A Retrospective Claims Analysis of Medication Adherence and Persistence Among Patients Taking Antidepressants for the Treatment of Major Depressive Disorder (MDD)

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ABSTRACT

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Background: Pharmacotherapy to treat Major Depressive Disorder (MDD) has proven to be effective, yet improving adherence and persistence (A&P) to antidepressant (AD) therapy continues to be challenging. Guidelines recommend initiating AD therapy through initiation phase (3 months of therapy), and continuation phase (6 months beyond initiation phase), with a recommended total duration of 9 months of therapy. Even at the minimal recommended duration of therapy (6 months), it is estimated that only 12-34% of patients remain adherent to AD therapy, increasing the chance of relapse back into the depressive episode and resource utilization. Further research on A&P is warranted due to lack of estimates for new AD therapy and incomparability among existing findings.

Methods: To date, this was the largest US insurance claims analysis conducted of A&P to initial AD therapy. Truven Marketscan® Commercial, Medicare, and Medicaid databases were queried for MDD patients between the years 2003-2014. Qualifying MDD diagnoses for inclusion included either one

inpatient, or one outpatient service claim with a second confirmatory claim (either inpatient or outpatient), after ensuring 6 months of negative MDD diagnosis and AD prescription history. Patients with a diagnosis of other mental disorders (Schizophrenia, Bipolar, Alzheimer's, Dementia, depressive type psychosis, or other mood disorders) were excluded if diagnosed from 6 months before to 12 months after the IDD. 527,907 patients were identified who initiated therapy with one AD within 60 days of a qualifying MDD diagnosis and had continuous insurance coverage from 6 months before to 12 months after this index AD prescription date (IPD). A&P was calculated to initial AD medication, to initial therapeutic class, and overall, to any AD therapy, over the first 3, 6, 9, and 12 months from the IPD, using Medication Possession Ratio (MPR)/Proportion of Days Covered (PDC) and days to discontinuation, respectively. Adherence to continuation phase, or adherence between 4-9 months, was calculated similarly. The proportion adherent was defined as the proportion whose MPR/PDC was greater than or equal to 0.80, where the proportion persistent was defined as the proportion remaining persistent over the time frame. Chi-squared testing was used to test differences in the proportion adherent or persistent, when grouped by initial AD or comparing proportions over time. Odds ratios of adherence comparing initial ADs to sertraline were estimated at 3, 6, 9, and 12 months after the IPD through multivariable logistic regression, adjusting for age, gender, insurance source, region, insurance plan type, MDD diagnosis code, Charlson Comorbidity Index, and comorbid anxiety or chronic pain disorders. In a separate logistic model adjusted for the same covariates, the odds ratio of adherence to continuation phase among those adherent/not adherent to initiation phase was estimated.

Results: The proportion adherent to initial AD medication over time frames was 0.43/0.41 (MPR/PDC) at 3 months, and 0.23/0.21 at 12 months (p value<0.0001). The proportion persistent to initial AD medication was 0.44 at 3 months and 0.17 at 12 months (p value<0.0001). A&P to initial therapeutic class and overall, to any AD therapy was slightly higher than to initial AD medication, yet each measure similarly decreased over time (p value<0.0001). For each logistic regression for the primary model, association of initial AD and adherence to the time frame was found to be significant (p value <0.0001). Compared to sertraline, patients initiating with desvenlafaxine, duloxetine, and venlafaxine XR had greater odds of adherence at 6 months (adjusted odds ratios of 1.30, 1.07, and 1.19, respectively; p values all <0.0001). In a separate logistic model, adherence to the first 3 months of treatment was associated with adherence

to continuation phase, or months 4-9 (p value<0.0001). Patients who were adherent to the first 3 months of therapy had 13.7 times greater odds of adherence to continuation phase, when adjusted for covariates (95% Confidence Interval 13.4-14.0).

Conclusion: Results support that the choice of initial AD is an important clinical decision, associated with A&P, and thus, has the potential to improve clinical outcomes and decrease resource utilization.

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BACKGROUND

Diagnosis of Major Depressive Disorder (MDD), also known as Major Depression or unipolar major depression, involves a physician or a psychiatrist's examination, including clinical history evaluation, physical evaluation, and mental evaluation. The Diagnostic and Statistical Manual of Mental Disorders- 5th Edition (DSM-5) from the American Psychological Association (APA) provides definitions and criteria for diagnosis of MDD.[1] Recent survey data support an increasing trend in the prevalence of depression both in the United States (US) and worldwide.[2,3] During 2013, it is estimated that 6.7% of the US population 18 years of age or older had a major depressive episode[4] and it is estimated that lifetime prevalence of depression is as high as 17%.[5] The cost of depression in the US was estimated to be $83.1 billion in 2000, attributed mostly to workplace costs ($51.5 billion), then direct medical costs ($26.1 billion), and lastly, costs due to suicide ($5.4 billion; the value of lost lifetime earnings).[6]

Guidelines from the APA support first line pharmacological treatment of MDD with selective serotonin reuptake inhibitor (SSRI) therapy. Alternative first line treatment includes several classes of antidepressants (ADs): serotonin-norepinephrine reuptake inhibitors (SNRI), and serotonin modulator (SM) therapies. SM therapy includes both Serotonin Antagonist and Reuptake Inhibitor (SARI) and Serotonin Modulator and Stimulator (SMS) mechanisms of action (Appendix 1).[7,8] First line alternatives also include ADs with atypical mechanisms of action, such as bupropion and mirtazapine.[7–9] Due to both adverse effects (AEs) and potential for death due to overdose, therapies such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are clinically reserved as second-line agents. ADs are also classified by generation, where TCAs and MAOIs are considered first generation ADs and SSRIs, SNRIs, and SMSs are considered second generation. Though effectiveness is thought to be similar, ADs differ in propensity to cause AEs and cost.[10,11]

Pharmacologic treatment of an episode of MDD begins with monotherapy, or a single AD agent. Treatment recommendations outline an initiation phase of 4-12 weeks, a continuation phase for 4-9 months, and if needed, maintenance therapy for an additional 12 to 36 months or indefinitely for a subset of patients.[8] The APA guidelines and other articles support treatment of a new episode of MDD for a minimum duration of 6 months, yet a duration of 9 months is recommended to complete both initiation

and continuation phases of treatment.[8,11] Depending on response and severity of the presenting episode, providers may attempt to switch the AD, combine AD therapies or add to therapy with an adjunctive agent, such as an antipsychotic or mood stabilizing medication.

The National Center for Quality Assurance (NCQA) also provides definitions of effective initiation and continuation phase for assessment of antidepressant medication management (AMM), largely adopted by health plans.[12,13] Effective treatment is defined through measuring adherence, or compliance, and persistence to AD therapy. In a recent study, patient noncompliance was the most common reason for failure to meet NCQA standards.[14] A large US insurance claims analysis estimated that only 12-34% of patients are adherent to initial AD therapy over 6 months.[15] Medication adherence and persistence to AD therapy is important and is associated with decreased probability and occurrence of relapse (reoccurrence of symptoms associated with presenting MDD episode)[11,16,17] and decreased costs of medical care.[18]

Previous analyses support the association of adherence to AD therapy with patient demographics (age[19–21], gender[22], socioeconomic status[19,23], and race[23–25]), clinical characteristics (MDD diagnosis code[26], severity of depression[26], comorbid conditions[23,24,27,28] and polypharmacy[22]) and medication characteristics (initial medication[15,19,29], dose of medication[30,31], formulation[32], and frequency of administration[29]). Observational claims analyses published since 2000 support that a greater proportion of patients were considered adherent to first line ADs (SSRIs and SNRIs) than to second line ADs (TCAs and MAOIs) over 6 months (first line 22-34%[15] versus second line 12- 22%[15,22]). For persistence, a greater proportion of patients were persistent to first line ADs over 6 months when compared with second line ADs (21-52%[33–35] versus 0-20%[33], respectively). For switching, a smaller proportion of patients switched from first line ADs over 6 months when compared with second line ADs (21-26%[34] versus 40%[15], respectively). Results may reflect fewer AEs and improved tolerability to first-line versus second-line ADs. These estimates differed in definitions and time periods over which adherence or persistence was calculated and demonstrated that some ADs are little studied, with only one study reporting adherence or persistence for certain AD therapy. There is a need for a comprehensive analysis of adherence and persistence to AD therapy.

Duloxetine is the most recent AD for which adherence has been estimated and substantiated through experimental or observational analyses, reported in an observational analysis published in 2008.[15] Since duloxetine, multiple medications and new formulations have received approval for treatment of MDD by the Food and Drug Administration (FDA): vortioxetine, levomilnacipran, vilazodone, trazodone extended release, desvenlafaxine, and selegiline transdermal patch. Adherence and persistence for these ADs have not been reported. Lack of adherence and persistence estimates for new therapy coupled with incomparability of existing adherence outcomes supported the need for further research.

OBJECTIVE

The aim of this study was to describe the MDD population through a large US insurance claims database and to calculate adherence and persistence to initial AD medication, to initial therapeutic class, and overall, to AD therapy.

METHODS

Data Source

We utilized the Truven Health Analytics MarketScan® Research Databases for this study. These databases contain inpatient and outpatient insurance claims and prescription medication claims representing US patients from commercial insurance plans, Medicare supplemental and Medicaid. Claims report information on diagnoses, billing codes, and dates of service. Detailed information on medication claims includes medication name, quantity of medication prescribed, date of dispensation, and the day's supply (the number of days that the quantity of medication will last from the prescription claim). Patient eligibility information includes age, gender, insurance plan type, geographic region of residence, and monthly insurance eligibility status.

Based on the criteria set forth by the University of Washington's Investigational Review Board this research was self-determined not to meet the definition of Human Subjects Research.[36] This determination was made based on the complete de-identification of the dataset at its source to ensure complete HIPAA compliance[37], and that the Truven Health Analytics research team did not serve as

investigators for the project.

Sample Selection

Inclusion criteria: All patients with new diagnosis of MDD and new prescription of an AD were eligible for this study. Commercial and Medicare supplemental claims databases were queried to identify claims between July 1, 2003 and January 1, 2014 (Figure 1). Qualifying diagnoses for MDD included either one inpatient, or one outpatient service claim with a second confirmatory claim (either inpatient or outpatient), after ensuring 6 months of negative MDD diagnosis and AD prescription history. The first qualifying MDD claim, or the index diagnosis date (IDD), was the primary reference point to determine diagnosis and prescription claim history. MDD claims were identified using the International Classification of Diseases, 9th Edition (ICD-9) codes in Appendix 2 for MDD (single episode 296.2, recurrent episode 296.3), dysthymic disorder (300.4), and depressive disorder, not otherwise specified (311).[15,30] The index prescription date (IPD) was established at the first pharmacy claim for an AD medication filled within 60 days before or after a qualifying diagnosis of MDD, and was the principle reference point to determine insurance eligibility status. Pharmacy claims included all ADs approved for treatment of MDD by the FDA and those ADs that are used off-label to treat MDD (Appendix 1).

Exclusion criteria: Patients who did not have continuous insurance coverage from 6 months before to 12 months after the IPD were excluded from the study. In order to ensure that ADs were being used to treat a new diagnosis of MDD, patients having claims for certain conditions were excluded from the dataset if they occurred within 6 months before to 12 months after the IDD. These include Schizophrenic disorder (ICD-9 Code: 295), Bipolar disorder (296.0-296.1 and 296.4-296.9), other psychosis related disorders, paranoid states (297), other mood disorders (293.83 and 301.13), drug-induced depression (292.84), depressive type psychosis (298), Alzheimer's disease (331), Parkinson's disease (332), and Dementia (290). In addition, individuals who had a claim for pregnancy (630-679) were excluded from the dataset due to the effect that pregnancy may have on discontinuation of therapy. Patients were excluded if they initiated with two medications, or had greater than three medications prescribed within the first 60 days after the IPD. Initiating with two medications was defined as having two prescriptions for AD therapy on the IPD, or prescriptions for two ADs that overlapped for greater than 30 days within the first 60 days of the IPD.

These days of overlap did not have to be consecutive.

Outcomes (Adherence and Persistence)

We measured adherence in the first year after the IPD. Specific calculations of adherence such as Medication Possession Ratio (MPR) and Proportion of Days Covered (PDC) are well-defined.[38–41] MPR was calculated as the total days supplied for a specified medication and divided by the period of follow up (MPR >1 was truncated to 1). PDC was calculated as the total number of days that the medication was available and divided by the period of follow up. PDC accounts for overlap of prescriptions, estimating adherence conservatively and is considered a preferred measure of adherence.[42] Adherence is commonly defined as the proportion of patients with an MPR or PDC ≥80% and was chosen for this analysis.[43] A follow up period of 6 months for assessing adherence was guided by the APA and NCQA, based on the minimum duration of treatment of a new episode of MDD.[8,13] However, the recommended duration of therapy is 9 months, including initiation and continuation phases. Adherence to initial AD was calculated using both MPR and PDC from the IPD over the following time frames: the first 3 months (initiation phase), first 6 months (minimal recommended duration), first 9 months (recommended duration), and first 12 months (extended duration). An outcome of secondary interest was adherence to continuation phase, or between months 4-9 as previously reported.[19,20] Time frames used in adherence calculations are presented in Figure 2a. We also calculated adherence to initial AD medication over the first 3, 6, 9, and 12 months after the IPD conditional on persistence over the same time frame, as previously reported.[15,22] Adherence over the time frames of interest to initial AD medication, to the initial therapeutic class, and overall, to any AD therapy, were separately calculated. Adherence outcomes were dichotomized as adherent or not adherent over each time period of interest. Unless noted otherwise, all discussion of adherence will refer to PDC.

Persistence was defined as the duration of treatment (days) without a significant gap in therapy and estimated over each subject's continuous enrollment period after the IPD. The definition of a significant gap has ranged from 15 to 45 days after the last AD prescription in observational studies. A 30 day gap in calculations of time to discontinuation and proportion persistent has successfully been used in prior analyses[44,45] and was chosen for this analysis. Persistence in days was converted to a dichotomous

outcome as persistent or not persistent over each time frame (Figure 2b). The proportion persistent to initial AD medication, initial therapeutic class, and overall, to AD therapy were calculated over the first 3, 6, 9, and 12 months after the IPD.

Primary and Secondary Analyses

Primary: The primary predictor variable for adherence outcomes was initial AD medication, in order to assess an association between initial AD medication and adherence to the following time frames: the IPD to 3, to 6, to 9, and to 12 months. The primary outcome variables were adherence to initial AD medication over these time frames.

Secondary: In order to assess the association between adherence to initiation phase and adherence to continuation phase, the secondary predictor of interest was adherence to initial AD medication over the first 3 months of treatment (initiation phase). The secondary outcome variable was adherence to initial AD medication between months 4-9 (continuation phase).

Subgroup Analyses

Patients meeting inclusion criteria who had comorbid anxiety or chronic non-cancer pain disorders were identified. These patients were of interest because certain AD therapy is FDA labeled or used off-label to treat these comorbidities. Patients were identified if diagnosis of these disorders occurred 60 days before or after the IDD through ICD-9 codes (Appendix 2). However, a diagnosis for low back pain was identified up to 6 months before to 60 days after the IDD, to capture the progression of treatment over time for this disorder. Diagnosis of cancer pain was not of interest because guidelines supported analgesic therapy for management of pain.[46] Furthermore, patients were identified if, over the first 3, 6, 9, or 12 months, a new prescription for AD therapy was identified. This was defined as patients with the presence of a prescription for a new AD medication over a specified time period that was different from the initial AD prescribed on the IPD.

We conducted three subgroup analyses, consisting of adherence and persistence outcomes over the first 3, 6, 9, and 12 months after the IPD. The first two subgroup analyses calculated the proportion adherent and persistent over these four time frames in those patients with comorbid anxiety or chronic

non-cancer pain disorders. The third analysis calculated the proportion adherent and persistent over these time frames in patients with the presence of a prescription for a new and different AD than prescribed on the IPD.

Covariates

Baseline demographic covariates were age, gender, source of insurance claim, region in which medical care was received, and type of health plan. Clinical covariates were MDD diagnosis code, Charlson Comorbidity Index score, presence of a comorbid anxiety disorder and presence of a chronic non-cancer pain disorder. The Charlson Comorbidity Index (CCI with Deyo modification), calculated as previously described over the year prior to the IDD,[47] was used as an indicator of disease burden and risk of mortality.

STATISTICAL ANALYSIS

Descriptive statistics were used to characterize baseline demographics, clinical characteristics, and subgroups. Means and standard deviations (SDs) were used to describe continuous variables, and counts and proportions for categorical variables. Bivariate statistics for differences in characteristics across initial AD medication or therapeutic class were conducted using Chi-squared tests (χ^2) for categorical variables and analysis of variance (ANOVA) for continuous variables.

Adherence outcomes for the primary analysis were descriptively interpreted. Inferential statistics were used to compare adherence over time. Specifically, we compared the proportion adherent from the IPD to 3 month time frame to the IPD to 6 month, 9 month and 12 month time frames using McNemar's χ^2 tests.

For subgroup analyses, we calculated the proportion adherent and persistent to initial AD medication, by each subgroup. We also conditioned on persistence over the time frame of interest. No inferential statistics were applied.

The adherence outcome for the secondary analysis was descriptively interpreted by the proportion adherent between months 4-9, conditioning on adherence from IPD to month 3. No inferential

statistics were applied.

