INTERACTIVE ASSOCIATIONS OF RACE AND COMORBIDITY IN MEDICATION TREATMENT AND OUTCOMES OF MEDICAID ENROLLED PATIENTS WITH MAJOR DEPRESSIVE DISORDER

by

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DEDICATION

This dissertation is dedicated with love to my fiancée,
Chi-Chuan (Emma) Wang

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LIST OF ABBREVIATIONS

MDD	Major Depressive Disorder
NCS-R	National Comorbidity Survey-Replication
NAMCS	National Ambulatory Medical Care Survey
NHANES III	National Health and Nutrition Examination Survey III
NSAL	National Survey of American Life
NESARC	National Epidemiologic Survey of Alcoholism and Related Conditions
HRQL	Health Related Quality of Life
MEPS	Medical Expenditure Panel Survey
SSRIs	Selective serotonin reuptake inhibitors
ICD-9-CM	International Classification of Disease, 9th Division, Clinical Modifications
IRB	Institutional Review Board
ER	Emergency Room
OLS	Ordinary Least Squares regression
GLS	General Least Squares regression
VIF	Variance Inflation Factor
PHQ-9	Patient Health Questionnaire – 9
HBM	The Health Belief Model
HCUP	Healthcare Cost and Utilization Project
AHRQ	Agency for Healthcare Research and Quality

ABSTRACT

Background

Comorbid anxiety disorders commonly occur in patients with Major Depressive Disorder (MDD). Treatment disparities of depression between African Americans and Caucasians still exist. Few studies have investigated the association of race and comorbid anxiety disorders with medication use-related outcomes in Medicaid enrollees with MDD.

Objectives

The objectives of this study was to examine the association of race, comorbid anxiety disorders, and the interaction between race and comorbid anxiety disorders with medication adherence, medication persistence, and health resource utilization in Medicaid enrollees with MDD.

Methods

The conceptual and analytical framework of the study primarily drew from the Behavioral Model of Health Service Use. The MarketScan® Multi-State Medicaid Database were used in this retrospective cohort study. Adult Medicaid enrollees between 18 and 64 years of age with MDD but without bipolar disorders who received an antidepressant between January 1, 2004 and December 31, 2006 were identified. Patients with a 24-month continuous enrollment and without dual eligibility of Medicaid and

Medicare were included. A Cox-propositional hazard regression was used to examine the risk of non-persistent antidepressant use. Multivariate logistic regressions were used to model the probability of adherence and health care utilization. Multivariate negative binominal regression analyses were used to assess the rate of change of health care utilization. Multivariate linear regressions with log-transformed costs were used to assess predictors of health care costs.

Results

Approximately 25% of 3,083 patients had comorbid anxiety disorders. After controlling for covariates, comorbid anxiety disorders were significantly associated with higher adherence and more frequent mental health-related health care utilization. African Americans were less likely than Caucasians to adhere to antidepressants and had higher risk of non-persistence. Additionally, African-American patients had fewer mental health-related office visits but were more likely to be hospitalized and have ER visits. The interaction effect (being African American and having comorbid anxiety disorders) reduced the individual association with health care utilization.

Conclusion

African-American patients were less likely than Caucasian patients to be adherent to or persistently use antidepressants. Comorbid anxiety disorders were associated with higher health resource utilization. Health policy makers and health care providers need to decrease the disease burden of comorbid anxiety disorders and reduce health disparities between Caucasians and African Americans among Medicaid enrollees with MDD.

CHAPTER 1

INTRODUCTION

Background

Major depressive disorder in the United States

Major depressive disorder (MDD) – also known as depression – is among the most prevalent mental illnesses in the United Sates. Its annual prevalence rate was estimated to be 6.7% in 2003,[1] and its lifetime prevalence rate has reached as high as 16.2%[2] based on the results of National Comorbidity Survey-Replication (NCS-R), a nationally representative survey conducted by Kessler et al.(2005).[1-2] The number of people who are at risk for MDD has also constantly increased. Prevalence of MDD has nearly doubled (3.3% - 7.1%) from 1991-1992 to 2001-2002.[3]

In addition to its high prevalence, MDD is a common clinical problem that primary care physicians face. MDD frequently occurs in 5% to 10% of patients in primary care settings in the U.S.[4] MDD has a significant impact on patients' physical, social and role functioning, and it can lower patients' quality of life.[5] There is evidence suggest that MDD is still inadequately or undertreated.[6]

MDD places a substantial burden on patients because MDD patients usually experience recurrence of symptoms. According to a report of the National Institute of

Mental Health Consensus Development Conference in 1985, between 50% and 85% of MDD patients can have a recurrence during their lifetime, and approximately, 50% of those patients experience recurrence in the first two years after they have had an initial episode.[7]

The economic burden of depression is very high and has constantly increased. Greenberg et al. (1993, 2003) conducted studies to estimate the cost of depression in 1990 and 2000, respectively.[8-9] They found that the annual cost of depression in the U.S. was nearly 43.7 billion dollars in 1990.[9] The economic burden increased from 77.4 billion dollars in 1990 to 83.1 billion dollars in 2000,[8] a total 7% increase in the economic burden over the 10 year period.[8] Due to lost work productivity and impaired work performance, depression costs several billion dollars per year from a social perspective in the U.S.[10]

Racial/Ethnic disparities in major depressive disorder patients

MDD prevalence between Caucasians and African Americans

Reports of MDD prevalence are inconsistent in their findings with respect to race/ethnicity. Some studies find a higher MDD prevalence rate in Caucasians than in African Americans. For example, Roiolo et al. (2005) reported significantly higher MDD prevalence in Caucasians than in African Americans by analyzing data from the National Health and Nutrition Examination Survey III (NHANES III).[11] Similarly, Williams et al. (2007) studied the difference in MDD prevalence among African Americans, Caribbean Blacks, and non-Hispanic Whites by using data from National Survey of American Life (NSAL). They found that lifetime MDD prevalence was higher in Caucasians (17.9%) than in African Americans (10.4%), but when compared with annual MDD prevalence,

the same study found that there was no significant difference between Caucasians and African Americans.[12] In addition, results of the NSAL study showed African Americans were more likely to have increased severity of role impairment related to their MDD.[12] African Americans also had higher MDD persistence (56.0%) than Caucasians (38.6%).[12] Similar results of a higher MDD prevalence rate in Caucasians have also been reported in several other studies.[13-14]

However, some studies reveal a similar MDD prevalence rate between African Americans and Caucasians.[15-16] For example, Crystal et al. (2003) analyzed Medicare claims data to investigate if health disparities exist in the diagnosis and treatment of depression in elderly patients. They found that there was no significant difference in the diagnosis of depression between African Americans and Caucasians.[15] Minsky et al. (2003) conducted a study in New Jersey using administrative claims, and found that Latinos had a higher MDD prevalence rate than African Americans and Caucasians, but the MDD prevalence rate was similar between African Americans and Caucasians.[16]

Racial/Ethnic disparities in MDD treatment

Pharmacotherapy is usually the first-line option of treatment for MDD patients. In contrast to the inconsistent study results of MDD prevalence in different racial/ethnic groups, consistent health disparities between Caucasians and African Americans exist in depression treatment. Several studies have shown that African American patients are less likely to receive MDD treatment when compared with Caucasians.[14, 17-23] For example, Sclar et al. (2008) investigated antidepressant use among different racial/ethnic groups in two different time periods, 1992-1997 and 2003-2004. Using data from the National Ambulatory Medical Care Survey (NAMCS), the researchers found that in 2004, the

treatment rate in African American patients (5.2 per 100) was less than half the treatment rate in Caucasian patients (11.4 per 100) even though the rate of antidepressant use in African American patients had increased by nearly 50% (2.6 per 100 in 1993 to 5.2 per 100 in 2004).[18]

Other studies conducted using data from administrative claims also show that African American patients with MDD were less likely to receive antidepressant treatment,[22] to initialize a treatment, to have an antidepressant prescription,[21] or to receive effective acute-phase treatment or continuation-phase treatment.[23] For example, a study conducted by Virning et al. (2004) investigated the quality of mental health care received by senior enrollees in Medicare.[23] The authors found that 46.7% of Caucasian patients with MDD received effective continuation-phase treatment after hospitalization, but only 32.7% of African-American patients with MDD received the same treatment.[23]

Comorbidity in major depressive disorder patients

Comorbid conditions frequently exist among patients with MDD. Findings from the NCS-R revealed that about 72% of patients with MDD can have some form of psychiatric comorbidity in their lifetime.[6] The annual prevalence rate of psychiatric comorbidity in MDD patients has been reported to be as high as 79%.[6] In addition to comorbid psychiatric conditions, comorbid physical conditions are also very common in MDD patients. A growing evidence shows that depression and painful symptoms are common comorbidities.[24]

In patients with MDD, psychiatric comorbid diseases usually refer to comorbid mental illnesses. Patients with MDD can simultaneously have other mental illnesses. Anxiety disorders have been reported as the most common comorbid psychiatric illnesses

in patients with MDD.[25-26] Moreover, patients with MDD can also have additional painful symptoms, which refer to comorbid physical illnesses in patients with MDD. Studies have shown that the common painful symptoms include abdominal pain, chest pain, chronic pain, headache, joint pain, lower back pain, and neck pain.[24, 27-34]

Psychiatric comorbidity in MDD patients

Psychiatric comorbidity commonly occurs in patients with MDD. In a review article of depression and psychiatric comorbidity, Otte (2008) reported that about 60% to 70% of MDD patients have at least one comorbid psychiatric disorder. Approximately, 30% to 40% of these patients have two or more comorbid psychiatric disorders.[26] Among those comorbid psychiatric disorders, anxiety disorders frequently coexist in patients with MDD.

The prevalence of comorbid anxiety disorders in patients with MDD is very high. Studies using nationally representative data consistently show that MDD patients can easily have comorbid psychiatric conditions, and among those conditions, anxiety disorders are the most common. In NCS-R, nearly 60% of lifetime MDD patients reported having anxiety disorders.[6] Findings from the National Epidemiologic Survey of Alcoholism and Related Conditions (NESARC), a nationally representative survey of the U.S. including Alaska and Hawaii, also revealed that about 41% of lifetime MDD patients have anxiety disorders.[25]

MDD patients with comorbid anxiety disorders have significantly poorer health outcomes, especially for those involving depressive symptoms, when compared with patients with MDD only. For example, Sherboune et al. (1997) conducted a study to evaluate the influence of comorbid anxiety disorders on depressive symptoms in patients

with depression.[35] They found the presence of comorbid anxiety disorders significantly impeded the clinical progress of depressive symptoms in depressed patients.[35] In addition, Felker et al. (2003) evaluated patients in a VA primary care trial, and found that MDD patients with comorbid anxiety disorders had more depressive symptoms, more impaired health status, and worse disability than patients with MDD alone.[36] In addition to more severe depressive symptoms, MDD patients with comorbid anxiety disorders have been shown to consume more health care resources[37] and also have a greater risk of developing persistent depression.[38]

Furthermore, depressed patients with comorbid anxiety disorders can have worse treatment outcomes and need a longer time to recover when compared with patients with depression alone. For example, Fava et al. (1997) studied 294 MDD outpatients treated with fluoxetine 20 mg/day for 8 weeks.[39] They found that MDD patients without anxiety disorders showed significant improvement in health outcomes during treatment compared with MDD patients with anxiety disorders.[39] Clayton et al. (1991) examined 327 inpatients and outpatients to assess the effect of anxiety disorders in depressed patients.[40] The study revealed that depressed patients with concurrent anxiety disorders took a longer time to recover compared to patients with depression alone.[40]

In summary, previous studies have shown that a majority of MDD patients can have significant psychiatric comorbidity.

Physical comorbidity in MDD patients

Comorbid physical conditions are common in patients with MDD. Comorbid painful symptoms are the most frequent physical comorbidity in patients with MDD. Findings from a review conducted by Bair et al. (2003) revealed that almost 65% of

MDD patients have some form of comorbid pain symptoms.[24] Prevalence of pain symptoms in patients with depression can be very high. For example, Bair et al. (2003) analyzed data from 573 clinically depressed patients in a primary care setting, and found that more than two thirds of depressed patients reported some degree of pain.[41]

Comorbid pain can have a negative impact on health outcomes such as Health Related Quality of Life (HRQL) in MDD patients. For example, Bao et al. (2003) conducted a national study to assess the effect of comorbid chronic pain on health care utilization and health outcomes in depressed patients.[42] In their study, patients' HRQL was measured using the SF-12, which consisted of physical and mental health components. They found depressed patients with comorbid pain had significantly lower scores in both components.[42] Moreover, studies have shown that depressed patients with comorbid pain can also have more severe psychiatric distress[42] and functional limitations[43] than patients with depression alone.

In addition, the presence of pain in depressed patients can increase the use of health services and health care expenditures. A study conducted by using a nationally representative household survey reveals that depressed patients with comorbid pain have 20% higher visits to medical providers than depressed patients without pain after adjusting for sociodemographic characteristics and severity of psychological distress.[42] Depression and comorbid pain are also associated with a higher economic burden for patients. Another nationally representative study, which was conducted by analyzing the Health and Retirement Study (HRS), has shown that senior patients with depression and severe pain have higher total health care expenditures than senior patients only with depression.[43] Similarly, in a study conducted in a primary care clinic, MDD patients with

comorbid disabling chronic pain had higher medical service costs than MDD patients without pain.[44]

Depressed patients with comorbid pain are usually under diagnosed. Depressed patients have been found to report physical conditions, such as painful symptoms, but not to report psychiatric symptoms when they talked to their doctors.[45] Wilson et al. (1983) conducted a study examining somatic symptoms in depressed patients in a family practice by reviewing nearly 4,000 medical charts, and noted that pain could be an onset signal of depression and it could also coexist with depression.[45] However, the authors also noted that pain in depressed patients was either under diagnosed or improperly treated.[45]

Findings from a review of depression and pain comorbidity reveal that the presence of pain can negatively affect treatment of depression,[41] depressive symptoms and worse depression outcomes.[24] For example, Bair et al. (2003) reported that the probability of poor treatment response was positively associated with an increased severity of pain in depressed patients.[41]

In summary, pain is the most common comorbid psychological condition in MDD patients. Depressed patients with comorbid pain have a greater decrement in health outcomes, such as having lower HRQL, more severe psychiatric distress, and more functional limitations. Study results from both nationally representative survey data and from primary care clinics show that the presence of pain in MDD patients is associated with higher health care utilization and health care expenditures.

Medication treatment, adherence and outcome in major depressive disorder patients

The goals of treatments for MDD patients are to achieve remission of symptoms, to prevent recurrence, and eventually to recover from the illness. Pharmacotherapy such as medication treatment with antidepressants is an essential element for achieving these goals. Antidepressants can treat depression and prevent future episodic disorders.[46] An increased rate of antidepressant treatment has been reported. For example, Olfson and Marcus (2009) studied trends of national patterns in antidepressant treatment using the Medical Expenditure Panel Survey (MEPS), and found that the rate of antidepressant use has increased from 5.84% in 1996 to 10.12% in 2005, which accounted for 13.3 (1996) to 27.0 (2005) million people in the U.S.[47] With a growing number of individuals in the U.S. using antidepressant treatment, it is important to know if patients are adherent to the treatment. Adherence decides whether antidepressant treatment can reach maximized effectiveness and attain optimal treatment outcomes.

Adherence to medication therapy is crucial for achieving successful depression treatment because depressed patients with good adherence are less likely to experience relapse or recurrence.[48-49] However, medication nonadherence to depression treatment is commonly reported in previous studies. Approximately, 28% of patients with newly prescribed antidepressants for depression stop taking medications during the first month of therapy, and 44% stop taking them by the third month of the therapy.[50] Findings from a review study conducted by Cramer and Rosenseck (1998) reported that the rate of compliance with antidepressants is only 65% (range 40% to 90%).[51] Moreover, the mean

rate of nonadherence among patients with recurrent depression is as high as 46.5% (range 39.7% to 52.7%).[52]

Reasons for nonadherence in depressed patients can vary. Side effects of taking antidepressants can be a common reason for nonadherence, but studies have shown several other reasons that might be also related to noncompliance with antidepressants. For example, findings from a review article conducted by Delgado[53] (2000) showed that reasons for nonadherence to antidepressants included beliefs about mental illness, cost of treatment, ineffectiveness of treatment, symptoms of diseases, and cultural or attitudinal factors. Other reasons for discounting medications can include believing in not needing medications, perceiving inefficacy of medicines, or feeling better.[50]

With a high rate of nonadherence of antidepressant treatment, the consequence can be serious. Discontinuation of antidepressant treatment is associated with ineffective treatment which can result in relapse of depression.

Better treatment outcomes are related to better medication adherence. For example, findings from a review article conducted by Keller et al. (2002) showed that compliance with antidepressant treatment is important in achieving treatment effectiveness, such as strengthening treatment outcomes and preventing relapse or recurrence of depression symptoms.[54]

In summary, understanding antidepressant treatment is important since a large amount of the population is using antidepressants. Antidepressant treatment can achieve remission in depressed patients but optimal treatment outcomes will not be reached without adherence. Better adherence can cure depression and eventually prevent relapse or recurrence in depressed patients.

Need for Research

MDD is a mental illness with high prevalence, high severity, and a high economic burden on society in the U.S. Studies have noted that MDD is prevalent in both Caucasians and African Americans,[15-16] but African American patients are less likely to receive antidepressant treatment.[18, 21-22] Potential health disparities of MDD treatment such as antidepressant use may exist between Caucasians and African American patients. With socioeconomic disadvantages, African American MDD patients can be less likely to access MDD treatment and less likely to receive antidepressants.[18, 21-22]

Comorbid conditions are common in MDD patients. Aforementioned studies have shown a high prevalence rate of psychiatric and physical comorbidity, such as anxiety disorders and painful symptoms, in patients with depression. Both psychiatric and physical comorbid conditions can result in more severe depressed symptoms, worse treatment outcomes, longer time to recover, a higher rate of health resource utilization, more frequent recurrence, and a lower rate of remission in MDD patients.

Previous studies have examined the influence of race/ethnicity and comorbidity respectively on health related outcomes. Most of the studies have examined the influence of comorbidity on health outcomes in MDD patients; however, there is a scarcity of the literature evaluating the impact of a combined effect of race/ethnicity and comorbidity on medication-related outcomes, such as adherence, medication utilization and medical expenditures. Furthermore, with a high rate of psychiatric and physical conditions coexisting in patients with MDD, it is necessary to evaluate the combined effect of race/ethnicity with either psychiatric or physical comorbidity on MDD patients' medication-related outcomes.

Medication adherence can ensure optimal pharmacotherapy. Persistent use of antidepressant treatment can achieve remission and prevent recurrence in MDD patients. However, previous studies have shown a lower adherence rate in MDD patients. It is important to investigate factors that are associated with medication adherence in MDD patients. It is also imperative to investigate the combined effect of race/ethnicity and comorbidity on medication adherence in MDD patients. After reviewing the existing literature, there is still a gap in examining the combined effect of race and comorbidity on medication adherence.

Medicaid enrollees have unique patient characteristics. Compared with beneficiaries covered by primary health care plans or Medicare, Medicaid enrollees usually have lower socioeconomic status, poorer education background, poorer understanding of medication use and preventive cares, and are more vulnerable to disease threats. Patients can have difficulty understanding their medications or treatments, which could relate to a lower adherence rate. With fluctuating eligibility, Medicaid enrollees may not have consistent and appropriate treatments to relieve MDD symptoms. Moreover, medical needs and medication utilization of Medicaid enrollees with MDD can be distinct from beneficiaries covered by other insurance plans. Although studies have been carried out assessing the association between comorbidity and health outcomes in patients with MDD, it is not clear whether the same study results can be applied in Medicaid populations. Hence, it is imperative to conduct research to investigate the association between the combined effect of race/ethnicity and comorbidity and medication-related health outcomes in MDD patients, especially for Medicaid populations.

Medication utilization, medication adherence, and health resource utilization in MDD patients alone can be different from that in MDD patients with comorbidity. With the combined influence of race and ethnicity, patterns of medication use in patients with MDD may be affected. However, there is a paucity of literature investigating the influence of race/ethnicity, comorbidity, and their combined effect on medication related outcomes in patients with MDD.

Significance of the Study

This study was important because it provided new insights into this combined effect on MDD patients. This study was the first study to investigate the combined effect of race and comorbidity together on medication use-related outcomes among Medicaid enrollees with MDD. There was a scarcity of research to investigate health outcomes among patients with MDD in Medicaid enrollees. Medicaid enrollees were an under-served and under-studied population. The results of this study would provide comprehensive understanding of the association of race and comorbidity with medication use-related outcomes among patients with MDD.

By examining the combined effect of race/ethnicity and comorbidity on medication related outcomes in MDD patients, this study provided supportive literature in helping clinicians, policymakers and health service researchers to comprehensively understand and explain differences of medication utilization in patients with MDD based on important parameters such as race and comorbidity. Identifying the influence of the combined effect of those factors would help to understand the influence of comorbidity in patients with MDD, to design strategies to reduce health disparities in antidepressant treatment, and improve health outcomes, especially in Medicaid MDD enrollees.

Specific Objectives

The objectives of this study were to assess the association between specific effects of race, comorbid anxiety disorders, and the combined effects of race and comorbid anxiety disorders on medication related outcomes in Medicaid-enrolled MDD patients. This section described the specific objectives.

This dissertation included two publishable manuscripts. The two manuscripts were included in the Chapter 4 and Chapter 5, respectively. The following seven objectives were addressed either in the first manuscript in the Chapter 4 or in the second manuscript in the Chapter 5. Based on preliminary studies and the literature review, the specific objectives of this study were as follows:

Objective 1: To describe select patient characteristics (sociodemographic factors and medication-related factors) in Medicaid-enrolled patients with and without comorbid anxiety disorders. (Addressed in the manuscript No. 1 & No. 2)

Objective 2: To examine the effect of race/ethnicity, comorbid anxiety disorders, and the combined effects of race/ethnicity and comorbid anxiety disorders on medication adherence in Medicaid-enrolled MDD patients after adjusting for select confounders. (Addressed in the manuscript No. 1)

Objective 3: To examine the effect of race/ethnicity, comorbid anxiety disorders, and the combined effects of race/ethnicity and comorbid anxiety disorders on medication persistence in Medicaid-enrolled MDD

patients after adjusting for select confounders. (Addressed in the manuscript No. 1)

Objective 4: To examine the effect of race/ethnicity, comorbid anxiety disorders, and the combined effects of race/ethnicity and comorbid anxiety disorders on mental health-related health care costs in Medicaid-enrolled MDD patients after adjusting for select confounders. (Addressed in the manuscript No. 2)

Objective 5: To examine the effect of race/ethnicity, comorbid anxiety disorders, and the combined effects of race/ethnicity and comorbid anxiety disorders on overall health care costs in Medicaid-enrolled MDD patients after adjusting for select confounders. (Addressed in the manuscript No. 2)

Objective 6: To examine the effect of race/ethnicity, comorbid anxiety disorders, and the combined effects of race/ethnicity and comorbid anxiety disorders on mental health-related health resource utilization (office visits, hospitalization and emergency room (ER) visits) in Medicaid-enrolled MDD patients after adjusting for select confounders. (Addressed in the manuscript No. 2)

Objective 7: To examine the effect of race/ethnicity, comorbid anxiety disorders, and the combined effects of race/ethnicity and comorbid anxiety disorders on overall health resource utilization (office visits, hospitalization and emergency room (ER) visits) in Medicaid-

enrolled MDD patients after adjusting for select confounders. (Addressed in the manuscript No. 2)

Study Hypotheses

The following study hypotheses anticipated directions of the associations. The hypotheses were formed based on findings from the literature and the theoretical frameworks which were described in the Chapter 2. The hypotheses were tested either in the first manuscript in the Chapter 4 or in the second manuscript in the Chapter 5. The hypotheses were as follows:

Hypothesis 1: Compared with Caucasian patients with MDD, African American patients with MDD have a lower rate of medication adherence, and a lower rate of medication persistence after adjusting for select confounders. (Tested in the manuscript No. 1)

Hypothesis 2: Compared with patients with MDD only, MDD patients with comorbid anxiety disorders have a higher rate of medication adherence, a higher rate of medication persistence after adjusting for select confounders. (Tested in the manuscript No. 1)

Hypothesis 3: African-American patients with comorbid anxiety disorders have a lower rate of medication adherence and persistence when compared with three other groups: African-American patients without comorbid anxiety disorders, Caucasian patients with comorbid anxiety disorders, and Caucasian patients without comorbid anxiety disorders. (Tested in the manuscript No. 1)

Hypothesis 4: Compared with Caucasian patients with MDD, African American patients with MDD have a lower rate of office visits, but have a higher rate of mental health-related and overall health resource utilization (hospitalization, ER visits, health care costs) after adjusting for select confounders. (Tested in the manuscript No. 2)

Hypothesis 5: Compared with patients with MDD only, MDD patients with comorbid anxiety disorders have a higher rate of mental health-related and overall health resource utilization (hospitalization, ER visits, health care costs) after adjusting for select confounders. (Tested in the manuscript No. 2)

Hypothesis 6: African-American patients with comorbid anxiety disorders have a higher rate of mental health-related and overall health resource utilization (office visits, hospitalization, ER visits, health care costs) after adjusting from select confounders when compared with three other groups: African-American patients without comorbid anxiety disorders, Caucasian patients with comorbid anxiety disorders, and Caucasian patients without comorbid anxiety disorders. (Tested in the manuscript No. 2)

CHAPTER 2

REVIEW OF LITERATURE

Major Depressive Disorder

Symptoms of major depressive order

Depression is a major mental illness that can interfere with a person's daily life. Depression can disable a person's normal functions such as working, sleeping, studying and eating,[55]and it creates a significant burden to both patients and their families. Results from the WHO collaborative study on psychological problems in general health care revealed that patients with MDD usually experience permanent disability.[56]

The symptoms of depression include feeling empty, persistently sad, anxious, hopeless, helpless, loss of interest, and loss of energy.[55] Patients with depressive disorders can have suicide attempts.[55] Physical symptoms of depressed patients can include pains, headaches, cramps, and digestive problems.[55] Although depressive disorders can exhibit a variety of symptoms, not every patient experiences all the same symptoms.

Prevalence of major depressive disorder

Major Depressive Disorder (MDD) is one of the most common mental disorders in the U.S.[57] Waraich et al. (2004) conducted a systemic review of 23 articles

investigating prevalence and incidence of mood disorders between 1980 and 2000.[58] The authors reported that the annual prevalence rate of MDD is about 4.1% and the lifetime prevalence rate is 6.7%.[58] More recently, the annual prevalence rate has been estimated to be 6.7% in 2003,[1] and the lifetime prevalence rate was 16.2%.[2] The prevalence rate of depression is more common in women than men.[59-60] In addition, MDD was found to have a prevalence rate close to 19% in urban general medicine practices.[61]

With a high prevalence rate, depression is also a recurrent disorder.[57] Approximately 80% of depressed patients have at least one more episode even though they have received treatment for depression.[57, 62] An average period of an episode is 16 weeks (95% CI, 15.1-17.3 weeks).[6, 57] About 60% of patients with MDD can have role impairment.[6] Furthermore, patients with depression can be associated with comorbid psychiatric disorders and medical illnesses.[57]

In summary, MDD is a highly prevalent mental illness. It is one of the most common illnesses seen in primary care settings. Patients with MDD can also have comorbid mental and somatic illnesses. The average MDD episode is long and can easily to result in role impairment.

Undertreatment among MDD patients

Although depression is a highly prevalent mental illness in the U.S., a substantial amount of patients still receive inappropriate treatment. A nationally cross-sectional telephone survey conducted over a one year period from 1997 to 1998 showed that only 19% of patients with depression received appropriate care.[63] At that time, the authors concluded that most adult patients did not receive optimal treatment of depression in the U.S.[63] In addition, treatment disparities exist across different gender or race/ethnicity

boundaries. Males and African Americans are less likely to receive appropriate treatment for depression.[63]

Results from a more recent study in 2003 shows that about 48% of MDD patients did not receive treatment.[6] Among those who have received treatment, only 21.7% of patients received appropriate treatment.[6] With a high prevalence rate and a recurrence rate, the consequence of inappropriate treatment can result in relapse. Therefore, to increase treatment and improve the quality of treatment among MDD patients need to be emphasized.

Major Depressive Disorder in the Medicaid population

Medicaid enrollees are usually a vulnerable population in society due to their lower socioeconomic status. Health resource utilization or medication related outcomes, such as medication adherence and medication persistence of Medicaid enrollees, can be different from the general population due to the socioeconomic disadvantages of Medicaid enrollees. Chen et al. (2008) conducted a study using national Medicaid pharmacy claims provided by the Centers for Medicare & Medicaid Services to investigate the utilization, price and spending trends for antidepressants in the U.S. Medicaid program.[64] They found a significantly increased amount of antidepressant use and expenditure among the Medicaid population. For example, from 1991 to 2005, the total number of antidepressant prescriptions increased 380% from 6.82 million to 32.72 million, and the total expenditure on antidepressants increased from 159 million dollars in 1991 to 2.26 billion dollars in 2004.[64]

In addition to the increased amount of antidepressant use, understanding medication use, such as adherence to antidepressants or medication persistence, is also an

important issue to be investigated in the Medicaid population. However, studies have revealed distinct adherence rates in Medicaid enrolled patients with MDD. For example, Stiles et al. (2009) used Florida Medicaid data to study adherence among Medicaid enrollees with severe mental illness such as schizophrenia or MDD.[65] In the findings, they reported an overall 57% adherence rate to recommended practice guidelines for patients with MDD.[65] In contrast, a fairly good prescription consistency rate in Medicaid patients with MDD was reported in another study.[66] Carnahan et al. (2008) conducted a study using data from the Iowa Medicaid Pharmaceutical Care Management program, and reported an 86% consistency rate among 1,122 persistent antidepressant users.[66]

The eligibility of Medicaid coverage or types of services can have an influence on medication related outcomes in patients with MDD. For example, Medicaid enrollees with MDD enrolled in the fee-for-service condition were more likely to receive treatment consistent with recommended practice guidelines compared with enrollees in either PMHP or HMO conditions.[65]

Kahn et al. (2008) conducted a study to investigate comorbidity between depression and diabetes in Medicaid enrollees.[67] The authors used the Patient Health Questionnaire (PHQ-9) to survey Medicaid enrollees and found that 56% of patients with diabetes also had depression. Only half (49%) of those patients had a diagnosis of depression in the claims.[67] They further concluded that among Medicaid enrollees, diabetic patients with comorbid depression were underdiagnosed.[67]

Regarding findings from the literature search above, there is still a gap in the literature about the influence of race and comorbidity on Medicaid enrolled patients with MDD. In addition, most studies conducted to investigate medication-related outcomes in

the Medicaid population were not national-wide studies.[65-67] A study with nationally representative data of Medicaid enrolled patients with MDD is necessary for comprehensively understanding health outcomes and the association with race and comorbidity.

Treatment Guidelines in Major Depressive Disorder

In April 2000, the American Psychiatric Association released a set of practice guideline: Treatment of Patients With Major Depressive Disorder, Second Edition.[68] However, it has been a decade since these guidelines have been updated.[68] In order to obtain the most current information regarding treatment of major depressive disorder, this literature reviewer adopted the most recent treatment information from the British Association for Psychopharmacology.[57] The most recent guidelines published in 2008 by this association is 'Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 British Association for Psychopharmacology guidelines'.[57] These guidelines provide the most updated information for treating depression through the use of antidepressants.

The antidepressant treatment in the guidelines is summarized in the following sections.

Choice of antidepressant medication

Selective serotonin reuptake inhibitors (SSRIs) are the first line choice for treating depression due to their safety and better tolerance.[57] Older tricyclic antidepressants (TCAs) can be a choice if the first line SSRIs have failed.[57] Factors associated with the choice of antidepressants include patient preference, previous treatment response to a particular antidepressant, side effects, and tolerability.[57] Furthermore, a drug interaction

between antidepressants and other medicines needs to be taken into consideration because depressed patients can have concurrent comorbid mental or physical illnesses.[57]

Treatment failure and treatment resistance

When they encounter treatment failure and treatment resistance, physicians need to evaluate the treatment dosage and medication nonadherence.[57] Several treatment strategies, such as increasing dosage to the therapeutic range, evaluating diagnoses, and considering social factors associated with depression, can be implemented in order to improve treatment.[57] If the symptom has mild improvement after implementing the treatment in the first four weeks, the treatment can be implemented for another 2-4 weeks.[57] After adequate treatment for 6-8 weeks, if the symptom has moderate or greater improvement, the treatment can be continuously implemented.[57] Longer trials are first recommended before patients switch to a new treatment if patients have failed several treatments.[57]

Comorbid condition

Potential drug-drug interactions influence the choice of antidepressants due to the high prevalence of comorbid conditions among depressed patients. An antidepressant with a lower risk of interaction is the first choice.[57] In addition, adverse effects need to be considered when choosing an antidepressant.[57] Patients with certain comorbid diseases, such as cardiovascular diseases, arrhythmias and cardiac failure need to avoid TCAs to treat depression.[57] SSRIs and SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors) are preferred for treating depressed patients with comorbid bleeding disorders.[57]

Side effects

Side effects are common when depressed patients take antidepressants. For example, Greist et al. (2004) studied duloxetine (SNRIs) and related induced nausea by taking duloxetine.[69] The authors revealed that duloxetine could induce mild to moderate nausea but nausea could be resolved after continuous treatment for one week.[69] Nausea is also commonly associated with SSRIs but can improve over time.[57, 69] Research on side effects of SSRI treatments shows that the number of adverse effects decreases over time.[70] However, anticholinergic side effects caused by taking TCAs do not diminish over time and can remain with long-term treatment.[71]

The strategies to manage side effects include reducing the dose, switching to a new drug, treating side effects caused by antidepressants by using another agent, or non-drug management for the side effects.[57] Newer antidepressants such as SSRIs or SNRIs usually have better tolerability than older antidepressants such as TCAs.

