Health care resource utilization and costs associated with nonadherence and nonpersistence to antidepressants in major depressive disorder

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What is already known about this subject

- Adherence and persistence to antidepressant therapy for major depressive disorder (MDD) are poor, with only 35%-55% of patients remaining adherent or persistent to antidepressant therapy at 6 months.
- Antidepressant nonadherence and nonpersistence are associated with increased health care resource utilization (HCRU), costs, and risk of relapse and recurrence.
- Contemporary real-world evidence on the effect of nonadherence and nonpersistence to antidepressants on HCRU and costs in patients with MDD is limited.

What this study adds

- This study provides a comprehensive update on the contemporary economic effect of antidepressant nonadherence and nonpersistence in a broad U.S. adult MDD population enrolled in commercial and Medicare supplemental plans.
- Our findings underscore the need for new strategies that promote better adherence and persistence to reduce health care burden among patients with MDD.

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ABSTRACT

BACKGROUND: Nonadherence and nonpersistence to antidepressants in major depressive disorder (MDD) are common and associated with poor clinical and functional outcomes and increased health care resource utilization (HCRU) and costs. However, contemporary real-world evidence on the economic effect of antidepressant nonadherence and nonpersistence is limited.

OBJECTIVE: To assess the effect of nonadherence and nonpersistence to antidepressants on HCRU and costs in adult patients with MDD enrolled in U.S. commercial and Medicare supplemental insurance plans.

METHODS: This was a retrospective new-user cohort study using administrative claims data from the IBM MarketScan Commercial and Medicare Supplemental databases from January 1, 2010, to December 31, 2018. We identified adult patients with MDD aged ≥18 years who initiated antidepressant therapy for a new MDD episode between January 1, 2011, and December 31, 2017. Twelve-month total all-cause HCRU and costs (2019 U.S. dollars) were characterized for patients who were adherent/nonadherent and persistent/nonpersistent to antidepressants at 6 months. Adherence was defined as having proportion of days covered (PDC) ≥80%, and persistence was defined as having continuous

antidepressant therapy without a ≥30-day gap. Multivariable negative binomial regression and 2-part models adjusted for baseline characteristics were used to estimate incidence rate ratios (IRRs) for HCRU and incremental costs of nonadherence and nonpersistence, respectively.

RESULTS: A total of 224,645 patients with MDD (commercial: n=209,422; Medicare supplemental: n=15,223) met all study inclusion criteria. Approximately half of patients were nonadherent (commercial: 48%; Medicare supplemental: 50%) or nonpersistent (commercial: 49%; Medicare supplemental: 52%) to antidepressants at 6 months. After

controlling for baseline characteristics, nonadherent patients experienced significantly more inpatient hospitalizations (commercial, adjusted IRR [95% CI]: 1.34 [1.29 to 1.39]; Medicare supplemental: 1.19 [1.12 to 1.28]) and emergency room (ER) visits (commercial, adjusted IRR [95% CI]: 1.43 [1.40 to 1.45]; Medicare supplemental: 1.28 [1.21 to 1.36]) compared with adherent patients. Similar results were observed in nonpersistent patients. Adjusted mean differences revealed that nonadherent and nonpersistent patients accumulated significantly higher medical costs (commercial: \$568 [95% CI: \$354 to \$764] and \$491 [\$284 to \$703]; Medicare supplemental: \$1,621 [\$314 to \$2,774] and \$1,764 [\$451 to \$2,925]), inpatient costs (commercial: \$650 [\$490 to \$801] and \$564 [\$417 to \$716]; Medicare supplemental: \$1,546 [\$705 to \$2,308] and \$1,567 [\$778 to \$2,331]), and ER costs (commercial: \$130 [\$115 to \$143] and \$129 [\$115 to \$142]; Medicare supplemental: \$82 [\$23 to \$150] and \$80 [\$18 to \$150]), and incurred significantly lower pharmacy costs (commercial: -\$561 [-\$601 to -\$521] and -\$576 [-\$616 to -\$540]; Medicare supplemental: -\$510 [-\$747 to -\$227] and -\$596 [-\$830 to -\$325]) compared with adherent and persistent patients, respectively.

CONCLUSIONS: This study found more hospitalizations and ER use and higher total medical costs among patients who were nonadherent and nonpersistent to antidepressants at 6 months. Strategies that promote better adherence and persistence may lower HCRU and medical costs in patients with MDD.

Major depressive disorder (MDD) affects more than 17 million Americans in the United States and is a leading cause of disability worldwide.^{1,2} MDD is associated with substantial clinical and economic burden; in 2010, MDD was estimated to account for \$210 billion in the United States, with total costs split approximately equally between direct medical costs and indirect workplace costs (i.e., absenteeism and presenteeism costs).³

American Psychiatric Association guidelines recommend a minimum of 6–12 weeks of initial treatment with antidepressants or other treatment modalities to induce remission of symptoms (i.e., acute phase), which is followed by 4–9 months of continuous treatment to prevent relapse (i.e., continuation phase) and maintenance treatment that may be required indefinitely to prevent recurrence for patients with 3 or more major depressive episodes, chronic depression, or risk factors for recurrence.⁴ The National Committee for Quality Assurance (NCQA) continues to endorse various Antidepressant Medication Management (AMM) Healthcare Effectiveness Data and Information Set (HEDIS) measures for effective acute and continuation phase treatment with antidepressants to improve the quality of depression care.⁵ Although clinical guidelines emphasize the importance of adherence and persistence

to antidepressants, adherence and persistence to antidepressants are suboptimal, with only 35%–55% of patients remaining adherent or persistent to antidepressant therapy at 6 months.^{6–10} Commonly cited reasons for nonadherence or nonpersistence to antidepressants include lack of efficacy,¹¹ intolerability,¹¹ regimen complexity,¹² out-of-pocket costs,^{12,13} and patient beliefs about antidepressant medications.^{14,15}

Both antidepressant nonadherence and nonpersistence are significant barriers to depression treatment effectiveness and subsequent remission,⁴ and failure to achieve adequate response or remission with antidepressant therapy is associated with poorer clinical and functional outcomes,^{16,17} increased health care resource utilization (HCRU) and costs,^{16–20} and work productivity loss.^{16–18} Previous research has demonstrated that antidepressant nonadherence is associated with increased risk of relapse and recurrence,^{21–23} more hospitalizations and emergency room (ER) visits,^{7,8,24} and higher health care costs.^{8,9,25,26} In addition, antidepressant nonpersistence, which has been assessed in previous studies as discontinuation in the first 30–180 days of antidepressant therapy, is independently associated with increased risk of relapse and recurrence¹⁰ and higher all-cause and psychiatric HCRU and costs in patients with MDD.^{7,9,27–29}