We then conducted simple logistic regressions on the complete cohort for the primary analysis to estimate the odds of adherence to initial AD medication for each time frame (from IPD to 3, 6, 9, or 12 months; Logistic Model 1 below). This was followed by multivariable logistic regression, adjusting for covariates (Appendix 3). PDC was chosen for logistic modelling as a more conservative estimate of adherence than MPR, where a PDC that was greater than or equal to 0.80 over a time frame was considered adherent (coded as 1) and a PDC less than 0.80 was considered non-adherent (coded as 0). Each logistic model was assessed for serious deviations from a mean logistic model by comparing Pearson residuals to predicted values. With only 5 observations, coefficients could not be accurately estimated for trimipramine; thus, these observations were excluded from all logistic models.

Logistic Model 1($\pi(X)$=Adherence Status, γ=Dummy categorical variable)

Unadjusted:
$\exp\{\text{logit}[\pi(X)]\}=\beta_0+\gamma_{\text{InitialAD}}$

Adjusted:
$\exp\{\text{logit}[\pi(X)]\}=\beta_0+\gamma_{\text{InitialAD}}+\gamma_{\text{Age}}+\gamma_{\text{Gender}}+\gamma_{\text{Source}}+\gamma_{\text{Region}}+\gamma_{\text{Plan}}+\gamma_{\text{MDD}}+\gamma_{\text{CCI}}+\gamma_{\text{Anxiety}}+\gamma_{\text{Pain}}$

For the secondary analysis, we conducted simple logistic regression on the complete cohort to estimate the odds of adherence to continuation phase (between months 4-9), comparing those adherent/not adherent to initiation phase (Logistic Model 2 below). This was subsequently followed by multivariable logistic regression, adjusting for covariates and initial AD medication.

Logistic Model 2 ($\pi(X)$=Adherence Status, γ=Dummy categorical variable)

Unadjusted:
$\exp\{\text{logit}[\pi(X)]\}=\beta_0+\gamma_{\text{AdMonth3}}$

Adjusted:
$\exp\{\text{logit}[\pi(X)]\}=\beta_0+\gamma_{\text{AdMonth3}}+\gamma_{\text{InitialAD}}+\gamma_{\text{Age}}+\gamma_{\text{Gender}}+\gamma_{\text{Source}}+\gamma_{\text{Region}}+\gamma_{\text{Plan}}+\gamma_{\text{MDD}}+\gamma_{\text{CCI}}+\gamma_{\text{Anxiety}}+\gamma_{\text{Pain}}$

Persistence outcomes were descriptively interpreted. Inferential statistics were used to compare persistence over time. Specifically, we compared the proportion persistent from the IPD to 3 month time

frame to the 6 month, 9 month and 12 month time frames using McNemar's χ^2 tests. Days until discontinuation were descriptively interpreted by initial AD medication. Simple linear regression was used to compare differences in mean days to discontinuation, when grouped by initial AD medication. Persistence to initial therapeutic class and overall, to AD therapy was described using time to discontinuation curves. These curves plotted days to discontinuation of initial therapeutic class and days to discontinuation of AD therapy. All analyses were performed using the statistical software package STATA® Version 13.[48] A significance level of alpha=0.05 was chosen for all analyses.

RESULTS

Of the estimated 200 million patients in Marketscan® Databases, we identified 6,562,955 patients with qualifying diagnoses of MDD from July 1st 2003 to January 1st 2014. After inclusion and exclusion criteria were applied, 574,753 patients received a new prescription for AD therapy. The 527,907 patients with one new prescription for AD therapy on the IPD, and did not meet the definition of initiating with two or more medications, were included in the analysis of adherence and persistence. The most commonly prescribed medications in this analytic cohort were sertraline, escitalopram, and citalopram (Table 1: 18.7%, 17.0%, and 16.0%). There were no patients who received isocarboxazid, likely due its use as second line therapy. There were no patients who received vortioxetine or levomilnacipran, most likely due to their recent approval by the FDA to treat MDD in mid-2013.[49,50] The most commonly prescribed therapeutic class was SSRIs (Table 2: 70.4%).

Demographics

Our study population had an average age of 38 years (S.D. 17). The majority of the subjects were female (64%) covered by commercial insurance (81%), with preferred provider organizations and health maintenance organizations (48% and 20%) as the most common insurance plan type (Table 1 and 2). Overall, the sample resided in the southern region (29%), yet geographic region varied by insurance claim source. The largest proportion of the commercial group resided in the Southern region (34%) and the largest proportion of the Medicare Supplemental group resided in the North Central region (36%). Importantly, the Medicaid subjects were without region data. Differences in means and proportions of demographic covariates, by initial AD medication or initial therapeutic class were significant (all p values

<0.001).

Clinical Characteristics and Subgroups

Of the four MDD specific diagnostic codes used, the most common was depression, not otherwise specified (56%). The analytic cohort had low mortality risk, as demonstrated by the majority having a CCI score of 0 (79%), yet 24% had comorbid anxiety disorders, 24% had comorbid chronic pain disorders, and 6% had both. A greater proportion of patients with comorbid anxiety disorders were prescribed SSRIs, MAOIs, and SMSs than chronic pain disorders, whereas a greater proportion of patients with comorbid chronic pain disorders were prescribed SNRIs, atypical ADs, SARIs and TCAs than comorbid anxiety disorders. The proportion of patients with the presence of a prescription for a new and different AD than prescribed on the IPD grew from 11% from the IPD to 3 months to 28% from the IPD to 12 months. A greater proportion of patients initiating with TCAs, MAOIs, and SARIs had subsequent prescription for a new and different AD over time than other classes (Table 2). Differences in the proportion of clinical characteristics and subgroups when grouped by initial AD medication and initial therapeutic class were significant (p values all <0.001).

Adherence

The proportion adherent to initial AD medication, initial therapeutic class, and overall, to AD therapy from IPD to 3 months, to 6 months, to 9 months and to 12 months is presented in Table 3. The proportions considered adherent using MPR calculations were similar to PDC calculations. Adherence to initial AD medication differed depending on initial AD and decreased over time. The overall proportion considered adherent to their initial AD decreased when comparing the IPD to 3 month time frame to the 12 month time frame (0.41 at 3 months to 0.21 at 12 months; p values <0.0001). Among the three most commonly prescribed antidepressants, the proportion adherent decreased similarly from 3 to 12 months (sertraline: 0.43 versus 0.22; escitalopram: 0.44 versus 0.22; citalopram: 0.42 versus 0.21; p values all <0.0001). Among the three highest proportions considered adherent at 3 months, the proportion adherent decreased similarly (tranylcypromine 0.62 versus 0.31, phenelzine 0.53 versus 0.24, and desvenlafaxine 0.50 versus 0.28 p values all <0.05). Among the three lowest proportions considered adherent at 3

months, the proportion adherent similarly decreased (trazodone 0.18 versus 0.08, maprotiline 0.18 versus 0.08, and trazodone ER 0.16 versus 0.14; p-values all <0.0001 except trazodone ER was not significant).

Subgroup analyses supported that the proportion adherent to initial AD medication for patients with anxiety disorders and chronic pain disorders was similar in magnitude to the overall cohort and similarly decreased from IPD to 3 month time frame to the IPD to 12 month time frame (Table 4: 0.41 versus 0.21 and 0.39 versus 0.20, respectively). However, for patients with the presence of a new and different AD prescription than prescribed on the IPD, the proportion adherent was lower (0.32 at 3 months to 0.13 at 12 months). Conditioning on persistence to the time frame, the proportion adherent to initial AD medication for the entire cohort was much higher (0.84 at 3 months and 0.92 at 12 months). This magnitude was similar in the chronic pain and anxiety disorder subgroups, and in patients with a new and different AD prescription than prescribed on the IPD.

Conditional on adherence to initial AD medication over the first 3 months of therapy (Table 5), the proportion adherent to initial AD medication during continuation phase (months 4-9) was slightly higher for each AD than the proportion adherent over the first 9 months of therapy. Patients prescribed protriptyline in this analysis had the highest proportion adherent (0.43), whereas in the overall cohort, the highest proportion adherent from IPD to 9 months was for patients prescribed tranylcypromine (Table 3: 0.31).

The proportion adherent to initial therapeutic class and overall, to AD therapy, was slightly higher than adherence to initial AD medication, yet similarly decreased when comparing the IPD to 3 month and IPD to 12 month time frames (Table 3). The overall proportion considered adherent to initial therapeutic class when comparing these time frames decreased by about half (0.43 versus 0.23; p value <0.0001), as did the proportion adherent overall, to AD therapy (0.44 versus 0.26; p value<0.0001). Patients prescribed MAOIs, SNRIs, and SSRIs had the highest proportions adherent to initial therapeutic class at 3 months and similarly decreased by the 12 month time frame (0.48 versus 0.18, 0.48 versus 0.28, and 0.44 versus 0.23, respectively; p values <0.0001). The lowest proportions adherent to initial therapeutic class were demonstrated by those prescribed TCAs and SARIs, similarly decreasing from the 3 month to 12 month time frame (0.25 versus 0.12 and 0.19 versus 0.09,respectively; p values <0.0001).

Logistic regressions results from the primary analyses of the odds of adherence to initial AD medication over each time frame (from the IPD to 3, 6, 9, or 12 months) are presented in Table 6. Sertraline was chose as the referent category, as it was the most common initial AD (Table 1: 18.7%) and a relatively high proportion remained adherent to sertraline over first year of therapy (Table 3). For each logistic regression, association of initial AD and adherence to the time frame was found to be significant (p value <0.0001). Among the SSRIs, the adjusted odds of adherence were lower or no different than sertraline. The odds of adherence to fluoxetine weekly versus sertraline were not significantly different over the four time frames. Though the odds of adherence to escitalopram versus sertraline did not statistically differ from the IPD to 6 months, the adjusted odds of adherence were 3% lower (OR 0.97; 95% CI 0.95-0.99) over the first 9 months, and 5% lower (OR 0.95; 0.93-0.97) over the first 12 months. The adjusted odds of adherence from the IPD to 6 months were 14% lower (OR 0.86; 95% CI 0.74-0.99) to fluvoxamine versus sertraline, yet the odds of adherence were not statistically different at the 9 and 12 month time frames. Among the SNRIs, the adjusted odds of adherence were significantly higher versus sertraline to desvenlafaxine, venlafaxine XR, and duloxetine. The odds of adherence were 30% higher to desvenlafaxine (OR 1.30; 95% CI 1.24-1.38) versus sertraline over the first 6 months, 28% higher (OR 1.28; 95% CI 1.21-1.36) over the first 9 months, and 27% higher (OR 1.27; 95% CI 1.20-1.35) over the first 12 months. The odds of adherence was 19% higher for venlafaxine XR (OR 1.19; 95% CI 1.15-1.23) versus sertraline over the first 6 months, 14% higher (OR 1.14; 95% CI 1.10-1.18) over the first 9 months, and 12% higher (OR 1.12; 95% CI 1.07-1.16) over the first 12 months. The odds of adherence were 7% higher for duloxetine (OR 1.07; 95% CI 1.03-1.10) versus sertraline over the first 6 months, 8% higher (OR 1.08; 95% CI 1.04-1.11) over the first 9 months, and 10% higher (OR 1.10; 95% CI 1.07-1.14) over the first 12 months. Odds of adherence to venlafaxine did not significantly differ from sertraline at 6 months, but were 5% higher at 9 months (OR 1.05 95% CI 1.01-1.10) and 9% higher (OR 1.09; 95% CI 1.04-1.14) at 12 months. Among those initiating with SARIs, all demonstrated significantly lower odds of adherence than sertraline, except for trazodone ER (not significantly different from sertraline at 9 and 12 months). Those initiating with vilazodone (an SMS) demonstrated significantly lower odds of adherence than sertraline. Among those initiating with atypical ADs, all demonstrated significantly lower odds of adherence than sertraline, except bupropion XL (not significantly different from sertraline at 6 and 9

months). Among those initiating with TCAs and MAOIs, all demonstrated significantly lower odds of adherence than sertraline, except for selegiline transdermal patch (at 6 and 9 months), amoxapine (at 6 and 12 months), phenelzine (at 6, 9, and 12 months), protriptyline (at 6 and 12 months), and tranylcypromine (at 6, 9, and 12 months). Those initiating with phenelzine, tranylcypromine, and amoxapine demonstrated less precise estimates due to small sample size (n=17, 13, and 11, respectively).

Logistic regression results for the secondary analysis supported that adherence to initiation phase, or the first 3 months of therapy, was associated with adherence to continuation phase, or months 4-9 (Table 7: p value<0.0001). The adjusted odds of adherence during continuation phase among those who were adherent to initiation phase is 13.7 times greater than those who were not adherent to initiation phase (95% CI: 13.4-14.0).

Persistence

Proportions remaining persistent over time to initial AD medication, initial therapeutic class, and overall to AD therapy are presented in Table 8. The proportion persistent to their initial AD medication was 0.44 from the IPD to 3 months and 0.17 from the IPD to 12 months (p value <0.0001). Those patients initiating with desvenlafaxine, tranylcypromine, and venlafaxine XR demonstrated the highest proportion persistent at the 3 month time frame and the proportion decreased when comparing the 3 and 12 month time frames (0.54 versus 0.23, 0.54 versus 0.15, and 0.51 versus 0.21; p values all <0.05). Those patients initiating with doxepin, maprotiline, and trazodone had the lowest proportion persistent at the 3 month time frame, and decreased similarly over time (all 0.21 versus 0.07; p values all <0.0001).

Subgroup analyses support that the proportion persistent to initial AD medication for patients with anxiety and chronic pain disorders was similar in magnitude to the overall cohort and similarly decreased from the first 3 months to the first 12 months from the IPD (Table 4: 0.45 versus 0.18 and 0.41 versus 0.16, respectively). Patients with the presence of a new and different AD prescription than prescribed on the IPD demonstrated a lower proportion persistent than the overall cohort over all time frames, yet the proportion decreased similarly when comparing the 3 and 12 month time frames (0.33 versus 0.10).

The proportion persistent to initial therapeutic class and the overall proportion persistent to AD therapy was slightly higher than persistence to initial AD medication. The overall proportion remaining persistent to their initial therapeutic class was 0.46 from the IPD to 3 months and 0.19 from the IPD to 12 months (p value<0.0001). Those prescribed SNRIs and SSRIs had the highest proportion persistent comparing persistence at 3 and 12 months (0.51 versus 0.24 and 0.48 versus 0.19, respectively; p values<0.0001). Those prescribed TCAs and SARIs had the lowest proportion persistent comparing the 3 month and 12 month time frame (0.27 to 0.10, and 0.21 to 0.07, respectively; p values <0.0001). The proportion remaining persistent AD therapy was 0.48 from the IPD to 3 month time frame, and 0.22 from the IPD to 12 month time frame (p value<0.0001).

The average time to discontinuation (days) to initial AD medication in the sample was 174 days (SD 206 days). Those prescribed phenelzine, desvenlafaxine, and venlafaxine XR had highest mean persistence (Table 8: 225, 218, and 203 days, respectively). Those prescribed trazodone, trimipramine and maprotiline had lowest mean persistence (93, 93 and 89 days, respectively). Time to discontinuation curves (Figures 3 and 4) demonstrated a pattern across ADs and therapeutic classes at 30, 60, and 90 days, which may correspond with the commonality among insurance plans of covering a 30 day supply of medication at a time. Time to discontinuation curves were different by initial therapeutic class, with a more pronounced drop in persistence for TCAs and SARIs, and at 270 days, MAOIs.

DISCUSSION

This retrospective analysis of insurance claims for the US MDD population analyzed adherence and persistence to initial medication, to initial therapeutic class, as well as to overall AD therapy. To date, it was the largest study of adherence and persistence to initial AD therapy using US insurance claims, and included commercial, Medicare supplemental, and Medicaid insurance data, with a sample size of 527,907 and estimates reported for 33 ADs. Adherence and persistence to initial AD therapy was found to be low over all time periods of interest, and only slightly higher to initial therapeutic class and overall, to any AD therapy. Differences in adherence were related to initial therapy and initial therapeutic class. The initial AD medication was associated with adherence, over all time periods of interest. Adherence to initiation phase, or the first 3 months of therapy, was associated with adherence to continuation phase, or

between months 4-9.

The cohort was predominantly female, with a CCI score of 0, between the ages of 18-65, with commercial insurance plans, and living the Southern region of the US. The primarily female MDD population across databases in the analytic cohort supports other literature of a higher prevalence of depression among females than males.[51,52] The sample was found to be representative of the US MDD population, with the exception of chronic pain disorders and anxiety disorders. The prevalence of comorbid chronic pain was lower than the previously reported US prevalence over one year (43%)[53] and conflicted with the results of survey analyses that supported higher prevalence of these disorders among patients who have depression.[5,54–56] Yet, prevalence of anxiety disorders was slightly higher than the previously reported US prevalence from a survey analysis over one year (18%)[5]. Around half of the sample presented with the depression, not otherwise specified diagnosis code, which was higher in prevalence when compared to previous depression claims analyses.[15,30]

Adherence across ADs decreased over time, regardless of the method used for calculating adherence (i.e. MPR or PDC). Compared to other literature assessing adherence in MDD, this analysis found that the proportion adherent at 6 months was higher to SSRI (0.33) or SNRI therapy (0.38) versus TCAs (0.17). This is similar to previously reported estimates (adherence to first line 22-34%[15] versus second line 12-22%[15,22]). Yet, the proportion adherent at 6 months to MAOIs was similar to SSRI or SNRI therapy, which was unexpected. Considering first line therapy and alternatives, many other SSRIs had lower odds of adherence when compared to sertraline, although the magnitude was small. The odds of adherence were greater or similar for the SNRIs versus sertraline, while the odds were lower for many atypical ADs and SARIs and the SMS. Persistence across ADs also exhibited a decreasing trend over time. Consistent with previous literature, the proportion persistent in our study at 6 months to SSRI (0.34) or SNRI (0.38) therapy was higher than persistence to TCAs (0.18). This was similar to previously reported estimates (persistence to first line 21-52%[33–35] versus second line 0-20%[33]). Yet, the proportion persistent at 6 months to MAOIs was similar to SSRI or SNRI therapy, which was unexpected.

