

# Burden of EPS in Commercial Patients With Schizophrenia Initiating Atypical Antipsychotics

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Schizophrenia is a chronic, disabling mental health condition characterized by positive and negative symptoms that affects approximately 1.1% of the population.<sup>1,2</sup> Relapse is common and positive patient outcomes are observed in only 20% of cases.<sup>1</sup> Antipsychotics remain the cornerstone of pharmacologic treatment and are utilized both for the treatment of acute episodes and as maintenance therapy.<sup>1,3,4</sup> Although antipsychotics have been shown to be effective in managing schizophrenia symptoms and preventing relapse, they are also associated with adverse effects (AEs) that impact treatment adherence, long-term health outcomes, and patient quality-of-life (QOL) outcomes.<sup>3,5,6</sup>

Extrapyramidal symptoms (EPS) are involuntary hyperkinetic movement disorders that frequently affect the face, tongue, and extremities and include acute symptoms such as dystonia, akathisia, and parkinsonism, as well as more chronic manifestations of tardive akathisia and tardive dyskinesia.<sup>7</sup> The severity of EPS varies, and increased symptoms are associated with increased stigma and QOL impairments. Although EPS can occur spontaneously, they are commonly linked to excessive dopaminergic blockade or depletion in the basal ganglia caused by antipsychotic treatment.<sup>8</sup> Newer atypical antipsychotics (AAPs) are associated with lower rates of EPS compared with first-generation (typical) antipsychotics.<sup>5,9-10</sup> However, the risk of AEs is not fully ameliorated with AAPs, as studies report EPS in up to 30% of patients treated with AAPs. In addition, AAPs are also associated with increased cardiometabolic AEs compared with typical antipsychotics.<sup>3,5,9,10</sup>

Medication nonadherence in schizophrenia is associated with poor outcomes including increased risks of relapse, hospitalization, and suicide, as well as increased health care costs.<sup>3,5,6,11,12</sup> Development of EPS has been associated with poor outcomes including increased antipsychotic nonadherence, partially due to the reversibility of acute EPS following antipsychotic discontinuation.<sup>6,9-11</sup> As tolerability issues are some of the strongest predictors of nonadherence, the development of EPS in patients with schizophrenia has been suggested to be associated with an incremental economic burden.<sup>6,9,11,13,14</sup> The objectives of this study were to (1) examine the incidence of EPS and (2) assess the

## ABSTRACT

**OBJECTIVES:** Extrapyramidal symptoms (EPS) affect 15% to 30% of patients with schizophrenia treated with antipsychotics and have been associated with poor outcomes. This study examined the incidence and economic burden of EPS in patients with schizophrenia initiating atypical antipsychotics (AAPs).

**STUDY DESIGN:** Retrospective analysis of secondary deidentified administrative claims database.

**METHODS:** Patients with schizophrenia initiating AAPs with no prior EPS were identified in the MarketScan Commercial and Medicare Supplemental databases from January 1, 2012, to December 31, 2018. Incidence of EPS (diagnosis or medication use) was assessed in the year following AAP initiation. Annual all-cause and schizophrenia-related health care resource utilization (HCRU) and costs were assessed in cohorts who did or did not develop EPS in the year following first EPS claim (EPS cohort) or randomly assigned index date (non-EPS cohort). Multivariate regression was used to compare all-cause and schizophrenia-related total health care costs and inpatient admissions between cohorts.

**RESULTS:** A total of 3558 patients with schizophrenia newly initiating AAPs were identified; 22.1% developed EPS in the year following AAP initiation (incidence: 26.9 cases per 100 person-years). Multivariate analyses revealed that patients with EPS had 34% higher odds of all-cause [odds ratio [OR], 1.3361; 95% CI, 1.0770-1.6575;  $P < .01$ ] and 84% increased odds of schizophrenia-related [OR, 1.8436; 95% CI, 1.0434-2.4219;  $P < .0001$ ] inpatient admission compared with the non-EPS cohort. The EPS cohort also evidenced significantly higher adjusted all-cause [\$26,632 vs \$21,273;  $P < .001$ ] and schizophrenia-related [\$9018 vs \$4475;  $P < .0001$ ] costs compared with the non-EPS cohort.

**CONCLUSIONS:** The 20% of patients who developed EPS in the year following AAP initiation evidenced significantly increased HCRU and costs over the postindex period. Schizophrenia therapies with reduced EPS risk are needed to improve patient care.