Relapse

Relapse means a return of depression before recovery from the disease.[57] Relapse is very common in depressed patients after antidepressant treatment. Results from a review article conducted by Belsher and Costello (1998) showed that 20-24% of patients can experience a relapse of depression in two months after recovery.[57, 72] The relapse rate in 4 months is 28-44%; in 6 months is between 28-44%, and in 12 months is between 37-54%.[57, 72] Despite the higher relapse rate, patients continuously receiving antidepressant treatment can reduce the relapse rate by 70% when compared with patients who receive treatment discontinuously.[73] Treatment can be effective for up to 36 months if patients adhere to treatment.[73] The treatment period for receiving antidepressants is usually 36

months. Therefore, continuing taking antidepressants can prevent the relapse of the disease.

Pharmacotherapy in Major Depressive Disorder

Several studies have shown that continuation and maintenance treatment is important for preventing recurrence and achieving remission when treating depressed patients.[74-77] Antidepressants are categorized into three major types: selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) and Tricycles (TCAs). The first class is SSRIs. Serotonin is a neurotransmitter associated with mood and behaviors. SSRIs block the reabsorption of serotonin and keep serotonin levels high in the brain.[78] Due to higher tolerability and efficacy, SSRIs are often the first treatment choice for depressed patients. The most prescribed SSRIs include Citalopram (Celexa®), Escitalopram (Lexapro®), Fluoxetine (Prozac®), Paroxetine (Paxil®), and Sertraline (Zoloft®).[78] In 1997, 58.3% depressed patients received SSRIs as antidepressant treatment in U.S. outpatient settings.[79]

The second class of antidepressants is SNRIs. SNRIs are also called dual inhibitors because SNRIs block both serotonin and norepinephrine reabsorption.[80] SNRIs increase the level of neurotransmitters (serotonin and norepinephrine) in the brain and improve mood.[80] Duloxetine (Cymbalta) and Venlafazine (Effexor) are two SNRIs that are commonly prescribed for treating depression.[80]

TCAs are an older group of antidepressants. In addition to blocking serotonin and norepinephrine reabsorption, TCAs inhibit one additional neurotransmitter, dopamine, from being reabsorbed by brain cells. The levels of serotonin, norepinephrine, and dopamine are believed to be associated with mood.[81] Results of a meta-analysis with 102

comparative and randomized clinical trials showed no significant difference in efficacy between SSRIs and TCAs.[82] However, the anticholinergic adverse effects of TCAs have resulted in treatment discontinuation.[83] The commonly prescribed TCAs include Amitriptyline, Amoxapine, Despramine (Norpramin), Doxepin (Sinequan), Imipramine (Tofranil), Nortriptyline (Pamelor), Protriptyline (Vivactil), and Trimipramine (Surmontil).[81]

In summary, depressed patients can benefit from continuing antidepressant treatment. The use of antidepressants can achieve remission and prevent relapse. SSRIs, SNRIs, and TCAs are three groups of antidepressants that are commonly used. Due to high tolerability,[84] SSRIs are the first line treatment option and have been widely prescribed for patients with depression.

Medication Use Behavior

Adherence is one of the most important medication use behaviors because adherence to a prescription treatment is essential to achieve remission of a disease. In studying medication use behaviors in depressed patients, issues of adherence are more important because better adherence to antidepressants can successfully achieve remission and prevent relapse. Understanding medication adherence among depressed patients is even more important because studies have revealed that depression is a predictor for poor medication adherence.[85-87] Therefore, issues of adherence to antidepressants and the impact of race/ethnicity or comorbidity on adherence are reviewed and described in the following sections.

The following sections begin with the definition of medication adherence. Factors associated with medication adherence in MDD patients are then reviewed. Also, the

influence of comorbidity on medication adherence in MDD patients is reviewed. The final section addresses the challenges of studying medication adherence in MDD patients.

Definition of medication adherence

Adherence to a medication regimen is usually defined as "the extent to which patients take medications as prescribed by their health care providers."[88-89] Two words, "adherence" and "compliance" are usually used to describe patients' complying with physicians' orders to use a medicine. Adherence is preferred because it means patients are more actively involved in the therapeutic decision and do not just passively follow the physicians' orders of a treatment.[88] Using adherence to describe medication use behaviors allows physicians and patients have a more balanced status when a treatment decision is made.

According to a World Health Care Organization report on adherence to long-term therapies, adherence to a medication treatment refers to several medication-taking behaviors such as seeking medical attention, filling prescriptions, and taking medication appropriately.[89] The benefit of medication adherence can be achieved only if patients closely adhere to medication regimens.[88]

Factors associated with medication adherence in MDD patients

Factors associated with medication adherence in MDD patients can be categorized into three groups.[83] They are physician-specific issues, patient-specific issues and medication-specific issues.[83] In physician-specific issues, for example, explicit communication between physicians and depressed patients can result in treatment continuation.[90] Bull et al. (2002) studied the impact of physician-patient communication on continuation of treatment with antidepressants.[90] The authors found that patients were

less likely to discontinue treatment if they have discussed side effects with their physicians.[90] Explicit communication regarding side effects and therapeutic duration can reduce discontinuation of antidepressants use.[90] Other physician-specific issues, such as patients' not receiving sufficient dosage from physicians, can also result in discontinuation of antidepressants.[91]

In addition to physician-specific issues, patient-specific issues can have an influence on adherence. Patients may stop taking antidepressants if they have negative perceptions regarding antidepressants, such as feeling stigmatized or disliking taking medication.[92] In addition, patients are less likely to adhere to antidepressant treatment if they do not perceive symptom relief or efficacy of the medications.[93]

The adverse effect is one of the most common medication-specific issues which causes patients to discontinue their medication treatment.[90] In a survey study, for example, 43% of patients had stopped taking antidepressants in the first 3 months of initiating therapy due to side effects.[93] Another medication-specific issues influencing medication adherence is the complicated dosing and titration schedule of the antidepressant treatment.[83] Simplifying the dosing schedule, such as prescribing a sustain-release formulation with a single tablet, can improve patients' adherence.[94-95]

In summary, antidepressants can effectively treat depression. However, patients cannot gain benefits from antidepressants unless they are adherent to the medication. If patients fully understand antidepressant treatment, such as the overall period of treatment, the onset time, side effects and the time when patients can start to experience the efficacy, then patients are more likely to adhere to the medication they are taking. Through explicit

physician-patient communication, adherence can be improved and optimal antidepressant treatment can be achieved.

Influence of comorbidity on medication adherence in MDD patients

Comprehensively understanding the influence of comorbidity on medication adherence in MDD patients is very important. Given the high incidence of physical and psychiatric comorbidity among MDD patients, MDD patients may experience several symptoms and use several medicines at the same time. For example, research has shown that 85% of depressed patients can experience overlapping symptoms of anxiety.[96] Research has also shown that MDD patients with comorbid diseases are less likely to respond to treatment and are more likely to experience negative treatment outcomes.[96]

With complex disease patterns and treatment regimens, MDD patients with comorbidity may have difficulty in understanding how to take medicines, because patients can have a more sophisticated dosing pattern and schedule of taking medicines. Patients may stop taking medications for several reasons, such as not understanding the medication treatment, not communicating well with physicians, not immediately experiencing symptom relief, and not tolerating adverse reactions.

Therefore, comorbid illnesses in MDD patients can lower the adherence rate. Comorbidity can hinder MDD patients' ability to understand and to take medication correctly. Eventually, it can result in not achieving treatment goals.

The combined effect of race and comorbidity on health outcomes

A number of studies have revealed differences of disease prevalence among different racial/ethnic groups.[97-100] Different racial/ethnic groups can have different prevalent disease patterns. For example, African-Americans have a higher prevalence rate

of diabetes.[98] In contrast, a higher prevalence rate of MDD in Caucasian patients than African-American patients is reported in several studies.[11-14] Race/ethnicity can be a factor affecting certain disease prevalence, but it may not be able to fully explain the difference of health outcomes between American and Caucasian patients without accounting for the disease burden, especially comorbidity. The occurrence of the co-existence of multiple chronic conditions may affect health outcomes such as health resource utilization or medication adherence between different racial/ethnic groups.[101] For example, the mortality rate between African-American males and Caucasian males becomes similar after considering the joint effect of the occurrence in chronic diseases.[101]

Incorporating the combined effect in a study can assist researchers in obtaining more comprehensive results. For example, Berkman et al. (2003) conducted a clinical trial to examine the effects of treating depression and to assess low perceived social supports on clinical events after myocardial infarction.[102] The authors incorporated the combined effects of treatment and gender, and found the combined effect had a significant influence on patients' health outcomes.[102] Schneiderman et al. (2004) examined the effect of psychosocial treatment within different genders by ethnic subgroups, and the authors concluded that it was necessary to incorporate the combined effect of gender and race when studying health outcomes in coronary heart diseases.[103]

Race and comorbidity and their combined effects can have a significant influence on patients' health outcomes. West et al. (1996) conducted a study to examine the effect of comorbidity on the breast cancer survival rate between African-American and Caucasian women.[104] The authors found that comorbidity could predict the survival rate in women with breast cancer.[104] The authors also emphasized the importance of

incorporating certain diseases by a certain ethnic group with a comorbidity index (Charlson) when conducting future research.[104]

The studies reviewed above have addressed the importance of incorporating the combined effects of race and comorbidity when conducting research. However, there is a scarcity of research conducted to evaluate the impact of the combined effect of race/ethnicity and comorbidity on medication related outcomes, such as adherence, medication utilization and health care utilization, in Medicaid patients with MDD. The combined effect of race and comorbidity on the health outcome is still not clear among patients with MDD. There exist differences in MDD prevalence,[11-14] and the treatment rate between African-American and Caucasian patients.[14, 17-23] In addition, comorbid diseases are highly prevalent in patients with MDD.[24-26] Therefore, it is very important to conduct a study which accounts for the combined effects of race and comorbidity, and to examine the combined effects on health outcomes. The results of such a study could potentially fill the gap of the literature and comprehensively understand medication related outcomes in patients with MDD.

Issues and challenges with medication adherence in MDD patients

The measurement of medication adherence is an important issue to be considered when studying medication use behaviors. Assessing adherence is to rate the percentage of prescribed doses of the medication that are actually taken by patients over a certain period of time.[88] Results can be extremely different when choosing different methods to measure adherence. Osterber and Blaschke (2005) conduced a review study of medication adherence.[88] In the article, the authors categorized adherence measurement into two primary different methods: direct measures of adherence and indirect measures

of adherence.[88] Direct methods include directly observed therapy, measurement of the level of medicine in blood, and measurement of biologic markers in blood.[88] Indirect methods include patient self report, pill counts, the rate of prescription refills, assessment of the patient's clinical response, electronic medication monitors, measurement of physical markers, patient diaries, and reports from a proxy.[88]

Each method of measuring adherence has its own advantages and disadvantages. For example, the advantage of directly measuring the level of medicine in blood in MDD patients can precisely detect the drug concentration in patients but the disadvantages of this method can be cost-ineffectiveness and this method may not to be feasible if patients are not hospitalized. In contrast, indirect measures, such as patient self report adherence, can be very inexpensive to implement but the precision can be suboptimal.

This study will assess medication adherence by measuring the rate of prescription refills. Measuring the rate of prescription refills has been widely used in measuring adherence in claim data. The advantages of this method are that it is reliable, inexpensive, and objective. Investigators can obtain prescription refill information through records in administrative claim data. However, timing of intake can be imprecise because it cannot be measured using administrative claim data. Another drawback of this method is that refilling prescriptions may not does not necessarily imply taking prescriptions.

Precisely measuring medication adherence in MDD patients can be more challenging because of several reasons. First, MDD patients can have several comorbid diseases. Patients may need to take several medications to relieve symptoms and maintain health. Taking several prescriptions at the same time increases the likelihood of nonadherence. Second, depressed patients usually have great difficulty in following their

medication treatment. Unlike other physical illnesses, MDD patients may have impairments of cognitive functions. These impairments increase the difficulty for MDD patients to adhere to their antidepressants. Third, MDD patients may be reluctant to take antidepressants because of the social and cultural stigmas that may be associated with these medicines. Different racial/ethnic groups can have different views of depression. Negative perceptions of taking antidepressants can result in a lower adherence rate.

In summary, precise measurement of medication adherence may pose real challenges because each method has its own advantages and disadvantages. From a clinical perspective, MDD patients with comorbidity need to take multiple medications, which may lower the medication adherence rate. Finally, from the cultural perspective, facing stigma of taking antidepressants may influence patients' adherence of taking medications.

Theoretical Framework

Developing and implementing a theoretical framework is critical in conducing health service research because a theoretical framework provides rationality for examining associations and identifying causality among variables. A theoretical framework assists researchers in conducting a study, generalizing testable hypotheses, developing instruments, collecting essential information, analyzing study data, and interpreting results. The theoretical framework informs researchers and guides research processes by conceptualizing study factors. Moreover, a conceptual framework can also serve as a basic structure for identifying or selecting potential factors (predictors) that can be associated with study outcomes. Researchers can articulately identify elements and

systematically think about the relationships between concepts and elements, which are specific for a behavior, a behavior change, or an outcome.

In order to comprehensively understand the combined effect of race/ethnicity and comorbidity on medication use related outcomes in MDD patients, a theoretical framework is proposed for conducting the study, identifying variables and assessing associations. The concepts in the proposed framework are derived from the Health Belief Model and the Aday-Andersen model. The Health Belief Model is one of the commonly used conceptual frameworks to explain health behaviors. The Aday-Andersen model is a framework that has been widely applied for studying access to health care and health care utilization in the health survey research area. The history, concepts and rationality of the two models are depicted in the following two sections.

Andersen-Newman framework for health care utilization

Health services utilization in the U.S. is a major concern because of the increasing size of the senior population and extremely high health care expenditures. In order to lower incremental health care expenditures and provide better health care, heath service researchers want to comprehensively understand the association between individual determinants and characteristics of health service utilization.

Andersen and Newman (1975) developed an initial model for identifying social and individual characteristics which were related to health service utilization in the 1960s.[105] In the model, the authors proposed that health care utilization is associated with several social and individual determinants.[105] Social determinants include technology and norms of a society that can influence the health services system.[105] The health care system consists of resources and organization, both of which have an impact on

individual determinants of health service utilization.[105] The resource of the health care system includes the volume of the resource and the distribution of the resource.[105] For example, the number of primary care physicians in a certain county's health care system can determine how many health care resources that this certain health care system can provide. The authors define two elements of the organization of the health care system: access and structure.[105] Access refers to gaining entry to the health care system and to continuously have medical treatment in the system.[105] Structure means how the system processes medical care for patients in the system.[105] For example, a patient may need to have a referral from a primary physician to a specialist when the patients need specific health care.

In addition to social determinants, individual determinants pay an important role in studying health care utilization. Figure 2.1 depicts three individual determinants: predisposing, enabling and illness levels in the model that Andersen and Newman proposed.[105] In the Predisposing component, variables are further categorized into three subcomponents: demographic variables, social structure variables and beliefs variables. Each individual can have a certain propensity to use health care resources based on their predisposing characteristics.[105] For example, disease patterns in males can be very different from those in females. Consequently, gender differences can be considered as a reason for an individual's seeking health care when studying health care utilization. Similarly, social structure variables, such as education, can have an influence on an individual's health care utilization.[105]

The last group of predisposing factors is the individual's beliefs. An individual's beliefs or attitudes about health can determine his/her health behaviors, which can

eventually change the pattern of health care utilization.[105] For example, an individual may think a certain screening procedure can be beneficial for his/her health. The person may be more willing to undergo the procedure than a person who does not believe the procedure is beneficial for his/her own health.

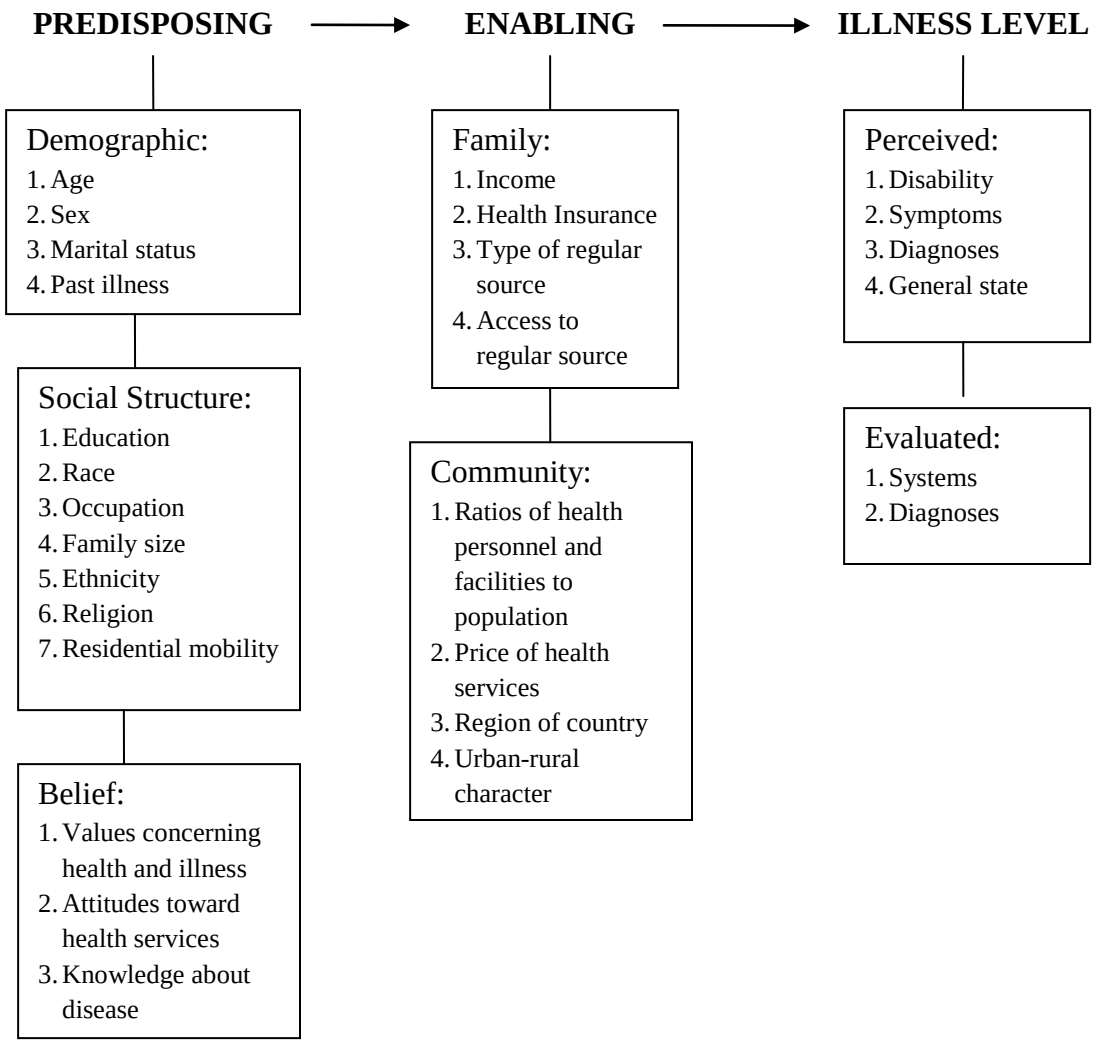


Figure 2.1 Individual determinants of health service utilization

Enabling factors in the Andersen-Newman framework are defined as the conditions under which an individual is able to obtain health care resources.[105] It also reflects an individual's ability to make use of those health care resources.[106] Enabling factors such as family income and insurance coverage can determine if an individual is able to use health care resources. Furthermore, whether a person has a regular source of care can also determine if he/she is able to access health care resources. The enabling characteristic, such as price of health services, can also affect health care utilization. For example, if the price of a certain health service is affordable for most individuals, the use rate may be elevated.[105]

Finally, the last component of the model is the illness level. Variables related to individuals' perceiving their personal health status or their experiencing severity of the illness are included in the component of illness level.[105-106] How people view their functional state and experience disease symptoms can influence their health care utilization.[106] The authors also argued that illness level can also immediately affect health care use.[105] Health care utilizations are directly related to how individuals perceive their own illness level.

In summary, the Andersen-Newman model explores social and individual determinants that are associated with health care utilization. Both social determinants and factors of health services system directly impact individual determinants, which can eventually influence health care utilization. An individual's health resources utilization can be well explained by the model when considering predisposing factors, enabling factors and factors of illness level in the model.

The Aday-Andersen framework for the study of access to health care

In the U.S., accessing health care is an important social concern. Policymakers seek strategies of increasing the access rate for the public. Health care researchers continuously put much effort into finding causes and barriers of accessing health care. Both of policymakers and health care researchers intend to improve and achieve the equity of access to health care.

In 1974, in order to comprehensively understand concepts of access to health care Aday and Andersen proposed a framework to study and investigate relevant issues of access to health care. (Figure 2.2)[107] Factors and concepts of access to health care are incorporated into the framework. Various relevant variables of access, such as characteristics of the health delivery system, as well as the population at risk, utilization of health services, and consumer satisfaction are integrated into the Aday-Andersen theoretical framework.[107]

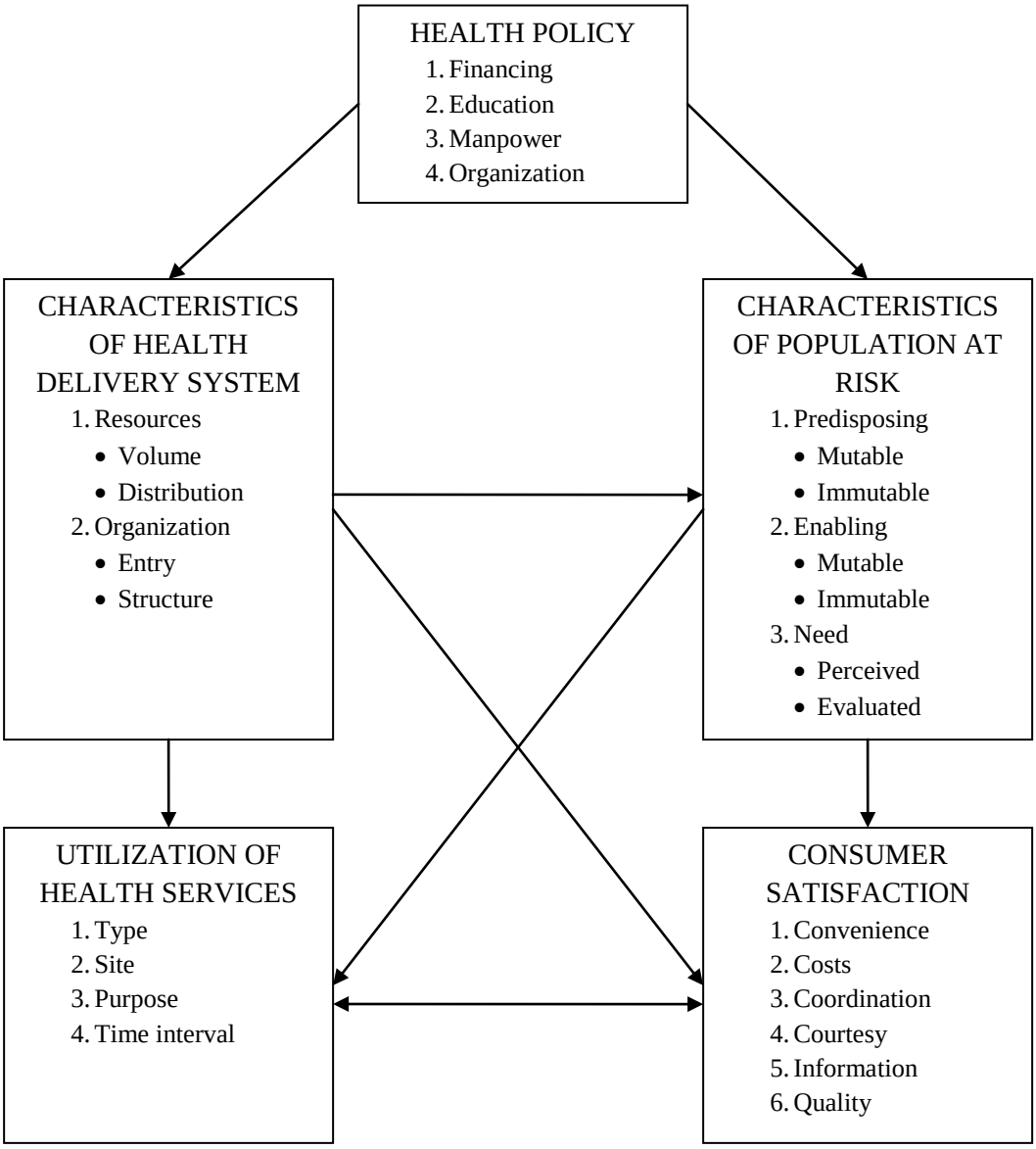


Figure 2.2 Aday-Andersen framework for the study of access

The Aday-Andersen framework conceptualizes access to health care as processing from the component of the Health Policy through the Characteristics of Health Delivery System and the Characteristics of Population at Risk and ending with outcomes as the Utilization of Health Services and the Consumer Satisfaction for individuals.[107] In this model, the Health Policy component is conceptualized as a starting point of access to

health care because improving access to health care is usually the main purpose of health policy.[107] The Health Policy component comprises of financing, education, manpower, and health care organizations, which include factors that are associated with health care access.

In this model, the Health Policy is proposed to influence the Characteristics of Health Delivery System and the Characteristics of Population at Risk. The component of the Characteristics of Health Delivery System in Aday-Andersen framework[107] is similar to the component of social determinants in the Andersen-Newman model.[105] The volume and distribution of health care resources are associated with access to health care. For example, the number of primary care physicians and whether primary care clinics are located in rural or urban areas can affect patients' opportunity to receive required health care resources. Furthermore, in the organization component, entry means the processes by which individuals navigate the health care system.[107] The process may include travel time to the hospital and the waiting time to see a doctor. The structure refers to things related to health care after patients enter the health care system.[107] For example, the structure may include the health care resources, health information or health care facility that patients receive after they have entered to a hospital.

The Characteristics of Population at Risk are the same as individual determinants in the Andersen-Newman model.[105, 107] There are respectively mutable and immutable variables in the components of predisposing and enabling factors. A variable that is useful for promoting access to health care needs to be mutable.[106] For example, a policy that changes the coverage of the public insurance can be considered mutable. Several variables such as age, gender and race/ethnicity are considered as variables with a low

degree of mutability. The need component in the characteristics of the population at risk is the component of illness level in the Andersen-Newman model.[105, 107] The need variables are the most frequent reasons that individuals seek for health care.[107] The degree of individual need for health care is determined by an individual's perception or an evaluation by a member of the health care system.[107]

The Utilization of Health Service is categorized into four parts: type, site, purpose and time interval.[107] The type means the kind of health service patients obtain. The site means where health service is performed. For example, the site of health service utilization can be in a hospital, a primary care clinic, or a pharmacy. The purpose refers to whether a visit is for preventative care or treatment.[107] The time interval refers to the contact, volume or continuity measures when patients enter the health care system.[107] For example, in a given period of time after patients are admitted to a hospital, patients are able to contact their physicians, to have a certain amount of visits and consistently receive medical treatment.[107]

The last component of the Aday-Andersen framework is the Consumer Satisfaction.[107] The Consumer Satisfaction expresses consumers' attitudes in terms of the health care they receive, the health care providers they encounter and the location where the service is provided. The Consumer Satisfaction refers to the quality and quantity of the actual health service that patients have experienced or received.[107] The Consumer Satisfaction is an important dimension of studying access to health care because the satisfaction that patients report can decide if patients eventually perceive satisfaction for the service that physicians provides.

In addition to addressing each component in the Aday-Andersen framework, the authors also proposed an interrelation among components.[107] The arrows in Figure 2.2 express the association. The Health Policy component is the beginning of the process. This component has a direct influence on the Characteristics of Health Delivery System and the Characteristics of Population at Risk. Both of them influence the Utilization of Health Services and the Consumer Satisfaction. Moreover, The Characteristics of Health Delivery System can influence the Characteristics of Population at Risk because the volume and distribution of health care resources can determine patients' ability to access health care. Finally, the Utilization of Health Services and the Consumer Satisfaction can interact with each other because not only health service use can decide patients' satisfaction but also the satisfaction can influence the subsequent use of services.[107]

In summary, the Aday-Andersen framework comprehensively addresses the components relevant to patients' access to health care. The framework conceptualizes variables associated with access to health care and it allows researchers to have a theoretical model when studying issues related to access to health care.

The change of the Behavioral Model of Health Services Utilization

The Behavioral Model of Health Service Use was first introduced in the 1960s. Andersen and Newman proposed the first framework to study health care utilization (Figure 2.1).[59, 105] In 1970s, the second phase of the model was developed by Lu Ann Aday and colleagues (Figure 2.2).[59, 107] The third phase of the model was developed during the 1980s and the1990s. The model incorporated external environment variables, such as physical, political, and economic components, as well as personal health practices such as diet, exercise and self care (Figure 2.3).[59, 106] In the 1990s, the model evolved into

a new stage. In addition to the major components, the model emphasized the dynamic nature of the health service utilization.[59, 106] It also incorporated feedback loops that showed the Outcomes component could influence the Population Characteristics component and the Health Behavior (Figure 2.4).[59, 106]

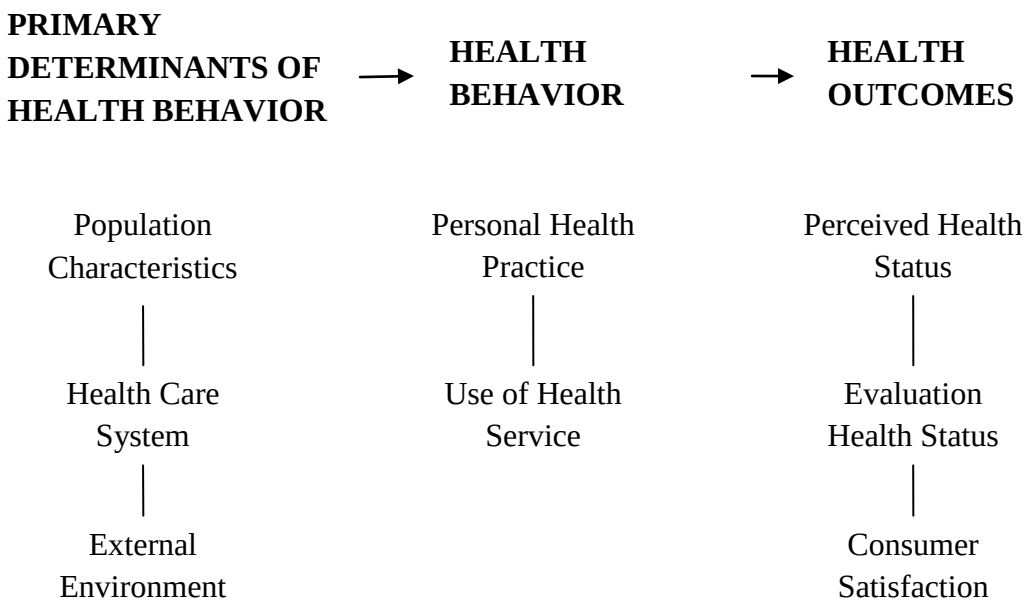


Figure 2.3 The Behavioral Model of Health Services Use: Phase 3 (1980s-1990s)

Figure 2.5 shows the most recent version of the Behavioral Model of Health Services Use. The model focuses on contextual and individual determinants.[59, 108] The Contextual Characteristics comprise health organization and provider relevant variables.[59, 108] Similar to the Individual Characteristics, variables in the Contextual Characteristics are categorized into predisposing, enabling and need factors. The model suggests that the Health Behaviors and the Outcomes can be respectively explained by

relevant predisposing, enabling, and need factors of both the Contextual and Individual Characteristics.

The use of the Behavioral Model of Health Services Use allows researchers to assess the association between multiple factors and the Health Behaviors, such as medication utilization. The model can also help researchers to examine the relationship between multiple factors in the Contextual or the Individual Characteristics and the Health Outcomes, such as medication expenditure. Finally, the model also provides a comprehensive perspective on evaluating the association among medication related health outcomes. Therefore, concepts in the model are adopted to study the association among variables in this study.