Adherence and persistence differed by initial AD and initial therapeutic class. However, clinical significance of these differences, as it relates to adherence and persistence is unknown. Further research

to ascertain a clinically meaningful change of adherence and persistence is warranted. Largely, our study supports the importance of choosing the appropriate initial therapy in order to improve adherence and persistence. Adherence is associated with improved clinical outcomes[11,16,17] and decreased costs of medical care[18], further stressing the importance of initial AD.

Although MDD may or may not become a chronic disease for certain patients, comparison of reported adherence and persistence to other chronic diseases is warranted. Yeaw et.al. reported 12-month adherence and 6-month persistence to medication therapy across 6 chronic disease states, calculated using similar methods to our analysis. Mean 12-month PDC was lowest for overactive bladder syndrome (0.35, S.D. 0.32) and prostaglandin analogs (0.37, S.D. 0.26), while it was highest for oral antidiabetic therapy (0.72, S.D. 0.32).[57] In comparison with our findings, mean 12-month PDC to AD therapy was moderate in comparison (Appendix 4: mean PDC 0.48, S.D. 0.33). The proportion persistent over 6 months, using a 30 day gap, was lowest for overactive bladder syndrome (0.21) and prostaglandin analogs (0.35), while it was highest for oral antidiabetic therapy (0.53). Our findings support persistence at 6-months was 0.36, and was moderate to low in comparison. Briesacher et. al. reported the proportion adherent at 12 months across 7 diseases, using MPR. Patients with gout had the lowest proportion adherent (0.37), and patients with hypertension had the highest (0.72).[58] In comparison to our findings, the proportion adherent 12 months was 0.31. Comparing adherence to other chronic diseases supports relatively poor to moderate adherence and persistence in the MDD population. However, when comparing adherence and persistence among complex diseases, it is important to reconcile clinically relevant periods that may differ by disease state.

Adherence and persistence to initiation phase (first 3 months of therapy) was low, yet, an adequate trial of AD therapy is between 8 and 12 weeks.[8] It is to be expected that patients may switch therapy at this point if initial therapy was not efficacious, supported by time to discontinuation curves (Figures 3 and 4).[8] Though switching likely occurred, as shown by the proportion of patients with the presence of a new and different AD prescription than prescribed on the IPD over time, switching did not completely account for low adherence and persistence demonstrated by the sample as a whole. Adherence and persistence overall, to any AD therapy, was only slightly higher than adherence to initial

AD medication, indicating that even with switching to other therapies, adherence and persistence remains low. For other periods of clinical relevance, adherence and persistence decreased after initiation phase, both at 6 months (minimally recommended duration of treatment) and also 9 months (recommended duration of therapy).[7,8]

Adherence was specifically calculated over continuation phase (between months 4 to 9) of therapy, which is another clinically relevant time period time. Adherence is related to persistence, and as such, low persistence over the interval, will attenuate adherence results. Many patients became non-persistent during continuation phase, as mean persistence was approximately 6 months. It was necessary to include this interval because calculating adherence from the IPD to month 6 does not adequately capture this drop in persistence. Calculations of adherence with a reference point of the IPD fail to distinguish adherence beyond initiation phase, as adherence past this point cannot be separated from the calculation. This limits the ability of conventional adherence calculations to reflect patterns of adherence and persistence. Description of adherence in the MDD population may require multiple time frames, as demonstrated here, in order to account for therapy changes and switching. More sophisticated methods, such as trajectory modelling,[59] are on the horizon that may allow modeling of adherence behavior using claims data.

Limitations

Limitations in this study were due to the use of insurance claims data. Use of insurance claims data may pose a risk of inaccurate information, due to consolidation of information across health plans, yet Truven Health Analytics ensures data quality through internal processes. The prevalence of AD prescription in the sample may not reflect prescribing practices, as prescription claims data relies on patients actually filling their AD prescriptions. Yet, as our sample was large and found to be representative of the MDD population, prescribing likely reflected current practice. Assessing adherence and persistence through analyses of claims data may not reflect true adherence and persistence, yet again, with our sample size, calculations likely approximated estimates with some certainty.

Using claims data did not allow for control for all possible predictors of adherence, yet many

important confounders and precision variables were controlled for in adjusted analyses: age, gender, source of insurance, geographical region, insurance plan type, MDD diagnosis code, CCI, and presence of anxiety or chronic pain comorbidities. Though switching of AD therapy could be used as another surrogate of MDD severity, MDD diagnosis code was used to adequately control for severity. Alternative clinical instructions may lead to underestimation of adherence. For example, trazodone is commonly used off-label at low doses as a sedative-hypnotic and is not typically used to treat MDD,[8] which possibly led to trazodone's low adherence and persistence in this sample. Certain psychosocial predictors of adherence, such as beliefs, patient-provider relationship, education, and economic and cultural factors, were not ascertained due to use of insurance claims data.[8]

CONCLUSION

Adherence and persistence to AD medication is low in the US MDD population, over the first 3, 6, 9, and 12 months of receipt of initial antidepressant. Adherence and persistence was found to differ by initial antidepressant and by initial therapeutic class. Initial antidepressant was associated with adherence at all time periods over the first year of therapy. Adherence over the first 3 months, or initiation phase of treatment, was associated with adherence over the next 4-9 months, or continuation phase of treatment. Results support that among first line ADs and alternatives, the odds of adherence versus sertraline may be higher for patients initiating with desvenlafaxine, duloxetine, or venlafaxine XR from IPD to month 3, month 6, month 9, and month 12. Suitable alternatives, showing no difference in the odds of adherence from sertraline at 6 months, include bupropion XL, fluoxetine weekly, escitalopram, or venlafaxine. The choice of initial antidepressant medication is an important clinical decision, associated with adherence and persistence, and thus, has the potential to improve clinical outcomes and decrease health care utilization.

TABLES

Table 1. Baseline Demographic, Clinical, and Subgroup Variables by Initial Antidepressant Medication (in Alphabetic Order)

	Amitriptyline	Amoxapine	Bupropion	Buproprion SR	Bupropion XL	Citalopram	Clomipramine	Desipramine	Desvenlafaxine	Doxepin	Duloxetine
DEMOGRAPHIC											
Initial AD prescription, n (%)	6,433 (1.2%)	11 (<1%)	22,958 (4.3%)	7,759 (1.5%)	28,509 (5.4%)	84,253 (16.0%)	158 (<1%)	210 (<1%)	6,269 (1.2%)	1,056 (<1%)	21,777 (4.1%)
Age, mean (SD)											
Years	41.5 (17.0)	41.0 (19.9)	38.2 (15.4)	37.7 (15.2)	37.6 (14.4)	39.9 (17.4)	38.0 (15.6)	44.9 (16.5)	40.5 (13.1)	45.0 (16.4)	44.1 (14.7)
Age Categories, n (%)											
<18 years old	829 (12.9%)	3 (27.3%)	2,692 (11.7%)	1,007 (13.0%)	3,126 (11.0%)	9,598 (11.4%)	20 (12.7%)	14 (6.7%)	173 (2.8%)	62 (5.9%)	737 (3.4%)
18-39 years old	1,927 (30.0%)	2 (18.2%)	9,275 (40.4%)	3,108 (40.1%)	12,284 (43.1%)	32,074 (38.1%)	67 (42.4%)	54 (25.7%)	2,760 (44.0%)	322 (30.5%)	7,430 (34.1%)
40-65 years old	3,252 (50.6%)	6 (54.5%)	10,305 (44.9%)	3,449 (44.5%)	12,547 (44.0%)	36,920 (43.8%)	65 (41.1%)	121 (57.6%)	3,215 (51.3%)	579 (54.8%)	12,235 (56.2%)
>65 years old	425 (6.6%)	0 (<1%)	686 (3.0%)	195 (2.5%)	552 (1.9%)	5,661 (6.7%)	6 (3.8%)	21 (10.0%)	121 (1.9%)	93 (8.8%)	1,375 (6.3%)
Gender, n (%)											
Male	1,912 (29.7%)	3 (27.3%)	9,386 (40.9%)	3,188 (41.1%)	11,205 (39.3%)	29,693 (35.2%)	81 (51.3%)	82 (39.0%)	2,040 (32.5%)	406 (38.4%)	7,339 (33.7%)
Female	4,521 (70.3%)	8 (72.7%)	13,572 (59.1%)	4,571 (58.9%)	17,304 (60.7%)	54,560 (64.8%)	77 (48.7%)	128 (61.0%)	4,229 (67.5%)	650 (61.6%)	14,438 (66.3%)
Insurance Claim Source, n (%)											
Medicaid	1,844 (28.7%)	1 (9.1%)	2,175 (9.5%)	1,451 (18.7%)	2,263 (7.9%)	10,097 (12.0%)	18 (11.4%)	36 (17.1%)	273 (4.4%)	199 (18.8%)	2,066 (9.5%)
Commercial	4,159 (64.7%)	9 (81.8%)	19,981 (87.0%)	6,106 (78.7%)	25,552 (89.6%)	68,003 (80.7%)	133 (84.2%)	152 (72.4%)	5,845 (93.2%)	754 (71.4%)	18,116 (83.2%)
Medicare	430 (6.7%)	1 (9.1%)	802 (3.5%)	202 (2.6%)	694 (2.4%)	6,153 (7.3%)	7 (4.4%)	22 (10.5%)	151 (2.4%)	103 (9.8%)	1,595 (7.3%)
Geographical Location, n (%)											
Northeast	694 (10.8%)	3 (27.3%)	3,700 (16.1%)	888 (11.4%)	3,351 (11.8%)	12,758 (15.1%)	31 (19.6%)	35 (16.7%)	654 (10.4%)	119 (11.3%)	2,680 (12.3%)
Northcentral	1,139 (17.7%)	2 (18.2%)	5,206 (22.7%)	1,748 (22.5%)	6,689 (23.5%)	22,048 (26.2%)	32 (20.3%)	50 (23.8%)	1,373 (21.9%)	198 (18.8%)	5,389 (24.7%)
South	1,633 (25.4%)	4 (36.4%)	6,188 (27.0%)	1,950 (25.1%)	10,262 (36.0%)	21,119 (25.1%)	53 (33.5%)	40 (19.0%)	2,981 (47.6%)	324 (30.7%)	8,245 (37.9%)
West	1,066 (16.6%)	1 (9.1%)	5,376 (23.4%)	1,623 (20.9%)	5,523 (19.4%)	17,271 (20.5%)	24 (15.2%)	48 (22.9%)	865 (13.8%)	207 (19.6%)	3,082 (14.2%)
Unknown	57 (<1%)	0 (<1%)	313 (1.4%)	99 (1.3%)	421 (1.5%)	960 (1.1%)	0 (<1%)	1 (<1%)	123 (2.0%)	9 (<1%)	315 (1.4%)
Missing	1,844 (28.7%)	1 (9.1%)	2,175 (9.5%)	1,451 (18.7%)	2,263 (7.9%)	10,097 (12.0%)	18 (11.4%)	36 (17.1%)	273 (4.4%)	199 (18.8%)	2,066 (9.5%)
Health Plan Type, n (%)											
Comprehensive	1,643 (25.5%)	3 (27.3%)	1,958 (8.5%)	1,403 (18.1%)	3,020 (10.6%)	10,008 (11.9%)	27 (17.1%)	41 (19.5%)	354 (5.6%)	226 (21.4%)	2,998 (13.8%)
EPO	34 (<1%)	0 (<1%)	232 (1.0%)	37 (<1%)	285 (<1%)	779 (<1%)	3 (1.9%)	1 (<1%)	86 (1.4%)	4 (<1%)	212 (<1%)
HMO	1,283 (19.9%)	0 (<1%)	5,052 (22.0%)	1,820 (23.5%)	4,621 (16.2%)	18,504 (22.0%)	26 (16.5%)	42 (20.0%)	673 (10.7%)	194 (18.4%)	2,972 (13.6%)
POS	397 (6.2%)	0 (<1%)	1,677 (7.3%)	625 (8.1%)	2,439 (8.6%)	5,803 (6.9%)	12 (7.6%)	18 (8.6%)	550 (8.8%)	69 (6.5%)	1,663 (7.6%)
PPO	2,551 (39.7%)	7 (63.6%)	11,430 (49.8%)	3,260 (42.0%)	15,633 (54.8%)	40,353 (47.9%)	77 (48.7%)	94 (44.8%)	3,998 (63.8%)	477 (45.2%)	12,261 (56.3%)
POS with Capitation	169 (2.6%)	0 (<1%)	371 (1.6%)	221 (2.8%)	538 (1.9%)	1,078 (1.3%)	3 (1.9%)	4 (1.9%)	21 (<1%)	28 (2.7%)	219 (1.0%)
CDHP	115 (1.8%)	0 (<1%)	865 (3.8%)	151 (1.9%)	974 (3.4%)	2,778 (3.3%)	4 (2.5%)	5 (2.4%)	290 (4.6%)	26 (2.5%)	688 (3.2%)
HDHP	66 (1.0%)	0 (<1%)	481 (2.1%)	59 (<1%)	464 (1.6%)	1,624 (1.9%)	1 (<1%)	3 (1.4%)	114 (1.8%)	14 (1.3%)	289 (1.3%)
Missing	175 (2.7%)	1 (9.1%)	892 (3.9%)	183 (2.4%)	535 (1.9%)	3,326 (3.9%)	5 (3.2%)	2 (<1%)	183 (2.9%)	18 (1.7%)	475 (2.2%)
CLINICAL											
MDD Diagnosis Code, n (%)											
Single Episode	725 (11.3%)	2 (18.2%)	2,818 (12.3%)	1,004 (12.9%)	4,123 (14.5%)	10,387 (12.3%)	30 (19.0%)	21 (10.0%)	810 (12.9%)	145 (13.7%)	2,768 (12.7%)
Recurrent Episode	1,059 (16.5%)	5 (45.5%)	4,381 (19.1%)	1,586 (20.4%)	6,171 (21.6%)	12,522 (14.9%)	62 (39.2%)	56 (26.7%)	1,377 (22.0%)	241 (22.8%)	4,801 (22.0%)
Dysthymia	999 (15.5%)	1 (9.1%)	2,958 (12.9%)	1,025 (13.2%)	3,626 (12.7%)	11,213 (13.3%)	14 (8.9%)	33 (15.7%)	755 (12.0%)	165 (15.6%)	2,668 (12.3%)
Depression, NOS	3,650 (56.7%)	3 (27.3%)	12,801 (55.8%)	4,144 (53.4%)	14,589 (51.2%)	50,131 (59.5%)	52 (32.9%)	100 (47.6%)	3,327 (53.1%)	505 (47.8%)	11,540 (53.0%)
CCI (Deyo Modification), n (%)											
0	4,440 (69.0%)	9 (81.8%)	18,635 (81.2%)	6,292 (81.1%)	23,911 (83.9%)	65,641 (77.9%)	134 (84.8%)	152 (72.4%)	5,101 (81.4%)	750 (71.0%)	16,019 (73.6%)
1	1,206 (18.7%)	0 (<1%)	2,963 (12.9%)	1,030 (13.3%)	3,311 (11.6%)	11,585 (13.8%)	15 (9.5%)	30 (14.3%)	835 (13.3%)	177 (16.8%)	3,377 (15.5%)
2	380 (5.9%)	1 (9.1%)	707 (3.1%)	231 (3.0%)	738 (2.6%)	3,420 (4.1%)	6 (3.8%)	15 (7.1%)	200 (3.2%)	65 (6.2%)	1,157 (5.3%)
3+	407 (6.3%)	1 (9.1%)	653 (2.8%)	206 (2.7%)	549 (1.9%)	3,607 (4.3%)	3 (1.9%)	13 (6.2%)	133 (2.1%)	64 (6.1%)	1,224 (5.6%)
SUBGROUP											
Comorbid Diagnoses*, n (%)**											
Anxiety Disorder	1,436 (22.3%)	5 (45.5%)	4,186 (18.2%)	1,161 (15.0%)	4,086 (14.3%)	21,510 (25.5%)	84 (53.2%)	53 (25.2%)	1,666 (26.6%)	288 (27.3%)	4,942 (22.7%)
Chronic Pain Disorder	3,601 (56.0%)	4 (36.4%)	5,145 (22.4%)	1,657 (21.4%)	5,703 (20.0%)	19,856 (23.6%)	33 (20.9%)	87 (41.4%)	1,563 (24.9%)	404 (38.3%)	8,750 (40.2%)
Presence of prescription for new and different AD*, n (%)**											
within first 3 months	1,114 (17.3%)	3 (27.3%)	3,946 (17.2%)	1,693 (21.8%)	4,133 (14.5%)	6,959 (8.3%)	41 (25.9%)	35 (16.7%)	713 (11.4%)	209 (19.8%)	2,410 (11.1%)
within first 6 months	1,729 (26.9%)	7 (63.6%)	6,270 (27.3%)	2,801 (36.1%)	6,784 (23.8%)	12,636 (15.0%)	57 (36.1%)	51 (24.3%)	1,208 (19.3%)	305 (28.9%)	4,220 (19.4%)
within first 9 months	2,105 (32.7%)	9 (81.8%)	7,655 (33.3%)	3,395 (43.8%)	8,523 (29.9%)	16,460 (19.5%)	66 (41.8%)	68 (32.4%)	1,570 (25.0%)	380 (36.0%)	5,460 (25.1%)
within first 12 months	2,410 (37.5%)	9 (81.8%)	8,864 (38.6%)	3,835 (49.4%)	9,970 (35.0%)	19,956 (23.7%)	75 (47.5%)	81 (38.6%)	1,892 (30.2%)	442 (41.9%)	6,600 (30.3%)

