Healthcare Resource Utilization and Costs Associated with Non-Adherence to Pharmacotherapy for Major Depressive Disorder

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Abstract

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BACKGROUND: Major Depressive Disorder (MDD) affects more than 16 million adults in the United States (US) and accounted for $210 billion in direct and indirect costs in the US in 2010. Pharmacological treatments for MDD include selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and other antidepressants; however, non-adherence to MDD pharmacotherapy is common and is associated with poorer clinical outcomes.

OBJECTIVE: To assess the impact of non-adherence to MDD pharmacotherapy on healthcare resource use (HCRU) and costs in MDD patients enrolled in commercial, Medicare Supplemental, and Medicaid insurance.

METHODS: This was a retrospective cohort study conducted using administrative claims data from the IBM® MarketScan® Commercial, Medicare Supplemental, and Medicaid Multi-State databases from January 1, 2010 – December 31, 2017. We identified adult MDD patients ≥ 18 years with an initial diagnosis of MDD and who newly initiated antidepressant therapy between January 1, 2011 and December 31, 2016. Included patients were required to have no MDD or antidepressant claims in the 12-month baseline period prior to initial MDD diagnosis and have ≥ 12 months of continuous medical, pharmacy, and mental health/substance abuse benefits prior to the initial diagnosis date and following the index prescription date (date of first antidepressant fill within 60 days after the initial diagnosis date). Adherence to MDD pharmacotherapy at 6 months following the index prescription date was calculated using the Proportion of Days Covered (PDC) metric and included all antidepressants and augmentation agents. Adherent patients were defined as having PDC for MDD pharmacotherapy ≥ 80%. Twelve-month total all-cause HCRU by setting of care (inpatient, emergency room (ER), outpatient) and costs (total healthcare, medical, pharmacy, adjusted to 2018 US dollars) were characterized for patients who were adherent and non-adherent to MDD pharmacotherapy at 6 months. Multivariable negative binomial regression and generalized linear models with a log-link function and gamma distribution were used to estimate incidence rate ratios (IRRs) for HCRU and incremental costs of non-adherence compared to adherence, respectively. All multivariable analyses were adjusted for age, sex, geographic region, insurance type, index year, Charlson Comorbidity Index (CCI) score (continuous), and 12-month baseline costs.

RESULTS: A total of 5,988,383 adult MDD patients were identified, of which 163,410 patients met study inclusion criteria. Mean [standard deviation (SD)] age was 42 [16] years and the majority of patients were female (61%), had commercial insurance (87%), and were enrolled in Preferred Provider Organization (PPO) plans (53%). Forty-eight percent of adult MDD patients were non-adherent to MDD pharmacotherapy at 6 months, and mean [SD] PDC among non-adherent and adherent patients was 42% [20%] and 95% [6%], respectively ($p<0.001$). In the 12-month period following index antidepressant initiation, non-adherent patients experienced more all-cause inpatient hospitalizations (1.5 vs. 1.4, $p<0.001$), ER visits (1.9 vs 1.6, $p<0.001$), and other outpatient visits (7.7 vs. 7.2, $p<0.001$) compared to adherent patients. Non-adherent patients incurred non-significantly higher 12-month total all-cause medical costs ($10,240 vs.

$9,891; mean unadjusted difference: $349, 95% CI: -$19, $716), but lower total 12-month total all-cause healthcare costs ($12,242 vs. $12,587; mean unadjusted difference: -$345, 95% CI: -$735, $45) as a result of lower all-cause pharmacy costs ($2,003 vs. $2,697; mean unadjusted difference: -$694, 95% CI: -$788, $600). Adjusted analyses revealed that non-adherent patients were 1.19 (95% CI: 1.15, 1.23), 1.37 (95% CI: 1.34, 1.40), and 0.86 (95% CI: 0.86, 0.88) times as likely to have inpatient hospitalizations, ER visits, and outpatient visits compared to adherent patients, respectively. Adjusted incremental total medical, total pharmacy, and total healthcare costs associated with non-adherence to MDD pharmacotherapy were $367 (95% CI: $26, $708), -$984 (95% CI: -$1107, -$861), and -$508 (95% CI: -$881, -$135), respectively.

CONCLUSIONS: This study found higher all-cause inpatient and ER utilization and total medical costs, but lower total healthcare costs among patients who were non-adherent to MDD pharmacotherapy at 6 months. Non-adherent patients spent less on medications and received care in more expensive settings (inpatient and ER) than adherent patients.

TABLE OF CONTENTS

BACKGROUND

Major Depressive Disorder (MDD) affects more than 16 million Americans in the United States (US)[1] and is the leading cause of disability worldwide.[2] MDD is associated with substantial clinical and economic burden; in 2010, MDD was estimated to account for $210 billion in the United States, with total costs split approximately 50% between direct medical costs and indirect costs.[3]

The treatment of MDD includes pharmacological treatment (i.e., selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), esketamine), psychotherapy (i.e., cognitive behavioral therapy (CBT)), and other somatic therapies (i.e., electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS)). While the American Psychiatric Association (APA) guidelines currently recommend either SSRIs, SNRIs, mirtazapine, or bupropion as initial pharmacotherapy for most patients, treatment selection is guided by a variety of considerations, including efficacy, severity of symptoms, comorbidities, and patient preferences.[4]

Treatment of an MDD episode consists of a minimum of 6-12 weeks of initial treatment with pharmacotherapy or other treatment modalities to induce remission of symptoms (i.e., acute phase), which is followed by 4-9 months of continuation treatment to prevent relapse (i.e., continuation phase) and maintenance treatment for individuals with 3 or more major depressive episodes, chronic depression, or risk factors for recurrence. A minimum of 4-6 weeks is typically required to assess response to antidepressant therapy, but patients may experience improvement as early as 1-2 weeks. Strategies to address incomplete response or non-response to initial antidepressant therapy include dose escalation of the initial antidepressant, switching to another antidepressant, combination antidepressant therapy, or augmentation with an antipsychotic agent.[4]

While existing pharmacological MDD agents remain widely used in the initial treatment of an MDD episode per the APA guidelines, non-adherence and non-persistence are common with these agents, with only 44% and 48% of patients remaining adherent or persistent to

antidepressant therapy at 3 months.[5] Commonly-cited reasons for non-adherence to MDD pharmacotherapy include lack of efficacy,[6] intolerability,[6] regimen complexity,[7] out-of-pocket costs,[7] and patient beliefs about antidepressant medications.[8,9] Non-adherence and non-persistence to MDD pharmacotherapy are associated with increased healthcare resource utilization (HCRU)[10,11] and risk of relapse and recurrence.[12,13]

Although non-adherence to MDD pharmacotherapy is well-documented, recent literature on the impact of non-adherence on HCRU and costs in MDD is limited. Most of these studies have focused on specific comorbid MDD populations, including patients with comorbid diabetes, chronic obstructive pulmonary disease, and coronary artery disease.[14–17] Additionally, there are inconsistent definitions of adherence to antidepressants used in the existing literature,[18] and studies that examine the impact of non-adherence on clinical and economic outcomes with standardized objective measures of adherence (i.e., PDC ≥ 80%) are needed. The aim of this study is to update the existing literature on the impact of non-adherence on HCRU and costs in MDD.

OBJECTIVE

The primary objective of this study was to assess the impact of non-adherence to MDD pharmacotherapy on HCRU and costs in MDD patients enrolled in commercial, Medicare Supplemental, and Medicaid insurance.

