AND ASSOCIATED LABOR MARKET PARTICIPATION AND QUALITY OF LIFE OUTCOMES IN THE UNITED STATES: 2004-2007)

Trends in Antidepressant Utilization, And Associated Labor Market Participation And Quality of Life Outcomes in the United States: 2004-2007

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Background: Innovative antidepressants have been widely adopted. However, the differences in patient factors and antidepressant use, and associated patient health and work outcomes were not jointly studied.

Objective: This study was trying to understand how patient factors and antidepressant utilization were associated with patient employment duration and quality of life.

Methods: A retrospective cross-sectional study was conducted using the 2004-2007 Medical Expenditure Panel Survey (MEPS) dataset. Proportional hazard duration models were used to examine MDD patient's employment duration. Linear regression models were implemented to study the impact of MDD patient factors and antidepressant utilization on associated patient physical and mental health status.

Results: Duration models did not show associations between patient antidepressant use and employment duration. However, differences in employment duration across several patient factors were found. Cox proportional hazard model showed that, compared to uninsured patients, MDD patients covered by private insurance had a lower level of hazard of job termination (hazard ratio=0.15, $p<0.01$). Patients who were in better physical health conditions had a lower level of hazard of job termination (hazard ratio=0.96, $p<0.01$). Results from OLS regressions showed that, compared to patient without antidepressant pharmacotherapy for MDD treatment, patients who took innovative antidepressants such as SSRIs/SNRIs and other newer ones had a huge increase in MCS (β=11.35, $p<0.01$). In addition, better antidepressant adherence was significantly associated with an increase of MCS (β=0.10, $p<0.01$).

Conclusions: This study suggested that effective policy interventions were needed for improving medication adherence, and the design of prescription drug benefit within health insurance should be tailored considering its associations with patient factors and related improvement in health status according to the findings of this study. Preexisting conditions might be barriers to health insurance and might in turn, be barriers to optimal health care services for those needed patients, which needs policy makers to enhance accessibility to optimal health care for those patients with mental health conditions. We

also need policy makers to be engaged in designing effective policy interventions to improve patient medication adherence, which may in turn, improve patient health status and labor market participation.

Keywords: employment duration; job termination; adherence; antidepressant; SSRI; SNRI; major depressive disorder (MDD); patient factor; antidepressant utilization

INTRODUCTION

Work is an important aspect of most human beings' lives. For many people, his or her identity is partly composed of their work, and the self-worth, self-perception and satisfaction from it.[1-3] However, health issues, including both psychical and mental disorders, interfere with people's work performance which may be likely to reduce people's satisfaction with current work status, health status and quality of life.[4-6] It is inevitable that the existence of medication is to treat patients' illnesses and in turn, raise their quality of life and work performance. To measure the influences of medications, there are several valid and useful measures developed to assess work outcomes; for example, perceived performances, absence from work, employment status, and productivity at paid work.

It is shown that mental health conditions are common not only in the United States but also in many developed countries. Estimation in recent research shows that 26.2 percent of Americans ages 18 and older suffer from a diagnosable mental disorder in a given year.[7] Among mental disorders, major depressive disorder (MDD) is attributed as the leading cause of disability in the U.S. for ages 15-44, and affects 6.7 percent of the U.S. population age 18 and older in a given year.[8]

MDD is regarded as both an acute and a chronic disease. Epidemiologic research shows the lifetime prevalence rate is between ten to twenty percent.[9, 10] According to the National Comorbidity Survey, the lifetime and annual prevalence of MDD are 17.1 percent and 10.3 percent, respectively.[11] In addition, the degree of relapse and reoccurrence is likely to be high for MDD patients and requires well maintenance. MDD patients are also recommended long-term maintenance treatment to prevent recurrence or

the emergency of a new episode of depression.[12-16] MDD is therefore regarded as a chronic disease to some extent,[9, 17] and antidepressant medication may be needed in a longer term. With the nature of being both acute and chronic disease, a person with untreated or poorly treated MDD cannot function well for his/her daily, business and social activities.

As Prozac™ (fluoxetine Hcl), the first selective serotonin reuptake inhibitors (SSRI) antidepressant, was introduced in 1988, SSRIs have become the major and preferable medication treatment for MDD patients. SSRIs, compared to old generation antidepressants (i.e. tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs)), have a unique treatment mechanism which selectively increases the level of serotonin.[18] SSRIs were soon adopted by physicians and patients because of their innovative mechanism of action and superior efficacy. In mid-1990, serotonin-norepinephrine reuptake inhibitor (SNRI), another innovative class of antidepressants, was introduced to treat MDD. Unlike SSRIs which act more selectively upon serotonin, SNRI increases both serotonin and norepinephrine to treat MDD. SNRIs have also been widely adopted by physicians and patients as a prescription for MDD treatment recently.

The influences of antidepressants on MDD patient's daily life, work performance and quality of care has been researched intensively. Work performance has been measured using psychometric scales and associated absenteeism (i.e. work loss) has been explored as well. Previous research shows significant differences between medication (either older or newer antidepressant) and placebo groups for work performance.[19-23] Studies in Europe in the 1980's show MDD patients treated by SSRIs had lower absenteeism compared to those treated by TCAs, and absenteeism was lower in patients

treated by TCAs than those who were untreated.[24, 25] However, these studies are out-of-date and the generalizability is low to Americans, which could not indicate adequate information for the U.S. mental health policy. Although previous studies explored the influences of antidepressants on patient's work outcomes by examining their employment status and work performance, none of them examined patient employment duration. Examining patient's employment duration could indicate how, how likely, and in how long a patient's job would be terminated, which could bring implications for labor market participation and mental health policy for patients with mental disorders.

In addition, patient antidepressant adherence could have association with patient health and work outcomes. Adherence, to some extent has the same meaning as compliance, is defined as patients taking the correct dose during the proper time interval for the appropriate time period.[26] Although SSRIs are widely accepted and used, it is however that, medication treatment adherence in patients with mental disorders is low in general. Even effective medications cannot improve patients' mental health status without good medication adherence. Research has shown poor medication adherence in both antidepressants and antipsychotics in patients with mental disorders. It has been shown that early discontinuation of antidepressants is widespread;[27] in particular, 28% to 40% of patients with depression discontinue antidepressant medication, which significantly increases health care expenditures.[28] Besides, reports reveal that rates of non-adherence to antipsychotics range from 20% to 89%, and 50% on average.[29, 30] In other words, research has shown that non-adherence in pharmacotherapy in mentally ill patients is indeed a serious problem and needs more research. Therefore, patient

antidepressant adherence was of this study's interest for its impact on patient health and work outcomes.

As previous literature concluded that health issues could interfere with people's work performance which may have negative impacts on people's quality of life,[4-6] this study analyzed patient employment duration and quality of life as two patient outcomes with MDD treatment. According to the aforementioned research motivations, the objective of this study was trying to examine the influences of innovative antidepressant choice and utilization on patient labor market participation and quality of life. This study used the Medical Expenditure Panel Survey (MEPS) along with the proportional hazard duration models and linear regressions to explore how patient factors, antidepressant choice and utilization influenced MDD patients' employment duration and quality of life in MDD treatment in the U.S.

