2016

Measuring Adherence with Antidepressant Medication: Comparison of HEDIS and PDC Methodologies

Carmen Monica Telinoiu
University of Rhode Island, ctelinoiu@my.uri.edu

MEASURING ADHERENCE WITH ANTIDEPRESSANT MEDICATION: COMPARISON OF HEDIS AND PDC METHODOLOGIES

BY

CARMEN MONICA TELINOIU

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE

REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

IN

PHARMACEUTICAL SCIENCES

UNIVERSITY OF RHODE ISLAND

2016

MASTER OF SCIENCE THESIS

OF

CARMEN MONICA TELINOIU

APPROVED:

Thesis Committee:

Major Professor Stephen Kogut

Rita Marcoux

Clinton Chichester

Nasser H. Zawia
DEAN OF THE GRADUATE SCHOOL

UNIVERSITY OF RHODE ISLAND
2016

ABSTRACT

Depression is a significant problem for the managed care system. Antidepressant medication helps ameliorate the symptoms of depression yet adherence to medication is known to be poor. The current approach to adherence measurement (i.e HEDIS) is limited or lacking. Other methods are used (e.g Proportion of Days Covered –PDC) in other chronic diseases to measure adherence. Medication adherence is a growing concern for clinicians and other health care stakeholders (e.g. payer) because of the increasing evidence that non-adherence is prevalent and places patients at an increased risk for adverse health outcomes and higher cost of care.

We conducted a retrospective cohort study of patients enrolled in a Medicaid plan. For inclusion in the study population patients had to meet HEDIS inclusion criteria and PDC criteria respectively. Patients included in the HEDIS study's cohort were adults at least 18 years of age with a new diagnosis of depression confirmed by outpatient medication use and an ICD-9 diagnostic code. The upper limit age was set at 75 years old in order to maintain the confidential information about the patients. Patients had to meet certain enrollment eligibility criteria as well. For the PDC study population patients met the same age requirement as for the HEDIS measurement inclusion criteria. Patients included in the study for the PDC cohort were not required to have a new diagnosis of depression certified by a diagnostic code; they only had to be antidepressant medication users during the study period. We evaluated antidepressant medication adherence by applying the HEDIS measures and PDC measures. The measure of effect was the odds ratio in separate models. We also applied HEDIS criteria to the PDS cohort to provide a head-to-head comparison of the rates of adherence. Adherence was assessed with seven medication classes as recommended by HEDIS: Miscellaneous Antidepressants. Monoamine Oxidase Inhibitors (MAOIs). Phenylpiperazine Antidepressants. Selective Serotonin-Norepinephrine Reuptake Inhibitors Antidepressants (SSNRIs). Selective Serotonin Reuptake Inhibitors Antidepressants (SSRIs). Tetracyclic Antidepressants (TeCAs). and Tricyclic Antidepressants (TCAs). Differences in baseline characteristics and the odds of adherence were assessed between the groups for each methodology separately as well as patient demographic and health related variables. We constructed multivariate logistic regression models to measure the odds of adherence with antidepressant medication for each methodology while controlling for

potential confounders and assessing for interaction terms. The level of significance and the corresponding 95% confidence intervals of the odds ratios were presented as well.

A total of 626 eligible antidepressant users were identified according to the HEDIS criteria, and 22,351 eligible antidepressant users were identified according to PDC criteria and were evaluated for adherence with antidepressant medication. In both study samples patients 50 years and older were significantly more likely to be adherent with antidepressant medication than the younger group (<35 years) patients. In both groups patients that had respiratory disease had an increased odds of adherence with antidepressant medication relative to patients that were not classified having a respiratory disease. Patients that had other mental health diagnoses in addition to depression had a statistically significant increased odds of adherence with antidepressant medication relative to patients that did not have such diagnoses. The beta coefficient representing the relationship between the antidepressant medication adherence and the therapy regimen was positive and statistically significant for both samples. Patients that were using more than one drug were significantly more likely to be adherent to antidepressant medication regimen than patients that were using only one type of antidepressant drugs.

Our results implicate older age and comorbid diseases such as respiratory and other mental health diseases and polymedication as risk factors associated with better adherence with antidepressant medication therapy among Medicaid insured patients. Interventions that strive to improve adherence with antidepressant medication therapy should continue to be implemented and evaluated.

ACKNOWLEDGMENTS

I would like to acknowledge and express my sincerest gratitude for the enduring expert guidance and support that I have been fortunate to receive from my major professor, **Dr. Kogut** throughout all my master's program and even before starting it.

I express my appreciation to Dr Chichester and Professor Marcoux for having served on my committee. Their thoughtful questions and comments were valued greatly.

I am extremely satisfied with the expansive and applicable education I have acquired through my experience in the program. I take this opportunity to express my thanks to all the faculty members of the program of Pharmacoeconomics & Pharmacoepidemiology for their help and encouragement and for all whom, directly or indirectly, have lent their helping hand in my academic journey.

PREFACE

The standard format was used in preparation of this thesis.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

Medication adherence is a growing concern for clinicians, and other health system stakeholders (e.g. payer) because of the increasing evidence that non-adherence is prevalent and associated with adverse outcomes and higher cost of care.[1] Adherence to a medication regimen is generally defined as the extent to which patients take medication as prescribed by their health care providers.[2] There are many different methods for assessing adherence to medication. While there is no consensus about a golden standard for measuring medication adherence, numerous subjective and objective medication adherence methods have been developed. Oesterberg et al[3] categorized these methods as either direct or indirect. Direct methods include directly observed therapy, measurement of the level of the medicine or metabolite in the blood, and measurement of the biological marker in the blood.[3] Indirect methods of adherence assessment include patient questionnaires, self reports, pill counts, rates of prescription refills, assessment of the patient's clinical response, electronic medication monitors, measurements of the psychological markers and patient diaries.[3]

The American Psychiatric Association defines 2 phases of antidepressant treatment: acute phase and continuation phase. The current *Practice Guideline for the Treatment of Patients with Major Depressive Disorder* recommends pharmacological treatment for each phase to reduce the risk of relapse. Patients having a successful acute phase treatment (adherence over 4-8 weeks) are encouraged to continue treatment with antidepressant agents for at least 4 to 9 months. Moreover, for patients that had multiple episodes of depression, further maintenance treatment is recommended for at least one year.[3]

An ideal measure would evaluate adherence for all patients with depression. Unfortunately, unlike other chronic diseases, no measures of medication adherence among chronic users of antidepressants have been developed. The Pharmacy Quality Alliance (PQA) recommends using a proportion of days covered (PDC) measure for calculating adherence for chronic users of medications for conditions such as diabetes and dyslipidemia. Their measures are endorsed by the National Quality Forum (NQF). The PDC measure calculates the percentage of patients that are taking the prescribed medications from a particular drug class

that exceed an 80% adherence benchmark. The Medication Possession Ratio (MPR) is another metric that measures medication adherence, yet this measure is considered inferior to the PDC because MPR is a mere summation of the day supply, and does not consider multiple therapies. The PDC measure offers a more conservative estimate of the medication adherence since it allows looking at each day in the designated time period to determine whether an individual has one or more dispensed study drugs. As a proportion, the PDC always ranges between 0 and 1. Typically, an 80% (0.8) threshold is applied to indicate good or poor adherence, with higher thresholds set for some therapies (e.g. 90% for antiretrovirals).[4]

Depression is one of the most common disorders and a leading cause for disability worldwide. Almost 50% of the U.S population has experienced at least one psychiatric disorder in their lifetime.[5] The lifetime prevalence of major depressive disorder is reported to be as high as 17% and the 12-month prevalence is 5%-9%.[6,7] The World Health Organization (WHO) considers major depressive disorder one of the most debilitating diseases to society. Its negative outcomes include suicide, substantial impairment, lower quality of life, increased health care utilization and cost, and adverse impact on employment productivity.[8] It is anticipated that major depressive disorder (MDD) will be the second leading cause of disability worldwide by 2020[9] with a lifetime risk of 7% - 12% for men and 20%-25% for women.[9]

Depression is a serious public problem, particularly among people with low income. Low socio-economic status is associated with a higher prevalence of depression. Moreover, the duration of new episodes of depression are longer in people with a low socio-economic level.[10] According to data from the National Health and Nutrition Examination Survey (2009-2012) persons living below poverty level are nearly 2½ times more likely to have depression than those at or below poverty level.[11]

The incidence of depression is rising and the costs are escalating. People that have depression cannot enjoy a fulfilled life because they experience sadness, a sense of isolation and feeling like they are a burden. Depressed people are 30 times more likely to commit suicide and each year in U.S. approximately 41.000 individuals complete suicide.[12]

Depression impacts the academic development of a person, the marriage perspective and an average loss of $10,400/year in income by the time the person reaches 50 years of age.[13] Depressed people are 7 times more likely to be unemployed.[8] According to Smith JP et al (2010) a person that suffers from

depression has a loss of 20% in potential income, and a lifetime loss for each family who has a depressed family member of $300,000.[14]

From the employer point of view depression is a big concern also. The employer is affected by the missed days of work (absenteeism) and the reduced productivity (presenteeism) of individuals with MDD. According to data from the National Health and Nutrition Examination Survey (2009-2012) almost 43% of individuals with severe depressive symptoms reported serious difficulties in work, home and social activities. The rate of difficulty in work, home or social related activities, increased with the severity of depression.[11]

The consequences of untreated depression or inadequately treated depression are significant, therefore adherence to antidepressant medication is crucial. Response to drug therapy occurs predominantly in patients who are strictly adherent to antidepressant medication regimens. Most patients experience good outcomes with appropriate antidepressants taken for the appropriate period of time. Patients must be closely monitored during the acute phase (first three months) and the initial continuation phase (the first six to nine months) of treatment for necessary drug dosage adjustments. Measuring adherence is important to make sure that patients comply with provider recommendations for a good outcome and a reduced economic burden on health care system. The antidepressant therapy must be coupled with the appropriate form of psychological therapy.