Nevertheless, contemporary literature on the effect of antidepressant nonadherence and nonpersistence on HCRU and costs in a broad MDD population is limited. Newer antidepressants have been introduced over the past decade (i.e., vilazodone, vortioxetine, levomilnacipran), and much of the existing literature on the association between antidepressant nonadherence^{8,25,26} or nonpersistence^{25,28,29} and HCRU and costs has been published before 2010.^{8,25,26,28,29}

Due to the high prevalence of MDD and burden associated with poor treatment outcomes in MDD, understanding the economic effect of antidepressant nonadherence and nonpersistence is of continued interest to health systems and managed care organizations. Additionally, there are inconsistent definitions and thresholds of antidepressant adherence and persistence used in the existing literature,^{30,31} and studies using standardized objective measures of adherence and persistence are needed.³⁰ Furthermore, much of the previous literature has focused on privately insured commercial populations,^{7,8,25–29} and MDD is prevalent in other insured populations, including the Medicare population where MDD affects approximately 15% of beneficiaries aged 65 years and older.³² Therefore, the objective of this study was to provide a contemporary update on the effect of antidepressant nonadherence and nonpersistence on HCRU and costs in adult patients with MDD enrolled in commercial and Medicare supplemental insurance plans.

FIGURE 1 Study Design

HCRU = health care resource utilization; MDD = major depressive disorder.

Methods

STUDY DESIGN AND DATA SOURCE

This was a retrospective new-user cohort study using administrative claims data from the IBM MarketScan Commercial and Medicare Supplemental databases from January 1, 2010, to December 31, 2018 (Figure 1). The IBM MarketScan Commercial database consists of employer and health plan medical and pharmacy claims data for more than 40 million commercial plan members annually.³³ Enrollees include employees, their spouses, and their dependents who are covered by employer-sponsored private health insurance.³³ A variety of fee-for-service, fully capitated, and partially capitated health plans are represented in the IBM MarketScan Commercial database, including point-of-service, exclusive provider organizations, preferred provider organization plans, indemnity plans, health maintenance organizations, consumer-driven health plans, and high-deductible health plans.³³ The IBM MarketScan Medicare Supplemental database contains data on the Medicare-covered portion of payment (i.e., coordination of benefits amount) and employer- and out-of-pocket patient expenses for health care services provided in inpatient and outpatient settings for U.S. Medicare beneficiaries.³³ Medical claims are linked to outpatient prescription drug claims and person-level enrollment information.³³

This study did not meet the definition of human subjects research and therefore did not require University of Washington Institutional Review Board approval, as the IBM MarketScan databases are deidentified and compliant with the Health Insurance Portability and Accountability Act of 1996.

STUDY POPULATION

Inclusion Criteria. The study population consisted of adult patients with MDD who were identified between January 1, 2011, and December 31, 2017, and initiated an antidepressant for the treatment of a new MDD episode. Patients with MDD were defined as having either of the following: ≥ 1 inpatient medical claim with a primary *International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification* (ICD-9-CM/ICD-10-CM) diagnosis code for MDD or ≥ 1 inpatient or outpatient medical claim with a secondary ICD-9-CM or ICD-10-CM diagnosis code for MDD, followed by a second confirmatory inpatient or outpatient claim with an ICD-9-CM or ICD-10-CM diagnosis code for MDD in any position within 6 months after the initial medical claim ([Supplementary Table 1](#), available in online article). The date of the first qualifying MDD diagnosis between January 1, 2011, and December 31, 2017, was defined as the initial MDD diagnosis date. Antidepressants for MDD included selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, tricyclic

antidepressants, and other antidepressants ([Supplementary Table 2](#), available in online article). To ensure antidepressant claims were for the treatment of MDD, the index antidepressant date was defined as the date of the first antidepressant pharmacy claim within 60 days after a qualifying MDD diagnosis.⁶ Patients were required to be aged ≥ 18 years at index antidepressant date and have continuous enrollment in medical and pharmacy benefits for 12 months before the initial MDD diagnosis date (baseline period) and 12 months after the index antidepressant date (post-index period).

Exclusion Criteria. To avoid potential bias from other neuropsychiatric conditions, patients were excluded if they had diagnoses for bipolar/manic disorder, mood disorders other than MDD, Alzheimer disease, Parkinson disease, or dementia during the study period. Additionally, patients with diagnoses of schizophrenic disorder, psychosis-related disorders, drug-induced depression, or depressive-type psychosis in the 12-month baseline period before the initial MDD diagnosis date were excluded. Patients were also excluded if they had evidence of pregnancy, childbirth, or breastfeeding at any time during the study period, as these conditions may affect antidepressant adherence and persistence. To ensure antidepressants were prescribed for a new MDD episode, additional exclusions included any MDD claims or claims for antidepressants or combination antidepressant/antipsychotic agents (i.e., amitriptyline/perphenazine, fluoxetine/olanzapine) in the 12-month baseline period and evidence of combination antidepressant therapy or augmentation therapy on or within 30 days after the index antidepressant date. Combination antidepressant therapy was defined as 1 of the following: initiating ≥ 2 different antidepressants on the index antidepressant date, initiating an additional antidepressant with a different active ingredient within 30 days after the index antidepressant date³⁴ that overlaps with the index antidepressant for ≥ 30 days during the first 60 days of the index date (overlap did not need to be consecutive), or having more than 3 antidepressants within the first 30 days after the index date.³⁴ Augmentation therapy was defined as having any claims for an antipsychotic, mood stabilizer, or combination antidepressant/antipsychotic agent on or within 30 days after the index antidepressant date ([Supplementary Table 3](#), available in online article).³⁴

STUDY MEASURES AND OUTCOMES

Baseline Demographic and Clinical Characteristics.

Baseline patient demographic and clinical characteristics were assessed during the 12-month baseline period before the initial MDD diagnosis date. Baseline demographic characteristics included age, sex, plan type, geographic region,

and all-cause health care costs during the 12-month baseline period. Baseline clinical characteristics included the Quan-Charlson Comorbidity Index (Quan-CCI)^{35,36} and the following selected comorbidities of interest: anxiety, alcohol-use disorder, substance-use disorder, sleep disorders, coronary heart disease, congestive heart failure, chronic pulmonary disease, and diabetes.

Antidepressant Adherence and Persistence. Adherence to antidepressants was estimated from pharmacy claims data using the proportion of days covered (PDC) calculation,^{37,38} which reflects the proportion of days covered by medication fills during a measurement period. PDC represents a more conservative measure of adherence than the formerly widely used medication possession rate, which tends to overestimate adherence and has been suggested as a preferred measure of adherence by the Pharmacy Quality Alliance and Centers for Disease Control and Prevention.³⁸⁻⁴⁰ Adherent patients were defined as having $PDC \geq 80\%$. Persistence was defined as continuous therapy without the presence of a ≥ 30 -day gap in therapy.^{6,7,41} Adherence and persistence were assessed at 6 months following the index antidepressant date,^{7,9,24,25,42} a time frame that consists of both the acute and continuation phases of MDD treatment. Adherence and persistence were calculated for antidepressant therapy overall; in other words, any antidepressant for MDD was used toward the calculation of adherence and persistence.