METHODS

Study sample

This was a retrospective cross-sectional study. This study used the 2004-2007 Medical Expenditure Panel Survey (MEPS) to obtain a nationally representative sample of MDD patients whose antidepressant utilization and its impacts on patient and labor market outcomes could be studied. The MEPS is a national probability survey cosponsored by the Agency for Healthcare Research and Quality (AHRQ) and the National Center for the Health Statistics (NCHS). The MEPS survey is designed to provide nationally representative estimates of health care use, expenditures, source of payments, and insurance coverage for the U.S. civilian noninstitutionalized population.

The MEPS dataset consists of four major components: the Household Component (HC), the Medical Provider Component (MPC), the Insurance Component (IC) and the Nursing Home Component (NHC).

For research purposes, this study used the HC component of the MEPS. First, the HC collects data from families and individuals in selected communities across the U.S. and are self-reported. The HC includes demographics, health conditions, health status, income, health insurance coverage, employment, and both use and expenditure and health care services collected using computer-assisted personal interviewing technology. For instance, the latest panel (Panel 11) of the MEPS-HC was collected in years 2006 and 2007 with five rounds of interviews and can be used to analyze changes in the two-year period. Secondly, although the MPC component was not used directly in this study, it supplements and/or replaces information on medical care expenditures reported by the HC by contacting all hospitals and pharmacies by the household respondents. The MPC is conducted through telephone interviews and record abstraction.[31]

There were several subsets of the HC component that were used in this study. In addition to the MEPS panel longitudinal data files (i.e. the pooled file of five rounds in two survey years) from year 2004 to year 2007, three additional groups of files were also used for the purpose of this study. First, the medical condition file which is an event file that provides detailed information of each medical condition reported by the household respondents, was used to identify patients with mental disorders (MDD and comorbid mental disorders). Second, the prescription drug files are also event files that provide data on all prescribed medicines which are self-reported by the HC respondents and supplemented by the MPC pharmacies. Specifically, counts of prescribed medicine

utilization are based entirely on HC, whereas drug information such as expenditure and payment data, as well as details of medications (e.g., strength, quantity, etc.) is from the Pharmacy Component (PC) within the MEPS-MPC. Third, the job files with job-level data which contain variables pertaining to household-reported job, including job start and end dates, wage rate, hours, industry and occupation, were also used in this study.

This study focused on patients with MDD, therefore only patients diagnosed with MDD were extracted from the MEPS datasets and included in this study. Sample extraction was according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR, American Psychiatric Association, 2000) classification of mental disorders identified by the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes contained in MEPS. Only subjects with ICD-9 codes 296.2x (major depressive disorder: single episode) and 296.3x (major depressive disorder: recurrent) were MDD patients to be extracted. In addition, this study excluded children from the study sample in order to avoid the heterogeneity of treatment between adults and children with MDD.

Unfortunately the public-available MEPS dataset only provides the first three-digit ICD-9 codes due to patient's confidentiality concerns. That is, in this study all patients with ICD-9 code 296 were extracted from the MEPS dataset. However, ICD-9 code 296.xx includes both MDD and bipolar disorder. It is recommended that patients with bipolar disorder to be treated by mood stabilizers (for depression episodes) and antipsychotics. Antidepressants such as SSRIs are very seldom used as monotherapy to treat depression episodes for bipolar disorder; clinical research shows that several types of antidepressants may trigger patient's maniac episodes unless mood stabilizers are

adjunctively used.[32] In order to exclude bipolar patients from the study sample, an extra exclusion strategy was accordingly implemented: patient who used mood stabilizers and antipsychotics were excluded from the study sample.

In terms of job records, in order to accurately capture the impact of antidepressants on patient's employment duration, only primary jobs were included in this study; miscellaneous jobs were excluded. Also, job termination records due to change of jobs, giving birth, and attending school were excluded in order to capture purer impact of diseases on employment duration.

Categories of antidepressants

In this study, antidepressants were categorized as SSRI/SNRI antidepressants, other newer antidepressants, and older antidepressants (TCAs, MAOIs and other older antidepressants.) The detailed list of antidepressants for each category in the MEPS dataset is shown in Table 6.1. Patients who took more than one types of antidepressants were classified as having combination therapy. The creation of the combination therapy category was to avoid double-counting of antidepressant utilization. Under this categorization, SSRIs and SNRIs were grouped for their similar pharmacological mechanisms. Other newer antidepressants, for example bupropion and mirtazapine, were separated from SSRI/SNRI category for their different drug mechanisms. This categorization benefited to examine the net effects of SSRI/SNRI antidepressants from other newer ones.

Table 6.1. Categories of Antidepressants

Type of Antidepressant	Medications
SSRI/SNRI antidepressants	citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine,
Other newer antidepressants	bupropion, mirtazapine, nefazodone, mianserin
Older antidepressants	amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, isocarboxazid, maprotiline, nortriptyline, phenelzine, protriptyline, selegiline, tranylcypromine, trazodone, trimipramine,

Measurements

The main purpose of this study was to examine the impact of innovative antidepressant use on MDD patient outcomes such as labor market participation and quality of life. The dependent variables used for measuring patient outcomes included employment duration and quality of life. Employment duration was calculated from the MEPS job files in monthly spells; the year and month of each job initiation and termination (if any) was identified for the calculation. Quality of life were represented by the SF-12 summary scores PCS and MCS directly from the MEPS longitudinal data files.

The independent variables fell into three groups. First, patient demographics such as gender, age, marital status, family size, education year, race/ethnicity, metropolitan area, and hourly wage rate were considered. Second, patient health insurance status, prescription drug insurance status, comorbid mental disorders, evaluated health status and total annual health expenditure were controlled. Third, patient antidepressant utilization including medication adherence and antidepressant choice were considered.

This study adopted the proportion of days covered (PDC) as the measure of medication adherence to capture the suggested long-term use of antidepressants and due to the data availability of MEPS. PDC is essentially a continuous, multiple-interval measure of medication availability according to Steiner and Prochazka's categorization, which is suggested to be more useful in testing cumulative drug dosage and longer-term exposure of medication.[33, 34] As discontinuation of antidepressants brings high likelihood of recurrence and serious withdrawal symptoms, antidepressants are suggested for long-term maintenance use. [12-16] Therefore, the use of PDC as a continuous, multiple-interval measure of medication availability is an appropriate measure for antidepressant adherence. In addition, the MEPS prescription data file provided exactly the needed drug information for PDC calculation.