Table 1. Continued (Letters E-Ph)

	Escitalopram	Fluoxetine	Fluoxetine weekly	Fluvoxamine	Imipramine	Maprotiline	Mirtazapine	Nefazodone	Nortriptyline	Paroxetine	Paroxetine CR	Phenelzine
DEMOGRAPHIC												
Initial AD prescription, n (%)	89,616 (17.0%)	70,537 (13.4%)	185 (<1%)	919 (<1%)	933 (<1%)	332 (<1%)	12,438 (2.4%)	294 (<1%)	1,895 (<1%)	22,004 (4.2%)	5,074 (<1%)	17 (<1%)
Age, mean (SD)												
Years	38.5 (16.8)	32.8 (17.8)	31.0 (17.7)	32.9 (16.1)	29.5 (21.2)	43.2 (17.5)	46.9 (22.6)	45.2 (13.2)	44.3 (16.4)	41.5 (17.1)	39.6 (16.2)	52.6 (17.9)
Age Categories, n (%)												
<18 years old	12,642 (14.1%)	21,956 (31.1%)	70 (37.8%)	204 (22.2%)	441 (47.3%)	36 (10.8%)	1,799 (14.5%)	8 (2.7%)	151 (8.0%)	1,892 (8.6%)	529 (10.4%)	0 (<1%)
18-39 years old	33,987 (37.9%)	22,836 (32.4%)	56 (30.3%)	401 (43.6%)	168 (18.0%)	92 (27.7%)	2,834 (22.8%)	84 (28.6%)	542 (28.6%)	8,220 (37.4%)	2,035 (40.1%)	4 (23.5%)
40-65 years old	38,501 (43.0%)	23,139 (32.8%)	55 (29.7%)	290 (31.6%)	277 (29.7%)	178 (53.6%)	5,131 (41.3%)	189 (64.3%)	1,042 (55.0%)	10,130 (46.0%)	2,217 (43.7%)	10 (58.8%)
>65 years old	4,486 (5.0%)	2,606 (3.7%)	4 (2.2%)	24 (2.6%)	47 (5.0%)	26 (7.8%)	2,674 (21.5%)	13 (4.4%)	160 (8.4%)	1,762 (8.0%)	293 (5.8%)	3 (17.6%)
Gender, n (%)												
Male	31,553 (35.2%)	23,937 (33.9%)	66 (35.7%)	442 (48.1%)	425 (45.6%)	64 (19.3%)	6,132 (49.3%)	119 (40.5%)	619 (32.7%)	8,310 (37.8%)	1,704 (33.6%)	9 (52.9%)
Female	58,063 (64.8%)	46,600 (66.1%)	119 (64.3%)	477 (51.9%)	508 (54.4%)	268 (80.7%)	6,306 (50.7%)	175 (59.5%)	1,276 (67.3%)	13,694 (62.2%)	3,370 (66.4%)	8 (47.1%)
Insurance Claim Source, n (%)												
Medicaid	10,004 (11.2%)	11,378 (16.1%)	59 (31.9%)	117 (12.7%)	362 (38.8%)	41 (12.3%)	2,809 (22.6%)	45 (15.3%)	308 (16.3%)	3,515 (16.0%)	1,568 (30.9%)	0 (<1%)
Commercial	74,970 (83.7%)	56,328 (79.9%)	123 (66.5%)	774 (84.2%)	517 (55.4%)	262 (78.9%)	6,987 (56.2%)	236 (80.3%)	1,415 (74.7%)	16,726 (76.0%)	3,255 (64.2%)	14 (82.4%)
Medicare	4,642 (5.2%)	2,831 (4.0%)	3 (1.6%)	28 (3.0%)	54 (5.8%)	29 (8.7%)	2,642 (21.2%)	13 (4.4%)	172 (9.1%)	1,763 (8.0%)	251 (4.9%)	3 (17.6%)
Geographical Location, n (%)												
Northeast	13,064 (14.6%)	8,719 (12.4%)	13 (7.0%)	179 (19.5%)	83 (8.9%)	95 (28.6%)	1,512 (12.2%)	20 (6.8%)	226 (11.9%)	3,018 (13.7%)	341 (6.7%)	2 (11.8%)
Northcentral	22,398 (25.0%)	15,589 (22.1%)	33 (17.8%)	178 (19.4%)	146 (15.6%)	54 (16.3%)	2,976 (23.9%)	59 (20.1%)	384 (20.3%)	5,128 (23.3%)	1,036 (20.4%)	3 (17.6%)
South	29,357 (32.8%)	16,640 (23.6%)	53 (28.6%)	296 (32.2%)	227 (24.3%)	62 (18.7%)	3,141 (25.3%)	73 (24.8%)	417 (22.0%)	5,643 (25.6%)	1,323 (26.1%)	9 (52.9%)
West	13,690 (15.3%)	17,315 (24.5%)	24 (13.0%)	139 (15.1%)	106 (11.4%)	78 (23.5%)	1,925 (15.5%)	93 (31.6%)	542 (28.6%)	4,408 (20.0%)	757 (14.9%)	3 (17.6%)
Unknown	1,103 (1.2%)	896 (1.3%)	3 (1.6%)	10 (1.1%)	9 (<1%)	2 (<1%)	75 (<1%)	4 (1.4%)	18 (<1%)	292 (1.3%)	49 (<1%)	0 (<1%)
Missing	10,004 (11.2%)	11,378 (16.1%)	59 (31.9%)	117 (12.7%)	362 (38.8%)	41 (12.3%)	2,809 (22.6%)	45 (15.3%)	308 (16.3%)	3,515 (16.0%)	1,568 (30.9%)	0 (<1%)
Health Plan Type, n (%)												
Comprehensive	12,656 (14.1%)	9,242 (13.1%)	63 (34.1%)	124 (13.5%)	300 (32.2%)	54 (16.3%)	3,635 (29.2%)	63 (21.4%)	340 (17.9%)	3,504 (15.9%)	1,785 (35.2%)	3 (17.6%)
EPO	745 (<1%)	508 (<1%)	2 (1.1%)	11 (1.2%)	7 (<1%)	6 (1.8%)	68 (<1%)	1 (<1%)	14 (<1%)	192 (<1%)	18 (<1%)	0 (<1%)
HMO	13,194 (14.7%)	18,821 (26.7%)	23 (12.4%)	157 (17.1%)	164 (17.6%)	57 (17.2%)	2,311 (18.6%)	59 (20.1%)	524 (27.7%)	4,937 (22.4%)	899 (17.7%)	3 (17.6%)
POS	7,480 (8.3%)	4,795 (6.8%)	20 (10.8%)	61 (6.6%)	47 (5.0%)	22 (6.6%)	767 (6.2%)	24 (8.2%)	138 (7.3%)	1,417 (6.4%)	357 (7.0%)	1 (5.9%)
PPO	46,885 (52.3%)	30,665 (43.5%)	66 (35.7%)	468 (50.9%)	344 (36.9%)	153 (46.1%)	4,696 (37.8%)	128 (43.5%)	745 (39.3%)	10,041 (45.6%)	1,701 (33.5%)	8 (47.1%)
POS with Capitation	2,005 (2.2%)	1,421 (2.0%)	9 (4.9%)	23 (2.5%)	41 (4.4%)	8 (2.4%)	409 (3.3%)	9 (3.1%)	29 (1.5%)	447 (2.0%)	253 (5.0%)	0 (<1%)
CDHP	2,880 (3.2%)	2,106 (3.0%)	0 (<1%)	25 (2.7%)	6 (<1%)	14 (4.2%)	232 (1.9%)	8 (2.7%)	32 (1.7%)	583 (2.6%)	41 (<1%)	1 (5.9%)
HDHP	1,212 (1.4%)	1,229 (1.7%)	0 (<1%)	12 (1.3%)	6 (<1%)	6 (1.8%)	102 (<1%)	1 (<1%)	21 (1.1%)	270 (1.2%)	4 (<1%)	1 (5.9%)
Missing	2,559 (2.9%)	1,750 (2.5%)	2 (1.1%)	38 (4.1%)	18 (1.9%)	12 (3.6%)	218 (1.8%)	1 (<1%)	52 (2.7%)	613 (2.8%)	16 (<1%)	0 (<1%)
CLINICAL												
MDD Diagnosis Code, n (%)												
Single Episode	13,431 (15.0%)	9,980 (14.1%)	25 (13.5%)	150 (16.3%)	151 (16.2%)	50 (15.1%)	2,146 (17.3%)	32 (10.9%)	254 (13.4%)	2,572 (11.7%)	739 (14.6%)	2 (11.8%)
Recurrent Episode	16,790 (18.7%)	12,030 (17.1%)	35 (18.9%)	293 (31.9%)	185 (19.8%)	62 (18.7%)	3,221 (25.9%)	87 (29.6%)	424 (22.4%)	3,483 (15.8%)	1,132 (22.3%)	8 (47.1%)
Dysthymia	11,821 (13.2%)	7,838 (11.1%)	26 (14.1%)	116 (12.6%)	139 (14.9%)	61 (18.4%)	1,005 (8.1%)	34 (11.6%)	282 (14.9%)	3,256 (14.8%)	647 (12.8%)	2 (11.8%)
Depression, NOS	47,574 (53.1%)	40,689 (57.7%)	99 (53.5%)	360 (39.2%)	458 (49.1%)	159 (47.9%)	6,066 (48.8%)	141 (48.0%)	935 (49.3%)	12,693 (57.7%)	2,556 (50.4%)	5 (29.4%)
CCI (Deyo Modification), n (%)												
0	72,221 (80.6%)	58,492 (82.9%)	156 (84.3%)	797 (86.7%)	712 (76.3%)	233 (70.2%)	8,203 (66.0%)	239 (81.3%)	1,324 (69.9%)	16,932 (76.9%)	4,065 (80.1%)	12 (70.6%)
1	11,195 (12.5%)	8,660 (12.3%)	25 (13.5%)	97 (10.6%)	156 (16.7%)	63 (19.0%)	2,018 (16.2%)	34 (11.6%)	345 (18.2%)	3,161 (14.4%)	702 (13.8%)	2 (11.8%)
2	3,160 (3.5%)	1,789 (2.5%)	4 (2.2%)	19 (2.1%)	35 (3.8%)	20 (6.0%)	886 (7.1%)	7 (2.4%)	110 (5.8%)	975 (4.4%)	184 (3.6%)	1 (5.9%)
3+	3,040 (3.4%)	1,596 (2.3%)	0 (<1%)	6 (<1%)	30 (3.2%)	16 (4.8%)	1,331 (10.7%)	14 (4.8%)	116 (6.1%)	936 (4.3%)	123 (2.4%)	2 (11.8%)
SUBGROUP												
Comorbid Diagnoses*, n (%)**												
Anxiety Disorder	21,453 (23.9%)	15,381 (21.8%)	19 (10.3%)	443 (48.2%)	234 (25.1%)	83 (25.0%)	3,192 (25.7%)	51 (17.3%)	453 (23.9%)	6,969 (31.7%)	1,136 (22.4%)	4 (23.5%)
Chronic Pain Disorder	19,098 (21.3%)	13,524 (19.2%)	37 (20.0%)	159 (17.3%)	235 (25.2%)	212 (63.9%)	3,552 (28.6%)	69 (23.5%)	1,100 (58.0%)	5,475 (24.9%)	1,090 (21.5%)	5 (29.4%)
Presence of prescription for new and different AD*, n (%)**												
within first 3 months	8,010 (8.9%)	6,052 (8.6%)	27 (14.6%)	151 (16.4%)	124 (13.3%)	77 (23.2%)	1,998 (16.1%)	46 (15.6%)	311 (16.4%)	2,073 (9.4%)	753 (14.8%)	6 (35.3%)
within first 6 months	14,532 (16.2%)	10,722 (15.2%)	45 (24.3%)	237 (25.8%)	207 (22.2%)	119 (35.8%)	3,140 (25.2%)	85 (28.9%)	507 (26.8%)	3,816 (17.3%)	1,432 (28.2%)	6 (35.3%)
within first 9 months	19,087 (21.3%)	13,977 (19.8%)	62 (33.5%)	293 (31.9%)	265 (28.4%)	151 (45.5%)	3,845 (30.9%)	110 (37.4%)	625 (33.0%)	5,001 (22.7%)	1,911 (37.7%)	6 (35.3%)
within first 12 months	23,050 (25.7%)	16,888 (23.9%)	75 (40.5%)	339 (36.9%)	318 (34.1%)	174 (52.4%)	4,412 (35.5%)	131 (44.6%)	728 (38.4%)	6,034 (27.4%)	2,271 (44.8%)	8 (47.1%)

Table 1. Continued (Letters Pr-V)