METHODS

Study Design and Data Source

This was a retrospective cohort study using administrative claims data from the IBM® MarketScan® Commercial, Medicare Supplemental, and Medicaid Multi-State databases from January 1, 2010 – December 31, 2017 (Figure 1). The IBM® MarketScan® Commercial Database consists of employer and health plan medical and pharmacy claims data for more than 40 million commercial plan members annually. Enrollees include employees, their spouses and dependents who are covered by employer-sponsored private health insurance. A variety of Fee for Service (FFS), fully capitated, and partially capitated health plans are represented in the MarketScan® Commercial database, including Point of Service (PPOs) and Exclusive Provider Organizations

(EPOs), Preferred Provider Organization (POS) plans, indemnity plans, Health Maintenance Organization (HMOs), Consumer-Driven Health Plans (CDHPs), and High-Deductible Health Plans (HDHPs). Medical claims are linked to outpatient prescription drug claims and person-level enrollment information. The IBM® MarketScan® Medicare Supplemental Database contains data on Medicare-covered portion of payment (i.e., Coordination of Benefits Amount (COB)), employer- and out-of-pocket patient expenses for healthcare services provided in inpatient and outpatient settings for US Medicare beneficiaries. Medical claims are linked to outpatient prescription drug claims and person-level enrollment information. The IBM® MarketScan® Multi-State Database contains data for inpatient services, inpatient admissions, outpatient services, prescription drug claims, long-term care, and other medical care for more than 44 million Medicaid enrollees nationally.[19]

This study did not meet the definition of human subjects research and therefore did not require University of Washington Institutional Review Board (IRB) approval, as the MarketScan® databases are de-identified and compliant with the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Study Population

Inclusion Criteria

The study population consisted of adult patients with MDD who were identified between January 1, 2011 and December 31, 2016 and initiated an antidepressant for the treatment of MDD within 60 days after a medical claim containing an MDD diagnosis. Patients with MDD were defined as having either having ≥ 1 inpatient medical claim with a primary International Classification of Diseases-9th Revision-Clinical Modification (ICD-9-CM) or ICD-10-CM diagnosis code of MDD or ≥1 inpatient or outpatient medical claim with a secondary ICD-9-CM or ICD-10-CM diagnosis code of MDD with a 2nd confirmatory inpatient or outpatient claim with an ICD-9-CM or ICD-10-CM diagnosis code of MDD in any position within 6 months after the inpatient medical claim (Appendix A). The date of the first qualifying MDD diagnosis between January 1, 2011 and December 31, 2016 was defined as the initial MDD diagnosis date. Antidepressants for MDD included SSRIs, SNRIs, MAOIs, TCAs, and other antidepressants (Appendix B.1). To ensure antidepressant claims were for the treatment of MDD, the index prescription date was

defined as the date of the first antidepressant pharmacy claim (Appendix B.1) within 60 days after a qualifying MDD diagnosis (Figure 1).[5] Patients were required to be ≥18 years at index prescription date and have continuous enrollment, defined as no gaps in coverage for ≥ 31 days, in medical, pharmacy, and mental health/substance abuse benefits for 12 months prior to the initial MDD diagnosis date (baseline period) and 12 months after the index prescription date. The baseline period was used to assess patient clinical and demographic characteristics at baseline. The post-index period was defined as the 12-month period following the index prescription date.

Exclusion Criteria

Patients were excluded if they had diagnoses for bipolar/manic disorder, Alzheimer's disease, Parkinson's disease, dementia, or evidence of pregnancy, childbirth, or breastfeeding at any time during the study period (Appendix C). Additionally, patients with diagnoses of schizophrenic disorder, psychosis-related disorders, drug-induced depression, or depressive type psychosis in the 12-month baseline period prior to the initial MDD diagnosis date were excluded (Appendix D). Additional exclusions included any MDD claims or claims for antidepressants or combination antidepressant/antipsychotic agents (Appendix B.2) (i.e., amitriptyline/ perphenazine, fluoxetine/olanzapine) in the 12-month baseline period and evidence of combination antidepressant therapy or augmentation therapy on or within 30 days of the index prescription date. Combination therapy was defined by either initiating a 2nd antidepressant with a different active ingredient on or within 30 days after the index prescription date[20] that overlaps with the index antidepressant for ≥ 30 days during the study period or initiating an antipsychotic, mood stabilizer, or combination antidepressant/antipsychotic agent on or within 30 days after the index prescription date[20] that overlaps with the index antidepressant for ≥ 30 days during the study period. The overlap did not need to be consecutive. Medicaid patients who were dually-eligible for Medicare benefits were excluded due to incompleteness of claims data for these enrollees.

Baseline Demographic and Clinical Characteristics

Baseline demographic characteristics included age, sex, insurance type, plan type, geographic region, and total all-cause healthcare costs during the 12-month baseline period. Baseline clinical

characteristics included the Charlson Comorbidity Index (CCI)[21,22] and the following selected comorbidities of interest: anxiety, alcohol use disorder, substance use disorder, sleep disorders, coronary heart disease, congestive heart failure, chronic pulmonary disease, and diabetes.

Exposure of Interest – Medication Adherence

Adherence to MDD pharmacotherapy was estimated from pharmacy claims data using the Proportion of Days Covered (PDC) calculation.[23,24] PDC reflects the proportion of days covered by medication fills during a measurement period and represents a more accurate measure of adherence than the formerly widely used Medication Possession Ratio (MPR).[23,25] PDC was calculated for MDD pharmacotherapy overall; in other words, any antidepressant or augmentation agent for MDD was used toward the calculation of PDC (Figure 2). Adherent patients were defined as having PDC ≥ 80% and non-adherent patients were defined as having PDC < 80% to MDD pharmacotherapy at 6 months following initiation of the index antidepressant.

Adherence was measured over a 6-month measurement period starting from the index prescription date to 180 days following the index prescription date, which is most commonly used in the literature[11,14,16,26,27] and consistent with the National Committee for Quality Assurance (NCQA) Healthcare Effectiveness Data and Information Set (HEDIS) Antidepressant Medication Management Continuation Phase measure specifications.[28]

Study Outcomes

Healthcare Resource Utilization (HCRU)

For the primary analysis, HCRU was assessed over a 12-month period following the index prescription date. HCRU was categorized as all-cause (HCRU regardless of diagnosis code) and by setting of care (inpatient, emergency room (ER), outpatient) using place of service codes. Outpatient visits were further categorized as physician office visits and other outpatient visits excluding physician office and ER visits. HCRU included counts and percentages of patients with ≥ 1 inpatient, ER, and outpatient visit, mean [SD] inpatient hospitalization length of stay, and mean [SD] inpatient, ER, and outpatient visits per patient per year (PPPY) among patients with ≥ 1 inpatient, ER, and outpatient visit.

Costs

Costs were assessed over a 12-month period following the index prescription date. Costs were categorized as all-cause (regardless of diagnosis) and reported for medical, pharmacy, and total healthcare costs. Medical costs were further categorized by setting of care (inpatient, ER, outpatient (all), physician office, other outpatient).

All costs were adjusted to 2018 US dollars (USD) using the Bureau of Labor Statistics (BLS) medical care component of the Consumer Price Index (CPI).[29] Costs reflect all payments made to providers by insurers (i.e., plan and coordination of benefits) and patients (i.e., copay, co-insurance, deductible). Patients with any evidence of capitated claims were excluded from cost analyses. Additionally, claims with potentially invalid cost data (i.e., negative total costs) were excluded. All costs were reported as mean [SD] cost PPPY.