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## TAKEAWAY POINTS

Extrapyramidal symptoms (EPS) are common adverse effects of antipsychotic treatment in schizophrenia and are associated with negative quality-of-life impacts, poor clinical outcomes, and morbidity and mortality. In this analysis, approximately 20% of commercially insured patients with schizophrenia initiating atypical antipsychotics developed EPS within 1 year. Development of EPS was associated with significantly higher rates of hospitalization and increased health care costs.

- ▶ Patients with EPS had 34% and 84% higher odds of all-cause and schizophrenia-related hospitalization, respectively.
- ▶ All-cause health care costs were 25% higher and schizophrenia-related health care costs were 200% higher for patients with EPS compared with those without.

xx) or EPS medication claims (deutetrabenazine, valbenazine, tetrabenazine, amantadine, bexmefoprol, trihexyphenidyl, or biperiden) during the preindex period. Additionally, patients with a fill or administration for a typical antipsychotic (chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, pimozide, prochlorperazine, thioridazine, thiothixene, or trifluoperazine) or a claim with a diagnosis for Parkinson disease at any time were excluded. Individuals who met these criteria were part of the EPS incidence analysis.

economic burden of EPS in patients with schizophrenia newly initiating AAPs.

## METHODS

### Data Source

This study utilized the MarketScan Commercial and Medicare Supplemental databases, composed of deidentified administrative claims data, from January 1, 2012, through December 31, 2018. The commercial database contains the full health care (inpatient, outpatient, and outpatient pharmacy) experience of employees and their dependents covered under a variety of employer-sponsored health plans. The Medicare Supplemental database includes the full health care experience of individuals with a Medicare supplemental insurance policy provided by an employer; both supplemental insurance and Medicare-paid portions of claims are represented. All study data were obtained using *International Classification of Diseases, Ninth Revision, Clinical Modification*, and *Tenth Revision, Clinical Modification (ICD-9-CM and ICD-10-CM)* codes; Current Procedural Terminology Fourth Edition codes; Healthcare Common Procedure Coding System codes; and National Drug Codes.

### Patient Selection

Eligible patients were adults diagnosed with schizophrenia newly initiating AAPs (aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, or ziprasidone) on or after January 1, 2012. The first AAP claim served as the index date; patients were required to have medical, pharmacy, and mental health/substance abuse (MHSA) coverage for 6 months prior to and 12 months following index. To ensure that patients were new AAP users, individuals with any evidence of AAP use (administrations or fills) in the preindex period were excluded. Patients were also required to have at least 1 inpatient or nondiagnostic outpatient claim for schizophrenia and could not have any EPS diagnoses (*ICD-9-CM* codes: 332.1, 333.1, 333.5, 333.72, 333.79, 333.81-333.83, 333.85, 333.89, 333.90, 333.99, 781.0; *ICD-10-CM* codes: G21.1x, G21.2, G21.8, G24.01, G24.02, G24.2-G24.9, G25.1-G25.4, G25.61, G25.7x, G25.89, G25.9, R25.

Patients who qualified for the incidence cohort (patients with schizophrenia initiating treatment with an AAP) could further qualify for either the EPS or non-EPS cohorts used in the economic burden analysis. The EPS cohort included patients who developed EPS during the 12-month postindex period. The first EPS diagnosis or medication fill during this period served as the EPS index date. Patients were also required to have evidence of medical, pharmacy, and MHSA coverage for 6 months prior and 12 months following the EPS index date. Individuals who did not have evidence of EPS in the 12-month postindex period could qualify for the non-EPS cohort. A random non-EPS index date was assigned, and continuous medical, pharmacy, and MHSA eligibility was required for the 6 months prior to and 12 months following the non-EPS index date. Individuals who had evidence of EPS diagnoses or medication fills in the 12 months following their random non-EPS index date were also excluded from the EPS cohort because of delayed development (> 12 months following AAP initiation) of EPS. As the EPS and non-EPS index dates were offset from the index date for the incidence cohort, it is possible that EPS or non-EPS patients did not exhibit any AAP use in the 6-month preindex period of the economic burden analysis; these patients were still included in the economic burden analysis because prior AAP use had been established as part of the incidence analyses. The final non-EPS cohort was established by matching non-EPS patients based on age group and gender at a 1:1 to 1:3 ratio depending on available sample sizes.