	Protriptyline	Selegiline Transdermal Patch	Sertraline	Tranylcypromine	Trazodone	Trazodone ER	Trimipramine	Venlafaxine	Venlafaxine XR	Vilazodone	Row Sum, n	Percentage of total	p value
DEMOGRAPHIC													
Initial AD prescription, n (%)	37 (<1%)	55 (<1%)	98,869 (18.7%)	13 (<1%)	14,576 (2.8%)	43 (<1%)	5 (<1%)	11,820 (2.2%)	17,476 (3.3%)	1,376 (<1%)	527,907	100%	-
Age, mean (SD)													*
Years	43.9 (14.6)	41.1 (14.3)	36.2 (18.4)	51.2 (17.0)	40.6 (17.0)	37.9 (14.0)	51.8 (14.2)	41.8 (14.9)	40.6 (14.8)	40.9 (13.4)	527,907	100%	
Age Categories, n (%)													**
<18 years old	3 (8.1%)	3 (5.5%)	21,795 (22.0%)	0 (<1%)	1,826 (12.5%)	2 (4.7%)	0 (<1%)	512 (4.3%)	1,128 (6.5%)	35 (2.5%)	83,293	16%	
18-39 years old	9 (24.3%)	19 (34.5%)	35,063 (35.5%)	3 (23.1%)	4,778 (32.8%)	21 (48.8%)	2 (40.0%)	4,671 (39.5%)	7,021 (40.2%)	575 (41.8%)	192,724	37%	
40-65 years old	23 (62.2%)	32 (58.2%)	36,085 (36.5%)	8 (61.5%)	7,104 (48.7%)	20 (46.5%)	3 (60.0%)	6,064 (51.3%)	8,609 (49.3%)	731 (53.1%)	222,532	42%	
>65 years old	2 (5.4%)	1 (1.8%)	5,926 (6.0%)	2 (15.4%)	868 (6.0%)	0 (<1%)	0 (<1%)	573 (4.8%)	718 (4.1%)	35 (2.5%)	29,358	6%	
Gender, n (%)													**
Male	11 (29.7%)	19 (34.5%)	34,836 (35.2%)	8 (61.5%)	5,794 (39.8%)	20 (46.5%)	3 (60.0%)	3,903 (33.0%)	5,866 (33.6%)	506 (36.8%)	189,681	36%	
Female	26 (70.3%)	36 (65.5%)	64,033 (64.8%)	5 (38.5%)	8,782 (60.2%)	23 (53.5%)	2 (40.0%)	7,917 (67.0%)	11,610 (66.4%)	870 (63.2%)	338,226	64%	
Insurance Claim Source, n (%)													**
Medicaid	7 (18.9%)	1 (1.8%)	14,426 (14.6%)	0 (<1%)	2,840 (19.5%)	5 (11.6%)	1 (20.0%)	965 (8.2%)	2,745 (15.7%)	91 (6.6%)	71,710	14%	
Commercial	27 (73.0%)	53 (96.4%)	78,335 (79.2%)	11 (84.6%)	10,815 (74.2%)	37 (86.0%)	3 (60.0%)	10,174 (86.1%)	13,994 (80.1%)	1,240 (90.1%)	425,106	81%	
Medicare	3 (8.1%)	1 (1.8%)	6,108 (6.2%)	2 (15.4%)	921 (6.3%)	1 (2.3%)	1 (20.0%)	681 (5.8%)	737 (4.2%)	45 (3.3%)	31,091	6%	
Geographical Location, n (%)													**
Northeast	7 (18.9%)	4 (7.3%)	14,360 (14.5%)	4 (30.8%)	1,677 (11.5%)	8 (18.6%)	0 (<1%)	1,954 (16.5%)	1,713 (9.8%)	231 (16.8%)	72,143	14%	
Northcentral	10 (27.0%)	6 (10.9%)	24,962 (25.2%)	3 (23.1%)	2,980 (20.4%)	12 (27.9%)	2 (40.0%)	2,868 (24.3%)	4,359 (24.9%)	280 (20.3%)	127,340	24%	
South	6 (16.2%)	24 (43.6%)	27,250 (27.6%)	2 (15.4%)	3,946 (27.1%)	12 (27.9%)	1 (20.0%)	3,508 (29.7%)	5,522 (31.6%)	602 (43.8%)	150,913	29%	
West	6 (16.2%)	19 (34.5%)	16,603 (16.8%)	4 (30.8%)	3,000 (20.6%)	6 (14.0%)	1 (20.0%)	2,336 (19.8%)	2,962 (16.9%)	162 (11.8%)	99,265	19%	
Unknown	1 (2.7%)	1 (1.8%)	1,268 (1.3%)	0 (<1%)	133 (<1%)	0 (<1%)	0 (<1%)	189 (1.6%)	175 (1.0%)	10 (<1%)	6,536	1%	
Missing	7 (18.9%)	1 (1.8%)	14,426 (14.6%)	0 (<1%)	2,840 (19.5%)	5 (11.6%)	1 (20.0%)	965 (8.2%)	2,745 (15.7%)	91 (6.6%)	71,710	14%	
Health Plan Type, n (%)													**
Comprehensive	8 (21.6%)	1 (1.8%)	14,460 (14.6%)	3 (23.1%)	2,696 (18.5%)	3 (7.0%)	0 (<1%)	1,011 (8.6%)	3,508 (20.1%)	95 (6.9%)	75,235	14%	
EPO	0 (<1%)	1 (1.8%)	884 (<1%)	1 (7.7%)	110 (<1%)	0 (<1%)	0 (<1%)	117 (<1%)	104 (<1%)	11 (<1%)	4,473	1%	
HMO	6 (16.2%)	15 (27.3%)	18,603 (18.8%)	3 (23.1%)	3,109 (21.3%)	4 (9.3%)	1 (20.0%)	2,112 (17.9%)	3,189 (18.2%)	143 (10.4%)	103,521	20%	
POS	1 (2.7%)	5 (9.1%)	7,100 (7.2%)	1 (7.7%)	1,079 (7.4%)	6 (14.0%)	0 (<1%)	746 (6.3%)	1,484 (8.5%)	111 (8.1%)	38,915	7%	
PPO	21 (56.8%)	25 (45.5%)	47,515 (48.1%)	5 (38.5%)	6,346 (43.5%)	28 (65.1%)	4 (80.0%)	6,432 (54.4%)	8,049 (46.1%)	871 (63.3%)	255,337	48%	
POS with Capitation	0 (<1%)	2 (3.6%)	2,534 (2.6%)	0 (<1%)	349 (2.4%)	0 (<1%)	0 (<1%)	118 (<1%)	458 (2.6%)	5 (<1%)	10,772	2%	
CDHP	0 (<1%)	4 (7.3%)	3,115 (3.2%)	0 (<1%)	396 (2.7%)	0 (<1%)	0 (<1%)	449 (3.8%)	294 (1.7%)	82 (6.0%)	16,164	3%	
HDHP	0 (<1%)	0 (<1%)	1,657 (1.7%)	0 (<1%)	193 (1.3%)	1 (2.3%)	0 (<1%)	294 (2.5%)	42 (<1%)	42 (3.1%)	8,208	2%	
Missing	1 (2.7%)	2 (3.6%)	3,001 (3.0%)	0 (<1%)	298 (2.0%)	1 (2.3%)	0 (<1%)	541 (4.6%)	348 (2.0%)	16 (1.2%)	15,282	3%	
CLINICAL													
MDD Diagnosis Code, n (%)													**
Single Episode	4 (10.8%)	10 (18.2%)	13,635 (13.8%)	1 (7.7%)	2,160 (14.8%)	8 (18.6%)	1 (20.0%)	1,267 (10.7%)	2,323 (13.3%)	168 (12.2%)	71,942	14%	
Recurrent Episode	11 (29.7%)	25 (45.5%)	16,373 (16.6%)	7 (53.8%)	3,328 (22.8%)	15 (34.9%)	0 (<1%)	1,947 (16.5%)	3,631 (20.8%)	304 (22.1%)	95,652	18%	
Dysthymia	7 (18.9%)	6 (10.9%)	12,683 (12.8%)	1 (7.7%)	1,667 (11.4%)	7 (16.3%)	0 (<1%)	1,650 (14.0%)	2,110 (12.1%)	187 (13.6%)	67,002	13%	
Depression, NOS	15 (40.5%)	14 (25.5%)	56,178 (56.8%)	4 (30.8%)	7,421 (50.9%)	13 (30.2%)	4 (80.0%)	6,956 (58.8%)	9,412 (53.9%)	717 (52.1%)	293,311	56%	
CCI (Deyo Modification), n (%)													**
0	21 (56.8%)	45 (81.8%)	79,030 (79.9%)	11 (84.6%)	11,008 (75.5%)	36 (83.7%)	3 (60.0%)	9,170 (77.6%)	14,184 (81.2%)	1,111 (80.7%)	419,089	79%	
1	10 (27.0%)	6 (10.9%)	12,929 (13.1%)	0 (<1%)	2,212 (15.2%)	2 (4.7%)	1 (20.0%)	1,598 (13.5%)	2,230 (12.8%)	183 (13.3%)	70,158	13%	
2	3 (8.1%)	1 (1.8%)	3,434 (3.5%)	2 (15.4%)	627 (4.3%)	2 (4.7%)	0 (<1%)	550 (4.7%)	597 (3.4%)	44 (3.2%)	19,370	4%	
3+	3 (8.1%)	3 (5.5%)	3,476 (3.5%)	0 (<1%)	729 (5.0%)	3 (7.0%)	1 (20.0%)	502 (4.2%)	465 (2.7%)	38 (2.8%)	19,290	4%	
SUBGROUP													
Comorbid Diagnoses*, n (%)**													
Anxiety Disorder	6 (16.2%)	12 (21.8%)	25,480 (25.8%)	4 (30.8%)	3,832 (26.3%)	14 (32.6%)	1 (20.0%)	3,502 (29.6%)	3,233 (18.5%)	400 (29.1%)	125,319	24%	**
Chronic Pain Disorder	27 (73.0%)	10 (18.2%)	20,815 (21.1%)	0 (<1%)	4,278 (29.3%)	17 (39.5%)	3 (60.0%)	3,395 (28.7%)	3,906 (22.4%)	360 (26.2%)	124,170	24%	**
Presence of prescription for new and different AD*, n (%)													
within first 3 months	7 (18.9%)	5 (9.1%)	7,981 (8.1%)	3 (23.1%)	4,073 (27.9%)	13 (30.2%)	0 (<1%)	1,446 (12.2%)	2,136 (12.2%)	187 (13.6%)	56,735	11%	**
within first 6 months	13 (35.1%)	16 (29.1%)	14,134 (14.3%)	3 (23.1%)	5,482 (37.6%)	18 (41.9%)	1 (20.0%)	2,487 (21.0%)	3,834 (21.9%)	316 (23.0%)	97,220	18%	**
within first 9 months	17 (45.9%)	20 (36.4%)	18,489 (18.7%)	4 (30.8%)	6,271 (43.0%)	21 (48.8%)	2 (40.0%)	3,118 (26.4%)	4,989 (28.5%)	392 (28.5%)	124,347	24%	**
within first 12 months	17 (45.9%)	22 (40.0%)	22,318 (22.6%)	6 (46.2%)	6,879 (47.2%)	23 (53.5%)	2 (40.0%)	3,701 (31.3%)	6,064 (34.7%)	462 (33.6%)	148,056	28%	**

Abbreviations: EPO- exclusive provider organization, HMO- health maintenance organization, POS-point of service, PPO- preferred provider organization, CDHP- consumer driven health plan, HDHP- high deductible health plan, SD-standard deviation, AD-Antidepressant, MDD-Major Depressive Disorder, NOS-Not Otherwise Specified, CCI-Charlson Comorbidity Index, SR- Sustained release, XL-Extended release, CR- Controlled release, XR-Extended Release, SD-standard deviation
Footnotes: * p value <0.0001, ** p value<0.001, ***Percentage does not add to 100% within one medication because percentage was cumulative over time and/or categories were not mutually exclusive
Testing: Pearson Chi-Squared test of independence of variables was undertaken for categorical variables to test equality of proportions when grouped by initial medication. Analysis of Variance (ANOVA) was undertaken to test equality of means for continuous variables with initial medication as the predictor variable.

Table 2. Baseline Demographic, Clinical, and Subgroup Variables by Initial Therapeutic Class

	SSRI	SNRI	Atypical	SARI (SM)	MAOI	TCA	SMS (SM)	Row Sum, n	Percentage of total	p value
DEMOGRAPHIC										
Initial therapeutic class prescription, n (%)	371,457 (70.4%)	57,342 (10.9%)	71,664 (13.6%)	14,913 (2.8%)	85 (<1%)	11,070 (2.1%)	1,376 (<1%)	527,907	100%	-
Age, mean (SD)										*
Years	37.3 (17.8)	42.2 (14.7)	39.4 (16.8)	40.7 (17.0)	45.0 (16.2)	41.4 (17.6)	40.9 (13.4)	527,907	100%	
Age Categories, n (%)										**
<18 years old	68,686 (18.5%)	2,550 (4.4%)	8,624 (12.0%)	1,836 (12.3%)	3 (3.5%)	1,559 (14.1%)	35 (2.5%)	83,293	16%	
18-39 years old	134,672 (36.3%)	21,882 (38.2%)	27,501 (38.4%)	4,883 (32.7%)	26 (30.6%)	3,185 (28.8%)	575 (41.8%)	192,724	37%	
40-65 years old	147,337 (39.7%)	30,123 (52.5%)	31,432 (43.9%)	7,313 (49.0%)	50 (58.8%)	5,546 (50.1%)	731 (53.1%)	222,532	42%	
>65 years old	20,762 (5.6%)	2,787 (4.9%)	4,107 (41.7%)	881 (5.9%)	6 (7.1%)	780 (7.0%)	35 (2.5%)	29,358	6%	
Gender, n (%)										**
Male	130,541 (35.1%)	19,148 (33.4%)	29,911 (41.7%)	5,933 (39.8%)	36 (42.4%)	3,606 (32.6%)	506 (36.8%)	189,681	36%	
Female	240,916 (64.9%)	38,194 (66.6%)	41,753 (58.3%)	8,980 (60.2%)	49 (57.6%)	7,464 (67.4%)	870 (63.2%)	338,226	64%	
Insurance Claim Source, n (%)										**
Medicaid	51,164 (13.8%)	6,049 (10.5%)	8,698 (12.1%)	2,890 (19.4%)	1 (1.2%)	2,817 (25.4%)	91 (6.6%)	71,710	14%	
Commercial	298,514 (80.4%)	48,129 (83.9%)	58,626 (81.8%)	11,088 (74.4%)	78 (91.8%)	7,431 (67.1%)	1,240 (90.1%)	425,106	81%	
Medicare	21,779 (5.9%)	3,164 (5.5%)	4,340 (6.1%)	935 (6.3%)	6 (7.1%)	822 (7.4%)	45 (3.3%)	31,091	6%	
Geographical Location, n (%)										**
Northeast	52,452 (14.1%)	7,001 (12.2%)	9,451 (13.2%)	1,705 (11.4%)	10 (11.8%)	1,293 (11.7%)	231 (16.8%)	72,143	14%	
Northcentral	91,372 (24.6%)	13,989 (24.4%)	16,619 (23.2%)	3,051 (20.5%)	12 (14.1%)	2,017 (18.2%)	280 (20.3%)	127,340	24%	
South	101,681 (27.4%)	20,256 (35.3%)	21,541 (30.1%)	4,031 (27.0%)	35 (41.2%)	2,767 (25.0%)	602 (43.8%)	150,913	29%	
West	70,207 (18.9%)	9,245 (16.1%)	14,447 (20.2%)	3,099 (20.8%)	26 (30.6%)	2,079 (18.8%)	162 (11.8%)	99,265	19%	
Unknown	4,581 (1.2%)	802 (1.4%)	908 (1.3%)	137 (<1%)	1 (1.2%)	97 (<1%)	10 (<1%)	6,536	1%	
Missing	51,164 (13.8%)	6,049 (10.5%)	8,698 (12.1%)	2,890 (19.4%)	1 (1.2%)	2,817 (25.4%)	91 (6.6%)	71,710	14%	
Health Plan Type, n (%)										**
Comprehensive	51,842 (14.0%)	7,871 (13.7%)	10,016 (14.0%)	2,762 (18.5%)	7 (8.2%)	2,642 (23.9%)	95 (6.9%)	75,235	14%	
EPO	3,139 (<1%)	519 (<1%)	622 (<1%)	111 (<1%)	2 (2.4%)	69 (<1%)	11 (<1%)	4,473	1%	
HMO	75,138 (20.2%)	8,946 (15.6%)	13,804 (19.3%)	3,172 (21.3%)	21 (24.7%)	2,297 (20.7%)	143 (10.4%)	103,521	20%	
POS	27,033 (7.3%)	4,443 (7.7%)	5,508 (7.7%)	1,109 (7.4%)	7 (8.2%)	704 (6.4%)	111 (8.1%)	38,915	7%	
PPO	177,694 (47.8%)	30,740 (53.6%)	35,019 (48.9%)	6,502 (43.6%)	38 (44.7%)	4,473 (40.4%)	871 (63.3%)	255,337	48%	
POS with Capitation	7,770 (2.1%)	816 (1.4%)	1,539 (2.1%)	358 (2.4%)	2 (2.4%)	282 (2.5%)	5 (<1%)	10,772	2%	
CDHP	11,528 (3.1%)	1,721 (3.0%)	2,222 (3.1%)	404 (2.7%)	5 (5.9%)	202 (1.8%)	82 (6.0%)	16,164	3%	
HDHP	6,008 (1.6%)	739 (1.3%)	1,106 (1.5%)	195 (1.3%)	1 (1.2%)	117 (1.1%)	42 (3.1%)	8,208	2%	
Missing	11,305 (3.0%)	1,547 (2.7%)	1,828 (2.6%)	300 (2.0%)	2 (2.4%)	284 (2.6%)	16 (1.2%)	15,282	3%	
CLINICAL										
MDD Diagnosis Code, n (%)										*
Single Episode	50,919 (13.7%)	7,168 (12.5%)	10,091 (14.1%)	2,200 (14.8%)	13 (15.3%)	1,383 (12.5%)	168 (12.2%)	71,942	14%	
Recurrent Episode	62,658 (16.9%)	11,756 (20.5%)	15,359 (21.4%)	3,430 (23.0%)	40 (47.1%)	2,105 (19.0%)	304 (22.1%)	95,652	18%	
Dysthymia	47,600 (12.8%)	7,183 (12.5%)	8,614 (12.0%)	1,708 (11.5%)	9 (10.6%)	1,701 (15.4%)	187 (13.6%)	67,002	13%	
Depression, NOS	210,280 (56.6%)	31,235 (54.5%)	37,600 (52.5%)	7,575 (50.8%)	23 (27.1%)	5,881 (53.1%)	717 (52.1%)	293,311	56%	
CCI (Deyo Modification), n (%)										*
0	297,334 (80.0%)	44,474 (77.6%)	57,041 (79.6%)	11,283 (75.7%)	68 (80.0%)	7,778 (70.3%)	1,111 (80.7%)	419,089	79%	
1	48,354 (13.0%)	8,040 (14.0%)	9,322 (13.0%)	2,248 (15.1%)	8 (9.4%)	2,003 (18.1%)	183 (13.3%)	70,158	13%	
2	12,985 (3.5%)	2,504 (4.4%)	2,562 (3.6%)	636 (4.3%)	4 (4.7%)	635 (5.7%)	44 (3.2%)	19,370	4%	
3+	12,784 (3.4%)	2,324 (4.1%)	2,739 (3.8%)	746 (5.0%)	5 (5.9%)	654 (5.9%)	38 (2.8%)	19,290	4%	
SUBGROUP										
Comorbid Diagnoses, n (%)* **										
Anxiety Disorder	92,391 (24.9%)	13,343 (23.3%)	12,625 (17.6%)	3,897 (26.1%)	20 (23.5%)	2,643 (23.9%)	400 (29.1%)	125,319	24%	*
Chronic Pain Disorder	80,054 (21.6%)	17,614 (30.7%)	16,057 (22.4%)	4,364 (29.3%)	15 (17.6%)	5,706 (51.5%)	360 (26.2%)	124,170	24%	*
Presence of prescription for new and different AD, n (%)* **										
within first 3 months	32,006 (8.6%)	6,705 (11.7%)	11,770 (16.4%)	4,132 (27.7%)	14 (16.5%)	1,921 (17.4%)	187 (13.6%)	56,735	11%	*
within first 6 months	57,554 (15.5%)	11,749 (20.5%)	18,995 (26.5%)	5,585 (37.5%)	25 (29.4%)	2,996 (27.1%)	316 (23.0%)	97,220	18%	*
within first 9 months	75,280 (20.3%)	15,137 (26.4%)	23,418 (32.7%)	6,402 (42.9%)	30 (35.3%)	3,688 (33.3%)	392 (28.5%)	124,347	24%	*
within first 12 months	90,931 (24.5%)	18,257 (31.8%)	27,081 (37.8%)	7,033 (47.2%)	36 (42.4%)	4,256 (38.4%)	462 (33.6%)	148,056	28%	*

Abbreviations: EPO- exclusive provider organization, HMO- health maintenance organization, POS-point of service, PPO- preferred provider organization, CDHP- consumer driven health plan, HDHP- high deductible health plan, SD-standard deviation, AD-Antidepressant, MDD-Major Depressive Disorder, NOS-Not Otherwise Specified, CCI-Charlson Comorbidity Index, SSRI- Selective Serotonin Reuptake Inhibitor, SNRI- Serotonin and Norepinephrine Reuptake Inhibitor, SARI - Serotonin Antagonist and Reuptake Inhibitor (Serotonin Modulator), MAOI- Monoamine Oxidase Inhibitor, TCA- Tricyclic Antidepressant, SMS -Serotonin Modulator and Stimulator (Serotonin Modulator), SD-standard deviation

Footnotes: * p value <0.0001, ** p value<0.001, ***Percentage does not add to 100% within one medication because percentage was cumulative over time and/or categories were not mutually exclusive

Testing: Pearson Chi-Squared test of independence of variables was undertaken for categorical variables to test equality of proportions when grouped by initial class. Analysis of Variance (ANOVA) was undertaken to test equality of means for continuous variables with initial class as the predictor variable.

