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Antipsychotic Prescriptions among Adults with Major Depressive Disorder in Office-based Outpatient Settings: National Trends from 2006 to 2015

Taeho Greg Rhee, PhD, MSW[1,2], **Somaia Mohamed, MD, PhD**[3,4,5], and **Robert A. Rosenheck, MD**[3,4,5]

[1]Section of Geriatrics, Department of Internal Medicine, School of Medicine, Yale University, New Haven, CT

[2]Yale Center for Outcomes Research and Evaluation (CORE), Yale-New Haven Hospital, New Haven, CT

[3]Department of Psychiatry, School of Medicine, Yale University, New Haven, CT

[4]Veterans Affairs (VA) New England Mental Illness Research, Education and Clinical Centers (MIRECC), West Haven, CT

[5]Veterans Affairs (VA) Connecticut Healthcare System, West Haven, CT

Abstract

Objectives—A recent moderately long-term study found an antipsychotic to be more effective than an antidepressant as the next-step treatment of unresponsive major depressive disorder (MDD). It is thus timely to examine recent trends the pharmaco-epidemiology of antipsychotic treatment of MDD.

Methods—Data from the 2006–2015 National Ambulatory Medical Care Survey, nationally representative samples of office-based outpatient visits in adults with MDD (ICD-9-CM codes 296.20–296.26 and 296.30–296.36) (n=4,044 unweighted), were used to estimate rates of

Corresponding Author: Greg Rhee, PhD, MSW, Yale University School of Medicine, 333 Cedar Street, PO Box #208025, New Haven, CT, 06520, USA (Phone: +1-773-398-9564; taeho.rhee@yale.edu).

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antipsychotic prescribing over these 10 years. Multivariable logistic regression analysis identified demographic and clinical factors independently associated with antipsychotic use in MDD.

Results—Antipsychotic prescribing for MDD increased from 18.5% in 2006–2007 to 24.9% in 2008–2009, and then declined to 18.9% in 2014–2015. Visits with adults aged 75 or older showed the greatest decline from 27.0% in 2006–2007 to 10.7% in 2014–2015 (OR for overall trend=0.73; 95% CI=0.56 – 0.95). The most commonly prescribed antipsychotic agents were aripiprazole, olanzapine, quetiapine, and risperidone. Antipsychotic prescription was associated with being black or Hispanic, having Medicare among adults under 65, or Medicaid, as a primary source of payment, and receiving mental health counseling, three or more concomitant medications, and diagnosis of cannabis use disorder ($p<0.01$).

Conclusion—Antipsychotics, prescribed for about one-fifth of adults with MDD, increased and then declined from 2006–2015 reflecting first, FDA approval, and then concern about adverse effects in the elderly. Future research should track evolving trends following the publication of evidence of greater long-term effectiveness of antipsychotic than antidepressant next-step therapy in adults with MDD.

Keywords

antipsychotics; major depressive disorder; outpatient care

INTRODUCTION

Major depressive disorder (MDD) is a one of the most common mental disorders, affecting 16.1 million US adults in 2015.[1] MDD is a chronic, recurring, and debilitating psychiatric disorder,[2] and remains one of the main causes of disability and comorbidity globally.[3] Conventionally, antidepressants have long been the first-line pharmacological therapy for MDD.[2,4] Despite the availability of numerous antidepressants, approximately two-thirds of individuals with MDD fail to achieve remission from a first antidepressant trial.[5,6] Patients who fail two trials are considered to have treatment-resistant depression (TRD).[7]

For patients who do not respond to antidepressants, switching to another antidepressant or augmentation with either an additional antidepressant or a non-antidepressant agent is common practice and is recommended in most guidelines.[8–10] Augmentation or adjunctive treatment of antidepressants with four second-generation antipsychotics are the only pharmacologic alternatives to antidepressants that have been approved by the US Food and Drug Administration (FDA), for this purpose.[11,12] Aripiprazole was the first approved by the FDA as an adjunctive treatment to antidepressants for treating MDD in November 1, 2007.[13] Subsequently, quetiapine and olanzapine plus fluoxetine were approved in December 4 and 14, 2009, respectively, and brexipiprazole on July 10, 2015.[13,14]