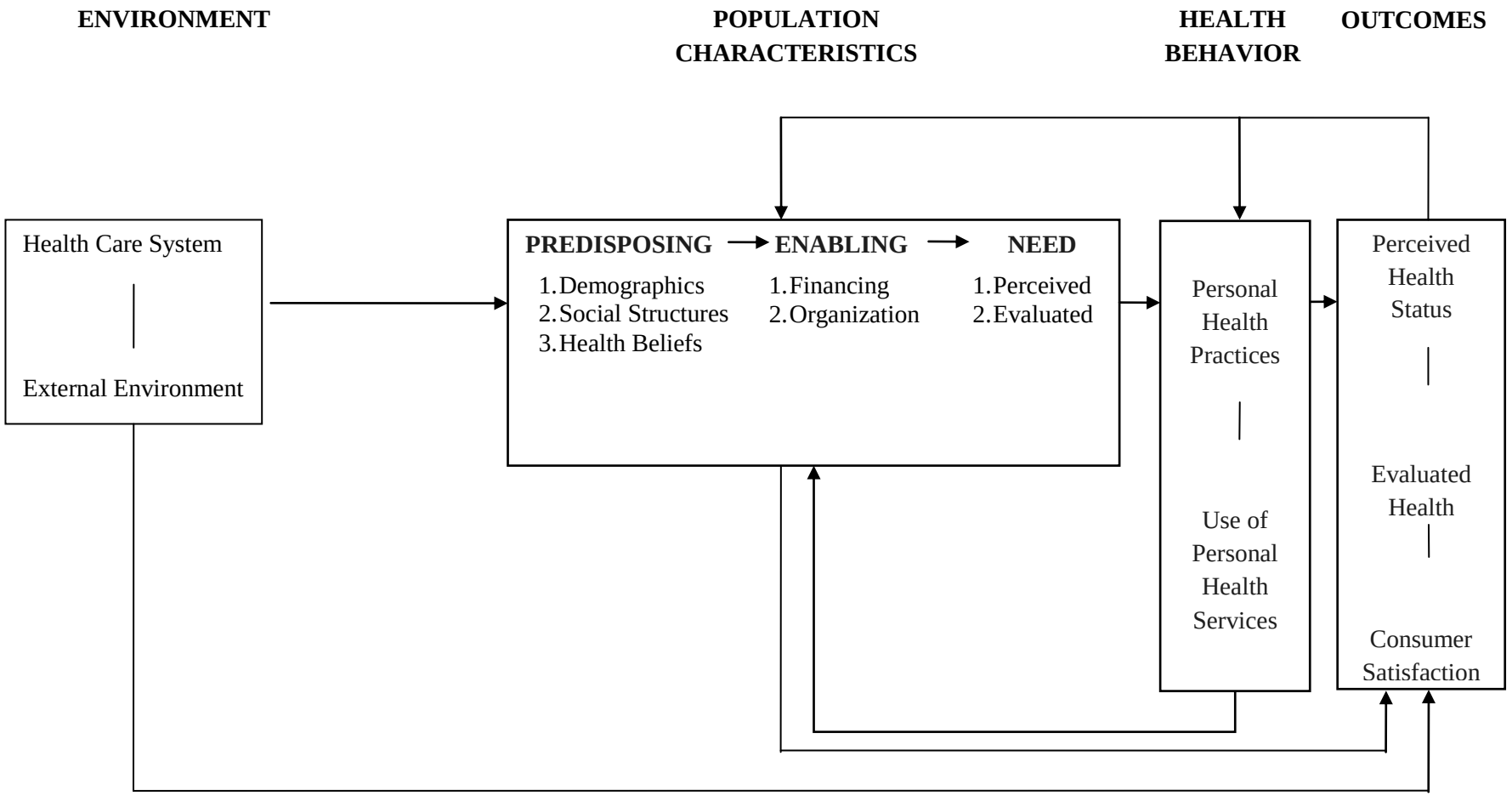


Figure 2.4 The Behavioral Model of Health Services Use: Phase 4 (1990s)

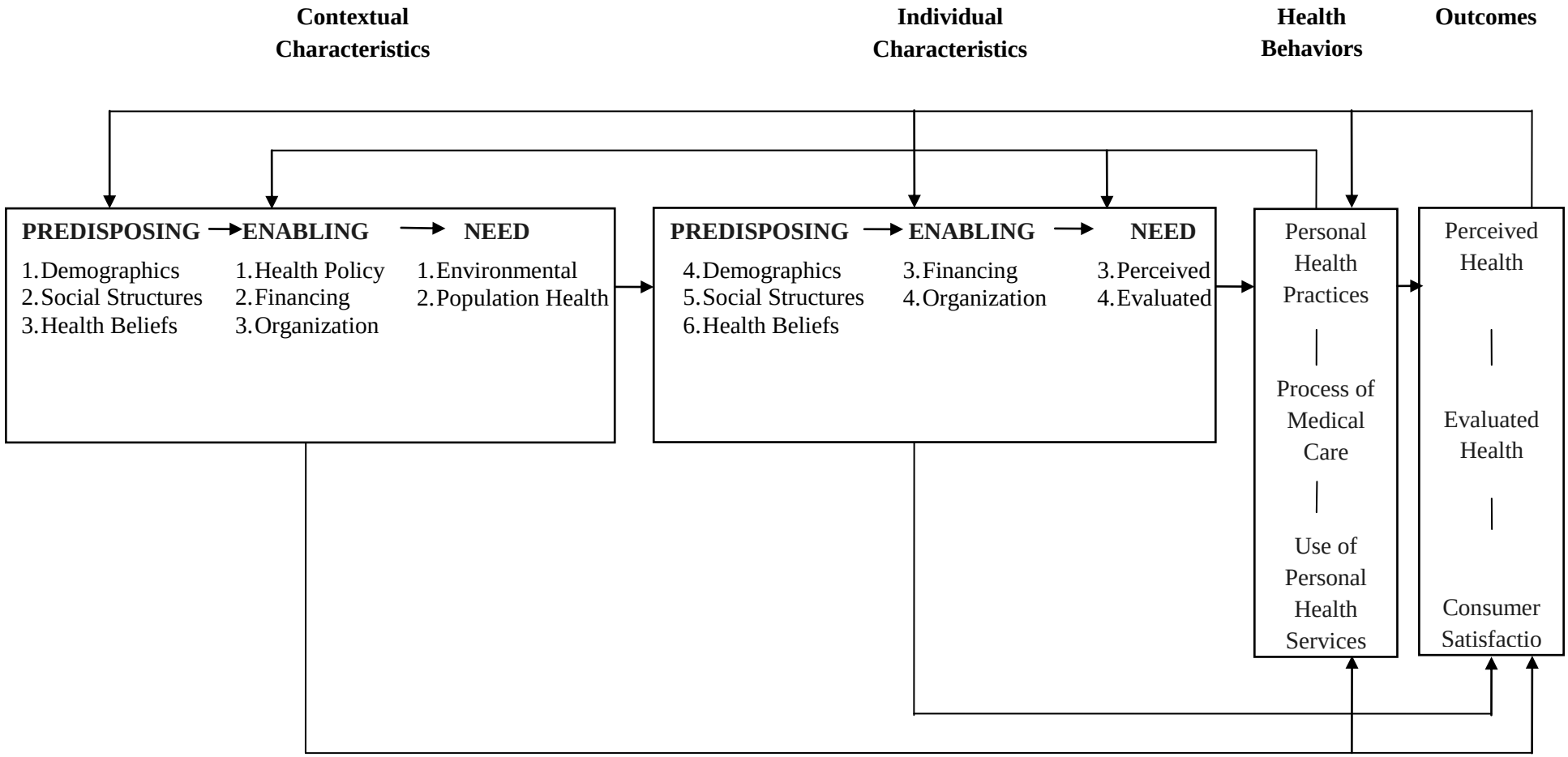


Figure 2.5 The Behavioral Model of Health Services Use: Phase 5 (2000s)

The Health Belief Model

The Health Belief Model was first introduced by Irwin M. Rosenstock in the 1950s.[109] The model was designed to investigative why people use health services.[109] The author believed that it is essential to understand the reasons why individuals behave as they do before starting to modify behavioral changes.[109]The model emphasizes individual behavioral changes which include changes of behaviors to prevent disease, detect illness and to make individuals healthy.[109] Variables incorporated in the Health Belief Model have been divided into two categories. The first category includes individual's psychological state in which he/she feels susceptible to a certain disease.[109] The second category includes beliefs that behavioral changes can result in benefits and reduce disease threats.[109]

Four major components comprise the Health Belief Model (Figure 2.6).[109] They are the Perceived Susceptibility, the Perceived Seriousness, the Perceived Benefits of Taking Action and the Barrier to Taking Action, and Cues to Action. The relations between components and behavioral changes are described in the following sections.

The Perceived Susceptibility refers to an individual's perception of the risk of having a disease.[109] Individuals may perceive the possibility of contracting a condition. For example, a personal may feel he/she is at a risk of having breast cancer if she has a family history of it.

The Perceived Seriousness expresses that a person perceives the seriousness of a condition which may lead to his/her death, morbidity, or impairments of mental or physical functions.[109] In addition, a person may perceive the seriousness of a disease can impair his/her work activity, family life or social relations.[109]

The Perceived Benefits of Taking Action and Barriers to Taking Action means the degree of the health consequences after an individual decides to make behavioral changes.[109] The balance between benefits and barriers can determine if a person is willing to make behavioral changes. The benefits of behavioral changes include a healthy life after taking an action. In contrast, perceived barriers can include inconvenient access, expensive care, painful treatment or unpleasant experience, which prevent individuals from making behavioral changes.[109]

The last component of the Health Belief Model is the Cues to Action. The cue is a trigger which activates an action of behavioral changes. The cues can be internal factors such as perception of bodily states, or external factors such as interpersonal interactions, the influence from media or influence from other people's experience.[109] Moreover, the intensity of a cue is important to trigger an action to make behavioral change,[109] especially when the perception of behavioral changes is low.

Studies have shown that each construct exists its own influence on behavioral changes. Janz and her colleges reviewed 46 articles relevant to the Health Belief Model (HBM) and found that perceived barriers are the most powerful predictors followed by perceived susceptibility, benefits and severity.[110]

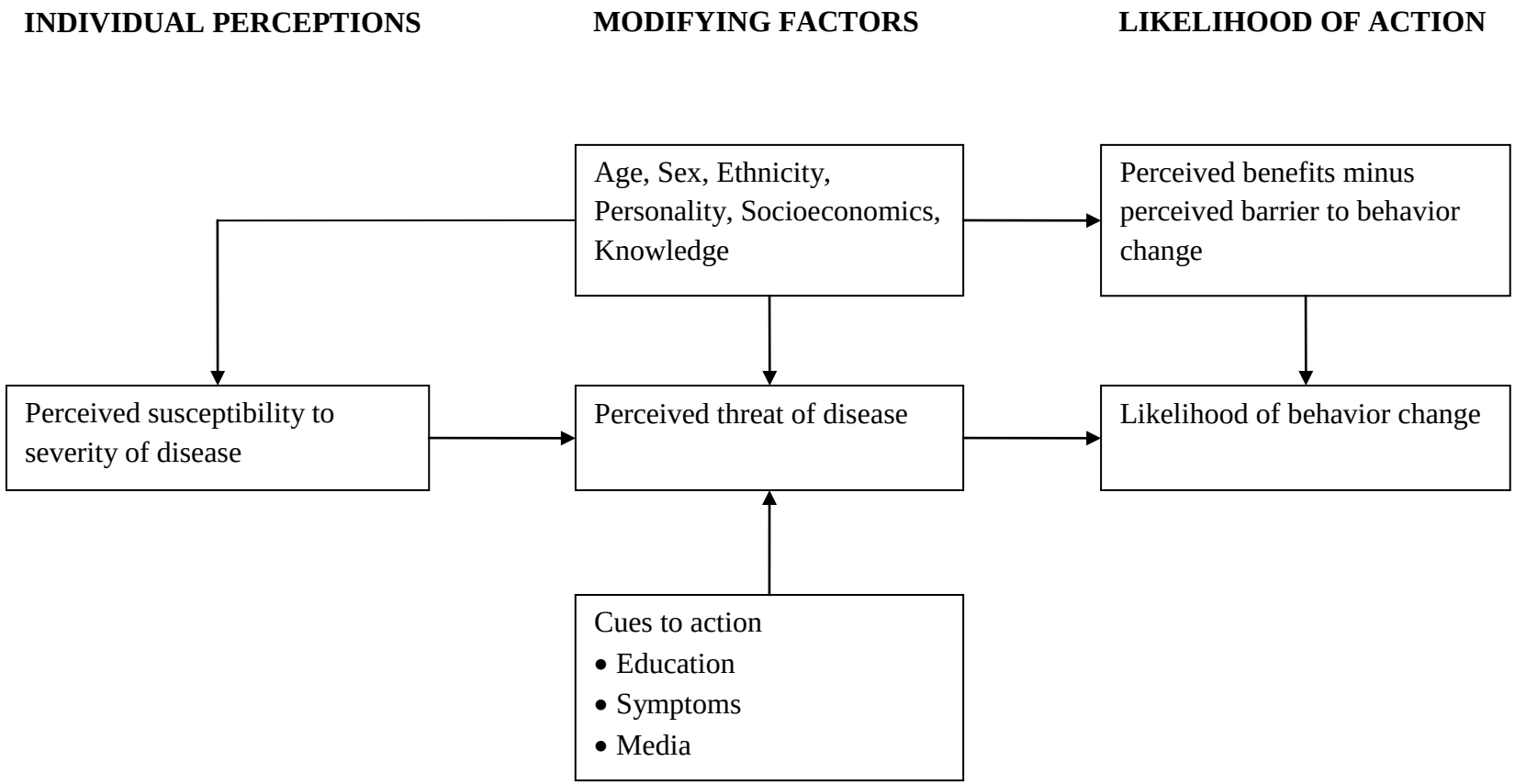


Figure 2.6 The Health Belief Model

The Health Belief Model is usually applied to explain behavioral changes. In 1975, Rosenstock used the Health Belief Model to further explain medication compliance behaviors.[111] In addition to the primary components in the Health Belief Model, the concepts of knowledge of the medical condition and the prescribed regimen were incorporated in the model.[111] Patients need to know what medical condition they have been diagnosed with, what prescription they should take, the rationale behind the condition and taking their prescriptions, and how to take their medicines. For example, patients need to know how to take the prescriptions and how long they should take the prescriptions even after symptoms are relieved. Improving patients' knowledge about taking medicines also lowers the barrier of compliance. It is difficult to improve patients' compliance if patients do not believe that their prescriptions are beneficial or they do not have enough knowledge about taking prescriptions.

Health care researchers further investigated adherence behavior regarding concepts of the Health Belief Model. Becker and colleagues (1975) conducted a review study and proposed a theoretical framework called the Becker-Maiman model (Figure 2.7), which is based on elements of the Health Belief Model, to further explain and predict compliance behavior.[112] The authors conducted a systematical review of the literature to identify social-psychological variables which were expected to be related to compliance behaviors.[112] Concepts of the Health Belief Model, such as perceived susceptibility, perceived severity, perceived benefits and costs, and motivation, were incorporated into the theoretical framework that they proposed. The impact of interactions between components was also incorporated into the new framework. For

example, a study has shown that the combined belief of perceived susceptibility and perceived severity was associated with compliance with penicillin prophylax.[113]

Moreover, the authors added on several modifying factors in their model in order to not only predict but also explain compliance behaviors. The first factor is the patient-practitioner repationship.[112] Studies have shown that mothers are more likely to be compliant to a prescribed regimen for their child if they perceive a cognitive and friendly encounter in the initial contact.[114-115] Second, the physician continuity is the second modifying factor. Visiting the same doctor can improve medication adherence.[116] Third, social influences from family or friends can also determine patients' compliance behavior.[117-118] Finally, demographic and personality variables are also related to compliance behavior.[112]

In summary, the Becker-Maiman model conceptualizes variables related to patients' compliance behavior. The model is more comprehensive than the Health Belief Model, which addresses individuals' health beliefs and whether they intend to undergo behavior change. The Becker-Maiman model provides a framework to further predict compliance with health and medical care recommendations.[116]

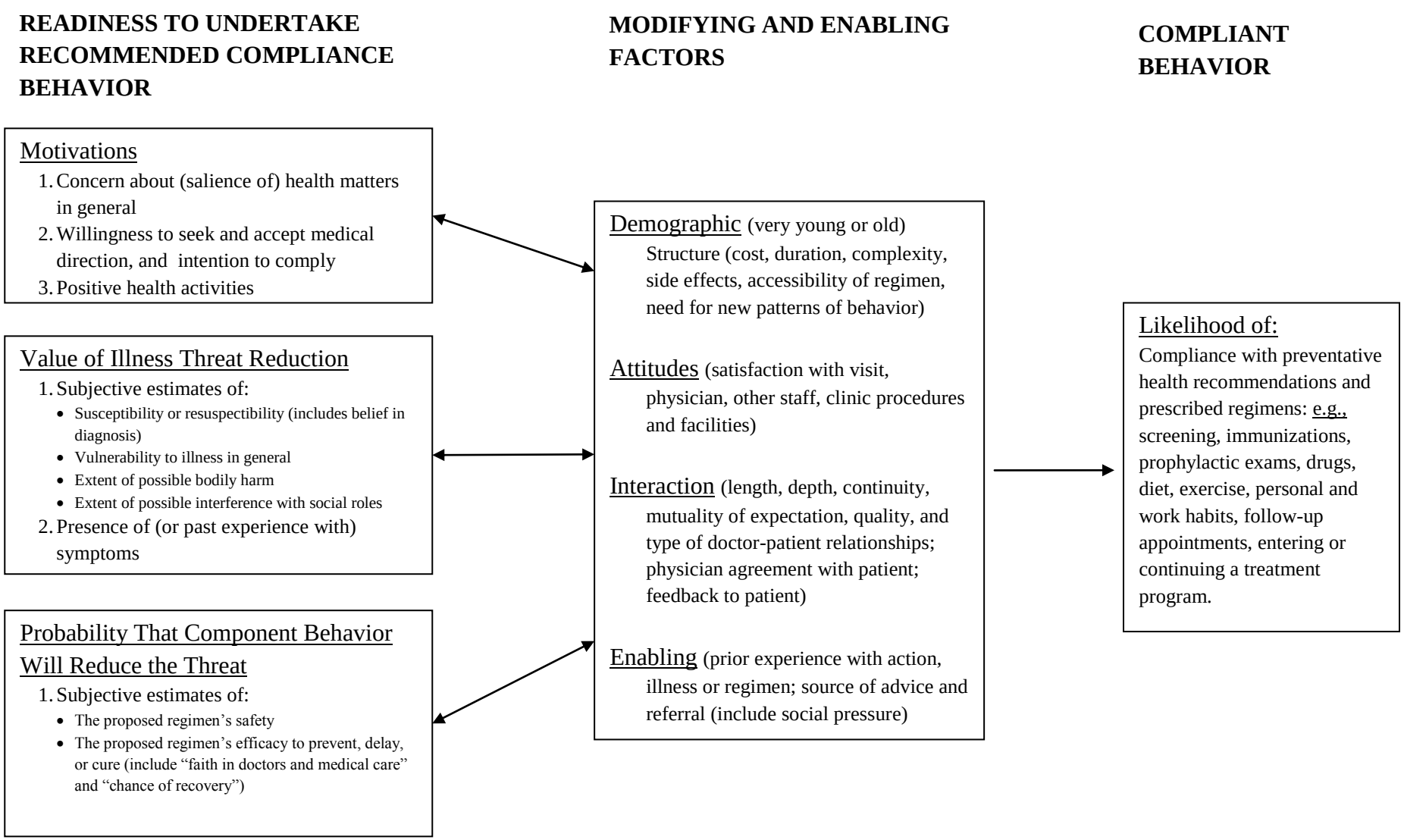


Figure 2.7 Becker-Maiman model for predicting and explaining compliance behavior

Proposition of the theoretical framework

Concepts from the Becker-Maiman model and the Aday-Andersen model are used to form the proposed theoretical framework in this study. The proposed study model of the current study is shown in Figure 2.8. Primarily, the framework is based on the Aday-Andersen model. The dependent variables (hospitalization, ER visits and prescription expenditure) of the current study belong to the Outcomes component of the Aday-Andersen model. In the Aday-Andersen model, health outcomes are assumed to be associated with predisposing, enabling, and need factors. These factors are incorporated in the current theoretical framework and used to identify the variables (covariates) that are associated with medication related outcomes in patients with MDD. Variables of the Contextual Characteristics component in the Aday-Andersen model are excluded because the current study only focuses on investigating the relationship between individual characteristics and health-related outcomes.

Predisposing factors include patient characteristics, such as age, gender, and race/ethnicity. The predisposing factors are less mutable. Enabling factors in this study include number of prescriptions, cost of prescriptions, health care utilization prior to being diagnosed with MDD, number of physician visits, and type of physicians. The need factors include comorbidity (Charlson Comorbidity Index) and the severity of disease.

The concept of medication adherence in the Becker-Maiman model is employed and the concept serves as one of the dependent variables in the current study. In addition, medication adherence also belongs to the Health Behavior component of the Aday-Andersen model. In the current study, medication adherence is assumed to be influenced by patients' predisposing, enabling and need factors. Medication adherence also affects

other health outcomes such as hospitalization, ER visits, and prescription expenditures among patients with MDD.

The uniqueness of the current theoretical framework is that the framework incorporates a new concept of the combined effect between race and comorbidity. The new concept is the combined effect of race and comorbidity. The combined effect recognizes the interaction term of race and comorbidity. The interaction term explicitly considers the level of influence on the dependent variables in the current study. Using the interaction term allows researchers to differentiate several levels of influence between race and comorbidity on medication related outcomes.[119] The level of influence is categorized into four groups: Caucasian MDD patients with a high degree of comorbidity, Caucasian MDD patients with a low degree of comorbidity (or without comorbidity), African-American MDD patients with a high degree of comorbidity, and African-American MDD patients with a low degree of comorbidity (or without comorbidity). The differences of medication related outcomes are examined by the combined effect after adjusting for predisposing, enabling, and need factors in MDD patients.

The concepts of perceived susceptibility, perceived severity, perceived benefits and perceived barriers in the Becker-Maiman model were assumed to influence medication adherence and health care utilization. Due to the nature of the dataset, these variables were not measured in the current study.

The relationships of each concept in the proposed theoretical framework are depicted in Figure 2.8. The arrows between each box depict the directions and associations among variables. Patients' predisposing, enabling, and need characteristics have a direct influence on health behaviors (medication adherence and medication

persistence) and health outcomes. The combined effect of race and comorbidity is an independent concept which derives from but does not belong to patients' predisposing, enabling, or need factors. The combined effect also has a direct impact on health behaviors and health outcomes among patients with MDD.

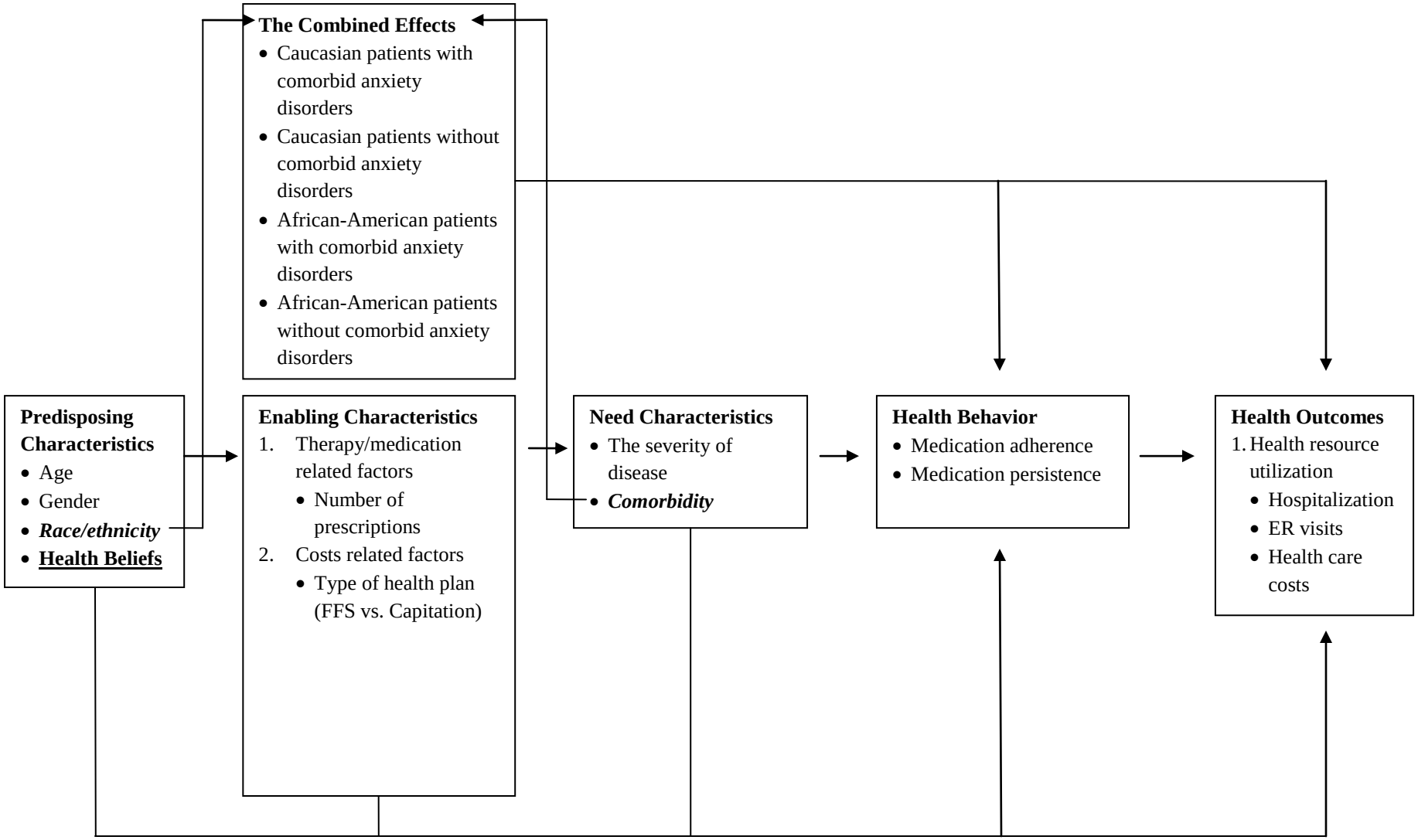


Figure 2.8 The proposed theoretical framework for the current study

CHAPTER 3

METHODOLOGY

This chapter provides detailed methodology which is required to conduct and implement the current study. The chapter begins by describing the data source. Then, detailed information of the study design, study perspective, database elements, and analytical framework are provided. The final part of the chapter includes a description of study variables, statistical analyses, hypothesis testing, and regression diagnoses.

Database and Management

In this section, the detailed information about the dataset and management of the dataset are provided.

Data source

The MarketScan® Multi-State Medicaid Database[120] serve as data sources for this study. The MarketScan® Multi-State Medicaid Database licensed from Thomson Reuters® is a pooled Medicaid asset set from eight geographically dispersed states.[120] Although the states are de-identified and dispersed, at least one state is selected from each of the six regions from the U.S. Therefore, the data still provide a nationally representative sample of Medicaid population in the U.S.[120]

The MarketScan® Multi-State Medicaid Database contains a variety of disease conditions that patients have. The disease conditions include diabetes, hypertension, hyperlipidemia, breast cancer, and major depression. The data also include Medicaid managed care plans, patient enrollment information, long-term care, claims of inpatient and outpatient services, and prescription during claims. Key demographic variables include gender, age and race. Additional variables include Medicaid and Medicare eligibility categories.

The time period of the MarketScan® Multi-State Medicaid Database is from January 1st, 2003 to December 31, 2007. The study duration is from January 1st, 2003 to December 31st, 2007.

Characteristics of the MarketScan® Multi-State Medicaid Database

The major strength of the MarketScan® Multi-State Medicaid Database is that it uses a unique enrollee identifier (ENROLID) to track individual patients and families longitudinally.[120] The personal level identifiers are identical across all years, all medical, surgical, and outpatient pharmaceutical claims.[120] To ensure confidentiality, the personal identifier cannot be linked to the recipient ID, social security number, or any other external identifier.[120]

Clinical variables in the MarketScan® Multi-State Medicaid Database are classified by diagnosis and procedure. The International Classification of Disease, 9th Division, Clinical Modifications (ICD-9-CM) are used as the Diagnosis Codes in MarketScan® Database.[120] The ICD-9-CM diagnosis codes are three to five digits long. For the Inpatient Service record, up to two diagnosis codes (DX1, DX2) are recorded.[120] The principal diagnosis on the Inpatient Admissions Table is generally identified as the

discharge diagnosis on a hospital claim.[120] The corresponding Inpatient Admission record includes up to 14 secondary diagnosis codes (DX2 through DX15) from individual Inpatient Service records.[120] Each Outpatient Service record has up to two diagnosis codes (DX1 and DX2).[120] Each Facility Header record has up to nine diagnosis codes (DX1 through DX9).[120]

Three major procedure code systems, the Current Procedural Terminology, the 4th Edition (CPT-4) procedure codes, the ICD-9-CM procedure codes, and the HCFA Common Procedural Coding System (HCPCS) procedure codes are used in the MarketScan® Multi-State Medicaid Database. The first two are more commonly used in the dataset. CPT-4 procedure codes exist in physician claims and many outpatient facility claims.[120] CPT-4 procedure codes have five-digit numbers. The ICD-9-CM are three to four digits and used mainly in hospital claims. One procedure code (PROC1) is stored on each Inpatient Service record,[120] which consists of one Inpatient Admission record. Each procedure code is identified and assigned as the principal procedure (PPROC).[120] Each individual Inpatient Service record has up to 14 secondary procedure codes (PROC2 through PROC15).[120] One procedure code (PROC1) is included on each Outpatient Service record.[120] Each Facility Header record has up to six procedure codes.[120] Thomson Reuters® has edited procedure and diagnosis codes if necessary from payers or administrators to ensure the quality of the data.[120]

Construction of the MarketScan® Multi-State Medicaid Database

The MarketScan® Multi-State Medicaid Database are constructed from paid medical and prescription drug claims.[120] Raw data are collected from appropriate payers. The raw data include service-level adjudicated paid claims, and inpatient and outpatient

services of capitation encounter claims.[120] The MarketScan® Multi-State Medicaid Database also include financial, clinical and demographic variables as well as variables specific to employers and health plans.[120] The Outpatient Pharmaceutical Claims Table includes clinical details, which include Therapeutic Class, Therapeutic Group, Manufacturer's Average, Wholesale Price, and Generic Product Identifier.[120]

After obtaining the raw data, Thomson Reuters® implements the case construction process by assembling the inpatient paid services into one record per inpatient admission.[120] To ensure high quality data, several reasonableness checks, such as diagnosis against age, diagnosis against gender, and charge against payment, are implemented.[120] The purpose of these data checking procedures is to ensure the validity of the data and eliminate improper coding during the data creation process. The detailed MarketScan® data creation process is shown in Figure 3.1.

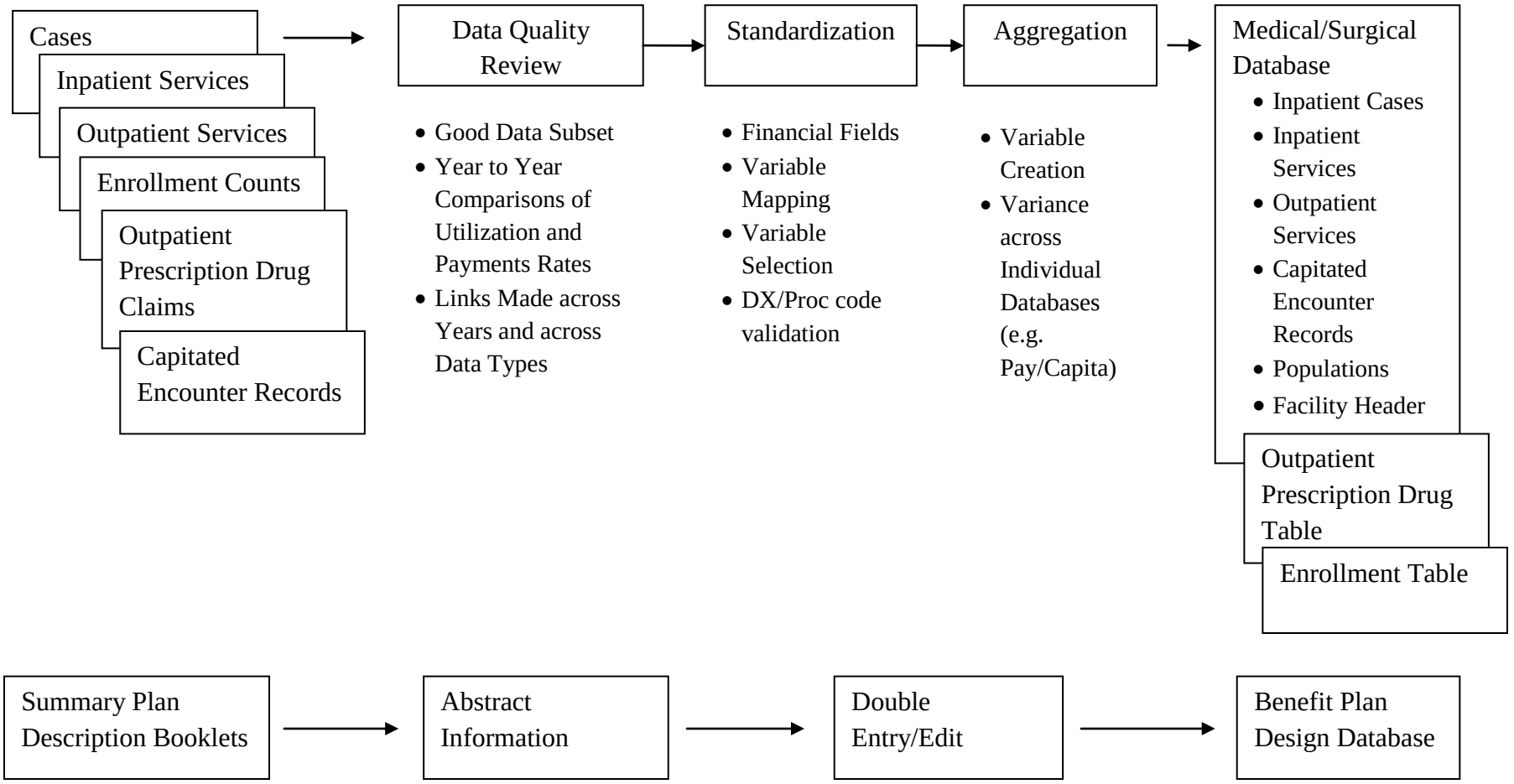


Figure 3.1 MarketScan® Data Flow

Study Design

This study was a retrospective cohort study. The cohorts were identified from MarketScan® Multi-State Medicaid Database.