All-Cause Health Care Resource Utilization and Costs. All-cause (regardless of diagnosis code) HCRU and costs were assessed over the 12-month post-index period following the index antidepressant date. HCRU and costs were reported by setting of care (inpatient, ER, outpatient, pharmacy). Outpatient visits were further categorized as physician office visits and other outpatient visits (i.e., outpatient visits excluding physician office and ER visits). HCRU was reported as counts and percentages of patients with ≥ 1 visit and mean visits or pharmacy claims per patient per year (PPPY). Costs were categorized as medical (sum of inpatient, ER, and outpatient costs); pharmacy; and total health care costs (sum of medical and pharmacy costs) and reported as mean costs PPPY. All costs were adjusted to 2019 U.S. dollars using the Bureau of Labor Statistics medical care component of the Consumer Price Index⁴³ and reflected all payments made to providers by insurers (i.e., plan and coordination of benefits) and patients (i.e., copay, co-insurance, deductible). Patients with evidence of capitated claims or negative total costs in any cost subcategory were excluded from cost analyses.

STATISTICAL ANALYSIS

Descriptive statistics were used to describe demographic and clinical characteristics during the 12-month baseline period and to calculate unadjusted 12-month post-index all-cause HCRU and costs. Unadjusted differences in HCRU and costs between nonadherent/adherent and nonpersistent/persistent patients were assessed using chi-square tests for categorical variables and unpaired t-tests with unequal variances for continuous variables. Additionally, multivariable negative binomial models were used to calculate adjusted incidence rate ratios (IRRs) to assess the association between nonadherence or nonpersistence to antidepressants and 12-month post-index HCRU. Adjusted incremental mean differences in health care costs associated with nonadherence and nonpersistence were assessed using multivariable 2-part models (logistic regression to determine the probability of having non-zero costs, followed by generalized linear models using a log-link function and gamma distribution). A nonparametric bootstrapping procedure with 500 iterations was used to estimate 95% CIs for the mean incremental cost differences, which were obtained using the 2.5th and 97.5th percentiles of the bootstrapped distribution. Multivariable HCRU and cost models were adjusted for the following variables: age, sex, geographic region, plan type, index year, Quan-CCI, index antidepressant class, and 12-month baseline total all-cause health care costs.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). P values ≤ 0.05 were considered statistically significant.

Results

BASELINE CHARACTERISTICS

A total of 5,745,208 adult patients with MDD were identified in IBM MarketScan Commercial and Medicare Supplemental databases between January 1, 2011, and December 31, 2017 (Figure 2). Of these, 224,645 adult patients with MDD (commercial: n=209,422; Medicare supplemental: n=15,223) met all study inclusion criteria. The mean (SD) ages for the commercial and Medicare supplemental populations were 40 (14) and 75 (8) years, and the majority of patients were female (commercial: 61%; Medicare supplemental: 62%; Table 1). Most patients were enrolled in preferred provider organization plans in the commercial population (59%), whereas most patients were enrolled in comprehensive plans in the Medicare supplemental population (44%). Compared with adherent and persistent patients, nonadherent and nonpersistent patients had a higher prevalence of anxiety, alcohol-use disorder, substance-use disorder, and chronic

pulmonary disease (Table 1). In both populations, the most commonly prescribed index antidepressants were selective serotonin reuptake inhibitors (commercial: 73%; Medicare supplemental: 74%), followed by other antidepressant classes (commercial: 16%; Medicare supplemental: 15%). At 6 months, 48% and 49% of patients in the commercial population and 50% and 52% of patients in the Medicare supplemental population were nonadherent and nonpersistent to antidepressants, respectively.

ALL-CAUSE HEALTH CARE RESOURCE UTILIZATION

A significantly greater proportion of nonadherent and nonpersistent patients had all-cause inpatient hospitalizations (commercial: 8% vs. 6% for both comparisons; all $P < 0.001$; Medicare supplemental: 24% vs. 21% for both comparisons; all $P < 0.001$) and ER visits (commercial: 24% vs. 19% for both comparisons; all $P < 0.001$; Medicare supplemental: 36% vs. 30% and 35% vs. 30%, respectively; all $P < 0.001$) compared with adherent and persistent patients, respectively. After adjustment for age, sex, plan type, geographic region, index year, Quan-CCI, index antidepressant class, and baseline 12-month total all-cause health care costs, nonadherent and nonpersistent patients in both the commercial and Medicare supplemental populations had significantly more hospitalizations (commercial, adjusted IRR [95% CI]: 1.34 [1.29 to 1.39] and 1.32 [1.27 to 1.36]; Medicare supplemental: 1.19 [1.12 to 1.28] and 1.18 [1.10 to 1.26]) and ER visits (commercial, adjusted IRR [95% CI]: 1.43 [1.40 to 1.45] and 1.41 [1.38 to 1.44]; Medicare supplemental: 1.28 [1.21 to 1.36] and 1.28 [1.21 to 1.36]) compared with adherent and persistent patients (Table 2). Nonadherent and nonpersistent patients had significantly fewer pharmacy claims compared with adherent and persistent patients (commercial, adjusted IRR [95% CI]: 0.67 [0.67 to 0.67] and 0.66 [0.66 to 0.66]; Medicare supplemental: 0.83 [0.81 to 0.84] and 0.81 [0.79 to 0.82]). In the commercial population, nonadherent and nonpersistent patients had fewer physician office visits, whereas mean physician office visits were not significantly different between nonadherent/adherent and nonpersistent/persistent patients in the Medicare supplemental population (Table 2).

ALL-CAUSE HEALTH CARE COSTS

Nonadherent and nonpersistent patients in the commercial and Medicare supplemental populations incurred significantly higher adjusted mean medical, inpatient, and ER costs and significantly lower adjusted mean pharmacy costs (Table 3). Nonadherence to antidepressants in the commercial/Medicare supplemental populations were associated with \$568 (95% CI: \$354 to \$764)/\$1,621 (\$314 to \$2,774) higher medical costs; \$650 (\$490 to \$801)/\$1,546 (\$705 to

FIGURE 2 Study Identification Flowchart ^aMDD ICD-9-CM codes: 296.20-296.24, 296.30-296.34, 300.4, 311; ICD-10-CM codes: F32.0-F32.3, F32.9, F33.0-F33.3, F33.9, F34.1^bExclusion diagnoses at any time during the study period included ICD-9-CM or ICD-10-CM codes for bipolar disorder/manic disorder, other mood disorders, Alzheimer disease, Parkinson disease, dementia, or evidence of pregnancy/childbirth/breastfeeding. Exclusion diagnoses during the baseline period included ICD-9-CM or ICD-10-CM codes for schizophrenia/schizophrenic disorders, psychosis-related disorders, drug-induced depression, and depressive type psychosis ([Supplementary Table 1](#), available in online article).

ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM=International Classification of Diseases, Tenth Revision, Clinical Modification; MDD=major depressive disorder.

TABLE 1 Demographic and Clinical Characteristics

Characteristic	Commercial					
	All Patients (N = 209,422)		Adherent (n = 108,777)		Nonadherent (n = 100,645)	
Age, mean [SD], years	40.1	[13.5]	41.0	[13.4]	39.1	[13.6] ^a
Female, n (%)	127,987	(61.1)	67,670	(62.2)	60,317	(59.9) ^a
Plan type, n (%) ^d						
Comprehensive	5,810	(2.8)	2,925	(2.7)	2,885	(2.9)
EPO	1,813	(0.9)	920	(0.9)	893	(0.9)
HMO	27,611	(13.2)	13,956	(12.8)	13,655	(13.6)
POS	14,524	(6.9)	7,279	(6.7)	7,245	(7.2)
PPO	123,545	(59.0)	64,293	(59.1)	59,252	(58.9)
POS with capitation	1,225	(0.6)	583	(0.5)	642	(0.6)
CDHP	20,685	(9.9)	10,921	(10.0)	9,764	(9.7)
HDHP	11,763	(5.6)	6,599	(6.1)	5,164	(5.1)
Unknown	2,446	(1.2)	1,301	(1.2)	1,145	(1.1)
Quan-CCI, mean [SD]	0.29	[0.88]	0.29	[0.88]	0.29	[0.89]
Quan-CCI, n (%) ^d						
0	175,366	(83.7)	91,166	(83.8)	84,200	(83.7)
1	20,569	(9.8)	10,528	(9.7)	10,041	(10.0)
2	8,698	(4.2)	4,673	(4.3)	4,025	(4.0)
3+	4,789	(2.3)	2,410	(2.2)	2,379	(2.4)
Comorbidities, n (%)						
Anxiety	38,125	(18.2)	18,685	(17.2)	19,440	(19.3) ^a
Alcohol disorder	5,081	(2.4)	2,091	(1.9)	2,990	(3.0) ^a
Substance use disorder	15,067	(7.2)	6,338	(5.8)	8,729	(8.7) ^a
Sleep disorders	16,081	(7.7)	8,461	(7.8)	7,620	(7.6)
Coronary heart disease	5,353	(2.6)	2,790	(2.6)	2,563	(2.6)
Congestive heart failure	1,896	(0.9)	998	(0.9)	898	(0.9)
Chronic pulmonary disease	19,496	(9.3)	9,914	(9.1)	9,582	(9.5) ^b
Diabetes	14,750	(7.0)	7,610	(7.0)	7,140	(7.1)
Geographic region, n (%) ^d						
Northeast	30,834	(14.7)	16,756	(15.4)	14,078	(14.0)
North Central	52,427	(25.0)	27,966	(25.7)	24,461	(24.3)
South	80,995	(38.7)	40,699	(37.4)	40,296	(40.0)
West	43,269	(20.7)	22,458	(20.7)	20,811	(20.7)
Unknown/N/A	1,897	(0.9)	898	(0.8)	999	(1.0)
Index antidepressant, n (%) ^d						
SSRI	153,244	(73.2)	80,389	(73.9)	72,855	(72.4)
SNRI	19,707	(9.4)	10,718	(9.9)	8,989	(8.9)
TCA	2,062	(1.0)	615	(0.6)	1,447	(1.4)
MAOI	17	(<0.1)	7	(<0.1)	10	(<0.1)
Other ^e	34,392	(16.4)	17,048	(15.7)	17,344	(17.2)

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TABLE 1 Demographic and Clinical Characteristics (*continued*)

Characteristic	Commercial				
	All Patients (N=209,422)	Adherent (n=108,777)	Nonadherent (n=100,645)	Persistent (n=105,919)	Nonpersistent (n=103,503)
12-month baseline all-cause health care costs, mean, 2019 USD^f					
Included patients, n (%)	171,648 (82.0)	89,467 (82.2)	82,181 (81.7)	87,095 (82.2)	84,553 (81.7)
Total health care [SD]	9,205 [31,030]	9,238 [30,246]	9,169 [31,862]	9,217 [30,153]	9,194 [31,908]
Total patient out-of-pocket [SD]	1,199 [1,785]	1,202 [1,723]	1,196 [1,850]	1,202 [1,724]	1,196 [1,846]
Characteristic	Medicare Supplemental				
	All Patients (N=15,223)	Adherent (n=7,648)	Nonadherent (n=7,575)	Persistent (n=7,333)	Nonpersistent (n=7,890)
Age, mean [SD], years	74.6 [7.6]	74.4 [7.4]	74.8 [7.7] ^a	74.4 [7.4]	74.8 [7.7] ^a
Female, n (%)	9,476 (62.3)	4,692 (61.4)	4,784 (63.2) ^c	4,477 (61.1)	4,999 (63.4) ^b
Plan type, n (%)^d					
Comprehensive	6,739 (44.3)	3,396 (44.4)	3,343 (44.1)	3,241 (44.2)	3,498 (44.3)
EPO	13 (0.1)	9 (0.1)	4 (0.1)	8 (0.1)	5 (0.1)
HMO	2,006 (13.2)	1,047 (13.7)	959 (12.7)	1,012 (13.8)	994 (12.6)
POS	523 (3.4)	277 (3.6)	246 (3.3)	277 (3.8)	246 (3.1)
PPO	5,560 (36.5)	2,715 (35.5)	2,845 (37.6)	2,598 (35.4)	2,962 (37.5)
POS with capitation	190 (1.3)	93 (1.2)	97 (1.3)	93 (1.3)	97 (1.2)
CDHP	44 (0.3)	26 (0.3)	18 (0.2)	22 (0.3)	22 (0.3)
HDHP	17 (0.1)	9 (0.1)	8 (0.1)	7 (0.1)	10 (0.1)
Unknown	131 (0.9)	76 (1.0)	55 (0.7)	75 (1.0)	56 (0.7)
Quan-CCI, mean [SD]	1.31 [1.90]	1.30 [1.90]	1.31 [1.90]	1.31 [1.90]	1.31 [1.90]
Quan-CCI, n (%)^d					
0	7,314 (48.1)	3,738 (48.9)	3,576 (47.2)	3,570 (48.7)	3,744 (47.5)
1	2,854 (18.8)	1,356 (17.7)	1,498 (19.8)	1,319 (18.0)	1,535 (19.5)
2	2,288 (15.0)	1,147 (15.0)	1,141 (15.1)	1,074 (14.7)	1,214 (15.4)
3+	2,767 (18.2)	1,407 (18.4)	1,360 (18.0)	1,370 (18.7)	1,397 (17.7)
Comorbidities, n (%)					
Anxiety	2,690 (17.7)	1,227 (16.0)	1,463 (19.3) ^a	1,185 (16.2)	1,505 (19.1) ^a
Alcohol disorder	307 (2.0)	127 (1.7)	180 (2.4) ^b	123 (1.7)	184 (2.3) ^b
Substance use disorder	1,020 (6.7)	452 (5.9)	568 (7.5) ^a	439 (6.0)	581 (7.4) ^a
Sleep disorders	1,883 (12.4)	926 (12.1)	957 (12.6)	899 (12.3)	984 (12.5)
Coronary heart disease	3,816 (25.1)	1,882 (24.6)	1,934 (25.5)	1,801 (24.6)	2,015 (25.5)
Congestive heart failure	1,792 (11.8)	907 (11.9)	885 (11.7)	888 (12.1)	904 (11.5)
Chronic pulmonary disease	3,697 (24.3)	1,766 (23.1)	1,931 (25.5) ^a	1,717 (23.4)	1,980 (25.1) ^c
Diabetes	3,893 (25.6)	1,987 (26.0)	1,906 (25.2)	1,925 (26.3)	1,968 (24.9)