### Outcomes and Descriptive Analyses

For the incidence analysis, patients were followed from index (first AAP claim) to the first EPS diagnosis, the first EPS medication claim, or the end of the 1-year follow-up. The incidence of EPS was reported as the percentage of patients who evidenced EPS over the 1-year follow-up and the rate of EPS per 100 person-years.

The economic analysis utilized the EPS and non-EPS cohorts and their respective EPS or non-EPS index dates. Demographics were measured on the EPS or non-EPS index date, whereas baseline clinical characteristics were measured over the 6-month preindex period except for AAP use, which was assessed over the preindex period and the index date. Health care resource utilization (HCRU) and cost outcomes were evaluated over the 6-month preindex and 12-month

postindex periods. All-cause and schizophrenia-related HCRU and costs were calculated based on inpatient admissions, outpatient (emergency department [ED] visits, office visits, and other services) encounters, and outpatient pharmacy fills. Schizophrenia-related HCRU and costs were identified by the presence of a diagnosis of schizophrenia on the claim line or by fills for AAPs or EPS medications in the outpatient pharmacy. Costs were calculated based on paid amounts on adjudicated claims including both insurer and patient payment and inflated to 2018 US\$; costs for capitated plans were estimated via payment proxy. All analyses were conducted using WPS version 4.1 (World Programming).

**Multivariate Analyses**

Risk of all-cause or schizophrenia-related inpatient admissions were assessed via logistic regression. All-cause and schizophrenia-related costs were adjusted using 2-part models with Firth logistic regression followed by gamma family general linear models with log link; covariate-adjusted costs were calculated using the recycled prediction method. Covariates for all models were measured during the preindex period or on the index date and included age; sex; region of residence; plan type; Charlson Comorbidity Index (CCI) score; AAP days' supply; diagnoses of depression, bipolar disorder, anxiety, or alcohol/substance abuse; inpatient admission or ED visit; and total health care costs.

**RESULTS**

**EPS Incidence**

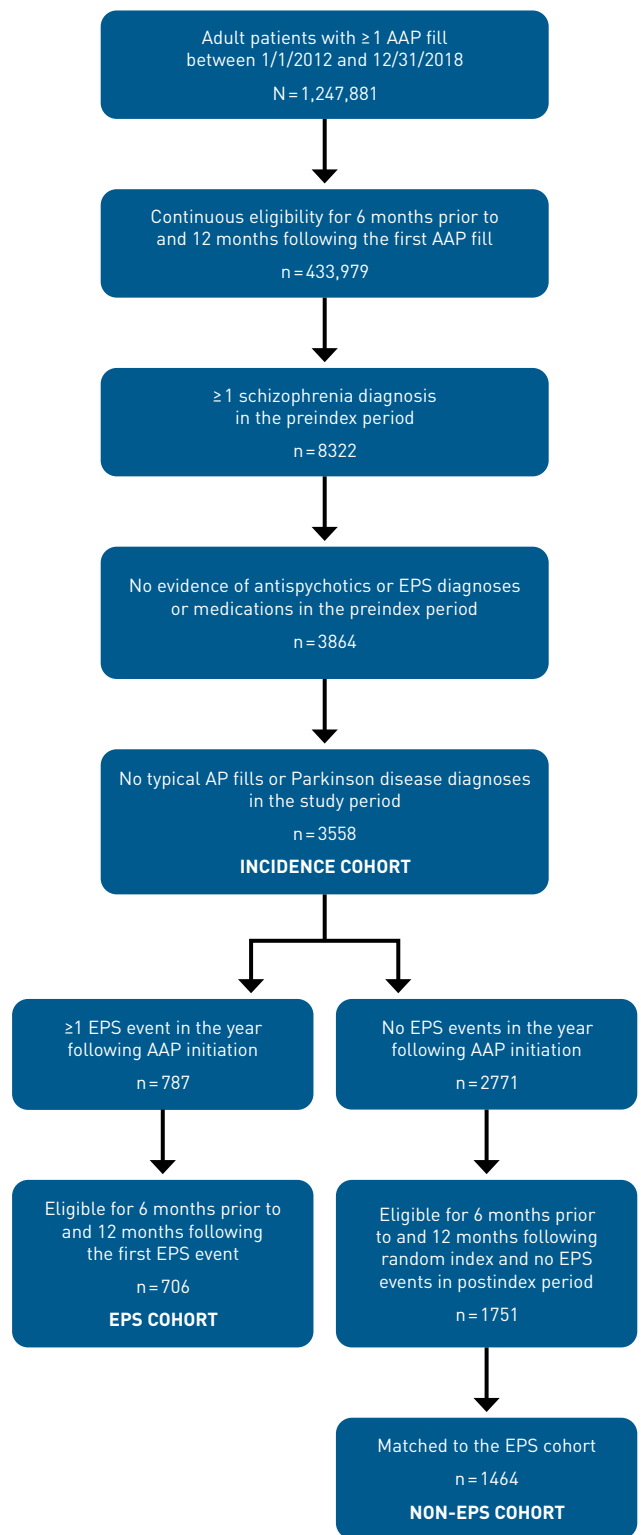
A total of 3558 patients qualified for the EPS incidence analysis (Figure 1). Of these, 787 (22.1%) of patients developed EPS in the year following AAP initiation, yielding an EPS incidence rate of 26.9 cases per 100 person-years. Mean (SD) time to EPS among patients who developed EPS was 77.3 (106.0) days.