Despite the positive evidence from *placebo* controlled randomized trials (RCTs) of antipsychotic efficacy in treating non-responsive MDD, until recently, there have been no comparative effectiveness studies comparing antipsychotic treatment to either switching to a new antidepressant or adding an additional antidepressant. However, the recent multi-site VA Augmentation and Switching for improving depression outcomes (VAST-D) study[10,15]

reported the results of an RCT that showed augmentation of antidepressant treatment with an antipsychotic agent, aripiprazole, was significantly more effective in promoting remission (i.e., virtual lack of depressive symptoms) than switching to a new antidepressant (bupropion) and significantly more effective in promoting response (reduction of symptoms by 50%) than either switching to another antidepressant or adding another antidepressant.[10] Because atypical antipsychotics carry well-known risks for adverse events (e.g., extrapyramidal side effects, tardive dyskinesia, weight gain, diabetes, morbidity, or mortality),[13,16] it is notable that aripiprazole treatment in VAST-D study was associated with greater weight gain than other treatments while buproprion was associated with greater anxiety. Since the results of VAST-D may be taken as generally supportive of greater antipsychtic use in MDD, it is timely to review trends in antipsychotic prescribing in recent years for the management of MDD in ambulatory care settings. To our knowledge, there have been only two pharmaco-epidemiological studies of antipsychotic prescribing patterns in MDD.[14,17] One study based on Medicaid Analytic eXtract (MAX) data from 2001–2010 found that 14% of patients with MDD were started an antipsychotic medication within one-year following onset of MDD.[14] Another study found that that 20.6% of veterans with MDD treated in the Veterans Health Administration (VHA) in fiscal year 2007 received antipsychotic medications.[17] These studies, however, focused on only Medicaid beneficiaries[14] or VHA patients;[17] used data from many years ago; and did not address time trends in prescribing patterns over the last decade.

To fill in existing gaps in literature, we address the following research questions: 1) What are the national prevalence rates of antipsychotic prescriptions from 2006 to 2015 in visits in which MDD was diagnosed? 2) What particular antipsychotic medications were most commonly prescribed from 2006 to 2015 in visits with MDD? And finally, 3) What demographic and clinical characteristics are associated with antipsychotic prescription in visits with MDD? This is, thus, the first descriptive study to investigate national trends in antipsychotic prescribing patterns among MDD seen in in office-based outpatient settings, and provides a benchmark for tracking future use of antipsychotics in adults with MDD in light of recently published research.

METHODS

Data source and study sample

We used data from 2006–2015 National Ambulatory Medical Care Survey (NAMCS), which are administrated by National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC).[18] The NAMCS is an annual, cross-sectional survey of visits to office-based physicians in outpatient settings.[18] The NAMCS was designed to represent office-based outpatient care at the national level. The NAMCS collects up to three clinical diagnoses using the *International Classification of Diseases, 9th edition, Clinical Modification* (ICD-9-CM) diagnostic codes. Using this information, we selected visits made by adults ages 18 or older who were diagnosed with MDD (296.20–296.26 and 296.30–296.36) (n=4,464 unweighted). We excluded those diagnosed with bipolar disorders (296.0X, 296.1X, 296.40–296.80), schizophrenia (295.XX), and other psychoses (297.XX-299.XX) (n=113 unweighted). We further excluded observations with all missing

covariates (n=307 unweighted), which were missing at random, leaving a final sample size of 4,044. Using publicly available deidentified data, the research procedure for this study was exempted from the Institutional Review Board (#2000021850) at Yale School of Medicine. Further details of the survey, including descriptions, questionnaires, sampling methodology and datasets, are publicly available on the NAMCS website.[19]

Measures

Antipsychotics—The NAMCS collects up to eight medications prescribed in 2006–2011, up to 10 medications in 2012–2013, and up to 30 medications in 2014–2015. For consistency across years, we only considered the first eight medications. Using the *2017 American Hospital Formulary Service* (AHFS) *Compendium*,[20] and previous studies,[17,21] we identified prescribed antipsychotic medications using generic names. We included 11 typical, or first generation, antipsychotics (haloperidol, chlorpromazine, fluphenazine, perphenazine, prochlorperazine, thioridazine, trifluoperazine, thiothixene, loxapine, molindone, pimozide) and 10 atypical, or second generation, antipsychotics (aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone). We constructed a binary variable (yes/no) for overall antipsychotic prescription status.