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TABLE 1 Demographic and Clinical Characteristics (continued)

Characteristic	Medicare Supplemental				
	All Patients (N = 15,223)	Adherent (n = 7,648)	Nonadherent (n = 7,575)	Persistent (n = 7,333)	Nonpersistent (n = 7,890)
Geographic region, n (%)^d					
Northeast	2,768 (18.2)	1,487 (19.4)	1,281 (16.9)	1,425 (19.4)	1,343 (17.0)
North Central	5,463 (35.9)	2,565 (33.5)	2,898 (38.3)	2,479 (33.8)	2,984 (37.8)
South	4,205 (27.6)	2,148 (28.1)	2,057 (27.2)	2,061 (28.1)	2,144 (27.2)
West	2,752 (18.1)	1,433 (18.7)	1,319 (17.4)	1,354 (18.5)	1,398 (17.7)
Unknown/N/A	35 (0.2)	15 (0.2)	20 (0.3)	14 (0.2)	21 (0.3)
Index antidepressant, n (%)^d					
SSRI	11,299 (74.2)	5,867 (76.7)	5,432 (71.7)	5,635 (76.8)	5,664 (71.8)
SNRI	1,448 (9.5)	694 (9.1)	754 (10.0)	673 (9.2)	775 (9.8)
TCA	194 (1.3)	72 (0.9)	122 (1.6)	66 (0.9)	128 (1.6)
MAOI	0	0	0	0	0
Other ^e	2,282 (15.0)	1,015 (13.3)	1,267 (16.7)	959 (13.1)	1,323 (16.8)
12-month baseline all-cause health care costs, mean, 2019 USD^f					
Included patients, n (%)	12,894 (84.7)	6,428 (84.0)	6,466 (85.4)	6,151 (83.9)	6,743 (85.5)
Total health care [SD]	28,153 [60,947]	28,653 [62,055]	27,655 [59,826]	28,925 [61,875]	27,448 [60,084]
Total patient out-of-pocket [SD]	1,273 [1,174]	1,289 [1,275]	1,258 [1,064]	1,294 [1,271]	1,254 [1,078]

Note: P values were calculated using chi-square tests for categorical values and t-tests for continuous values.
^aP < 0.001 for comparison of nonadherent versus adherent patients or nonpersistent versus persistent patients.
^bP < 0.01 for comparison of nonadherent versus adherent patients or nonpersistent versus persistent patients.
^cP < 0.05 for comparison of nonadherent versus adherent patients or nonpersistent versus persistent patients.
^dP < 0.05 for overall distribution of nonadherent versus adherent patients or nonpersistent versus persistent patients across all categories.
^eOther antidepressants include bupropion, mirtazapine, nefazodone, and trazodone.
^fCosts were adjusted to 2019 USD. Patients with any evidence of capitated claims or negative costs in any cost subcategory were excluded from cost analyses. Patient out-of-pocket costs represent sum of deductibles, copays, and coinsurance.
CDHP = consumer-driven health plan; EPO = exclusive provider organization; FFS = fee-for-service; HDHP = high-deductible health plan; HMO = health maintenance organization; MAOI = monoamine oxidase inhibitor; MDD = major depressive disorder; N/A = not applicable; POS = point of service; PPO = preferred provider organization; Quan-CCI = Quan-Charlson Comorbidity Index; SNRI = selective norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; USD = U.S. dollars.

\$2,308) higher inpatient costs; \$130 (\$115 to \$143)/\$82 (\$23 to \$150) higher ER costs; and \$561 (–\$601 to –\$521)/\$510 (–\$747 to –\$227) lower pharmacy costs (Table 3). Similarly, incremental mean (95% CI) medical, inpatient, ER, and pharmacy costs associated with nonpersistence in the commercial/Medicare supplemental populations were \$491 (\$284 to \$703)/\$1,764 (\$451 to \$2,925), \$564 (\$417 to \$716)/\$1,567 (\$778 to \$2,331), \$129 (\$115 to \$142)/\$80 (\$18 to \$150), and –\$576 (–\$617 to –\$540)/–\$596 (–\$830 to –\$325), respectively. Adjusted outpatient and total health care costs were not significantly different between nonadherent/adherent and nonpersistent/persistent patients in both the commercial and Medicare supplemental populations (Table 3).

Discussion

This large retrospective U.S. administrative claims database study assessed the effect of nonadherence and nonpersistence to antidepressants on 12-month all-cause HCRU and costs among adult patients with MDD who initiated antidepressant therapy for a new MDD episode. Consistent with previous studies, adherence and persistence to antidepressants at 6 months were poor among both commercially insured patients and Medicare beneficiaries with Medicare supplemental insurance, with only approximately 50% of patients remaining adherent or persistent to antidepressants at 6 months.