In the calculation of PDC, medication adherence was defined as the proportion of "days covered" by a given drug in each time interval, based on number of days supplied and quantity of medication dispensed for each filled prescription. The PDC standardizes the time period over which adherence is examined.[48] The PDC can be calculated by the following formula according to its definition:

$$\text{PDC}(\%) = \frac{\text{Number of days with drug on hand}}{\text{Number of days in specified time interval}} \times 100.$$

The denominator for PDC is a clinically meaningful number of days that is the same for all intervals and patients. In this study, 365 days (one year) was defined as the duration of study in order to capture the suggested long-term use of antidepressants and due to the data structure of MEPS. Regarding the numerator, however, the MEPS dataset did not provide information regarding "days supply" of medication. Therefore, the days of supply was calculated as "quantity of prescriptions dispensed" divided by "number of

times took per day". "Quantity of prescriptions dispensed" could be obtained simply from the MEPS prescription drug files, and "number of times took per day" for every single antidepressant was obtained from the daily dosing recommendation at EPROCRATES ONLINE®, an online drug dictionary. The MEPS prescription drug files contained all drug dispense records of every single patient within one survey year, therefore the numerator in the PDC formula was in fact the days supply aggregated from every single drug records within one year. According to the definition of PDC and all the available information, PDC in this study was calculated and defined as follows:

$$\text{PDC}(\%) = \frac{\text{Number of days with drug on hand}}{\text{Number of days in specified time interval}} \times 100$$

$$= \frac{\Sigma\,(\text{Quantity of drugs dispensed} / \#\text{ of times took per day})}{365} \times 100.$$

Note that differential dosage forms of drugs were considered in the coding of drug entries by MEPS already as well as in compiling daily dosing recommendation from EPOCRATES ONLINE. For example, the suggested "number of times took per day" from EPOCRATES ONLINE for Wellbutrin-SR™ is 2, whereas "number of times took per day" for Wellbutrin-XL™ is 1. That is, the calculation of PDC in this study implicitly considered differential dosage forms for each medication. This method of PDC calculation in this study provided a drug- and strength- specific measure which was more accurate than the measures in previous studies.

Statistical Analyses

The primary dependent variables used for this study were the employment duration and quality of life for MDD patients. Two separate statistical methods were

implemented to conduct the statistical analyses for these two different patient outcomes. First, regarding MDD patient's labor market participation, the non-parametric Kaplan-Meier plot was drawn as a preliminary examination for the duration dependence of antidepressant choice upon MDD patient's employment duration. Then the semiparametric Cox-proportional hazard duration models, which did not required specifying the probability distribution of the baseline hazard and associated covariates, were used. Finally, the parametric proportional hazard model with exponential distribution was also used to cross-compare the impact antidepressant choice on MDD patient's employment duration with previous models.

A general form for the duration model in this study can be represented as:

Distribution Function:

$$F(t) = \int_0^t f(s)\mathrm{d}s = \Pr(T \le t) \text{ for } t > 0$$

where $f(t)$ is the density function, T is the random variable indicating duration (in monthly spells in this study), t is a realization of T, $F(\ )$ is a distribution function for the corresponding duration.

Survival Function:

$$S(t) = 1 - F(t)$$

where $S(\ )$ is the survival function, which indicates the probability that a spell lasts at least t periods.

Hazard Function:

$$\lambda(t) = \lim_{h \downarrow 0} \frac{\Pr(t \le T < t + h \mid T \ge t)}{h} = \frac{f(t)}{S(t)} = -\frac{d \ln S(t)}{dt}$$

where $\lambda(\ )$ is the hazard function, which indicates the probability of the spell ending at a given time *t*, given that it has lasted until at least *t*.

A general form for the semi-parametric Cox-proportional hazard model in this study can be represented as:

$$\lambda(t;X) = \lambda_0(t) \cdot \exp[\beta_0 + \beta_1(\text{demographics})_{it} + \beta_2(\text{insurance and health condition})_{it} + \beta_3(\text{antidepressant utilization and adherence})_{it}] + \varepsilon_{it}$$

where $\lambda_0(\ )$ is the baseline hazard, which will be cancelled in the likelihood function. Therefore, the assumption considering the distribution of the baseline hazard is not needed in the Cox-proportional hazard model, which illustrates its semi-parametric characteristic.

A general form for the parametric proportional hazard model in this study can be represented as:

$$\lambda(t;X) = \lambda_0(t) \cdot \kappa[\beta_0 + \beta_1(\text{demographics})_{it} + \beta_2(\text{insurance and health condition})_{it} + \beta_3(\text{antidepressant utilization and adherence})_{it}] + \varepsilon_{it}$$

where $\lambda_0(\ )$ is the baseline hazard and $\kappa(\ )$ is a particular probability distribution (i.e. exponential distribution in this study.) In this study, the Akaike Information Criteria (AIC) were compared for these models' goodness-of-fit.

Secondly, regarding the impact of antidepressant utilization and patient's quality of life, the linear OLS models were implemented. The OLS model in this study is shown as follows:

$$\text{Patient quality of life (SF-12 PCS or MCS)}$$

$$= \beta_0 + \beta_1(\text{demographics})_{it} + \beta_2(\text{insurance and health condition})_{it}$$

$$+ \beta_3(\text{antidepressant utilization and adherence})_{it}] + \varepsilon_{it}.$$

Besides, in order to obtain national estimates, all analyses were weighted. However, the three-stage weighting scheme in MEPS was lost because of the complicated sample extraction process. This study alternatively adopted the weighting strategy suggested by Lee et al.,[35] which divided each weight by the average weight for the whole study sample. This weighting method provided the advantage that the MEPS weighting scheme could be retained and incorporated without inflating the sample size. Statistical software Stata® version 11 was used to conduct all statistical analyses.

RESULTS

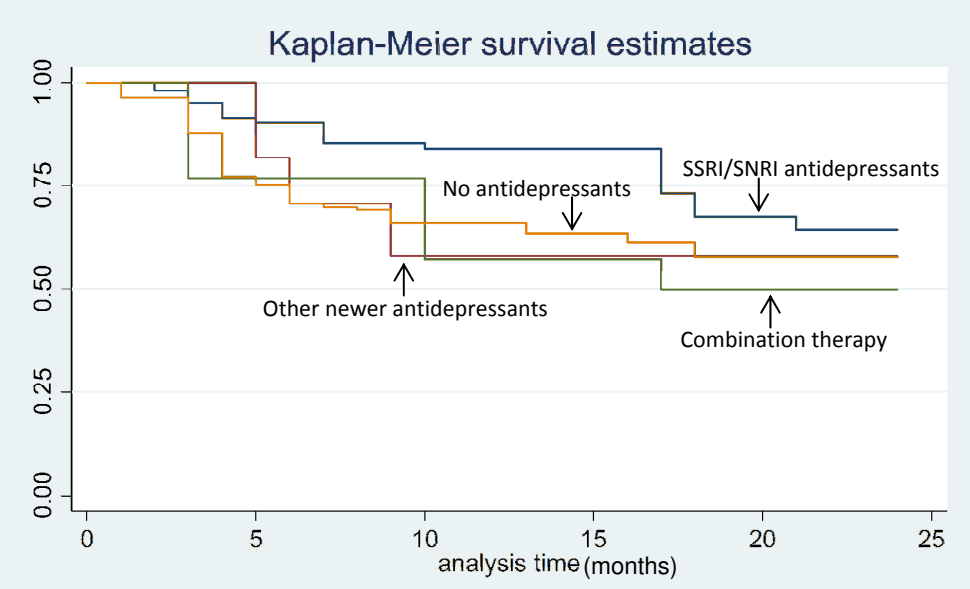
[Insert Table 6.2.]