Antidepressant medications are the standard approach for treating depression. According to the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, depressive disorder is challenging to treat.[14] STAR*D is the largest study of its kind. The results demonstrated that after exposure to four different levels of medication intervention options, approximately one-third of the patients in this study failed to achieve remission.[14] Also, approximately 50% of the patients in this trial prematurely discontinued antidepressant therapy for a number of different reasons, including patient-related (e.g. side effects, misperception about medication), and clinician-related factors (e.g. poor instruction by the clinician about the medication, lack of follow-up care). Depression itself is a condition that causes patients to have difficulty following the medication regimen, yet they can have the greatest potential to benefit from treatment adherence.[15]

Currently, there are more than 20 antidepressant medications available worldwide, and they are used singularly or in combination with other antidepressants to treat the disabling affects of depression for many patients.

According to IMS Health National Prescription Audit PLUS, in 2010 antidepressants were the second most commonly prescribed medication, second to drugs to lower cholesterol. Approximately 254 million antidepressant prescriptions were written in 2010, resulting in nearly $ 10 billion in costs.[16] Eleven percent of Americans aged 12 years and over take antidepressant medication and more than 60% of patients have taken therapy for 2 years or longer, with 14% having taken the medication for 10 years or more.[11] For most patients, the course of major depressive disorder (MDD) is recurrent or chronic. The goal of antidepressant treatment is the full remission of symptoms and prevention of relapse. Remission of symptoms is related to improved functioning and prognosis.[17] Antidepressants are recommended to be continued for at least 4 months beyond the initial symptom resolution. However, reported levels of non-adherence have been consistently high and this remains a serious concern.[18] Thus, a majority of antidepressant users are chronic users of these medications, and as in other chronic diseases such as diabetes and hypertension, the health system must direct resources towards promoting patient adherence with prescribed chronic therapies.

The National Committee for Quality Assurance (NCQA) is a private standards-setting organization which aims to improve the quality of health care and reduce the overall burden of illness. To evaluate antidepressant adherence, NCQA uses the Antidepressant Medication Management (AMM) measure from the Health Plan Employer Data and Information Set (HEDIS) standardized performance measurement tool. HEDIS is a tool used by more than 90% of American health plans to measure performance on important dimensions of care, including medication adherence. The HEDIS measure focuses on newly diagnosed cases of depression, thus this measure is limited because it omits the majority of the patients that are chronic users of antidepressants. The question that arises is how is adherence measured for patients that use antidepressants chronically?

Another organization that has as a mission to improve quality of medication management is the Pharmacy Quality Alliance (PQA). Among the quality measures developed by the Pharmacy Quality Alliance (PQA), three quality measures are related to measuring medication adherence for chronic diseases

such as diabetes, hypertension and cholesterol. The PQA adherence measures are endorsed by the National Quality Forum (NQF) and are currently used by Centers for Medicare and Medicaid Services (CMS) Medicare Part D plans.

The PQA identified medication adherence as an important component of medication-use quality and endorsed the proportion of days covered (PDC) as standard method for calculating medication adherence across prescription drug plans and pharmacies.[4]

Purpose and Hypothesis

The purpose of this study was to investigate the suitability of the PDC approach applied to antidepressant adherence, in comparison with the HEDIS AMM measure. We sought to determine if the percentage of patients identified as adherent with antidepressant medication according to the HEDIS (AMM) specifications was similar to the percentage of patients identified as adherent with antidepressant medication according to the PDC specifications during the chronic phase of treatment. In patients with a confirmed diagnosis of depression (HEDIS) we calculated adherence with antidepressant treatment according to the HEDIS specifications for chronic phase of adherence. Adherence was calculated for patients that are users of antidepressant medication in the PDC group as well using 80% threshold standard to the PDC methodology. Furthermore, we applied the HEDIS inclusion criteria to the PDC population to determine the correlation between HEDIS and PDC adherence measurement methodologies in a unified sample. Additionally, we evaluated several factors as predictors of adherence for both measures.

CHAPTER 2

METHODOLOGY

The study was conducted as a retrospective cohort study using health care claims data describing pharmacy utilization for a period spanning July 1, 2013-September 30, 2014. The data for this research represent a sample of Medicaid recipients. These data contained information on enrollment and demographics, as well as pharmacy and medical claims for approximately 40,000 enrollees utilizing antidepressant medication.

HEDIS methodology inclusion and exclusion criteria.

Patients were at least 18 years of age as of July 1, 2013 and continuously enrolled for at least 180 days of a 231 day period between the period of July 1, 2013 to September 30, 2014. Patients older than 75 years of age were excluded from the study in order to maintain the confidentiality of subjects. All patients were confirmed to have a diagnostic code for depression. International classification of disease ninth edition (ICD-9) codes from the 2014 Healthcare Effectiveness Data and Information Set (HEDIS)[19] were used to identify the presence of any code indicative of depression or a depression related complication (Appendix D). Also patients had to have a diagnosis of depression in an inpatient, outpatient, emergency department, intensive outpatient or partial hospitalization setting during the 60 days prior of the starting of medication through 60 days after the Index Prescription Start Date (IPSD). All patients were confirmed to have used a medication for treatment of depression or a depression related disease, defined as the presence of a claim for any oral or injectable antidepressant agent during each patient's continuous enrollment period. Medication use was evaluated 105 days prior to the IPSD with seven medication classes (Appendix E) in order to test the negative medication history (NMH). Patients that had a prescription during the NMH period were excluded from the study, thus providing a sample of newly treated patients.

PDC methodology inclusion and exclusion criteria.

Patients were at least 18 years of age as of July 1, 2013 and continuously enrolled for 365 days during the study period. Patients older than 75 years of age were excluded from the study in order to maintain the confidentiality of subjects. No ICD-9 codes for a diagnostic of depression were required for the PDC methodology inclusion criteria. Patients that used any of the antidepressant medications from the seven classes (Appendix E) were included in the study. Patients were also required to have at least 91 days between the index medication and the end of the study period.

Defining Adherence

Eligibility for the HEDIS methodology required that all patients have at least one antidepressant claim during the index period associated with an ICD-9 diagnostic of depression 60 days prior or after the first prescription. This will ensure that the patients has a new diagnosis of depression according to HEDIS requirements. Patient must not have an antidepressant claim during a 105 days period prior to the index date. Patient with a claim during the negative medication history were excluded from the study population. The continuation phase of the treatment lasts 231 days, during which a patient needs to fill a sufficient number of antidepressant prescriptions to provide medication for at least 180 days. Medication gap due to washout or refill can total a maximum of 51 days during the 231-day period. Adherence was determined as the proportion between the days supply of dispensing divided by the days of follow up during the chronic phase (231 days) . Patients were classified as adherent if they remained on antidepressant medication for at least 180 days (6 months) of the 231 days in the period.

For the PDC methodology, all patients were required to have at least one antidepressant claim during the index period. The index date should occur at least 91 days prior to the end of the study period. Adherence was also evaluated as a dichotomous variable and calculated as the proportion between the days supply of dispensing during the study period divided by the number of days between the fill days and the end of the study period. According to the Pharmacy Quality Alliance (PQA) patients will be considered adherent to their medication if the PDC is equal to or exceeds 80% and non-adherent if the PDC is less than 80%. Adherence with antidepressant medication was evaluated separately for the two methodologies as the inclusion criteria for the measures were different, yielding different samples.

Independent Variables

Age: We created three age groups, approximately the youngest, middle aged, and older patients in the population. Most older adults 65 years old or older receive their prescription drugs benefit through Medicare Part D plans, and were not included in this study.

Gender: Analyzed as a dichotomous variable.

Individual Comorbid Diseases: The presence of diabetes, cardiovascular, respiratory and mental health diseases (other than depression) was identified during the entire study period using the ICD-9 codes from the HEDIS 2015 (Appendix A, B, C, D). The diabetes disease variable comprised codes for diabetes with and without complications and also codes for the drug therapeutic class.(Appendix A). The cardiovascular disease variable comprised codes for congestive heart failure, coronary artery disease, myocardial infarction, and other forms of ischemic and non-ischemic cardiovascular disease (Appendix B). Respiratory disease comprised codes for bronchitis, emphysema and asthma. Mental health disorders comprised codes for schizophrenia, bipolar disorder, paranoia, psychosis, anxiety, autism, panic disorder, personality disorders, acute stress disorders, impulse control disorders, anger/ aggression disorders, attention deficit disorder, and attention hyperactivity deficit disorder. These four conditions were selected based on high prevalence and high health expenditure.

Physician care visits: We analyzed if patients visited a physician providing a basis for qualifying patients as seeing a medical doctor or not visiting a physician during the follow-up period.

Medication regimen: The antidepressant medication regimen was calculated as the number of unique antidepressant types dispensed during the study period providing a basis to classify patients as users of antidepressant monotherapy or polytherapy.

Statistical Analysis

The analysis of the data was performed using Statistical Analysis Software Version 9.4 (SAS® Version 9.4). The Pearson Chi-Square test was used to assess differences between groups (within each measure separately). Continuous variables were compared using t-tests for independent samples. The

relationship between HEDIS/PDC and adherence, are presented as frequencies and percentages of patients that were adherent to antidepressant medication according to each characteristic. Results with a P-value <=0.05 were considered statistically significant while p-values <0.2 were used in selecting variables for inclusion in the multivariate model. Univariate logistic regression was used to assess each individual variable and the results with the P-values are presented with odds ratios and corresponding 95% confidence intervals. Multivariate logistic regression was used to assess the relationship between the independent variables describing patient and provider characteristics, and the dependent variable of medication adherence, measured by the AMM and PDC methods. Antidepressant medication adherence was the risk factor of interest, with all other independent variables considered potential confounders of the relationship with the dependable variable of adherence. These models were created using a stepwise approach removing the least statistically significant interaction terms at each step. Two-way interactions were assessed using a hierarchical approach. The likelihood ratio test was used to compare models in order to evaluate if the inclusion of interaction terms improved the model fit. The difference in the -2 log statistic between the full model and the reduced model was compared to the corresponding Chi-square statistic with the degrees of freedom equal to the difference in the number of terms in the models. Multivariable colinearity was assessed for all the possible confounders for each model (both for HEDIS and PDC measures). The adherence beta estimate for the full model with all variables was used as the standard for comparison. The final multivariate model for both HEDIS and PDC measures contained all important variables for model inclusion. The Akanke Information Criterion statistic and the Hosmer-Lemeshow goodness of fit test were used to assess the fit of the final models.