**Demographics and Clinical Characteristics**

A total of 2170 patients (706 EPS patients and 1464 non-EPS patients) qualified for the economic burden analysis (Figure 1). Most patients were male; the EPS cohort was slightly younger than the non-EPS cohort (Table 1). Physical comorbidity burden was similar between cohorts in the preindex period. A greater proportion of EPS patients had a diagnosis of anxiety or alcohol/substance abuse in the preindex period, whereas non-EPS patients were more likely to have a dementia diagnosis (Table 1). The most filled co-medications during the preindex period were anticonvulsants, antidepressants, and anxiolytics; a significantly greater proportion of non-EPS patients had a fill for an antidepressant ( $P < .0001$ ).

Examination of AAPs during the preindex period or on the index date revealed an increased proportion of EPS patients using AAPs; however, among AAP users, non-EPS patients exhibited a higher mean days' supply ( $P < .001$ ) (Table 1). Most patients in both cohorts had a days' supply of 1 to 30 days in the preindex period or on the index date.

**FIGURE 1. Sample Attrition**



AAP, atypical antipsychotic; AP, antipsychotic; EPS, extrapyramidal symptoms.

**TABLE 1.** Demographics and Clinical Characteristics<sup>a</sup>

Characteristics	EPS cohort		Non-EPS cohort		P	Standardized difference
	n = 706		n = 1464			
	N/mean	%/SD	N/mean	%/SD		
<b>Demographics<sup>b</sup></b>						
Age in years (mean, SD)	33.1	16.9	37.2	18.0	<b>&lt;.0001</b>	<b>-0.2324</b>
Age category in years (n, %)						
18-24	383	54.2%	627	42.8%	<b>&lt;.0001</b>	<b>0.2637</b>
25-34	88	12.5%	168	11.5%		
35-44	48	6.8%	144	9.8%		
45-54	70	9.9%	195	13.3%		
55-64	65	9.2%	195	13.3%		
65-74	40	5.7%	99	6.8%		
≥ 75	12	1.7%	36	2.5%		
Sex (n, %)						
Male	417	59.1%	795	54.3%	<b>.0364</b>	0.0787
Female	289	40.9%	669	45.7%		
Geographic region (n, %)						
Northeast	162	22.9%	290	19.8%	.1422	<b>0.1202</b>
North Central	156	22.1%	372	25.4%		
South	276	39.1%	536	36.6%		
West	107	15.2%	257	17.6%		
Unknown	5	0.7%	9	0.6%		
Insurance plan type (n, %)						
Comprehensive	67	9.5%	174	11.9%	.2034	<b>0.1157</b>
EPO/PPO	390	55.2%	775	52.9%		
HMO	110	15.6%	197	13.5%		
POS	45	6.4%	93	6.4%		
CDHP/HDHP	86	12.2%	212	14.5%		
Unknown	8	1.1%	13	0.9%		
Index year (n, %)						
2012	189	26.8%	395	27.0%	.9022	0.0716
2013	131	18.6%	277	18.9%		
2014	97	13.7%	219	15.0%		
2015	110	15.6%	208	14.2%		
2016	86	12.2%	182	12.4%		
2017	77	10.9%	159	10.9%		
2018	16	2.3%	24	1.6%		