A total weighted number of 2,302,650 subjects, who were diagnosed as MDD and were ever employed within the studied survey periods, were included in this study. Table 6.2 outlines the descriptive statistics of the study sample. First regarding patient demographics, less than half of study subjects were male (44.22%) and aged 39 years old on average. A majority of the study subjects (80.12%) were non-Hispanic white patients. A large proportion of the study subjects resided in metropolitan areas (76.21%). Regarding patient health insurance and health status, more than two-thirds of the study subjects were covered by private health insurance (67.99%) and prescription drug insurance (66.43%). Only a small fraction of patients were diagnosed comorbid psychotic

disorders (2.43%) whereas more than one-quarter study subjects were diagnosed with comorbid anxiety disorders (29.22%).

Regarding patient antidepressant utilization, nearly half of the study subjects were not treated by antidepressant pharmacotherapy (45.68%), and more than one-third were treated by innovative SSRI/SNRI antidepressants (36.90%) whereas no patients were treated by older generation antidepressants as monotherapy. The study sample performed a poor PDC on average (43.28 out of 100), which indicated merely partial adherence to antidepressants. Regarding patient's labor market outcomes, the average employment duration was 16.65 months and more than one-third jobs were terminated within the study periods (39.41%).

Figure 6.1. Kaplan-Meier survival plot in MDD patients with respect to antidepressant utilization



The non-parametric Kaplan-Meier survival plot shown as Figure 6.1 provided a preliminary picture of employment duration dependence upon antidepressant utilization.

Patients who took SSRI/SNRI antidepressants had higher probabilities of surviving from job termination over the analysis time, which provided a clear indication of employment duration dependence.

[Insert Table 6.3.]

The results of the semi-parametric Cox proportional hazard model examining the impact of patient factors and antidepressant utilization on employment duration are reported in Table 6.3, in which model (1) did not include patient antidepressant utilization as covariates, whereas patient antidepressant utilization was controlled in model (2). Hazard ratios are reported in Table 6.3 in which some particular covariate is associated with a higher hazard of job termination relatively to the baseline hazard if the hazard ratio is larger than one; and some particular covariate is associated with a lower hazard of job termination relatively to the baseline hazard if the hazard ratio is less than one.

In model (1), an increased year of age was associated with a decreased hazard of job termination ($p<0.01$). Compared to uninsured patients, MDD patients who were covered by private insurance had a lower level of hazard of job termination ($p<0.01$). In addition, MDD patients who were in better physical or mental health conditions had a lower level of hazard of job termination ($p<0.01$).

Model (2) added more results on model (1), given antidepressant utilization was controlled. Besides the same results that age and private insurance status were associated with an increased or decreased hazard of job termination, male patients tended to have higher hazard of job termination then female patients ($p<0.05$). Patients having longer education years and were covered by prescription drug insurance were more likely to face

job termination (p<0.05). However, patient antidepressant utilization, including choice of antidepressant and medication adherence, was not shown to be associated with an increase or decrease of the likelihood of job termination (p<0.05).

[Insert Table 6.4.]

Table 6.4 shows the results of the proportional hazard model with exponential distribution, examining the impact of patient factors and antidepressant utilization upon employment duration. The results were almost the same with the results of the Cox model shown in Table 6.3.

In model (1), an increased year of age was associated with a decreased hazard of job termination (p<0.01). Compared to uninsured patients, MDD patients who were covered by private insurance had a lower level of hazard of job termination (p<0.01. In addition, MDD patients who were in better heath physical or mental conditions had a lower level of hazard of job termination (p<0.01 and p<0.05, respectively).

Similarly, model (2) added more results on model (1), given antidepressant utilization was controlled. Besides the same results that age and private insurance coverage were associated with an increased or decreased hazard of job termination, patients having longer education years were more likely to face job termination (p<0.05). It was the same as the results of the Cox model that, however, patient antidepressant utilization, including choice or antidepressant and medication adherence, was not shown to be associated with an increase or a decrease in the likelihood of job termination (p<0.05).

[Insert Table 6.5.]

Regarding the impact of patient factors and innovative antidepressant use on MDD patient's quality of life, Table 6.5 reports the results of the linear regression model examining patient's physical health (measured by SF-12 PCS) controlling for patient factors and antidepressant utilization. Similarly with the aforementioned duration models, model (1) did not include patient antidepressant utilization as covariates, whereas patient antidepressant utilization was controlled in model (2). Beta coefficients of linear regression models are reported in Table 6.5.

In model (1), an increase of education year was associated with an increased PCS ($p<0.05$). Hourly wage was positively associated with PCS as well ($p<0.05$). In model (2), patient antidepressant utilization was controlled in addition to patient factors. Statistical results of model (2) in Table 6.5 show a positive association between being married and higher PCS ($p<0.1$). Compared to patients with Hispanic ethnicity, non-Hispanic black patients had lower PCS while antidepressant use was controlled ($p<0.01$). Antidepressant utilization, including patient antidepressant choice and medication adherence, was not significantly revealed either positive or negative associations with PCS.

[Insert Table 6.6]

Regarding patient mental health status as another measure for patient quality of life, Table 6.6 shows the results of linear regression models examining the impact of patient factors and use of innovative antidepressants on MDD patient's mental health status (measured by SF-12 MCS). Similarly with Table 6.5, model (1) did not control for patient antidepressant use whereas model (2) did. Beta coefficients of linear regression models are reported in Table 6.6 as well.

Table 6.6 shows somewhat varied results from those in Table 6.5. The results of model (1) show that an increase in age was associated with a decrease of MCS ($p<0.05$). Patients diagnosed with comorbid anxiety disorders had lower MCS ($p<0.05$). In addition, patients who spent more on health care were those who possessed lower MCS ($p<0.05$). Model (2) considered patient antidepressant utilization. Coverage of prescription drug insurance was associated with a decrease in MCS ($p<0.01$). Patients diagnosed with comorbid anxiety disorders had relatively lower MCS ($p<0.05$).

Regarding patient antidepressant utilization, both patient antidepressant choice and adherence had significant association with patient MCS. Compared to patient without antidepressant pharmacotherapy for MDD treatment, patients who took innovative antidepressants such as SSRIs/SNRIs and other newer ones had a huge increase in MCS ($p<0.01$). In addition, better antidepressant adherence was significantly associated with an increase of MCS ($p<0.01$).

DISCUSSION

While innovative antidepressants such as SSRIs and SNRIs have been widely adopted for MDD treatment, this study noticed that patient employment duration varied with several patient factors. Furthermore, patient mental health status as a part of patient quality of life was revealed to have positive associations with the use of innovative antidepressants. However, patient antidepressant use did not show significant associations with patient employment duration and physical health status.