Study population

The study population is comprised of patients aged between 18 to 64 years who were diagnosed with Major Depressive Disorders (MDD) and were prescribed at least one new antidepressant during the index period. The study duration was from January 1st, 2003 to December 31st, 2007. The study protocol was approved by the Institutional Review Board (IRB) at the University of Michigan.

The following sections describe the specific terms, inclusion criteria, and exclusion criteria used to identify the study population. The patient selection criteria flow is shown in Figure 9.

Definitions of the terms used

The definitions of several terminologies used to describe the time periods of this study are defined as follows:

1. The study duration:

   January 1st, 2003 to December 31st, 2007

2. Index period (Identification Period):

   January 1st, 2004 to December 31st, 2006

3. Study period (Follow-up period):

   One year follow-up period after the index diagnosis date

4. Pre-study period:

   One year before the index diagnosis date

5. Drug naïve patients:

   Patients with no claims of any antidepressant prescription during the pre-index period

Inclusion criteria

Patients who met the following inclusion criteria were selected in the final study cohort.

1. Age

   Patients aged between 18 to 64 years during the index period were included in this study. The study population was all adults in this study. Patients aged 65 years and above were excluded to prevent dual eligible enrollees with Medicaid and Medicare. Patients with dual eligible enrollees could have been reimbursed from either Medicaid or Medicare. It was difficult to obtain complete health care utilization data from dual eligible enrollees. Therefore, the age of study subjects was limited to patients aged between 18 and 64 years.

2. Study periods and the continuous eligibility

   The index period of this study is between January 1st, 2004 and December 31st, 2006. Subjects were included in the study population must meet two criteria. First, they must be diagnosed with MDD during the index period, and second, they must be prescribed at least one antidepressant during the one year follow up period (the study period) after they have been diagnosed with MDD. Each patient was assigned an index diagnosis date and an index prescription date. A 12-month pre-study period,

which was a one-year period before the index diagnosis date, was used for verifying new antidepressant users (drug naïve patients or new cases). Medication use behaviors such as medication adherence and medication persistence could be dramatically different between current users and new users. Medication use behaviors could be contaminated if patients have taken antidepressants before. Subjects were included only if they did not have any antidepressant claims during the pre-index period of this study.

The same 12-month pre-study period was also used to determine maintained continuous Medicaid eligibility. Subjects were included only if they had at least 12 months continuous eligibility before the index diagnosis date. Moreover, the continuous Medicaid eligibility of the study period, which was a 12-month follow up period after the index diagnosis date, was necessary to ensure patients have the continuous eligibility during the study period. Overall, patients should have a 24-month (12 months before and 12 months after the index diagnosis date) continuous eligibility to be included in the study population.

3. Diagnosis

The study population was identified using ICD-9-CM for MDD patients. The ICD-9-CM codes used for this study included 296.2 (Major depressive disorder, single episode), and 296.3 (Major depressive disorder, recurrent episode). Patients diagnosed with the above ICD-9-CM codes during the index period (New diagnosis) were included in this study.

4. Prescription used

During the study period (one year follow up after the index diagnosis date), patients who were prescribed an antidepressant were included in the study. An index prescription date was assigned for each patient. Evidence of antidepressant use was identified using Therapeutic Class in the MarketScan® Multi-State Medicaid Database. Therapeutic Class refers to a 3-digit code that indicates the therapeutic/pharmacologic category of the drug product. For example, the Therapeutic Class value equal to 69 refers to patients who had an administrative claim of taking antidepressants. The Therapeutic Class was used to identify patients' antidepressant use status.

Exclusion criteria

1. Patients aged <18 years or >64 years.
2. Patients diagnosed Bipolar disorders (ICD-9-CM: 296.4, 296.5, 296.6, 296.7, 2968, and 296.9) were excluded.
3. Patients already taking an antidepressant during the pre-study period were excluded.

Figure 3.2 depicts the selection criteria for identifying the current study cohort.

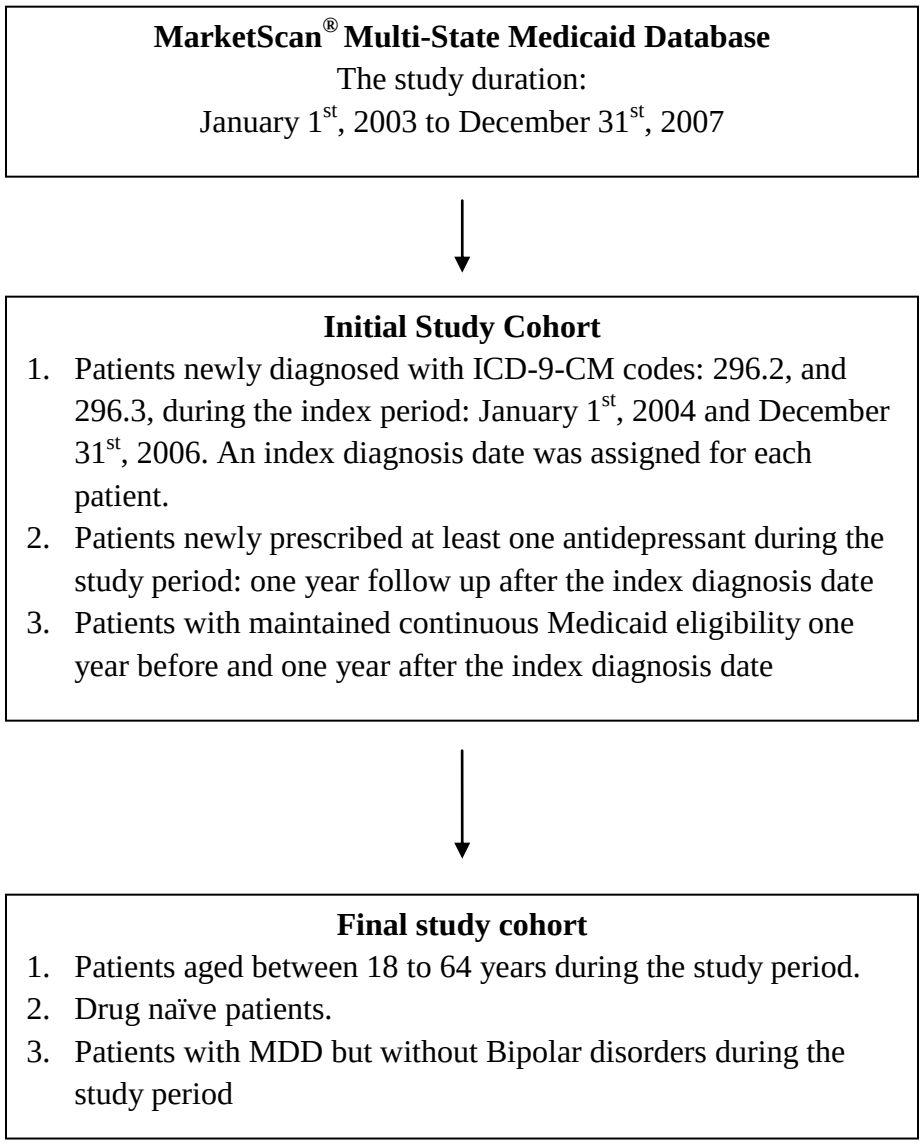


Figure 3.2 Patient selection criteria flow of the current study

Study Perspective

This study is conducted from the payer's perspective. This study is to investigative and evaluate the impact of the combined effect of race and comorbidity on medication use related outcomes in MDD patients. Understanding the association between the combined effect of race and comorbidity and medication use can further improve patients' medication adherence. It also helps to develop intervention programs or patient education programs which could potentially reduce medication non-adherence and eventually lower overall health service utilization in MDD patients.

The Medicaid program offers national health insurance for low-income families and individuals. These vulnerable groups would benefit from the study findings which are essential for making informed decisions about coverage of Medicaid enrollees. The outcomes measured in this study are also essential for policymakers and Medicaid reimbursement, because improving adherence in MDD patients means lower health care cost and lower reimbursement from the Medicaid program. Finally, the findings of the study can help to allocate limited health care resources.

Database Elements

The dataset in this study was retrieved from the MarketScan® Multi-State Medicaid Database. Variables were further categorized into five groups: eligibility/enrollment, inpatient admissions, inpatient services, outpatient claims, and prescription drugs. Social demographic variables such as age, gender and race/ethnicity were also retrieved. Variables associated with health service utilization such as hospitalizations and emergency room visits were also included in the study. Selected variables are listed in Table 3.1.

Table 3.1 Selected variables retrieved from the MarketScan® Multi-State Medicaid Database

1. Eligibility/enrollment file
Enrollee ID (ENROLID)
BOE category (BOE)
Date enrollment start (DTSTART)
Day enrollment end (DTEND)
Patient birth year (DOBYR)
Gender of patient (SEX)
Race (STDRACE)
Medicaid case number (MCASENUM)
Medicare eligibility (MEDICARE)
Member days (MEMDAYS)
Medicaid Capitation flag (CAP)
2. Inpatient admission
Enrollee ID (ENROLID)
Date of admission (ADMDATE)
Date of discharge (DISDATE)
Diagnosis related group (DRG)
Major diagnostic category (MDC)
Diagnosis principal (PDX)
Diagnosis 1 (DX 1)
Diagnosis 2 (DX 2)
Discharge status (DSTATUS)
Date claim paid (PDDATE)
Procedure principal (PPROC)
Procedure 1 (PROC 1)
Length of stay (DAYS)
COB and other savings total case (TOTCOB)
Coinsurance total case (TOTCOINS)
Copayment total case (TOTCOPAYS)
Deductible total case (TOTDED)
Payments net case (TOTNET)
Payments total case (TOTPAY)
3. Inpatient services
Enrolled ID (ENROLID)
Case and services link (CASEID)
COB and other savings (COB)
Coinsurance (COINS)
Copayment (COPAY)
Diagnosis primary (PDX)

Quantity of services (QTY)
Revenue code (REVCODE)
Sequence number (SEQNUM)
Place of service (STDPLAC)
Service type (STDSVC)
Type of provider (STDPROV)
Date service incurred (SVCDATE)
Date of service ending (TSVCDAT)

4. Outpatient claims
Enrollee ID (ENROLID)
Date service incurred (SVCDATE)
Date of service ending (TSVCDAT)
Date year incurred (YEAR)
Diagnosis 1 (DX1)
Diagnosis 2 (DX2)
Procedure 1 (PROC 1)
Procedure group (PROCGRP)
Procedure code type (PROCTYPE)
Place of service (STDPLAC)
Provider type (STDPROV)
Quantity of services (QTY)
Major diagnostic category (MDC)
Payment (PAY)
Payment net (NETPAY)
Date claim paid (PDDATE)
COB and other savings (COB)
Coinsurance (COINS)
Copayment (COPAY)
Coverage indicator drug (DRUGCOVG)

5. Prescription drug
Enrollee ID (ENROLID)
Date service incurred (SVCDATE)
Coverage indicator drug (DRUGCOVG)
Date claim paid (PDDATE)
National Drug Code (NDCNUM)
Day supplied (DAYSUPP)
Quantity of services (QTY)
Average wholesale price (AWP)
Ingredient cost (INGCOST)
COB and other savings (COB)
Coinsurance (COINS)

Copayment (COPAY)
Payment (PAY)
Generic indicator (GENIND)
Generic product ID (GENERID)
Dispensing fee (DISPFEE)
Metric quantity (METQTY)
Refill Number (REFILL)
Therapeutic class (THERCLS)
Therapeutic group (THERGRP)

Analytical Framework

The steps involved in identifying the study cohort are described in Figure 3.3.

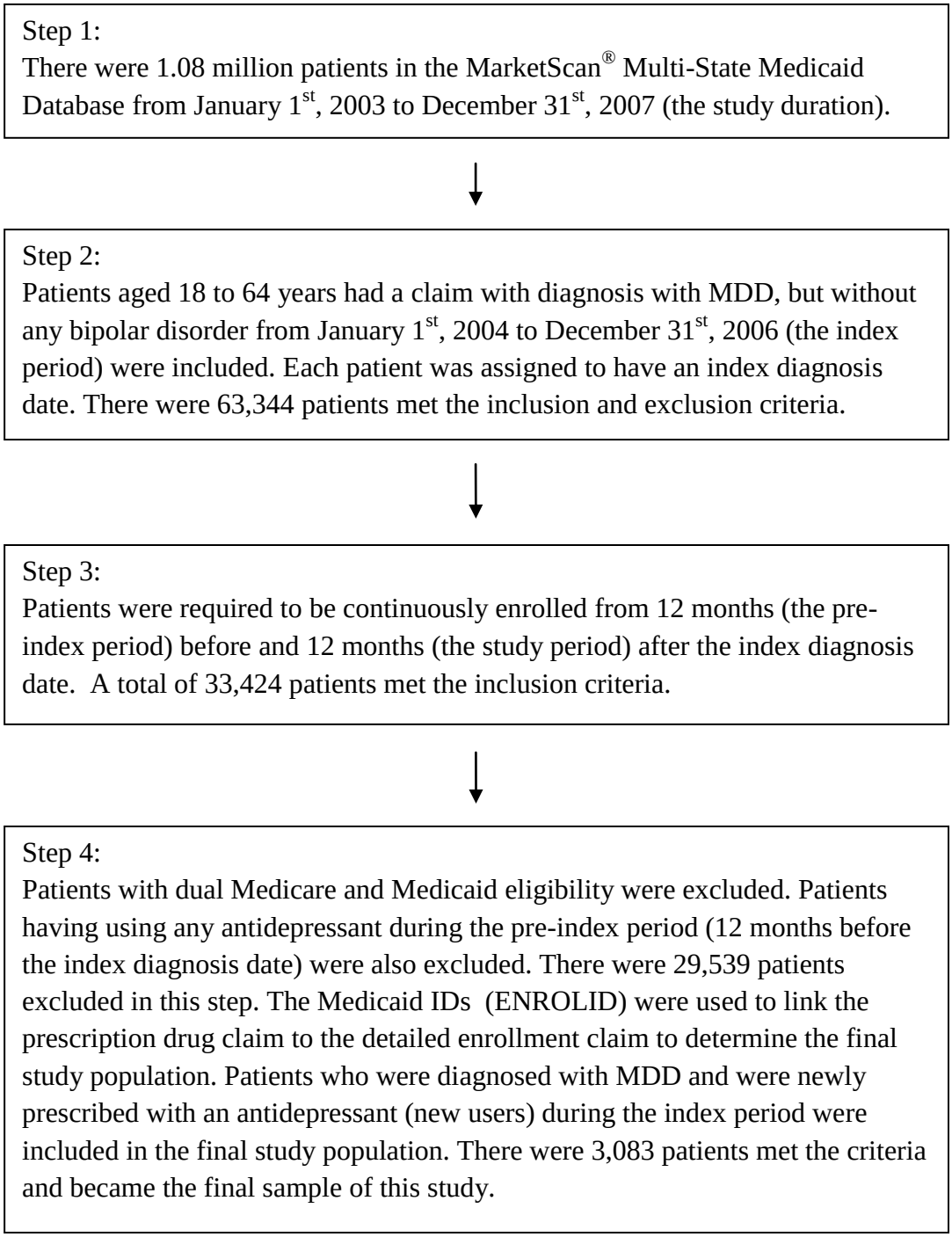


Figure 3.3 Steps involved in identifying the study cohort

Study Variables and Measurement

The operational definitions of the study variables and their measurements were described in this section. The dependent variables in this study include medication adherence, medication persistence, hospitalizations, and emergency room (ER) visits. The key tested hypothesized independent variables were race, comorbidity, and the interaction effect of race and comorbidity. Other independent variables (covariates) included age, gender, access to health care, and the disease severity. A detailed operational definition of each variable was described in the following sections.

Dependent variables

Medication adherence

Medication adherence was the first dependent variable in this study. Medication adherence refers to the level of conformity to the treatment recommendation regimens by the provider regarding the timing, dosage, and frequency.[121] It can be further defined as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen."[121] With respect to the threat/severity of the disease and their behavioral change, patients develop a habit of taking medicines in accordance with physicians' orders.[121]

Medication Possession Ratio (MPR) was used to measure medication adherence in this study. MPR is widely used to measure refill adherence. MPR is an indirect measurement of patients' medication adherence, especially when using administrative claim data. Using administrative claims data to measure medication adherence provides several advantages. For example, the adherence rate can be measured in an inexpensive and efficient way.[122] Patients do not realize they have been measured which can prevent

the Hawthorne effect.[122] A review study conducted by Karve et al. (2008) reviewed eight different measurements for assessing medication adherence in administrative claims data.[123] The authors concluded that MPR has the highest predictive validity for measuring medication adherence.

The data of the current study are Medicaid administrative claims data. Therefore, MPR was used to measure medication adherence. MPR was defined as the number of days' supply in the index period divided by the number of days in the study period.[123] In order to take the last day supply into consideration, MPR was further adjusted as MPR, modified (MPRm), which is defined as the total days' supply of medications divided by the period between the last claim date and the first claim date plus the last days supply of medications.[124-125] The basic assumption of measuring adherence using MPR is "a prescription filled is a prescription taken."[122] In this study, the MPRm is used and defined as follows:

$$\text{MPRm} = \frac{Number\ of\ days'\ supply\ obtained}{(Date\ of\ last\ claim - Date\ of\ first\ claim + Days'\ supply\ of\ the\ last\ claim)} \times 100$$

In spite of the advantages, using MPR to measure adherence could have several limitations. For example, MPR may not be able to cover prescription records if patients refill prescriptions at multiple pharmacies.[126] Moreover, MPR cannot accurately indicate the actual medication taking behaviors if patients do not take the medicine that they refill.

In addition, medication adherence was further categorized into a dichotomous variable in this study. The cut-off point was set as 0.8, which was based on an empirical study conducted by Karve et al. (2009).[127] By using an administrative claims dataset, the

authors concluded that selecting a 0.8 cut-off point was appropriate for predicting hospitalization resulting from non-adherence in several chronic diseases.[127]

Medication persistence

Medication persistence is a distinct concept from medication adherence. Medication persistence refers to the patients' accordance with continuing the treatment for the period of taking prescription.[121] It was defined as "the duration of time from initiation to discontinuation of therapy."[121] The administrative claims data provides a perspective to measure medication persistence because of the detailed prescription refill record.[126]

Medication persistence in this study is operationally defined as the duration for which antidepressants were taken. It is the number of days determined by the initiation of taking the medicine to the end of stopping taking the medicine. Measuring the gap between refills is important to understand medication persistence. A late refill may mean poor medication adherence but it does not necessarily mean non-persistence. Different medications can have different clinical declines or adverse events for different patients. Therefore, identifying a gap threshold for MDD patients who use antidepressants is very important for studying medication persistence. The gap threshold of medication persistence in this study was set as 15 days based on the literature search.[128-130] Patients were defined as non-persistent if they had a refill gap greater than 15 days.

Office visits

The number of office visits was a count variable identified from the MarketScan® Multi-State Medicaid Database. In the data, each procedure was assigned to have a procedure code. Patients who had the procedure code equal to 101 (office visits for new

patients) or 104 (office visit for existing patients) were determined as having an office visit during the study period.

Hospitalization

Hospitalization was a dichotomous dependent variable in this study. Patients were identified as having a hospital admission if they had an event of any hospital admission in the claims. Variables such as Date of Admission and Date of Discharge in the MarketScan® Multi-State Medicaid Database were used to identify patients' hospitalization.

Emergency Room (ER) visit

Patients were identified as having an ER visit if they had any of the following events reported in the MarketScan® Multi-State Medicaid Database. Based on the procedure codes, the MarketScan® Multi-State Medicaid Database provides an indicator variable for the type of related outpatient procedures. Patients who had the procedure group (PROCGRP) value equal to 110 (emergency room visit for new patients) or 114 (emergency room visits) were determined as having an ER visit during the study period. The ER visit variable was coded as dichotomous (yes/no).

Health care costs

Patients' health care costs were directly identified from the MarketScan® Multi-State Medicaid Database. The overall health care costs included patients' inpatient, outpatient, and prescription expenditures during the study period. Mental health-related health care costs were the expenditures that were relevant to the mental illnesses identified by the above ICD-9-CM codes.

In addition to overall office visits, hospitalization, and ER visits, the study also examined mental health-related health resource utilization. All of the above dependent variables were assessed over a 12-month period after the index diagnosis date. The term "mental health-related" was defined as patients having at least one primary or secondary diagnosis of a mental illnesses. These illnesses included schizophrenia (295.xx), depression (296.2x, 296.3x, 296.9x, 300.4x, 309.0x, or 311.xx), anxiety (300.0x, 300.2x, 300.3x, 306.9x, 308.xx, 309.2x, 309.4x, or 309.9x), other psychoses (297.xx, 298.xx, 299.xx, 300.1x, 302.8x, or 307.9x), and dementia (290.xx, 291.2x, 310.9x, or 331.0).[131] Any patient utilization related to the above ICD-9-CM codes was defined as mental health-related health care utilization. For example, a mental health-related office visit, coded as dichotomous (yes/no), was determined by whether patients had an office visit related to any of the above mental illnesses during the study period. Similarly, mental-health related hospitalization and mental health-related ER visits were also categorized as a dichotomous variable.

Key tested independent variables

The key tested independent variables of this study were race, comorbid anxiety disorders and the combined effects of race and comorbid anxiety disorders. The definitions and descriptions of each key tested variable were described in the following section.

Race

Race was self-reported information obtained from patients when they were first enrolled in the Medicaid program. The variable was directly derived from the

MarketScan® Multi-State Medicaid Database. It was categorized as either Caucasian or African American.

Comorbid anxiety disorders

Comorbid anxiety disorders were identified based on medical claims of any anxiety disorder diagnosis during the 12-month study period after the index diagnosis date. MDD patients with a diagnosis of anxiety disorders were classified as having comorbid anxiety disorders. MDD patients concurrently having one of the anxiety disorders listed in Table 3.2 were identified as having comorbid anxiety disorders. [132] The variable of having a comorbid psychiatric disorder was coded as dichotomous (yes/no).

Diagnosis	**ICD-9-CM**
Panic disorder without agoraphobia	300.01
Panic disorder with agoraphobia	300.02
Agoraphobia without history of panic disorder	300.22
Social phobia (social anxiety disorder)	300.23
Obsessive-compulsive disorder	300.30
Post-traumatic stress disorder	309.81
Acute stress disorder	308.30
Generalized anxiety disorder	300.02
Anxiety disorder due to general medical condition	293.89
Anxiety disorder, not otherwise specified	300.00

Table 3.2 Comorbid anxiety disorders and the ICD-9-CM codes

The combined effect

The combined effect of race and comorbidity was the interaction term between race and comorbidity.

Other independent variables (covariates)

The selection of covariates was based on the proposed theoretical framework in Figure 2.8. Variables were categorized into three groups: predisposing factors, enabling factors, and need factors. Predisposing factors included sociodemographic variables, such as age and gender. Enabling factors included variables related to access to health care and economic variables. Need factors were variables related to the severity of the disease. Each group of covariates is described in the following sections.

Predisposing factors

Sociodemographic variables

Sociodemographic variables in this study included patients' age and gender. Patients' age was calculated as the year of index date minus the year of birth. All sociodemographic variables were identified from the MarketScan® Multi-State Medicaid Database.

Enabling factors

Economic variables

The economic variable in the current study was determined by the type of health plan (FFS vs. Capitation). The type of health plan was directly identified from the MarketScan® Multi-State Medicaid Database.

Need factors

Need factors in the Andersen model were referred as the severity of the disease. Need factors in this study included comorbid painful symptoms, variables of the pre-index period and comorbidity measured by the Elixhauser comorbidity index.

Comorbid painful symptoms

Research has shown that painful symptoms frequently co-exist among MDD patients. One of the study objectives was to examine the influence of comorbid physical disorders on medication-related outcomes in MDD patients. In the current study, comorbid physical disorders were defined as painful symptoms. The selection of comorbid painful symptoms was based on a literature search.[24, 27-34] Table 3.3 lists the comorbid pain symptoms used for the current study and their related ICD-9-CM codes. MDD patients having a claim of any one of the painful symptoms listed in Table 3.3 were identified as having comorbid painful symptoms. The variable of having comorbid painful symptoms was coded as dichotomous (yes/no).

Diagnosis	**ICD-9-CM**
Abdominal pain	789.0
Chest pain	786.5, 786.50, 786.51, 786.52
Chronic pain (Chronic pain associated with significant psychosocial dysfunction)	338.4
Headache	346, 784.0
Joint pain (pain in joint)	719.4
Lower back pain	724.2
Neck pain (pain in neck, Cervicalgia)	723.1
Pain	338
Pain associated with psychological factors	307.8, 307.81, 307.82, 307.89

Table 3.3 Comorbid painful symptoms and the ICD-9-CM codes

Variables of the pre-index period resource utilization

Several variables in the pre-index period considered to have an influence on medication-related outcomes in the index period needed to be included and adjusted when performing data analyses. Patients having high health resource utilization in the pre-index period could also have high health resource utilization in the index period.

Therefore, variables in the pre-index period related to health resource utilization needed to be controlled. Variables related to health resource utilization in the pre-index period include the number of prescriptions used in the pre-index period, ER visits in the pre-index period (yes/no), and hospitalization in the pre-index period (yes/no).

A comorbidity index was used to adjust the influence of comorbid conditions other than MDD on health outcomes. The Elixhauser index, was used to adjust the comorbid conditions in this study, was discussed in the following sections.

The Elixhauser comorbidity index

The Elixhauser comorbidity index was introduce by Dr. Ann Elixhauser in 1998.[133] She and her colleagues studied the influence of comorbid conditions on health outcomes, such as length of stay, hospital charges, and in-hospital death from 1,779,167 adult nonmaternal inpatients from 438 acute care hospitals in California.[133] The index included a comprehensive set of disease conditions and provided a measurement of comorbidity from administrative inpatient datasets.[133] The Elixhauser comorbidity index assumes each comorbid condition could have an independent effect on health outcomes. Composing the effect of each condition to a single score was not appropriate and did not sufficiently evaluate the impact of a condition on health outcomes. Consequently, the Elixhauser index was used as an expanded set of comorbid conditions (30 different diseases). The names of the conditions and their related ICD-9-CM codes are listed in Table 3.6.[133]

The Elixhauser comorbidity index provided a more comprehensive measurement of comorbid conditions in this study. In addition to the physical conditions, the Elixhauser comorbidity index also incorporates mental illness. Therefore, the Elixhauser

comorbidity index served as a measurement of comorbidity in the current study. The index was categorized as the number of comorbid conditions (0, 1, 2, and 3^{+}) to control for overall severity of illness in the study population. The SAS codes of counting comorbid conditions in this study were derived and modified from the Healthcare Cost and Utilization Project (HCUP) Comorbidity Software website.[134] The HCUP was a database project founded by a federal-state-industry partnership and sponsored by the Agency for Healthcare Research and Quality (AHRQ).

Table 3.4 Definitions and ICD-9-CM codes of the Elixhauser Index

Comorbidity	ICD-9-CM Codes
1. Congestive Heart Failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0-428.9
2. Cardiac Arrhythmias	426.10, 426.11, 426.13, 426.2-426.53, 426.6-426.89, 427.0, 427.2, 427.31, 427.60, 427.9, 785.0, V45.0, V53.3
3. Valvular Disease	093.20-093.24, 394.0-397.1, 397.9, 424.0-424.99, 746.3-746.6, V42.2, V43.3
4. Pulmonary Circulation Disorders	416.0-416.9, 417.9
5. Peripheral Vascular Disorders	440.0-440.9, 441.00- 441.9, 442.0-442.9, 443.1-443.9, 447.1, 557.1, 557.9, V43.4
6. Hypertension (combines uncomplicated and complicated)	
Hypertension, uncomplicated	401.1, 401.9, 642.00-642.04
Hypertension, complicated	401.0, 402.00-405.99, 642.10-642.24, 642.70-642.94
7. Paralysis	342.0-344.9, 438.20-438.53
8. Other Neurological Disorders	330.0-331.9, 332.0, 333.4, 333.5, 334.0-335.9, 340, 341.1-341.9, 345.00-345.11, 345.2-345.3, 345.40-345.91, 347.00-347.01, 347.10-347.11, 780.3, 780.39, 784.3
9. Chronic Pulmonary Disease	490-492.8, 493.00-493.92, 494-494.1, 495.0-505, 506.4
10. Diabetes without Chronic Complications	250.00-250.33, 648.00-648.04
11. Diabetes with Chronic Complications	250.40-250.93, 775.1
12. Hypothyroidism	243-244.2, 244.8, 244.9
13. Renal Failure	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585, 586, V42.0, V45.1, V56.0-V56.32, V56.8

14.	Liver Disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 456.0, 456.1, 456.20, 456.21, 571.0, 571.2, 571.3, 571.40-571.49, 571.5, 571.6, 571.8, 571.9, 572.3, 572.8, V42.7
15.	Chronic Peptic Ulcer Disease (includes bleeding only if obstruction is also present)	531.41, 531.51, 531.61, 531.70, 531.71, 531.91, 532.41, 532.51, 532.61, 532.70, 532.71, 532.91, 533.41, 533.51, 533.61, 533.70, 533.71, 533.91, 534.41, 534.51, 534.61, 534.70, 534.71 534.91
16.	HIV and AIDS	042-044.9
17.	Lymphoma	200.00-202.38, 202.50-203.01, 203.8-203.81, 238.6, 273.3
18.	Metastatic Cancer	196.0-199.1
19.	Solid Tumor Without Metastasis	140.0-172.9, 174.0-175.9, 179-195.8
20.	Rheumatoid Arthritis/Collagen Vascular Diseases	701.0, 710.0-710.9, 714.0-714.9, 720.0-720.9, 725
21.	Coagulation Deficiency	286.0-286.9, 287.1, 287.3-287.5
22.	Obesity	278.0, 278.00, 278.01
23.	Weight Loss	260-263.9, 783.21, 783.22
24.	Fluid & Electrolyte Disorders	276.0-276.9
25.	Blood Loss Anemia	280.0, 648.20- 648.24
26.	Deficiency Anemias	280.1-281.9, 285.21-285.29, 285.9
27.	Alcohol Abuse	291.0-291.3, 291.5, 291.8, 291.81, 291.89, 291.9, 303.00-303.93, 305.00-305.03
28.	Drug Abuse	292.0, 292.82-292.89, 292.9, 304.00-304.93, 305.20-305.93, 648.30-648.34
29.	Psychoses	295.00-298.9, 299.10-299.11
30.	Depression	300.4, 301.12, 309.0, 309.1, 311

Statistical Analyses and Hypothesis Testing

The objective of the current study was to examine the association between the combined effects of race/ethnicity and comorbidity and medication-related outcome (medication utilization, medication persistence, medication adherence, and medication expenditures) in Medicaid-enrolled MDD patients. The required statistical analyses employed in examining the study objectives and hypothesis testing were described in the following sections.

Study objectives

Objective 1: To describe select patient characteristics (sociodemographic factors and medication-related factors) in Medicaid-enrolled patients with and without comorbid anxiety disorders. (Addressed in the manuscript No.1 & No. 2)

Descriptive statistics were used to describe patient characteristics, which include sociodemographic factors and medication-related factors such as health care costs, prescription utilization, and health service utilization, between MDD patients with and without comorbid anxiety disorders. The average value (mean) was used to describe the continuous variables and a proportion (%) was used to describe the categorical variables. The Student's t-test was used to differentiate the mean difference of the continuous variables between MDD patients with and without comorbid anxiety disorders. Chi-square tests were used to assess the difference of the categorical variables between MDD patients with and without comorbid anxiety disorders.

Objective 2: To examine the effect of race/ethnicity, comorbid anxiety disorders, and the combined effects of race/ethnicity and comorbid anxiety disorders on medication adherence in Medicaid-enrolled MDD patients, after adjusting for select confounders. (Addressed in the manuscript No. 1)

Medication adherence was assessed by MPRm, which is the dependent variable in the regression model. An Ordinary Least Squares (OLS) regression model was used to assess the association between MPRm and key tested variables as well as other covariates. When the dependent variable was skewed and heteroskedastic, a log-transformation for the dependent variable was needed. Shapiro-Wilk test and White test[135] were used to test

the normality and heteroskedasticity. A log-transformed MPRm was not necessary due to the normal distribution of the MPRm values in this study.

The OLS regression model was used to examine the association between medication adherence and race/ethnicity, comorbid anxiety disorders and the combined effect. The key tested variables were race/ethnicity, comorbid anxiety disorders, and the combined effect of race/ethnicity and comorbid anxiety disorders. The selection of covariates was based on the proposed theoretical framework in Figure 2.8. Covariates were categorized into predisposing, enabling, and need factors. Predisposing factors included age and gender. Enabling factors in this study were determined by the type of health plan (FFS vs. Capitation). Need factors in the current study refer to the severity of the disease. The factors were determined by the Elixhauser comorbidity index, whether patients had been hospitalized in the pre-study period (yes/no), whether patients had ER visits in the pre-study period (yes/no), and the number of prescriptions used during the pre-study period. Due to the high prevalence of co-occurring painful symptoms in patients with MDD, whether patients were with comorbid painful symptoms (yes/no) was also adjusted with all other covariates in the regression model. The same principle of variable selection was applied in all of the regression models in the current study.

The following equations show the OLS regression model that includes key tested variables, predisposing factors, enabling factors, and needed factors as well as their relationship with MPRm.

$$Y: MPRm = \beta_0 + \beta_1\,(race/ethnicity) + \beta_2\,(comorbid\ anxiety\ disorders) + \beta_3\,(the\ combined\ effect) + \beta_4\,(predisposing\ factors) + \beta_5(enabling\ factors) + \beta_6\,(need\ factors) + error$$

The interpretation of the association between MPRm and covariates is that for every unit increase in a particular covariate, the value of MPRm was assumed to change with a parameter unit of the particular covariates, holding all other variables in the model constant.

