

Off-Label Use of Antipsychotic Medications in Medicaid

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Antipsychotic medications have long been an important component of effective treatment for schizophrenia. They also make up a large and growing share of Medicaid prescription drug programs, which covered nearly 75% of all prescriptions for antipsychotic medications in the United States in 2002,¹ although since 2006 the public share of financing for antipsychotic medications has been roughly equally divided between Medicaid and Medicare.² In addition to schizophrenia, most second-generation antipsychotics have also been approved to treat bipolar disorder. More recently, the Food and Drug Administration (FDA) approved aripiprazole (in 2007) and olanzapine (in 2009) for the adjunctive treatment of major depressive disorder and risperidone (in 2006) and aripiprazole (in 2009) for irritability in children and adolescents with autism. However, once a drug has been approved by the FDA, clinicians are free to prescribe it as they see fit. Because there often is not the same level of high-quality clinical research demonstrating the safety and efficacy of these drugs for non-FDA-approved indications, the benefits of such off-label use are usually unclear. Given that these drugs are expensive and have serious side effects (including weight gain, diabetes mellitus, tardive dyskinesia, and extrapyramidal symptoms), their off-label use may represent significant risk and cost with undemonstrated clinical benefit.

Several previous studies have investigated off-label use of antipsychotic medications.^{3,4} A recent study using data from the US Department of Veterans Affairs (VA) found that 60.2% of veterans who had a prescription for an antipsychotic medication in fiscal year 2007 did not have a diagnosis of either schizophrenia or bipolar disorder in the same year.⁵ Two reports by the Agency for Healthcare Research and Quality (AHRQ) found that off-label use of second-generation antipsychotics is common, especially in the treatment of agitation in dementia, depression, obsessive-compulsive disorder, posttraumatic stress disorder (PTSD), personality disorders, Tourette's syndrome, and autism; however, there was moderate to strong evidence of efficacy in the literature for only a few of the drugs and for only a small number of the off-label indications.^{6,7} Another study by Walton and colleagues⁸ found that several of the second-generation antipsychotics (quetiapine, risperidone, and

olanzapine) had a high rate of off-label prescribing in the absence of good evidence of effectiveness.

Medicaid is the primary payer for patients with schizophrenia

Objectives: To determine how often antipsychotics are prescribed off-label to adults without schizophrenia or bipolar disorder who are enrolled in Medicaid, which pays for more than 70% of antipsychotic prescriptions in the United States.

Study Design: Retrospective analysis of 2003 administrative data from 42 state Medicaid programs.

Methods: Continuously enrolled patients with at least 1 prescription for an antipsychotic medication were identified. For these patients, inpatient and outpatient records were checked for any diagnosis of schizophrenia or bipolar disorder; those without any such diagnoses were considered to have received these medications off-label. Off-label antipsychotic use was compared across sociodemographic groups (age, race/ethnicity, sex). Multivariate logistic regression models identified characteristics associated with off-label use.

Results: Of the 372,038 individuals given an antipsychotic medication, 214,113 (57.6%) received these agents for off-label disorders. Off-label use among patients receiving an antipsychotic was more prevalent among individuals under age 21 years (75.9%) and those 65 years and older (64.8%) than it was among those aged 21 to 64 years (49.0%). Rates of off-label use were relatively high for Hispanics (65.7%) and low for African Americans (52.3%) compared with whites (58.2%). Off-label use was most common among patients receiving risperidone and least common among patients receiving clozapine.

Conclusions: Off-label use of antipsychotic medications is common, particularly among the elderly and children/adolescents. Given that these drugs are expensive, have potentially severe side effects, and have limited evidence supporting their effectiveness off-label, they should perhaps be used with greater caution.

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Take-Away Points

This study documented rates of off-label use of antipsychotic medications in 42 state Medicaid programs in 2003.