There were several strong associations that are of great interest. First, for labor market concerns, gender difference was revealed in employment duration in one of the

models given antidepressant use was controlled, whereas the difference was not shown when antidepressant use was not considered. This echoed the study done by Zadoroznyj and colleagues that drug use as well as employment status was associated by women's reproduction role which in turn, caused gender difference.[36] In other words, while patient's medication use was controlled, gender difference was significantly revealed in patient's employment duration.

The second association that was of great interest was the association between education years and patient employment duration. The findings of this study showed a negative correlation between education years and employment duration. This finding could be explained by the association between "employability" and higher education,[37] which indicated a possible higher likelihood of voluntary job termination for those who had longer education years.

The third association that was of great interest was the associations between patient's health insurance status and employment duration. The study findings indicated that patient health insurance coverage was associated with lower hazard of job termination. A possible explanation was the impact of "job-lock" on employment status concluded by Madrian.[38] As a large proportion of employees were covered by employer-sponsored health insurance, a part of employees were "locked" in current jobs because of preexisting condition exclusion which made their health insurance premium more expensive, or simply because employees were afraid of losing their health insurance, which resulted in reducing their voluntary job termination.[39] This concern was particularly significant given all the study subjects were diagnosed MDD and a proportion of them had comorbidities and relatively poorer health status in this study.

Fourth, the statistical results showed a negative association between patient prescription drug insurance and patient mental health status. A possible explanation was patient's self-selection for drug insurance coverage in those who were medically needed for medication treatment, which was in turn, associated with a decrease mental health status. However, severities in this study were not considered, which limited the ability to clarify the association between patient needs and related patient outcomes. Future studies considering severities of MDD need to be conducted.

Finally, although antidepressant utilization was revealed neither a positive nor a negative association with employment duration, it did show a significant positive association with an improvement in patient mental health status. Both use of antidepressant and better antidepressant adherence were strongly associated with better mental health status in MDD patients. Given the poor medication adherence for pharmacotherapy in mental disorders,[28-30] the findings of this study strongly called for urgent needs for effective policy intervention to improve patient medication adherence, which would in turn improve patient health status and therefore augment patient quality of life. In addition, given the findings in this study that use of pharmacotherapy had positive association with patient mental health status, accommodating patient factors, tailoring drug formularies and prescription drug benefit design within health insurance, and adjusting patient payment schemes for antidepressant were strongly suggested.

The above five associations brought strong implications with respect to mental health policies. First, the study results indicated that a part of employees might be locked in current jobs because of preexisting conditions. As the high volume of uninsured people and the elevating costs of pharmaceuticals in the U.S., this study results implied that

preexisting conditions might be barriers to health insurance and might in turn be barriers to optimal health care services for those needed patients. Therefore, how to enhance accessibility to optimal health care for those patients with mental health conditions is indeed an issue for policy makers to concern with.

The second implication for mental health policy came from the study results indicating that better antidepressant adherence was strongly associated with better mental health status in MDD patients. Therefore, we need policy makers to be engaged in designing effective policy interventions to improve patient medication adherence, which may in turn, improve patient health status. Example interventions include patient education regarding the knowledge of taking antidepressants, related drug side effects, and possible drug-drug interactions; increasing financial incentives for health care providers to follow up patient medication utilization; implementing monitoring devices for medication use; and so on.

Finally, the study results indicated that MDD patients who were in better physical or mental health conditions had a lower level of hazard of job termination. This implied that patient labor market participation could be enhanced as a consequence of an improvement in their health status. All of the aforementioned implications call for policy makers' efforts to ameliorate patient antidepressant adherence and in turn, to improve patient mental health status and labor market participation.

CONCLUSION

The main objective of this study was trying to examine the influences of innovative antidepressant choice and utilization on patient work outcomes, labor market

participation and related quality of life. This study used the Medical Expenditure Panel Survey (MEPS) along with the proportional hazard duration models and linear regressions to explore how patient factors, antidepressant choice and utilization influenced MDD patients' employment durations and quality of life in the U.S. The results provide evidence that MDD patient's labor market participation varied across patient factors such as gender, education and health insurance. The study results also evidenced that patient quality of life varied across patient factors such as health insurance, antidepressant treatment, and medication adherence.

There were limitations that could be drawn from this study. First, the MEPS dataset contains only three-digit ICD-9 codes which limited the accuracy for sample extraction. Second, the episodes and severities of MDD were not taken into account in this study. Severities may contribute to patient use of pharmacotherapies. Third, the MEPS dataset contains self-reported information which may be inaccurate due to recall bias, respondent bias, or interview bias. Fourth, PDC as the measure for antidepressant adherence is based on a strong assumption that all refilled drugs on hand are taken truly and timely by patients, which is not likely to be held in real life. However, we believe these limitations did not outweigh the relative contribution of this study.

This study did not conclude that there was a positive or a negative association between patient antidepressant use and employment durations. However, differences in employment duration across several patient factors were found in this study. Patient health status and quality of life varied across patient factors as well, in which patient utilization of innovative antidepressants were found to have positive association with patient mental health status.

Such differences could have important policy implications for drug formularies and payment schemes in medications. This study suggested that effective policy interventions were needed for improving medication adherence, and the design of prescription drug benefit within health insurance should be tailored considering its associations with patient factors and related improvement in health status according to the findings of this study.

This study analyzed a large nationally representative survey dataset, the Medical Expenditure Panel Survey (MEPS), to examine patient factors associated with SSRI/SNRI antidepressant adherence for MDD patients, and its impact on patient labor market participation and quality of life. This study provided the first investigation for SSRI/SNRI adherence and its association with patient work and health outcomes using such large dataset with multiple-year cross-sectional data. Besides, this study considered type of antidepressants when examining antidepressant adherence and associated outcomes, alone with an innovative way to calculate medication adherence, which could bring alternative insights in utilizing public dataset (such as MEPS) to study medication adherence. Finally, this study accommodated the issue of limited ICD-9 codes in MEPS and successfully excluded subjects with bipolar disorder, which could reveal more accurate estimates of antidepressant utilization in MDD patients; this was never done in previous studies using MEPS.

As patients themselves are getting more and more involved in their own health care decisions, this study was helpful for health care providers to better understand how to assist patients to adhere to antidepressant medications, and for policy makers to revisit and tailor current policies and insurance benefit design which may fail to improve patient

antidepressant adherence and in turn, fail to improve patient work and health outcomes due to inadequate MDD treatment.