Covariates—Based on previous studies,[4,17,22] we identified a number of covariates. We included the following demographic variables: age, gender, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanics, or other), region (Northeast, Midwest, South, or West), primary source of payment (Private, Medicare (<65), Medicare (≥65), Medicaid, or other), reason for visit (acute problem, routine chronic problem, preventive care, or pre- or post-surgery care), and repeat of visits within the past 12 months (none, 1–2, 3–5, or 6+). For clinical characteristics, we included the following variables: physician specialty (primary care, psychiatry, or other), metropolitan statistical area (MSA) status (yes/no), psychotherapy provided (yes/no), mental health counseling other than psychotherapy provided (yes/no), time spent with a doctor (<15, 15–20, 21–30, or >30 min.), antidepressants prescribed (yes/no),[4] number of chronic conditions (1, 2–3, or 4+), and number of medications (0–3, 4–5, or 6+). The number of chronic conditions was based on 14 chronic conditions (yes/no) collected by the NAMCS (e.g., arthritis, congestive heart failure, and diabetes). We also constructed variables identifying co-morbid psychiatric disorders (dementia, post-traumatic stress disorder, anxiety disorders, adjustment disorders, personality disorders, depressive disorders other than MDD, and mild cognitive impairment) and seven specific substance use psychiatric disorders (alcohol, opiates, cocaine, cannabis, barbiturates, amphetamines, and hallucinogens) using the ICD-9-CM diagnostic codes.[21]

Data Analysis

First, we examined the extent to which patients with MDD who were prescribed antipsychotic medication differed on demographic and clinical characteristics from those not prescribed such medication. We used design-based *F*-tests (i.e., weight-corrected Pearson's chi-squared statistics) to test differences by the antipsychotic prescription status. Second, we estimated antipsychotic prescribing trends over time from 2006 to 2015. After estimating the overall proportion of visits in which antipsychotics were prescribed, we performed stratified

analyses for MDD with psychotic features (ICD-9-CM codes 296.24 and 296.34) and without psychotic features, as well as by age, gender, race/ethnicity, primary source of payment, and physician specialty. In trend analyses, we combined years into 2-year intervals, assigning values ranging from 1 to 5 (1=2006–2007, 2=2007–2008, etc.). We transformed this variable by subtracting 1 and dividing by 4, resulting in values between 0 and 1. This allowed us to interpret the odds ratio as the change in odds of receiving a prescription for an antipsychotic across the 10-year period.

Third, we estimated prevalence of each antipsychotic agent prescribed over time by antipsychotic classification and generic names with summary data for first and second generation antipsychotics. We again used design-based *F*-tests to investigate the differences in patterns across years. Lastly, we ran a multivariable-adjusted logistic regression analysis to identify demographic and clinical factors independently associated with antipsychotics prescriptions. In this analysis, we only included variables that had significance differences by antipsychotic prescription status at the level of $p<0.01$. We used Stata 13.1[23] for all analyses, and we employed the *svy* commands to account for the complex survey sampling design of the NAMCS (i.e., unequal probability of selection, clustering and stratification).

RESULTS

Selected characteristics of the sample

Altogether, 20.0% of visits with a diagnosis of MDD involved prescription of an antipsychotic. Table 1 presents demographic and clinical characteristics of visits among adults with MDD by the antipsychotic prescription status. Overall, the majority of visits were made by adults with MDD aged less than 65 (84.5%) and female adults (66.2%). 27% of adults with MDD prescribed an antipsychotic were of racial/ethnic minority status (Table 1), which was a significantly higher proportion than among those without antipsychotic prescriptions (18.6%) ($p<0.001$). In addition, while 52.8% of MDD patients who were prescribed an antipsychotic had Medicare or Medicaid as their primary sources of payment, only 27.6% of those without antipsychotics had such government insurance coverage ($p<0.001$).

More than 90% of antipsychotics were prescribed in visits to psychiatrists as contrasted with other precribers. Other clinical characteristics, such as urban metropolitan statistical area (MSA) status, mental health counseling provided, and the total number of medications prescribed were also significantly more frequent at visits in which antipsychotics were prescribed. Among those with MDD who had antipsychotics prescribed, 85.9% also had antidepressants prescribed. Among co-diagnosed psychiatric and substance use psychiatric disorders, post-traumatic stress disorder, adjustment disorder, personality disorder, and cannabis-related disorders were all significantly associated with receipt of antipsychotic prescriptions.

Trends of antipsychotic prescriptions

Table 2 shows stratified analyses of the proportion of visits in which antipsychotics were prescribed by year among adults with MDD. Overall, the percentage of visits at which

antipsychotics were prescribed increased from 16.4% in 2006–2007 to 22.8% in 2008–2009, and then declined to 18.9% in 2014–2015. The antipsychotic use was particularly common for those with MDD with psychotic features, ranging from 68.4% in 2006–2007 to 75.2% in 2014–2015. Among visits with adults aged 75 or older, the percentage receiving antipsychotic prescriptions decreased most substantially over time from 26.9% in 2006–2007 to only 11.5% in 2014–2015 (OR=0.73; 95% CI=0.56 – 0.95). In cases of visits among non-Hispanic blacks and Medicare beneficiaries aged 65 or older, the proportions of visits at which antipsychotics were prescribed fluctuated over time with no consistent trend (p=0.044 and 0.049, respectively).

