Medication Adherence and Persistence in Patients with Severe Major Depressive Disorder with Psychotic Features: Antidepressant and Second-Generation Antipsychotic Therapy Versus Antidepressant Monotherapy

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ABSTRACT

BACKGROUND: Major depressive disorder with psychotic features, or psychotic depression, is a severe mental health disorder often associated with a worse depression-related symptom profile when compared with major depressive disorder without psychotic features. While combination pharmacotherapy with an antidepressant and an antipsychotic is recommended as first-line therapy, antidepressant monotherapy has been found to be useful and efficacious in psychotic depression.

OBJECTIVE: To assess the rates of antidepressant adherence and antidepressant persistence in Texas Medicaid patients with psychotic depression who used antidepressant plus second-generation antipsychotic (AD/SGA) therapy or antidepressant (AD) monotherapy.

METHODS: Using Texas Medicaid prescription and medical claims data from September 2007 to December 2012, adult patients aged 18-63 years were included if they had no confounding psychiatric disorders, no antidepressant claims during a 6-month pre-index period, and at least 1 diagnosis for severe major depressive disorder with psychotic features (ICD-9-CM codes 296.24 and 296.34). The first claim date for an antidepressant served as the index date. All patients were required to have at least 2 antidepressant claims, and those in the AD/SGA cohort were required to have 2 or more claims for an SGA. Study covariates included age, gender, race/ethnicity, residence, Charlson Comorbidity Index (CCI) score, and tobacco use/dependence. Statistical analyses included descriptive statistics, univariate analyses, logistic regression, and Cox proportional hazards regression.

RESULTS: A total of 926 patients met study criteria (AD cohort=510; AD/SGA cohort=416). The overall sample had a mean [$\pm$ SD] age of 40.5 [$\pm$ 13.2] years and was primarily female (66.8%) and non-Caucasian (74.8%). When compared with the AD cohort, patients in the AD/SGA cohort had a 52.3% higher likelihood of being adherent to antidepressant therapy based on proportion of days covered (PDC; OR=1.523; 95% CI=1.129-2.053; $P=0.006$). Similarly, antidepressant adherence was 42.0% higher for the AD/SGA cohort based on medication possession ratio (MPR; OR=1.420; 95% CI=1.062-1.898; $P=0.018$). Younger patients, African Americans, and tobacco users/dependents had significantly worse likelihoods of antidepressant medication adherence based on PDC and MPR. The risk of antidepressant nonpersistence was 23.2% lower for patients in the AD/SGA cohort (HR=0.768; 95% CI=0.659-0.896; $P=0.001$), compared with those in the AD cohort. Antidepressant nonpersistence was significantly higher in younger patients, African Americans, Hispanics, and tobacco users/dependents.

CONCLUSIONS: Better antidepressant adherence and persistence outcomes were associated with combination pharmacotherapy with an AD and an SGA antipsychotic. This study provides real-world estimates that support the current first-line treatment recommendations for psychotic depression; however, it should be noted that the majority of study patients used AD therapy only. Future research in psychotic depression is needed.

J Manag Care Spec Pharm. 2016;22(5):588-96

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What is already known about this subject

- Previous research has reported worse health-related outcomes in psychotic depression when compared with major depressive disorder without psychotic features.
- While an antidepressant plus an antipsychotic agent is advocated as first-line therapy by the American Psychiatric Association and the Texas Medication Algorithm Project practice guidelines, other therapy such as antidepressant monotherapy has been shown to be effective in the treatment of major depressive disorder with psychotic features.
- Little is known about antidepressant adherence in major depressive disorder with psychotic features; however, adherence in patients with major depressive disorder is generally low.

What this study adds

- This study provides estimates of proportion of days covered, medication possession ratio, and persistence in patients with major depressive disorder with psychotic features.
- Study results found that patients on combination pharmacotherapy with an antidepressant plus a second-generation antipsychotic had significantly better antidepressant adherence and persistence compared with those on antidepressant monotherapy.
- Compared with Caucasians, African Americans had worse antidepressant adherence and persistence outcomes, whereas Hispanics had poorer rates of antidepressant persistence.