TABLE 2 12-Month All-Cause Health Care Resource Utilization

Commercial Population						
	Adherent (n=108,777)	Nonadherent (n=100,645)	Incidence Rate Ratio (95% CI)	Persistent (n=105,919)	Nonpersistent (n=103,503)	Incidence Rate Ratio (95% CI)
Unadjusted HCRU, mean [SD]						
Inpatient hospitalizations	0.08 [0.39]	0.11 [0.50] ^a	1.36 (1.31 to 1.41)	0.08 [0.40]	0.11 [0.48] ^a	1.33 (1.28 to 1.38)
Emergency room	0.29 [0.83]	0.42 [1.20] ^a	1.45 (1.42 to 1.48)	0.29 [0.84]	0.42 [1.19] ^a	1.44 (1.41 to 1.47)
Outpatient (all)	19.39 [18.48]	17.22 [17.95] ^a	0.89 (0.88 to 0.89)	19.46 [18.58]	17.21 [17.85] ^a	0.88 (0.88 to 0.89)
Physician office	14.45 [13.52]	12.21 [12.18] ^a	0.85 (0.84 to 0.85)	14.51 [13.56]	12.22 [12.17] ^a	0.84 (0.84 to 0.85)
Other	4.94 [9.98]	5.01 [10.73]	1.01 (1.00 to 1.03)	4.96 [10.10]	4.99 [10.59]	1.01 (1.00 to 1.02)
Pharmacy	27.22 [19.60]	18.30 [17.15] ^a	0.67 (0.67 to 0.68)	27.57 [19.64]	18.19 [17.05] ^a	0.66 (0.66 to 0.66)
Adjusted HCRU, mean^c						
Inpatient hospitalizations	0.07	0.10 ^a	1.34 (1.29 to 1.39)	0.07	0.10 ^a	1.32 (1.27 to 1.36)
Emergency room	0.28	0.40 ^a	1.43 (1.40 to 1.45)	0.28	0.40 ^a	1.41 (1.38 to 1.44)
Outpatient (all)	19.21	17.14 ^a	0.89 (0.89 to 0.90)	19.27	17.13 ^a	0.89 (0.88 to 0.90)
Physician office	14.51	12.35 ^a	0.85 (0.85 to 0.86)	14.55	12.36 ^a	0.85 (0.84 to 0.86)
Other	4.51	4.65 ^a	1.03 (1.02 to 1.04)	4.52	4.64 ^a	1.03 (1.01 to 1.04)
Pharmacy	25.73	17.24 ^a	0.67 (0.67 to 0.67)	26.03	17.15 ^a	0.66 (0.66 to 0.66)
Medicare Supplemental Population						
	Adherent (n=7,648)	Nonadherent (n=7,575)	Incidence Rate Ratio (95% CI)	Persistent (n=7,333)	Nonpersistent (n=7,890)	Incidence Rate Ratio (95% CI)
Unadjusted HCRU, mean [SD]						
Inpatient hospitalizations	0.28 [0.63]	0.34 [0.78] ^a	1.21 (1.13 to 1.29)	0.29 [0.64]	0.34 [0.77] ^a	1.17 (1.09 to 1.26)
Emergency room	0.53 [1.10]	0.68 [1.37] ^a	1.29 (1.21 to 1.37)	0.53 [1.09]	0.68 [1.36] ^a	1.28 (1.21 to 1.36)
Outpatient (all)	30.61 [27.31]	31.40 [28.00]	1.03 (1.00 to 1.05)	30.87 [27.63]	31.13 [27.68]	1.01 (0.98 to 1.03)
Physician office	17.29 [15.03]	16.86 [14.04]	0.97 (0.95 to 1.00)	17.34 [15.09]	16.83 [14.03] ^b	0.97 (0.95 to 1.00)
Other	13.31 [21.48]	14.55 [22.61] ^a	1.09 (1.05 to 1.14)	13.53 [21.88]	14.30 [22.21] ^b	1.06 (1.02 to 1.10)
Pharmacy	43.30 [27.27]	35.86 [24.84] ^a	0.83 (0.81 to 0.84)	43.95 [27.52]	35.55 [24.53] ^a	0.81 (0.79 to 0.82)
Adjusted HCRU, mean^c						
Inpatient hospitalizations	0.26	0.31 ^a	1.19 (1.12 to 1.28)	0.26	0.31 ^a	1.18 (1.10 to 1.26)
Emergency room	0.51	0.65 ^a	1.28 (1.21 to 1.36)	0.50	0.65 ^a	1.28 (1.21 to 1.36)
Outpatient (all)	30.13	30.82 ^c	1.02 (1.00 to 1.05)	30.33	30.61	1.01 (0.99 to 1.03)
Physician office	17.09	16.92	0.99 (0.97 to 1.02)	17.16	16.86	0.98 (0.96 to 1.01)
Other	12.02	13.12 ^a	1.09 (1.05 to 1.13)	12.12	12.98 ^a	1.07 (1.03 to 1.11)
Pharmacy	43.46	35.87 ^a	0.83 (0.81 to 0.84)	44.05	35.60 ^a	0.81 (0.79 to 0.82)

Note: P values for unadjusted HCRU comparisons were calculated using chi-square tests for categorical variables and t-tests for means of continuous values. Adjusted mean HCRU estimates and IRRs were calculated using multivariable negative binomial regression adjusted for age, sex, plan type, geographic region, index year, Quan-CCI, index antidepressant class, and baseline 12-month total all-cause health care costs. IRRs reflect comparison of nonadherent versus adherent patients and nonpersistent versus persistent patients.

^aP<0.001 for comparison of nonadherent versus adherent patients or nonpersistent versus persistent patients.

^bP<0.05 for comparison of nonadherent versus adherent patients or nonpersistent versus persistent patients.

^c17 patients in the commercial population (<0.0001%) and 3 patients in the Medicare population (<0.001%) with negative baseline costs were excluded from multivariable negative binomial models due to convergence issues.

HCRU=health care resource utilization; IRR=incidence rate ratio; PPPY=per patient per year; Quan-CCI=Quan Charlson Comorbidity Index.