Table 3. Proportion Adherent to Initial Antidepressant Medication, to Initial Therapeutic Class, and Overall, to Antidepressant Therapy

		Index prescription date (IPD) to 3 months		IPD to 6 months (Minimum)				IPD to 9 months (Recommended)				IPD to 12 months (Extended)			
		MPR	PDC	MPR		PDC		MPR		PDC		MPR		PDC	
Initial AD	N(%)	Proportion Adherent	Proportion Adherent	Proportion Adherent	p value	Proportion Adherent	p value	Proportion Adherent	p value	Proportion Adherent	p value	Proportion Adherent	p value	Proportion Adherent	p value
Total	527,907 (100%)	0.43	0.41	0.33	*	0.31	*	0.26	*	0.24	*	0.23	*	0.21	*
Tranylcypromine	13 (<1%)	0.62	0.62	0.46	NS	0.38	NS	0.38	NS	0.31	****	0.38	NS	0.31	****
Phenelzine	17 (<1%)	0.53	0.53	0.35	NS	0.35	NS	0.35	NS	0.29	****	0.29	****	0.24	****
Desvenlafaxine	6,269 (1.2%)	0.51	0.50	0.43	*	0.40	*	0.34	*	0.32	*	0.31	*	0.28	*
Venlafaxine XR	17,476 (3.3%)	0.50	0.49	0.41	*	0.37	*	0.32	*	0.29	*	0.29	*	0.25	*
Duloxetine	21,777 (4.1%)	0.48	0.47	0.39	*	0.36	*	0.32	*	0.29	*	0.30	*	0.26	*
Bupropion XL	28,509 (5.4%)	0.46	0.45	0.37	*	0.34	*	0.28	*	0.26	*	0.25	*	0.22	*
Escitalopram	89,616 (17.0%)	0.45	0.44	0.36	*	0.34	*	0.28	*	0.26	*	0.25	*	0.22	*
Venlafaxine	11,820 (2.2%)	0.46	0.44	0.38	*	0.35	*	0.32	*	0.29	*	0.30	*	0.26	*
Selegiline	55 (<1%)	0.45	0.44	0.35	****	0.33	****	0.24	**	0.18	**	0.16	**	0.13	*
Sertraline	98,869 (18.7%)	0.45	0.43	0.36	*	0.33	*	0.28	*	0.26	*	0.26	*	0.22	*
Fluoxetine	70,537 (13.4%)	0.44	0.43	0.35	*	0.31	*	0.26	*	0.24	*	0.24	*	0.20	*
Citalopram	84,253 (16.0%)	0.43	0.42	0.34	*	0.31	*	0.26	*	0.24	*	0.24	*	0.21	*
Trimipramine	5 (<1%)	0.40	0.40	0.40	NC	0.40	NC	0.20	NC	0.00	NC	0.00	NC	0.00	NC
Vilazodone	1,376 (<1%)	0.41	0.39	0.32	*	0.30	*	0.25	*	0.24	*	0.23	*	0.21	*
Fluoxetine weekly	185 (<1%)	0.39	0.39	0.29	**	0.26	*	0.24	*	0.22	*	0.20	*	0.18	*
Fluvoxamine	919 (<1%)	0.39	0.38	0.32	*	0.29	*	0.27	*	0.25	*	0.25	*	0.21	*
Paroxetine	22,004 (4.2%)	0.39	0.38	0.30	*	0.28	*	0.23	*	0.22	*	0.21	*	0.19	*
Paroxetine CR	5,074 (<1%)	0.38	0.37	0.27	*	0.25	*	0.18	*	0.17	*	0.14	*	0.12	*
Amoxapine	11 (<1%)	0.36	0.36	0.36	NC	0.27	NS	0.27	NS	0.27	NS	0.27	NS	0.27	NS
Nefazodone	294 (<1%)	0.35	0.34	0.27	*	0.25	*	0.19	*	0.18	*	0.15	*	0.14	*
Bupropion	22,958 (4.3%)	0.35	0.34	0.24	*	0.22	*	0.17	*	0.16	*	0.15	*	0.13	*
Mirtazapine	12,438 (2.4%)	0.33	0.32	0.26	*	0.23	*	0.20	*	0.19	*	0.18	*	0.16	*
Desipramine	210 (<1%)	0.32	0.31	0.25	***	0.22	**	0.21	*	0.18	*	0.20	*	0.18	*
Nortriptyline	1,895 (<1%)	0.30	0.29	0.21	*	0.19	*	0.17	*	0.15	*	0.15	*	0.14	*
Imipramine	933 (<1%)	0.30	0.29	0.23	*	0.21	*	0.17	*	0.15	*	0.16	*	0.13	*
Clomipramine	158 (<1%)	0.30	0.28	0.24	****	0.19	***	0.19	**	0.15	*	0.19	**	0.15	**
Protriptyline	37 (<1%)	0.27	0.27	0.19	NS	0.16	NS	0.19	NS	0.19	NS	0.19	NS	0.14	****
Buproprion SR	7,759 (1.5%)	0.26	0.25	0.16	*	0.14	*	0.10	*	0.09	*	0.08	*	0.07	*
Amitriptyline	6,433 (1.2%)	0.24	0.23	0.17	*	0.15	*	0.13	*	0.12	*	0.12	*	0.11	*
Doxepin	1,056 (<1%)	0.20	0.20	0.14	*	0.13	*	0.11	*	0.10	*	0.11	*	0.09	*
Trazodone	14,576 (2.8%)	0.19	0.18	0.14	*	0.12	*	0.11	*	0.10	*	0.10	*	0.08	*
Maprotiline	332 (<1%)	0.18	0.18	0.13	**	0.12	**	0.09	*	0.09	*	0.09	*	0.08	*
Trazodone ER	43 (<1%)	0.19	0.16	0.19	NS	0.19	NS	0.16	NS	0.16	NS	0.14	NS	0.14	NS

Table 3. Continued

		Index prescription date (IPD) to 3 months		IPD to 6 months (Minimum)				IPD to 9 months (Recommended)				IPD to 12 months (Extended)			
		MPR	PDC	MPR		PDC		MPR		PDC		MPR		PDC	
Initial Class	N (%)	Proportion Adherent	Proportion Adherent	Proportion Adherent	p value	Proportion Adherent	p value	Proportion Adherent	p value	Proportion Adherent	p value	Proportion Adherent	p value	Proportion Adherent	p value
Total	527,907 (100%)	0.44	0.43	0.36	*	0.33	*	0.28	*	0.26	*	0.26	*	0.23	*
MAOI	85 (<1%)	0.49	0.48	0.36	***	0.34	***	0.28	*	0.22	*	0.22	*	0.18	*
SNRI	57,342 (11%)	0.49	0.48	0.42	*	0.38	*	0.34	*	0.31	*	0.32	*	0.28	*
SSRI	371,457 (70%)	0.45	0.44	0.37	*	0.33	*	0.29	*	0.27	*	0.27	*	0.23	*
SMS	1,376 (<1%)	0.41	0.40	0.33	*	0.30	*	0.25	*	0.24	*	0.23	*	0.21	*
Atypical	71,664 (14%)	0.41	0.39	0.32	*	0.30	*	0.26	*	0.23	*	0.23	*	0.20	*
TCA	11070 (2%)	0.26	0.25	0.19	*	0.17	*	0.15	*	0.14	*	0.14	*	0.12	*
SARI	14,913 (3%)	0.19	0.19	0.14	*	0.13	*	0.11	*	0.10	*	0.10	*	0.09	*
Adherence to any AD therapy		0.46	0.44	0.39	*	0.35	*	0.33	*	0.29	*	0.31	*	0.26	*

Abbreviations: PDC- proportion of days covered, MPR-medication possession ratio, SR- Sustained release, XL-Extended release, CR- Controlled release, XR-Extended Release, IPD- Index Prescription Date (AD), SSRI- Selective Serotonin Reuptake Inhibitor, SNRI- Serotonin and Norepinephrine Reuptake Inhibitor, SARI - Serotonin Antagonist and Reuptake Inhibitor (Serotonin Modulator), MAOI- Monoamine Oxidase Inhibitor, TCA- Tricyclic Antidepressant, SMS -Serotonin Modulator and Stimulator (Serotonin Modulator), NS-not significant with significance level alpha=0.05, NC- Not able to calculate (due to small sample size)

Footnotes: *= p value <0.0001 **=p value <0.001 ***=<0.01, ****=p value<0.05

Testing: A Chi-Squared test (McNemar's paired chi-squared test) was performed to test equality of the proportion adherent for each time frame compared to Initiation phase (IPD to 3 month time frame), separately for both PDC and MPR calculations.

Notes: Adherence was determined if the MPR or PDC greater than or equal to 0.80 over time period, if not, the patient was considered non adherent

Table 4. Proportion Adherent and Persistent, and Proportion Adherent conditioning on Persistence, to Initial Antidepressant Medication, by Subgroup and Time frame

	IPD to 3 months (Initiation)	Total number of patients	IPD to 6 months (Minimum)	Total number of patients	IPD to 9 months (Recommended)	Total number of patients	IPD to 12 months (Extended)	Total number of patients
Entire Cohort								
Proportion Adherent	0.41	527,907	0.31	527,907	0.24	527,907	0.21	527,907
Proportion Persistent	0.44	527,907	0.31	527,907	0.23	527,907	0.17	527,907
Proportion Adherent given Persistence	0.84	234,047	0.88	163,645	0.90	120,345	0.92	90,562
Subgroup with Anxiety disorders								
Proportion Adherent	0.41	125,319	0.31	125,319	0.25	125,319	0.21	125,319
Proportion Persistent	0.45	125,319	0.32	125,319	0.24	125,319	0.18	125,319
Proportion Adherent given Persistence	0.84	56,341	0.88	39,636	0.90	29,547	0.92	22,579
Subgroup with Chronic Pain Disorders								
Proportion Adherent	0.39	124,170	0.29	124,170	0.23	124,170	0.20	124,170
Proportion Persistent	0.41	124,170	0.29	124,170	0.22	124,170	0.16	124,170
Proportion Adherent given Persistence	0.84	51,415	0.89	36,292	0.91	26,846	0.93	20,426
Subgroup with a prescription for a new and different AD over time interval								
Proportion Adherent	0.32	56,735	0.21	97,220	0.15	124,347	0.13	148,056
Proportion Persistent	0.33	56,735	0.19	97,220	0.13	124,347	0.10	148,056
Proportion Adherent given Persistence	0.81	18,997	0.87	18,935	0.89	16,495	0.92	14,363

Abbreviations: IPD-Index Prescription Date, Antidepressant-AD

Table 5. Adherence to Initial Antidepressant Medication during Continuation phase (Between Months 4-9), conditioning on Adherence to Initiation Phase (IPD to month 3)

	MPR		PDC	
	Number adherent to Initiation Phase	Proportion Adherent	Number adherent to Initiation Phase	Proportion Adherent
Protriptyline	7	0.43	7	0.43
Venlafaxine	4915	0.48	4779	0.40
Trazodone ER	6	0.50	5	0.40
Desvenlafaxine	2921	0.43	2878	0.38
Fluvoxamine	304	0.44	292	0.37
Desipramine	53	0.38	52	0.37
Venlafaxine XR	8005	0.43	7753	0.36
Doxepin	166	0.40	165	0.36
Duloxetine	9529	0.42	9274	0.35
Sertraline	41084	0.41	40114	0.34
Mirtazapine	3434	0.40	3356	0.34
Amitriptyline	1222	0.37	1184	0.34
Paroxetine	7888	0.39	7712	0.34
Citalopram	33738	0.39	33039	0.33
Amoxapine	3	0.33	3	0.33
Escitalopram	37787	0.38	37092	0.33
Bupropion XL	11569	0.39	11308	0.32
Vilazodone	499	0.36	489	0.31
Fluoxetine	29012	0.38	28120	0.31
Maprotiline	45	0.40	44	0.30
Trazodone	1736	0.33	1699	0.29
Tranylcypromine	7	0.43	7	0.29
Nortriptyline	484	0.34	470	0.29
Imipramine	242	0.38	234	0.28
Paroxetine CR	1718	0.32	1675	0.27
Clomipramine	35	0.37	33	0.27
Bupropion	6801	0.30	6649	0.25
Nefazodone	88	0.32	86	0.24
Buproprion SR	1662	0.23	1634	0.20
Fluoxetine weekly	64	0.27	64	0.19
Selegiline	23	0.17	22	0.18
Phenelzine	6	0.33	6	0.17
Trimipramine	2	0.00	2	0.00

Abbreviations: SR- Sustained release, XL-Extended release, CR- Controlled release, XR-Extended Release, PDC-Proportion of days covered, MPR- Medication Possession Ratio

Notes: Adherence was determined if the MPR or PDC greater than or equal to 0.80 over time period, if not, the patient was considered non adherent. Included only patients who did not have presence of a new and different AD prescription during Initiation Phase

Table 6. Logistic Regression Model 1: Odds Ratios of Adherence to Initial Antidepressant versus sertraline

Medication	IPD to Month 3 (Unadjusted)				IPD to Month 3 (Adjusted)				IPD to Month 6 (Unadjusted)				IPD to Month 6 (Adjusted)			
		95% CI		p value		95% CI		p value		95% CI		p value		95% CI		p value
	Odds Ratio	Low	High		Odds Ratio	Low	High		Odds Ratio	Low	High		Odds Ratio	Low	High	
Tranylcypromine	2.09	0.68	6.39	NS	1.52	0.52	4.44	NS	1.27	0.42	3.89	NS	0.92	0.29	2.94	NS
Desvenlafaxine	1.32	1.25	1.39	*	1.26	1.20	1.33	*	1.38	1.31	1.45	*	1.30	1.24	1.38	*
Venlafaxine XR	1.23	1.19	1.27	*	1.22	1.18	1.26	**	1.22	1.18	1.26	*	1.19	1.15	1.23	*
Phenelzine	1.47	0.57	3.81	NS	1.19	0.44	3.24	NS	1.11	0.41	3.00	NS	0.89	0.33	2.41	NS
Duloxetine	1.14	1.11	1.17	*	1.07	1.03	1.10	*	1.16	1.13	1.20	*	1.07	1.03	1.10	**
Bupropion XL	1.08	1.05	1.11	*	1.05	1.03	1.08	**	1.05	1.02	1.08	**	1.03	1.00	1.06	NS
Escitalopram	1.04	1.02	1.06	*	1.01	0.99	1.03	NS	1.03	1.01	1.05	***	0.99	0.97	1.01	NS
Fluoxetine	0.98	0.96	1.00	NS	1.01	0.99	1.03	NS	0.92	0.90	0.94	*	0.96	0.94	0.98	*
Fluoxetine weekly	0.83	0.62	1.12	NS	1.00	0.74	1.35	NS	0.73	0.53	1.02	NS	0.88	0.63	1.22	NS
Venlafaxine	1.04	1.00	1.08	NS	0.95	0.92	0.99	****	1.08	1.04	1.13	**	0.99	0.95	1.03	NS
Selegiline	1.01	0.59	1.72	NS	0.91	0.54	1.54	NS	0.99	0.56	1.74	NS	0.89	0.51	1.56	NS
Citalopram	0.95	0.93	0.97	*	0.90	0.88	0.91	*	0.93	0.91	0.95	*	0.87	0.86	0.89	*
Paroxetine CR	0.76	0.71	0.80	*	0.82	0.77	0.87	*	0.68	0.64	0.73	*	0.73	0.68	0.78	*
Fluvoxamine	0.79	0.69	0.91	**	0.82	0.71	0.94	NS	0.83	0.72	0.96	****	0.86	0.74	0.99	****
Vilazodone	0.85	0.76	0.95	***	0.80	0.72	0.89	*	0.86	0.77	0.97	****	0.80	0.71	0.90	**
Paroxetine	0.79	0.77	0.81	*	0.75	0.73	0.78	*	0.78	0.75	0.80	*	0.73	0.71	0.76	*
Amoxapine	0.75	0.22	2.55	NS	0.68	0.19	2.46	NS	0.76	0.20	2.88	NS	0.69	0.17	2.78	NS
Imipramine	0.54	0.47	0.62	*	0.65	0.56	0.75	*	0.55	0.47	0.64	*	0.65	0.55	0.77	*
Bupropion	0.66	0.64	0.68	*	0.63	0.61	0.65	*	0.58	0.56	0.60	*	0.54	0.53	0.56	*
Nefazodone	0.67	0.53	0.86	***	0.60	0.47	0.77	**	0.69	0.53	0.89	***	0.61	0.47	0.79	**
Mirtazapine	0.61	0.58	0.63	*	0.56	0.54	0.58	*	0.62	0.59	0.65	*	0.56	0.54	0.59	*
Desipramine	0.60	0.45	0.80	**	0.54	0.40	0.72	*	0.59	0.42	0.81	***	0.52	0.37	0.72	**
Nortriptyline	0.54	0.49	0.60	*	0.50	0.45	0.56	*	0.49	0.43	0.55	*	0.45	0.40	0.50	*
Clomipramine	0.50	0.36	0.71	**	0.49	0.34	0.70	**	0.48	0.32	0.71	**	0.46	0.30	0.68	**
Protriptyline	0.48	0.23	1.00	****	0.46	0.22	0.99	****	0.39	0.16	0.94	****	0.37	0.15	0.90	****
Buproprion SR	0.44	0.42	0.46	*	0.44	0.41	0.46	*	0.34	0.32	0.36	*	0.34	0.31	0.36	*
Amitriptyline	0.39	0.36	0.41	*	0.40	0.38	0.43	*	0.37	0.34	0.40	*	0.38	0.35	0.41	*
Doxepin	0.32	0.28	0.38	*	0.30	0.26	0.35	*	0.31	0.26	0.37	*	0.28	0.24	0.34	*
Trazodone	0.29	0.28	0.31	*	0.28	0.27	0.30	*	0.28	0.27	0.30	*	0.27	0.26	0.29	*
Trazodone ER	0.25	0.11	0.57	**	0.25	0.11	0.56	**	0.47	0.22	1.00	NS	0.45	0.21	0.96	****
Maprotiline	0.28	0.21	0.37	*	0.25	0.19	0.33	*	0.29	0.21	0.40	*	0.25	0.18	0.35	*