- 57.6% of patients given an antipsychotic had no diagnoses of schizophrenia or bipolar disorder during the year.
- Rates of off-label use were higher among children/adolescents and the elderly, among patients given risperidone, and among those diagnosed with depression.
- Given healthcare reform and widespread crisis in state revenues, state Medicaid programs will be under pressure to serve larger patient populations, increasing their fiscal stress. Reducing off-label antipsychotic use may generate savings with little impact on patient outcomes.

in the United States, with over a third of individuals with schizophrenia receiving their care through state Medicaid programs.⁹ Hence, antipsychotic medications make up a considerable share of Medicaid prescriptions and pharmacy budgets.^{1,2,10} It is unknown, however, how much of antipsychotic use in Medicaid is off-label. The objective of the current study was to determine the prevalence of off-label use of antipsychotic medications in state Medicaid plans and to explore patient sociodemographic and clinical characteristics associated with off-label use of these drugs.

METHODS

Sources of Data

Medicaid Analytic eXtract (MAX) data for 2003 were obtained from the Centers for Medicare & Medicaid Services (CMS) for 42 states. MAX files were developed by CMS to support research and policy analysis on Medicaid populations. MAX files include person-level data with information on Medicaid eligibility, service utilization, and payments. They are organized into 5 files: a Personal Summary File (which contains enrollment information) and 4 claims files (Inpatient, Other Therapy, Long Term Care, and Prescription Drug). The claims files represent final action claims, and have undergone extensive edit checks.

The states studied include the District of Columbia and all but the following 9 states: Colorado, Delaware, Michigan, Montana, North Dakota, South Dakota, Tennessee, Utah, and Washington. These states were excluded because they had a relatively high proportion of managed care enrollees during the study period. Medicaid claims information for managed care enrollees is typically not as complete as that for fee-for-service enrollees.¹¹

The study was approved by the Institutional Review Board of the Penn State College of Medicine.

Measures

First, all Medicaid patients who were continuously enrolled for the entire year in a fee-for-service plan and who

were not dually enrolled in Medicare were identified. For these patients, all prescriptions for antipsychotic medications were identified and categorized as aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone, and first-generation antipsychotics considered as a class. Next, inpatient and outpatient records were examined to determine whether patients who received these medica-

tions had any visits or hospitalizations with a diagnosis of either schizophrenia (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 295) or bipolar disorder (ICD-9-CM codes 296.0, 296.1, 296.4-296.8). Patients without any diagnosis of schizophrenia or bipolar disorder during 2003 who received an antipsychotic medication were considered to have received these medications off-label. Although some of these drugs are now approved for treatment of other disorders (eg, autism, depression), we considered only schizophrenia and bipolar disorder since they were the only approved indications in 2003.

Among these patients, the average daily dose was computed for the first prescription of the year by multiplying the number of pills by the strength per pill and dividing by the number of days of supply. Dosages of first-generation antipsychotics were converted to chlorpromazine equivalents. Patients without a diagnosis of schizophrenia or bipolar disorder were assigned to the following diagnostic groups based on whether they had any visits with the corresponding non-exclusive ICD-9-CM codes: adjustment reaction (309, excluding 309.81), alcohol abuse/dependence (303, 305.00), anxiety disorder (300, excluding 300.4), autism spectrum disorder (299, excluding 299.9), conduct disorder (309.3, 309.4, 312.0-312.9, 313.3-313.9), drug abuse/dependence (292, 304, 305.2-305.9), major depression (296.2-296.3), minor depression (300.4, 296.9, 311, 301.1), organic brain syndrome/Alzheimer disease (290, 293-294, 331.00, 310), other psychosis (297-299), PTSD (309.81), other mental disorder (290-319, excluding 305.1, not elsewhere specified), and no mental disorder. Patients could belong to more than 1 mental disorder diagnostic group.

Analysis

First, the number and proportion of off-label users who received each drug was determined. Second, all patients belonging to any of the 13 diagnostic groups listed above (excluding those with any comorbid diagnosis of schizophrenia or bipolar disorder) were identified. The proportion of patients

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in each of these diagnostic groups who received a prescription for an antipsychotic medication was determined, along with the average daily dose of each antipsychotic among users of that medication.