Statistical Analysis

Descriptive statistics were used to describe demographic and clinical characteristics during the 12-month baseline period, 12-month post-index all-cause HCRU, and 12-month post-index all-cause healthcare costs for the entire study population and cohorts categorized by 6-month adherence to MDD pharmacotherapy based on PDC. Unadjusted differences in HCRU and costs between adherent and non-adherent cohorts were assessed using chi-squared tests for categorical variables and unpaired t-tests with unequal variances for continuous variables. Additionally, unadjusted and adjusted multivariable negative binomial models were used to calculate incidence rate ratios to assess the association between adherence to MDD pharmacotherapy and 12-month post-index prescription hospitalization, ER visits, and outpatient visits. Differences in post-index all-cause pharmacy, medical, and total healthcare costs were assessed using unadjusted and adjusted multivariable generalized linear models (GLMs) using a log-link function and gamma distribution. Incremental costs of non-adherence compared to adherence were assessed using the recycled predictions method. Multivariable HCRU and cost models were adjusted for the following variables: age, sex, geographic region, insurance type, index year, CCI score (continuous), and 12-month baseline all-cause healthcare costs.

All statistical analyses were performed using RStudio version 1.1.463 (RStudio Inc., Boston, MA) and STATA/SE version 14.2 (StataCorp, College Station, TX). P-values ≤ 0.05 were considered statistically significant.

RESULTS

Baseline Characteristics

Of approximately 152 million patients identified in IBM® MarketScan® databases, a total of 5,988,383 adult MDD patients were identified between January 1, 2011 and December 31, 2016 (Figure 3). Of these, 163,410 adult MDD patients (3%) met all study inclusion criteria. The mean [SD] age for the overall study population was 42 [16] years (Table 1). The majority of patients were female (61%), had commercial insurance (87%), and were enrolled in Preferred Provider Organization (PPO) plans (53%). Thirty-five percent of the MDD study population resided in the South, and the prevalence of comorbidities was low for the overall MDD study population (mean [SD] CCI: 0.52 [1.24])). Compared to adherent patients, non-adherent patients were younger (mean [SD]: 41 [16] vs. 43 [16] years), a greater proportion were enrolled in Medicaid insurance (9% vs. 4%), had similar mean [SD] CCI (0.52 [1.24] vs 0.52 [1.23]), had a higher prevalence of substance use disorder (11% vs 7%), and lower baseline 12-month total all-cause healthcare costs ($10,370 [$37,318] vs $10,884 [37,543]). The most commonly prescribed index antidepressants were SSRIs (73%), followed by other antidepressant classes (16%). At 6 months, 48% of patients were non-adherent to MDD pharmacotherapy. Mean [SD] PDC among adherent and non-adherent patients was 95% [6%] and 42% [20%], respectively (Table 2).

Healthcare Resource Utilization

Non-adherent patients had significantly more all-cause inpatient hospitalizations (mean [SD]: 1.5 [1.2] hospitalizations vs. 1.4 [0.9] hospitalizations, p<0.001), ER visits (1.9 [2.4] visits vs. 1.6 [1.5] visits, p<0.001), and other outpatient visits (7.7 [18.5] vs. 7.2 [16.1] visits, p<0.001) compared to adherent patients in the 12-month period following the index prescription date (Table 3). Additionally, a greater proportion of non-adherent patients had all-cause inpatient hospitalizations (9% vs. 8%, p<0.001) and ER visits (27% vs. 20%, p<0.001) compared to adherent patients. However, mean [SD] length of stay per patient per inpatient hospitalization

was not significantly different between non-adherent and adherent patients (4.6 [4.8] vs. 4.4 [4.9], p=0.73). Adherent patients had an average [SD] of 15.1 [14.0] physician office visits per year, whereas non-adherent patients had an average [SD] of 12.6 [12.5] physician office visits.

After adjustment for age, sex, insurance type, geographic region, index year, CCI score, and baseline 12-month total all-cause healthcare costs, non-adherent patients were 1.19 (95% CI: 1.15, 1.23), 1.37 (95% CI: 1.34,1.40), and 0.86 (95% CI: 0.86,0.88) times as likely to have all-cause inpatient hospitalizations, ER visits, and outpatient visits compared to adherent patients, respectively (Table 4).

Costs

Non-adherent patients incurred non-significantly greater mean [SD] total 12-month all-cause medical costs ($10,240 [$36,902] vs. $9,891 [$31,858]; mean unadjusted difference: $349, 95% CI: -$19, $716), lower pharmacy costs ($2,003 [$8,671] vs. $2,697 [$8,973]; mean unadjusted difference: -$694, 95% CI: -$788, $600), and lower 12-month total healthcare ($12,242 [$38,797] vs. $12,587 [$34,215]; mean unadjusted difference: -$345, 95% CI: -$735, $45) compared to adherent patients (Table 5). Within medical costs, mean [SD] inpatient hospitalization ($3,272 [$26,071] vs. $2,697 [$21,286]; mean unadjusted difference: $575, 95% CI: $321, $829) and ER costs ($418 [$1,745] vs. $319 [$1,400]; mean unadjusted difference: $99, 95% CI: $82, $115) were significantly higher among non-adherent patients, while total outpatient costs were lower among non-adherent patients ($6,550 [$20,463] vs. $6,874 [$18,964]; mean unadjusted difference: -$324, 95% CI: -$534, -$115).

After adjustment for age, sex, insurance type, geographic region, index year, CCI score, and baseline 12-month total all-cause healthcare costs, non-adherence to MDD pharmacotherapy was significantly associated with $367 (95% CI: $26, $708) higher 12-month total all-cause medical costs, $984 (95% CI: -$1107, -$861) lower pharmacy costs, and $508 (95% CI: -$881, -$135) lower 12-month total healthcare costs, respectively (Table 5). Pharmacy costs accounted for the greatest difference in costs between non-adherent and adherent patients.

DISCUSSION

This retrospective study assessed the impact of non-adherence to MDD pharmacotherapy on 12-month all-cause total HCRU and costs among adult patients with newly diagnosed or new episodes of MDD who initiated antidepressant therapy for MDD. Consistent with prior studies, adherence to MDD pharmacotherapy at 6 months was poor, with only 48% remaining adherent to MDD pharmacotherapy at 6 months.

This study found a significantly higher risk of inpatient hospitalizations and ER visits among non-adherent patients compared to adherent patients, a finding that is consistent with previous studies.[11,15,17] Adherence to antidepressant therapy for MDD is also associated with better medication adherence and improved clinical outcomes in other chronic disease states, including diabetes, chronic obstructive pulmonary disease, and coronary artery disease,[14–17] which may subsequently result in reduced all-cause HCRU among patients who are adherent to MDD pharmacotherapy.