Major depressive disorder with psychotic features is a severe subtype of major depressive disorder characterized as major depressive episodes with delusions, hallucinations, or both.¹ This disorder, also termed *psychotic depression*, is associated with worse outcomes related to depressive episodes, suicide, hospitalizations, financial assistance, and social functioning when compared with patients with major depressive disorder without psychotic features.²⁻⁴ Epidemiological studies have estimated the prevalence of psychotic depression to be as low as 0.4%-0.6% in general populations and as high as 25.3%-44.7% in populations of patients with major depressive disorder.^{2,5-7} The financial burden of psychotic depression is apparent—1 study from the United Kingdom reported inpatient costs for first-episode psychotic depression that were nearly equal to the inpatient costs associated with first-episode schizophrenia at estimates of £2.6 million and £2.8 million, respectively.⁸

Treatment goals for psychotic depression include depressive episode remission, attainment of baseline psychosocial functioning, and prevention of depression relapse and recurrence.^{9,10} While algorithms for psychotic depression exist, there is a lack of consensus among international practice guidelines. Generally, the American Psychiatric Association and the Texas Medication Algorithm Project guidelines recommend the use of combination therapy with an antidepressant and antipsychotic as first-line therapy, while the National Institute for Health and Clinical Excellence, the Danish Board of Health, and the Dutch National Steering Committee of Health guidelines support the use of antidepressant monotherapy.⁹⁻¹³ In general, the Texas Medication Algorithm Project guidelines recommend using an antipsychotic during the acute phase to achieve remission of symptoms and then continuing use for 1 to 2 months before slowly tapering off the antipsychotic, while antidepressants should be continued after symptom remission for 6 to 9 months at the full therapeutic doses used during the acute phase.¹⁰

A number of studies have found combination therapy with antidepressants plus second-generation antipsychotics (e.g., olanzapine, quetiapine, aripiprazole, and risperidone) to be effective in achieving a response or remission of depressive episode symptoms in psychotic depression.¹⁴⁻²¹ Combination therapy is more beneficial when compared with antipsychotic monotherapy,^{16,21} while the results are not as clear when combination therapy is directly compared with antidepressant monotherapy.^{14,15,22} For example, a meta-analysis found that combination therapy with an antidepressant plus antipsychotic was superior to antidepressant monotherapy in relation to study-defined inefficacy and Clinical Global Impressions scores.²³ However, superiority was not found in depression ratings and psychosis ratings. Similarly, a Cochrane Review found that combination therapy was not necessarily more effective than antidepressant monotherapy.²⁴ This is noteworthy, since antidepressant monotherapy of imipramine, nortriptyline, sertraline, or fluoxetine has been reported to be useful in

treating psychotic depression.^{14,22,25,26} Furthermore, antidepressant monotherapy and antidepressant/antipsychotic therapy have successfully treated acute depressive episode and have been shown to be efficacious in the long term.¹⁵

Previous related studies have primarily compared psychotically depressed patients with those with nonpsychotic depression. While these studies have reported outcomes associated with depression scores, relapse rates, psychosocial impairment, hospitalizations, length of stay, and outpatient visits, none have compared medication treatment regimens among patients with psychotic depression.^{2,4,27} Similarly, there is a lack of medication adherence and persistence studies focusing on psychotic depression. One study on psychotic depression evaluated medication use as a percentage of time and found that, at 24 months, 31.4% of patients continued to use their antidepressant medications 75%-100% of the time.²⁸ In general, patients with major depressive disorder have low antidepressant adherence and high rates of antidepressant discontinuation.^{29,30} One study reported an antidepressant adherence rate of 43.3% based on medication possession ratio,³¹ and another estimated antidepressant persistence rates of 43.7%-45.2%.²⁹ While these studies provide insight into antidepressant adherence and persistence in patients with major depressive disorder, the effect of psychotic features cannot be clearly delineated.²⁹⁻³¹ Therefore, in order to provide more insight into the real-world treatment of psychotic depression, the objective of this study was to compare medication adherence and persistence among Texas Medicaid patients using combination pharmacotherapy with an antidepressant plus second-generation antipsychotic versus those on antidepressant therapy alone.