In order to identify patient-level factors associated with off-label use of these agents, logistic regression models were then estimated in which off-label use of antipsychotic medications was the dependent variable and the independent variables included the following: age group, female sex, black race, Hispanic ethnicity, other/missing race, and diagnostic group. Because these models intended to predict off-label use, the sample was again restricted to all individuals without any diagnoses of schizophrenia or bipolar disorder. Separate models were run using receipt of the following antipsychotic drugs as the dependent variable: aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, and first-generation antipsychotics. Because so few patients received clozapine off-label, a separate model was not estimated for clozapine. A final model was estimated for receipt of any antipsychotic medication off-label. In each of the models, standard errors were adjusted to account for the clustering of individuals within states.

RESULTS

Off-Label Use

We identified 372,038 unique patients who were continuously enrolled in a fee-for-service Medicaid program and received a prescription for an antipsychotic medication across all 42 states in 2003. Of these patients, 214,113 (57.6%) did not have a diagnosis of schizophrenia or bipolar disorder during the year and were considered to have received these drugs off-label. Characteristics of off-label users of antipsychotic medications are presented in **Table 1**. The average age was 30.5 years and they were evenly divided by sex. Whites were the most common racial group (53.1%), with blacks comprising 22.4% of off-label users.

The diagnostic breakdown of off-label users is also presented in **Table 1**. The most common diagnostic group was other mental disorder (35.0%), followed by minor depression (25.4%), major depression (23.2%), no mental disorder (18.8%), conduct disorder (18.8%), and anxiety disorder (16.2%). Very few off-label users were diagnosed with PTSD (5.6%) or alcohol abuse (5.0%). There was a considerable

Table 1. Characteristics of Off-Label Users (N = 214,113)

Characteristic	Value ^a
Age, y, mean ± SD	30.5 ± 18.67
Sex	
Male	107,105 (50.0)
Female	107,005 (50.0)
Race/ethnicity	
White	113,785 (53.1)
Black	47,982 (22.4)
Hispanic	22,823 (10.7)
Other/missing	29,523 (13.8)
Diagnosis	
Adjustment reaction	12,564 (5.9)
Alcohol abuse/dependence	10,697 (5.0)
Anxiety disorder	34,775 (16.2)
Autism spectrum disorder	12,759 (6.0)
Conduct disorder	40,302 (18.8)
Drug abuse/dependence	16,747 (7.8)
Minor depression	54,375 (25.4)
Major depression	49,606 (23.2)
Organic brain syndrome/Alzheimer disease	12,285 (5.7)
Other psychosis	17,304 (8.1)
PTSD	12,058 (5.6)
Other mental disorder	74,888 (35.0)
No mental disorder	40,343 (18.8)
Antipsychotic prescribed	
Aripiprazole	13,225 (6.2)
Clozapine	665 (0.3)
Olanzapine	53,968 (25.2)
Quetiapine	49,253 (23.1)
Risperidone	88,571 (41.4)
Ziprasidone	8787 (4.1)
First-generation antipsychotic	44,759 (20.9)
PTSD indicates posttraumatic stress disorder.	
^a Values represent number (percentage) unless indicated otherwise.	

degree of comorbidity among these disorders, as evidenced by the fact that the proportions of patients in these diagnostic groups sum to more than 100%.

Risperidone was the most commonly prescribed medication among those given antipsychotic medications off-label (41.4%), followed by olanzapine (25.2%) and quetiapine (23.1%). First-generation antipsychotics were also fairly common (20.9%), while relatively few patients were given aripiprazole (6.2%), ziprasidone (4.1%), or clozapine (0.3%) off-label.