Types and prevalence of antipsychotic agents

Table 3 presents types and prevalence of individual antipsychotic agents by the time period. Overall, more than 90% of commonly prescribed antipsychotics were atypical (second generation) medications. The most commonly prescribed agents were: quetiapine (36%), aripiprazole (27.7%), risperidone (22%), lurasidone (8.7%), and ziprasidone (5.1%) (not mutually exclusive), which were all atypical. The prescribing patterns for individual agents were relatively stable over time, with no significant differences across the time periods.

Multivariable Logistic Regression Analysis of Antipsychotic prescription

Table 4 presents the results of multivariable-adjusted logistic regression model, which estimated the odds that an antipsychotic was prescribed at any given visit. Two demographic factors were associated with higher odds of antipsychotic prescription. When compared to non-Hispanic whites, both non-Hispanic blacks and Hispanics had 2.56 and 1.69 times higher odds of receiving an antipsychotic prescription, respectively (p<0.01). In the case of health insurance coverage, those covered Medicare (and aged <65) and Medicaid had 2.16 and 2.06 times higher odds, respectively, of receiving an antipsychotic prescription, when compared to those with Private insurance coverage (p<0.01).

Turning to clinical characteristics, visits to physicians other than a psychiatrist (i.e., primary care and other specialties) had 0.29 times lower odds of receiving an antipsychotic prescription than visits to a psychiatrist (p<0.001; 95% CI=0.18 – 0.48). Visits which included mental health counseling had 1.47 times higher odds that antipsychotics were prescribed, compared to visits with no mental health counseling (p<0.01; 95% CI=1.12 – 1.94). Visits with three or more medications prescribed had 5.78 times higher odds of receiving an antipsychotic prescription, compared to visits with two or fewer medications prescribed (p<0.001; 95% CI=4.39 – 7.60). Finally, visits in which an adjustment disorder was diagnosed had 0.11 times lower odds that antipsychotics would be prescribed (p<0.01; 95% CI=0.02 – 0.58), while visits in which a cannabis use disorder was diagnosed had 2.66 times higher odds that antipsychotics would be prescribed (p<0.05; 95% CI=1.17 – 6.06).

DISCUSSION

This study evaluated antipsychotic prescribing trends among adults who received a diagnosis of MDD, with no co-morbid psychotic disorders, in a nationally representative sample of office-based outpatient visits from 2006 to 2015. Overall, the antipsychotic prescription rate

increased from 18.5% in 2006–2007 to 24.9% in 2008–2009 (when several antipsychotic agents receive FDA approval for use in MDD), and then declined to 18.9% in 2014–2015. On the one hand, these prescribing rates are generally stable and broadly similar to those in previous studies,[14,17] which found that 14% of non-elderly Medicaid adults with depression had antipsychotics prescribed within a year of depression onset,[14] and 20.6% of VHA patients with MDD were prescribed antipsychotics.

On the other hand, it appears that the prescribing rates did increase in response to FDA approvals for use in MDD from 2007–2009, and decreased in elderly patients in response to subsequent findings of increased mortality in this group. The decreasing rate from 27% in 2006–2007 to 10.7% in 2014–2015 in adults ages 75 or older may reflect physicians' responsiveness to the FDA's black-box warning concerning the increased risk of death with antipsychotics in the ederly,[24,25] and/or to other clinical guidelines such as the Beers criteria which identified potentially inappropriate medication use in older adults.[26] The FDA black-box warning issued in 2008, stated that both conventional and atypical antipsychotics increased a risk of mortality in older adults treated for dementia-related psychosis.[25] In the similar vein, Beers criteria have recommended against the use of antipsychotics due to its increased risks of developing cognitive impairment, including dementia, and stroke among older patients.[26]

Of the visits with antipsychotics prescribed among adults with MDD, 85.9% also had antidepressants prescribed. A previous study suggests that 71.3% of patients for whom antipsychotics for MDD were initiated did not have minimally adequate antidepressant treatment prior to the initiation of antipsychotic treatment as recommended by the FDA.[14] However, due to cross-sectional nature of our study, we were not able to identify whether such concomitant prescribing of antipsychotics followed adequate antidepressant trials or previous antidepressant switching or augmentation. Future population-based observational research should investigate this pattern to address whether the use of antipsychotics among patients with MDD in office-based outpatient settings follows recommended use in patients unresponsive to standard antidepressants.