Methods

Data Source

A retrospective cohort design was employed using Texas Medicaid prescription and medical claims data from September 1, 2007, to December 31, 2012. Patients with a diagnosis of severe major depressive disorder with psychotic features were included if they had a 6-month pre-index period with no antidepressant or antipsychotic medication claims and a 12-month post-index period where they received antidepressant therapy. The first antidepressant claim date served as the index date, where possible index dates (i.e., the index period) ranged from as early as March 1, 2008, to as late as December 31, 2011, to allow for the minimum 18-month study period (Figure 1). All claims data were in de-identified form, and the study protocol was deemed as nonhuman subjects research and approved by The University of Texas at Austin Institutional Review Board.

Inclusion and Exclusion Criteria

Texas Medicaid patients with a diagnosis of severe major depressive disorder with psychotic features based on *International Classification of Diseases, Ninth Revision, Clinical Modification*

FIGURE 1 Data Extraction and Subject Identification Period

(ICD-9-CM) codes 296.24 and 296.34 were included if they met the following criteria: (a) were adults aged 18 to 63 years at index; (b) had at least 2 prescription claims for an antidepressant (AD cohort), or had at least 2 claims for an antidepressant and at least 2 claims for an oral or injectable second-generation antipsychotic agent (AD/SGA cohort); and (c) were continuously enrolled for 18 months (6-month baseline pre-index period and 12-month follow-up post-index period) in Texas Medicaid.

For the purpose of controlling for disease-related confounders, patients were excluded if they had an ICD-9-CM diagnosis of dementia (290.xx); schizophrenia (295.xx); pervasive development disorder (299.xx); mental retardation (317.xx-319.xx); other cerebral degenerations (331.xx); Parkinson's disease (332.xx); senility without mention of psychosis (797.xx); or manic depression, bipolar disorder, or cyclothymic disorder (296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.80, 296.81, 296.89, and 301.13). Patients were excluded if they had a claim at any time for clozapine, a first-generation antipsychotic agent, or electroconvulsive therapy based on ICD-9-CM codes 94.26 and 94.27 or procedural codes 90870 and 90871. Patients with SGA antipsychotic use during the pre-index period were also excluded. Patients were not included in the AD/SGA cohort if their first claim for an SGA did not occur on the index date or if there was less than a 30-day overlap of combined pharmacotherapy usage between the AD therapy and SGA therapy.

Study Outcomes

AD adherence was the study outcome of interest and included the following: (a) AD adherence based on proportion of days covered (PDC) $\geq 80\%$ (defined as the number of days with medication available divided by 365 days); (b) AD adherence based on medication possession ratio (MPR) $\geq 80\%$ (calculated as the sum of the days supply divided by 365 days); and (c) time until AD nonpersistence (i.e., the time, in days, before a 45-day gap in therapy occurred), with sensitivity analyses using 30-day and 60-day permissible gaps.

Study Covariates

The patient cohorts, AD versus AD/SGA, were the primary independent variables. Multivariate analyses controlled for the following demographic and clinical variables: age, gender, race/ethnicity, place of residence, pre-index Charlson Comorbidity Index (CCI) score (Dartmouth-Mannitoba³²), and post-index tobacco use/dependence based on ICD-9-CM codes 305.1, V15.82, 989.84, and 649.00 through 649.04.