(continued)

**Preindex Period HCRU and Costs**

A significantly greater proportion of EPS patients had at least 1 all-cause hospitalization or ED visit compared with non-EPS patients during the 6-month preindex period ( $P < .0001$ ) (Table 1). Conversely, the non-EPS cohort had a greater proportion of patients with at least 1 office visit (77.8% vs 72.1%;  $P < .01$ ) or outpatient pharmacy fill (88.3% vs 77.6%;  $P < .0001$ ). Trends in schizophrenia-related HCRU were similar: A greater proportion of EPS patients had at least 1 schizophrenia-related hospitalization (67.0% vs 39.1%;  $P < .0001$ ) or ED visit (14.6% vs 8.6%;  $P < .0001$ ), and a greater proportion of

non-EPS patients had at least 1 office visit (22.1% vs 17.7%;  $P < .05$ ) or outpatient pharmacy fill (69.5% vs 56.7%;  $P < .0001$ ). All-cause total preindex period health care costs were significantly higher in the EPS cohort compared with the non-EPS cohort ( $P < .05$ ) (Table 1).

**Postindex Period HCRU and Costs**

EPS patients evidenced increased postindex period HCRU, with a higher proportion having at least 1 hospitalization, ED visit, office visit, other outpatient service, or outpatient pharmacy fill compared with the non-EPS cohort ( $P < .05$ ) (Table 2). The trend toward increased

**TABLE 1.** (Continued) Demographics and Clinical Characteristics<sup>a</sup>

Characteristics	EPS cohort		Non-EPS cohort		P	Standardized difference
	n = 706		n = 1464			
	N/mean	%/SD	N/mean	%/SD		
<b>Clinical characteristics<sup>c</sup></b>						
CCI score (mean, SD)	0.4	1.0	0.5	1.2	.1143	-0.0749
Physical and psychiatric comorbidities (n, %)						
Diabetes	54	7.6%	127	8.7%	.4180	-0.0309
Cardiovascular disease	116	16.4%	243	16.6%	.9215	-0.0037
Hypertension	154	21.8%	320	21.9%	.9811	-0.0009
Hyperlipidemia	75	10.6%	181	12.4%	.2391	-0.0451
Obesity	53	7.5%	81	5.5%	.0734	0.0639
Bipolar disorder	253	35.8%	510	34.8%	.6477	0.0171
Anxiety	124	17.6%	161	11.0%	<b>&lt;.0001</b>	<b>0.1492</b>
Depression	270	38.2%	520	35.5%	.2165	0.0460
Personality disorders	38	5.4%	75	5.1%	.7988	0.0095
Alcohol/substance abuse	275	39.0%	466	31.8%	<b>.0010</b>	<b>0.1210</b>
Dementia	26	3.7%	83	5.7%	<b>.0471</b>	-0.0797
AAP fills in the preindex period or on index (n, %)	691	97.9%	1302	88.9%	<b>&lt;.0001</b>	<b>0.3379</b>
AAP days' supply in preindex period or on index (mean, SD)	40.2	63.6	51.6	66.4	<b>.0002</b>	<b>-0.1750</b>
Co-medication use (n, %)						
Antidepressants	241	34.1%	628	42.9%	<b>&lt;.0001</b>	<b>-0.1486</b>
Anticonvulsants	176	24.9%	380	26.0%	.6076	-0.0193
Anxiolytics	157	22.2%	344	23.5%	.5143	-0.0246
Mood stabilizers	43	6.1%	96	6.6%	.6774	-0.0157
<b>All-cause HCRU and costs<sup>c</sup></b>						
Inpatient admissions (n, %)	524	74.2%	711	48.6%	<b>&lt;.0001</b>	<b>0.4562</b>
Emergency department visits (n, %)	343	48.6%	552	37.7%	<b>&lt;.0001</b>	<b>0.1795</b>
Total health care costs (mean, SD)	\$25,120	\$40,990	\$19,320	\$43,300	<b>.0030</b>	<b>0.1376</b>
Inpatient costs	\$18,754	\$38,147	\$11,621	\$30,953	<b>&lt;.0001</b>	<b>0.2054</b>
Outpatient costs	\$5197	\$11,715	\$6034	\$20,513	.3138	-0.0501
Outpatient pharmacy costs	\$1169	\$3626	\$1665	\$11,256	.2533	-0.0593

AAP, atypical antipsychotic; CCI, Charlson Comorbidity Index; CDHP, consumer-directed health plan; EPO, exclusive provider organization; EPS, extrapyramidal symptoms; HCRU, health care resource utilization; HDHP, high-deductible health plan; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization.