The most commonly prescribed antipsychotic medications were quetiapine (36%), aripiprazole (27.7%), risperidone (22.0%), and olanzapine (8.74%), which were all second generation medications and together accounted for more than 85% of all antipsychotic prescriptions in any given time interval. It appear that these patterns are in accordance to the FDA approvals and other clinical guidelines for antipsychotic use in the treatment of MDD.[8–10] Furthermore, this trend was also similar to those in previous studies, which showed predominant exposure of second generation antipsychotics in patients treating with MDD.[14,17]

One key correlate of antipsychotic prescription was being a minority (i.e, non-Hispanic black or Hispanic). Additional correlates suggest greater clinical severity or dysfunction, for example a predominance of patients younger than 65 covered by Medicare or by Medicaid, receiving mental health counseling in addition to pharmacotherapy, receiving three or more medications, or being diagnosed with co-morbid cannabis use disorders.[17] Future research is needed to determine why racial/ethnic minority adults were more likely to receive

antipsychotics. Predictors associated with the decreased likelihood of antipsychotic prescription were visits to specialties other than psychiatry and having diagnosed with adjustment disorders, suggestive of less severe clinical status.

There are two notable clinical implications from this study. This is the first study to investigate patterns of antipsychotic prescribing among adults with MDD in office-based outpatient settings and found antipsychotics were prescribed in one in five visits for MDD with limited change over time. While the recent VAST-D study[10] provided robust support for the greater effectiveness of augmentation with aripiprazole and perhaps other antipsychotics than switching to or augmenting treatment with another antidepressant, further studies are needed to address the balance of effectiveness, safety and cost-effectiveness. Further planned analyses of data from VAST-D should provide some of this information, especially with respect to effects on elderly patients, at greatest risk for adverse effects. Second, it will be important to assess increasing antipsychotic prescribing in adults with MDD with either aripiprazole or other antipsychotics in response to the findings of VAST-D. While FDA approval seems to have had limited impact on use of this approach, the likely impact of publication of a major comparative effectiveness trial for MDD is currently unknown and deserves future study.

There are several limitations in this study. First, NAMCS does not capture outpatient visits to hospital-affiliated clinics and emergency departments, which account for about 8.5% of all outpatient visits. Furthermore, NAMCS excludes prescriptions ordered by phone. Second, NAMCS collected patient information in a randomly selected visit, which may have resulted in incomplete documentation of the patient services. For example, NAMCS cannot identify if patients with MDD received antipsychotic prescriptions at a different clinic. For these reasons, our findings may underestimate the magnitude of antipsychotic prescribing patterns. Third, the NAMCS does not collect dosing information (e.g., strength and duration) of each drug. This limits the ability to investigate appropriate or potentially inappropriate use of antipsychotics in adults with MDD.

Despite these limitations, this study shows that antipsychotics have been prescribed at one in five office-based outpatient visits at which MDD was diagnosed with general stability over time except in the elderly. Most prescribed antipsychotic medications were second generation agents, in accordance with FDA approvals and other clinical guidelines. Yet, the degree of appropriate use and the impact of a recent landmark effectiveness trial supporting the use of antipsychotics in treating MDD are as yet unknown and this study should spur additional research.

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Clinical points

- Although recent research supports the effectiveness of antipsychotics in unresponsive MDD, little is known about prescribing nationally in MDD.
- FDA-approved second generation antipsychotics are prescribed at about one in five office-based visits at which MDD is diagnosed with little change in recent years.
- Pharmaco-surveillance data are needed to provide better information on long-term effectiveness and safety of antipsychotics for MDD.

Table 1

Selected characteristics (weighted column %) of US adults ages 18 and older with major depressive disorder (MDD) by antipsychotics prescription status in office-based outpatient settings, 2006–2015 NAMCS.