A third sample was created by applying the inclusion and exclusion criteria for PDC methodology to patients that met the HEDIS inclusion and exclusion criteria. The sample was analyzed to determine if there is a correlation between measuring adherence with antidepressant medication using HEDIS and PDC methodology using a continuous measure of adherence.

Resources required

The journal articles, clinical guidelines and other important information necessary for the successful completion of this research were obtained using the University library or interlibrary exchange services, PubMed through the College of Pharmacy, or other professional services available on World Wide Web such as government information policy on HEDIS and PDC measures. Data used in this study were provided by Major Professor Stephen Kogut. This study was approved by URI Institutional Review Board. Analyses of the data were conducted using SAS® Version 9.4 -University of Rhode Island.

CHAPTER 3

RESULTS

The two separate samples were created after applying the inclusion/exclusion criteria for both HEDIS and PDC methods that were subsequently statistically analyzed. The main difference between the samples created is that patients included in the HEDIS sample have a new diagnosis of depression documented by an ICD-9 code, whereas the patients in the PDC sample are simply antidepressant users irrespective of diagnosis.

Application of inclusion and exclusion criteria for HEDIS methodology

The final cohort comprised a total of 626 Medicaid patients that met all the inclusion and exclusion criteria for HEDIS methodology (Figure 1). The initial cohort was comprised of 32,052 patients initially from which a number of 15,056 patients were excluded because they did not met the enrollment criteria and had no prescription for an antidepressant drug during the study period. Further 22,370 patients were excluded from the cohort for (1) not having a diagnosis of depression according to a ICD-9 code, (2) not being prescribed an antidepressant agent during the intake period and (3) not meeting the eligibility criteria according to HEDIS requirements.

Application of inclusion and exclusion criteria for PDC methodology

The final cohort was comprised of 22,351 patients (Figure 2). Initially a total number of 34,481 patients were identified as using an antidepressant medication agent. After selecting only the patients that had an antidepressant prescription during the study period, 1,352 patients were excluded. After applying the continuous enrollment criteria another 1,591 patients were excluded from the sample. Further, 5,190 patients were excluded from the sample because they (1) did not use an antidepressant agent included in the study criteria and (2) their index medication was not greater than 91 days prior to the end of the study period.

HEDIS Baseline Characteristics

The analytic cohort for the HEDIS measure was comprised of 626 patients (Table 1). Patients in this cohort had a new diagnosis of depression documented by o a ICD-9 code. The mean (standard deviation [SD]) age of enrolled patients was 37.59 [12.16]. The majority of the cohort was female representing 79.52% of the cohort sample and only 20.48% were male . The prevalence of diabetes, cardiovascular, respiratory and mental health disease was different between groups. Patient with diabetes comprised 7.35% of the HEDIS group. Patients with cardiovascular disease made up 13.42% of the HEDIS group, patients with respiratory disease made up 6.55%, whereas patients with mental health disorders made up 33.07% of this sample. In terms of the health care utilization, 27.48% of HEDIS patients were hospitalized during the study period and 74.60% visited a psychiatrist. Variability existed with regard to the therapeutic regimen, with 57.99% of patients taking a single antidepressant drug during the study period. Approximately sixty-six percent of the patients were prescribed a selective serotonin reuptake inhibitor (SSRI) medication, 12.62% of the patients were prescribed trazodone, while 8.31% of the patients were prescribed bupropion. Selective norepinephrine reuptake inhibitors (SNRIs) agents and tricyclic (TCAs) antidepressants were prescribed to 4.95% of the patients and 4.63%, respectively. Patients that were prescribed mirtazapine accounted for 3.35% of the sample.

PDC Baseline Characteristics

The analytic cohort for PDC measure was comprised of 22,351 patients (Table 1). Patients in this cohort are users of antidepressant drugs and did not have a diagnostic of depression according to an ICD-9 code. The mean (standard deviation [SD]) age of enrolled patients was 42.76 [12.42]. The majority of the cohort was female representing 72.14%% of the cohort sample, and only 27.86% were males. The prevalence of diabetes, cardiovascular, respiratory and mental health disease was different between groups. Patient with diabetes made up 11.69% of the group. Patients with cardiovascular disease made up 14.45% while patients with respiratory disease made up 6.17% of the group. Other mental health disease was present in 21.28% of the PDC group. In terms of the health care utilization, 16.71% of patients were hospitalized during the study period and 36.54% had a physician visit. Therapeutic regimens varied and 69.50% of patients took a single antidepressant drug during the study period. Approximately 66% percent

of the patients were prescribed a serotonin reuptake inhibitor (SSRI) medication, while 11.91% of the patients were prescribed trazodone, and 10.04% of the patients were prescribed bupropion. Selective norepinephrine reuptake inhibitors (SNRIs) agents and tricyclic (TCAs) antidepressants were prescribed to patients in 7.49% and 9.98% of the cases, respectively . Patients that were using mirtazapine accounted for 3.62% of the PDC sample.

Adherence with antidepressant medication according to HEDIS methodology

The bivariate relationships between the dependent variable, adherence with antidepressant medication according to HEDIS methodology, and all other variables are presented as frequencies and percentages in Table 2. Patients were considered adherent if they met or exceeded the HEDIS adherence threshold of 180 of 231 days else they were considered non-adherent. The overall adherence for the HEDIS measure was 37.38% with 234 of the 626 patients taking their medication as prescribed by their provider. Significant differences between adherent and non-adherent patients existed across all three age stratum (P-value <0.001). The highest level of adherence was registered among older patients in the over 50 age group, and the lowest level of non-adherence (28.67%) was among the younger group of individuals (less than 35 years of age). Approximately thirty-eight percent of females were adherent to the antidepressant medication regimen compared with 35.16% of males, without a statistical significant difference (P-value= 0.6091). Among patients that had a diagnosis of diabetes, 45.65% were adherent to the antidepressant medication therapy, but without significant difference from patients without diabetes (P-value=0.2678). Patients with cardiovascular disease were adherent to antidepressant medication therapy at 44.05%, which did not differ from the rate among patients without cardiovascular disease (P-value=0.1838). Patients with respiratory disease were more frequently adherent (56.10%) than patients without this condition (P-value= 0.0123). Adherence among patients with other mental health disease (42.03%) did not differ statistically in terms of adherence with antidepressant medication compared with the patients that did not have diagnoses for other mental health conditions (P-value= 0.0958). Related to health care utilization, 39.40% of patients that visited a psychiatric practitioner and 39.79% of hospitalized patients, were adherent to the medication regimen; however, neither of these comparisons yielded statistically significant differences (P-value= 0.0874 and P-value=0.9264, respectively). Adherence rates varied among the antidepressant medication

drug classes with no statistical difference between the adherent and non-adherent groups. Adherence among patients utilizing antidepressant polytherapy was 49.43%, which was statistically significantly greater than adherence among users of monotherapy (P-value<0.001).

Adherence with antidepressant medication according to PDC methodology.

The bivariate relationship between the dependent variable, adherence with antidepressant medication according to the PDC methodology, and all other variables are presented as frequencies and percentages in Table 2. Patients were considered adherent if they met or exceeded the adherence threshold of 80%, else they were considered non-adherent. The overall adherence rate according to the PDC measure was 50.37% with 11,259 of 22,351 patients taking their medication as prescribed by their provider. Significant differences between adherent and non-adherent patients existed across all three age stratum (P-value<0.001). The highest level of adherence was registered among older patients in the >50 years of age group, 61.85% compared with 37.12% in the youngest age group (P-value<0.001). The proportion of female patients that were adherent to the antidepressant medication regimen compared to the proportion of males that adherent was 50.00% to 51.33% , without a statistically significant difference (P-value= 0.0758). In terms of the comorbid conditions, all the differences between the presence/absence of the condition with adherence rates were statistically significant with a P-value<0.001. Among patients that had a diagnosis of diabetes, 61.35% were adherent to the antidepressant medication therapy, which exceeded adherence rates for patients without diabetes (P-value <0.001). Patients with cardiovascular disease were adherent to antidepressant medication therapy at 58.85%, which exceeded adherence among patients without cardiovascular disease (P-value <0.001). Patients with respiratory disease (62.19%) and other mental health diseases (54.38%) that were adherent to the antidepressant medication therapy differed statistically significant from those without these conditions (37.81% and 45.62%, respectively) with P-values<0.001. Related to health care utilization, the group of patients that visited a psychiatric practitioner during the follow up period were adherent in a proportion 56.01%, which exceeded the rate among patients lacking such visits (P-value <0.001). Among patients with at least 1 hospitalization during the period, 51.75% were adherent to the medication regimen; the adherence rate among patients that were not

hospitalized was not statistically significantly different (P-value=0.0645). Users of SNRIs and trazodone were more frequently adherent than users of SSRIs. TCAs, and mirtazapine (P-value<0.001).

Univariate Logistic Regression Analyses for HEDIS and PDC methodologies

Univariate logistic regression analyses were performed for both methodologies in order to test the association of each explanatory variable separately with the outcome (adherence with antidepressant medication) in order to identify variables for inclusion in the multivariate analyses. We also excluded the variables from the further analysis that did not show significant association with the outcome (adherence with antidepressant medication) on their own as they are not likely to be associated with the outcome after adjusting for other variables. The results of the univariate logistic regression for all the variables considered in the analysis are presented in Table 3. For both methodologies, the middle and older age groups had statistically significant positive beta coefficients that showed the association of age with the outcome (adherence with antidepressant medication). The Odds Ratios were >1 for both age groups for both methodologies, having 95% confidence intervals that did not overlap unity. A statistically significant positive association [Odds (95% CI)] between the respiratory disease and the outcome was found for both methodologies with [OR 2.265 (1.159 - 4.293)] for HEDIS cohort and [1.672 (1.494 - 1.870)] for PDC cohort, with P-values<0.001.