<sup>a</sup>Bold cells indicate significant differences between cohorts measured by either a *P* < .05 or a standardized mean difference < -0.1 or > 0.1.

<sup>b</sup>Demographics were measured on the index date.

<sup>c</sup>Clinical characteristics and HCRU and costs were measured over the preindex period.

HCRU in the EPS cohort was also observed for schizophrenia-related HCRU, although differences were amplified between groups, with 2-fold more EPS patients with a schizophrenia-related hospitalization or ED visit compared with non-EPS patients (*P* < .0001) (Table 2).

Despite the increased HCRU in the EPS cohort, all-cause health care costs were similar between the EPS and non-EPS cohorts during the postindex period (*P* = .5109); schizophrenia-related costs were more than 2-fold higher in the EPS cohort (*P* < .0001) (Table 2).

### Multivariate Analyses

Multivariate regression confirmed that EPS patients had 34% higher odds of all-cause inpatient admission and 84% higher odds

of schizophrenia inpatient admission compared with non-EPS patients (Figure 2). Risk factors for postindex period all-cause admissions included preindex anxiety (odds ratio [OR], 1.61; 95% CI, 1.22-1.12; *P* < .001) or alcohol/substance abuse (OR, 1.53; 95% CI, 1.21-1.92; *P* < .001) diagnoses; presence of at least 1 preindex inpatient admission or ED visit (OR, 1.72; 95% CI, 1.20-2.48; *P* < .01); and preindex costs in the 10th decile (OR, 1.93; 95% CI, 1.03-3.60; *P* < .05). Risk factors for postindex period schizophrenia-related inpatient admissions were preindex alcohol or substance abuse diagnoses (OR, 1.52; 95% CI, 1.13-2.05; *P* < .01) and presence of at least 1 preindex inpatient admission or ED visit (OR, 2.45; 95% CI, 1.47-4.10; *P* < .001); preindex bipolar diagnoses (OR, 0.59; 95% CI,

**TABLE 2.** Postindex Period Health Care Resource Utilization and Costs<sup>a</sup>

	EPS cohort		Non-EPS cohort		P
	n = 706		n = 1464		
	N/mean	%/SD	N/mean	%/SD	
<b>All-cause HCRU</b>					
<b>Inpatient</b>					
Patients with an admission (n, %)	224	31.7%	336	23.0%	<b>&lt;.0001</b>
Number of inpatient admissions (mean, SD) <sup>b</sup>	1.8	1.2	1.7	1.4	.4531
<b>Outpatient</b>					
<b>ED visits</b>					
Patients with an ED visit (n, %)	279	39.5%	494	33.7%	<b>.0085</b>
Number of ED visits (mean, SD) <sup>b</sup>	2.3	2.4	2.3	2.8	.9427
<b>Office visits</b>					
Patients with a visit (n, %)	641	90.8%	1274	87.0%	<b>.011</b>
Number of visits (mean, SD) <sup>b</sup>	9.1	8.0	8.3	7.5	<b>.028</b>
<b>Other outpatient services</b>					
Patients with service (n, %)	683	96.7%	1333	91.1%	<b>&lt;.0001</b>
Number of services (mean, SD) <sup>b</sup>	21.8	25.2	18.2	22.6	<b>.0013</b>
<b>Outpatient pharmacy</b>					
Patients with a prescription (n, %)	705	99.9%	1334	91.1%	<b>&lt;.0001</b>
Number of prescriptions (mean, SD) <sup>b</sup>	34.7	31.6	29.9	31.8	<b>.0010</b>
<b>All-cause health care costs</b>					
Inpatient costs (mean, SD)	\$10,867	\$31,659	\$7185	\$28,878	<b>.0071</b>
Outpatient costs (mean, SD)	\$9021	\$15,667	\$10,378	\$47,602	.4603
ED visit costs (mean, SD)	\$988	\$2638	\$848	\$3006	.2882
Office visit costs (mean, SD)	\$949	\$1178	\$855	\$1546	.1516
Other outpatient services costs (mean, SD)	\$7084	\$14,718	\$8676	\$46,670	.3760
Outpatient pharmacy costs (mean, SD)	\$4688	\$9017	\$4962	\$36,127	.8427
Total medical costs (mean, SD)	\$19,888	\$38,214	\$17,563	\$64,904	.3786
Total costs (mean, SD)	\$24,576	\$39,869	\$22,525	\$78,080	.5109

(continued)

0.44-0.80;  $P < .001$ ) were negatively associated with schizophrenia-related hospitalization risk.