Table 2 shows rates of off-label use as a percentage of antipsychotic users by age, sex, and race/ethnicity. Among an-

■ **Table 2.** Rates of Off-Label Use Among Patients Receiving an Antipsychotic

Characteristic	Received an Antipsychotic	Off-Label Use	
		No.	%
Age group, y			
<21	114,290	86,734	75.9
21-64	250,458	122,658	49.0
≥65	7290	4721	64.8
Sex			
Male	182,369	107,105	58.7
Female	189,666	107,005	56.4
Race/ethnicity			
White	195,460	113,785	58.2
Black	91,691	47,982	52.3
Hispanic	34,740	22,823	65.7
Other/missing	50,147	29,523	58.9

tipsychotic users, off-label use was most common in patients younger than 21 years (75.9%), followed by patients 65 years and older (64.8%). Off-label use among antipsychotic users was only slightly more common among males (58.7%) than females (56.4%). In addition, there were substantial differences by race/ethnicity, with off-label use among antipsychotic users being most common among Hispanics (65.7%) and least common among blacks (52.3%).

Off-Label Use Among Diagnostic Groups

Table 3 shows the use of an-

■ **Table 3.** Average Daily Dose of Off-Label Antipsychotics by Diagnostic Group (N = 5,888,286)

Drug	Any Mental Disorder (n = 1,084,951)	Adjustment Reaction (n = 96,186)	Alcohol Abuse (n = 63,404)	Anxiety Disorder (n = 169,497)	Autism Spectrum (n = 32,523)	Conduct Disorder (n = 166,780)	Drug Abuse (n = 90,523)
Aripiprazole							
% taking	1.1%	1.0%	0.8%	1.5%	4.3%	2.1%	0.9%
Average daily dose ^a	11.1	10.6	12.2	11.0	11.4	10.4	12.7
Clozapine							
% taking	0.0%	0.0%	0.0%	0.0%	0.2%	0.1%	0.0%
Average daily dose ^a	231	192	187	182	249	215	163
Olanzapine							
% taking	4.2%	3.1%	6.0%	6.1%	7.7%	5.2%	6.8%
Average daily dose ^a	8.2	7.4	9.9	7.4	9.3	7.7	11.4
Quetiapine							
% taking	4.1%	3.8%	5.6%	6.4%	7.8%	6.0%	6.2%
Average daily dose ^a	146	129	136	132	232	161	143
Risperidone							
% taking	7.2%	5.9%	5.0%	7.1%	25.6%	14.3%	5.2%
Average daily dose ^a	1.54	1.28	1.68	1.47	1.97	1.38	1.79
Ziprasidone							
% taking	0.7%	0.6%	0.6%	1.0%	2.3%	1.3%	0.7%
Average daily dose ^a	64.1	56.1	67.9	63.4	63.5	59.0	66.0
First-generation antipsychotic							
% taking	2.4%	1.8%	3.0%	3.8%	4.5%	1.9%	3.3%
Average daily dose ^a	225	205	223	190	265	266	217
Any antipsychotic							
% taking	16.0%	13.1%	16.9%	20.5%	39.2%	24.2%	18.5%

^aThe recommended dosing ranges for schizophrenia are 10 to 30 mg/day for aripiprazole, 150 to 600 mg/day for clozapine, 5 to 20 mg/day for olanzapine, 150 to 750 mg/day for quetiapine, 2 to 6 mg/day for risperidone, 40 to 160 mg/day for ziprasidone, and 300 to 1000 mg/day for first-generation drugs.

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tipsychotic medications and average daily doses among patients with specific mental illness diagnoses, exclusive of comorbid schizophrenia or bipolar disorder. In contrast to Tables 1 and 2, in which the sample consists only of patients receiving antipsychotics off-label (N = 372,038), Table 3 includes all patients who did not have schizophrenia or bipolar disorder (N = 5,888,286). Rates of antipsychotic use were highest among patients diagnosed with other psychosis (62.7%), followed by autism spectrum disorder (39.2%), organic brain syndrome/Alzheimer disease (36.5%), PTSD (35.0%), and major depression (34.0%). Relatively few patients diagnosed with no mental disorder (0.8%), adjustment reaction (13.1%), other mental disorder (14.5%), or alcohol or drug abuse (16.9% and 18.5%, respectively) received an antipsychotic medication.