Table 6.2. Descriptive statistics of adult MDD patients

Variable	% or mean (std)
Demographics	
Gender: male	44.22
Age	39.20 (13.42)
Marrital status: married	39.39
Family size	2.22 (1.22)
Education year	13.05 (2.40)
Race/ethnicity:	
Non-Hispanic white	80.12
Non-Hispanic black	10.27
Hispanic	6.25
Other	3.37
Region:	
Northeast	14.94
Midwest	24.44
South	37.33
West	23.30
Metropolitan area	76.21
Hourly wage	10.05 (10.14)
Health insurance and health condition	
Health insurance status:	
Private insurance	67.99
Public insurance only	18.48
Uninsured	13.52
Prescription drug insurance	66.43
Comorbidity:	
Psychotic disorders	2.43
Anxiety disorders	29.22
SF-12 PCS (out of 100)	48.60 (9.60)
SF-12 MCS (out of 100)	42.32 (9.86)
Total annual health expenditure	8,578.40 (9,564.23)
Antidepressant utilization	
Antidepressant Used:	
SSRI/SNRI antidepressants	36.90
Other newer antidepressants	10.79
Other older antidepressants	0
Combination therapy	6.64
No antidepressant therapy	45.68
PDC (out of 100)	43.28 (35.16)
Employment	
Employment duration (month)	16.65 (8.46)
Terminated jobs	39.41

Notes:
1. *N* (total weighted) = 2,302,650
2. Data source: MEPS 2004-2007

Table 6.3. Cox proportional hazard duration models: employment duration of MDD patients

Dependent variable: employment duration

Statistical model	(1)		(2)	
Independent variables ↓	hazard ratio	(Std. err.)	hazard ratio	(Std. err.)
Demographics				
Gender: male	1.6136	(0.6821)	9.0320*	(8.3583)
Age	0.7523**	(0.0764)	0.5921**	(0.1136)
Age squre	1.0028*	(0.0012)	1.0062**	(0.0023)
Marrital status: married	3.4024	(2.1817)	0.3063	(0.4076)
Family size	0.8994	(0.1732)	1.3354	(0.4793)
Education year	1.0227	(0.1179)	2.0602*	(0.6592)
Race/ethnicity:				
Non-Hispanic white	0.4849	(0.3811)	0.1245	(0.1752)
Non-Hispanic black	2.9578	(2.8544)	5.3051	(11.7796)
Hispanic	---	---	---	---
Other	0.0000	(0.0000)	0.0000	(0.0000)
Metropolitan area	1.0330	(0.4788)	1.5678	(1.5498)
Hourly wage	0.9760	(0.0258)	1.0164	(0.0458)
Health insurance & health condition				
Health insurance status:				
Private insurance	0.1536**	(0.0990)	0.0534*	(0.0621)
Public insurance only	0.3166	(0.1981)	0.9921	(1.0580)
Uninsured	---	---	---	---
Prescription drug insurance	2.5344	(1.2813)	8.1104*	(9.4257)
Comorbidity:				
Psychotic disorders	0.0000	(0.0000)	0.0000	(0.0000)
Anxiety disorders	0.6247	(0.3035)	0.7466	(0.6929)
SF-12 PCS (out of 100)	0.9278**	(0.0257)	0.9640	(0.0615)
SF-12 MCS (out of 100)	0.9629	(0.0204)	1.0017	(0.0605)
Total annual health expenditure	1.0000	(0.0000)	1.0000	(0.0000)
Antidepressant utilization				
Antidepressant Used:				
SSRI/SNRI antidepressants only			0.4057	(0.5151)
Other newer antidepressants only			0.1321	(0.2134)
Combination therapy			---#	---
No antidepressants			---	---
PDC (out of 100)			0.9967	(0.0106)
AIC	294.4896		155.3067	
Weighted sample size	1,649,101		953,567	

Notes:

1. *p <0.05; **p <0.01
2. Data source: MEPS 2004-2007
3. Proportional hazard models are estimated with exponential distribution
4. #: dropped due to perfect predicts

Table 6.4. Proportional hazard duration models: employment duration of MDD patients

Dependent variable: employment duration

Statistical model	(1)		(2)	
Independent variables ↓	hazard ratio	(Std. err.)	hazard ratio	(Std. err.)
Demographics				
Gender: male	1.6414	(0.6934)	4.9630	(4.0834)
Age	0.7562**	(0.0746)	0.6846*	(0.1099)
Age squre	1.0028*	(0.0012)	1.0044*	(0.0020)
Marrital status: married	3.2253	(1.9501)	0.3527	(0.4575)
Family size	0.8931	(0.1681)	1.1094	(0.3974)
Education year	1.0210	(0.1177)	1.7549*	(0.5007)
Race/ethnicity:				
Non-Hispanic white	0.4759	(0.3680)	0.3919	(0.4633)
Non-Hispanic black	2.4287	(2.3040)	11.3147	(23.4634)
Hispanic	---	---	---	---
Other	0.0000	(0.0006)	0.0000	(0.0008)
Metropolitan area	1.0034	(0.4543)	1.0291	(0.9272)
Hourly wage	0.9759	(0.0256)	1.0213	(0.0428)
Health insurance & health condition				
Health insurance status:				
Private insurance	0.1454**	(0.0917)	0.1146*	(0.1225)
Public insurance only	0.3408	(0.2074)	0.8766	(0.8665)
Uninsured	---	---	---	---
Prescription drug insurance	2.6036	(1.3022)	4.7962	(5.0843)
Comorbidity:				
Psychotic disorders	0.0000	(0.0000)	0.0000	(0.0000)
Anxiety disorders	0.5807	(0.2767)	0.5480	(0.4848)
SF-12 PCS (out of 100)	0.9243**	(0.0249)	0.9715	(0.0569)
SF-12 MCS (out of 100)	0.9598*	(0.0200)	0.9819	(0.0522)
Total annual health expenditure	1.0000	(0.0000)	1.0000	(0.0000)
Antidepressant utilization				
Antidepressant Used:				
SSRI/SNRI antidepressants only			0.7368	(0.9052)
Other newer antidepressants only			0.3744	(0.5392)
Combination therapy			---#	---
No antidepressants			---	---
PDC (out of 100)			0.9948	(0.0101)
AIC	192.3834		120.7474	
Weighted sample size	1,649,101		953,567	

Notes:

1. *p <0.05; **p <0.01
2. Data source: MEPS 2004-2007
3. Proportional hazard models are estimated with exponential distribution
4. #: dropped due to perfect predicts

Table 6.5. Regression models: patient quality of life (SF-12 physical component summary scale) of MDD patients

Dependent variable: SF-12 physical component summary scale (PCS)

Statistical model	(1)		(2)	
	(R^2=27.54%)		(R^2=40.25%)	
Independent variables↓	beta coeff.	(Std. err.)	beta coeff.	(Std. err.)
Demographics				
Gender: male	0.9589	(1.7728)	-0.2661	(2.3107)
Age	-0.7051	(0.4033)	0.1404	(0.5134)
Age squre	0.0059	(0.0048)	-0.0037	(0.0061)
Marrital status: married	1.7506	(2.6527)	9.1233	(5.3149)
Family size	-0.6560	(0.8711)	-0.9045	(1.2621)
Education year	0.7805*	(0.3648)	0.3449	(0.4235)
Race/ethnicity:				
Non-Hispanic white	-3.4242	(3.7432)	-8.5184	(4.7350)
Non-Hispanic black	-4.6991	(4.9939)	-23.4130**	(8.3329)
Hispanic	---	---	---	---
Other	-2.3165	(7.2764)	-3.3035	(9.5283)
Metropolitan area	-2.3559	(2.0854)	-1.5702	(3.3054)
Hourly wage	0.2237*	(0.1030)	0.0629	(0.1353)
Health insurance & health condition				
Health insurance status:				
Private insurance	-5.2122	(3.4368)	-6.1536	(3.8494)
Public insurance only	-0.6257	(3.2111)	3.7580	(3.8676)
Uninsured				
Prescription drug insurance	3.6861	(2.6217)	1.2582	(3.0151)
Comorbidity:				
Psychotic disorders	-10.9869	(8.3066)	8.6355	(12.8876)
Anxiety disorders	-3.5325	(2.0393)	-1.3412	(2.8972)
Total annual health expenditure	-0.0002	(0.0001)	-0.0003	(0.0002)
Antidepressant utilization				
Antidepressant Used:				
SSRI/SNRI antidepressants only			-2.9532	(3.4833)
Other newer antidepressants only			-3.6914	(4.3805)
Combination therapy			---#	---
No antidepressants			---	---
PDC (out of 100)			0.0357	(0.0361)
Intercept	63.1414**	(8.8665)	61.0835**	(11.8575)
Weighted sample size	2,076,957		1,156,187	