TABLE 3 12-Month All-Cause Health Care Costs Following Index Antidepressant

Commercial Population						
	Adherent (n = 89,468)	Nonadherent (n = 82,145)	Incremental Difference (95% CI)	Persistent (n = 87,096)	Nonpersistent (n = 84,517)	Incremental Difference (95% CI)
Unadjusted health care costs, mean [SD], 2019 USD						
Total	10,875 [28,306]	11,058 [36,362]	183 (–127 to 493)	10,938 [28,551]	10,988 [35,961]	50 (–258 to 358)
Medical	8,466 [25,853]	9,264 [34,414] ^a	798 (508 to 1,088)	8,511 [26,029]	9,196 [34,067] ^a	685 (397 to 972)
Inpatient	1,868 [15,120]	2,566 [23,067] ^a	699 (512 to 885)	1,907 [15,337]	2,506 [22,734] ^a	599 (415 to 783)
Emergency room	332 [1,311]	470 [1,784] ^a	138 (123 to 153)	329 [1,302]	469 [1,779] ^a	139 (125 to 154)
Outpatient (all)	6,267 [17,005]	6,228 [19,864]	–39 (–214 to 137)	6,274 [16,959]	6,221 [19,830]	–54 (–228 to 121)
Physician office	2,406 [4,975]	2,098 [4,624] ^a	–309 (–354 to –263)	2,411 [4,942]	2,102 [4,670] ^a	–309 (–355 to –264)
Other	3,860 [15,306]	4,130 [18,526] ^b	270 (109 to 432)	3,864 [15,321]	4,119 [18,431] ^b	256 (95 to 416)
Pharmacy	2,408 [8,295]	1,794 [8,617] ^a	–615 (–695 to –534)	2,427 [8,310]	1,792 [8,593] ^a	–635 (–715 to –555)
Adjusted health care costs, mean, 2019 USD						
Total	9,026	9,030	4 (–204 to 216)	9,072	8,982	–89 (–303 to 144)
Medical	7,059	7,627	568 (354 to 764)	7,089	7,580	491 (284 to 703)
Inpatient	1,633	2,283	650 (490 to 801)	1,666	2,230	564 (417 to 716)
Emergency room	310	440	130 (115 to 143)	309	438	129 (115 to 142)
Outpatient (all)	5,415	5,389	–26 (–130 to 79)	5,429	5,376	–52 (–161 to 57)
Physician office	2,347	2,090	–257 (–289 to –220)	2,355	2,090	–265 (–295 to –225)
Other	3,356	3,642	286 (183 to 387)	3,362	3,629	267 (166 to 374)
Pharmacy	1,930	1,370	–561 (–601 to –521)	1,947	1,371	–576 (–617 to –540)

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Our findings support and extend previous work on the association between nonadherence and nonpersistence to antidepressants and all-cause HCRU and costs in patients with MDD. Similar to previous studies, our study found greater all-cause inpatient hospitalizations and ER use among nonadherent and nonpersistent patients compared with adherent and persistent patients, respectively.^{7,8,27} Also consistent with previous research,^{8,9,25,26,28} nonadherence and nonpersistence were associated with significantly higher adjusted medical costs in both the commercial and Medicare supplemental populations, which were largely driven by approximately 20%–40% higher inpatient hospitalization and ER costs among nonadherent and nonpersistent patients. Given the association between nonremission and poor depression treatment outcomes, the higher medical costs and rates of hospitalizations and ER visits among antidepressant nonadherent and nonpersistent patients may, in part, reflect higher rates of nonremission among these patients.

Of note, Medicare supplemental patients who were nonadherent and nonpersistent to antidepressants incurred

the highest HCRU and health care costs. Compared with younger patients, older adults with depression are more likely to experience higher comorbidity burden,⁴⁴ which was similarly reflected in our study; Medicare supplemental patients with MDD in our study had a markedly higher prevalence of comorbid coronary heart disease, congestive heart failure, chronic pulmonary disease, and diabetes. There is also evidence that older patients with MDD have a poorer depression prognosis compared with younger patients with MDD.⁴⁴ These factors may therefore contribute to higher health care spending compared with younger, healthier patients with depression.

Total health care costs were not significantly different between nonadherent/adherent and nonpersistent/persistent patients in this study, as medical cost savings due to reductions in HCRU among adherent and persistent patients may not sufficiently offset the higher pharmacy costs due to improved antidepressant adherence and persistence in the short term. It is plausible that the potential benefits of improved antidepressant adherence and persistence may not be fully realized in the short term, as various

TABLE 3 12-Month All-Cause Health Care Costs Following Index Antidepressant (*continued*)

Medicare Supplemental Population						
	Adherent (n=6,430)	Nonadherent (n=6,466)	Incremental Difference (95% CI)	Persistent (n=6,153)	Nonpersistent (n=6,743)	Incremental Difference (95% CI)
Unadjusted health care costs, mean [SD], 2019 USD						
Total	26,242 [62,525]	26,867 [62,200]	625 (–1,528 to 2,778)	26,133 [61,547]	26,940 [63,096]	807 (–1,346 to 2,959)
Medical	21,538 [60,632]	22,745 [60,465]	1,207 (–884 to 3,297)	21,372 [59,602]	22,848 [61,396]	1,476 (–614 to 3,565)
Inpatient	6,531 [26,473]	7,913 [30,041] ^b	1,383 (405 to 2,360)	6,625 [29,071]	7,770 [27,619] ^c	1,146 (165 to 2,127)
Emergency room	612 [3,164]	665 [3,165]	53 (–56 to 162)	616 [3,208]	659 [3,124]	43 (–66 to 153)
Outpatient (all)	14,396 [46,664]	14,167 [44,025]	–229 (–1,795 to 1,337)	14,131 [43,389]	14,418 [47,087]	287 (–1,275 to 1,848)
Physician office	4,071 [9,455]	3,642 [7,717] ^b	–429 (–727 to –131)	4,092 [9,552]	3,639 [7,688] ^b	–453 (–754 to –152)
Other	10,325 [44,036]	10,525 [42,447]	200 (–1,293 to 1,693)	10,039 [40,524]	10,778 [45,587]	740 (–747 to 2,226)
Pharmacy	4,703 [9,873]	4,121 [9,825] ^a	–58 (–922 to –242)	4,761 [9,752]	4,092 [9,933] ^a	–669 (–1,009 to –329)
Adjusted health care costs, mean, 2019 USD						
Total	23,304	24,309	1,005 (–414 to 2,237)	23,226	24,320	1,094 (–305 to 2,327)
Medical	18,625	20,246	1,621 (314 to 2,774)	18,494	20,258	1,764 (451 to 2,925)
Inpatient	6,361	7,907	1,546 (705 to 2,308)	6,309	7,876	1,567 (778 to 2,331)
Emergency room	471	553	82 (23 to 150)	470	550	80 (18 to 150)
Outpatient (all)	12,177	12,300	123 (–709 to 930)	12,084	12,370	286 (–476 to 1,009)
Physician office	3,824	3,720	–104 (–311 to 109)	3,841	3,710	–131 (–335 to 71)
Other	8,783	8,983	200 (–568 to 973)	8,654	9,078	424 (–370 to 1,161)
Pharmacy	4,494	3,985	–510 (–747 to –227)	4,546	3,951	–596 (–830 to –325)

Note: Costs were adjusted to 2019 USD. Patients with any evidence of capitated claims or negative total costs in any cost subcategory were excluded from cost analyses. Unadjusted cost differences were determined using 2-sample t-tests with unequal variances, and adjusted incremental cost differences were calculated using multivariable 2-part models (logistic regression followed by generalized linear models with log-link and gamma distribution) adjusted for age, sex, plan type, geographic region, index year, Quan-CCI, index antidepressant class, and baseline 12-month total all-cause health care costs. Significance of adjusted incremental cost differences based on 95% CIs obtained via nonparametric bootstrapping procedure (N=500).