In addition to evaluating medication adherence as a continuous variable, medication adherence was further categorized into a dichotomous variable. A value of MPRm smaller than 80% (MPRm < 80%) was defined as non-adherent.[127] Logistic regression was used to examine the association between the likelihood of being adherent to the medication and race/ethnicity adjusting for other covariates. The following logistic regression model describes the association.

$$Y: Medication\ adherence\ (yes/no) = \beta_0 + \beta_1\,(race/ethnicity) + \beta_2\,(comorbid\ anxiety\ disorders) + \beta_3\,(the\ combined\ effect) + \beta_4\,(predisposing\ factors) + \beta_5(enabling\ factors) + \beta_6\,(need\ factors) + error$$

Objective 3: To examine the effect of race/ethnicity, comorbid anxiety disorders, and the combined effects of race/ethnicity and comorbid anxiety disorders on medication

persistence in Medicaid-enrolled MDD patients, after adjusting for select confounders. (Addressed in the manuscript No. 1)

Medication persistence in this study was operationally defined as the duration for which prescriptions were taken. It was the number of days determined by the initiation of taking the medicine to the end of taking the medicine. Medication persistence was a time-dependent variable. The censored time referred to the time of persistently taking antidepressants during the study period. Unadjusted Kaplan-Meier survival curves were used to compare the differences of censored time between Caucasian and African American patients as well as MDD patients with and without comorbid anxiety disorders, respectively. A Cox proportional hazard model was used to estimate the different hazard ratios in patients with different race/ethnicity who are on the time to first stop taking antidepressants after adjusting for other covariates. The following equation describes the Cox proportional hazard model.

$$Y: Medication\ persistence\ (time)$$
$$= \beta_0 + \beta_1\ (race/ethnicity) + \beta_2\ (comorbid\ anxiety\ disorders)$$
$$+ \beta_3\ (the\ combined\ effect) + \beta_4\ (predisposing\ factors)$$
$$+ \beta_5 (enabling\ factors) + \beta_6\ (need\ factors) + error$$

Objective 4: To examine the effect of race/ethnicity, comorbid anxiety disorders, and the combined effects of race/ethnicity and comorbid anxiety disorders on mental health-related health care costs in Medicaid-enrolled MDD patients after adjusting for select confounders. (Addressed in the manuscript No. 2)

An OLS regression model with log transformation was used to assess the association between mental health-related health care costs and key tested variables as well as covariates in the regression model. The health care costs was a highly skewed variable, which needed log transformation to obtain normality. The log-transformed OLS model was an exponential model, which had non-linear estimated regression coefficients. In order to obtain the incremental effect of a one-unit change of the estimated regression coefficients, retransformation was necessary. A "smearing" term was incorporated in the retransformation process.[136-137] The assumption of the retransformation with a smearing term in the estimated coefficients was that homoscedasticity exists among the errors. However, it was not common to have an unrelated error in health care expenditure data. A Breusch-Pagan test was used to test the heteroskedasticity in this study and it was found that the prescription expenditure data was not homoscedastic.[138] Therefore, the log-transformed estimated regression coefficients did not need the retransformation process. The interpretation of a parameter in the log-transformed regression model was assumed to be percent difference. However, researchers need to be cautious when interpreting the log-transformed regression coefficients because the values of the coefficients are not linear. The following OLS regression model assesses the influence of race/ethnicity, comorbid anxiety disorders and their combined effect on mental health-related health care costs after adjusting for other covariates.

$$Y: Ln\ (Mental\ health - related\ health\ care\ costs) =$$

$$\beta_0 + \beta_1\ (race/ethnicity) + \beta_2\ (comorbid\ anxiety\ disorders) +$$

$$\beta_3\ (the\ combined\ effect) + \beta_4\ (predisposing\ factors) +$$
$$\beta_5(enabling\ factors) + \beta_6\ (need\ factors) +\ error$$

Objective 5: To examine the effect of race/ethnicity, comorbid anxiety disorders, and the combined effects of race/ethnicity and comorbid anxiety disorders on overall health care costs in Medicaid-enrolled MDD patients after adjusting for select confounders. (Addressed in the manuscript No. 2)

The dependent variable of Objective 5 is the overall health care costs. The statistical analysis of the Objective 5 is similar to the analysis implemented in examining the hypothesis testing in Objective 4. The following equation illustrates the OLS regression model with log-transformed overall health care costs.

$$Y: Ln\ (Overall\ health\ care\ costs) =\ \ \beta_0\ +\ \beta_1\ (race/ethnicity) +$$
$$\beta_2\ \ (comorbid\ anxiety\ disorders) + \beta_3\ (the\ combined\ effect) +$$
$$\beta_4\ (predisposing\ factors) + \beta_5(enabling\ factors) + \beta_6\ (need\ factors) +$$
$$error$$

Objective 6: To examine the effect of race/ethnicity, comorbid anxiety disorders, and the combined effects of race/ethnicity and comorbid anxiety disorders on mental health-related health resource utilization (office visits, hospitalization and emergency room (ER) visits) in Medicaid-enrolled MDD patients after adjusting for select confounders. (Addressed in the manuscript No. 2)

Mental health-related health resource utilization such as office visits, hospitalization, and ER visits were considered as count dependent variables in this study. OLS regression was not appropriate to obtain a robust estimate for assessing the association between health care utilization and race/ethnicity. Due to the difference between the variance and the mean, the negative-binominal distribution is more appropriate to be used for assessing the association. A highly skewed number of mental health-related hospitalization and ER visits existed in the study population. Therefore, a two-part of regression model was used to model the association of mental health-related health resource utilizations and race/ethnicity, comorbid anxiety disorders, and combined effects, adjusting for other covariates. Multivariate logistic regression analyses were the first part of the two-part model. The logistic regression analyses were used to estimate the probability of any event of health resource utilization. Then, the second part is multivariate negative binominal regression analyses. They were used to estimate the level change of health resource utilization among patients having at least one event of health resource utilization.

Logistic regression analyses:

$$Y: Mental\ health - related\ office\ visits\ \ (yes/no)$$
$$= \beta_0 + \beta_1\ (race/ethnicity) + \beta_2\ (comorbid\ anxiety\ disorders)$$
$$+ \beta_3\ (the\ combined\ effect) + \beta_4\ (predisposing\ factors)$$
$$+ \beta_5 (enabling\ factors) + \beta_6\ (need\ factors) + error$$

$$Y: Mental\ health - related\ hospitalization\ \ (yes/no)$$

$$= \beta_0 + \beta_1\ (race/ethnicity) + \beta_2\ \ (comorbid\ anxiety\ disorders)$$

$$+ \beta_3\ (the\ combined\ effect) + \beta_4\ (predisposing\ factors)$$

$$+ \beta_5 (enabling\ factors) + \beta_6\ (need\ factors) + \ error$$

$$Y: Mental\ health - related\ ER\ visits\ \ (yes/no)$$

$$= \beta_0 + \beta_1\ (race/ethnicity) + \beta_2\ \ (comorbid\ anxiety\ disorders)$$

$$+ \beta_3\ (the\ combined\ effect) + \beta_4\ (predisposing\ factors)$$

$$+ \beta_5 (enabling\ factors) + \beta_6\ (need\ factors) + \ error$$

Negative binominal distribution regression analyses

$$Y: Mental\ health$$

$$- related\ office\ visits\ \ (a\ count\ variable, the\ number\ of\ office\ visits)$$

$$= \beta_0 + \beta_1\ (race/ethnicity) + \beta_2\ \ (comorbid\ anxiety\ disorders)$$

$$+ \beta_3\ (the\ combined\ effect) + \beta_4\ (predisposing\ factors) + \beta_5 (enabling\ factors)$$

$$+ \beta_6\ (need\ factors) + \ error$$

$$Y: Mental\ health$$

$$-related\ hospitalization\ \ (a\ count\ variable, the\ number\ of\ hospitalization)$$

$$= \beta_0 + \beta_1\ (race/ethnicity) + \beta_2\ \ (comorbid\ anxiety\ disorders)$$

$$+ \beta_3\ (the\ combined\ effect) + \beta_4\ (predisposing\ factors) + \beta_5(enabling\ factors)$$

$$+ \beta_6\ (need\ factors) + \ error$$

$$Y: Mental\ health$$

$$-related\ ER\ visits\ \ (a\ count\ variable, the\ number\ of\ ER\ visits)$$

$$= \beta_0 + \beta_1\ (race/ethnicity) + \beta_2\ \ (comorbid\ anxiety\ disorders)$$

$$+ \beta_3\ (the\ combined\ effect) + \beta_4\ (predisposing\ factors)$$

$$+ \beta_5(enabling\ factors) + \beta_6\ (need\ factors) + \ error$$

Objective 7: To examine the effect of race/ethnicity, comorbid anxiety disorders, and the combined effects of race/ethnicity and comorbid anxiety disorders on overall health resource utilization (office visits, hospitalization and emergency room (ER) visits) in Medicaid-enrolled MDD patients after adjusting for select confounders. (Addressed in the manuscript No. 2)

The regression analyses of examining hypothesis testing in Objective 7 were similar to analyses implemented in Objective 6. However, the dependent variables in Objective 7 are the overall health resource utilization (office visits, hospitalization, ER visits). Two-part models including logistic regressions and negative binominal regressions were used to assess the association of overall health resource utilization and

race, comorbid anxiety disorders, and the combined effect, adjust for all other covariates in the models.

Propensity score matching

Propensity score matching were used to match patient characteristics between MDD patients with and without comorbid anxiety disorders. The propensity score is a scoring method to create a single variable (a propensity score) which incorporates effects of covariates on the treatment and collapses the value of the effects into a single score.[139] The propensity score is the probability that a patient will receive treatment after adjusting for covariates.[139] It is a predicted probability of exposure.[139] In contrast to a randomized trial, the drawbacks of an observational study are selection bias and potential confounders that may influence the dependent variable. The advantage of using a propensity score in an observational study is that matching based on the propensity score provides a similar magnitude to a randomized clinical trial. Propensity score matching can remove selection bias and potential confounders, which creates a balance between groups with and without treatment. Although propensity score matching provides a condition similar to a randomized trial, the result of matching in groups with and without treatments still cannot substitute the randomized trial because the propensity score matching only matches observed variables. The matching cannot remove the effect of unobserved variables. Confounding effects from the unobserved variables can only be removed by a randomized trial.

In the current study, propensity score matching was used to eliminate the confounding effect of covariates between MDD patients with and without comorbid psychiatric conditions (comorbid anxiety disorders). A logistic regression was employed,

and variables listed in Table 3.5 were used to generate a propensity score for each subject. Two different matching techniques were implemented in the study. The first matching technique was that MDD patients with comorbid anxiety disorders were matched to MDD patients without comorbid anxiety disorders within a 0.01 caliper of propensity.[140] Each pair of patients was matched based on a two-digit match with the propensity score. The second matching technique is called "Greedy Match." In this technique, matching between patients with and without comorbid anxiety disorders is based on the best matching on the propensity score from the highest digit (set as 5 in the study) to the lowest digit (set as 1 in the study).[141] Figure 3.4 illustrates the result of the two-digit matching on the propensity score between MDD patients with and without comorbid anxiety disorders. Figure 3.5 illustrates the result of the greedy match. Both figures illustrate that patient characteristics of MDD patients with and without comorbid anxiety disorders become similar based on the propensity score after they have been matched. After the propensity score matching, the medication-related outcomes were compared between MDD patients with comorbid anxiety disorders and MDD patients without comorbid anxiety disorders. The results of the comparison were not presented in the two article manuscripts in Chapter 4 and Chapter 5 because more than one of the key test independent variables were included in the regression model.

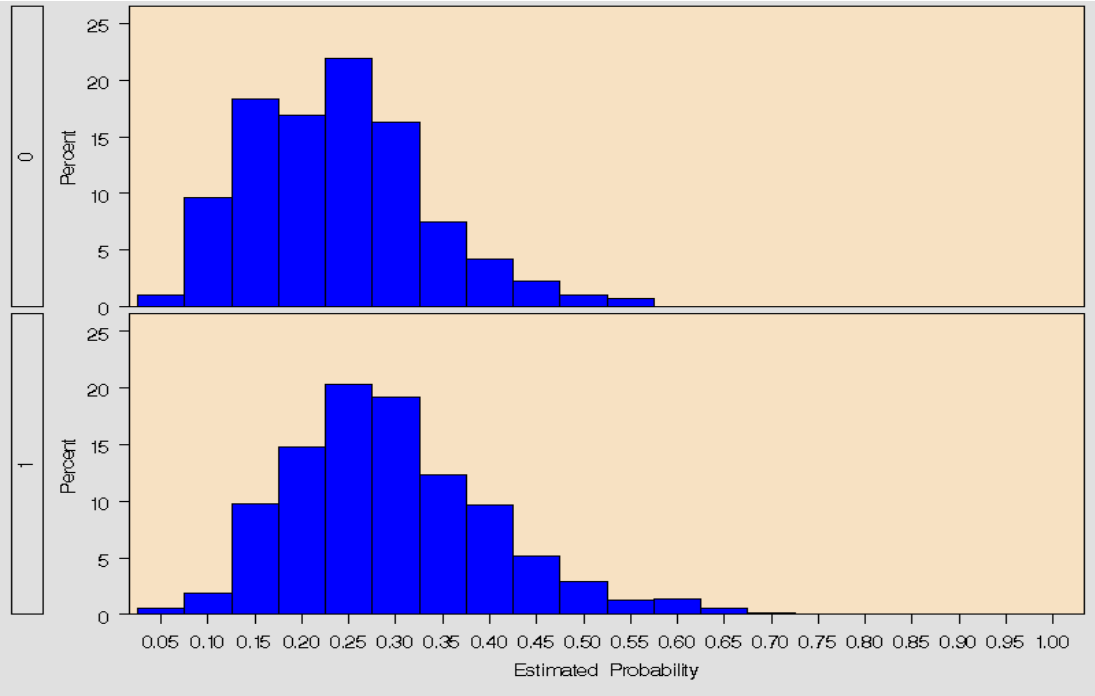
Table 3.5 Variables used in the propensity score matching modeling

Variables
Age
Gender
Race/ethnicity
Physician visit
Comorbidity
Type of health plan
Number of prescription medicines

Number of hospitalizations in the pre-index period
Number of ER visits in the pre-index period
Number of prescription medicines in the pre-index period

Figure 3.4 Results of the two-digit matching on the propensity score: matching variables listed in the Table 3.7

Before matching



After matching

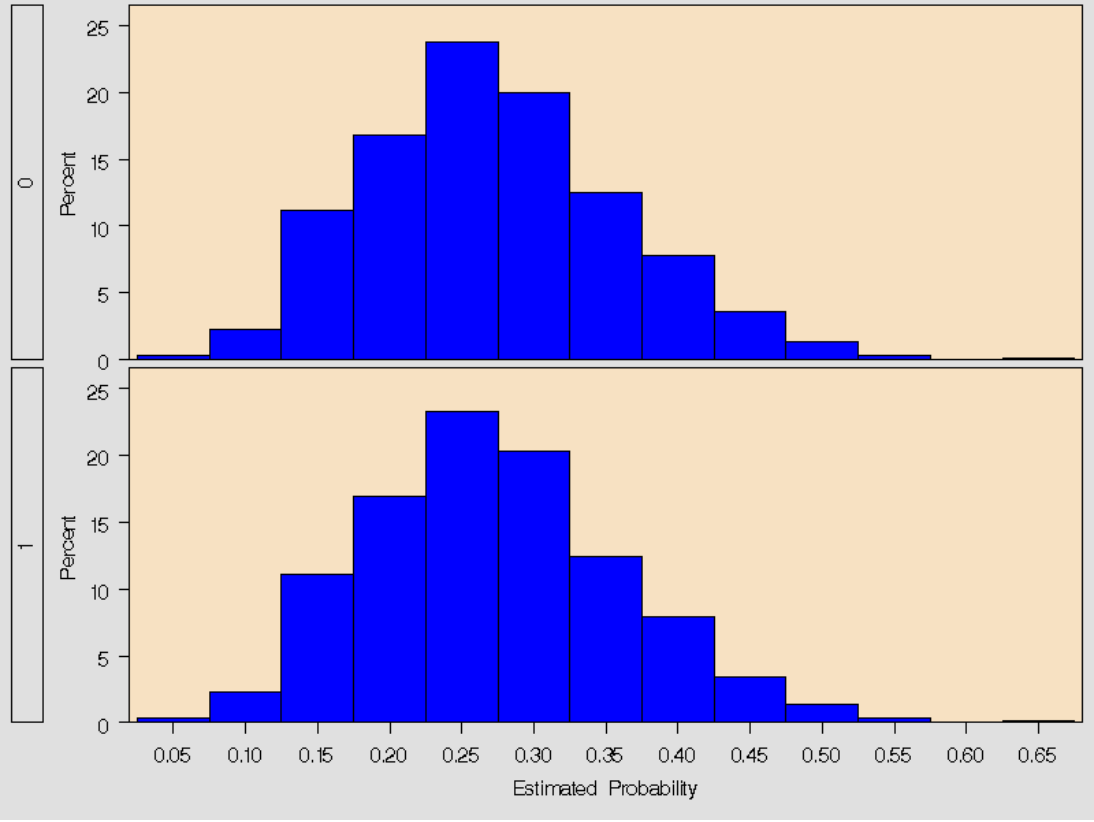
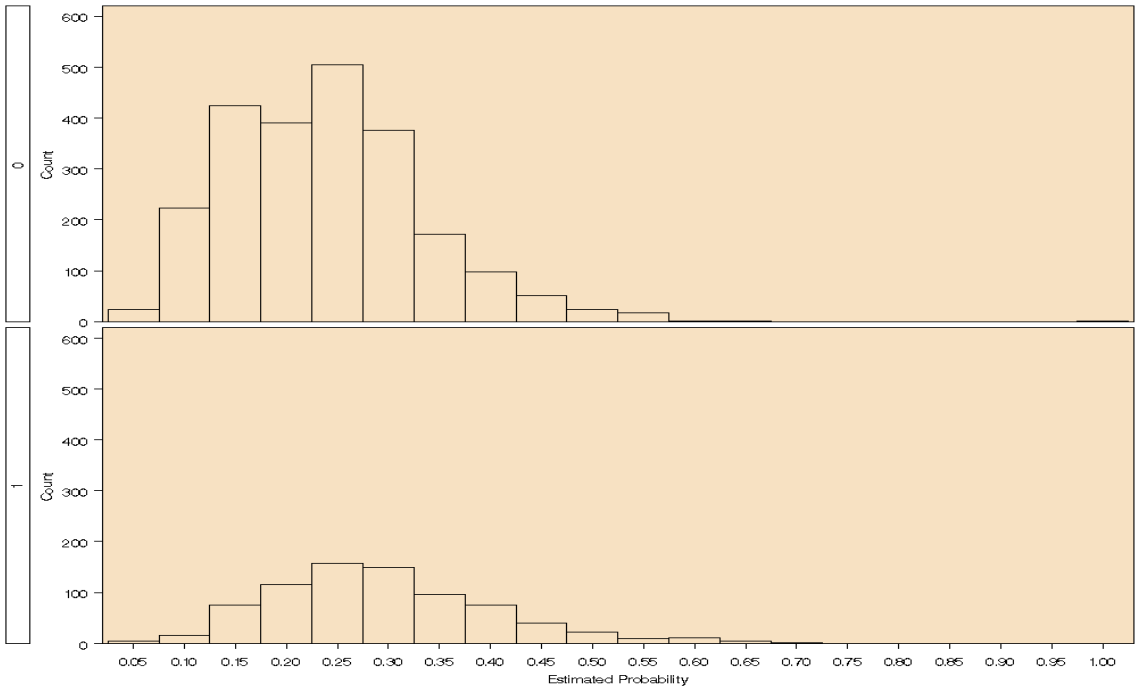
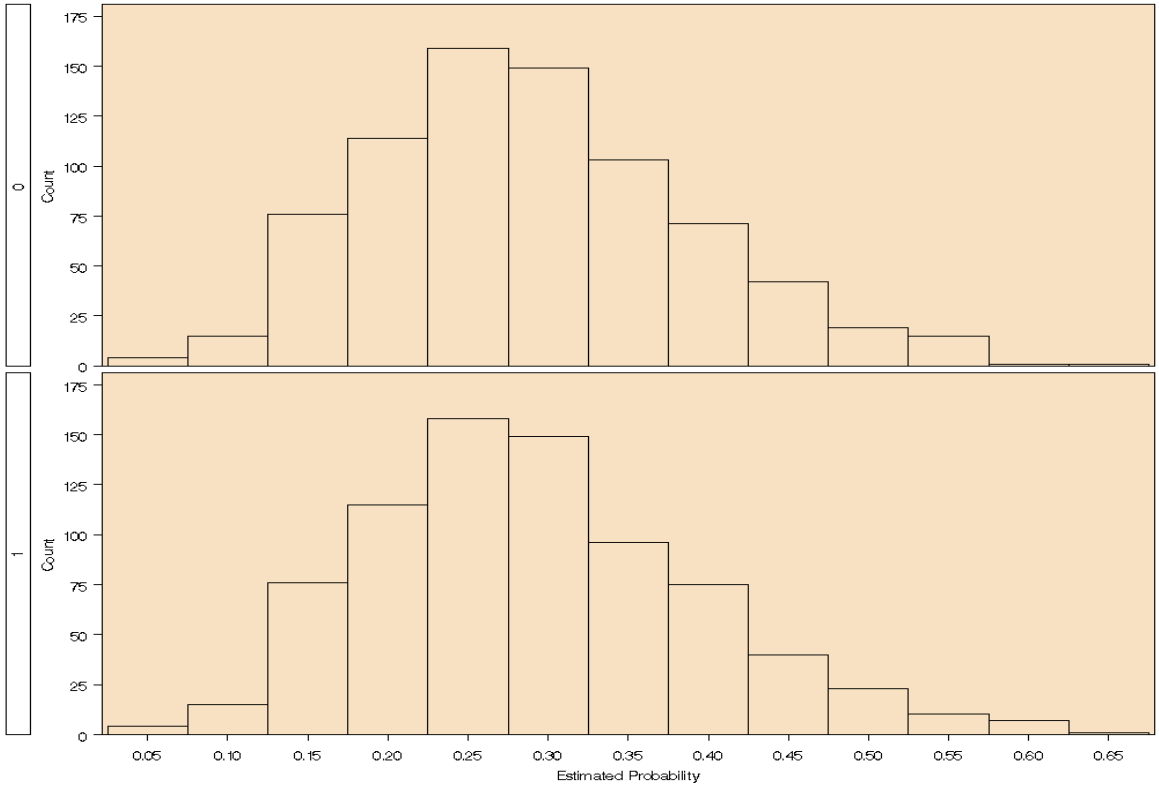


Figure 3.5 Results of greedy match based on propensity score: matching variables listed in the Table 3.7

Before matching



After matching



Regression Diagnostics

In order to obtain robust estimates, an OLS regression model needs to meet several statistical assumptions. These assumptions include Existence, Linearity, Independence, Homoscedasticity, and Normality.[142] Existence means the dependent variable, Y, is random and has a finite mean and variance in a population.[142] The mean and the variance of Y depends on the value of the independent variable, X. Basically, our study population meets the Existence statistical assumption. Linearity means that the mean value of Y is a straight-line function of X.[142] The current study also meets this statistical assumption. For example, the MPR is a linear function of the key tested independent variables and other covariates.

For other statistical assumptions such as Independence, Homoscedasticity and Normality, several regression diagnoses were implemented to ensure the OLS regression models performed in this study met the criteria of the assumption. Specific tests for each statistical assumption are described in the following sections.

Autocorrelation

Independence assumes that the value of each dependent variable is independent from the others.[142] This assumption implies that the value of each Y is not correlated. It assumes a correlation between each Y does not exist. Most cross sectional studies usually meet this assumption. However, the Independence assumption can be violated in certain situations. For example, the values of multiple observations in the same subject over a different period time can be correlated. This is called autocorrelation.

Autocorrelation can exist especially when studying medication adherence behavior in patients with chronic diseases. The OLS regression cannot obtain robust

estimations when autocorrelation exists. Using the Durbin-Watson statistic test can determine if autocorrelation exists or not in the regression model.[142] The null hypothesis of the Durbin-Watson test is that there is no autocorrelation over time. The value of the Durbin-Watson statistic test is between 0 and 4.[143] If the value of the Durbin-Watson statistic is 2, it means there is no autocorrelation between Y values over time.[143] A positive autocorrelation exists if the value is close to 0.[143] In contrast, a negative autocorrelation exists if the value is close to 4.[143] Using lagged variables in the OLS regression or GLS (general least squares) regression can correct the autocorrelation if it exists.

Heteroskedasticity

One of the assumptions in the OLS regression model is homoscedasticity, which means the variance of Y (the dependent variable) is the same for any given X (the independent variable). Heteroskedasticity is a violation of the assumption with a constant variance.[142] The presence of outliners and skewness can result in heteroskedasticity.[143] The consequence of heteroskedasticity can result in a narrow range of the confidence interval which leads to easily rejecting the null hypotheses even though the point estimates (OLS coefficients) are still unbiased.

The Breusch-Pagan-Godfrey test is often used to test for the presence of heteroskedasticity in the OLS regression model.[143] It tests whether the estimated variance of the residuals from an OLS regression model is dependent on the values of the independent variables. If heteroskedasticity exists in the OLS regression model, the estimated variance of the residuals can be correlated with independent variables. The

correction of heteroskedasticity includes using GLS regression, which accounts for equal weight to each observation.[143]

Normality

Normality means that for any fixed value of X, Y has a normal distribuation.[142] An OLS regression model has to meet the normality assumption to obtain robust point estimates and confidence intervals. The inference made by the OLS regression model is accurate and reliable if the normality assumption is not violated.[142] The Shiparo-Wilk test and a plot histogram of residuals[143] are usually used to test the normality.[135] When the normality assumption is unsatisfied, a log-transformation of the Y (dependent)-value is needed.[142] However, researchers need to ascertain that other assumptions, such as homoscedasticity, are not violated after log-transformation. In general, normality and homoscedasticity assumptions are not violated after implementing log transformation.[142]

Multicollinearity

In addition to satisfying the basic statistical assumptions described above when implementing an OLS regression model, multicollinearity between independent variables (covariates) also needs to be considered. "Collinearity occurs when two or more of the explanatory variables are correlated to the extent that they convey essentially the same information about the observed variation in Y."[144] The consequence of multicollinearity can result in an instability of the point estimate and the standard error.[144]

Variance Inflation Factor (VIF) is often used to detect multicollinearity in an OLS regression model.[142] VIF is an index which measures the magnitude of the variance change of an estimated coefficient due to multicollinearity. The larger the VIF value is, the greater multicollinearity is between independent variables.[142] Severe multicollinearity

is observed in an OLS regression model when the VIF value is greater than 10.[142] When multicollinearity occurs, the model needs to be re-specified. The presence of multicollinearity was checked in the OLS regression models in the current study.

Data Management and Analyses

The analytical data extracted from the MarketScan® Multi-State Medicaid Database was in SAS format. SAS v.9.2 software (SAS Institute, Cary, North Carolina)[145] was used for data management procedures. All statistical analyses were computed with using SAS v.9.2, and Stata 11 (StataCorp LP, College Station, Texas).[146] Estimates of means, proportions, and standard errors with 95% confidence intervals (CI) were derived from the statistical estimation. Two-tailed tests and a 0.05 level of significance were used to determine statistical significance. The study protocol was approved by the Institutional Review Board (IRB) at the University of Michigan. (Appendix 1).

CHAPTER 4

MANUSCRIPT ONE

Title: Associations of Race and Comorbid Anxiety Disorders with Medication Adherence and Persistence in Medicaid Enrollees with Major Depressive Disorders

Abstract

Background

Depressed patients often have comorbid anxiety disorders. Depressed African-American patients are less likely to receive antidepressants than Caucasian patients. Few studies have investigated the association of race and comorbid anxiety disorders with antidepressant adherence and persistence in Medicaid enrollees.

Objective

The objective of this study was to examine the association of race, comorbid anxiety disorders, and the interaction between race and comorbid anxiety disorders with medication adherence and persistence in Medicaid enrollees with Major Depressive Disorders (MDD).

Methods

Data from the MarketScan® Multi-State Medicaid Database were used in this retrospective cohort study. Adult Medicaid enrollees between 18 and 64 years of age with MDD but without bipolar disorders who received an antidepressant between January 1, 2004 and December 31, 2006 were identified. An index diagnosis date was assigned to each patient. Patients with a 24-month continuous enrollment (12 months before and after the index diagnosis date) and without dual eligibility of Medicaid and Medicare were included in the study population. Adherence was determined by Medication Possession Ratio, modified (MPRm). Persistence was measured by the time duration to discontinuously stop taking antidepressants. Multivariate logistic regressions were used to model the probability of adherence. A Cox-propositional hazard regression was used to examine the association of race and comorbid anxiety disorders with the risk of non-persistent antidepressant use.

Results

There were 3,083 Medicaid patients with MDD included in this study. Approximately, 25% of the patients had comorbid anxiety disorders. The expected odds of adhering to antidepressants was 40% lower in African-American than Caucasian patients, adjusting for all other covariates in the model (OR = 0.6, 95% CI = 0.51-0.72, $p < 0.001$). MDD patients with comorbid anxiety disorders were more likely to be adherent to antidepressants than patients with MDD alone (OR= 1.55, 95% CI=1.27-1.90, $p < 0.001$). For medication persistence, African Americans had a higher hazard of not persistently taking antidepressants (Hazard Ratio = 1.55, 95% CI = 1.38-1.75, $p < 0.001$).

Conclusion

In Medicaid enrollees with MDD, African-American patients were less likely than Caucasian patients to be adherent to or persistently use antidepressants. MDD patients with comorbid anxiety disorders had higher antidepressant adherence when compared with MDD patients without comorbid anxiety disorders. The mental health policy implications needed to reduce health disparities between African-American and Caucasian patients and improve antidepressant use behaviors among Medicaid enrollees with MDD.

Key words: adherence, administrative data, African Americans, comorbid anxiety disorders, major depressive disorders, Medicaid, persistence, race.

Introduction

Major Depressive Disorder (MDD) is a prevalent mental disorder in the United States.[57] In 2003, the annual prevalence rate was estimated to be 6.7%,[1] and the lifetime prevalence rate was 16.2%.[2] Additionally, MDD was found to have a prevalence rate close to 19% in urban general medicine practices.[61] Anxiety disorders commonly co-occur in patients with depression. Results from two U.S. national representative surveys showed that about 41%-60% of lifetime MDD patients experience comorbid anxiety disorders.[6, 25]

Co-occurring depression and anxiety disorders have increased the diseases' severity in patients with MDD. MDD patients with comorbid anxiety disorders can have

poor health outcomes, [36] less symptom improvement,[35] and need longer time to recover [40] than MDD patients without comorbid anxiety. Pharmacotherapy such as medication treatment with antidepressants has become a favorable option for treating patients with depression, anxiety disorders, or co-occurring depression and anxiety disorders. However, comorbid anxiety disorders can make pharmacotherapy more challenging and reduce treatment outcomes.[39]

Medication use behaviors in minority groups can be different when compared with non-minorities. Due to cultural differences, minorities may have different perceptions or beliefs concerning antidepressant treatments. For example, African-American patients found antidepressant prescription less acceptable when compared with Caucasian patients.[147] Additionally, studies have shown that African Americans were less likely than Caucasians to receive antidepressants after they have been diagnosed with depression,[21] to fill an antidepressant prescription,[17] and to use prescriptions.[148] For medication treatment of anxiety disorders, African Americans with panic disorders were less willing than Caucasians to consider medication treatment.[149] Given these findings, more investigations on medication use behaviors such as adherence and persistence between African Americans and Caucasians are needed

High adherence and persistently taking medicines can ascertain the success of treatment. However, low adherence and high discontinuation of taking antidepressants have been reported in several studies.[50-51, 150-151] For example, findings from a review study conducted by Cramer and Rosenseck reported that the rate of compliance with antidepressants is about 65%.[51] Moreover, the rate of discontinuation of antidepressant treatment was as high as 72% over a 3-month period.[151]

Given high disease prevalence of depression and comorbid anxiety disorders as well as a low adherence rate of antidepressant use, the association between adherence and comorbid anxiety disorders requires more investigation. However, there is a scarcity of research conducted to evaluate such an association. Stein et al. conducted a study using a large managed care database and reported that patients with co-occurring depression and anxiety disorders were more likely to adhere to antidepressant therapy than patients with anxiety disorders only.[152]

Furthermore, the influence of race on medication use behaviors needs more investigation, especially in Medicaid enrollees with MDD. Due to socioeconomic and educational factors, the gap of health outcomes between African-American and Caucasian patients with MDD could be expanded. African-American Medicaid enrollees might have difficulty in understanding the complexity of medication treatment. Accordingly, it is imperative to understand whether certain factors such as race and comorbid anxiety disorders could alter medication-taking behaviors among Medicaid enrollees with MDD.

The objective of this study was to investigate the association of race, comorbid anxiety disorders, and the interaction between race and comorbid anxiety disorders with medication adherence and persistence among Medicaid enrollees with MDD. Using the MarketScan® Multi-State Medicaid Database,[120] we evaluated the difference of medication adherence between MDD patients with and without comorbid anxiety disorders by different racial groups (Caucasian and African American). Furthermore, we examined the association of medication use behaviors (adherence and persistence,

respectively) with race, comorbid anxiety disorders, and the interaction effect between race and comorbid anxiety disorders, controlling for select confounders.