Notes:
1. *p <0.05; **p <0.01
2. Data source: MEPS 2004-2007
3. #: dropped due to collinearity

Table 6.6. Regression models: patient quality of life (SF-12 mental component summary scale) of MDD patients

Dependent variable: SF-12 mental component summary scale (MCS)

Statistical model	(1)		(2)	
	(R^2=23.63%)		(R^2=56.80%)	
Independent variables↓	beta coeff.	(Std. err.)	beta coeff.	(Std. err.)
Demographics				
Gender: male	1.2263	(1.8761)	2.8436	(1.9400)
Age	-1.0409*	(0.4268)	-0.3943	(0.4310)
Age squre	0.0150**	(0.0051)	0.0040	(0.0051)
Marrital status: married	-3.6225	(2.8073)	4.4006	(4.4622)
Family size	0.3722	(0.9219)	-0.7581	(1.0596)
Education year	0.1904	(0.3861)	-0.3073	(0.3555)
Race/ethnicity:				
Non-Hispanic white	6.3342	(3.9613)	7.1496	(3.9754)
Non-Hispanic black	-0.4026	(5.2849)	-4.4738	(6.9960)
Hispanic	---	---	---	---
Other	6.6852	(7.7004)	2.6321	(7.9997)
Metropolitan area	-1.1367	(2.2069)	4.0363	(2.7751)
Hourly wage	0.1215	(0.1090)	0.0539	(0.1136)
Health insurance & health condition				
Health insurance status:				
Private insurance	0.8994	(3.6371)	6.1109	(3.2318)
Public insurance only	-2.1057	(3.3982)	0.7055	(3.2471)
Uninsured	---	---	---	---
Prescription drug insurance	-2.2357	(2.7745)	-10.6603**	(2.5314)
Comorbidity:				
Psychotic disorders	0.8772	(8.7907)	-5.5083	(10.8200)
Anxiety disorders	-4.6525*	(2.1581)	-5.3627*	(2.4324)
Total annual health expenditure	-0.0003*	(0.0001)	-0.0001	(0.0001)
Antidepressant utilization				
Antidepressant Used:				
SSRI/SNRI antidepressants only			11.3516**	(2.9245)
Other newer antidepressants only			14.3695**	(3.6777)
Combination therapy			---#	---
No antidepressants			---	---
PDC (out of 100)			0.0954**	(0.0303)
Intercept	54.4936**	(9.3832)	38.0659**	(9.9552)
Weighted sample size	2,076,957		1,156,187	

Notes:
1. *p <0.5; **p <0.01
2. Data source: MEPS 2004-2007
3. #: dropped due to collinearity

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CHAPTER 7

OVERALL CONCLUSION

7.1 Conclusion And Policy Implications

The overarching topic of this research was to study the adoption and utilization of innovative antidepressants and its associations with patient work and health outcomes. As mentioned and analyzed in previous chapters, the differences in adoption across patient and physician characteristics, geographic regions, insurance status, and other related factors needed further research. Besides, the adoption of SSRIs/SNRIs was characterized by the prescription volume and reflected in physician's adherence to practice guidelines and patient's adherence to SSRI/SNRI medications.

The objective of this research was trying to jointly understand the pattern of prescribe and use of SSRI/SNRI medications for MDD patients and the process of its adoption, and patients adherence to these medications. In addition, patient outcomes such as employment duration and quality of life associated with the use of SSRI/SNRI antidepressants were studied as well. Understanding how sociological factors influence physician prescribing decision on antidepressants and patient medication utilization for MDD treatment could complement previous study findings and have important implications for the U.S. mental health policy especially for several specific groups whose mental disorders are undertreated. This study could help policy makers identify sources of variation in mental healthcare while reducing undertreatment.

There were three interlinked specific objectives examining physician adoption and patient use of innovative antidepressants, and its associated patient work and health outcomes. The conceptual framework of this study (Figure 3.1 on page 33) showed the associations among three interlocked objectives. An overall big picture capturing the overarching objective of this study could be drawn by integrating the results and findings in three separate manuscripts (Chapters 4-6).

In sum, we observed an association between sociological factors and physician's innovative antidepressant prescribing patterns. Differences in antidepressant adherence and health care spending across patient factors were revealed as well. In addition, patient health status and quality of life varied across patient factors, in which patient utilization of innovative antidepressants were found to have positive associations with patient mental health status. The study results indicated and implied following concerns and corresponded policy implications discussed as follows.

First, health disparities came across as a possible issue regarding physician prescribing and patient utilization of antidepressants. Physician adoption of innovative antidepressants varied with races/ethnicities, whereas substantial racial/ethnic differences in patient antidepressant adherence and health care utilization were also revealed, which jointly implied that Hispanic patients had less access to appropriate health care and were undertreated for mental disorders. Although racial/ethnic health disparities have been researched substantially, effective policy interventions are still urgently needed to solve the issue.

Second, patient's health insurance coverage had a strong association with physician's adoption as well as patient's use of innovative antidepressants. Compared to

public health insurance or uninsurance, private insurance did associate with an increased likelihood of physician antidepressant prescribing. In addition, the findings of this study significantly showed substantially higher medication adherence in patient with health insurance compared to those who were uninsured. Uninsured MDD patients were more likely suffering from under-treatment of MDD, implied by the significantly lower total heath care expenditure and MDD-specific drug expenditure. All these results jointly implied that there were certain patient populations that might be at higher risk for inadequate health care. Health insurance in turn, could play a more important role regarding MDD patient's access to pharmacotherapy.

As the existence of managed care, the high volume of uninsured people, and the elevating costs of pharmaceuticals in the U.S., this study confirmed previous study findings that sociological factors, such as race/ethnicity and patient health insurance status, imposed substantial influences on physician prescribing and patient medication utilization, in particular in MDD treatment. As the health care reform committing in reducing the number of U.S. uninsured people being proposed by President Obama, health insurance is hoped to increase people's accessibility to optimal health care especially for those whose health care need is unmet. While enhancing the accessibility to health insurance and in turn, health care services, policy makers have to make sure optimal health care for people's mental health could be appropriately provided and delivered. Specifically, solutions for gaps between optimal and suboptimal health care for patient mental health caused by systematic differences in sociological factors, for example patient's race/ethnicity, need to be well tailored.