Likelihood of antidepressant medication adherence according to HEDIS selected characteristics

The results of the multivariate logistic regression analysis of the effect of antidepressant therapy on medication adherence according to HEDIS methodology are presented in Table 5. Collinearity was not found between any of the independent variables assessed for the inclusion into the model. Interaction between variables was assessed as well to decide whether any interaction terms should be included into the final model. No significant interactions were found. The likelihood ratio chi-square was used to decide on the best model and was calculated by subtracting the -2log likelihood of the model with the variable from the nested model (Nested model= the model without the variable). The Hosmer-Lemeshow goodness of fit test showed that that the model was an appropriate one ($p > 0.05$) The beta coefficients representing the relationship between antidepressant medication adherence and age group 35-49, and group age older than

50 years, were statistically significant (0.3190 and 0.9463 respectively [P-value<0.001]). Patients 50 years and older were significantly more likely to be adherent with antidepressant medication than those less than 35 years old (OR 2.576 [95% CI 1.626 – 4.083]). Patients that had respiratory disease had an increased odds of adherence with antidepressant medication relative to patients that were not-adherent and suffered from a respiratory disease (OR 1.745 [95% CI 0.894 – 3.406]). Patients that had a mental health disease had increased odds of adherence with antidepressant medication relative to patients that were not-adherent and had the same comorbid condition (OR 1.379 [95% CI 0.964 – 1.973]). The beta coefficient representing the relationship between the antidepressant medication adherence and the therapy regimen was positive and statistically significant (0.3213 [P-value<0.001]. Patients that were using more than one antidepressant were significantly more likely to be adherent to antidepressant medication regimen than patients that were using only one type of antidepressant drugs (OR 2.214 [95% CI 1.570 – 3.121]).

Likelihood of antidepressant medication adherence according to PDC selected characteristics

The results of the multivariate logistic regression analysis of the effect of antidepressant therapy on medication adherence according to PDC methodology are presented in Table 6. Collinearity was not found between any of the independent variables assessed for the inclusion into the model. Interaction between variables was assessed as well to decide whether any interaction terms should be included into the final model. The interactions found between the independent variables are discussed in the limitations section of the paper, as the interactions terms were not suited to be included in the final model. The likelihood ratio chi-square was used to decide on the best model and was calculated by subtracting the -2log likelihood of the model with the variable from the nested model. The goodness of fit test showed that that the model was an appropriate one. The beta coefficients representing the relationship between antidepressant medication adherence and age group 35-49, and group age older than 50 years, were statistically significant (0.5484 and 1.0101 respectively [P-value<0.001]). Patients 50 years and older were significantly more likely to be adherent with antidepressant medication than the less than 35 years old patients (OR 2.746 [95% CI 2.564 – 2.940]).

The beta coefficient representing the relationship between adherence with antidepressant medication and diabetes was statistically significant (0.5051 [P-value<0.001]). Patients that had diabetes

were significantly more likely to be adherent with antidepressant medication than patients that did not have diabetes (OR 1.657 [95% CI 1.524 – 1.802]). The beta coefficient representing the relationship between adherence with antidepressant medication and cardiovascular disease was statistically significant (0.4003 [P-value<0.001]). Patients that had cardiovascular disease were significantly more likely to be adherent with antidepressant medication than patients that did not have cardiovascular disease (OR 1.492 [95% CI 1.384 - 1.609]). Patients that had respiratory disease had a statistically increased odds of adherence with antidepressant medication relative to patients that were not-adherent and suffered from a respiratory disease (OR 1.672 [95% CI 1.594 – 1.870]). The beta coefficient representing the relationship between the adherence with antidepressant medication and other mental health disease was statistically significant (0.2042 [P-value<0.001]. Patients that had a mental health disease had a statistically increased odds of adherence with antidepressant medication relative to patients that were not-adherent and had the same comorbid condition (OR 1.227 [95% CI 1.150 - 1.308]). Patients that were using more than one antidepressant were significantly more likely to be adherent to antidepressant medication regimen than patients that were using only one type of antidepressant drugs (OR 4.807 [95% CI 4.509 - 5.125]). Patients that used SNRIs were statistically more likely to be adherent to antidepressant regimen compared with those that were not taking an SNRI drug (OR 1.740 [95% CI 0.789 - 0.878]).

Correlation between adherence with antidepressant medication using HEDIS and adherence with antidepressant medication using PDC methodology

The final cohort comprised a total of 626 Medicaid patients that met all the inclusion and exclusion criteria for HEDIS methodology applied to the PDC sample. The sample was analyzed to determine if there is a correlation between measuring adherence with antidepressant medication using HEDIS and PDC methodology. We calculated the correlation coefficient of the two variables and we found that the two methodologies are highly positively correlated with a correlation coefficient of 0.95. This means that the two variables are closely correlated and that if we measure adherence with antidepressant medication according to HEDIS methodology for patients that meet the PDC criteria, in 95% of the cases they will be found adherent. A correlation matrix plot is presented in Figure 3.

CHAPTER 4

DISCUSSION

Major depressive disorder is a prevalent and debilitating disease among the U.S adult population. Effective treatment and adherence with antidepressant medication regimen is essential for optimal therapeutic outcome and for lower economic implications. Depression is a chronic disease, and many patients will be taking medication for long periods of time, maybe lifelong. According to the World Health Organization (2003) "adherence is the extent to which a person's behavior in taking medication corresponds with agreed recommendations from the health care provider"[2] and that adherence is a multidimensional phenomenon determined by the interplay of five sets of factors: socio economic, health care system, condition related, therapy related and patient related. Moreover, WHO stresses the fact that the consequences of non-adherence are may be very serious, and if non-adherence were a disease, it could be termed an "epidemic".[2]

Efforts are being made by institutions, clinicians and professional organizations to determine the most effective interventions to improve patient's adherence. While medication adherence for chronic diseases such as diabetes and hypertension have well established measures, adherence with antidepressant medication is only measured for new diagnosed patients, leaving aside the chronic users of antidepressants. Further research is needed to better address how medication adherence is measured among patients with chronic depression.

The present study investigated if there is a difference between the percentage of patients identified as adherent with antidepressant medication according to AMM specifications and the percentage of patients identified as adherent with antidepressant medication according to the PDC specifications during the chronic phases of treatment. It was hypothesized that the predictors of non-adherence will be similar for the HEDIS and PDC methodologies. The effect of older age on adherence with antidepressant medication [Odds ratio (95% CI)] was consistent between the two groups, as age was a significant risk factor for non-adherence with antidepressant medication for both HEDIS [OR 2.576 [95% CI 1.626 – 4.083])] and PDC

patients (OR 2.746 [95% CI 2.564 – 2.940]). This is possibly explained by the fact that older people take more medication as compared to the younger patients, hence more prone to be considered adherent.

As expected, the effect of polymedication on adherence [Beta estimate (P-value)] was consistent between the two analyzed groups [0.3213 (P-value<0.001)] for HEDIS and [1.5701(P-value<0.001)] for PDC we considered in our analysis that no more than two drugs were prescribed for same medical condition and coded polytherapy by looking at the drugs filled in the same day. We excluded from our analysis one of the drugs refilled in the same day during our study period. A limitation of the HEDIS method is that it does not adequately discern between combination therapy and medication switch. Thus, patients using more than more type of antidepressant are more likely to be classified as adherent. The univariate models for HEDIS methodology [Odds ratios (95% CI)] supported to lack of direct association between diabetes and cardiovascular diseases and adherence with antidepressant medication [OR 1.447 (95% CI 0.971 - 2.648)] and [OR 1.379 (95% CI 0.866 – 2.195)] respectively. The multivariate model for PDC methodology [Odds ratios (95% CI)] supported the association between adherence with antidepressant medication and chronic comorbid conditions such as diabetes and cardiovascular diseases [OR 1.675 (95% CI 1.524 – 1.802)] and [OR 1.492 (95% CI 1.384 – 1.609)] respectively. The latter finding aligns with the findings of a study by Katon et al[20] concerning adherence with antidepressant drug therapy in patients with evidence of diabetes or cardiovascular disease, or both. Patients adherent with antidepressant medication were more likely to be adherent to comorbid therapy versus those non-adherent to antidepressant drug therapy (Odds ratio [OR], 2.13 for cardiovascular, [OR] 1.85 for diabetes, [OR] 1.45, P-values<0.001 for both).[20]

Factors associated with medication adherence are dependent upon the characteristics of the patient population, the medication class and data source evaluated. According to the World Health Organization (2003) "adherence is the extent to which a person's behavior in taking medication corresponds with agreed recommendations from the health care provider"[2] and that adherence is a multidimensional phenomenon determined by the interplay of five sets of factors: socio economic, health care system, condition related, therapy related and patient related. A study by Akincgil el al[21] looked at adherence with antidepressant medication among privately insured patients diagnosed with depression. The study used medical and pharmacy claims data for 4312 subjects that were continuously enrolled in the health plan with a new

diagnostic of depression and who initiated antidepressant treatment. Treatment adherence was assessed for acute phase and continuation phase using the Health Plan Employer Data and Information Set (HEDIS) quality measures for outpatient depression care. The results showed that 51% of patients were adherent through acute phase. Older age and higher economic status were associated with better adherence. Alcohol and other substance abuse predicted lower acute-phase adherence (OR=0.49 and OR=0.72 respectively) for patients having two or more cardiovascular/metabolic conditions (OR=0.65), and for those who started treatment with an older generation antidepressant (OR=0.69). The presence of follow up visits from a psychiatrist positively influenced adherence. (OR=1.19). Among patient adherent during the acute phase, 41.5% remained adherent during the continuation phase. Adherence was significantly lower for Health Maintenance Organizations (HMO) enrollees compared with indemnity enrollees (OR=0.62).[22] According to Jeon-Slaughter[22] low level income combined with health insurance status and race/ethnicity, predict non-adherence to antidepressant treatment. The study extracted data from the National Comorbidity Survey-Replication (NCR-R) and the sample study comprised 280 adults between age 18 and 64 who were diagnosed with major depressive episode according to DSM-IV at some point during their lifetime and medicated with SSRIs in the past 12 months. The study results stated that African Americans were at higher risk of medication noncompliance that whites (Odds ratio, 4.53) and major depressive episode comorbidity was positively associated with medication noncompliance (Odds ratio, 4.52).[23]

Strategies to improve adherence with antidepressant medication therapy involve pharmacists, educational interventions involving physicians, nurses, different tools and structures that health plans may use to improve depression care. Finley et al[23] assessed the effect of collaborative care model with emphasis on the clinical pharmacist in providing drug management and treatment follow up to patients with depression. They compared the outcomes of subjects treated in the collaborative model (75 patients) with subjects receiving usual care (50 patients). After 6 months, the intervention group demonstrated a significantly higher drug adherence rate than the control group (67% vs 48%, odds ratio 2.17, 95% confidence interval 1.04 -4.51, p=0.038).[23] Another study by Hoffman et al[24] evaluated the impact of mail-based physician and member educational interventions on patients adherence with antidepressant medication. The study was a prospective randomized controlled one that followed 9564 patients over 6 months after filling a new prescription of antidepressant medication. A pharmacy claim claims database

was used to identify patients and track medication adherence. Practitioners were randomly assigned to intervention and control group. Patient assignment was linked to their physician's assignment. After adjusting the variables, the intervention statistically significant impacted the adherence [95% CI (1.003 – 1.197) $p<0.01$] proving that a monthly mail-based educational intervention program can positively influence patient adherence to therapy.[24]

Correlation between the two methodologies proved that adherence with antidepressant medication can be measured using the PDC method used for measuring adherence with medication for chronic diseases.