Similar to previously published studies,[10,14] non-adherent patients had significantly higher total 12-month medical costs compared to adherent patients after adjusting for age, sex, insurance type, geographic region, index year, CCI score, and baseline 12-month total healthcare costs. Consistent with greater inpatient hospitalizations and ER visits, non-adherent patients incurred significantly higher inpatient hospitalization and ER costs compared to adherent patients. Despite higher total medical costs, non-adherent patients had significantly lower total 12-month healthcare costs compared to adherent patients, which was driven by lower pharmacy costs. This finding is consistent with Birnbaum et al., which found lower total healthcare costs among non-compliant employees compared to compliant employees as a result of lower pharmacy costs.[30] Other studies have reported both higher total healthcare and total medical costs among non-adherent patients compared to adherent patients.[10,14,26] This discrepancy may be explained by several reasons. First, the MDD population reflected in this study may reflect a relatively healthier and less severe MDD population than prior studies, as this study was limited to patients with newly diagnosed or new episodes of MDD who newly initiated antidepressant therapy for MDD (i.e., absence of MDD and antidepressant claims in the 12-month baseline period), whereas other previous studies have included patients regardless of the presence of MDD claims

at baseline prior to initiation of antidepressant therapy. Indeed, the overall comorbidity burden in the MDD study population in this study was low (mean [SD] CCI: 0.52 [1.24]). Healthcare costs and mental health services utilization have been found to be substantially higher among patients with severe MDD compared to patients with mild MDD.[31] Therefore, reduced medical utilization and costs may not sufficiently offset the higher pharmacy costs associated with greater adherence to MDD pharmacotherapy in this study population. Additionally, recent literature has focused on the importance of prolonged or early gaps in therapy[14,32] and specific treatment patterns (i.e., switching, dose escalation)[20] on HCRU and costs in MDD. Early discontinuation within 30-90 days of initiation of antidepressant therapy has been independently associated with increased all-cause and psychiatric HCRU and costs in MDD patients.[14,32] Gauthier et al. found the greatest HCRU and healthcare costs among patients who switched within 6 weeks of initiating a first-line antidepressant, followed by patients who required dose escalation of initial antidepressant therapy.[20] Patients who require treatment switches or dose escalation following first-line antidepressant therapy may represent more complex, difficult-to-treat patients, regardless of medication adherence.

There are several strengths of the present study. First, this study provides a comprehensive update to the existing literature on the impact of non-adherence to MDD pharmacotherapy on HCRU and costs. To our knowledge, this is the largest real-world claims database study to evaluate the association of adherence to MDD pharmacotherapy and HCRU and costs to date, with over 160,000 adult MDD patients represented in this study. The study population was also representative of MDD patients with various insurance types (commercial, Medicare supplemental, Medicaid), plan types, and geographic regions.

Limitations

Several limitations of this study should be noted. First, the calculation of adherence to MDD pharmacotherapy was based on pharmacy claims data, which do not indicate whether a patient actually took their medication. Additionally, the PDC adherence calculation used in this study required only the supply of at least one medication used for MDD, even if it were an augmentation agent, which may inflate adherence to combination antidepressant therapy or augmentation therapy. For example, patients with only supply of an augmentation agent in the

absence of an antidepressant may be classified as adherent to MDD pharmacotherapy. Similarly, patients on combination antidepressant therapy who only have supply of only 1 antidepressant may be classified as adherent. As with other retrospective claims database studies, this study is subject to limitations inherent to administrative claims databases, including data coding errors, omissions, and misclassification. However, bias resulting from these errors would be expected to affect both adherence cohorts similarly. Importantly, this study did not consider indirect costs such as absenteeism or presenteeism costs, which have been found to be substantial in MDD[33] and estimated to account for up to 50% of the economic burden of MDD in the US.[3] Burton et al. found that employees who were non-adherent to acute and continuation phase antidepressant therapy were 38.7%-46.1% more likely to have short-term disability claims compared to adherent employees.[34] Therefore, the costs associated with non-adherence to MDD pharmacotherapy are likely to be underestimated in this study. Future studies are warranted to evaluate indirect costs in addition to direct costs in order to more fully characterize the economic burden of non-adherence to MDD pharmacotherapy. Furthermore, additional factors which may contribute to adherence, HCRU, and healthcare costs in MDD, such as disease severity,[31] prescriber specialty,[35] or other clinical characteristics, are not measured or adequately captured in claims databases. Other non-pharmacological interventions used for MDD such as psychotherapy and electroconvulsive therapy, which may influence HCRU and costs, were also not considered in this study. Finally, this study was limited to MDD patients without various comorbid psychiatric and cognitive disorders (i.e., schizophrenia, dementia) at baseline or during the entire study period. After applying all other exclusion criteria, the final study population represented only 3% of all adult MDD patients identified in MarketScan® databases during the study period. Therefore, these findings may not be generalizable to the broader U.S. MDD population consisting of patients with different characteristics from our study population, including patients with comorbid psychiatric and cognitive disorders, more severe MDD or treatment-resistant depression (TRD), insurance coverage outside of commercial, Medicare supplemental, or Medicaid plans, and uninsured individuals.

CONCLUSIONS

The results of this study found higher all-cause inpatient and ER HCRU and total medical costs, but lower total healthcare costs among patients who were non-adherent to MDD

pharmacotherapy at 6 months. Future studies are warranted to assess indirect costs in addition to direct costs to more fully characterize the economic burden of non-adherence to MDD pharmacotherapy.