Statistical Analyses

Statistical analyses were performed using PASW Statistics 18 (formally SPSS Statistics, Chicago IL). All statistical analyses were two-tailed and utilized an a priori significance level of $P < 0.05$. Descriptive statistics (means, standard deviations [SD], and frequencies) were calculated for all variables in the study. Other statistical analyses included Pearson's chi-square test for dichotomous variables, independent samples t-tests for normally distributed continuous variables, and Mann-Whitney U tests for nonparametric data. Multiple logistic regression analyses were used to assess the medication adherence variables of PDC and MPR. Time until AD nonpersistence was compared using Cox proportional hazards regression.

Results

A total of 926 patients met study criteria, with 416 and 510 patients in the AD/SGA and AD cohorts, respectively (Figure 2). Baseline and post-index characteristics for the total sample and individual cohorts are displayed in Table 1. At baseline, the AD/SGA cohort was, on average, significantly older and had a lower number of comorbidities based on CCI scores when compared with the AD cohort. Also, the AD/SGA cohort had a significantly lower percentage of females, Caucasians, and rural dwellers. There was no difference between the 2 cohorts regarding post-index tobacco use/dependence. The mean [$\pm$ SD] SGA persistence rate was 178.6 [$\pm$ 127.9] days, where 49.3% of the AD/SGA cohort utilized SGA therapy for 5 months or longer.

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FIGURE 2 Patient Selection in Texas Medicaid Database

^aDuring period of September 1, 2007, to December 31, 2012.

^bConfounding disease states include schizophrenia, dementia, pervasive development disorder, mental retardation, other cerebral degenerations, Parkinson's disease, senility without mention of psychosis, manic depression, bipolar disorder, and cyclothymic disorder.

AD = antidepressant; FGA = first-generation antipsychotic; SGA = second-generation antipsychotic.

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TABLE 1 Sociodemographic and Clinical Characteristics

	Total (N=926)	AD (n=510)	AD/SGA (n=416)	P Value ^a
Age, mean [±SD] ^{b,c}	40.5 [±13.2]	39.2 [±13.3]	42.0 [±13.0]	0.001
Gender (%) ^d				<0.001
Female	66.8	72.2	60.3	
Male	33.2	27.8	39.7	
Race/ethnicity (%) ^d				<0.001
Caucasian	25.2	30.0	19.2	
African American	34.9	28.0	43.3	
Hispanic	36.7	39.2	33.7	
Other ^e	3.2	2.7	3.8	
Residence (%) ^d				<0.001
Rural	20.5	25.7	14.2	
Urban	79.5	74.3	85.8	
CCI, mean [±SD] ^{f,g}	0.6 [±1.3]	0.8 [±1.4]	0.5 [±1.2]	<0.001
Tobacco use/dependence (%) ^{d,h}	19.7	21.8	17.1	0.074

^aSignificance at $P < 0.05$.

^bIndependent samples *t*-test.

^cRepresents age, in years, at the time of first AD prescription claim.

^dPearson's chi-square test.

^eOther includes Asian, unknown.

^fMann-Whitney *U* test.

^gWeighted index based on the Dartmouth-Mannitoba adaptation.

^hRepresents the only post-index characteristic.

AD=antidepressant; CCI=Charlson Comorbidity Index; SD=standard deviation; SGA=second-generation antipsychotic.

Approximately 33.0% and 38.3% of the total sample were adherent to their antidepressant medication therapy based on PDC and MPR, respectively. Specifically, the AD/SGA cohort had higher antidepressant adherence rates based on PDC (38.7% vs. 28.4%) and MPR (43.5% vs. 34.1%), compared with the AD cohort. A multivariate logistic regression analysis showed patients who used AD/SGA therapy had a 52.3% significantly higher likelihood of being adherent to AD therapy based on PDC (odds ratio [OR]=1.523; 95% confidence interval [CI]=1.129-2.053; $P=0.006$) versus the AD cohort (Table 2). Similarly for MPR, the likelihood of AD adherence was significantly higher by approximately 42.0% in the AD/SGA cohort (OR=1.420; 95% CI=1.062-1.898; $P=0.018$), while controlling for other variables in the model (Table 3). In both regression models, younger age, African-American race, and tobacco use/dependence were associated with lower likelihoods of AD adherence ($P < 0.05$).