	Antipsychotics prescription (%)		Total	*P*-value[†]
	No	Yes		
Sample size (row %)				
Unweighted sample (n)	80.3 (3,249)	19.7 (795)	100 (4,044)	
Weighted visits (N)	80.0 (6,380,114)	20.0 (1,596,826)	100 (7,976,941)	
Age				
18–44	36.9	35.0	36.5	0.220
45–64	47.0	52.2	48.0	
65–74	10.3	7.9	9.8	
75+	5.8	4.9	5.6	
Gender				
Female	67.0	63.3	66.2	0.186
Male	33.0	36.7	33.8	
Race/ethnicity				
Non-Hispanic White	81.4	73.0	79.7	<0.001
Non-Hispanic Black	5.2	8.8	5.9	
Hispanic	10.0	15.5	11.1	
Other[a)]	3.4	2.7	3.3	
Region				
Northeast	24.5	26.2	24.9	0.030
Midwest	15.4	18.3	16.0	
South	30.8	34.5	31.5	
West	29.3	20.9	27.6	
Primary source of payment				
Private	52.9	39.0	50.1	<0.001
Medicare (<65)	7.8	15.4	9.3	
Medicare (≥65)	10.8	9.8	10.6	
Medicaid	9.0	17.2	10.6	
Other[b)]	19.5	18.7	19.4	
Reason for visit				
Acute problem	9.2	5.5	8.4	0.033
Routine chronic problem	88.1	92.2	88.9	
Preventive care	0.2	0.0	0.2	
Pre- or post-surgery	2.5	2.3	2.5	
Repeat of visits in the past 12 months				
0 visit	2.1	1.2	1.9	<0.001
1–2 visits	21.2	15.5	20.1	
3–5 visits	32.6	26.2	31.3	

	Antipsychotics prescription (%)		Total	*P*-value[†]
	No	Yes		
6+ visits	44.1	57.1	46.7	
Physician specialty				
Primary care	13.6	4.8	11.9	<0.001
Psychiatry	83.9	93.1	85.7	
Other specialties[c)]	2.5	2.0	2.4	
MSA status				
MSA	94.0	90.7	93.4	0.008
Non-MSA	6.0	9.3	6.6	
Psychotherapy provided				
Yes	40.7	40.9	40.7	0.954
No	59.3	59.1	59.3	
Mental health counseling provided				
Yes	22.8	32.5	24.8	<0.001
No	77.2	67.5	75.3	
Time spent with doctor				
< 15 min.	9.9	9.7	9.8	0.064
15–20 min.	30.6	35.4	31.6	
21–30 min.	26.7	29.9	27.4	
> 30 min.	32.8	25.1	31.2	
Antidepressants prescribed				
Yes	80.9	85.9	81.9	0.041
No	19.1	14.1	18.1	
Multiple chronic conditions				
1	64.3	62.3	63.9	0.156
2–3	28.3	32.1	29.0	
4+	7.5	5.6	7.1	
Number of medications				
<3	56.7	23.3	49.5	<0.001
3–5	34.2	62.6	40.4	
6+	9.0	14.1	10.2	
Co-diagnosed psychiatric disorders				
Dementia	0.6	0.3	0.6	0.397
PTSD	5.4	8.1	5.9	0.035
Anxiety	20.4	24.1	21.2	0.122
Adjustment disorders	1.1	0.2	0.9	0.001
Personality disorders	2.4	4.2	2.8	0.038
Depressive disorders other than MDD	3.1	4.3	3.3	0.357
Mild cognitive impairment	0.1	0.0	0.1	0.535
Co-diagnosed substance use psychiatric disorders				
Alcohol	3.0	3.9	3.2	0.337

	Antipsychotics prescription (%)		Total	*P*-value[†]
	No	Yes		
Opiates	0.7	0.6	0.7	0.560
Cocaine	0.1	0.3	0.1	0.308
Cannabis	0.3	1.2	0.5	<0.001
Barbiturates	0.0	0.0	0.0	0.579
Amphetamines	0.1	0.2	0.2	0.698
Hallucinogens	0.0	0.0	0.0	-

Note:

[†] compares proportion differences by antipsychotics prescription status using a weight-corrected Pearson's chi-squared statistic; and

a) includes Asians, American Indian/Alaska Natives (AIANs), Native Hawaiian or Other Pacific Islanders (NHOPI), and other mixed races;

b) includes worker's compensation, self-pay, no charge, and others; and

c) includes general surgery, obstetrics/gynecology, orthopedic surgery, cardiovascular diseases, dermatology, urology, neurology, ophthalmology, otolaryngology, and others.

Table 2

Stratified analysis of visit proportions (weighted column %) in which antipsychotics were prescribed among US adults ages 18 and older with major depressive disorder (MDD), 2006–2015 NAMCS.