Risperidone was the drug most commonly prescribed off-label across all the mental disorder diagnostic groups, ranging from 5.0% of patients with alcohol abuse to 28.0% of all pa-

tients diagnosed with other psychosis. Other than clozapine, which very few patients received off-label, ziprasidone (0.7%) and aripiprazole (1.1%) were the drugs least commonly prescribed off-label.

Average daily doses of these drugs are also displayed in Table 3. Average dosages were generally high among patients with other psychosis or drug abuse and low among patients with adjustment reaction or anxiety disorder. All of the doses were at the low end of the therapeutic range for schizophrenia.

Predictors of Off-Label Use

Results of the regression models predicting off-label use of antipsychotic medications are presented in Table 4. Because of the large sample sizes, almost all of the estimates are statistically significant. In the model predicting any off-label use (first columns of Table 4), odds ratios (ORs) were highest for patients with other psychosis (OR = 9.09), autism spectrum disorder (OR = 5.91), major depression (OR = 5.51),

Minor Depression (n = 240,021)	Major Depression (n = 146,088)	Organic Brain Syndrome/Alzheimer Disease (n = 33,654)	Other Psychosis (n = 27,622)	Posttraumatic Stress Disorder (n = 34,495)	Other Mental Disorder (n = 516,943)	No Mental Disorder (n = 4,803,335)
1.6%	2.5%	1.8%	5.5%	3.1%	1.0%	0.0%
11.1	11.8	11.8	12.6	10.8	10.7	13.1
0.0%	0.1%	0.2%	0.5%	0.1%	0.0%	0.0%
184	237	161	225	198	224	307
6.7%	9.7%	13.2%	21.5%	8.3%	3.4%	0.2%
7.8	8.5	7.7	9.8	7.7	7.8	8.6
6.9%	11.6%	8.7%	14.4%	13.2%	3.2%	0.1%
132	138	146	197	153	157	174
8.5%	12.7%	15.1%	28.0%	15.6%	8.0%	0.2%
1.45	1.58	1.66	2.06	1.38	1.50	1.86
1.1%	2.0%	1.3%	3.9%	2.2%	0.6%	0.0%
62.2	68.1	68.8	75.5	64.2	63.1	74.0
3.6%	4.3%	7.8%	11.2%	3.0%	1.8%	0.4%
205	218	287	335	204	231	210
22.7%	34.0%	36.5%	62.7%	35.0%	14.5%	0.8%

■ **Table 4.** Logistic Regression Models Predicting Use of Antipsychotic Medications Off-Label (N = 5,888,286)

Independent Variable	Any Antipsychotic		Aripiprazole		Olanzapine	
	OR	95% CI	OR	95% CI	OR	95% CI
Age, y						
<21	0.39	0.39-0.40	0.94	0.90-0.98	0.28	0.28-0.29
≥65	1.11	1.07-1.15	0.32	0.25-0.41	1.28	1.21-1.35
Female	0.73	0.72-0.74	0.83	0.80-0.86	0.63	0.62-0.64
Race						
Black	0.90	0.88-0.91	0.87	0.83-0.92	0.90	0.88-0.92
Hispanic	0.80	0.79-0.82	0.77	0.72-0.82	0.87	0.84-0.89
Other/missing	1.10	1.08-1.12	1.11	1.05-1.17	1.02	0.99-1.06
Diagnosis						
Adjustment reaction	0.91	0.89-0.93	0.86	0.81-0.92	0.82	0.79-0.86
Alcohol abuse/dependence	0.77	0.75-0.79	0.69	0.63-0.76	0.83	0.79-0.86
Anxiety disorder	1.26	1.24-1.28	1.34	1.28-1.41	1.19	1.16-1.22
Autism spectrum disorder	5.91	5.75-6.06	4.52	4.25-4.81	2.80	2.67-2.93
Conduct disorder	3.46	3.41-3.51	2.34	2.24-2.45	2.45	2.39-2.52
Drug abuse/dependence	1.02	1.00-1.05	0.78	0.73-0.85	1.20	1.16-1.24
Minor depression	1.60	1.58-1.63	1.51	1.44-1.57	1.50	1.46-1.53
Major depression	3.51	3.46-3.56	3.11	2.98-3.25	2.49	2.44-2.55
Organic brain syndrome/Alzheimer disease	2.54	2.48-2.61	1.33	1.21-1.45	2.21	2.13-2.29
PTSD	2.94	2.86-3.01	2.17	2.02-2.32	2.01	1.92-2.10
Other psychosis	9.09	8.83-9.35	4.44	4.18-4.72	4.42	4.28-4.57
Other mental disorder	1.69	1.67-1.71	1.22	1.17-1.27	1.30	1.27-1.32
No mental disorder	0.20	0.19-0.20	0.10	0.09-0.10	0.14	0.14-0.15