Method

Data sources

The MarketScan® Multi-State Medicaid Database was used for this study.[120] The database includes information on Medicaid enrollees from eight geographically dispersed states in the United States.[120] It also contains patients' enrollment history, disease conditions, clinical and demographic variables, and claims of inpatient and outpatient services and prescriptions.[120] ICD-9-CM were used for categorized clinical diagnoses. [120] A confidential enrollee identifier tracks individual patients, and the identifier of each patient was identical across different sections and calendar years of claims.[120]

Sample selection

This is a retrospective cohort study. The study duration was from January 1st, 2003 to December 31st, 2007. Figure 4.1 illustrates the sample selection process for obtaining the study population. Patients aged between 18 and 64 years who were diagnosed with a MDD but without bipolar disorders between January 1st, 2004 and December 31st, 2006 (the index period), were first included in the study. Each patient was then assigned an index diagnosis date.

Continuous enrollment for 24 months overall (12 months before and 12 months after the index diagnosis date) was also required. Patients with dual Medicare and Medicaid eligibility were excluded. Racial/ethnic groups other than Caucasians and or African Americans were also excluded. In order to obtain new drug users (drug naïve

patients), patients having claims of using antidepressants during the 12 months before the index diagnosis date were also excluded. Our study only included patients with newly prescribed antidepressants during the index period. After fulfilling (incorporating) the above inclusion and exclusion criteria, the final study sample came to 3,083 patients. ICD-9-CM codes relative to disease diagnosis in the sample selection process are listed in Table 4.1.

Study variables

Dependent variables

Adherence

Medication adherence of antidepressants use was the first dependent variable in our study. Medication adherence was evaluated by Medication Possession Ratio (MPR), which is widely implemented to measure medication adherence in administrative claim data. MPR was defined as the number of days' supply in the index period divided by the number of days in the study period.[123] In order to take the last day supply into consideration, MPR is further adjusted as MPR, modified (MPRm), which is defined as the total days supply of medications divided by the period between the last claim date and the first claim date plus the last days supply of medications.[124-125] In our study, MPRm was further categorized, using 0.8 value of MPRm as a cut-off point, into a dichotomous variable. [127] A high MPRm value (MPRm > 0.8) was defined as adherent and a low MPRm value (MPRm ≤ 0.8) was defined as non-adherent.

Persistence

Medication persistence of antidepressant use was the second dependent variable in our study. Persistence was defined as "the duration of time from initiation to discontinuation of therapy."[121] In our study, medication persistence was operationally determined as the number of days from the initiation of antidepressant use to the cessation of antidepressant use. A refill gap was allowed because a late refill may mean poor medication adherence but it does not necessary mean non-persistence. For this study, the gap threshold of medication persistence was set as 15 days, based on a literature search.[128-130] Patients were defined as non-persistent if they had a refill gap longer than 15 days.

Key tested independent variables

In our study, race, comorbid anxiety disorders, and the interaction between race and comorbid anxiety disorders were three tested independent variables. Their association with medication adherence and persistence was evaluated. Race, which was categorized as Caucasian or African American, was self-reported information obtained from patients when they were first enrolled in the Medicaid program. Comorbid anxiety disorders were identified based on medical claims of any anxiety disorder diagnosis (Table 4.1) during the 12-month study period after the index diagnosis date. MDD patients with a diagnosis of anxiety disorders were determined as having comorbid anxiety disorders. The interaction term is the interaction effect between race and comorbid anxiety disorders. MDD prevalence was different between Caucasian and African American patients. However, race might not be able to fully explain the difference of medication use-related outcomes without accounting for comorbid anxiety disorders because of the high prevalent rate of concurrent anxiety disorders in patients

with MDD. Therefore, the interaction effect became a key tested independent variable in our study.

Covariates

Selection of the covariates in this study was based on Andersen's Behavioral Model of Health Services Use.[59, 108] In the model, health care utilization is considered to be associated with predisposing, enabling, and need factors.[59, 105-106, 108] In our study, predisposing factors were age (categorized as 18-30, 31-40, 41-50, 51-60, and 61-64 years) and gender. Enabling factors are variables that could determine patients' capability to access health care.[105-106] In our study, the enabling factor was the type of the health plan, categorized as fee-for-service, capitation, and dual. In the Andersen model, the severity of disease is included as a need factor. [105-106] In our study, need factors included whether patients had comorbid painful symptoms (yes/no), the number of prescriptions used during the pre-study period, hospitalization during the pre-study period, and ER visits during the pre-study visit. This study utilized the Elixhauser comorbidity index (categorized as 0, 1, 2, and 3^{+}), to control for overall severity of illness in the study population.[133] The Elixhauser comorbidity index, a comprehensive set of comorbidity index containing 30 different diseases, was designed to measure comorbidity for predicting hospitalization and in-hospital mortality using administrative data.[133]

Statistical analyses

Patient characteristics of the study population were performed using descriptive statistics. For evaluating medication adherence, comparisons of MPRm between MDD patients with and without comorbid anxiety disorders for both Caucasians and African Americans were examined using Student's t-tests. A multivariate linear regression

analysis was used to evaluate the association between MPRm and race, comorbid anxiety disorders and the interaction term controlling for covariates in the model. A multivariate logistic regression was implemented to model the probability of adhering to antidepressants (MPRm $\geq$ 0.8) after adjusting for covariates.

For evaluating medication persistence, survival analysis and a Cox proportional hazards model were implemented. The censored time referred to the time of persistently taking antidepressants during the study period. Unadjusted Kaplan-Meier survival curves were used to compare the differences of censored time between Caucasian and African American patients as well as MDD patients with and without comorbid anxiety disorders, respectively. A Cox proportional hazard regression model was used to assess the effect of race, comorbid anxiety disorders, and the interaction effect on the hazards of time to discontinue taking antidepressants, after adjusting for covariates.

In this study, data management and statistical analyses were performed using SAS v.9.2 (SAS Institute, Cary, NC).[145] Two-tailed tests with a 0.05 level of significance were used to determine statistical significance. The study protocol was approved by the Institutional Review Board (IRB) at the University of Michigan.

Results

Patient characteristics of the study population are depicted in Table 4.2. A total of 3,083 Medicaid enrollees met all inclusion and exclusion criteria. The study population was 77% female, 37% African American, 25% with comorbid anxiety disorders, 47% with comorbid painful symptoms, and 61% with fee-for-service health plan. Approximately 27% of the population had been hospitalized, and 60% had had at least one ER visit in the pre-study period. (Table 4.2)

Table 4.3 shows the chi-square comparison of the rate of comorbid anxiety disorders by racial groups. Compared with African-American patients with MDD, Caucasian patients with MDD were significantly more likely to have comorbid anxiety disorders (30.2% vs. 16.4%, $p < 0.01$).

Adherence

Table 4.4 shows the comparisons of MPRm between Caucasian and African-American patients, as well as MPRm between MDD patients with and without comorbid anxiety disorders. When compared to Caucasian patients, African-American patients had a significantly lower MPRm value (0.56 vs. 0.65, $p < 0.001$). MDD patients with comorbid anxiety disorders had a significantly higher MPRm value than patients with MDD alone (0.71 vs. 0.59, $p<0.001$).

Table 4.5 shows the comparisons of MPRm between study subgroups by race and comorbid anxiety disorders. In Caucasians, MDD patients with comorbid anxiety disorders had a higher value of MPRm when compared with MDD patients without comorbid anxiety disorders (0.73 vs. 0.62, $p < 0.001$). Similarly, in African Americans, MDD patients with comorbid anxiety disorders had a higher value of MPRm than patients only with MDD (0.65 vs. 0.54, $p < 0.001$).

Using multivariate regression models, table 4.6 illustrates the associations of medication adherence with race, comorbid anxiety disorders, and the interaction between race and comorbid anxiety disorders. MPRm served as a continuous dependent variable modeled by a multivariate linear regression. Results showed that African Americans were negatively associated with MPRm value when holding all other variables in the model constant ($\beta = -0.09$, SE= 0.02, $p < 0.001$). The expected value of MRPm significantly

increased by 0.09 in MDD patients with comorbid anxiety disorders when compared to patients with MDD alone, after holding all other covariates constant in the model (β = 0.09, SE= 0.02, $p < 0.001$).

Table 4.6 also shows results from a multivariate logistic regression model. MPRm was further dichotomized as adherent (MPRm > 0.8) vs. non-adherent (MPRm ≤ 0.8). When compared with Caucasian patients, the expected odds of adhering to antidepressants was 40% lower in African-American patients than in Caucasian patients when holding all other covariates constant (OR = 0.6, 95% CI = 0.51-0.72, $p < 0.001$). The adjusted odds of adhering to antidepressants in MDD patients with comorbid anxiety disorders was 1.55 times greater than the adjusted odds in MDD patients without comorbid anxiety disorders, after adjusting for all other covariates in the model (OR=1.55, 95% CI = 1.27-1.90, $p< 0.001$). The interaction effect of race and comorbid anxiety disorders was not significantly associated with medication adherence in either the multivariate linear regression model or the multivariate logistic regression model.

Persistence

Figure 4.2 depicts the Kaplan-Meier survival curves of medication persistence between Caucasian and African-American patients. The Log-Rank test ($p<0.001$) shows the difference of equality of the two survival curves. African-American patients were less likely to persistently use antidepressants. Table 4.7 illustrates the comparisons of survival distribution between Caucasian and African-American patients. A greater proportion of Caucasian patients than their African-American cohorts tended to persistently use antidepressants during the study period (45.2% vs. 43.7%). The estimated median time

that patients persistently used antidepressants was longer in Caucasian patients when compared with African-American patients (248 days vs. 187 days).

Figure 4.3 and Table 4.8 illustrate the Kaplan-Meier survival curves and the comparisons of survival distribution of medication persistence between MDD patients with and without comorbid anxiety disorders. MDD patients with comorbid anxiety disorders more persistently used antidepressants than those without comorbid anxiety disorders (The Log-Rank test of homogeneity, $p<0.01$). Furthermore, when compared with MDD patients without comorbid anxiety disorders, MDD patients with comorbid anxiety disorders had a longer estimated median time of persistently using antidepressants. (237 days vs. 216 days).

The study results of the Cox-proportional hazards regression analysis are shown in Table 4.9. The hazard of non-persistent antidepressant use in African-American patients was 1.55 times greater than the hazard of non-persistent antidepressant use in Caucasian patients, after adjusting for all other covariates in the model (Hazard Ratio = 1.55, 95% CI = 1.38-1.75, $p < 0.001$).

Sensitivity analysis

Table 4.10 shows the result of the adherence rate by varying the range of cut-off points of MPRm from the 0.4 level to the 0.9 level. The adherence rate decreased when the cut-off points increased. The adherence rate dropped 4.9% when the cut-off point increased from the 0.7 level to the 0.8 level. The 4.9% drop was greater than any other drop when the cut-off point had a 0.1 point increase in the sensitivity analysis.

Discussion

Our study results show that African-American Medicaid enrollees with MDD were less likely than Caucasians to be adherent to and consistent with taking antidepressants. For medication adherence, the results of bivariate group comparisons and multivariate regression analyses all have shown that African-American patients were significantly less likely to be adherent to their antidepressants than their Caucasian cohorts. Results from survival analyses and Cox-proportional hazards regression analyses reveal African-American patients were less persistently taking antidepressants when compared to Caucasian patients.

The difference of antidepressant adherence and persistence between Caucasian and African-American patients could result from several different factors. Lower adherence in African-American patients may result from lower access to depressant treatment,[153] their being less likely to receive antidepressants,[21] their being less likely to use antidepressants,[154-155] and their perceiving less acceptability for antidepressant treatment.[147] For example, Alegria et al. conducted a study using nationally representative data to study the health disparity of depression among racial groups. They reported that close to 60% of African Americans with depressive disorders did not access health treatment, whereas only 40% of Caucasians did not do so.[153] Cooper et al. reported that African Americans found antidepressant treatments less acceptable than Caucasians did.[147] Additionally, lower antidepressant adherence and persistence in African Americans could result from negative attitudes or opinions toward depression treatment such as disease stigma.[156] Accordingly, the consequence of non-adherence would lower the quality of care of antidepressant treatment in African-American patients, and it could

also increase the disparity of antidepressant treatment between African Americans and Caucasians.

The results of our study also confirmed the association of having comorbid anxiety disorders with higher antidepressant adherence among Medicaid enrollees with MDD. In a study conducted by Stein et al., found patients with co-occurring depression and anxiety disorders were more likely to be adherent to their antidepressants than patients with only anxiety disorders.[152] However, our study found patients with MDD and comorbid anxiety disorders had higher antidepressant adherence rate than patients only with MDD alone. Furthermore, our study found a lower hazard of non-persistence in MDD patients with comorbid anxiety disorders although the result was not significant.

Having comorbid anxiety disorders in patients with MDD was associated with higher antidepressant adherence. This could result from several factors. The therapeutic effect of antidepressants can reduce symptoms of both depression and anxiety disorders. Patients with comorbid anxiety disorders had increased the severity of the depression symptoms.[7, 35-36] By taking antidepressants, patients with concurrent depression and anxiety disorders could perceive the symptoms release for both diseases and tend to be more adherent to their medications.

Results of the sensitivity analysis in our study show a deep drop in the adherence rate when the cut-off point was increased from 0.7 to 0.8. A study conducted Karve et al. has concluded that 0.8 is a reasonable cut-off point to measure medication adherence (MPR) when using administrative claim data.[127]

One of the original objectives of our study was to investigate the association between the interaction effect of race and comorbid anxiety disorders with antidepressant

adherence and persistence. However, the interaction effect was not significantly associated with adherence or persistence after adjusting for all other covariates in the regression models.

Finally, our study provided a high generalizability for the Medicaid population because the results were obtained from a comprehensive database which included Medicaid enrollees in eight states from 2003 to 2007. The high generalizability from the study findings of the Medicaid population could become thoughtful resources for health policy makers and health care providers. From mental health policy perspectives, the policy implications, which could reduce health disparities between African-American and Caucasian patients and could improve antidepressant use behaviors among Medicaid enrollees with MDD, needed to be stressed and implemented. For example, policy intervention could focus on increasing the number of minority mental health care providers who could have better cultural understanding and provide culturally appropriate treatment with minority patients.[157] With better cultural understanding, the stigmatization of depression could be reduced. Consequently, African-American patients could become more willing to take antidepressants, and the adherence and persistence rate could be increased. From clinical perspectives, health care providers needed to realize the influence of comorbid anxiety disorders on antidepressant use behaviors and improve adherence as well as persistence when they encountered Medicaid patients, especially for minority patients, with concurrent depression and anxiety disorders.

Our study has some limitations which deserve to be mentioned. Due to the nature of the administrative claim data, we were unable to incorporate variables such as beliefs or attitudes of antidepressant treatment, concerns of side effects, or behavioral intentions

of taking medication. Previous studies have confirmed the association between these variables and medication taking behaviors in patients with depression.[53, 158-159] Additionally, Medicaid enrollees can have difficulty to understand the complexity of medication treatment due to their lower educational background. Without fully understanding the treatment process, patients may have a higher chance of not adhering to their medications or of ceasing to take them. However, our data did not provide enrollees' educational background. Therefore, with unique patient characteristics in the Medicaid population, the adherence rate in our study population could still be overestimated even though they already had a lower adherence rate.

Furthermore, the basic assumption of measuring adherence using MPR is "a prescription filled is a prescription taken."[122] However, it is very difficult for investigators to tell whether patients indeed take the medicine after they refill. In the future, medication adherence could be more precisely measured if patients could fill out a survey instrument along with analyzing administrative claims.

Conclusion

In Medicaid enrollees with MDD, African-American patients were less likely than Caucasian patients to be adherent to antidepressants. In addition, African-American patients have lower medication persistence and a higher hazard of not persistently taking antidepressants. MDD patients with comorbid anxiety disorders had higher antidepressant adherence when compared with MDD patients without comorbid anxiety disorders. Future studies could investigate the difference of antidepressant adherence in other minority populations such as Latinos\Latinas or Asia Americans, as well as the influence of comorbid anxiety disorders on their medication use behaviors.

Acknowledgments

The authors would like to thank Ms. Yuhong Zhang (B.S.) in the Center for Medication Use, Policy and Economics (CMUPE) in the College of Pharmacy, at the University of Michigan for constructing files of the MarketScan® Multi-State Medicaid Database.

Disclosure

This study is a part of Mr. Wu's original doctoral dissertation. The title of the dissertation is "Interactive Associations of Race and Comorbidity in Medication Treatment and Outcomes of Medicaid Enrolled Patients with Major Depressive Disorder".

Figure 4.1 The Analytic Framework of Obtaining the Study Population.

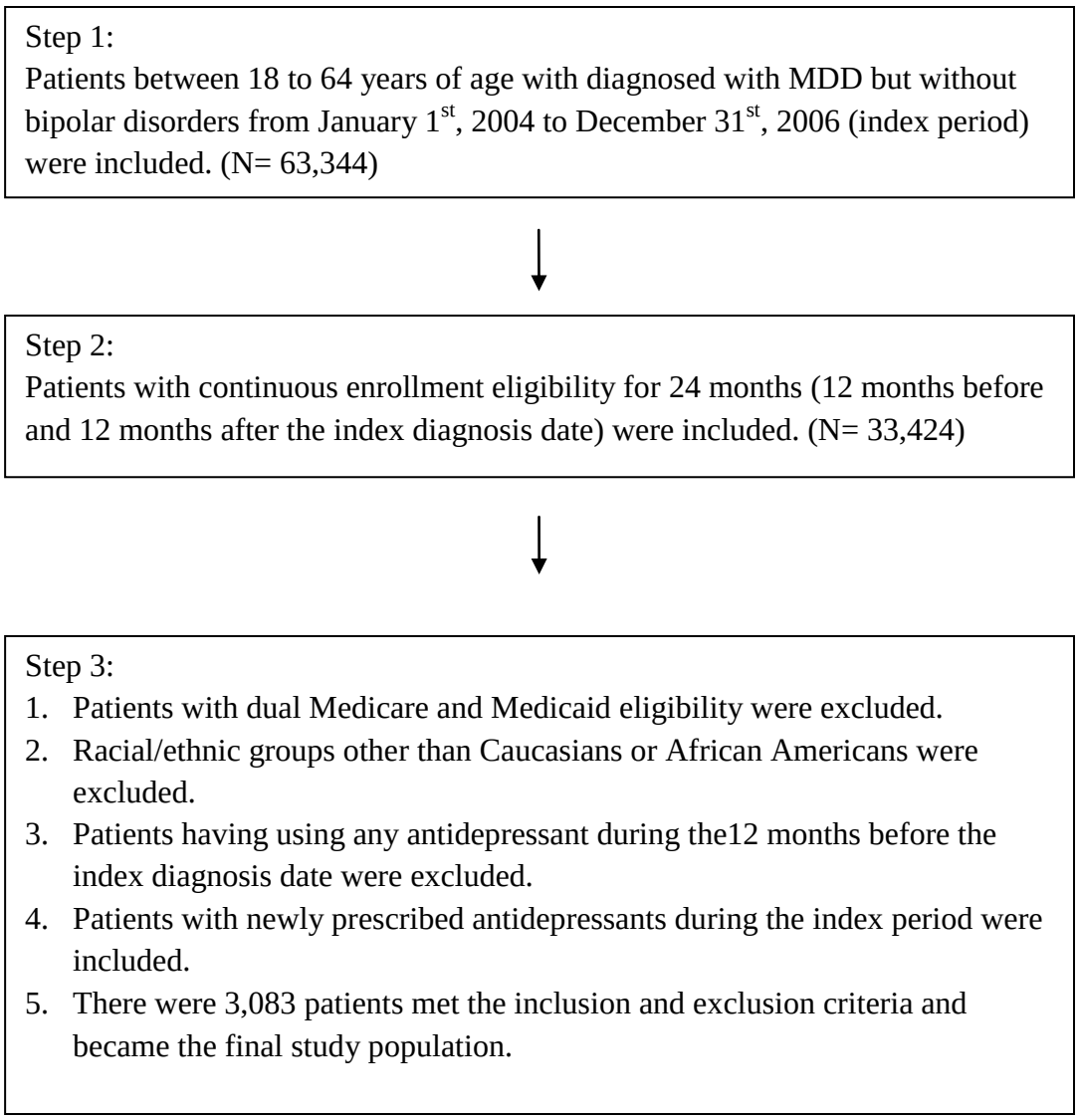
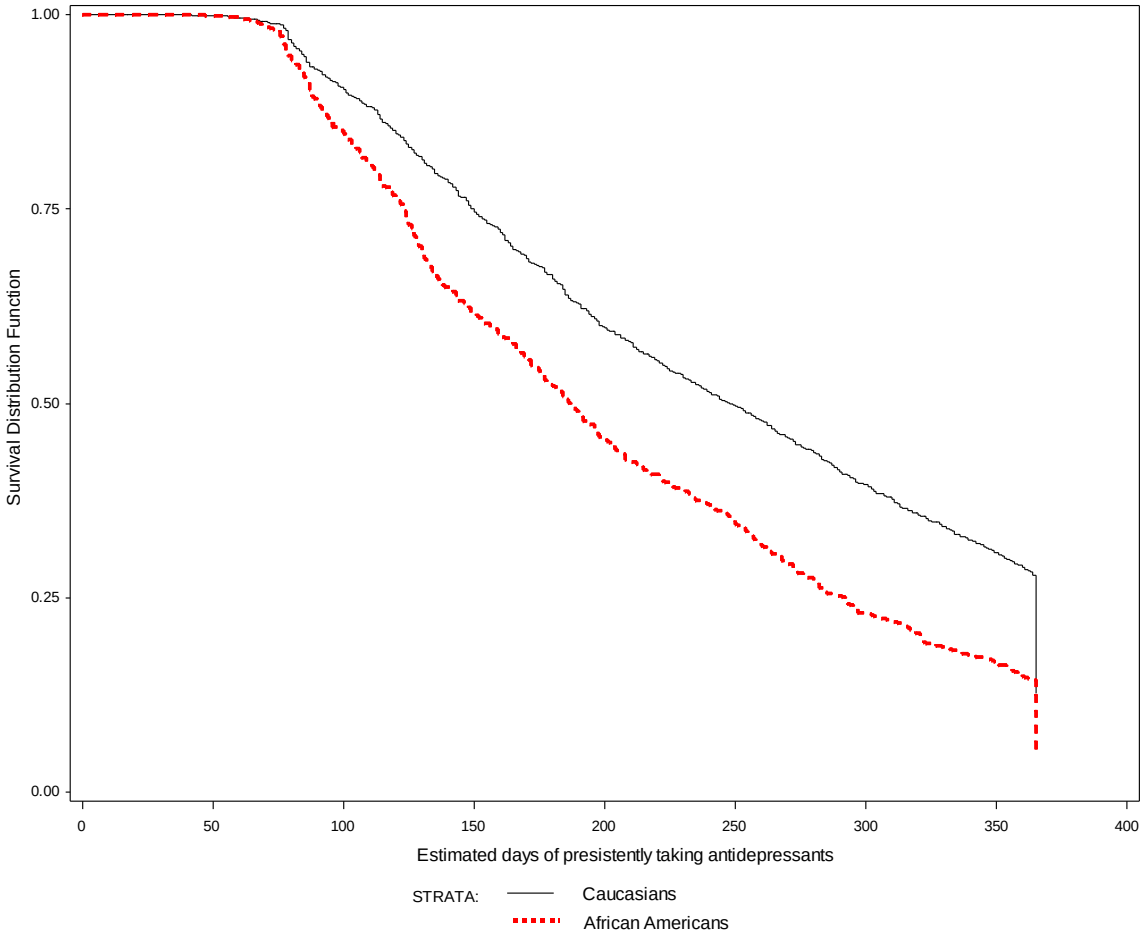
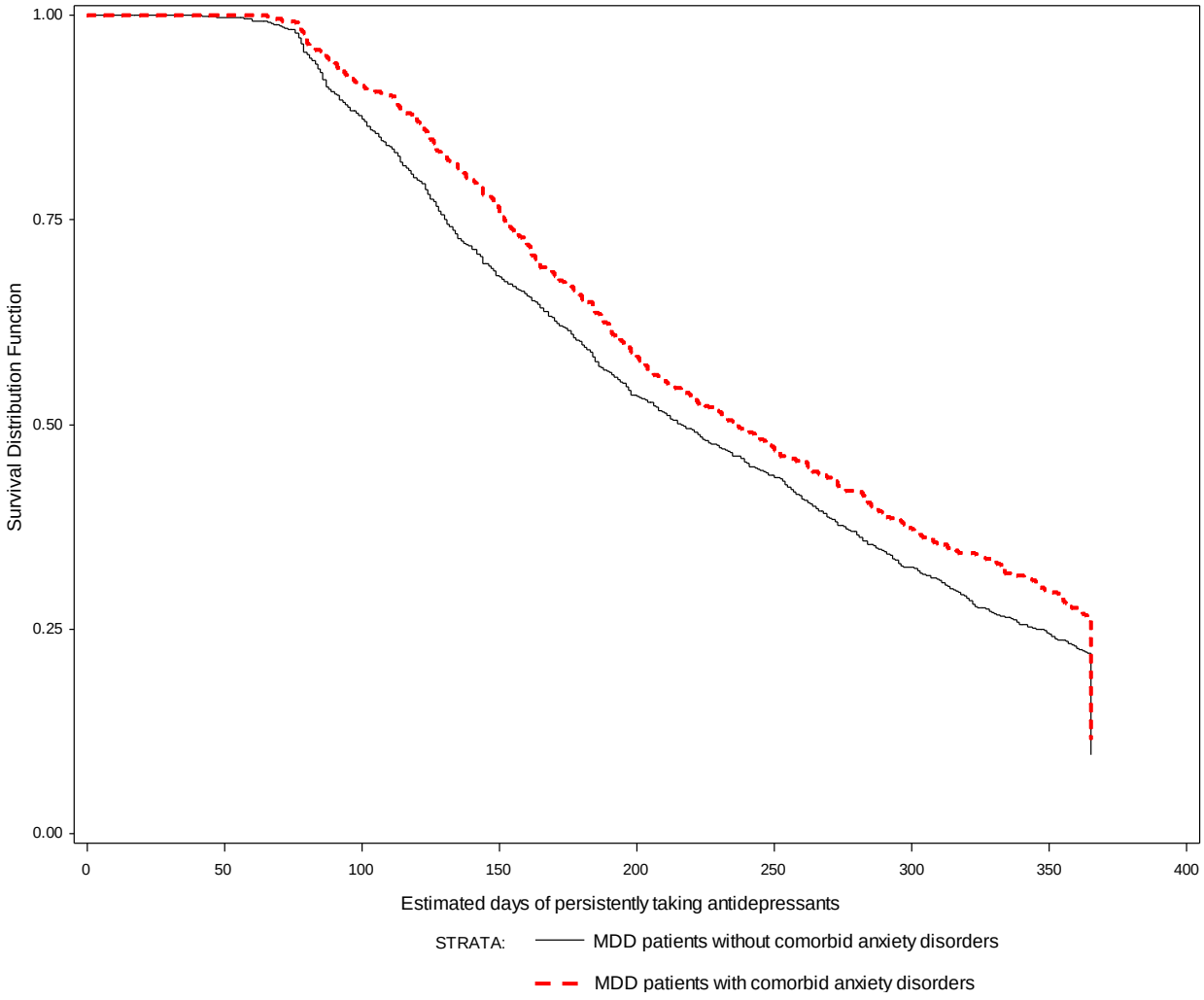


Figure 4.2 The Kaplan-Meier Survival Curves of Antidepressant Persistence between Caucasian and African-American Patients[§]



§: Log-Rank Test, $p<0.001$

Figure 4.3 The Kaplan-Meier Survival Curves of Antidepressant Persistence between MDD Patients with and without Comorbid Anxiety Disorders[§]



§: Log-Rank Test, $p<0.01$

Table 4.1 ICD-9-CM codes[#]

Diseases	Diagnoses	Codes[±]
Major Depressive Disorders	Major depressive disorder, single episode	296.2
	Major depressive disorder, recurrent episode	296.3
Bipolar Disorders	Bipolar affective disorder, manic	296.4x
	Bipolar affective disorder, depressed	296.5x
	Bipolar affective disorder, mixed	296.6x
	Bipolar affective disorder, unspecified	296.7x
	Manic-depressive psychosis, other	296.8x
Anxiety Disorders	Panic disorder without agoraphobia	300.01
	Panic disorder with agoraphobia	300.02
	Agoraphobia without history of panic disorder	300.22
	Social phobia (social anxiety disorder)	300.23
	Obsessive-compulsive disorder	300.30
	Post-traumatic stress disorder	309.81
	Acute stress disorder	308.30
	Generalized anxiety disorder	300.02
	Anxiety disorder due to general medical condition	293.89
	Anxiety disorder, not otherwise specified	300.00

#: ICD-9-CM is an abbreviation of International Classification of Diseases, Ninth Revision, Clinical Modification

±: An "x" means all sub-codes were included

Table 4.2 Patient Characteristics of the Study Population (N= 3,083)

Variables	Frequency	%
Age (years)		
18-30	1,250	40.5
31-40	817	26.5
41-50	641	20.8
51-60	325	10.5
61-64	50	1.6
Gender		
Male	699	22.7
Female	2,384	77.3
Race		
Caucasian	1,958	63.5
African American	1,125	36.5
Comorbidity (Elixhauser Index)		
0	860	27.9
1	804	26.1
2	559	18.1
≥3	860	27.9
Comorbid anxiety disorders		
Yes	776	25.2
No	2,307	74.8
Comorbid painful symptoms		
Yes	1,437	46.6
No	1,646	53.4
FFS vs. Capitation		
FFS	1,893	61.4
Capitation	822	26.7
Dual	368	11.9
Hospitalization during pre-study period		
Yes	833	27.0
No	2,250	73.0
ER visits during the pre-study period		
Yes	1,846	59.9
No	1,237	40.1
Outpatient Mental Health Facilities		
Yes	342	11.1
No	2,741	88.9
Outpatient psychiatric services		

Yes	469	15.2
No	2,614	84.8
Inpatient psychiatric services		
Yes	206	6.7
No	2,877	93.3

Table 4.3. Comparisons of Comorbid Anxiety Disorders by Race (N=3,083)

	Comorbid Anxiety Disorders				
	With (N=776)		Without (N=2,307)		
Variables	Frequency	%¤	Frequency	%¤	P-value±
Race					<0.01
Caucasians	592	30.2	1,366	69.8	
African Americans	184	16.4	941	83.6	

¤: Row percentages

±: Chi-square test

Table 4.4 Comparisons of Medication Possession Ratio by Race and Comorbid Anxiety Disorders, Respectively (N=3,083)[§]

	Caucasian (N=1,958)		African American (N=1,125)		Comorbid anxiety disorders (no) (N=2307)		Comorbid anxiety disorders (yes) (N=776)	
Variables	Mean	SD	Mean[#]	SD	Mean	SD	Mean[¤]	SD
MPRm[Ω]	0.65	0.39	0.56***	0.40	0.59	0.40	0.71***	0.37

Ω: Medication Possession Ratio modified

§: MPRm of the study population is 0.62

#: Student's T-test of MPRm between Caucasian and African American

¤: Student's T-test of MPRm between MDD patients with and without comorbid anxiety disorders

Note: * p < 0.05, ** p < 0.01, *** p < 0.001

Table 4.5 Comparisons of Medication Possession Ratio between Subgroups by Race and Comorbid Anxiety Disorders[§]

	Caucasian				African American			
	Comorbid anxiety disorders (no) (N=1,366)		Comorbid anxiety disorders (yes) (N=592)		Comorbid anxiety disorders (no) (N=941)		Comorbid anxiety disorders (yes) (N=184)	
Variables	Mean	SD	Mean[#]	SD	Mean	SD	Mean[#]	SD
MPRm[Ω]	0.62	0.40	0.73***	0.36	0.54	0.39	0.65***	0.38

Ω: Medication Possession Ratio modified

§: MPRm of the study population is 0.62

#: T-test between patients with and without comorbid anxiety disorders in Caucasians and African Americans, respectively

Note: * p < 0.05, ** p < 0.01, *** p < 0.001

Table 4.6 Factors Associated with Antidepressant Adherence in Medicaid Enrollees with Major Depressive Disorders: Multivariate Linear Regression Model and Multivariate Logistic Regression Model (N=3,083)

	Adherence			
	MPRm[#]		Odds ratio for medication adherence (80% of MPRm)[±]	
Variables	β coefficient	SE	Odds Ratio	95% CI
Race				
African American	-0.09	0.02***	0.60	(0.51–0.72)***
Caucasians	Reference	Reference	Reference	Reference
Comorbid anxiety disorders				
Yes	0.09	0.02***	1.55	(1.27–1.90)***
No	Reference	Reference	Reference	Reference
Interaction between race and comorbid anxiety disorders	0.00	0.04	1.09	(0.75–1.60)
Age (years)				
18-30	Reference	Reference	Reference	Reference
31-40	0.06	0.02***	1.39	(1.15–1.67)***
41-50	0.10	0.02***	1.73	(1.40–2.14)***
51-60	0.10	0.03***	1.90	(1.45–2.49)***
61-64	0.13	0.06*	1.91	(1.05–3.46)**
Gender				
Male	Reference	Reference	Reference	Reference
Female	0.03	0.02	1.09	(0.91–1.31)
Comorbid painful symptoms				
Yes	0.03	0.01*	1.16	(0.99–1.35)
No	Reference	Reference	Reference	Reference
Comorbidity (Elixhauser Index)				
0	Reference	Reference	Reference	Reference
1	0.01	0.02	1.02	(0.83–1.25)
2	0.04	0.02	1.30	(1.03–1.63)*
≥3	0.07	0.02**	1.34	(1.06–1.69)*
FFS vs. Capitation				
FFS	Reference	Reference	Reference	Reference
Capitation	-0.01	0.02	0.97	(0.81–1.15)
Dual	-0.01	0.02	1.00	(0.79–1.26)
Hospitalization during pre-				

study period				
Yes	0.01	0.02	1.09	(0.92−1.29)
No	Reference	Reference	Reference	Reference
ER visits during the pre-study period				
Yes	-0.03	0.02	0.84	(0.71−0.98)*
No	Reference	Reference	Reference	Reference
No. of prescriptions used during the pre-study period	0.00	0.00	1.01	(0.99−1.02)
Constant	0.49	0.04	0.55	(0.37−0.79)**
Adjusted R^2	0.05		0.04	