FIGURES

Figure 1. Study Design

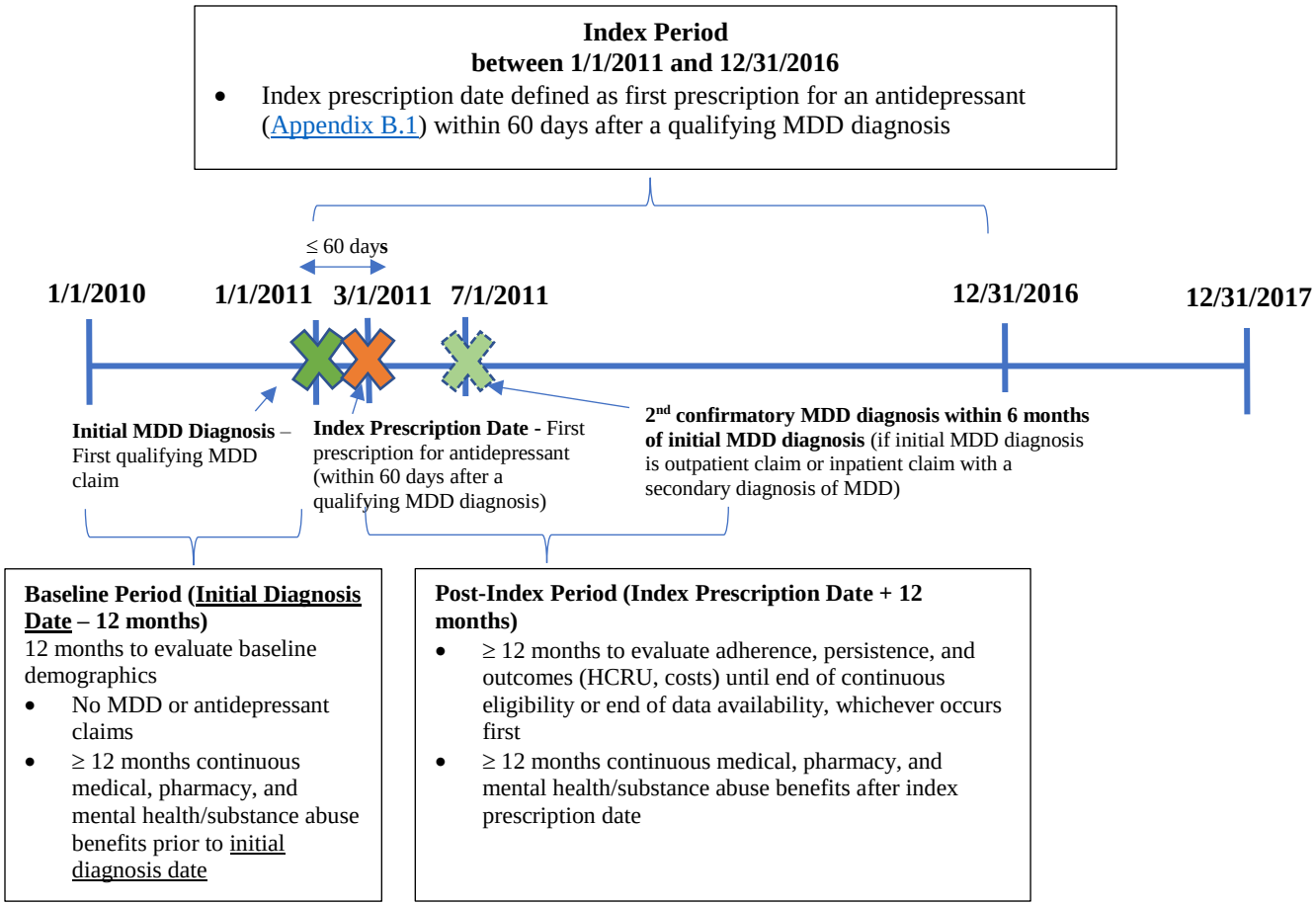
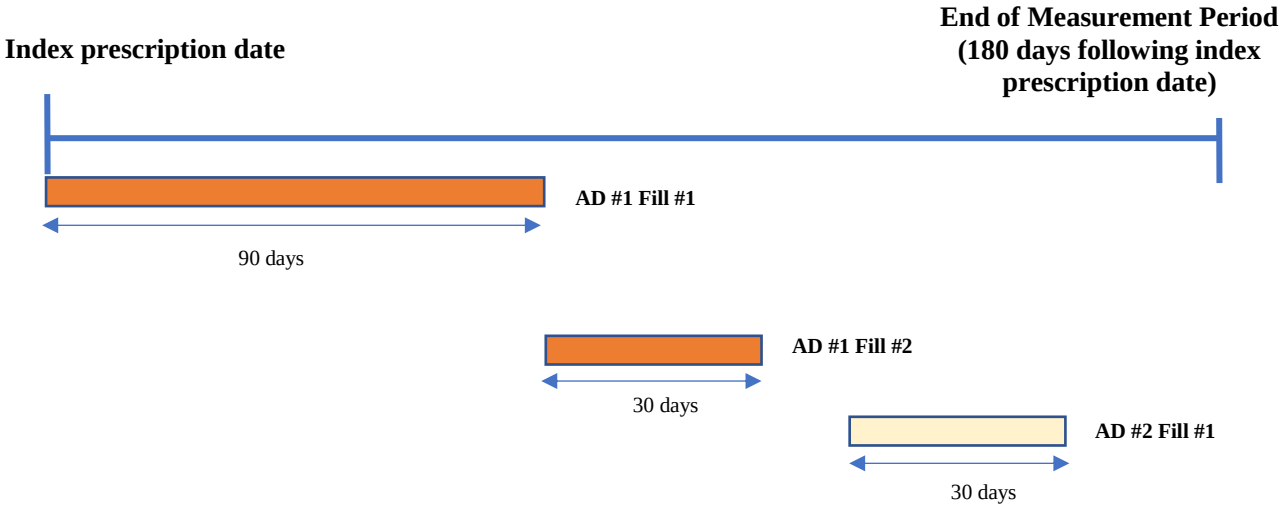


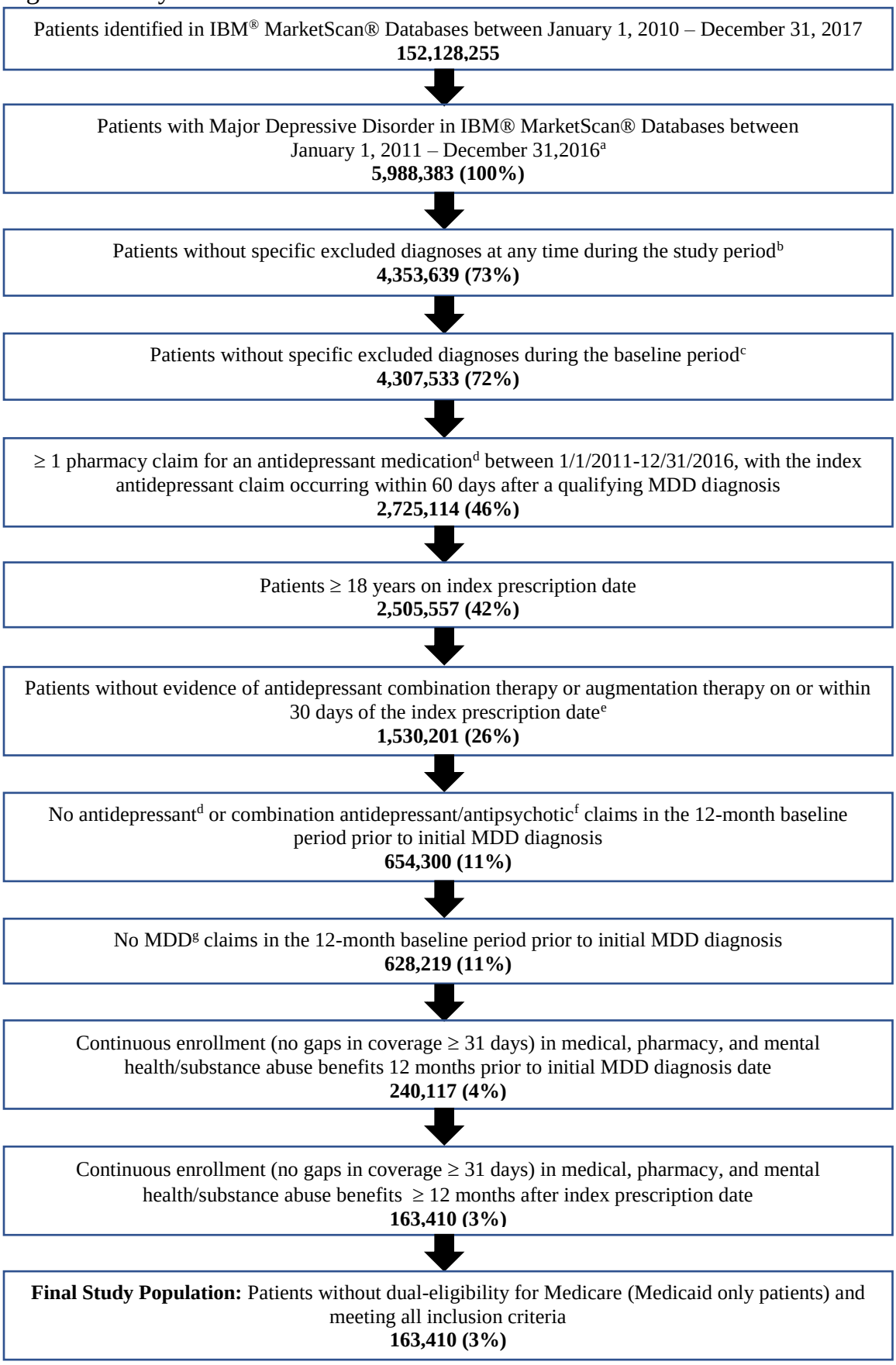
Figure 2. Calculation of Proportion of Days Covered (PDC)



$$PDC = \frac{90\ days + 30\ days + 30\ days}{180\ days} = 0.83$$

Calculation of PDC to MDD pharmacotherapy overall consists of days supply of 1st antidepressant (AD) (orange) and 2nd AD (yellow) claims. The PDC calculation accounts for early refills and switching.