CHAPTER 5

LIMITATIONS AND CONCLUSIONS

The present study utilized a retrospective cohort design with variables derived from data based claims of insured patients in a Medicaid state program. Because of the nature of the data we lack information on race/ethnicity, disease severity, social support of perceived stigma of patients with depression. Adherence is a problem that touches more than one level and poor adherence can be influenced by factors such as knowledge, attitudes, skills, environment of the patient and providers' practices. Due to the retrospective, not-randomized study design and the use of claims data we couldn't analyze all the variables that might have influenced adherence with antidepressant medication regimen. Because we captured only comorbid disease states through ICD-9 coding only during the study period, we might have underestimated the comorbid disease prevalence. There is a potential for misclassification surrounding the outcome (adherence) considering that patients that were prescribed two drugs on the same day were classified as using polytherapy. Some interactions were found between age and therapeutic regimen. Adults over 35 years old were more likely [OR (95% CI)] to use more than one drug and be adherent more often compared with the younger patients; the age group 35-49 years [1.415 (1.205 – 1.661), the age group older than 50 years [1.642 (1369 – 1.970)] with statistical P-value<0.001. Also, when more drugs were dispensed, the SSRIs were more likely to be prescribed [0.402 (0.318 – 0.509)] with a P-value<0.001. We derived measures of adherence from claims data rather than observing actual medication use. It is possible that patients picked up medication but then did not proceed to take it, resulting in a misclassification of baseline adherence.

Our study is believed to be the first evaluating the correlation between the measuring adherence with antidepressant medication according to HEDIS methodology and PDC methodology, so there was no evidence in the literature to support our findings. The generalization of our results is limited and confirmation of our results is to be warranted.

In conclusion, in both cohorts age (over 35 years) was found to be a risk factor for adherence with antidepressant medication for both groups. Patients that had respiratory disease had an increased odds of

adherence with antidepressant medication relative to patients that did not have a respiratory disease. Patients that had a mental health disease had increased odds of adherence with antidepressant medication relative to patients that did not have these comorbid conditions. Patients that were using more than one drug were significantly more likely to be adherent to antidepressant medication regimen than patients that were using only one type of antidepressant drugs.

The methodologies of measuring adherence are closely correlated and that if we measure adherence with antidepressant medication according to HEDIS methodology for patients that meet the PDC criteria, in 95% of the cases they will be found adherent. The findings of this study suggest that PDC methodology may be a suitable method of measuring adherence with antidepressant medication. The larger sample size for PDC methodology gives it some advantages over the HEDIS methodology sample: (1) is more representative of the population being analyzed and the results can be generalized to larger population with confidence, (2) greater accuracy of the results, (3) diversity and outliers are captured and observing them would give a more accurate picture of the characteristics of the population, dividing the sample into smaller sample groups can give deeper and valuable information about the population.

Patients using antidepressants should be adherent regardless of indication for use. Because HEDIS methodology limits the measuring of adherence only to new patients with and ICD-9 diagnosis of depression, a large percent of patients that might have another diagnosis/ or no diagnosis at all, are not considered for adherence measurement. Another aspect is represented by the fact that there is currently no measure in place to quantify adherence with antidepressant medication for chronic depression.

HEDIS methodology of measuring adherence with antidepressant medication has some limitations. Antidepressants may be prescribed by non-psychiatrists to treat medical disorders in the absence of a psychiatric diagnosis According to US Department of Health and Human Services 2008[25], 23 % of U.S. adults had a mental health problem treated in the past year by a general medical provider (physician, nurse, or other health professional), 16 % by a non-psychiatrist mental health specialist, 12 % by a psychiatrist, 8 % by a human services provider, and 7 % by a complementary and alternative medical provider. Not all of these professions might be a as expert in diagnosis and treating depression.[25]

Other limitation of HEDIS is that looking back 105 days might not be long enough and thus some cases are not new users; it does not exclude patients that were misdiagnosed with depression; it relies on

pharmacy dispensing records which may not represent medication actually taken by the patient. People might be dually enrolled during the study period they might be eligible for Medicare, but not have the Medicaid part. Another limitation of the approach is the duration of therapy. Not all patients need to use antidepressant medication indefinitely, regardless of diagnosis. This means that some patients may be considered non-adherent with antidepressant medication when applying the method, although the patient may have legitimately ended the treatment at the provider's recommendation.

Figure 1. Eligibility Flowchart: Application of Inclusion and Exclusion Criteria for HEDIS methodology

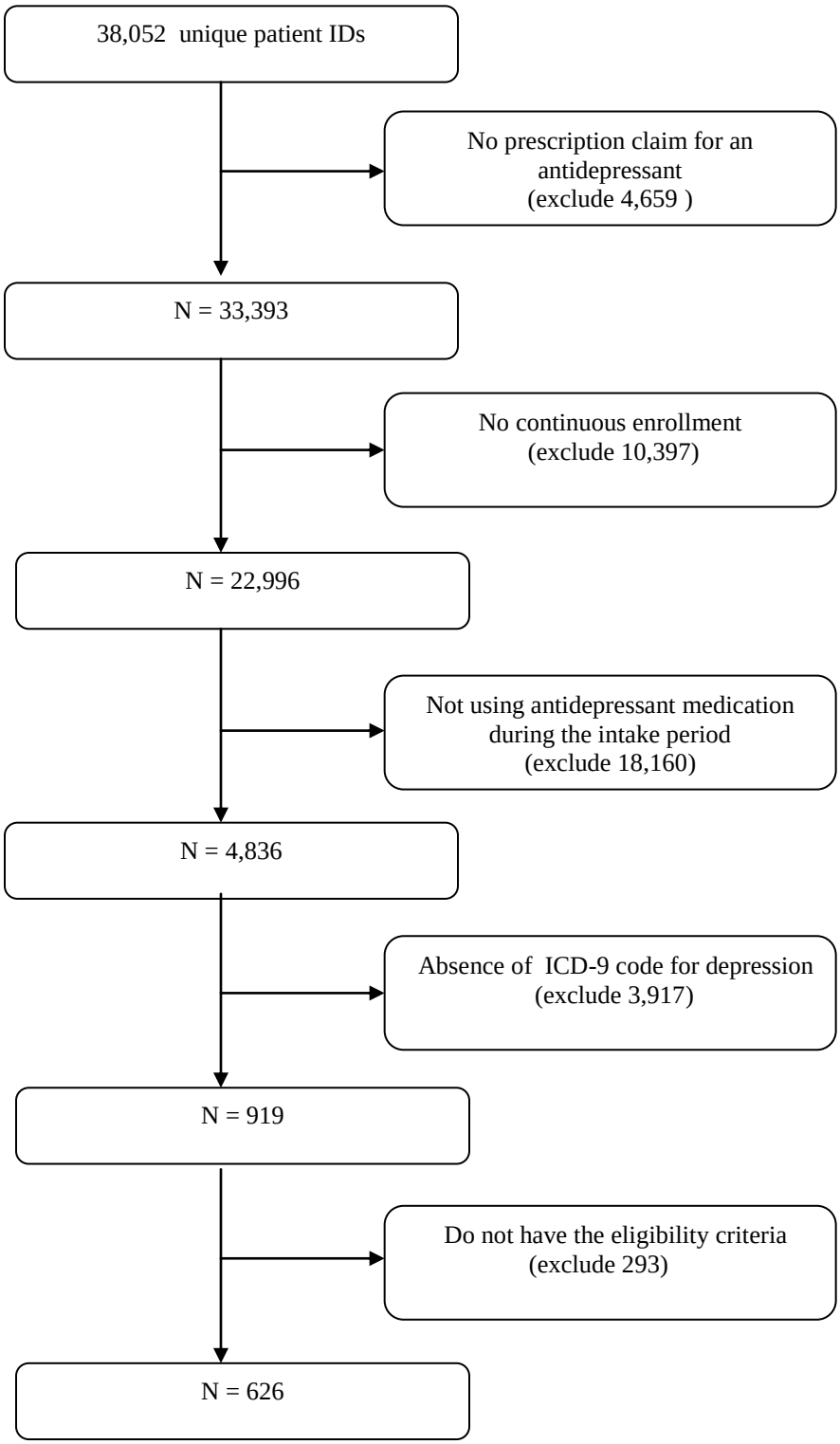


Figure 2. Eligibility criteria for Inclusion and Exclusion Criteria for PDC methodology