Table 6. Continued

Medication	IPD to Month 9 (Unadjusted)				IPD to Month 9 (Adjusted)				IPD to Month 12 (Unadjusted)				IPD to Month 12 (Adjusted)			
		95% CI				95% CI				95% CI				95% CI		
	Odds Ratio	Low	High	p value	Odds Ratio	Low	High	p value	Odds Ratio	Low	High	p value	Odds Ratio	Low	High	p value
Tranylcypromine	1.27	0.39	4.12	NS	0.88	0.26	2.94	NS	1.54	0.47	4.99	NS	1.06	0.33	3.42	NS
Desvenlafaxine	1.36	1.29	1.44	*	1.28	1.21	1.36	*	1.35	1.28	1.43	*	1.27	1.20	1.35	*
Venlafaxine XR	1.17	1.13	1.22	*	1.14	1.10	1.18	*	1.16	1.11	1.20	*	1.12	1.07	1.16	*
Phenelzine	1.19	0.42	3.38	NS	0.92	0.32	2.61	NS	1.06	0.35	3.26	NS	0.80	0.26	2.46	NS
Duloxetine	1.19	1.16	1.23	*	1.08	1.04	1.11	*	1.23	1.19	1.28	*	1.10	1.07	1.14	*
Bupropion XL	1.00	0.97	1.03	NS	0.98	0.95	1.01	NS	0.97	0.94	1.00	NS	0.95	0.92	0.98	***
Escitalopram	1.01	0.99	1.03	NS	0.97	0.95	0.99	***	0.99	0.97	1.01	NS	0.95	0.93	0.97	*
Fluoxetine	0.88	0.87	0.91	*	0.93	0.91	0.95	*	0.87	0.85	0.89	*	0.92	0.90	0.95	*
Fluoxetine weekly	0.81	0.57	1.15	NS	0.99	0.69	1.40	NS	0.78	0.54	1.13	NS	0.95	0.66	1.39	NS
Venlafaxine	1.17	1.12	1.22	*	1.05	1.01	1.10	****	1.21	1.16	1.27	*	1.09	1.04	1.14	*
Selegiline	0.63	0.32	1.26	NS	0.56	0.28	1.12	NS	0.50	0.23	1.11	NS	0.44	0.20	0.98	****
Citalopram	0.92	0.90	0.94	*	0.86	0.84	0.88	*	0.92	0.90	0.94	*	0.86	0.84	0.88	*
Paroxetine CR	0.57	0.53	0.62	*	0.60	0.55	0.64	*	0.47	0.43	0.52	*	0.49	0.45	0.53	*
Fluvoxamine	0.93	0.80	1.08	NS	0.96	0.82	1.13	NS	0.91	0.78	1.07	NS	0.95	0.81	1.12	NS
Vilazodone	0.88	0.78	1.00	NS	0.81	0.71	0.92	***	0.92	0.81	1.05	NS	0.84	0.73	0.96	***
Paroxetine	0.79	0.76	0.81	*	0.73	0.70	0.76	*	0.79	0.76	0.82	*	0.73	0.70	0.75	*
Amoxapine	1.07	0.28	4.03	NS	0.95	0.24	3.85	*	1.30	0.34	4.88	NS	1.16	0.28	4.74	NS
Imipramine	0.52	0.44	0.62	*	0.62	0.52	0.75	*	0.52	0.43	0.63	*	0.63	0.51	0.76	*
Bupropion	0.52	0.50	0.54	*	0.50	0.48	0.51	*	0.50	0.48	0.52	*	0.47	0.45	0.49	*
Nefazodone	0.61	0.45	0.83	***	0.53	0.40	0.72	*	0.56	0.40	0.78	***	0.48	0.35	0.67	*
Mirtazapine	0.65	0.62	0.68	*	0.57	0.54	0.60	*	0.66	0.63	0.70	*	0.57	0.54	0.60	*
Desipramine	0.61	0.43	0.87	***	0.53	0.37	0.75	**	0.76	0.54	1.09	NS	0.65	0.46	0.93	****
Nortriptyline	0.52	0.46	0.59	*	0.47	0.42	0.53	*	0.54	0.48	0.62	*	0.49	0.43	0.56	*
Clomipramine	0.51	0.33	0.79	***	0.48	0.31	0.75	***	0.62	0.40	0.96	****	0.59	0.37	0.92	****
Protriptyline	0.67	0.29	1.52	NS	0.61	0.26	1.41	*	0.54	0.21	1.39	NS	0.49	0.19	1.27	NS
Buproprion SR	0.27	0.25	0.29	*	0.27	0.25	0.29	*	0.24	0.22	0.27	*	0.24	0.22	0.26	*
Amitriptyline	0.40	0.37	0.43	*	0.40	0.37	0.43	*	0.41	0.38	0.45	*	0.41	0.38	0.45	*
Doxepin	0.33	0.27	0.40	*	0.29	0.24	0.36	*	0.35	0.29	0.44	*	0.31	0.25	0.39	*
Trazodone	0.30	0.29	0.32	*	0.29	0.27	0.30	*	0.32	0.30	0.34	*	0.30	0.28	0.31	*
Trazodone ER	0.55	0.25	1.25	NS	0.54	0.24	1.19	NS	0.56	0.24	1.33	NS	0.54	0.23	1.28	NS
Maprotiline	0.27	0.19	0.40	*	0.23	0.16	0.34	*	0.31	0.21	0.45	*	0.26	0.17	0.39	*

Abbreviations: CI- Confidence Interval, NS- Not Significant

Footnotes: * p value<0.0001, ** p value <0.001, ***p value <0.01, **** p value <0.05

Testing: Wald tests of association were performed. A significant test indicated that the Odds Ratio of adherence for a specific medication was significantly different than 1 when compared to sertraline. A Wald test of overall association was performed, and p values were all <0.0001 for time frames. This tested overall association of initial medication and adherence over time frame.

Notes: Adherence was determined if the Proportion of Days Covered (PDC) was greater than or equal to 0.80 over time period, if not, the patient was considered not adherent.

Table 7. Logistic Regression Model 2: Odds Ratio of Adherence to Continuation Phase comparing those Adherent/Not Adherent to Initiation Phase

	Model 2 (Unadjusted)				Model 2 (Adjusted)			
	Odds Ratio	95% CI		p value	Odds Ratio	95% CI		p value
		Low	High			Low	High	
	14.6	14.3	14.9	*	13.7	13.4	14.0	*

Abbreviations: CI-Confidence Interval, PDC-Proportion of days covered

Footnotes: * p value<0.0001, ** p value <0.001, ***p value <0.01, **** p value <0.05

Testing: Wald test of association of adherence to initiation and continuation phase

Notes: Adherence was determined if the Proportion of Days Covered (PDC) was greater than or equal to 0.80 over time period, if not, the patient was considered not adherent.

Table 8. Persistence to Initial Antidepressant Medication, to Initial Therapeutic Class, and Overall, to Antidepressant Therapy

		Days to discontinuation, mean (S.D.)	IPD to 3 Months (Initiation)	IPD to 6 Months (Minimum)		IPD to 9 Months (Recommended)		IPD to 12 Months (Extended)	
	N(%)		Proportion Persistent	Proportion Persistent	p value	Proportion Persistent	p value	Proportion Persistent	p value
Total	527,907 (100%)	174 (206)	0.44	0.31	*	0.23	*	0.17	*
Desvenlafaxine	6,269 (1.2%)	218 (227)	0.54	0.40	*	0.31	*	0.23	*
Tranylcypromine	13 (<1%)	172 (155)	0.54	0.38	NS	0.23	****	0.15	****
Venlafaxine XR	17,476 (3.3%)	203 (220)	0.51	0.37	*	0.28	*	0.21	*
Duloxetine	21,777 (4.1%)	201 (222)	0.49	0.36	*	0.27	*	0.21	*
Bupropion XL	28,509 (5.4%)	185 (208)	0.48	0.34	*	0.24	*	0.18	*
Escitalopram	89,616 (17.0%)	186 (209)	0.48	0.34	*	0.25	*	0.19	*
Phenelzine	17 (<1%)	225 (249)	0.47	0.41	NS	0.29	NS	0.24	****
Sertraline	98,869 (18.7%)	186 (213)	0.47	0.34	*	0.25	*	0.19	*
Fluoxetine	70,537 (13.4%)	175 (201)	0.47	0.32	*	0.23	*	0.17	*
Venlafaxine	11,820 (2.2%)	198 (227)	0.46	0.35	*	0.28	*	0.23	*
Amoxapine	11 (<1%)	148 (164)	0.45	0.27	NS	0.27	NS	0.18	NS
Citalopram	84,253 (16.0%)	176 (208)	0.44	0.31	*	0.23	*	0.18	*
Fluvoxamine	919 (<1%)	174 (209)	0.44	0.31	*	0.23	*	0.18	*
Vilazodone	1,376 (<1%)	163 (195)	0.42	0.29	*	0.21	*	0.16	*
Paroxetine	22,004 (4.2%)	162 (203)	0.40	0.28	*	0.21	*	0.16	*
Trimipramine	5 (<1%)	93 (86)	0.40	0.20	NS	0.00	NS	0.00	NS
Paroxetine CR	5,074 (<1%)	131 (152)	0.40	0.25	*	0.16	*	0.10	*
Fluoxetine	185 (<1%)	154 (199)	0.39	0.25	*	0.18	*	0.14	*
Nefazodone	294 (<1%)	153 (199)	0.39	0.26	*	0.18	*	0.12	*
Selegiline	55 (<1%)	131 (146)	0.38	0.29	****	0.18	**	0.07	**
Bupropion	22,958 (4.3%)	131 (168)	0.35	0.22	*	0.15	*	0.10	*
Desipramine	210 (<1%)	158 (220)	0.35	0.24	*	0.21	*	0.16	*
Mirtazapine	12,438 (2.4%)	142 (195)	0.34	0.23	*	0.17	*	0.13	*
Protriptyline	37 (<1%)	176 (239)	0.32	0.30	NS	0.22	****	0.19	****
Imipramine	933 (<1%)	130 (181)	0.32	0.21	*	0.15	*	0.11	*
Clomipramine	158 (<1%)	145 (207)	0.31	0.23	**	0.20	*	0.15	**
Nortriptyline	1,895 (<1%)	127 (185)	0.30	0.19	*	0.15	*	0.11	*
Buproprion SR	7,759 (1.5%)	96 (127)	0.27	0.14	*	0.08	*	0.05	*
Trazodone ER	43 (<1%)	115 (174)	0.26	0.16	****	0.14	****	0.14	****
Amitriptyline	6,433 (1.2%)	106 (163)	0.25	0.16	*	0.12	*	0.09	*
Doxepin	1,056 (<1%)	95 (159)	0.21	0.14	*	0.10	*	0.07	*
Maprotiline	332 (<1%)	89 (134)	0.21	0.14	*	0.09	*	0.07	*
Trazodone	14,576 (2.8%)	93 (149)	0.21	0.13	*	0.09	*	0.07	*

Table 8. Continued

Initial Class	N (%)	IPD to 3 Months (Initiation) Proportion Persistent	IPD to 6 Months (Minimum) Proportion Persistent	IPD to 6 Months (Minimum) p value	IPD to 9 Months (Recommended) Proportion Persistent	IPD to 9 Months (Recommended) p value	IPD to 12 Months (Extended) Proportion Persistent	IPD to 12 Months (Extended) p value
Total	527,907 (100%)	0.46	0.33	*	0.25	*	0.19	*
SNRI	57,342 (11%)	0.51	0.38	*	0.30	*	0.24	*
SSRI	371,457 (70%)	0.48	0.34	*	0.26	*	0.19	*
MAOI	85 (<1%)	0.44	0.33	**	0.21	*	0.12	*
Atypical	71,664 (14%)	0.43	0.30	*	0.22	*	0.17	*
SMS	1,376 (<1%)	0.42	0.29	*	0.21	*	0.17	*
TCA	11070 (2%)	0.27	0.18	*	0.13	*	0.10	*
SARI	14,913 (3%)	0.21	0.13	*	0.09	*	0.07	*
Persistence to any AD therapy		0.48	0.36	*	0.27	*	0.22	*

Abbreviations: SR- Sustained release, XL-Extended release, CR- Controlled release, XR-Extended Release, IPD- Index Prescription Date (AD), SSRI- Selective Serotonin Reuptake Inhibitor, SNRI- Serotonin and Norepinephrine Reuptake Inhibitor, SARI - Serotonin Antagonist and Reuptake Inhibitor (Serotonin Modulator), MAOI- Monoamine Oxidase Inhibitor, TCA- Tricyclic Antidepressant, SMS -Serotonin Modulator and Stimulator (Serotonin Modulator), NS-not significant with significance level alpha=0.05

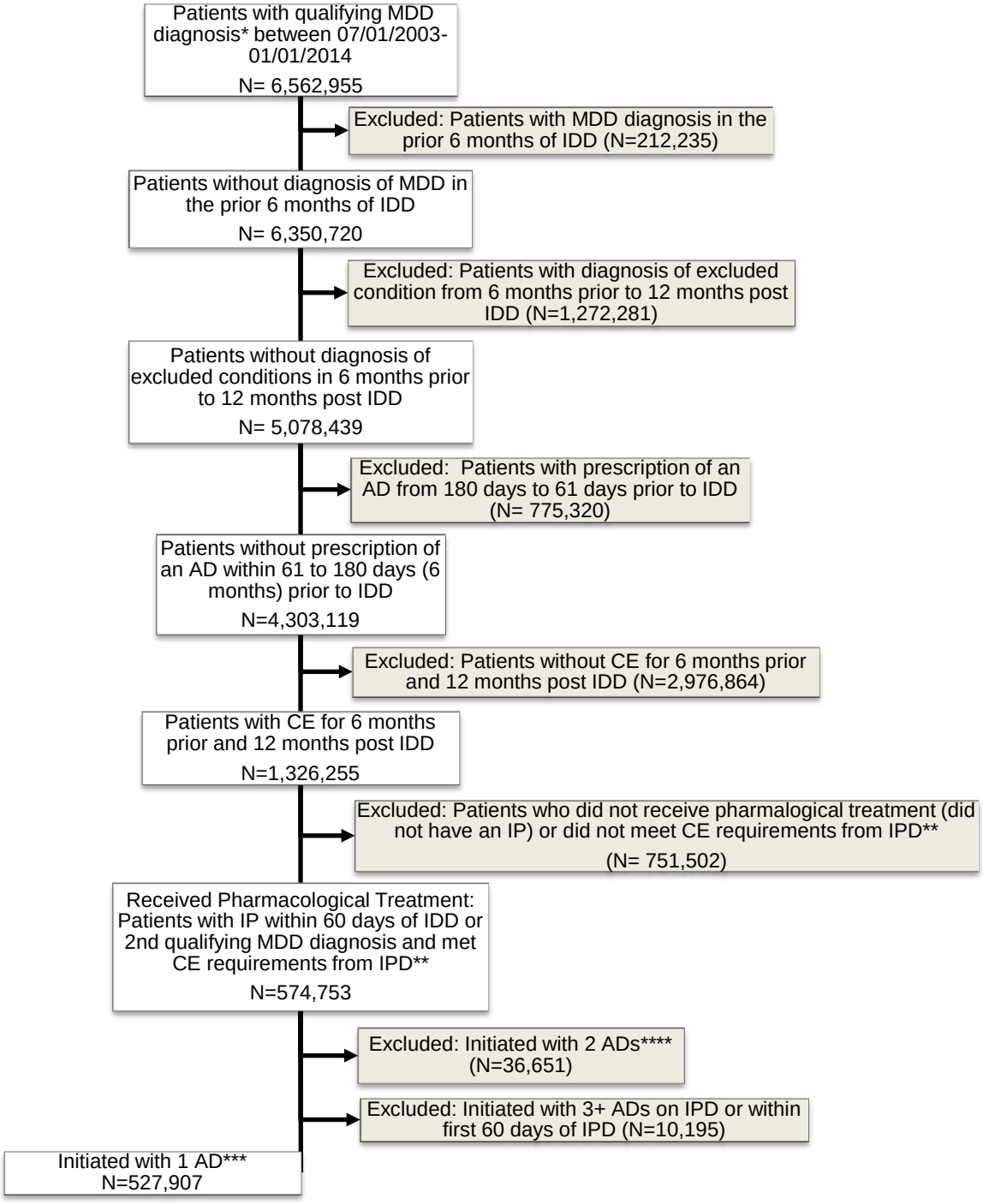
Footnotes: * p value <0.0001 **p value <0.001 ***p value<0.01, ****p value<0.05

Testing: A Chi-Squared test (McNemar's paired test) was performed to test equality of the proportion persistent for each time frame compared to Initiation phase (IPD to 3 month time frame).

Notes: Persistence was determined if the patient remained persistent over time frame, if not, the patient was considered not persistent.