CI indicates confidence interval; OR, odds ratio; PTSD, posttraumatic stress disorder.

and conduct disorder (OR = 3.46) compared with patients without these disorders. Having no mental disorder (OR = 0.20) or a diagnosis of adjustment reaction or alcohol abuse/dependence (OR = 0.91 and OR = 0.77, respectively), being under age 21 (OR = 0.39), or being female (OR = 0.73), of black race (OR = 0.90), or of Hispanic ethnicity (OR = 0.80) decreased the odds of receiving an antipsychotic medication off-label. The logistic regression results were fairly consistent across the other models predicting off-label use of each medication individually, although the effect sizes varied.

DISCUSSION

In this study, we used administrative data from the Medicaid programs of 42 states from 2003 to determine the extent to which antipsychotic medications are used off-label and to identify factors associated with off-label use. We found a considerable degree of off-label use of these drugs, with 57.6% of patients who were given antipsychotic medications having no visit with a diagnosis of either schizophrenia or bipolar dis-

order during the year. The most frequently prescribed drugs for off-label use were risperidone and olanzapine, with first-generation antipsychotics and quetiapine also being relatively common. Patients diagnosed with other psychosis or autism spectrum disorder had the highest odds of being given an antipsychotic off-label.

The rate of off-label use found in state Medicaid programs is similar to that found in a recent study of off-label use in the VA, which found that 60.2% of patients who received a prescription for an antipsychotic medication did not have a diagnosis of schizophrenia or bipolar disorder in fiscal year 2007.⁵ There are some notable differences between the study populations in these studies, however. The average age of patients receiving antipsychotic medications is lower in state Medicaid programs than in the VA, in large part due to the fact that Medicaid covers children whereas the VA does not. As a result, and also because of the different experiences of military veterans compared with Medicaid enrollees, the diagnostic breakdown of patients receiving antipsychotics off-label is quite different in the