^aP<0.001 for comparison of nonadherent versus adherent patients or nonpersistent versus persistent patients.

^bP<0.01 for comparison of nonadherent versus adherent patients or nonpersistent versus persistent patients.

^cP<0.05 for comparison of nonadherent versus adherent patients or nonpersistent versus persistent patients.

Quan-CCI=Charlson Comorbidity Index; USD=U.S. dollar.

real-world observational studies have found a significantly lower risk of relapse or recurrence (e.g., evidence of mental health-related ER visit, psychiatric hospitalization, suicide attempt, evidence of electroconvulsive therapy (ECT), or re-initiation of MDD pharmacotherapy after a gap of 6 months) over follow-up periods of up to 2 years among patients who were adherent to antidepressants during the first 6 months of treatment compared with those who were nonadherent to antidepressants.^{21–23} Furthermore, adherence and persistence to antidepressant therapy for MDD are associated with better medication adherence and improved clinical outcomes for comorbid conditions, including diabetes, chronic obstructive pulmonary disease, and cardiovascular disease.^{9,24,26,45} Similarly, the effect of improved antidepressant adherence and persistence on

other comorbid conditions may be associated with longer-term cost savings.

Overall, the high rates of antidepressant nonadherence and nonpersistence in our study, which were associated with greater all-cause hospitalizations and ER use, suggest inadequate depression treatment for a large proportion of patients with MDD and, therefore, highlight a continued need for effective strategies to improve antidepressant adherence and persistence, which may improve outcomes and reduce the health care burden associated with MDD. Interventions to improve antidepressant adherence and persistence may have important implications for health systems and managed care organizations, given the potential cost savings attributable to improved depression treatment outcomes,^{16,17,19} as well as continued efforts to incentivize

quality depression care in health care organizations.⁴⁶⁻⁴⁸ Such efforts are evidenced by the continued adoption of NCQA HEDIS AMM measures for effective acute and continuation phase antidepressant treatment in provider pay-for-performance initiatives and merit-based incentive programs,⁴⁶ as well as the emergence of the NCQA HEDIS Depression Remission or Response outcomes measures, which evaluate the percentage of health plan members achieving treatment response and remission,⁴⁹ in various value-based payment arrangements.^{47,50} Previous research has highlighted the clinical and economic benefits of interventions aimed at improving the quality of depression care in diverse practice settings, including collaborative care programs⁵¹⁻⁵⁵ and psychosocial interventions,^{56,57} which have been found to improve antidepressant adherence and longer-term depression outcomes.^{53,54} In the context of continued industry efforts to improve the quality of depression care, these findings therefore underscore the contemporary importance of strategies that promote better antidepressant adherence and persistence to improve depression care, and various measures, such as pay-for-performance initiatives, expansion of mental health benefits, and coverage of disease management and collaborative care programs, have been suggested as effective strategies to improve antidepressant adherence/persistence and depression treatment.^{13,48,55,58,59}

LIMITATIONS

Several limitations of this study should be noted. First, the calculation of adherence and persistence to antidepressants was based on pharmacy claims data, which do not confirm whether patients consumed their medication. The PDC and persistence calculations used in this study also did not account for the effect of hospitalization on adherence and persistence estimates.⁶⁰

Second, as with other retrospective claims database studies, this study is subject to limitations inherent to administrative claims databases, including data coding errors, omissions, and misclassification.

Third, this study did not consider indirect costs such as absenteeism or presenteeism costs, which have been found to be substantial in MDD and estimated to account for up to 50% of the economic burden of MDD in the United States.³ Burton et al. (2007) found that employees who were nonadherent to acute and continuation phase antidepressant therapy were 39%-46% more likely to have short-term disability claims compared with adherent employees.⁶¹ Therefore, the costs associated with nonadherence and nonpersistence to antidepressants are likely underestimated in this study.

Fourth, although various baseline characteristics were adjusted for in multivariable analyses, additional factors that may contribute to adherence, persistence, HCRU, and health care costs in MDD, such as depression severity,^{13,62} prescriber specialty,^{63,64} specific treatment patterns (e.g., combination antidepressant therapy, augmentation therapy, switching, dose escalation),^{28,29,34,65-67} or other clinical characteristics, were not assessed or adequately captured and, therefore, could not be controlled for. For example, patients who require treatment switches, dose escalation, combination antidepressant therapy, or augmentation therapy may represent more complex, difficult-to-treat patients, regardless of adherence or persistence.

Finally, the study population was limited to adult patients with MDD who initiated antidepressant therapy for a new MDD episode and were enrolled in commercial and Medicare supplemental insurance plans. Therefore, these findings may not be generalizable to patients with MDD who have different characteristics from our study population, including patients with treatment-resistant depression, patients with insurance coverage outside of commercial or Medicare supplemental insurance plans, and uninsured individuals.

Despite these limitations, there are several strengths of this study. First, this study provides a comprehensive update to the existing literature on the economic effect of antidepressant nonadherence and nonpersistence in MDD; to our knowledge, this study is the largest real-world observational study to assess the association between antidepressant nonadherence and nonpersistence and HCRU and costs in adult MDD patients to date, with more than 200,000 adult patients with MDD included in this study. Our patient population was representative of patients with MDD from diverse geographic regions across the United States and enrolled in various insurance plans (i.e., commercial and Medicare supplemental insurance plans) and plan types (i.e., capitated and noncapitated plans). Additionally, our study includes newer antidepressants that have been introduced since 2010, so this study serves to provide a contemporary update on the current landscape of MDD medication adherence and persistence and their effect on HCRU and costs in patients with MDD.

Conclusions

The results of our study suggest that greater hospitalization and ER use and total medical costs are incurred among patients who are nonadherent and nonpersistent to antidepressant therapy compared with those who are adherent and persistent, which was observed in both the commercial and Medicare supplemental populations. Higher medical

costs were largely driven by significantly higher inpatient hospitalization and ER costs among nonadherent and nonpersistent patients. Although clinical guidelines emphasize the importance of adherence and persistence to achieve remission and prevent depressive relapse and recurrence, adherence and persistence to existing MDD treatments remain suboptimal. The low rates of antidepressant adherence and persistence observed in this study reflect a continued unmet need for effective strategies that promote better adherence and persistence, which may increase the likelihood of achieving long-term recovery from depression and reduce the health care burden associated with MDD.

DISCLOSURES

This study was sponsored by Allergan, which was involved in the study design; data collection, analysis, and interpretation of data; and decision to present these results. Ta was supported by a training grant provided to the University of Washington by Allergan at the time this study was conducted. Tung and Gillard are employees of Allergan. Oliveri is an employee of Genesis Research. Sullivan and Devine have no financial disclosures.

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