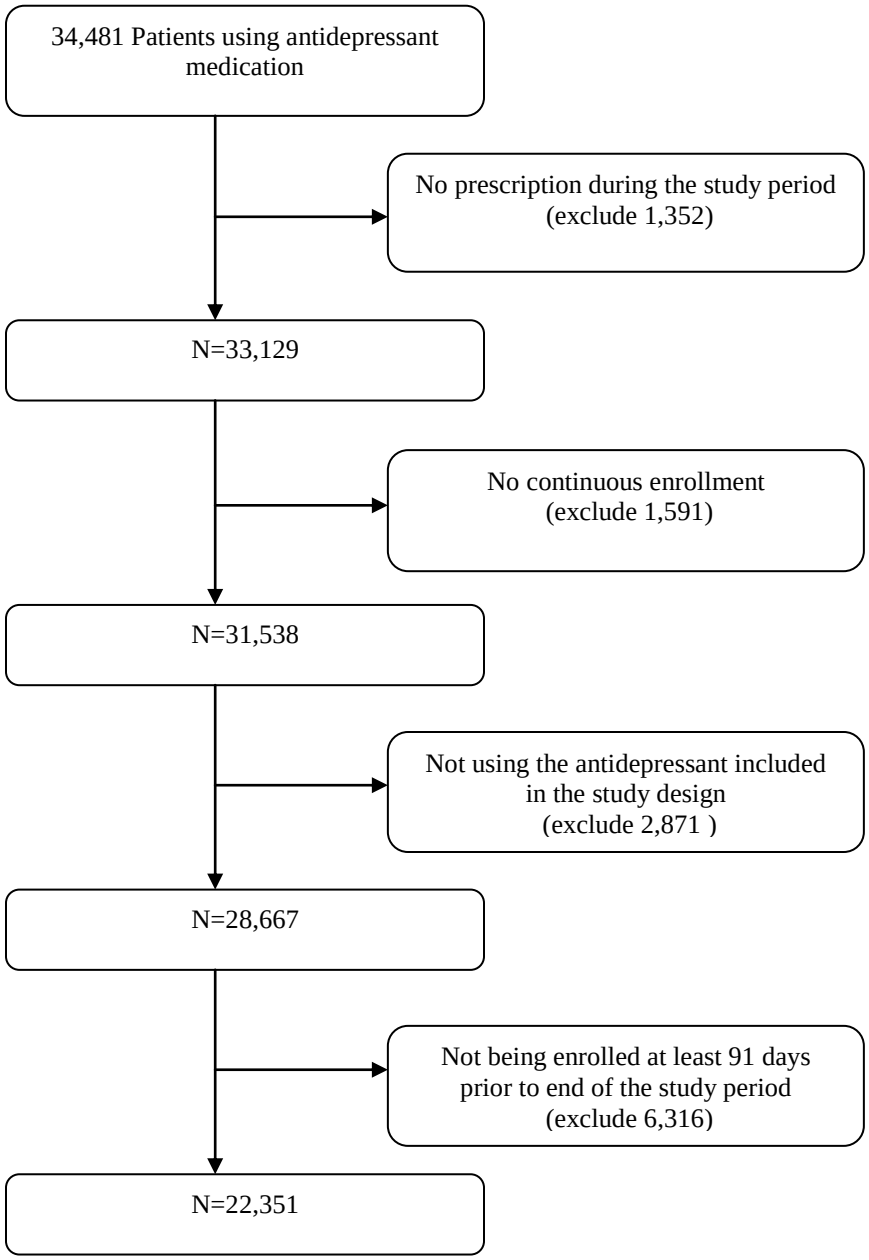


Table 1. Baseline Characteristics of Patients Identified for Antidepressant Adherence Measurement Using HEDIS[1] and PDC[2] methodology

Characteristic	HEDIS[1] N = 626 % (n)		PDC[2] N = 22,351 % (n)		P value
Age, years Mean Age [SD]	37.59 [12.16]		42.76 [12.42]		< 0.001
	% (n)		**% (n)**		
Age < 35	44.73 (280)		29.43 (6579)		
35≤ Age <49	35.30 (221)		37.06 (8242)		
50 ≤ Age	19.97 (125)		33.50 (7488)		
	% (n)				
Gender	**% (n)**		**% (n)**		< 0.001
Male	20.48 (128)		27.86 (6228)		
Female	79.52 (497)		72.14 (16123)		
Comorbid Disease	**Present**	**Absent**	**Present**	**Absent**	**P value**
	% (n)		**% (n)**		
Diabetes	7.35 (46)	92.65 (580)	11.69 (2613)	88.31 (19738)	0.008
Cardiovascular	13.42 (84)	85.58 (542)	14.45 (3230)	85.55 (19121)	0.468
Respiratory	6.55 (41)	93.45 (585)	6.17 (1178)	20973 (93.83)	0.694
Mental Health	33.07 (207)	66.93 (419)	21.28 (4757)	78.92 (17594)	<0.001
Health Care Utilization	**Present**	**Absent**	**Present**	**Absent**	**P value**
	% (n)		**% (n)**		
Psychiatric visits	74.60 (467)	25.40 (159)	36.54 (8168)	63.46 (14183)	< 0.001
Hospitalization	27.48 (172)	72.52 (454)	16.71 (3735)	83.29 (18616)	<0.001
Therapy Regimen	**Present**	**Absent**	**Present**	**Absent**	**P value**
	% (n)		**% (n)**		
Monotherapy	57.99 (363)	42.01 (263)	69.50 (15534)	30.50 (6817)	<0.001
SSRI[3]	65.81 (412)	34.19 (214)	56.81 (12643)	43.19 (9611)	<0.001
SNRI[4]	4.95 (31)	95.05 (595)	7.49 (1667)	92.51 (28587)	0.017
Trazodone	12.62 (79)	87.38 (547)	11.91 (2651)	88.09 (19603)	0.590
TCA[5]	4.63 (29)	95.37 (597)	9.98 (2221)	90.02 (20033)	<0.001
Bupropion	8.31 (52)	91.69 (574)	10.04 (2235)	20019 (89.96)	0.153
Mirtazapine	3.35 (21)	96.65 (605)	3.62 (805)	96.38 (21449)	0.728

[1]HEDIS - patients have a diagnosis of depression
[2]PDC- includes all users of antidepressants irrespective of diagnosis
[3]SSRI-Selective Serotonin Reuptake Inhibitors Antidepressants,
[4]SNRI-Selective Serotonin-Norepinephrine Reuptake Inhibitors Antidepressants,
[5]TCA-Tricyclic antidepressants

* P value is significant. Pearson chi-square test was used for all categorical comparisons and the independent t-test for continuous variables with equal variance

Table 2. Descriptive statistics. Adherence results for HEDIS and PDC methodologies

Characteristics	HEDIS[1] N = 626 % (n)			PDC[2] N =22.351 % (n)		P Value
[1]Overall adherence	37.38% (234)			50.37 % (11,259)		
Age, years	Adherent	Non-adherent		Adherent	Non-adherent	
	% (n)		P Value	% (n)		P Value
Age < 35	28.67 (80)	71.33 (199)	<0.001*	37. 12 (2442)	62.88 (4137)	<0.001*
35 ≤ Age <49	38.91 (86)	38. 91 (135)		50.53 (4186)	49. 47 (4098)	
50 ≤ Age	53. 60 (67)	46. 40 (58)		61. 85 (4631)	38. 15 (2857)	
Gender	%(n)		P Value	% (n)		P Value
Male	35. 16 (45)	64. 84 (83)	0.6091	51.33 (3197)	48.67 (3031)	0.0758
Female	37.95 (189)	62.05 (309)		50.00 (8062)	50.00 (8061)	
Comorbid Disease	% (n)		P Value	% (n)		P Value
Diabetes	45.65 (21)	54.35 (25)	0.2678	61.35 (1603)	38.65 (1010)	<0.001*
Cardiovascular	44.05 (37)	55.95 (47)	0.1838	58.85 (1901)	41.15 (1329)	<0.001*
Respiratory	56.10 (23)	43.90 (18)	0.0123	62.19 (857)	37.81 (521)	<0.001*
Mental Health	42.03 (87)	57.97 (120)	0.0958	54.38 (2587)	45.62 (2170)	<0.001*
Health Care Utilization	% (n)		P Value	% (n)		P Value
Psychiatric visits	39.40 (184)	60.60 (283)	0.0874	56.00 (4574)	44.00 (3594)	<0.001*
Hospitalization	37.79 (65)	62.21 (107)	0.9264	8.65 (1933)	8.06 (1802)	0.0645
Therapy Regimen	% (n)		P Value	% (n)		P Value
Polytherapy	49.43 (130)	50.57 (133)	<0.001*	75.66 (5158)	24.34 (1659)	<0.001*
SSRI[3]	34.47 (142)	65.53 (270)	0.0450*	48.41 (6121)	51.59 (6522)	<0.001*
SNRI[4]	58.06 (18)	41.94 (13)	0.210	62.93 (1049)	37.07 (618)	<0.001*
Trazodone	36.71 (29)	63.29 (50)	1.000	56.21 (1490)	43.79 (1161)	<0.001*
TCA[5]	44.83 (13)	55.17 (16)	0.4342	42.73 (949)	57.27 (1272)	<0.001*
Bupropion	44.23 (23)	55.77 (29)	0.2975	51.01 (1140)	48.99 (1095)	0.5471
Mirtazapine	38.10 (8)	61.90 (13)	1.000	44.10 (355)	63.90 (450)	0.0016

[1]HEDIS - patients have a diagnosis of depression
[2]PDC- includes all users of antidepressants irrespective of diagnosis
[3]SSRI-Selective Serotonin Reuptake Inhibitors Antidepressants,
[4]SNRI-Selective Serotonin-Norepinephrine Reuptake Inhibitors Antidepressants,
[5]TCA-Tricyclic antidepressants
Patients will be considered adherent to their medication if PDC >80% and non-adherent if PDC <80%.
* P value is significant.

Table 3. Likelihood of adherence associated with antidepressant use for HEDIS[1] methodology. Univariate Logistic Regression Analyses

Characteristic	Beta Coefficient	Odds Ratio	95% Confidence Interval
Age, years			
Age < 35	-	-	Reference
35 ≤ Age <49	0.4478*	1.565*	1.077 - 2.275
50 ≤ Age	1.0430*	2.838*	1.834 - 4.389
Gender			
Female	-	-	Reference
Male	-0.1206	0.886	0.591 - 1.330
Comorbid Disease			
Diabetes	0.3697	1.447	0.971 - 2.648
Cardiovascular	0.3211	1.379	0.866 - 2.195
Respiratory	0.8174*	2.265*	1.159 - 4.293
Mental Health	0.2938	1.341	0.954 - 1.887
Health Care Utilization			
Psychiatric visits	0.3488	1.417	0.967 - 2.078
Hospitalization	0.0242	1.024	0.713 - 1.472
Therapy Regimen			
Polytherapy	08895*	2.434*	1.746 - 3.392
SSRI[2]	-0.3604	0.697*	0.497 - 0.978
SNRI[3]	0.8875	2.429*	1.167 - 5.054
Trazodone	0.0328	0.968	0.593 - 1.578
TCA[4]	0.3238	1.382	0.653 - 2.928
Bupropion	0.3107	1.364	0.769 - 1.300
Mirtazapine	0.0316	1.032	0.421 - 2.528

[1]HEDIS - patients have a diagnosis of depression
[2]SSRI-Selective Serotonin Reuptake Inhibitors Antidepressants,
[3]SNRI-Selective Serotonin-Norepinephrine Reuptake Inhibitors Antidepressants,
[4]TCA-Tricyclic antidepressants

* P value<=0.2 is significant.