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Quetiapine		Risperidone		Ziprasidone		First-Generation Antipsychotic	
OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
0.58	0.57-0.60	0.83	0.82-0.85	0.70	0.66-0.74	0.15	0.14-0.15
0.89	0.83-0.97	1.32	1.25-1.40	0.41	0.32-0.54	0.99	0.94-1.05
0.91	0.89-0.93	0.61	0.60-0.62	0.93	0.89-0.98	1.12	1.10-1.15
0.79	0.77-0.81	1.01	0.99-1.03	0.81	0.77-0.86	0.87	0.84-0.89
0.80	0.77-0.83	0.76	0.74-0.78	0.73	0.68-0.80	0.93	0.90-0.96
0.98	0.94-1.01	1.20	1.17-1.23	0.99	0.92-1.07	1.00	0.96-1.03
0.91	0.88-0.94	0.88	0.85-0.91	0.79	0.73-0.87	0.95	0.90-1.00
1.01	0.97-1.05	0.68	0.65-0.71	0.79	0.70-0.88	0.77	0.73-0.81
1.31	1.28-1.34	1.09	1.07-1.12	1.30	1.22-1.37	1.17	1.13-1.20
3.05	2.92-3.19	5.09	4.95-5.24	4.40	4.05-4.77	3.30	3.11-3.50
2.45	2.39-2.52	2.99	2.93-3.05	2.43	2.29-2.57	1.89	1.82-1.97
1.30	1.26-1.34	0.70	0.67-0.72	0.90	0.82-0.98	1.05	1.01-1.10
1.60	1.57-1.64	1.41	1.39-1.44	1.40	1.33-1.47	1.16	1.13-1.20
3.69	3.61-3.77	2.89	2.83-2.95	3.56	3.38-3.75	1.36	1.32-1.40
1.75	1.68-1.83	2.08	2.01-2.15	1.36	1.23-1.51	2.04	1.95-2.13
2.84	2.74-2.94	2.33	2.25-2.41	2.34	2.16-2.53	1.23	1.15-1.31
3.05	2.94-3.17	4.81	4.67-4.97	4.59	4.28-4.93	3.47	3.33-3.62
1.25	1.22-1.28	1.70	1.67-1.73	1.13	1.07-1.19	1.30	1.26-1.33
0.10	0.09-0.10	0.11	0.11-0.11	0.09	0.08-0.10	0.41	0.40-0.43

2 study populations. Rates of PTSD are higher in the VA than in Medicaid, and autism spectrum disorder and conduct disorder are more common among Medicaid enrollees than in the VA.

The rate of off-label use of antipsychotic medications was also comparable to the 63.6% rate seen in the Georgia Medicaid population in 2000-2001.¹² However, our estimate of off-label use of antipsychotics is higher than that found in many previous studies. A previous VA study reported that 42.8% of VA patients who were prescribed second-generation antipsychotics during a 4-month period in 1999 received these drugs for an off-label use.⁴ At the time, second-generation antipsychotics had not been FDA approved for treating bipolar disorder, however. If patients with a diagnosis of bipolar disorder are removed, the rate of off-label use falls to 33.4%, perhaps reflecting the lower use of antipsychotics generally at that time. In addition, a more recent study based on national Medical Expenditure Panel Survey data reported that the percentages of antipsychotic medication users with an affective disorder or anxiety spectrum disorder without comorbid

schizophrenia in 2004-2005 were 22% and 19%, respectively,³ as compared with 21.7% (minor depression) and 20.1% in this study.

It is important to note that different rates of off-label use of antipsychotic medications may be partly due to differences in the length of time these drugs have been on the market. The more experience physicians have with a medication, the more comfortable they may be prescribing it off-label. We found that rates of off-label use were highest with risperidone and olanzapine, which are the drugs that have been on the market the longest.

The rate of off-label use of antipsychotics is high compared with that of other medications. Using data from a survey of office-based physicians, Radley et al¹³ found that 21% of all prescriptions were for an off-label use, and fewer than one-third of these (27%) were supported by strong scientific evidence of clinical efficacy. Rates of off-label use were highest for cardiac medications (46%), anticonvulsants (46%), and antiasthmatics (42%). Antipsychotic medications were not well represented in the study (only 2 were included), but this

is not surprising given that the population surveyed was not limited to mental health providers.