Note: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

#: Multivariate linear regression analysis

±: Multivariate logistic regression analysis

Table 4.7 Comparisons of Survival Distributions between Caucasian and African-American Patients with MDD (N=3,083)[Ω]

Variables	Caucasian (N=1,958)	African American (N=1,125)
Censored (cases, %)[#¤]	885 (45.2%)	492 (43.7%)
Median time (days, 95%CI)[§]	248 (235-262)	187 (176-197)

#: No. of patients who persistently used antidepressants until the end of the follow-up period

¤: The follow-up period is one year (365 days)

§: Estimated median time that patients persistently used antidepressants

Ω: Log-Rank test, p<0.001

Table 4.8 Comparisons of Survival Distributions between MDD Patients with and without Comorbid Anxiety Disorders (N=3,083)[Ω]

Variables	Comorbid anxiety disorders (no) (N=2307)	Comorbid anxiety disorders (yes) (N=776)
Censored (cases, %)[#¤]	1,079 (46.8%)	298 (38.4%)
Median time (days, 95%CI)[§]	216 (206-230)	237 (216-256)

#: No. of patients who persistently used antidepressants until the end of the follow-up period

¤: The follow-up period is one year (365 days)

§: Estimated median time that patients persistently used antidepressants

Ω: Log-Rank test, p<0.01

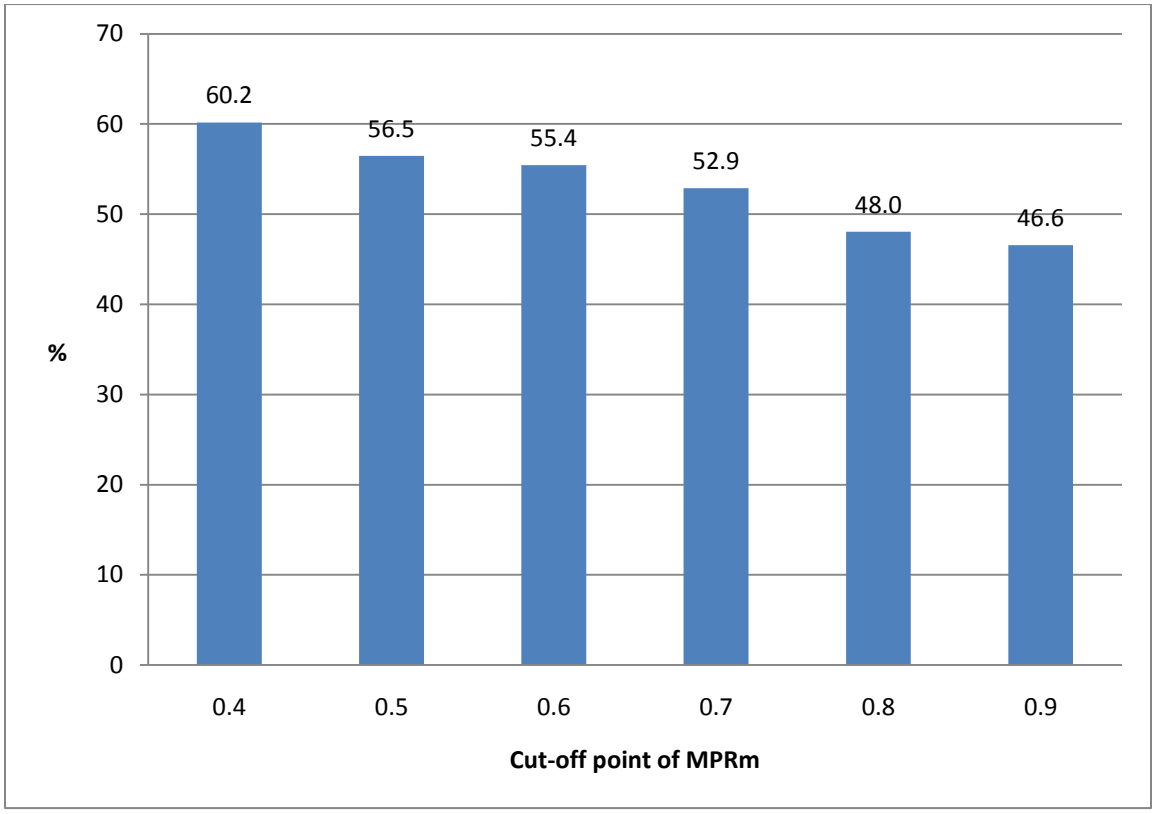
Table 4.9 Factors Associated with Antidepressant Persistence in Medicaid Enrollees with Major Depressive Disorders: Cox-proportional Hazard Regression Analysis (N=3,083)

	Cox Propositional Hazard Analysis	
	Hazard Ratio	95% CI
Variables		
Race		
African American	1.55	(1.38−1.75)***
Caucasian	Reference	Reference
Comorbid anxiety disorders		
Yes	0.93	(0.82−1.06)
No	Reference	Reference
Interaction between race and comorbid anxiety disorders	0.85	(0.67−1.09)
Age (years)		
18-30	Reference	Reference
31-40	0.88	(0.78−0.99)*
41-50	0.82	(0.71−0.93)**
51-60	0.56	(0.47−0.68)***
61-64	0.82	(0.57−1.19)
Gender		
Male	Reference	Reference
Female	1.21	(1.07−1.36)**
Comorbid painful symptoms		
Yes	1.02	(0.92−1.13)
No	Reference	Reference
Comorbidity (Elixhauser Index)		
0	Reference	Reference
1	0.89	(0.77−1.02)
2	0.91	(0.78−1.06)
≥3	0.90	(0.77−1.05)
FFS vs. Capitation		
FFS	Reference	Reference
Capitation	1.07	(0.95−1.20)
Dual	1.06	(0.91−1.23)
Hospitalization during pre-study period		
Yes	1.01	(0.90−1.13)
No	Reference	Reference
ER visits during the pre-study period		

Yes	1.19	(1.07−1.32)**
No	Reference	Reference
No. of prescriptions used during the pre-study period	0.99	(0.98−1.00)

Note: * p < 0.05, ** p < 0.01, *** p < 0.001

Table 4.10 Results of Sensitivity Analysis for Adherence



CHAPTER 5

MANUSCRIPT TWO

Title: Association of Race and Comorbid Anxiety Disorders on Health Care Utilization in Medicaid Enrollees with Major Depressive Disorders

Abstract

Background:

Comorbid anxiety disorders commonly occur in patients with depression. Treatment disparities of depression between African Americans and Caucasians still exist. Few studies have investigated the influence of race and comorbid anxiety disorders on health care utilization among Medicaid patients with major depressive disorders (MDD).

Objective:

The objective of this study is to examine the association of race, comorbid anxiety disorders, and the interaction effect between race and comorbid anxiety disorders with health care utilization among Medicaid patients with MDD.

Methods:

The study was a retrospective cohort study using the MarketScan® Multi-State Medicaid Database to identify patients with MDD who received an antidepressant between January 1, 2004 and December 31, 2006. An index diagnosis date was assigned to each patient. The inclusion criteria included patients between 18 and 64 years of age, with 12 months continuous eligibility before and after the index diagnosis date, and with no use of antidepressants during the 12 months before the index diagnosis date. Patients with bipolar disorders and dual eligibility in Medicaid and Medicare were excluded. Measures of health resource utilization included mental health-related and overall health care utilization (office visits, hospitalization, ER visits, and health care costs). The probability of office visits, ER visits, and hospitalization, was assessed using multivariate logistic regression models. Multivariate negative binominal regression analyses were used to examine the rate of change of office visits, ER visits, and hospitalization. Multivariate linear regressions with log-transformed costs were used to assess predictors of health care costs.

Results:

A total of 3,083 patients were included in this study. Approximately, 25% of patients had comorbid anxiety disorders. After controlling for covariates, comorbid anxiety disorders were significantly associated with more frequent mental health-related office visits, hospitalization, ER visits, and higher costs. When compared to Caucasian patients, African Americans were significantly less likely to have mental health related office visits but more likely to be hospitalized and have ER visits. The interaction effect (being

African American and having comorbid anxiety disorders) reduced the individual association with health care utilization.

Conclusion:

Comorbid anxiety disorders increased health care utilization and costs in adult Medicaid patients with MDD. Health disparities in health care utilization between African American and Caucasian patients still exist in the Medicaid population with MDD.

Key words: administrative data, comorbid anxiety disorders, health care utilization, major depressive disorders, Medicaid, race.

Introduction

Major depressive disorder (MDD) is among the most prevalent mental illnesses in the United Sates. Its annual prevalence rate was estimated to be 6.7% in 2003,[1] and its lifetime prevalence rate has reached as high as 16.2%[2] based on the results of the National Comorbidity Survey-Replication (NCS-R).[1-2] Patients with MDD can simultaneously have other mental illnesses, and anxiety disorders have been reported as the most common comorbid psychiatric illnesses in patients with MDD.[25-26] An estimated 40%-60% of lifetime MDD patients are reported to have comorbid anxiety disorders.[6, 25]

Numerous studies have shown that MDD patients with comorbid anxiety disorders have significantly poorer health outcomes.[35-36, 38-40] For example, depressed patients with comorbid anxiety disorders can have less treatment improvement and need a longer time to recover when compared with patients with depression alone.[39-40] The

presence of comorbid anxiety disorders significantly impedes the clinical progress of depressive symptoms in depressed patients.[35] Furthermore, MDD patients with comorbid anxiety disorders have a greater risk of developing persistent depression, more depressive symptoms, more impaired health status, and worse disability than patients with MDD alone.[36, 38]

Although the lifetime prevalence of anxiety disorders in African-American patients is lower when compared with Caucasian patients, the disease burden of anxiety disorders is more persistent among African American patients.[160] Additionally, African American patients with anxiety disorders are more likely to be functionally impaired and have higher disease severity when compared with Caucasian patients.[161]

Pharmacotherapy usually is the first-line option of treatment for patients with MDD and anxiety disorders. However, treatment disparities between Caucasian and African American patients still exist. Several studies have shown that African-American patients are less likely to receive medication treatment when compared with Caucasians.[14, 17-23] For example, using data from the National Ambulatory Medical Care Survey (NAMCS), Sclar et al. have found the antidepressant treatment rate in African American patients was less than half the treatment rate in Caucasian patients.[18] Other studies have also shown that African American patients with MDD were less likely to receive antidepressant treatment,[22] to have an antidepressant prescription,[21] or to receive effective acute-phase treatment or continuation-phase treatment.[23]

Previous studies have examined the impact of concurrent depression and anxiety disorders on health care utilization, and the results have shown that patients with both depression and anxiety disorders have greater health care utilization when compared with

patients with depression or anxiety disorders alone.[152, 162-163] However, limited studies have investigated such an impact specifically on Medicaid enrollees with MDD. Additionally, little is known about the impact of the association between race and comorbid anxiety disorders on health resource utilization. Given the high prevalence of comorbid anxiety disorders in patients with MDD, and treatment disparities of antidepressants between Caucasian and African American patients, it is important to comprehensively understand the influence of race and comorbid anxiety disorders on health resource utilization in Medicaid enrollees with MDD.

The objective of this study was to investigate the association of race, comorbid anxiety disorders, and the interaction between race and comorbid anxiety disorders with health care utilization among Medicaid enrollees with MDD. Using The MarketScan® Multi-State Medicaid Database,[120] we evaluated whether MDD patients with comorbid anxiety disorders by different racial groups (Caucasians and African Americans) have higher mental health-related health care utilization than MDD patients without comorbid anxiety disorders. We further investigated whether the association among race, comorbid anxiety disorders, their combined interaction effect, and health care utilization persisted after adjusting for select confounders.

Method

Data sources

Data were obtained from the MarketScan® Multi-State Medicaid Database,[120] which is a pooled Medicaid asset set from eight geographically dispersed states in the U.S.[120] The MarketScan® Multi-State Medicaid Database contains a variety of disease conditions, clinical variables, and key demographic variables.[120] The data also include

claims of enrollment information, inpatient and outpatient services, and prescriptions.[120] Clinical diagnoses are in ICD-9-CM format.[120] A confidential enrollee identifier is used to track individual patients longitudinally, and the identifier of each patient is identical across different sections of claims.[120]

Sample selection

This was a retrospective cohort study. The study duration was from January 1st, 2003 to December 31st, 2007. Patients aged between 18 to 64 years, who were diagnosed with MDD (see Table 5.1 for a complete list of ICD-9-CM codes) and who were prescribed at least one new antidepressant between January 1st, 2004 and December 31st, 2006, were identified from the database. The study excluded patients with bipolar disorders (Table 5.1) because antidepressants can also be used to treat patients with bipolar disorders. Each patient who met inclusion and exclusion criteria was assigned an index diagnosis date. (Table 5.1)

In order to obtain drug naïve patients, a 12-month pre-study period before the index diagnosis date, was used for verifying new antidepressant users. Patients who had a claim of using antidepressants during the pre-study period were excluded. The same 12-month pre-study period was also used to determine maintained continuous Medicaid eligibility. Overall, patients should have a 24- month (12 months before and 12 months after the index diagnosis date) continuous eligibility to be included in the study population. Finally, patients who had dual Medicare and Medicaid eligibilities were excluded in this study. After incorporating all inclusion and exclusion criteria, 3,083 patients were included in the study. These patients were followed for one year to examine their health care utilization.

Study variables

Dependent variables

The dependent variables of this study were mental health-related health care utilization and overall health care utilization. Health care utilization included office visits, hospitalization, Emergency Room (ER) visits, and health care costs. The dependent variables were assessed over a 12-month period after the index diagnosis date. The term "mental health-related" was defined as patients having at least one primary or secondary diagnosis of a mental illnesses. These illnesses included schizophrenia (295.xx), depression (296.2x, 296.3x, 296.9x, 300.4x, 309.0x, or 311.xx), anxiety (300.0x, 300.2x, 300.3x, 306.9x, 308.xx, 309.2x, 309.4x, or 309.9x), other psychoses (297.xx, 298.xx, 299.xx, 300.1x, 302.8x, or 307.9x), and dementia (290.xx, 291.2x, 310.9x, or 331.0).[131] Any patient-utilization related to the above ICD-9-CM codes was defined as mental health-related health care utilization. For example, a mental health-related office visit, coded as dichotomous (yes/no), was determined by whether patients had an office visit related to any of the above mental illnesses during the study period. Similarly, mental-health related hospitalization and mental health-related ER visits were also categorized as a dichotomous variable.

Health care costs also served as a dependent variable in this study. Overall health care cost was defined as patients' total health care expenditures during the study period. Mental health-related health care costs were patients' health care expenditures related to mental illnesses which were identified by the above ICD-9-CM codes.

Key independent variables

Race, comorbid anxiety disorders, and the interaction between race and comorbid anxiety disorders were three tested independent variables in the study. Race was self-reported information obtained from patients when they were first enrolled in the Medicaid program. It was categorized as either Caucasian or African American. Comorbid anxiety disorders were identified based on medical claims of any anxiety disorder diagnosis (Table 5.1) during the 12-month study period after the index diagnosis date. MDD patients with a diagnosis of anxiety disorders were classified as having comorbid anxiety disorders. The interaction term is the interaction effect between race and comorbid anxiety disorders. MDD prevalence was different between Caucasian and African American patients. However, race might not be able to fully explain the difference of medication use-related outcomes without accounting for comorbid anxiety disorders because of the high prevalent rate of concurrent anxiety disorders in patients with MDD. Therefore, the interaction effect became a key tested independent variable in our study.

Covariates

Covariates in this study were determined by using Andersen's Behavioral Model of Health Services Use.[59, 108] In the model, health care utilization is considered to be associated with predisposing, enabling, and need factors.[59, 105-106, 108] In this study, predisposing factors included age (categorized as 18-30, 31-40, 41-50, 51-60, and 61-64) and gender. Enabling factors refer to certain conditions that allow an individual to be able to access health care.[105-106] The enabling factor of this study was the type of the health plan, categorized as fee-for-service, capitation, dual. Need factors included whether patients had comorbid painful symptoms (yes/no), the number of prescriptions used

during the pre-study period, hospitalization during the pre-study period, and ER visits during the pre-study visit. The Medication Possession Ratio, modified (MPRm), which takes the last day supply into consideration, was used to assess patients' medication adherence to antidepressants.[124] The MPRm, serving as a covariate in the study, was further categorized using 0.8 value of MPRm as a cut-off point into a dichotomous variable: adherent (MPRm > 0.8) vs. non-adherent (MPRm ≤ 0.8).[127] This study utilized the Elixhauser comorbidity index (categorized as 0, 1, 2, and 3^{+}) to control for overall severity of illness in the study population.[133] The Elixhauser comorbidity index, a comprehensive set of comorbidity indices containing 30 different diseases, was designed to measure comorbidity for predicting hospitalization and in-hospital mortality using administrative data.[133]

Statistical analyses

The statistical analyses started with descriptive statistics (frequencies), which included the calculation of patients' characteristics in the study sample. Differences in patients' characteristics between MDD patients with and without comorbid anxiety disorders were further assessed using chi-square tests.

Next, comparisons of health care utilization (office visits, hospitalization, and ER visits) between patients with comorbid anxiety disorders and patients with MDD alone for both Caucasian and African American were examined using Student's t-tests. Similarly, comparisons of health care costs (mental health-related health care costs and overall health care costs) between patients with comorbid anxiety disorders and patients with MDD alone for both Caucasian and African American were examined using Student's t-tests.

Finally, multivariate regression analyses were conduced to evaluate the association between mental health related health care utilizations (dependent variables), and race, comorbid anxiety disorders, and their interaction (key independent variables) after adjusting for other covariates. For modeling health care utilization, multivariate logistic regression analyses were first used to estimate the probability of any event of health care utilization. Then, multivariate negative binominal regression analyses were used to estimate the level change of health care utilization among patients having at least one event of health care utilization. Multivariate linear regression analyses were used to model the health care costs as a function of race, comorbid anxiety disorders, the interaction effect, and other covariates. Health care costs were log-transformed.

In this study, data management was performed using SAS v.9.2 (SAS Institute, Cary, NC).[145] All statistical analyses were computed using Stata 11 (StataCorp LP, College Station, Texas).[146] Two-tailed tests and a 0.05 level of significance were used to determine statistical significance. The study protocol was approved by the Institutional Review Board (IRB) at the University of Michigan.

Results

Table 5.2 shows the characteristics of the study population. Of the 3,083 Medicaid enrollees with MDD, approximately 41% were aged between 18 and 30, 77% were female, 37% were African American, 61% were with fee-for-service health plan, 25% had comorbid anxiety disorders, and 47% had comorbid painful symptoms. About 27% of the population had been hospitalized, and 60% had at least one ER visit in the pre-study period. (Table 5.2)

Table 5.3 shows the chi-square comparison of characteristics between MDD patients with and without comorbid anxiety disorders. Females were more likely to have comorbid anxiety disorders than males (26.2% vs. 21.8%, $p < 0.05$). Compared with Caucasian patients, African-American patients were less likely to have comorbid anxiety disorders (16.4% vs. 30.2%, $p < 0.01$). Patients who had comorbid painful symptoms (32.6% vs. 18.7%, $p < 0.01$), and had at least one ER visit in the pre-study period (27.0% vs. 22.4% $p < 0.01$) were also more likely to have comorbid anxiety disorders. (Table 5.3).

Table 5.4 illustrates the mean differences of health care utilization between MDD patients with and without comorbid anxiety disorders by different racial/ethnical groups. In both Caucasians and African Americans, patients with comorbid anxiety disorders had a significantly higher number of mental health-related office visits and mental health-related ER visits than patients without comorbid anxiety disorders. In Caucasians, patients with comorbid anxiety disorders also had a significantly greater number of mental health-related hospitalizations than patients without comorbid anxiety disorders (0.19 vs. 0.07, $p < 0.01$). For overall health care utilization, patients with comorbid anxiety disorders had a higher number of office visits, hospitalizations, and ER visits in both racial groups. Caucasian patients with comorbid anxiety disorder also had a higher number of hospitalizations than patients without anxiety disorders (0.55 vs. 0.33, $p < 0.01$).

Table 5.5 illustrates the association among mental health-related health care utilization, race, comorbid anxiety disorders, and the interaction effect in the Medicaid patients with MDD. For mental health-related office visits, the adjusted odds of having a

mental health-related office visit in patients with comorbid anxiety disorders is 2.27 times greater than the adjusted odds of having a mental health-related office visit in patients without comorbid anxiety disorders when holding race, the interaction, age, gender, comorbid painful symptoms, comorbidity, type of health plans, previous hospitalization, previous ER visits, number of prescriptions used, and medication adherence constant (OR =2.27, 95% CI = (1.85-2.78), p <0.01). The adjusted odds of having a mental health-related office visit was significant lower in African-American patients when compared with the adjusted odds of having a mental health-related office visit in Caucasian patients, after holding all other covariates in the model constant (OR = 0.54, 95% CI = 0.45-0.66, p < 0.001). Furthermore, the expected number of mental health-related office visits in patients with comorbid anxiety disorders was 1.11 times the expected number of mental health-related office visits in patients without comorbid anxiety disorders (RR = 1.11, 95% CI = 1.02-1.21, p < 0.05). When compared with Caucasian patients, the expected number of mental health-related office visits decreased by 20% (RR =0.80, 95% CI = 0.72-0.88, p < 0.001) in African-American patients, holding all other covariates constant.

For mental health-related hospitalization, African-American patients were 2.57 times more likely to have at least one hospitalization when compared with Caucasian patients holding all covariates in the model constant (OR = 2.57, 95% CI=1.84-3.60, p < 0.001). The adjusted odds of hospitalization in patients with comorbid anxiety disorders were 1.82 times greater than the adjusted odds of hospitalization in patents without comorbid anxiety disorders (OR = 1.82, 95% CI=1.25-2.67, p < 0.01). The interaction between race and comorbid anxiety disorders was significant. Being African American

with a comorbid anxiety disorder reduced the probability of being hospitalized (OR = 0.32, 95% CI =0.16-0.65, $p < 0.01$).

For mental health-related ER visits, the odds of having an ER visit for African American patients were 1.52 times greater than the odds of having an ER visit for Caucasian patients after adjusting for all other covariates (OR = 1.52, 95% CI = 1.05-2.19, $P < 0.05$). Patients with comorbid anxiety had significantly greater odds of having an ER visit when compared with patients without comorbid anxiety disorders, holding all other covariates constant (OR=4.39, 95% CI =3.13-6.15, $p < 0.01$).

Table 5.6 illustrates the relationships among overall health care utilization, race, comorbid anxiety disorders, and the interaction effect in the study. The adjusted odds of having an office visit for African Americans was 50% lower than the adjusted odds of having an office visit for Caucasians, holding all other covariates in the model constant (OR = 0.50, 95%CI = 0.39-0.46, $p < 0.001$). When compared with Caucasian patients, the expected number of office visits in African-American patients was 15% lower (RR=0.85, 95% CI = 0.79-0.91, $p < 0.001$). The expected number of office visits in patients with comorbid anxiety disorders was 16% higher than the expected number of office visits in patients without comorbid anxiety disorders (RR=1.16, 95% CI=1.08-1.25, $P< 0.001$).

The odds of being hospitalized in African-American patients was 1.42 times greater than the odds of Caucasian patients being hospitalized after adjusting for all the covariates in the model (OR=1.42, 95% CI=1.15-1.76, $p < 0.01$).

For ER visits, MDD patients with comorbid anxiety disorder were 42% -more likely to have an ER visit when compared with MDD patients without comorbid anxiety disorders (OR = 1.42, 95% CI = 1.14-1.77, $p<0.01$). Considering the interaction effect,

African-American patients having comorbid anxiety disorders were less likely to have an ER visit (OR = 0.61, 95% CI= 0.40-0.92, P<0.05).

Table 5.7 shows the log-transformed mental health-related health care costs and overall health care costs, and their association with race, comorbid anxiety disorders, and the interaction effect. African-American patients had 34% higher mental health-related health care costs than Caucasian patients after adjusting for all other covariates in the regression model ($\beta = 0.34$, $p < 0.001$). Patients with comorbid anxiety disorders had significantly higher more mental health-related health care costs (27%) when compared with patients without comorbid anxiety disorders ($\beta = 0.27$, $p < 0.001$). For the interaction effect, African-American patients having comorbid anxiety disorders was negatively associated with mental health-related health care costs ($\beta = -0.33$, $p < 0.001$). For overall health care costs, race appeared to be significantly associated with the change of overall health care costs after adjusting for all other covariates in the model. African-American patients averaged 17% greater overall health care costs than Caucasian patients ($\beta = 0.17$, $p < 0.001$).

Discussion

In this study, approximately 25% of Medicaid enrollees with MDD also had comorbid anxiety disorders. Although the rate of comorbid anxiety disorders among patients with MDD was lower than the epidemiologic findings from previous studies,[6, 25-26] our study provides unique finding of the prevalence of comorbid anxiety disorders among Medicaid enrollees with MDD.

Additionally, in our study population, more than 45% of patients had comorbid painful symptoms, and about 27% and 60% of the patients had either a hospitalization or

an ER visit, respectively, in the pre-study period. These study results also illustrate the poorer health status and higher health resource utilization among Medicaid enrollees with MDD.

From the results of chi-square tests and multivariate regression analyses in our study, comorbid anxiety disorders consistently presented positively influenced all mental health-related overall health care utilizations as well as health care costs. After controlling for confounders, patients with comorbid anxiety disorders had significantly greater opportunity to utilize more mental health-related office visits, hospitalizations, and ER visits when compared with patients without comorbid anxiety disorders. Furthermore, among patients having utilized health care resources, comorbid anxiety disorders were positively associated with an increased rate of mental health-related and overall office visits.

Our findings about the influence of comorbid anxiety disorders on health care utilization and costs were consistent with previous studies.[152, 162-163] When compared with patients with depression or anxiety disorders alone, patients with co-occurred depression and anxiety had higher health resource utilization.[152, 162-163] The higher health care utilization in patients with co-occurred depression and anxiety disorders can result from the increased disease severity of depression in MDD patients also experiencing anxiety disorders. [35-36, 38-40] Inevitably, higher health resource utilization resulted in increased mental health-related health care costs among MDD patients with comorbid anxiety disorders.

Although African American patients with MDD were less likely to have comorbid anxiety disorders when compared with their Caucasian cohorts, our findings suggest that

they were more likely to having mental health-related hospitalization and ER visits, and overall hospitalization after controlling for confounders in the regression models. African American patients also consumed more health care costs. Our study results also show that African-American patients were significantly less likely to have office visits when compared with Caucasians patients. Fewer office visits could result in fewer opportunities to obtain high quality care. Without having appropriate treatment, African-American patients could eventually have a higher rate of mental health–related hospitalizations and ER visits. Based on our findings, health disparities of mental health care between African Americans and Caucasians among Medicaid patients with MDD still exist.

Our study results reveal a significant association between the interaction effect of race and comorbid anxiety disorders, and mental health-related hospitalization and costs. African-American patients with comorbid anxiety disorders reduced the influence of individual effects (race or having comorbid anxiety disorders) on health care utilization. Medicaid enrollees had unique patient characteristics. Due to lower educational background and lower socioeconomic status, these patients may not be able to access mental health care and obtain appropriate treatment. For these patients, difficulty in accessing health care and not understanding how to use health care resources may illustrate a negative association between the interaction effect and health care utilization. Therefore, the interaction term (being African American and having comorbid anxiety disorders) represents a reduced effect for the health care utilization.

Our study results also provide insights for health care policy makers especially when considering the policy implications on Medicaid enrollees with MDD. Polices

which can reduce health disparities between African-American and Caucasian patients with MDD need to be stressed and implemented. For example, Policy intervention should focus on reducing the barrier and increasing access to mental health care providers especially for African-American patients. This could reduce the mental health-related hospitalization or ER visits which result in high health resource utilization.

Form clinical perspectives, health care providers need to be aware of the high prevalence rate of comorbid anxiety disorders among patients with MDD, and realize the impact of comorbid anxiety disorders on health care utilization when treating Medicaid enrollees with MDD. For example, routine screening for depression and anxiety disorders, especially for African-American patients, in mental health care setting is necessary.[157] Furthermore, health care providers need to actively inquire patients' somatic symptoms because African-American patients might express their depressive symptoms as somatic discomfort.[164]

Finally, one of the uniqueness must be emphasized of our study is that we implemented Andersen's Behavioral Model of Health Services Use[59, 108] for the variable selection to evaluate factors associated with health care utilization in our study population. Using the Andersen's model allowed us to control predisposing, enabling, and need factors when evaluating association between race, comorbid anxiety disorders and the interaction with health care utilization.

There are some limitations in our study that deserve to be mentioned. First, the prevalence rate of comorbid anxiety disorders in our study is much lower when compared with findings reported in previous studies. [6, 25-26] The diagnosis of comorbid anxiety disorders was determined by using ICD-9 CM codes in administrative claims. Fewer

diagnoses could exist due to overlap of symptoms between depression and anxiety disorders. Due to the lower prevalence, the effect of comorbid anxiety disorders on health care utilization in our study population could be underestimated. Second, information of measures of mental health-specific disease severity did not exist in our study variables. Adding information about the severity of mental health diseases in the analyses would provide a more comprehensive assessment, especially when determining the influence of race or comorbid anxiety disorders on the rate change of mental health-related hospitalization or ER visits among patients who have utilized health care resources.

Furthermore, gender representation was disproportionate in our study population. Most of the enrollees were female. In addition to the higher disease prevalence of depression in the female population,[59-60] the high proposition of female enrollees in our study population could be a result of the nature of the Medicaid population.

Conclusion

Among Medicaid enrollees, MDD patients with comorbid anxiety disorders had higher mental health-related and overall health care utilization when compared with MDD patients without comorbid anxiety disorders. Comorbid anxiety disorders were also positively associated with higher health care costs. In terms of the influence of race, African-American patients were less likely to have mental health-related office visits but were more likely to have hospitalizations, ER visits, and consume more health care costs when compared with their Caucasian cohorts.

This study provides a comprehensive understanding of the influence of race, comorbid anxiety disorders, and the interaction effect on health care utilization among Medicaid enrollees with MDD. Future studies could evaluate depression severity in

patients with and without anxiety disorders, as well as the association with health care utilization among the Medicaid population.

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Disclosure

This study is a part of Mr. Wu's original doctoral dissertation. The title of the dissertation is "Interactive Associations of Race and Comorbidity in Medication Treatment and Outcomes of Medicaid Enrolled Patients with Major Depressive Disorder".