Table 4. Likelihood of adherence associated with antidepressant medication use for PDC[1] methodology. Univariate Logistic Regression Analyses

Characteristic	Beta Coefficient	Odds Ratio	95% Confidence Interval
Age, years			
Age < 35	-	-	Reference
35 ≤ Age <49	0.5484*	1.730*	1.620 - 1.849
50 ≤ Age	1.0101*	2.746*	2.564 - 2.940
Gender			
Female	-	-	Reference
Male	0.0532	1.055	0.995 - 1.118
Comorbid Disease			
Diabetes	0.5051*	1.657*	1.524 - 1.802
Cardiovascular	0.4003*	1.492*	1.384 - 1.609
Respiratory	0.5138*	1.672	1.494 - 1.870
Mental Health	0.2042*	1.227*	1.150 - 1.308
Health Care Utilization			
Psychiatric visits	0.3559*	1.427	1.351 - 1.508
Hospitalization	0.0663	1.069	0.996 - 1.146
Therapy Regimen			
Polytherapy	1.5701*	4.807*	4.509 - 5.125
SSRI[2]	-0.1835*	0.832*	0.789 - 0.878
SNRI[3]	0.5539*	1.740*	1.570 - 1.929
Trazodone	0.2651*	1.304*	1.201 - 1.415
TCA[4]	-0.3428*	0.710	0.650 - 0.776
Bupropion	0.0272	1.028	0.942 - 1.121
Mirtazapine	0.2296*	1.258	1.092 - 1.405

[1]PDC- includes all users of antidepressants irrespective of diagnosis
[2]SSRI-Selective Serotonin Reuptake Inhibitors Antidepressants,
[3]SNRI-Selective Serotonin-Norepinephrine Reuptake Inhibitors Antidepressants,
[4]TCA-Tricyclic antidepressants

* P value<=0.2 is significant for model selection.

Table 5. Fitted Reduced Model for HEDIS[1] methodology. Likelihood of antidepressant medication adherence according to selected characteristics

Characteristic	Beta Coefficient	Odds Ratio	95% Confidence Interval
Age, years			
Age < 35	-	-	Reference
35 ≤ Age <49	0.3190*	1.376	0.932 - 2.030
50 ≤ Age	0.9463*	2.576	1.626 - 4.083
Gender			
Female	-	-	Reference
Male	-0.3017	0.740	0.481 – 1.138
Comorbid Disease			
Respiratory	0.5567*	1.745	0.894 - 3.406
Mental Health	0.3213	1.379	0.964 - 1.973
Therapy Regimen			
Polytherapy	0.3213*	2.214	1.570 - 3.121

[1]HEDIS - patients have a diagnosis of depression
* P < 0.05

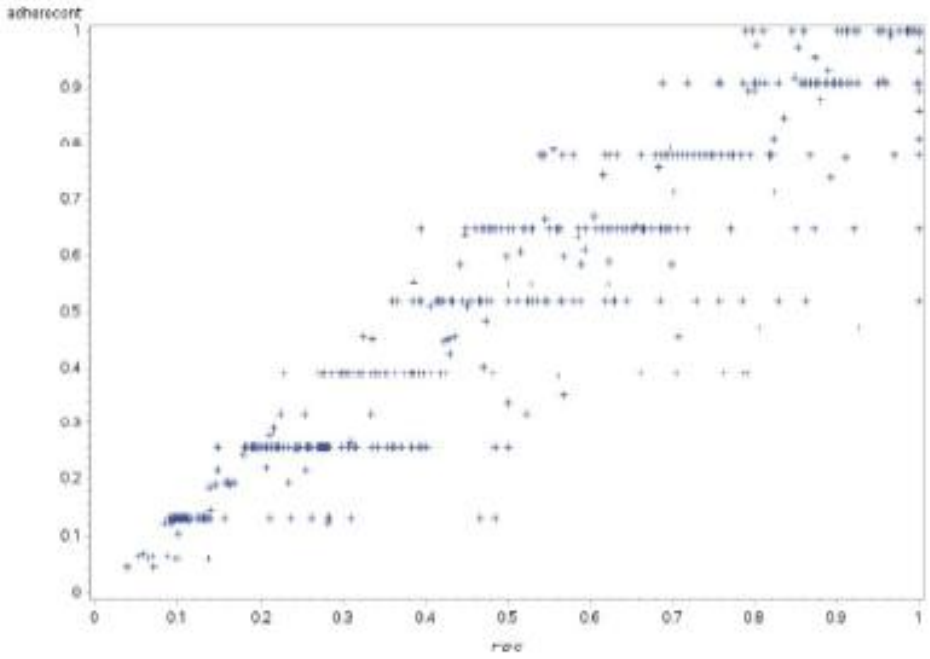
Table 6. Fitted Reduced Model for PDC[1] methodology. Likelihood of antidepressant medication adherence according to selected characteristics

Characteristic	Beta Coefficient	Odds Ratio	95% Confidence Interval
Age, years			
Age < 35	-	-	Reference
35 ≤ Age <49	0.5484*	1.730	1.620 - 1.849
50 ≤ Age	1.0101*	2.746	2.564 - 2.940
Gender			
Female	-	-	Reference
Male	0.0532	1.055	0.995 - 1.118
Comorbid Disease			
Diabetes	0.5051*	1.657	1.524 -1.802
Cardiovascular	0.4003*	1.492	1.384 - 1.609
Respiratory	0.5138*	1.672	1.594 - 1.870
Mental Health	0.2042*	1.227	1.150 - 1.308
Therapy Regimen			
Polytherapy	1.5701*	4.807	4.509 - 5.125
SNRI[2]	0.5339*	1.740	1.570 - 1.929
SSRI[3]	-0.1835*	0.832	0.789 - 0.878

[1]PDC- includes all users of antidepressants irrespective of diagnosis
[2]SSRI-Selective Serotonin Reuptake Inhibitors Antidepressants,
[3]SNRI-Selective Serotonin-Norepinephrine Reuptake Inhibitors Antidepressants,

* $P < 0.05$

Figure 3. Correlation between continuous adherence measures comparing HEDIS method and PDC adherence calculation method applied to HEDIS cohort



LIST OF REFERENCES

1. Iuga AO, McGuire MJ. Adherence and health care costs. Risk Manag Healthc Policy. 2014;7:35-44. 10.2147/RMHP.S19801.

2. World Health Organization. Adherence to long-term therapies: Evidence for action. Geneva, Switzerland: World Health Organization, 2003.

3. Osterberg L, Blaschke T. Adherence to Medication. N Engl J Med. 2005;353(5):487-497.

4. American Psychiatric Association. Practice Guideline for the Treatment of Patients with Major Depressive Disorder, 3rd Edition. Washington, DC: American Psychiatric Press Inc; 2010.

5. Pratt LA, Brody DJ. Depression in the United States household population, 2005-2006. NCHS Data Brief. 2008; (7)(7):1-8.

6. Pratt LA, Brody DJ, Gu Q. Antidepressant use in persons aged 12 and over: United States, 2005-2008. NCHS Data Brief. 2011;(76)(76):1-8.

7. Kessler RC, Barber C, Birnbaum HG, et al. Depression in the workplace: Effects on short-term disability. Health Aff (Millwood). 1999;18(5):163-171.

8. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: Results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003;289(23):3095-3105. .

9. Lerner D, Adler DA, Chang H, et al. Unemployment, job retention, and productivity loss among employees with depression. Psychiatr Serv. 2004;55(12):1371-1378.

10. Murray CJ, Lopez AD. Measuring the global burden of disease. N Engl J Med. 2013;369(5):448-457.

11. Lorant V, Deliege D, Eaton W, Robert A, Philippot P, Ansseau M. Socioeconomic inequalities in depression: A meta-analysis. Am J Epidemiol. 2003;157(2):98-112.

12. Pratt LA, Brody DJ. Depression in the U.S. household population, 2009-2012. NCHS Data Brief. 2014;(172)(172):1-8.

13. Centers for disease control and prevention (CDC). Web-based injury statistics query and reporting system (WISQARS) (2013, 2011) National Center for Injury Prevention and Control, CDC. Available at www.cdc.gov/injury/wisqars/index.html. Accessed last 3/15/2016

14. Smith JP, Smith GC. Long-term economic costs of psychological problems during childhood. Soc Sci Med. 2010;71(1):11011.

15. Gaynes BN, Warden D, Trivedi MH, Wisniewski SR, Fava M, Rush AJ. What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. Psychiatr Serv. 2009;60(11):1439-1445.

16. Nose M, Barbui C, Gray R, Tansella M. Clinical interventions for treatment non-adherence in psychosis: Meta- analysis. Br J Psychiatry. 2003;183:197-206.

17. IMS Health National Prescription Audit PLUS 2010. Available at https://www.google.com/webhp?sourceid=chrome-instant&ion=1&espv=2&ie=UTF-8#q=IMS+Health+National+Prescription+Audit+PLUS+2010. Accessed last 3/15/2016

18. Nemeroff CB. Prevalence and management of treatment-resistant depression. J Clin Psychiatry. 2007;68 Suppl 8:17-25.

19. HEDIS- Antidepressant Medication Management (AMM). Available at: https://www.google.com/webhp?sourceid=chrome-instant&ion=1&espv=2&ie=UTF. Accessed last 3/10/2016

19. Katon W, Cantrell CR, Sokol MC, Chiao E, Gdovin JM. Impact of antidepressant drug adherence on comorbid medication use and resource utilization. Arch Intern Med. 2005;165(21):2497-2503.