Figure 3: Study Identification Flowchart



[a] As defined in Inclusion Criteria for identification of MDD patients. Qualifying diagnosis codes for MDD provided in Appendix A

[b] Exclusion diagnoses at any time during the study period include ICD-9-CM or ICD-10-CM codes for: Bipolar Disorder/manic disorder, other mood disorders, Alzheimer's disease, Parkinson's disease, dementia, or evidence of pregnancy/childbirth/breastfeeding (Appendix C)

[c] Exclusion diagnoses during the baseline period include ICD-9-CM or ICD-10-CM codes for: schizophrenic disorder, psychosis-related disorders, drug-induced depression and depressive type psychosis (Appendix D)

[d]Antidepressant medications include but are not limited to: SSRIs, SNRIs, TCAs, MAOIs, and other antidepressants. All antidepressant medications listed in Appendix B.1

[e] Evidence for combination antidepressant or augmentation therapy as defined in Exclusion Criteria.

[f] Combination antidepressant/antipsychotic agents are listed in Appendix B.2

[g] Qualifying diagnosis codes for MDD provided in Appendix A

TABLES

Table 1. Demographic and Clinical Characteristics of Adult MDD Population

		Adherence (PDC)	
Characteristic	**All Patients (n=163,410)**	**Adherent (n= 84,866)**	**Non-Adherent (n=78,544)**
Age (years), mean [SD]	42 [16]	43 [16]	41 [16]
Female, n (%)	100,102 (61%)	52,420 (62%)	47,682 (61%)
Insurance Type, n (%)			
Commercial	142,082 (87%)	75,573 (89%)	66,509 (85%)
Medicare	10,821 (6%)	5,774 (7%)	5,047 (6%)
Medicaid	10,507 (7%)	3,519 (4%)	6,988 (9%)
Index Year			
2011	28,623 (18%)	14,465 (17%)	14,158 (18%)
2012	26,942 (17%)	13,496 (16%)	13,446 (17%)
2013	25,297 (16%)	12,925 (15%)	12,372 (16%)
2014	27,883 (17%)	14,777 (17%)	13,106 (17%)
2015	30,267 (19%)	16,207 (19%)	14,060 (18%)
2016	24,398 (15%)	12,996 (15%)	11,402 (15%)
Plan type, n (%)			
EPO	1,210 (1%)	632 (1%)	578 (1%)
PPO	85,742 (53%)	45,672 (54%)	40,070 (51%)
HMO	24,623 (15%)	12,169 (14%)	12,454 (16%)
POS/POS with capitation	13,733 (8%)	6,895 (8%)	6,838 (9%)
CDHP	13,172 (8%)	7,162 (9%)	6,010 (8%)
HDHP	7,692 (5%)	4,427 (5%)	3,265 (4%)
Comprehensive	16,195 (10%)	7,341 (9%)	8,854 (11%)
Unknown/Missing	1,043 (1%)	568 (<1%)	475 (<1%)
CCI, mean [SD]	0.52 [1.24]	0.52 [1.23]	0.52 [1.24]
CCI, n (%)			
0	119,926 (74%)	62,464 (74%)	57,462 (73%)
1	26,013 (16%)	13,335 (16%)	12,678 (16%)
2	8,203 (5%)	4,310 (5%)	3,893 (5%)
3+	9,268 (6%)	4,757 (6%)	4,511 (6%)
Selected Comorbidities			
Anxiety	43,265 (26%)	22,291 (26%)	20,974 (27%)
Alcohol disorder	4,232 (3%)	1,867 (2%)	2,365 (3%)
Substance use disorder	14,782 (9%)	6,286 (7%)	8,496 (11%)
Sleep Disorders	15,880 (10%)	8,504 (10%)	7,376 (9%)
Coronary Heart Disease	6,834 (4%)	3,553 (4%)	3,281 (4%)
Congestive Heart Failure	2,735 (2%)	1,426 (2%)	1,309 (2%)
Chronic Pulmonary Disease	18,713 (11%)	9,459 (11%)	9,254 (12%)
Diabetes	14,300 (9%)	7,343 (9%)	6,957 (9%)
Geographic Region			
North East	24,155 (15%)	13,401 (16%)	10,754 (14%)
North Central	41,483 (25%)	22,421 (26%)	19,062 (24%)

South	57,061 (35%)	29,444 (35%)	27,617 (35%)
West	29,394 (18%)	15,702 (19%)	13,692 (18%)
Unknown/N/A	11,317 (7%)	3,898 (5%)	7,419 (9%)
Index Prescription			
SSRI	119,705 (73%)	62,918 (74%)	56,787 (72%)
SNRI	15,509 (10%)	8,338 (10%)	7,171 (9%)
TCA	1,816 (1%)	592 (1%)	1,224 (2%)
MAOI	15 (<1%)	6 (<1%)	9 (<1%)
Other	26,365 (16%)	13,012 (15%)	13,353 (17%)
12-Month Baseline All-Cause Healthcare Costs, 2018 USD, mean [SD]			
Total	$10,640 [$37,437]	$10,884 [$37,543]	$10,370 [$37,318]
Total Patient Out-of-Pocket	$1,158 [$1,730]	$1,192 [$1,673]	$1,120 [$1,790]

Abbreviations: CCI = Charlson Comorbidity Index; CDHP = Consumer-Driven Health Plan; EPO = Exclusive Provider Organization; FFS = Fee-For-Service; HDHP = High-Deductible Health Plan; HMO = Health Maintenance Organization; MAOI = monoamine oxidase inhibitor; MDD = Major Depressive Disorder; N/A = not applicable; PDC = proportion of days covered; POS = point of service; PPO = Preferred Provider Organization; SD = standard deviation; SNRI = selective norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; USD = US dollars

Table 2. 6-Month Post-Index Adherence to MDD Pharmacotherapy for Adult MDD Population

	All Patients (n=163,410)	**Adherent (n=84,866)**	**Non-Adherent (n=78,544)**	**p-value**
Proportion of Days Covered (%), mean [SD]	70% [30%]	95% [6%]	42% [20%]	<0.001

Table 3. 12-Month All-Cause Healthcare Resource Utilization for Adult MDD Population

	All Patients (n=163,410)	Adherent (n= 84,866)	Non-Adherent (n=78,544)	p-value
Inpatient				
Number of patients with ≥1 hospitalization, n (%)	13,811 (9%)	6,634 (8%)	7,177 (9%)	<0.001
Number of hospitalizations per patient, mean [SD] (among patients with ≥ 1 hospitalization)	1.4 [1.1]	1.4 [0.9]	1.5 [1.2]	<0.001
Length of stay per hospitalization, mean [SD] (among patients with ≥ 1 hospitalization)	4.9 [6.2]	4.9 [6.0]	5.0 [6.3]	0.33
Length of stay per patient per hospitalization, mean [SD] (among patients with ≥ 1 hospitalization)	4.6 [4.8]	4.4 [4.9]	4.6 [4.8]	0.73
Emergency Room				
Number of patients with ≥ 1 visit, n (%)	38,157 (23%)	17,239 (20%)	20,918 (27%)	<0.001
Number of visits, mean [SD] (among patients with ≥1 ER visit)	1.8 [2.1]	1.6 [1.5]	1.9 [2.4]	<0.001
Outpatient				
All Outpatient				
Number of patients with ≥ 1 visit, n (%)	163,136 (99.8%)	84,834 (100%)	78,302 (99.7%)	<0.001
Number of visits, mean [SD] (among patients with ≥1 outpatient visit)	18.3 [20.7]	19.3 [20.4]	17.1 [20.9]	<0.001
Physician office				
Number of patients with ≥ 1 visit, n (%)	160,981 (99%)	84,147 (99%)	76,834 (98%)	<0.001
Number of visits per patient, mean [SD] (among patients with ≥1 physician office visit)	13.9 [13.4]	15.1 [14.0]	12.6 [12.5]	<0.001
Other outpatient				
Number of patients with ≥ 1 visit, n (%)	132,735 (81%)	69,220 (82%)	63,515 (81%)	<0.001
Number of visits, mean [SD] (among patients with ≥1 other outpatient visit)	7.4 [17.3]	7.2 [16.1]	7.7 [18.5]	<0.001