A high rate of off-label antipsychotic use would not necessarily be of concern if there were scientific evidence supporting the effectiveness of these medications for conditions other than schizophrenia and bipolar disorder. In fact, off-label use of some medications is supported by the medical community, such as the American Academy of Neurology's endorsement of quinine for treatment-resistant leg cramps despite the FDA warning against such off-label use.¹⁴ Since 2003, antipsychotic medications have been approved by the FDA for the treatment of other disorders in addition to schizophrenia and bipolar disorder: risperidone and aripiprazole for irritability in autism, and aripiprazole, olanzapine, and quetiapine for adjunctive use with antidepressants in patients with treatment-resistant depression. Hence, such uses of these drugs would not be considered off-label today, although they were at the time these data were collected. However, evidence supporting the effectiveness of antipsychotic medications for other disorders is generally lacking or weak. While a meta-analysis by Schneider et al¹⁵ found a small but statistically significant benefit for aripiprazole and risperidone in treating agitation in dementia, the Alzheimer disease arm of the Clinical Antipsychotic Trials of Intervention Effectiveness found that second-generation antipsychotics were no more effective than placebo in treating Alzheimer disease.^{16,17} In addition, according to 2 recent AHRQ reports,^{6,7} the scientific evidence supporting the effectiveness of off-label antipsychotic medication use is weak for most of the drugs and for many of the conditions for which they are commonly prescribed; however, the updated report did find that some of the conditions for which the first report concluded there was little evidence of efficacy now had an adequate evidence base suggesting efficacy or had been approved by the FDA for these conditions (eg, depression, autism).

There may be several reasons why prescription drugs are used off-label. For example, patients enrolled in clinical trials may bear little resemblance to patients typically seen in clinical practice, leading clinicians to question the generalizability of the results. Furthermore, efficacy data may not exist for some conditions or populations (eg, children), although manufacturers have a powerful incentive to conduct clinical trials to show efficacy in conditions other than those for which their drug has been approved for use. Another possible explanation for off-label use is that clinicians try these medications as a last resort in patients who have not responded to other treatments. However, journalistic accounts suggest that some pharmaceutical manufacturers have illegally marketed antipsychotic medications for off-label use,¹⁸⁻²⁰ and manufacturers have incurred heavy fines for such off-label marketing.^{21,22}

The average dose prescribed when antipsychotic medications were used off-label varied considerably across drugs and diagnostic groups. Doses tended to be higher for patients with other psychosis or drug abuse, and lower for patients with adjustment reaction or anxiety disorder. This suggests that clinicians are tailoring their choice of drug and prescribed dose to the particular characteristics of the patient. Further research is needed to explore the reasons for off-label use and why the prescribed dose varies by drug and clinical condition.

A number of limitations are associated with these administrative data. First, although detailed information is available on the medication and dose prescribed and days of supply, we cannot determine what condition a medication is intended to treat since many patients received multiple psychiatric diagnoses. Hence, while we can determine whether a patient who was prescribed an antipsychotic medication had a diagnosis of major depression, we cannot say that the diagnosis of depression was the reason for the antipsychotic prescription. In addition, diagnoses are based on ICD-9-CM codes, which may be miscoded or incomplete. This could be particularly problematic for serious mental disorders like schizophrenia, which may be underreported due to stigma associated with the diagnosis. Finally, the study sample was limited to those continuously enrolled in fee-for-service Medicaid programs who were not dually enrolled in Medicare; hence, generalizability may be limited.

Antipsychotic medications are expensive,^{23,24} with second-generation antipsychotics costing up to \$10 per day at doses recommended for patients with schizophrenia, although risperidone is now available generically. Total US sales of second-generation antipsychotics grew from \$8.4 billion in 2003 to \$14.6 billion in 2009, making it the highest selling medication class.²⁵ In addition, Medicaid bears a significant proportion of these costs.^{1,2} Hence, off-label use may be responsible for a considerable portion of state Medicaid budgets, with little or no documented clinical benefit and a substantial risk of adverse effects. With the recent passage of the healthcare reform bill and widespread crises in state revenues, state Medicaid programs will be under increasing pressure to serve larger patient populations, increasing their fiscal stress. Off-label use of antipsychotic medications may be an area of potential savings with little impact on patient outcomes. More research is needed to determine whether off-label use of antipsychotic medications yields substantial clinical benefit and to identify the basis for clinical decision making among clinicians who prescribe these drugs for non-FDA-approved conditions. Greater caution should probably be used to avoid hazardous side effects when there is limited evidence of clinical benefit.

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