	Years (%)						Trend (2006–2015)		
	2006–2007	2008–2009	2010–2011	2012–2013	2014–2015	Total	OR	95% CI	*P*-value
Total proportion of visits with antipsychotics in MDD	18.5	24.9	20.5	17.6	18.9	20.0	0.96	0.88 – 1.04	0.326
Visits with antipsychotics in MDD with non-psychotic features	15.9	22.0	17.8	16.7	16.3	17.7	0.97	0.89 – 1.05	0.425
Visits with antipsychotics in MDD with psychotic features	68.4	83.6	55.8	52.1	75.2	66.9	0.96	0.74 – 1.26	0.786
Total proportion of visits in which antidepressants were prescribed along with antipsychotics	18.5	24.5	22.5	18.5	20.9	21.0	0.99	0.91 – 1.08	0.891
Visits in which antidepressants were prescribed along with antipsychotics in MDD with non-psychotic features	16.1	21.7	19.6	17.3	17.7	18.5	0.99	0.91 – 1.08	0.850
Visits in which antidepressants were prescribed along with antipsychotics in MDD with psychotic features	70.8	82.8	67.4	63.8	75.2	72.6	0.98	0.73 – 1.33	0.913
Age									
18–44	14.1	25.4	22.7	14.6	18.4	19.2	0.98	0.88 – 1.10	0.761
45–64	20.5	25.1	21.2	21.3	20.9	21.7	0.98	0.87 – 1.11	0.778
65–74	20.7	24.2	8.3	16.0	15.7	16.1	0.90	0.67 – 1.22	0.504
75+	27.0	21.9	19.8	10.9	10.7	17.5	0.73	0.56 – 0.95	0.019
Gender									
Female	17.1	22.6	21.9	15.6	18.6	19.1	0.97	0.88 – 1.08	0.595
Male	21.7	30.2	17.9	22.0	19.6	21.8	0.93	0.80 – 1.08	0.331
Race/ethnicity									
Non-Hispanic White	17.2	22.9	17.9	16.4	17.9	18.3	0.97	0.89 – 1.06	0.470
Non-Hispanic Black	35.1	43.1	31.9	21.9	16.9	29.8	1.09	0.54 – 0.99	0.044
Hispanic	22.7	28.0	30.3	26.4	31.4	28.0	1.08	0.78 – 1.48	0.646
Other[a)]	12.5	16.3	18.8	11.5	19.2	16.6	1.09	0.72 – 1.64	0.686
Source of payment									
Private	11.7	20.7	14.2	14.3	17.7	15.9	1.06	0.93 – 1.20	0.395
Medicare (<65)	35.9	42.8	37.4	24.6	21.6	33.0	0.78	0.61 – 1.00	0.054
Medicare (≥65)	30.9	25.3	13.6	16.3	13.5	18.6	0.77	0.59 – 1.00	0.049
Medicaid	31.7	31.7	34.3	26.0	39.2	32.3	1.03	0.85 – 1.26	0.736

	Years (%)						Trend (2006–2015)		
	2006–2007	2008–2009	2010–2011	2012–2013	2014–2015	Total	OR	95% CI	*P*-value
Other[b)]	20.6	18.2	22.4	19.3	16.6	19.3	0.95	0.81 – 1.11	0.491
Physician specialty									
Primary care	6.4	20.9	7.2	2.8	7.7	8.2	0.79	0.55 – 1.13	0.191
Psychiatry	20.0	25.6	22.4	20.4	20.4	21.8	0.97	0.89 – 1.06	0.533
Other[c)]	3.0	4.6	22.5	23.8	15.8	16.9	1.20	0.74 – 1.94	0.458
Sample Size								**Total**	
Unweighted sample	632	671	782	1,318	641			4,044	
Weighted visits	1,412,102	1,458,356	1,726,968	1,545,536	1,833,979			7,976,941	

Note:

[a)] includes Asians, American Indian/Alaska Natives (AIANs), Native Hawaiian or Other Pacific Islanders (NHOPI), and other mixed races;

[b)] includes worker's compensation, self-pay, no charge, and others; and

[c)] includes general surgery, obstetrics/gynecology, orthopedic surgery, cardiovascular diseases, dermatology, urology, neurology, ophthalmology, otolaryngology, and others.

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Table 3

Type and prevalence of antipsychotic agents among US adults ages 18 and older with major depressive disorder (MDD) who were antipsychotics prescribed, 2006–2015 NAMCS.