Third, in order to eliminate variations among physician practices and to obtain optimal health care for patients, we need policy makers to design effective policy interventions to improve physician practice guidelines adherence, given the indication from previous studies showing associations between better depression guideline adherence and improved patient outcomes.[109-111]

Fourth, although antidepressant utilization and medication adherence was revealed neither a positive nor a negative association with employment durations, it did show a significant positive association with an improvement in patient mental health status. In addition, given the facts and the study findings that (1) poor medication adherence for pharmacotherapy in mental disorders; (2) the the use of innovative antidepressants such as SSRIs and SNRIs were associated with an improvement in mental health status; and (3) improvement in health status from effective MDD treatment might in turn, result in lower future total health care costs, we urgently need effective policy interventions to efficiently improve patient medication adherence and quality of life. Therefore, we need policy makers to be engaged in designing effective policy interventions to improve patient medication adherence, which may in turn improve patient health status and labor market participation.

Overall, while differences in antidepressant adherence and health care spending across patient factors could have important policy implications for drug formularies and health disparities, effective policy interventions are needed for improving medication adherence and accommodating patient factors. Tailoring drug formularies and prescription drug benefit design within health insurance, and adjusting patient payment schemes for antidepressant were also strongly suggested according to the findings of this

study. All of this calls for policy makers to try to enhance appropriate treatment for MDD to eliminate treatment variation due to systematic sociological factors. Policy makers should take into account the sources of heterogeneity in MDD treatment indicated by this study.

7.2 Contribution And Study Limitations

The purpose of this study was to understand the patterns of physician prescribing innovative antidepressant medications, patient utilizing antidepressants, as well as the associated patient health and work outcomes. Understanding the sociological influences on patient, physician and healthcare system that may impact the successful treatment of the MDD patient, as well as the determinants of medication adoption and the predictors of antidepressant prescribing would help identify demographic, clinical and socioeconomic obstacles to pharmacotherapy adoption, prescribing and utilization. It would help policy makers to develop strategies to improve practice guideline adherence and medication adherence in MDD patients.

There are some limitations of this study. First, we discussed the SSRI/SNRI innovation and adoption from a patient's and a physician's perspectives but not from a pharmaceutical firm's standpoint. Dataset such as IMS provides pharmaceutical sales data which may provide another view of SSRI/SNRI adoption process. Second, the NAMCS dataset contained only ambulatory care data; emergency department visits and inpatient care data were not included which may not include the very severe cases. Third, the episodes and severities of MDD were not taken into account in this study. Severities may contribute to patient's non-adherence to pharmacotherapies. Fourth, the MEPS

dataset contains only three-digit ICD-9 codes which limited the accuracy for sample extraction. Fifth, the NAMCS and MEPS dataset contained self-reported information which may be inaccurate due to recall bias, respondent bias, or interview bias. In addition, PDC as the measure for antidepressant adherence is based on a strong assumption that all refilled drugs on hand are taken truly and timely by patients, which is not likely to be held in real life. Finally, this study used a simplified Anderson model which did not consider the preceding of predisposing factors to enabling factors to need factors proposed in the original Anderson model. A hierarchical model may be used to model these relationships. However I believe these limitations would not overweigh the contribution of this study.

This study was the first one which analyzed the large nationally representative survey datasets, the National Ambulatory Medical Care Survey (NAMCS) and the Medical Expenditure Panel Survey (MEPS), to examine physician, patient and healthcare system factors associated with SSRI/SNRI prescribing and utilization for MDD and its associated patient outcomes. This study provided the first investigation for SSRI/SNRI adoption using such large datasets with long-term cross-sectional data. Since the NAMCS and the MEPS are nationally representative datasets, the study results performed good generalizability and helped formulate national policies in this area.

As patients themselves are getting more and more involved in their own health care decisions, this study may be helpful for health care providers to assist patients to make decisions on antidepressant medication, and for policy makers to adapt and revise current policies which may distort a patient's decision making. Finally, this study may help disentangle the dilemma of overuse or underuse of drug utilization for mental health,

in particular, MDD treatment. For example, policy interventions such as patient education and counseling designed based on the study results would be a cornerstone for promoting medication adherence in these patients.

This research was also expected to contribute in innovative methodology such as using the longer-term cross-sectional data with the Heckman two-step selection model to capture the two-stage decision of innovative antidepressant, and invented an innovative way to calculate and measure medication adherence using the national representative MEPS dataset. This study considered choice of antidepressants when examining antidepressant adherence and associated outcomes jointly, alone with an innovative way to calculate medication adherence, which could bring alternative insights in utilizing public dataset (such as MEPS) to study medication adherence. Besides, this study accommodated the issue of limited ICD-9 codes in MEPS and successfully excluded subjects with bipolar disorder, which could reveal more accurate estimates of antidepressant utilization in MDD patients; this was never done in previous studies using MEPS. All of these were never done in the past.

7.3 Future Research

There are several topics in this field for further research. First, similar studies regarding physician prescribing and patient utilization of antidepressants can consider disease severities which control the spectrum of needs. Second, a longer term study following up patient antidepressant utilization would examine the possible long-term economic returns of using innovative medications for MDD treatment. Finally, evaluation

regarding the costs and effectiveness of different interventions for improving patient medication adherence would benefit the understanding of relevant issues.

APPENDIX

INSTITUTION REVIEW BOARD (IRB) EXEMPTION FOR DATA ACCESS

Health Sciences and Behavioral Sciences Institutional Review Board •
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fax (734) 998-9171 • irbhsbs@umich.edu

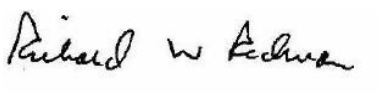
To: Hsien-Chang Lin
From: Richard Redman
Cc: Daniel Eisenberg
Rajesh Balkriahnan
Hsien-Chang Lin

Subject: Notice of Determination of "Not Regulated" Status for [HUM00035961]

SUBMISSION INFORMATION:
Title: TECHNOLOGY DIFFUSION AND MEDICATION UTILIZATION AND PATIENT OUTCOMES: THE CASE OF SSRIS IN MDD PATIENTS
Full Study Title (if applicable):
Study eResearch ID: HUM00035961
Date of this Notification from IRB: 12/9/2009
Date of IRB Not Regulated Determination : 12/9/2009

IRB NOT REGULATED STATUS:

Category	Description	Sort Order
Research Using Publicly Available Data Sets	Based on the information provided, the proposed study falls under the University of Michigan's policy for research using publicly available data sets (http://www.research.umich.edu/hrpp/Documents/datasets.html). Under this policy and in accordance with federal regulations for human subjects research (45 CFR Part 46) IRB approval is not required as the data cannot be tracked to a human subject.	13



Richard Redman

Chair, IRB HSBS

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Note: please refer to pages 87, 122 and 158 for separate bibliography for three separate manuscripts.

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