Table 5.1 ICD-9-CM codes*

Diseases	Diagnoses	Codes±
Major Depressive Disorders	Major depressive disorder, single episode	296.2
	Major depressive disorder, recurrent episode	296.3
Bipolar Disorders	Bipolar affective disorder, manic	296.4x
	Bipolar affective disorder, depressed	296.5x
	Bipolar affective disorder, mixed	296.6x
	Bipolar affective disorder, unspecified	296.7x
	Manic-depressive psychosis, other	296.8x
Anxiety Disorders	Panic disorder without agoraphobia	300.01
	Panic disorder with agoraphobia	300.02
	Agoraphobia without history of panic disorder	300.22
	Social phobia (social anxiety disorder)	300.23
	Obsessive-compulsive disorder	300.30
	Post-traumatic stress disorder	309.81
	Acute stress disorder	308.30
	Generalized anxiety disorder	300.02
	Anxiety disorder due to general medical condition	293.89
	Anxiety disorder, not otherwise specified	300.00

* ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

± An "x" means all sub-codes were included

Table 5.2 Characteristics of the Study Population (N= 3,083)

Variables	Frequency	%
Age (years)		
18-30	1,250	40.5
31-40	817	26.5
41-50	641	20.8
51-60	325	10.5
61-64	50	1.6
Gender		
Male	699	22.7
Female	2,384	77.3
Race		
Caucasians	1,958	63.5
African Americans	1,125	36.5
Comorbidity (Elixhauser Index)		
0	860	27.9
1	804	26.1
2	559	18.1
≥3	860	27.9
Comorbid anxiety disorders		
Yes	776	25.2
No	2,307	74.8
Comorbid painful symptoms		
Yes	1,437	46.6
No	1,646	53.4
FFS vs. Capitation		
FFS	1,893	61.4
Capitation	822	26.7
Dual	368	11.9
Hospitalization during pre-study period		
Yes	833	27.0
No	2,250	73.0
ER visit during the pre-study period		
Yes	1,846	59.9
No	1,237	40.1
Outpatient Mental Health Facilities		
Yes	342	11.1
No	2,741	88.9
Outpatient psychiatric services		
Yes	469	15.2
No	2,614	84.8
Inpatient psychiatric services		
Yes	206	6.7
No	2,877	93.3

Table 5.3 Characteristics of Medicaid MDD Patients with and without Comorbid Anxiety Disorders: chi-squared comparisons (N=3,083)#

	Comorbid Anxiety Disorders				
	With		Without		
	(N=776)		(N=2307)		
Variables	Frequency	%*	Frequency	%*	P-value±
Age (years)					0.10
18-30	303	24.2	947	75.8	
31-40	212	26.0	605	74.1	
41-50	181	28.2	460	71.8	
51-60	72	22.2	253	77.9	
61-64	8	16.0	42	84.0	
Gender					<0.05
Male	152	21.8	547	78.3	
Female	624	26.2	1,760	73.8	
Race					
Caucasians	592	30.2	1,366	69.8	<0.01
African Americans	184	16.4	941	83.6	
Comorbidity (Elixhauser Index)					<0.05
0	182	21.2	678	78.8	
1	206	25.6	598	74.4	
2	150	26.8	409	73.2	
≥3	238	27.7	622	72.3	
Comorbid painful symptoms					<0.01
Yes	469	32.6	968	67.4	
No	307	18.7	1,339	81.4	
FFS vs. Capitation					<0.01
FFS	503	26.6	1,390	73.4	
Capitation	172	20.9	650	79.1	
Dual	101	27.5	267	72.6	
Hospitalization during pre-study period					0.25
Yes	222	26.7	611	73.4	
No	554	24.6	1,696	75.4	
ER visits during the pre-study period					<0.01
Yes	499	27.0	1,347	73.0	
No	277	22.4	960	77.6	
Outpatient Mental Health Facilities					0.78
Yes	84	24.6	258	75.4	
No	692	25.3	2,049	74.8	

Outpatient psychiatric services					<0.01
Yes	152	32.4	317	67.6	
No	624	23.9	1,990	76.1	
Inpatient psychiatric services					0.76
Yes	50	24.3	156	75.7	
No	726	25.2	2,151	74.8	

MDD: Major Depressive Disorders

* Row percentage

± Chi-square test

Table 5.4 Health Care Utilization by Race and Comorbid Anxiety Disorders in Medicaid Patients with Major Depressive Disorders (N= 3,083)

	Caucasian Patients				African-American Patients			
	Comorbid anxiety disorders (no) (N=1,366)		Comorbid anxiety disorders (yes) (N=592)		Comorbid anxiety disorders (no) (N=941)		Comorbid anxiety disorders (yes) (N=184)	
Variables	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Mental health-related health care utilization								
No. of Office visits	0.62	1.24	1.55***	2.10	0.36	0.84	0.72***	1.15
No. of Hospitalizations	0.07	0.40	0.19**	0.94	0.16	0.61	0.11	0.43
No. of ER visits	0.08	0.44	0.42***	1.26	0.15	0.67	0.46**	1.50
Overall health care utilization								
No. of Office visits	6.14	5.70	8.47***	7.29	4.97	8.21	6.48**	5.65
No. of Hospitalizations	0.33	0.91	0.55**	1.59	0.52	1.35	0.46	1.12
No. of ER visits	2.60	6.06	4.04***	7.26	2.53	4.78	4.56***	7.37

Note: Student's t-test between patients with and without comorbid anxiety disorders in Caucasians and African Americans, respectively

Note: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 5.5 Factors Associated with Mental Health-Related Health Care Utilization in Medicaid Patients with Major Depressive Disorder: multivariate logistic models and negative binominal regression models

	Office Visit				Hospitalization				ER visit			
	Odds ratio for having at least one office visit# (N=3,083)		Rate ratio in number of one office visit± (N=1,086)		Odds ratio of having at least one hospitalization# (N=3,083)		Rate ratio in number of hospitalization± (N=243)		Odds ratio of having at least one ER visit# (N=3,083)		Rate ratio in number of ER visits± (N=286)	
	Odds Ratio	95% CI	Rate Ratio	95% CI	Odds Ratio	95% CI	Rate Ratio	95% CI	Odds Ratio	95% CI	Rate Ratio	95% CI
Variables												
Race												
African American	0.54	(0.45–0.66)***	0.80	(0.72–0.88)***	2.57	(1.84–3.60)***	0.94	(0.73–1.21)	1.52	(1.05–2.19)*	0.87	(0.64–1.18)
Caucasian	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Comorbid anxiety disorders												
Yes	2.27	(1.85–2.78)***	1.11	(1.02–1.21)*	1.82	(1.25–2.67)**	1.10	(0.84–1.45)	4.39	(3.13–6.15)***	1.28	(0.97–1.69)
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Interaction between race and comorbid anxiety disorders	0.88	(0.59–1.30)	1.05	(0.88–1.26)	0.32	(0.16–0.65)**	0.69	(0.41–1.14)	0.70	(0.41–1.23)	0.99	(0.63–1.54)
Age (years)												
18-30	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
31-40	0.91	(0.75–1.11)	0.99	(0.90–1.08)	0.99	(0.70–1.40)	0.82	(0.63–1.07)	0.88	(0.63–1.24)	0.93	(0.72–1.22)
41-50	0.79	(0.63–0.99)*	1.13	(1.02–1.25)*	1.00	(0.69–1.46)	1.16	(0.90–1.51)	0.84	(0.59–1.20)	0.93	(0.69–1.25)
51-60	0.67	(0.50–0.90)**	0.99	(0.86–1.14)	0.42	(0.23–0.77)**	0.91	(0.59–1.38)	0.64	(0.39–1.04)	0.78	(0.52–1.15)
61-64	1.32	(0.72–2.43)	1.16	(0.91–1.49)	1.04	(0.38–2.83)	0.71	(0.34–1.47)	0.61	(0.20–1.84)	0.58	(0.23–1.44)
Gender												
Male	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Female	1.88	(1.53–2.30)***	1.18	(1.07–1.31)**	0.59	(0.44–0.81)**	0.93	(0.74–1.16)	0.57	(0.42–0.76)***	0.96	(0.76–1.22)
Comorbid painful symptoms												
Yes	1.22	(1.03–1.43)*	1.30	(1.20–1.40)***	1.25	(0.94–1.67)	1.17	(0.95–1.46)	1.53	(1.16–2.02)**	1.48	(1.18–1.86)**
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Comorbidity (Elixhauser Index)												
0	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
1	1.09	(0.88–1.35)	1.17	(1.06–1.29)**	1.15	(0.77–1.72)	1.13	(0.81–1.57)	1.46	(0.96–2.21)	1.26	(0.89–1.79)
2	1.12	(0.88–1.44)	1.22	(1.09–1.37)**	0.85	(0.53–1.37)	1.12	(0.76–1.66)	1.61	(1.02–2.52)*	1.67	(1.14–2.44)**
≥3	1.29	(1.01–1.65)*	1.43	(1.28–1.60)***	1.73	(1.13–2.64)*	1.56	(1.12–2.16)**	2.84	(1.86–4.35)***	1.79	(1.25–2.56)**
FFS vs. Capitation												
FFS	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Capitation	0.78	(0.65–0.94)**	0.91	(0.83–1.00)*	0.90	(0.65–1.24)	0.87	(0.69–1.10)	1.21	(0.90–1.64)	0.96	(0.76–1.22)
Dual	0.94	(0.74–1.21)	0.92	(0.83–1.03)	0.88	(0.57–1.35)	0.74	(0.53–1.03)	1.29	(0.88–1.89)	0.94	(0.70–1.27)
Hospitalization during pre-study period												
Yes	0.84	(0.70–1.01)	0.98	(0.90–1.07)	1.92	(1.43–2.58)***	1.77	(1.42–2.20)***	1.31	(0.98–1.74)	1.28	(1.01–1.61)*
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
ER visit during the pre-study period												
Yes	0.85	(0.72–1.00)	0.95	(0.88–1.03)	1.47	(1.08–2.01)*	1.09	(0.86–1.38)	1.79	(1.32–2.43)***	1.62	(1.25–2.10)***
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
No. of prescriptions used during the pre-study period	1.01	(0.99–1.02)	1.04	(1.03–1.04)***	0.95	(0.92–0.97)***	1.01	(0.99–1.03)	0.96	(0.93–0.98)**	1.00	(0.98–1.02)
Adherence												
Yes (MPR > 80%)	0.94	(0.80–1.10)	1.19	(1.11–1.28)***	2.58	(1.93–3.46)***	0.99	(0.79–1.23)	1.68	(1.29–2.20)***	1.05	(0.84–1.30)
No (MPR ≤ 80%)	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Constant	0.19	(0.13–0.30)***	3.24	(2.60–4.03)***	0.06	(0.03–0.12)***	1.35	(0.81–2.27)	0.04	(0.02–0.09)***	3.03	(1.75–5.25)***
Adjusted R^2	0.06		0.06		0.09		0.10		0.13		0.04	

Note: * p < 0.05, ** p < 0.01, *** p < 0.001

#: Multivariate logistic regression analysis

±: Negative binominal regression analysis

Table 5.6 Factors Associated with Overall Health Care Utilization in Medicaid Patients with Major Depressive Disorder: multivariate logistic regression models and negative binominal regression

	Office Visit				Hospitalization				ER visit			
	Odds ratio for having at least one office visit# (N=3,083)		Rate ratio in number of one office visit± (N=2,630)		Odds ratio of having at least one hospitalization# (N=3,083)		Rate ratio in number of hospitalization± (N=718)		Odds ratio of having at least one ER visit# (N=3,083)		Rate ratio in number of ER visits± (N=1,755)	
	Odds Ratio	95% CI	Rate Ratio	95% CI	Odds Ratio	95% CI	Rate Ratio	95% CI	Odds Ratio	95% CI	Rate Ratio	95% CI
Variables												
Race												
African American	0.50	(0.39–0.64)***	0.85	(0.79–0.91)***	1.42	(1.15–1.76)**	1.13	(0.98–1.31)	1.20	(1.00–1.45)	0.89	(0.80–0.99)*
Caucasian	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Comorbid anxiety disorders												
Yes	1.23	(0.87–1.74)	1.16	(1.08–1.25)***	1.03	(0.81–1.31)	1.16	(0.98–1.37)	1.42	(1.14–1.77)**	1.12	(1.00–1.25)
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Interaction between race and comorbid anxiety disorders	1.27	(0.68–2.38)	0.90	(0.79–1.04)	0.70	(0.45–1.10)	0.75	(0.56–1.02)	0.61	(0.40–0.92)*	1.22	(0.99–1.50)
Age (years)												
18-30	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
31-40	0.64	(0.49–0.83)**	1.00	(0.93–1.07)	0.76	(0.60–0.96)*	1.06	(0.90–1.25)	0.64	(0.52–0.78)***	0.88	(0.79–0.98)*
41-50	0.89	(0.64–1.24)	1.03	(0.95–1.11)	0.84	(0.66–1.08)	1.25	(1.06–1.48)**	0.49	(0.39–0.61)***	0.86	(0.76–0.97)*
51-60	0.70	(0.46–1.05)	1.05	(0.95–1.15)	0.58	(0.42–0.80)**	1.29	(1.04–1.60)*	0.39	(0.29–0.53)***	0.75	(0.63–0.89)**
61-64	0.62	(0.24–1.63)	1.21	(0.98–1.48)	0.89	(0.47–1.70)	0.98	(0.66–1.48)	0.26	(0.14–0.48)***	0.66	(0.45–0.98)*
Gender												
Male	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Female	2.36	(1.85–3.01)***	1.09	(1.01–1.17)*	0.81	(0.66–1.00)	0.90	(0.78–1.03)	1.06	(0.88–1.29)	0.82	(0.74–0.92)***
Comorbid painful symptoms												
Yes	2.12	(1.66–2.71)***	1.35	(1.28–1.43)***	1.41	(1.17–1.69)***	1.13	(0.99–1.29)	2.77	(2.35–3.27)*	1.58	(1.44–1.73)***
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Comorbidity (Elixhauser Index)												
0	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
1	1.94	(1.47–2.56)***	1.19	(1.10–1.29)***	1.43	(1.10–1.86)**	0.94	(0.76–1.16)	1.43	(1.16–1.77)**	1.09	(0.96–1.24)
2	2.21	(1.57–3.11)***	1.34	(1.22–1.46)***	1.41	(1.05–1.89)*	0.93	(0.74–1.18)	1.90	(1.48–2.43)***	1.24	(1.08–1.42)**
≥3	2.79	(1.95–4.00)***	1.52	(1.40–1.66)***	2.46	(1.86–3.26)***	1.32	(1.07–1.64)**	2.30	(1.79–2.96)***	1.39	(1.21–1.60)***
FFS vs. Capitation												
FFS	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Capitation	1.16	(0.90–1.49)	0.94	(0.88–1.01)	0.79	(0.64–0.97)*	0.92	(0.79–1.07)	1.09	(0.91–1.31)	0.91	(0.83–1.01)
Dual	1.71	(1.16–2.52)**	0.97	(0.89–1.05)	0.96	(0.73–1.27)	1.01	(0.84–1.21)	1.16	(0.90–1.49)	1.06	(0.93–1.21)
Hospitalization during pre-study period												
Yes	0.79	(0.61–1.03)	0.99	(0.93–1.05)	1.85	(1.53–2.24)***	1.54	(1.36–1.74)***	1.13	(0.94–1.36)	1.16	(1.06–1.28)**
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
ER visit during the pre-study period												
Yes	0.72	(0.57–0.91)**	0.92	(0.87–0.98)**	1.23	(1.01–1.49)*	1.05	(0.91–1.21)	2.50	(2.12–2.95)***	1.70	(1.53–1.89)***
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
No. of prescriptions used during the pre-study period	1.13	(1.10–1.17)***	1.03	(1.03–1.04)***	1.01	(0.99–1.03)	1.00	(0.99–1.01)	1.00	(0.99–1.02)	1.01	(1.00–1.02)
Adherence												
Yes (MPR > 80%)	1.20	(0.96–1.51)	1.11	(1.05–1.17)***	1.44	(1.20–1.72)***	1.05	(0.93–1.19)	1.26	(1.08–1.48)**	1.13	(1.04–1.23)**
No (MPR ≤ 80%)	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Constant	0.46	(0.28-0.75)**	3.15	(2.70-3.67)***	0.15	(0.09-0.23)***	1.16	(0.83-1.62)	0.31	(0.20-0.46)***	2.76	(2.18-3.49)***
Adjusted R^2	0.15		0.05		0.07		0.07		0.13		0.04	

Note: * p < 0.05, ** p < 0.01, *** p < 0.001

#: Multivariate logistic regression analysis

±: Negative binominal regression analysis

Table 5.7 Factors Associated with Health Care Costs in Medicaid Patients with Major Depressive Disorders: multivariate linear regression models

	Mental Health Related Health Costs (N=3,083)		Overall Health Care Costs (N=3,083)	
Variables	β coefficient	SE	β coefficient	SE
Race				
Caucasians	0.34	0.06***	0.17	0.05***
African Americans	Reference	Reference	Reference	Reference
Comorbid anxiety disorders				
Yes	0.27	0.07***	0.08	0.05
No	Reference	Reference	Reference	Reference
Interaction between race and comorbid anxiety disorders	-0.33	0.13*	-0.20	0.10
Age (years)				
18-30	Reference	Reference	Reference	Reference
31-40	0.04	0.06	0.00	0.05
41-50	0.23	0.07**	0.24	0.06***
51-60	0.01	0.09	0.27	0.07***
61-64	-0.15	0.20	0.23	0.16
Gender				
Male	Reference	Reference	Reference	Reference
Female	-0.40	0.06***	-0.30	0.05***
Comorbid painful symptoms				
Yes	0.02	0.05	0.28	0.04***
No	Reference	Reference	Reference	Reference
Comorbidity (Elixhauser Index)				
0	Reference	Reference	Reference	Reference
1	0.06	0.07	0.32	0.05***
2	0.12	0.08	0.54	0.06***
≥3	0.32	0.08***	0.94	0.06***
FFS vs. Capitation				
FFS	Reference	Reference	Reference	Reference
Capitation	-0.24	0.06***	-0.35	0.05***
Dual	-0.09	0.08	-0.03	0.06
Hospitalization during pre-study period				
Yes	0.27	0.06***	0.26	0.05***

No	Reference	Reference	Reference	Reference
ER visit during the pre-study period				
Yes	0.18	0.05**	0.06	0.04
No	Reference	Reference	Reference	Reference
No. of prescriptions used during the pre-study period	-0.03	0.01***	0.03	0.00***
Adherence				
Yes (MPR > 80%)	1.02	0.05***	0.56	0.04***
No (MPR ≤ 80%)	Reference	Reference	Reference	Reference
Constant	6.86	0.13***	7.92	0.10***
Adjusted R^2	0.17		0.32	

Note: * p < 0.05, ** p < 0.01, *** p < 0.001

CHAPTER 6

OVERALL CONCLUSION

This chapter provides the overall conclusion of this dissertation. The chapter begins with the conclusion of study findings obtained from the previous two manuscripts. Then, the implications and limitations of this study are addressed. Finally, several new directions in future studies are discussed.

The Conclusion of Study Findings

MDD is a prevalent mental illness in the U.S. Anxiety disorders commonly co-occur in patients with MDD. Health disparities of MDD treatment still exist between Caucasians and African Americans. African-American patients are less likely than Caucasian patients to receive antidepressant treatment. With lower socioeconomic status and education background, Medicaid enrollees with MDD could suffer more severe disease burden when they have comorbid anxiety disorders. Additionally, health disparities of antidepressant treatment could also be severe between Caucasian and African-American Medicaid enrollees. It is very important to understand the association between medication use-related outcomes and comorbid anxiety disorders, race and the interaction effect between race and comorbid anxiety disorders in Medicaid enrollees with MDD.

The objectives of our study were to investigate the association of medication adherence and medication persistence with race and comorbid anxiety disorders as well as the interaction effect. This study also examined the association of health outcomes with race and comorbid anxiety disorders, and the interaction effect.

For medication use-related outcomes, this study found that among Medicaid enrollees with MDD, African-American patients were less likely than Caucasian patients to be adherent to antidepressants. In addition, African-American patients have lower medication persistence and a higher hazard of not persistently taking antidepressants. MDD patients with comorbid anxiety disorders had higher antidepressant adherence when compared with MDD patients without comorbid anxiety disorders.

This study further investigated overall and mental health-related health resource utilization such as office visits, hospitalization, ER visits, and health care costs. Results showed that among Medicaid enrollees, MDD patients with comorbid anxiety disorders had higher mental health-related and overall health care utilization when compared with MDD patients without comorbid anxiety disorders. Comorbid anxiety disorders were also positively associated with higher health care costs. In terms of the influence of race, African-American patients were less likely to have mental health-related office visits but were more likely to have hospitalizations, ER visits, and consume more health care costs when compared with their Caucasian cohorts.

Implications of the Study

In addition to filling the gap of the literature, the findings of this study also provided unique implications on Medicaid enrollees with MDD. The implications were discussed in the following two sections.

Overall implications

The findings of this study provide several implications in health service research. First, this study provides a high generalizability for the Medicaid population because the results are obtained from a comprehensive database which includes Medicaid enrollees in eight states from 2003 to 2007. Although this study does not provide causality among variables, it still reveals several significant associations among race, comorbid anxiety disorders, and medication use-related outcomes in Medicaid enrollees with MDD. The high generalizability from this study can still become thoughtful resources when health care providers consider treatment or policy makers make health policies for Medicaid patients with MDD. Second, this study provides insights for health care policy makers especially when considering the policy implications on Medicaid enrollees with MDD. Polices which can reduce health disparities between African-American and Caucasian patients with MDD need to be stressed and implemented. The policy implications also need to be relevant to reduce the disease severity among Medicaid enrollees with co-occurring depression and anxiety disorders. Third, this study also provides a wider clinical perspective on treating MDD patients with comorbid anxiety disorders. Health care providers when considering medical treatment for Medicaid patients with MDD must realize that medication use related-outcomes as well as health resource utilization are significant different between MDD patients with and without comorbid anxiety disorders. Fourth, the influence of the out-of-pocket costs could be minimized because Medicaid enrollees usually have a low amount of copayments. A high amount of copayments could change patients' medication taking behaviors. Patients could decide to stop taking antidepressants if they could not afford the copayment. Unlike enrollees who

may have high out-of-pocket costs of commercial health care plans, Medicaid enrollees usually have very low or are without any out-of-pocket costs. Consequently, the influence from out-of-pocket costs could be minimized or eliminated when the study was conducted by using Medicaid data. The findings of this study strengthened the association between race, comorbid anxiety disorders, and interaction effect with medication use-related outcomes in the Medicaid enrollees.

Finally, one of the uniqueness must be emphasized of our study is that Andersen's Behavioral Model of Health Services Use was implemented for the variable selection to evaluate factors associated with health care utilization in our study population. Using the Andersen's model allows us to control predisposing, enabling, and need factors when evaluating association between race, comorbid anxiety disorders and the interaction with health care utilization. The model also provides a theoretical background for the associations among study variables.

Policy implications of race, comorbid anxiety disorders, and the interaction effect

The policy implications of race, comorbid anxiety disorders, and the interaction effect were respectively discussed in this section.

When compared with Caucasians, African Americans with MDD had lower prevalence of comorbid anxiety disorders. However, African Americans were less likely to be adherent to and consistent with antidepressants, and had fewer mental health physician visits, but had higher health resource utilization (hospitalization, ER visits, and health care costs). From a policy perspective especially for Medicaid enrollees, policy intervention needed to be able to reduce the overall poverty, and improve access to mental health specific care for minority patients. For example, policy intervention could

improve access to mental health care for poor community where minority patients tended to live. Then, policy intervention could focus on increasing the number of minority (mental) health care providers[157] who could have better cultural understanding with minority patients because minority patients could perceive depression or anxiety differently when compared with Caucasians. For example, African Americans patients were more likely to express depression as stigma.[164] The stigmatization of depression among African-American population could result in a lower rate of mental health office visits and could further delay the diagnosis. Minority health care providers who have a similar cultural background with their patients could have better cultural understanding, and consequently could improve adherence and treatment outcomes. Finally, policy intervention could focus on the training of the patient education for minority depressed patients. For example, medical or pharmacy students should be trained to have specific communication skills for different racial/ethnic groups. Only through high quality physician-patient communication could reduce the burden of mental illness and improve medication adherence and persistence for minority patients.

The implication of the study results implied MDD patients with comorbid anxiety disorders had higher health resource utilization (office visits, hospitalization, and ER visits) and also more likely to be adherent to their antidepressants. Policy intervention could improve physicians' awareness of the high prevalent rate of comorbid anxiety disorders among patients with MDD in order to reduce patients' health resource utilization. Also, mental health policies could provide financial funding or research grants for evidence-based cares and research which could improve treatment for MDD patients with or without comorbid anxiety disorders.

The interaction effect reduced the individual effect (race and comorbid anxiety disorders) in some of the analyses. In addition to the policy intervention addressed above, additional policy intervention such as increasing routine screens for depression and anxiety disorders in African Americans was also needed. Physicians or other health care providers were encouraged to actively inquire patients about physical symptoms which might be related to depression or anxiety in order to diagnose the mental illness in the early stage. Instead of describing psychiatric symptoms such as sadness, African-Americans were more likely to express complains of physical symptoms when they had depression.[164] Health care providers need to understand that somatic symptoms could have been associated with depression in African-American patients. Finally, policy intervention which could improve cultural understanding was also necessary. For example, physicians' bias such as African American could tolerate more severe depression, could result in a late diagnosis with more severe depressed symptoms. Similar bias perception need to be removed.

Limitations of the Study

In spite of wider implications derived from this study, there are still several limitations. First, a lower prevalence rate of comorbid anxiety disorders was founded in our study when compared with findings reported in previous studies. The discrepancy may be because the diagnosis of comorbid anxiety disorders was determined by using ICD-9 CM codes in administrative claims. Fewer diagnoses could exist due to overlap of symptoms between depression and anxiety disorders. Due to the lower prevalence, the effect of comorbid anxiety disorders on health care utilization in our study population

could be underestimated. Second, information of measures of mental health-specific disease severity did not exist in our study variables. Adding information about the severity of mental health diseases in the analyses would provide a more comprehensive assessment, especially when determining the influence of race or comorbid anxiety disorders on the rate change of mental health-related hospitalization or ER visits among patients who have utilized health care resources. Third, due to the nature of the administrative claim data, we were unable to incorporate variables such as beliefs or attitudes of antidepressant treatment, concerns of side effects, or behavioral intentions of taking medication. Fourth, there is no variable in the database related to education, but a person's education background is important for understanding patients' medication use behaviors. A Medicaid enrollee with a lower education background may not be able to fully understand the complexity of medication treatment. It can result in not adhering to their medications or of ceasing to take them. Finally, the basic assumption of measuring adherence using MPR is that a prescription filled is a prescription taken. However, it is very difficult for investigators to tell whether patients indeed take the medicine after they refill. Using administrative claim data is not able to identify such a limitation.

Future Studies

Future studies could be conducted to investigate medication use-related outcomes not just in Medicaid enrollees with MDD but in different populations such as senior citizens or working adults with MDD. Results from other populations could reveal different associations among race, comorbid anxiety disorders, and medication use-related outcomes due to distinct patient characteristics from different populations. In addition to different study populations, other chronic mental illness such as the

Alzheimer disease or schizophrenia could be considered for further investigations in the future. For example, future studies could examine the association between comorbid mental illness and medication use in patients with schizophrenia. Furthermore, future research could evaluate depression severity in patients with and without anxiety disorders, as well as the association with health care utilization among the Medicaid population. Additionally, medication use patterns between different types of antidepressants in Medicaid-enrolled MDD patients with and without comorbid anxiety disorders can also be further investigated. One of the limitations of this study is the absence of including behavioral variables such as patients' beliefs, perception, or intention of taking antidepressants. Future studies could implement survey questionnaires to capture behavioral and psychological factors in order to comprehensively understand patients' medication use behaviors as well as the association with health resource utilization. For health disparities of different racial groups, future studies could investigate the difference of antidepressant adherence in other minority populations such as Latinos\Latinas or Asia Americans, as well as the influence of comorbid anxiety disorders on their medication use behaviors.

In conclusion, this study provides a comprehensive understanding of the influence of race, comorbid anxiety disorders, and the interaction effect on medication adherence and persistence as well as health care utilization among Medicaid enrollees with MDD. In spite of the limitations, the findings of this study still provide clinical and policy implications on medication use-related outcomes and health resource utilization among Medicaid enrollees with MDD.

APPENDICES

Appendix 1: The University of Michigan IRB Approval

Health Sciences and Behavioral Sciences Institutional Review Board • 540 East Liberty Street, Suite 202, Ann Arbor, MI 48104-2210 • phone (734) 936-0933 • fax (734) 998-9171 • irbhsbs@umich.edu

To: Mr. Chung-Hsuen Wu

From:

Richard Redman

Cc:

Chung-Hsuen Wu
Rajesh Balkrishnan

Subject:Initial Study Approval for [HUM00035510]

SUBMISSION INFORMATION:
Study Title: The Combined Effects of Race and Comorbidity on Medication Use Related Outcomes in Medicaid Enrolled Patients with Major Depressive Disorder
Full Study Title (if applicable): The Combined Effects of Race and Comorbidity on Medication Use Related Outcomes in Medicaid Enrolled Patients with Major Depressive Disorder
Study eResearch ID: HUM00035510
Date of this Notification from IRB:12/9/2009
Initial IRB Approval Date: 12/9/2009
Current IRB Approval Period:**12/9/2009 - 12/8/2011**
Expiration Date: Approval for this expires at **11:59 p.m. on 12/8/2011**
UM Federalwide Assurance (FWA): FWA00004969 expiring on 11/17/2011
OHRP IRB Registration Number(s): IRB00000245

Approved Risk Level(s):

Name	Risk Level
HUM00035510	No more than minimal risk

NOTICE OF IRB APPROVAL AND CONDITIONS:
The IRB HSBS has reviewed and approved the study referenced above. The IRB determined that the proposed research conforms with applicable guidelines, State and federal regulations, and the University of Michigan's Federalwide Assurance (FWA) with the Department of Health and Human Services (HHS). You must conduct this study in accordance with the description and information provided in the approved application and associated documents.

APPROVAL PERIOD AND EXPIRATION:
The approval period for this study is listed above. Please note the expiration date. If the approval lapses, you may not conduct work on this study until appropriate approval has been re-established, except as necessary to eliminate apparent immediate hazards to research subjects. Should the latter occur, you must notify the IRB Office as soon as possible.

IMPORTANT REMINDERS AND ADDITIONAL INFORMATION FOR INVESTIGATORS

APPROVED STUDY DOCUMENTS:
You must use any date-stamped versions of recruitment materials and informed consent documents available in the eResearch workspace (referenced above). Date-stamped materials are available in the "Currently Approved Documents" section on the "Documents" tab.

RENEWAL/TERMINATION:
At least two months prior to the expiration date, you should submit a continuing review application either to renew or terminate the study. Failure to allow sufficient time for IRB review may result in a lapse of approval that may also affect any funding associated with the study.

AMENDMENTS:
All proposed changes to the study (e.g., personnel, procedures, or documents), must be approved in advance by the IRB through the amendment process, except as necessary to eliminate apparent immediate hazards to research subjects. Should the latter occur, you must notify the IRB Office as soon as possible.

AEs/ORIOs:
You must inform the IRB of all unanticipated events, adverse events (AEs), and other reportable information and occurrences (ORIOs). These include but are not limited to events and/or information that may have physical, psychological, social, legal, or economic impact on the research subjects or other.

Investigators and research staff are responsible for reporting information concerning the approved research to the IRB in a timely fashion, understanding and adhering to the reporting guidance (http://www.med.umich.edu/irbmed/ae_orio/index.htm), and not implementing any changes to the research without IRB approval of the change via an amendment submission. When changes are necessary to eliminate apparent immediate hazards to the subject, implement the change and report via an ORIO and/or amendment submission within 7 days after the action is taken. This includes all information with the potential to impact the risk or benefit assessments of the research.

SUBMITTING VIA eRESEARCH:
You can access the online forms for continuing review, amendments, and AEs/ORIOs in the eResearch workspace for this approved study (referenced above).

MORE INFORMATION:
You can find additional information about UM's Human Research Protection Program (HRPP) in the Operations Manual and other documents available at: www.research.umich.edu/hrpp.

Richard Redman
Chair, IRB HSBS

Appendix 2: Data use agreement

AMENDMENT NUMBER 1
to the
Services and License Agreement

by and between

Thomson Reuters (Healthcare) Inc.
and
The Reagents of University of Michigan

When fully executed by both parties, this document will constitute the first (1st) formal Amendment to the Services and License Agreement by and between Thomson Reuters (Healthcare) Inc. ("TRH") and The Reagents of University of Michigan ("Customer"), dated effective September 28, 2009 ("Agreement"). The purpose of this Amendment is to provide expanded use of the licensed data.

Exhibit A to this Amendment describes licensed Data and the expanded permitted use of the Data.

This Amendment will be deemed fully executed and in effect as of the date of this last signature below. All other terms and conditions of the Agreement as previously amended that are not affected by this first (1st) amendment remain in full force and effect.

FOR THOMSON REUTERS (HEALTHCARE) INC	FOR THE REAGENTS OF UNIVERSITY OF MICHIGAN
By: [signature]	By: [signature]
Name: Doreen S. Osterhaus	Name: Lalit Sharma
Title: Financial Plan Mgr.	Title: IT Purchasing Manager
Date: 4/2/2010	Date: 3/31/10

Services and License Agreement
Exhibit A
Licensed Data and License Fees

Customer's Facility:
The Data described herein are licensed to Customer for access in the Customer offices located at:
The University of Michigan
428 Church Street
Ann Arbor, MI 48109-1065

Description of the Data Licensed to Customer:
Thomson Reuters (Healthcare) Inc. will provide five complete years (2003-2007) of the MarketScan Medicaid Database and three complete years (2005-2007) of the MarketScan Commercial Claims and Encounters Database.

Authorized Users for the Data:

Thomson Reuters (Healthcare) Inc. had previously provided the following authorized use of license data within the original Exhibit A to Services and License Agreement.

These data may be used by authorized faculty and staff within the "Center for Medication Use, Policy, and Economics, University of Michigan College of Pharmacy". Graduate students within the department may use the data in support of faculty-directed research and under the supervision of faculty and/or staff within the department.

Thomson Reuters (Healthcare) Inc. is now providing via this Amendment #1 additional expanded use of the licensed data as follows:

These data may be used by authorized faculty and staff within the "Center for Medication Use, Policy, and Economics, University of Michigan College of Pharmacy" at the University of Michigan.

Graduate students may ONLY use data in support of faculty-directed research and under the supervision of faculty and/or staff within department.

Ph.D. students are not permitted to use the MarketScan Data licensed under this agreement for dissertation research with the exception of the four students listed below. Ph.D. students may apply to use the MarketScan Dissertation Database for their dissertation research.

The four University of Michigan doctoral students listed below are authorized to use the MarketScan Medicaid Database in support of the named dissertation studies below through August 31, 2010 or when they have graduated from the university whichever date is soonest.

Any use of these data by students after graduation must be covered under a MarketScan Data Rider agreement signed by an authorized representative of the University of Michigan.

List of students and dissertation research:

Huang Tz-Ou: *PREDICTIVE PERFORMANCE OF COMORBIDITY MEASURES IN MEDICATION ADHERENCE, QUALITY OF CARE, HEALTHCARE RESOURCE UTILIZATION, AND COSTS IN TYPE 2 DIABETES*

Meg Kong: *RACIAL DIFFERENCES IN MEDICATION ADHERENCE AND ASSOCIATED OUTCOMES IN A HIV-INFECTED MEDICAID POPULATION WITH POSTPARTUM DEPRESSION*

Chung-Hsuen Wu: *THE COMBINED EFFECTS OF RACE AND COMORBIDITY ON MEDICATION USE RELATED OUTCOMES IN MEDICAID ENROLLED MAJOR DEPRESSIVE DISORDER PATIENTS*

Jun Wu: *STATIN MEDICATION USE BEHAVIORS IN TYPE 2 DIABETES PATIENTS PRESENTING COMORBID HYPERLIPIDEMIA IN MEDICAID POPULATION*

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