Table 4. Incidence Rate Ratios for 12-month All-Cause Healthcare Resource Utilization in Non-Adherent vs. Adherent Patients

	Unadjusted Incidence Rate Ratio (95% CI)	**Adjusted Incidence Rate Ratio* (95% CI)**
Inpatient		
Number of hospitalizations	1.25 (1.20, 1.30)	1.19 (1.15, 1.23)
Emergency Room		
Number of emergency room visits	1.56 (1.53, 1.60)	1.37 (1.34, 1.40)
Outpatient		
Number of outpatient visits	0.88 (0.88, 0.89)	0.86 (0.86, 0.88)

* Controlled for age, sex, insurance type, geographic region, index year, CCI score (continuous), baseline 12-month total all-cause healthcare costs

Table 5. 12-Month Mean [SD] All-Cause Total Healthcare, Medical, and Pharmacy Costs following Index Antidepressant

	All Patients (n=136,557)	**Adherent** (n=71,698)	**Non-Adherent** (n=64,859)	**Unadjusted Difference* (95% CI)**	**Adjusted Incremental Difference** (95% CI)**
Total	$12,424 [$36,463]	$12,587 [$34,215]	$12,242 [$38,797]	-$345 (-$735, $45)	-$508 (-$881, -$135)
Medical	$10,056 [$34,346]	$9,891 [$31,858]	$10,240 [$36,902]	$349 (-$19, $716)	$367 ($26, $708)
Inpatient	$2,970 [$23,681]	$2,697 [$21,286]	$3,272 [$26,071]	$575 ($321, $829)	--
Emergency Room	$366 [$1,574]	$319 [$1,400]	$418 [$1,745]	$99 ($82, $115)	--
Outpatient (All)	$6,720 [$19,691]	$6,874 [$18,964]	$6,550 [$20,463]	-$324 (-$534, -$115)	--
Physician Office	$2,302 [$4,820]	$2,487 [$5,170]	$2,098 [$4,391]	-$390 (-$440, -$339)	--
Other	$4,418 [$18,215]	$4,387 [$17,321]	$4,452 [$19,155]	-$65 (-$129, $259)	--
Pharmacy	$2,367 [$8,838]	$2,697 [$8,973]	$2,003 [$8,671]	-$694 (-$788, $600)	-$984 (-$1107, -$861)

* 2-sample t-test using unequal variances

**Controlled for age, sex, insurance type, geographic region, index year, CCI score (continuous), baseline 12-month total all-cause healthcare costs; adjusted incremental difference reflects comparison of non-adherent vs. adherent patients

APPENDICES

Appendix A: International Classification of Diseases (ICD) Codes for Inclusion Criteria

Condition	ICD-9 Codes	ICD-10 Codes
Major Depressive Disorder (MDD)[36]		
Major depressive affective disorder, single episode, unspecified	296.20	F32.9
Major depressive affective disorder, single episode, mild	296.21	F32.0
Major depressive affective disorder, single episode, moderate	296.22	F32.1
Major depressive affective disorder, single episode, severe, without psychotic features	296.23	F32.2
Major depressive disorder, single episode, severe with psychotic features	296.24	F32.3
Major depressive affective disorder, recurrent episode, unspecified	296.30	F33.9
Major depressive affective disorder, recurrent episode, mild	296.31	F33.0
Major depressive affective disorder, recurrent episode, moderate	296.32	F33.1
Major depressive affective disorder, recurrent episode, severe, without psychotic features	296.33	F33.2
Major depressive disorder, recurrent, severe with psychotic symptoms	296.34	F33.3
Dysthymic Disorder	300.4	F34.1
Depressive disorder, not elsewhere classified	311	N/A

Appendix B.1: Antidepressants for MDD

Antidepressant Medication
SSRIs
Citalopram
Escitalopram
Fluoxetine
Fluvoxamine
Paroxetine
Sertraline
Vilazodone
Vortioxetine
SNRIs
Desvenlafaxine
Duloxetine
Levomilnacipran
Venlafaxine
TCAs
Amitriptyline
Amoxapine
Clomipramine
Desipramine
Doxepin
Imipramine
Maprotiline
Nortriptyline
Protriptyline
Trimipramine
MAOIs
Isocarboxazid
Phenelzine
Selegiline
Tranylcypromine
Other
Bupropion
Mirtazapine
Nefazodone
Trazodone

Appendix B.2: Augmentation Agents for MDD

Antipsychotic medications
Aripiprazole
Asenapine
Brexpiprazole
Cariprazine
Clozapine
Iloperidone
Lurasidone Hydrochloride
Olanzapine
Paliperidone
Quetiapine fumarate
Risperidone
Ziprasidone
Mood stabilizers
Carbamazepine
Lamotrigine
Lithium
Valproic acid
Combination Antidepressant/Antipsychotic
Amitriptyline/Perphenazine
Fluoxetine/Olanzapine

Appendix C: International Classification of Diseases (ICD) Codes for Exclusion at Any Time during the Study Period

Condition	ICD-9 Codes	ICD-10 Codes
Bipolar Disorder/Manic Depression	29600, 29601, 29602, 29603, 29604, 29605, 29606, 29610, 29611, 29612, 29613, 29614, 29615, 29616, 29640, 29641, 29642, 29643, 29644, 29645, 29646, 29650, 29651 29652, 29653, 29654, 29655, 29656, 29660, 29661, 29662, 29663, 29664, 29665, 29666, 2967, 29680, 29681, 29682, 29689	F310, F3110, F3111, F3112, F3113, F312, F3130, F3131, F3132, F314, F315, F3160, F3161, F3162, F3163, F3164, F3170, F3171, F3172, F3173, F3174, F3175, F3176, F3177, F3178, F3181, F3189, F319
Other Mood Disorders	29383, 29690, 29699, 30113	F0630, F0631, F0632, F0633, F0634, F3281, F3289, F338, F3481, F3489, F39, F340
Alzheimer's disease	3310	G300, G301, G308, G309
Parkinson's disease	3320, 3321, 33182	G20, G210, G2111, G2119, G212, G213, G214, G218, G219
Dementia	2900, 29010, 29011, 29012, 29013, 29020, 29021, 2903, 29040, 29041, 29042, 29043, 29410, 29411, 29420, 29421, 29282	F0150, F0151, F0280, F0281, F0390, F0391, F1997
Pregnancy/Childbirth/ Breastfeeding	630-679	O00-O9A

Appendix D: International Classification of Diseases (ICD) Codes for Exclusion during the Baseline Period