The mean [±SD] time until AD nonpersistence was 172.3 [±130.4] days for the total sample. The AD persistence rate was, on average, significantly longer in the AD/SGA cohort than in the AD cohort by approximately 34 days (191.3 [±132.1] vs. 156.8 [±127.1] days). A Cox proportional hazards regression model found that the risk of AD nonpersistence was 23.2% significantly lower in the AD/SGA cohort, compared with the AD cohort (hazard ratio [HR]=0.768; 95% CI=0.659-0.896;

$P=0.001$). Younger age, African-American race, Hispanic ethnicity, and tobacco use/dependence were associated with significantly higher risks of AD nonpersistence (Table 4). Sensitivity analyses showed comparable results favoring the AD/SGA cohort when using a 30-day permissible gap (158.9 [±126.6] vs. 130.7 [±115.4]; HR=0.782; 95% CI=0.670-0.913; $P=0.002$) and a 60-day permissible gap (216.2 [±133.9] vs. 174.8 [±130.9] days; HR=0.719; 95% CI=0.611-0.840; $P < 0.001$).

Discussion

This study assessed medication adherence and persistence among 2 cohorts (AD/SGA vs. AD) of Texas Medicaid patients who were diagnosed with severe major depressive disorder with psychotic features. Somewhat unexpectedly, more than half of the total sample used AD monotherapy (n=510) compared with AD/SGA therapy (n=416). This deviation from first-line recommendations could be explained by a number of reasons, which this study was unable to measure. Since it is standard practice for providers to weigh the risks versus benefits of treatment when prescribing therapy,¹⁰ present comorbidities (e.g., diabetes mellitus) and the known adverse events of antipsychotics, such as weight gain and increased risks of elevated blood glucose and lipids, could potentially influence prescribing habits favoring AD monotherapy. This may be the case in this study, since patients on AD monotherapy had a significantly higher mean CCI score when compared with patients

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TABLE 2 Logistic Regression Analysis Comparing Likelihood of Antidepressant Adherence Based on PDC $\geq$ 80% Among Cohorts (N = 926)

	OR	95% CI		Wald χ^2	P Value ^a
AD/SGA vs. AD ^b	1.523	1.129	2.053	7.606	0.006
Age ^c	1.039	1.027	1.052	39.506	<0.001
Female vs. male	0.827	0.610	1.121	1.494	0.222
African American vs. Caucasian	0.612	0.419	0.894	6.462	0.011
Hispanic vs. Caucasian	0.744	0.505	1.096	2.242	0.134
Other ^d vs. Caucasian	1.232	0.552	2.748	0.259	0.611
Urban vs. rural	0.738	0.509	1.069	2.580	0.108
CCI ^e	0.919	0.817	1.034	1.957	0.162
Tobacco use/dependence vs. none ^f	0.636	0.437	0.927	5.546	0.019

^aSignificance at $P < 0.05$.

^bAdherent (PDC $\geq$ 80%): AD/SGA cohort = 38.7%; AD cohort = 28.4%.

^cRepresents age, in years, at the time of first AD prescription claim.

^dOther includes Asian, unknown.

^eWeighted index based on the Dartmouth-Mannitoba adaptation.

^fRepresents the only post-index characteristic.

AD = antidepressant; CCI = Charlson Comorbidity Index; CI = confidence interval; OR = odds ratio; PDC = proportion of days covered; SGA = second-generation antipsychotic.