	Years (%)					Overall (%)	*P*-value[†]
	2006–2007	2008–2009	2010–2011	2012–2013	2014–2015		
Any typical (first generation) agents	5.7	8.0	5.0	2.2	3.1	4.9	0.253
Typical (first generation) - Butyrophenones							
Haloperidol	1.7	3.8	0.4	0.0	1.5	1.6	0.124
Typical (first generation) - Phenothiazines							
Chlorpromazine	1.8	0.9	0.0	0.0	0.0	0.5	0.587
Fluphenazine	0.6	0.0	0.0	0.0	0.9	0.3	0.776
Perphenazine	1.1	0.0	2.7	0.3	0.7	1.0	0.132
Prochlorperazine	0.0	1.1	0.0	0.0	0.0	0.2	0.761
Thioridazine hydrochloride	0.0	0.2	0.0	0.9	0.0	0.2	0.724
Trifluoperazine hydrochloride	0.5	0.4	0.0	1.0	0.0	0.3	0.708
Typical (first generation) - Thiothixene							
Thiothixene	0.0	1.2	1.9	0.9	0.0	0.9	0.611
Typical (first generation) - Miscellaneous							
Loxapine succinate	0.0	0.0	0.0	0.0	0.0	0.0	-
Molindone hydrochloride	0.0	0.0	0.0	0.0	0.0	0.0	-
Pimozide	0.0	0.5	0.0	0.0	0.0	0.1	0.896
Any atypical (second generation) agents	96.1	95.6	96.1	98.1	98.3	96.8	0.562
Atypical (second generation)							
Aripiprazole[≠]	15.9	30.9	26.1	30.5	32.9	27.7	0.147
Asenapine	0.0	0.0	0.0	2.4	0.3	0.5	0.321
Clozapine	0.0	1.0	0.0	0.2	0.0	0.3	0.733
Iloperidone	0.0	0.0	0.0	0.0	0.0	0.0	-
Lurasidone	0.0	0.0	0.3	2.6	2.9	1.2	0.168
Olanzapine[≠]	15.8	6.0	8.3	6.5	8.5	8.7	0.130

	Years (%)					Overall (%)	*P*-value†
	2006–2007	2008–2009	2010–2011	2012–2013	2014–2015		
Paliperidone	0.0	0.0	2.2	2.7	0.3	1.0	0.340
Quetiapine≠	42.1	37.1	35.0	28.0	37.6	36.0	0.459
Risperidone≠	24.6	20.9	20.8	23.4	21.2	22.0	0.971
Ziprasidone≠	3.7	7.0	6.5	5.4	2.3	5.1	0.491

Note:

†compares proportion differences across years using a weight-corrected Pearson's chi-squared statistic.

≠indicates approved and off-label uses by the FDA for MMD.

Table 4

Adjusted odds ratios (AOR) for antipsychotic prescriptions among adults ages 18 and older with major depressive disorder, 2006–2015 NAMCS.

(Reference group in a parenthesis)	AOR	95% CI
Race/ethnicity (Non-Hispanic White)		
Non-Hispanic Black	2.56**	1.50 – 4.36
Hispanic	1.69**	1.16 – 2.46
Other*a)*	0.93	0.47 – 1.82
Primary source of payment (Private)		
Medicare (<65)	2.16***	1.50 – 3.10
Medicare (≥65)	1.16	0.77 – 1.76
Medicaid	2.06**	1.36 – 3.12
Other*b)*	1.18	0.88 – 1.57
Repeat of visits in the past 12 months (None)		
1–2 visits	1.02	0.47 – 2.20
3–5 visits	1.12	0.53 – 2.35
6+ visits	1.64	0.79 – 3.42
Physician specialty (Psychiatry)		
Other*c)*	0.29***	0.18 – 0.48
MSA status (MSA)		
Non-MSA	1.17	0.78 – 1.77
Mental health counseling provided (No)		
Yes	1.47**	1.12 – 1.94
Number of medications (<3)		
3+	5.78***	4.39 – 7.60
Adjustment disorder (No)		
Yes	0.12**	0.02 – 0.60
Cannabis use disorder (No)		
Yes	2.66*	1.17 – 6.06
Sample size		
Unweighted sample	4,044	
Weighted visits	7,976,941	
F-statistic	18.26***	

Note:

*** <0.001;

** <0.01;

* <0.05.

a) includes Asians, American Indian/Alaska Natives (AIANs), Native Hawaiian or Other Pacific Islanders (NHOPI), and other mixed races;

[b] includes worker's compensation, self-pay, no charge, and others; and

[c] includes primary care, general surgery, obstetrics/gynecology, orthopedic surgery, cardiovascular diseases, dermatology, urology, neurology, ophthalmology, otolaryngology, and others.