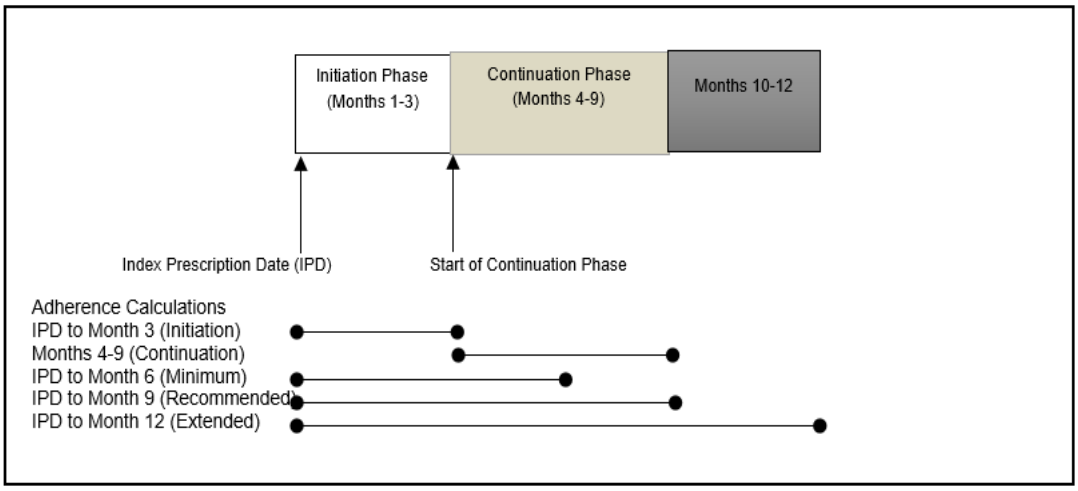
FIGURES

Figure 1. Patient Selection Flowchart



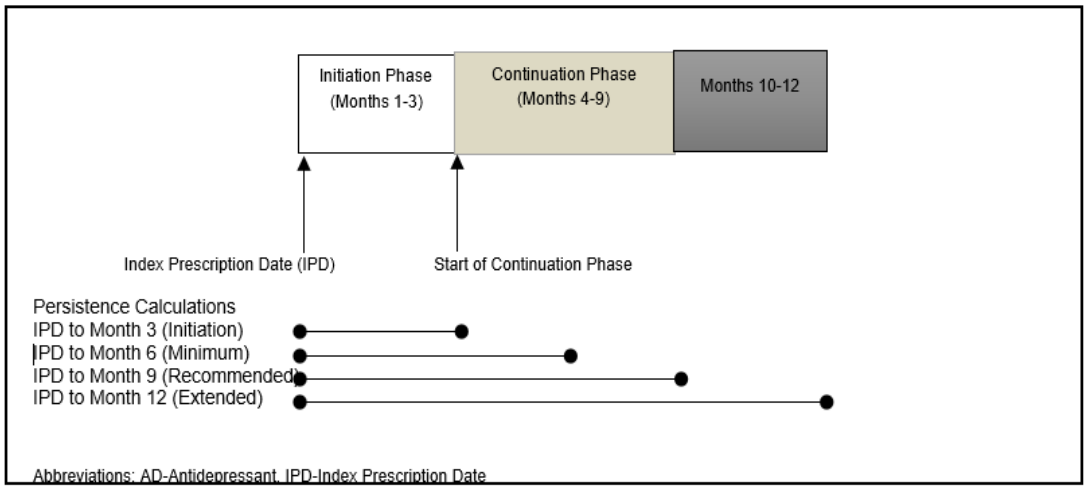
Abbreviations: AD-Antidepressant, IP- Index Prescription, IPD-Index Prescription Date, IDD-Index Diagnosis Date
Footnotes: *One inpatient or one outpatient diagnosis with a confirmatory outpatient or inpatient diagnosis within 60 days
**If IPD was before IDD, CE re-evaluated for 6 months prior to IPD. If IPD was after IDD, CE re-evaluated for 12 months post IPD
***Initiates with 1 AD on IPD and may include patients who start a second AD/adjunctive agent within 60 days of IPD if overlap is not >30 days. Also includes patients who may switch or add therapy beyond the first 60 days.
****Initiates with 2 ADs on IPD or starts 1 AD on IPD and starts a second AD/adjunctive agent within 60 days of IPD where the two prescriptions overlap for >30 days.

Figure 2a. Time Periods for Adherence Calculations



Abbreviations: AD-Antidepressant, IPD-Index Prescription Date

Figure 2b. Time Periods for Persistence Calculations



Abbreviations: AD-Antidepressant, IPD-Index Prescription Date

Figure 3. Time to Discontinuation of Initial Therapeutic Class (until 30 day treatment gap)

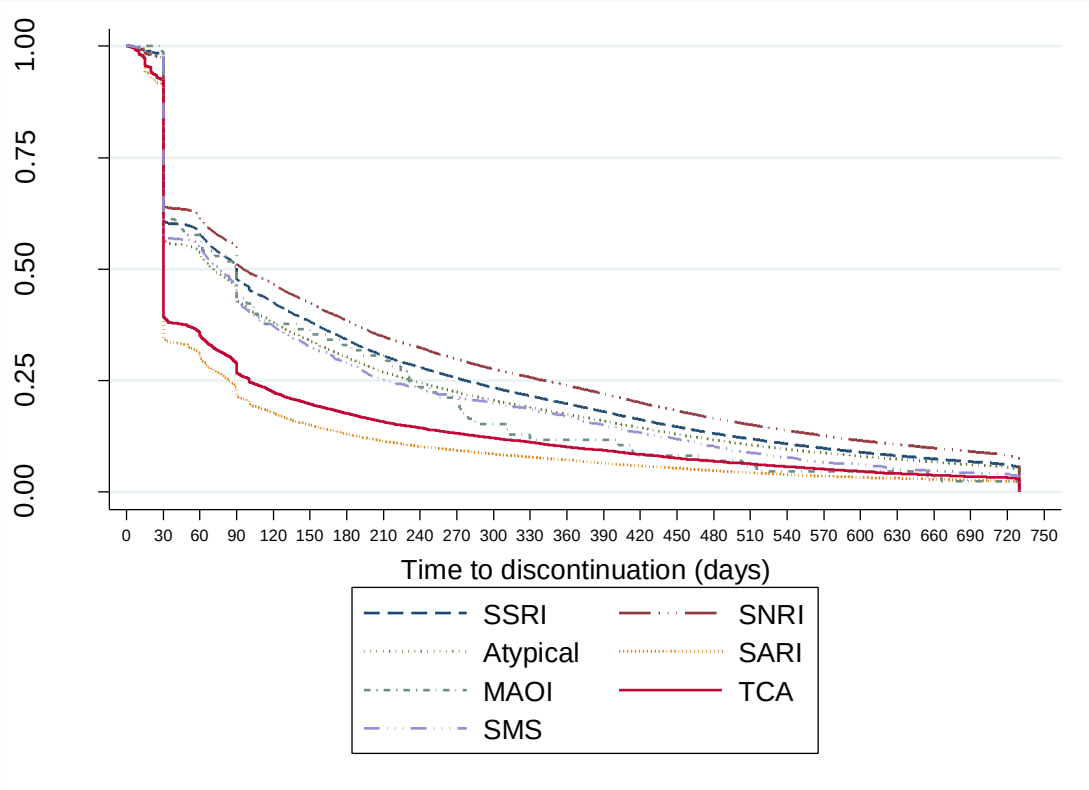
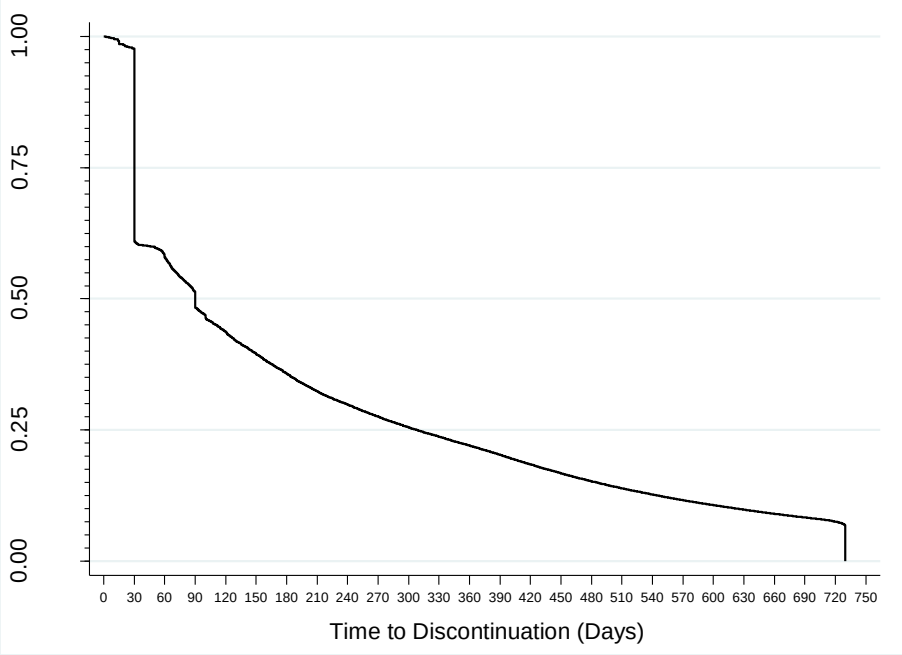


Figure 4. Overall Time to Discontinuation of Antidepressant therapy (until 30 day treatment gap)



APPENDICES

Appendix 1. Characteristics of Antidepressants, by therapeutic class

Abbreviations: MDD-Major Depressive Disorder, CPD-chronic pain disorders, AnD- anxiety disorders

Medication	Therapeutic Class	Clinical Use
Bupropion	Atypical Agent	MDD
Bupropion SR	Atypical Agent	MDD
Bupropion XL	Atypical Agent	MDD
Mirtazapine	Atypical Agent	MDD
Isocarboxazid	Monoamine Oxidase Inhibitor	MDD
Phenelzine	Monoamine Oxidase Inhibitor	MDD
Selegiline (transdermal patch)	Monoamine Oxidase Inhibitor	MDD
Tranylcypromine	Monoamine Oxidase Inhibitor	MDD
Citalopram	Selective Serotonin Reuptake Inhibitor	MDD, AnD
Escitalopram	Selective Serotonin Reuptake Inhibitor	MDD, AnD
Fluoxetine	Selective Serotonin Reuptake Inhibitor	MDD, AnD
Fluoxetine weekly	Selective Serotonin Reuptake Inhibitor	MDD, AnD
Fluvoxamine	Selective Serotonin Reuptake Inhibitor	MDD , AnDŁ
Paroxetine	Selective Serotonin Reuptake Inhibitor	MDD, AnD
Paroxetine CR	Selective Serotonin Reuptake Inhibitor	MDD, AnD
Sertraline	Selective Serotonin Reuptake Inhibitor	MDD, AnD
Desvenlafaxine	Serotonin and Norepinephrine Reuptake Inhibitor	MDD, CPD, AnD
Duloxetine	Serotonin and Norepinephrine Reuptake Inhibitor	MDD, CPD, AnD
Levomilnacipran	Serotonin and Norepinephrine Reuptake Inhibitor	MDD, CPD, AnD
Venlafaxine	Serotonin and Norepinephrine Reuptake Inhibitor	MDD, CPD, AnD
Venlafaxine XR	Serotonin and Norepinephrine Reuptake Inhibitor	MDD, CPD, AnD
Nefazodone	Serotonin Antagonist and Reuptake Inhibitor (Serotonin Modulator)	MDD
Trazodone	Serotonin Antagonist and Reuptake Inhibitor (Serotonin Modulator)	MDD
Trazodone ER tablets	Serotonin Antagonist and Reuptake Inhibitor (Serotonin Modulator)	MDD
Vilazodone	Serotonin Modulator and Stimulator (Serotonin Modulator)	MDD
Vortioxetine	Serotonin Modulator and Stimulator (Serotonin Modulator)	MDD
Maprotiline	Tetracyclic Antidepressant	MDD, CPD
Amitriptyline	Tricyclic Antidepressant	MDD, CPD
Amoxapine	Tricyclic Antidepressant	MDD, CPD
Clomipramine	Tricyclic Antidepressant	AnD, CPDŁ
Desipramine	Tricyclic Antidepressant	MDD, CPD
Doxepin	Tricyclic Antidepressant	MDD, CPD
Imipramine	Tricyclic Antidepressant	MDD, CPD
Nortriptyline	Tricyclic Antidepressant	MDD, CPD
Protriptyline	Tricyclic Antidepressant	MDD, CPD
Trimipramine	Tricyclic Antidepressant	MDD, CPD

Appendix 2. International Classification of Disease (ICD-9) Codes (inclusion and exclusion criteria)

Condition	ICD-9 Code
MDD Codes[20]	
Major depressive disorder, single episode	296.2
Major depressive disorder, recurrent episode	296.3
Dysthymic disorder	300.4
Depressive disorder, not otherwise specified (NOS)	311.xx
Anxiety Disorders[20,48]	
Generalized Anxiety Disorder	300.02
Panic disorders and phobias	300.01, 300.21, 300.22, 300.23
Obsessive-compulsive disorder	300.3
Post-traumatic stress disorder	309.81
Acute stress disorder	308.3
Anxiety and anxiety, not otherwise specified	300.00, 300.5X, 300.09, 300.20, 300.29, 300.3
Chronic Pain Disorders[43,48]	
Fibromyalgia	729.1
Diabetes with neurological manifestations	250.6x, 357.2x
Osteoarthritis	715.xx
Low back pain	721.3x, 722.10, 722.32, 722.52, 722.83, 722.93, 724.02, 724.2-7, 738.5, 739.3, 739.4, 846.xx, 847.2x
Headache (chronic type) and migraine	339.12, 346.xx, 784.0
Neuropathic pain conditions	337.1, 337.2x, 337.9, 344.6, 350.1, 350.2 354.0, 353.xx, 354.1, 354.2, 354.3, 354.4, 354.5, 354.8, 354.9,355.0, 355.1, 355.2, 355.3, 355.4, 355.5, 355.6, 355.71, 355.79, 355.8, 355.9, 357.1, 357.3, 357.4, 357.5, 357.6, 357.7,357.8, 357.9, 721.1, 721.41, 721.42, 721.91,722.7x, 724.3, 724.4, 729.2
Exclusion Codes [20,28,29]	
Pregnancy	630-679
Schizophrenic disorder	295.xx
Bipolar disorder, psychosis related disorders (paranoid states)	296.0-296.1, 296.4-296.9, 297.xx
Other mood disorders	293.83, 301.13
Drug-induced depression	292.84
Depressive type psychosis	298
Alzheimer's disease	331.xx
Parkinson's disease	332.xx
Dementia	290.xx

Appendix 3. Coding of Covariates in Logistic Regression Models

Variable	Definition
π(X)	Adherence Status from IPD to 3,6,9, or 12 months for Logistic Model 1, and for Logistic Model 2, over months 4-9 [Adherent=1, Not Adherent=0]
0	Not Adherent (PDC less than 0.80 over time period)
1	Adherent (PDC greater than or equal to 0.80 over time period)
γInitialAD	Dummy Variable for Initial AD (Sertraline=1; referent)
1	Sertraline
2	Amitriptyline
3	Amoxapine
4	Bupropion
5	Buproprion SR
6	Bupropion XL
7	Clomipramine
8	Desipramine
9	Desvenlafaxine
10	Doxepin
11	Duloxetine
12	Escitalopram
13	Fluoxetine
14	Fluoxetine weekly
15	Fluvoxamine
16	Imipramine
17	Maprotiline
18	Mirtazapine
19	Nefazodone
20	Nortriptyline
21	Paroxetine
22	Paroxetine CR
23	Phenazaline
24	Protriptyline
25	Selegiline
26	Citalopram
27	Tranylcypromine
28	Trazodone
29	Trazodone ER
30	Venlafaxine
31	Venlafaxine XR
32	Vilazodone
γAge	Dummy Variable for Age Categories (Age<18=1; referent)
1	<18 years old
2	18-39 Years Old
3	40-65 Years Old
4	>65 Years Old
γGender	Dummy Variable for Gender (Male=1; referent)
1	Male
2	Female
γSource	Dummy Variable for Insurance Claim Source (Medicaid=1; referent)
1	Medicaid
2	Commercial
3	Medicare
γRegion	Dummy Variable for Region where Patient Resides (Northeast=1; referent)
1	Northeast
2	Northcentral
3	South
4	West
5	Unknown
6	Missing

Appendix 3. Continued

Variable	Definition
γPlan	Dummy Variable for Insurance Plan (Comprehensive=1; referent)
1	Comprehensive
2	EPO
3	HMO
4	POS
5	PPO
6	POS with Capitation
7	CDHP
8	HDHP
9	Missing
γMDD	Dummy Variable for Diagnosis Code (MDD, single episode=1; referent)
1	Single Episode
2	Recurrent Episode
3	Dysthymia
4	Depression, Not otherwise specified
γCCI	Dummy Variable for Charleson Comorbidity Index (Deyo Modification) (CCI of 0=0; referent)
0	CCI = 0
1	CCI = 1
2	CCI = 2
3	CCI = 3 or greater
γAnxiety	Dummy Variable for Anxiety Diagnosis (Deyo Modification) (No anxiety diagnosis 0; referent)
0	No Anxiety disorder diagnosis within 60 days of IDD (pre or post)
1	Anxiety disorder diagnosis within 60 days of IDD (pre or post)
γPain	Dummy Variable for Chronic Pain Diagnosis (No chronic pain disorder diagnosis 0; referent)
0	No chronic pain disorder diagnosis within 60 days of IDD (pre or post)
1	Chronic Pain Disorder diagnosis within 60 days of IDD (pre or post)
γAdMonth3	Dummy Variable for Adherence from IPD to Month 3 (Not Adherent 0; referent)
0	Not Adherent (PDC less than 0.80 from IPD to Month 3)
1	Adherent (PDC greater than or equal to 0.80 from IPD to Month 3)

Appendix 4. Overall Adherence to Antidepressant Therapy, by time frame

	Initiation (IPD to Month 3)		Minimum Recommended Duration (IPD to Month 6)		Recommended Duration (IPD to Month 9)		Extended Duration (IPD to Month 12)	
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Medication Possession Ratio	0.69	0.29	0.59	0.33	0.54	0.35	0.51	0.35
Proportion of Days Covered	0.67	0.28	0.57	0.31	0.51	0.32	0.48	0.33

Abbreviations: IPD- Index Prescription Date

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