20. Akincigil A, Bowblis JR, Levin C, Walkup JT, Jan S, Crystal S. Adherence to antidepressant treatment among privately insured patients diagnosed with depression. Med Care. 2007; 45(4):363-369.

21. Jeon-Slaughter H. Economic factors in of patients' non-adherence to antidepressant treatment. Soc Psychiatry Psychiatr Epidemiol. 2012;47(12):1985-1998.

22. Finley PR, Rens HR, Pont JT, et al. Impact of a collaborative care model on depression in a primary care setting: A randomized controlled trial. Pharmacotherapy. 2003;23(9):1175-1185.

23. Hoffman L1, Enders J, Luo J, Segal R, Pippins J, Kimberlin C. Impact of an antidepressant management program on medication adherence. Am J Manag Care. 2003 Jan;9(1):70-80.

24. US department of health and human services 2008. Available at: https://store.samhsa.gov/shin/content/SMA10- 4590/SMA10- 4590.pdf. Accessed last 3/20/2016.

APPENDIX A

ICD-9 CODES TO IDENTIFY DIABETES

25000 25001 25002 25003 25010 25011 25012 25013 25020 25021 25022 25023 25030 25031
25032 25033 25040 25041 25042 25043 25050 25051 25052 25053 25060 25061 25062 25063
25070 25071 25072 25073 25080 25081 25082 25083 25090 25091 25092 25093 3572 36201
36202 36203 36204 36205 36206 36207 36641 64801 64802 64803 64804

DRUG THERAPEUTIC CLASS TO IDENTIFY DIABETES

C4G C4F C4K C4L C4N C4R C4S C4T

-Diabetes mellitus type I

-Diabetes mellitus type II

APPENDIX B

ICD-9 CODES TO IDENTIFY CARDIOVASCULAR DISEASE

401 40100 4010 4011 4019 425 4250 4251 42511 42518 4352 4253 4254 4255 4257 4258 4259 428 4280 4281 4282 42820 42821 42822 42823 4283 42830 42831 42832 42833 4284 42840 42841 42842 42843 4289 413 4130 41300 41310 41390 41000 41001 41002 41010 41011 41012 41020 41021 41022 41030 41031 41032 41040 41041 41042 41050 41051 41052 41060 41061 41062 41070 41071 41080 41081 41082 41090 41091 41092 41100 41110 41181 41189 41200 41300 41310 41390 41401 41403 41404 41405 41406 41407 41410 41411 41412 41419 41480 41490 42800 42810 42820 42821 42822 42823 42830 42831 42832 42833 42840 42841 42842 42843 42890 40201 40211 40291 40401 40411 40491 40403 40413 40493 39891

-High blood pressure

-Hyperpiesia

-Hypertensive heart disease

-Malignant hypertensive heart disease

-Benign hypertensive heart disease

-Unspecified hypertensive heart disease

-Acute myocarditis

-Acute percarditis

-Heart failure

APPENDIX C

ICD-9 CODES TO IDENTITY RESPIRATORY DISEASE

493 4930 29300 49301 49302 4931 49310 49311 49312 4938 49381 49382 4939 49390 49391 49392 4932 49320 49321 49322 496 4960 49600 49100 466 491 4910 49100 4911 4912 49120 49121 49122 4918 4919 4912 49120 49121 49122

-Bronchitis

-Emphysema

-Asthma

-Bronchiectasis

-Extrinsic allergic alveolitis

-Chronic airway obstruction

APPENDIX D

ICD-9 CODES TO IDENTIFY MENTAL HEALTH DISEASE

296 2960 29600 29601 29602 29603 29604 29605 29606 2961 29611 29612 29613 29614 29615 29616 2964 29640 29616 2964 29640 29641 29642 29643 29644 29645 29646 2965 29650 29651 29652 29653 29654 29656 2966 29660 29662 29663 29664 29665 2967 300 3000 30000 30001 30002 30009 30021 3003 3009 295 29500 30001 30002 30009 30021 3003 3009 295 2950 29500 29501 29502 29503 29504 29505 2951 29510 29511 29512 29513 29515 2952 29520 29521 29522 29523 29524 29525 2953 29530 29531 25932 29533 29534 29535 2954 29540 29541 29542 29543 29544 29545 2955 29550 29551 29552 29553 29554 29555 2956 29561 29562 29563 29564 29565 2957 29570 29571 29572 29573 29574 29575 2958 29580 29581 29582 29583 29584 29585 2959 29591 29592 29593 29594 29595

-Episodic mood disorders

-Bipolar disorder

-Manic disorder

-Major depressive disorder

-Schizophrenia

-Anxiety

-Phobic disorders

-Somatoform disorders

APPENDIX E

ANTIDEPRESSANT MEDICATIONS LIST

- Selective Serotonin Reuptake Inhibitors Antidepressants (SSRIs)

  Citalopram; Escitalopram; Fluoxetine; Fluvoxamine; Paroxetine; Sertraline

- Selective Serotonin-Norepinephrine Reuptake Inhibitors Antidepressants (SSNRIs)

  Desvenlafaxine; Duloxetine; Venlafaxine;

- Tetracyclic Antidepressants (TeCAs)

  Maprotiline; Mirtazapine;

- Monoamine Oxidase Inhibitors (MAOIs)

  Isocarboxazid; Selegiline; Phenelzine; Tranylcypromine

- Phenylpiperazine Antidepressants

  Nefazodone; Trazodone

- Psychotherapeutic combinations

  Amitriptyline-clordiazepoxide; Amitriptyline-perphenazine ; Fluoxetine-olanzapine;

- Tricyclic antidepressants (TCAs)

  Amitriptyline; Amoxapine; Clomipramine; Desipramine; Doxepin; Imipramine;

  Nortryptiline; Protryptyline; Trimipramine

- Miscellaneous Antidepressants

  Bupropion; Vilazodone

BIBLIOGRAPHY

Iuga AO, McGuire MJ. Adherence and health care costs. Risk Manag Healthc Policy. 2014;7:35-44. 10.2147/RMHP.S19801.

World Health Organization. Adherence to long-term therapies: Evidence for action. Geneva, Switzerland: World Health Organization, 2003.

Osterberg L, Blaschke T. Adherence to Medication. N Engl J Med. 2005;353(5):487-497. 353/5/487.

American Psychiatric Association. Practice Guideline for the Treatment of Patients with Major Depressive Disorder, 3rd Edition. Washington, DC: American Psychiatric Press Inc; 2010.

Pratt LA, Brody DJ. Depression in the United States household population, 2005-2006. NCHS Data Brief. 2008; (7)(7):1-8.

Pratt LA, Brody DJ, Gu Q. Antidepressant use in persons aged 12 and over: United States, 2005-2008. NCHS Data Brief. 2011;(76)(76):1-8.

Kessler RC, Barber C, Birnbaum HG, et al. Depression in the workplace: Effects on short-term disability. Health Aff (Millwood). 1999;18(5):163-171.

Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: Results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003;289(23):3095-3105. 10.1001/jama.289.23.3095.

Lerner D, Adler DA, Chang H, et al. Unemployment, job retention, and productivity loss among employees with depression. Psychiatr Serv. 2004;55(12):1371-1378. 55/12/1371.

Murray CJ, Lopez AD. Measuring the global burden of disease. N Engl J Med. 2013;369(5):448-457. 10.1056/NEJMra1201534.

Lorant V, Deliege D, Eaton W, Robert A, Philippot P, Ansseau M. Socioeconomic inequalities in depression: A meta-analysis. Am J Epidemiol. 2003;157(2):98-112.

Pratt LA, Brody DJ. Depression in the U.S. household population, 2009-2012. NCHS Data Brief. 2014;(172)(172):1-8.

Centers for disease control and prevention (CDC). Web-based injury statistics query and reporting system (WISQARS) (2013, 2011) National Center for Injury Prevention and Control, CDC. Available at www.cdc.gov/injury/wisqars/index.html. Accesed last 3/15/2016

Smith JP, Smith GC. Long-term economic costs of psychological problems during childhood. Soc Sci Med. 2010;71(1):11011

Gaynes BN, Warden D, Trivedi MH, Wisniewski SR, Fava M, Rush AJ. What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. Psychiatr Serv. 2009;60(11):1439-1445. 10.1176/appi.ps.60.11.1439.

Nose M, Barbui C, Gray R, Tansella M. Clinical interventions for treatment non-adherence in psychosis: Meta- analysis. Br J Psychiatry. 2003;183:197-206.

IMS Health National Prescription Audit PLUS 2010. Available at https://www.google.com/webhp?sourceid=chrome-instant&ion=1&espv=2&ie=UTF-8#q=IMS+Health+National+Prescription+Audit+PLUS+2010. Accessed last 3/15/2016

Nemeroff CB. Prevalence and management of treatment-resistant depression. J Clin Psychiatry. 2007;68 Suppl 8:17-25.

HEDIS- Antidepressant Medication Management (AMM). Available at https://www.google.com/webhp?sourceid=chrome-instant&ion=1&espv=2&ie=UTF. Accesed last 3/10/2016

Katon W, Cantrell CR, Sokol MC, Chiao E, Gdovin JM. Impact of antidepressant drug adherence on comorbid medication use and resource utilization. Arch Intern Med. 2005;165(21):2497-2503.165/21/2497.

Akincigil A, Bowblis JR, Levin C, Walkup JT, Jan S, Crystal S. Adherence to antidepressant treatment among privately insured patients diagnosed with depression. Med Care. 2007;45(4):363-369. 10.1097/01.mlr.0000254574.23418.f6.

Jeon-Slaughter H. Economic factors in of patients' non-adherence to antidepressant treatment. Soc Psychiatry Psychiatr Epidemiol. 2012;47(12):1985-1998. 10.1007/s00127-012-0497-6.

Finley PR, Rens HR, Pont JT, et al. Impact of a collaborative care model on depression in a primary care setting: A randomized controlled trial. Pharmacotherapy. 2003;23(9):1175-1185.

Hoffman L1, Enders J, Luo J, Segal R, Pippins J, Kimberlin C. Impact of an antidepressant management program on medication adherence. Am J Manag Care. 2003 Jan;9(1):70-80.

US department of health and human services 2008. Available at https://store.samhsa.gov/shin/content/SMA10- 4590/SMA10- 4590.pdf. Accessed last 3/20/2016.