TABLE 3 Logistic Regression Analysis Comparing Likelihood of Antidepressant Adherence Based on MPR $\geq$ 80% Among Cohorts (N = 926)

	OR	95% CI		Wald χ^2	P Value ^a
AD/SGA vs. AD ^b	1.420	1.062	1.898	5.596	0.018
Age ^c	1.044	1.031	1.056	51.360	<0.001
Female vs. male	0.922	0.684	1.242	0.285	0.594
African American vs. Caucasian	0.649	0.448	0.938	5.290	0.021
Hispanic vs. Caucasian	0.800	0.548	1.168	1.336	0.248
Other ^d vs. Caucasian	1.363	0.607	3.060	0.564	0.453
Urban vs. rural	0.758	0.528	1.089	2.249	0.134
CCI ^e	0.940	0.841	1.051	1.183	0.277
Tobacco use/dependence vs. none ^f	0.669	0.467	0.959	4.788	0.029

^aSignificance at $P < 0.05$.

^bAdherent (MPR $\geq$ 80%): AD/SGA cohort = 43.5%; AD cohort = 34.1%.

^cRepresents age, in years, at the time of first AD prescription claim.

^dOther includes Asian, unknown.

^eWeighted index based on the Dartmouth-Mannitoba adaptation.

^fRepresents the only post-index characteristic.

AD = antidepressant; CCI = Charlson Comorbidity Index; CI = confidence interval; MPR = medication possession ratio; OR = odds ratio; SGA = second-generation antipsychotic.

on AD/SGA therapy. Therefore, it is a possibility that patients deemed to have “less severe” psychotic depression were initiated with AD monotherapy after weighing the risks versus benefits of dual therapy.

To our knowledge, medication adherence measures using MPR and PDC have not been previously used in evaluating treatment adherence in psychotic depression. Craig et al. (2007) analyzed AD usage based on patient interviews,²⁸ but the present study represents the first known rates of AD adherence in psychotic depression based on PDC and MPR. Similarly, there are no known studies that evaluate medication persistence in severe major depressive disorder with psychotic

features. The authors support that the results of this study can help offer insight into practice guideline adherence among providers. For example, the Texas Medication Algorithm Project guidelines recommend using an antipsychotic medication for 1 to 2 months after a clinical response is achieved,¹⁰ and Wijkstra et al. (2010) support the continued use of an SGA for 4 months after a successful 2-month acute treatment course.¹⁵ These recommendations are comparable with the result of this study in which SGA therapy was continuously used for approximately 6 months before a treatment gap occurred. Conversely, our results show that patients persisted on their AD medications for less than 6 months, which is less than the recommended

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TABLE 4 Cox Proportional Hazards Regression Model Comparing Time to Nonpersistence (Based on 45-Day Permissible Gap of No Antidepressant Medication) Among Cohorts (N=926)

	HR	95% CI		Wald χ^2	P Value ^a
AD/SGA vs. AD ^b	0.768	0.659	0.896	11.283	0.001
Age ^c	0.982	0.976	0.988	36.684	<0.001
Female vs. male	1.025	0.876	1.200	0.097	0.755
African American vs. Caucasian	1.455	1.192	1.776	13.613	<0.001
Hispanic vs. Caucasian	1.301	1.061	1.594	6.408	0.011
Other ^d vs. Caucasian	1.204	0.783	1.852	0.713	0.398
Urban vs. rural	1.133	0.934	1.375	1.610	0.205
CCI ^e	1.010	0.956	1.067	0.124	0.725
Tobacco use/dependence vs. none ^f	1.249	1.040	1.501	5.678	0.017

^aSignificance at $P < 0.05$.

^bMean [$\pm$ SD] antidepressant persistence, in days, based on a 45-day permissible gap: AD/SGA cohort = 191.3 [$\pm$ 312.1]; AD cohort = 156.8 [$\pm$ 127.1].

^cRepresents age, in years, at the time of first AD prescription claim.

^dOther includes Asian, unknown.

^eWeighted index based on the Dartmouth-Mannitoba adaptation.