Condition	ICD-9 Codes	ICD-10 Codes
Psychosis-Related Disorders	2970, 2971, 2972, 2973, 2978, 2979, 2981, 2982, 2983, 2984, 2988, 2989, 29381, 29382, 29211, 29212	F22, F23, F24, F28, F29, F062, F060, F19950, F19951
Schizophrenia/Schizophrenic Disorders	29500, 29501, 29502, 29503, 29504, 29505, 29510, 29511, 29512, 29513, 29514, 29515, 29520, 29521, 29522, 29523, 29524, 29525, 29530, 29531 29532, 29533, 29534, 29535, 29540, 29541, 29542, 29543, 29544, 29545, 29550, 29551, 29552, 29553, 29554, 29555, 29560, 29561, 29562, 29563, 29564, 29565, 29570, 29571, 29572, 29573, 29574, 29575, 29580, 29581, 29582, 29583, 29584, 29585, 29590, 29591, 29592, 29593, 29594, 29595	F200, F201, F202, F203, F205, F2081, F2089, F209, F21, F250, F258, F259
Depressive Type Psychosis	2980	F251
Drug-Induced Depression	29284	F1994

Appendix E: International Classification of Diseases (ICD) Codes for Charlson Comorbidities

Condition	ICD-9 Codes	ICD-10 Codes
Charlson Comorbidities[21,22]		
Acute myocardial infarction	410, 412	I21, I22, I252
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4, 425.5, 425.6, 425.7, 425.8, 425.9, 428	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5, I42.6, I42.7, I42.8, I42.9, I43, I50, P29.0
Peripheral vascular disease	093.0, 437.3, 440, 441, 443.1-443.9, 47.1, 557.1, 557.9, V43.4	I70, I71, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Cerebrovascular Disease	362.34, 430-438	G45, G46, H34.0, I60-I69
Dementia	290, 294.1, 331.2	F00-F03, F05, G30, G31.1
Chronic Pulmonary Disease	416.8, 416.9, 490-505, 506.4, 508.1, 508.8	I27.8, I27.9, J68.4, J40-J47, J60-J67, J70.1, J70.3
Rheumatic Disease	446.5, 710.0 – 710.4, 714.0 - 714.2, 714.8, 725	M05, M06, M31.5, M32, M33, M34, M35.1, M35.3, M36.0
Peptic Ulcer Disease	531-534	K25-K28
Mild Liver Disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570, 571, 573.3, 573.4, 573.8, 573.9, V42.7	B18, K70.0, K70.1, K70.2, K70.3, K70.9, K71.3, K71.4, K71.5, K71.7, K73, K74, K76.0, K76.2, K76.3, K76.4, K76.8, K76.9, Z94.4
Diabetes (mild to moderate)	250.0 – 250.3, 250.8, 250.9	E10.0, E10.l, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Diabetes with complications	250.4-250.7	E10.7, E11.7, E12.7, E13.7, E14.7, E10.2-E10.5, E11.2-E11.5, E12.2-E12.5, E13.2-E13.5, E14.2-E14.5
Hemiplegia or Paraplegia	334.1, 342, 343, 344.0-344.6, 344.9	G04.1, G11.4, G80.1, G80.2, G81, G82, G83.0-G83.4, G83.9
Renal Disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582, 583.0 – 583.7, 5837, 585, 586, 588.0, V42.0, V45.1, V56	I12.0, I13.1, N18, N19, N25.0, N03.2-N03.7, Z49, Z94.0, Z99.2
Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin	140-172, 174-195.8, 200-208, 238.6,	C43, C88, C00-C26, C30-C34, C37-C41, C45-C58, C60-C76, C81-C85, C90-C97
Metastatic Solid Tumor	196-199	C77, C78, C79, C80
Moderate or Severe Liver Disease	572.2-572.8, 456.0-456.2	I85.0, I85.1, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
AIDS	042, 043, 044	B20, B21, B22, B24

Appendix F: International Classification of Diseases (ICD) Codes for Selected Comorbidities of Interest

Condition	ICD-9 Codes	ICD-10 Codes
Anxiety Disorders[5]		
Generalized Anxiety Disorder	300.02	F41.1
Panic disorders and phobias	300.01, 300.21, 300.22, 300.23	F40.01, F41.0, F40.02, F40.10,
Obsessive-compulsive disorder	300.3	F42.2, F42.3, F42.8, F42.9
Post-traumatic stress disorder	309.81	F43.1, F43.12
Acute stress disorder	308.3	F43.0
Anxiety, not otherwise specified	300.00, 300.5, 300.09, 300.20, 300.29	F41.8, F41.9, F40.9, F40.218, F40.240, F40.241, F40.8
Alcohol Disorder/Alcohol Dependence [37,38]	291.0, 291.1, 291.2, 291.3, 291.4, 291.5, 291.81, 291.82, 291.89, 291.9, 303.00, 303.01, 303.02, 303.03, 303.90, 303.91, 303.92, 303.93, 305.00, 305.01, 305.02, 305.03	F1010-F1099
Substance Use Disorder/Drug Dependence[37,38]	292.0, 292.11, 292.12, 292.2, 292.81, 292.82, 292.83, 292.84, 292.85, 292.89, 292.9, 304.01, 304.02, 304.03, 304.10, 304.11, 304.11, 304.12, 304.13, 304.20, 304.21, 304.22, 304.23, 304.30, 304.31, 304.32, 304.33, 304.40, 304.41, 304.42, 304.43, 304.50, 304.51, 304.52, 304.53, 304.60, 304.61, 304.62, 304.63, 304.70, 304.71, 304.72, 304.73, 304.80, 304.81, 304.82, 304.83, 304.90, 304.91, 304.92, 304.93, 305.1, 305.20, 305.21, 305.22, 305.23, 305.30, 305.31, 305.32, 305.33, 305.40, 305.41, 305.42, 305.43, 305.50, 305.51, 305.52, 305.53, 305.60, 305.61, 305.62, 305.63, 305.70, 305.71, 305.72, 305.73, 305.80, 305.81, 305.82, 305.83, 305.90, 305.91, 305.92, 305.93	F1110-F1999
Sleep Disorders/Insomnia	78050, 78051, 78052, 78053 78054, 78055, 78056, 78057 78058, 78059	G4700-G479
Coronary Heart Disease[37]	41000, 41001, 41002, 41010, 41011, 41012, 41020, 41021, 41022, 41030, 41031, 41032, 41040, 41041, 41042, 41050, 41051, 41052, 41060, 41061,	I200-I259

	41062, 41070, 41071, 41072, 41080, 41081, 41082, 41090, 41091, 41092, 4110, 4111, 41181, 41189, 412, 4130, 4131, 4139, 41400, 41401, 41402, 41403, 41404, 41405, 41406, 41407, 41410, 41411, 41412, 41419, 4142, 4143, 4144, 4148, 4149	
Congestive Heart Failure[21]	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4, 425.5, 425.6, 425.7, 425.8, 425.9, 428	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5, I42.6, I42.7, I42.8, I42.9, I43, I50, P29.0
Chronic Pulmonary Disease[21]	416.8, 416.9, 490-505, 506.4, 508.1, 508.8	I27.8, I27.9, J68.4, J40-J47, J60-J67, J70.1, J70.3,
Diabetes[21]	250.0 – 250.3, 250.8, 250.9 250.4-250.7	E10.0, E10.l, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9, E10.7, E11.7, E12.7, E13.7, E14.7, E10.2-E10.5, E11.2-E11.5, E12.2-E12.5, E13.2-E13.5, E14.2-E14.5

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