^fRepresents the only post-index characteristic.

AD=antidepressant; CCI=Charlson Comorbidity Index; CI=confidence interval; HR=hazard ratio; SD=standard deviation; SGA=second-generation antipsychotic.

6-9 months of AD continuation treatment after the remission of symptoms occurs.¹⁰ However, the possibility that patients were appropriately titrated by their physicians once their symptoms improved cannot be ruled out.

Finally, this study provides a unique addition to the present literature, since there remains a dearth of information regarding minority and Medicaid-qualifying indigent populations with psychotic depression. African-American and Hispanic minorities had poorer AD adherence and/or persistence compared with Caucasians, which has also been supported in other depression studies.^{29,31} Additionally, this study offered more insight with regard to tobacco use/dependence—tobacco users and dependents had significantly worse rates of AD adherence (based on MPR and PDC) and AD persistence. Ultimately, the authors believe that further research on tobacco use and dependence may be necessary in order to better understand the treatment outcomes associated with psychotic depression.

Limitations

While this is the first known study to analyze psychotic depression in relation to PDC, MPR, and medication persistence, there are several limitations to consider while interpreting the study results. First, the data only represent prescription claims—they are not necessarily indicative of actual prescription usage. However, this limitation was partially reduced by including only the patients that had at least 2 prescription claims as a proxy for medication usage. Second, tobacco use/dependence is likely to be underreported in large claims databases. Third, the study's generalizability is limited to similar populations—in this case, Medicaid-qualifying indigent populations with high rates of African Americans and Hispanics

who were first-time users (or those with at least a 6-month wash-out period) of antidepressant and antipsychotic therapy for psychotic depression. Fourth, the authors cannot rule out coding inaccuracies associated with administrative claims data. Finally, since propensity scoring was not possible due to the already limited sample sizes and randomization was not an option, cohorts were significantly different at baseline, that is, patients in the AD cohort were younger and sicker based on CCI scores, which may have affected the overall adherence and persistence rates. However, in order to better control for this limitation, multivariate statistical analyses were employed.

Overall, selection bias was problematic in this study, since outcomes may have been due in part to inherent differences among patients instead of to the type of medication therapy received. Mental health scores and relapse rates were not available for this study, and as a result, the authors were unable to assess whether 1 cohort was more likely to consist of patients with a higher degree of depression or psychosis severity over the other. Similarly, the effect of physician-prescribing behavior and guideline adoption rates on study outcomes could not be assessed. It is possible that the lack of guideline adoption may have contributed to the larger sample of AD monotherapy users in this study³³; although notably, the Texas Medication Algorithm Project guidelines, which advocate the use of combination pharmacotherapy as first-line, have been available since 1999.¹⁰ Finally, it is estimated that 36.6%-59.0% of patients with major depressive disorder smoke tobacco in order to self-relieve the psychological and physical symptoms of depression³⁴; therefore, the lack of information on patient self-medication with tobacco may be an important limitation.

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Conclusions

Overall, the results of this study indicate that users of combination pharmacotherapy with an AD and an SGA had significantly better AD adherence compared with those on AD therapy alone. Also, combination pharmacotherapy users fared significantly better with regard to AD persistence. Nonetheless, there were a high number of AD monotherapy users in this study, indicating a notable deviation from the first-line treatment recommendations recommended by U.S. practice guidelines for psychotic depression.

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DISCLOSURES

Kim-Romo received funding to conduct this study from the PhRMA Foundation Pre-Doctoral Fellowship in Health Outcomes. Rascati, Richards, Ford, Wilson, and Beretvas declare no conflict of interest in relation to this manuscript.

Kim-Romo and Rascati collaborated on the study design, data analysis, study interpretation, and writing of this manuscript. Richards, Ford, Wilson, and Beretvas provided critical evaluation of the study design, analysis, and interpretation, as well as edited this manuscript.

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