Multivariate adjustment of postindex period all-cause and schizophrenia-related costs for baseline demographic and clinical characteristics revealed that among patients with postindex period costs, EPS patients had significantly higher all-cause (\$26,632 vs \$21,273;  $P < .001$ ) and schizophrenia-related (\$9018 vs \$4475;  $P < .0001$ ) postindex period costs compared with non-EPS patients (Figure 3; eAppendix Tables 1 and 2 [available at [ajmc.com](http://ajmc.com)]). Increased all-cause total costs in the postindex period were associated with having EPS (OR, 1.21; 95% CI, 1.08-1.36;  $P < .001$ ), increased age (OR, 1.01; 95% CI, 1.00-1.01;  $P < .001$ ), higher preindex CCI score (OR, 1.17; 95% CI, 1.11-1.24;  $P < .0001$ ), preindex depression (OR, 1.23; 95% CI, 1.09-1.38;  $P < .001$ ) or alcohol/substance abuse (OR, 1.31; 95% CI, 1.16-1.49;  $P < .0001$ ) diagnoses, and preindex total all-cause costs above the third decile compared with the first decile (range: OR, 1.57; 95% CI, 1.22-2.03;  $P < .001$  to OR, 7.44; 95% CI, 5.52-10.03;  $P < .0001$ ). Reduced all-cause health care costs were

associated with residence in the South/unknown (OR, 0.84; 95% CI, 0.73-0.97;  $P < .05$ ) or West (OR, 0.83; 95% CI, 0.70-0.99;  $P < .05$ ) regions compared with the Northeast; comprehensive (OR, 0.75; 95% CI, 0.62-0.91;  $P < .01$ ) or unknown (OR, 0.59; 95% CI, 0.35-0.99;  $P < .05$ ) plan type compared with preferred provider organization/exclusive provider organization; preindex through the index date AAP days' supply of 0 days (OR, 0.79; 95% CI, 0.64-0.99;  $P < .05$ ), 31 to 60 days (OR, 0.81; 95% CI, 0.69-0.96;  $P < .05$ ), or 61 to 90 days (OR, 0.73; 95% CI, 0.60-0.90;  $P < .01$ ) compared with 1 to 30 days; and preindex inpatient admission or ED visits (OR, 0.64; 95% CI, 0.54-0.76;  $P < .0001$ ). Increased schizophrenia-related total costs were associated with the presence of an EPS diagnosis (OR, 1.65; 95% CI, 1.42-1.92;  $P < .0001$ ), preindex through the index date AAP days' supply of 0 vs 1 to 30 days (OR, 1.56; 95% CI, 1.05-2.31;  $P < .05$ ), and preindex total all-cause costs above the third decile compared with the first decile (range: OR, 1.62; 95% CI, 1.14-2.29;  $P < .01$  to OR, 5.25; 95% CI, 3.48-7.93;  $P < .0001$ ). Reduced schizophrenia-related costs were associated with female sex (OR, 0.81; 95% CI, 0.69-0.95;



**TABLE 2.** (Continued) Postindex Period Health Care Resource Utilization and Costs<sup>a</sup>

	EPS cohort		Non-EPS cohort		P
	n = 706		n = 1464		
	N/mean	%/SD	N/mean	%/SD	
<b>Schizophrenia-related HCRU</b>					
<b>Inpatient</b>					
Patients with an admission (n, %)	135	19.1%	139	9.5%	<b>&lt;.0001</b>
Number of inpatient admissions (mean, SD) <sup>b</sup>	1.6	1.0	1.3	0.7	<b>.0480</b>
<b>Outpatient</b>					
<b>ED visits</b>					
Patients with an ED visit (n, %)	81	11.5%	69	4.7%	<b>&lt;.0001</b>
Number of ED visits (mean, SD) <sup>b</sup>	1.6	2.3	1.7	1.2	.9091
<b>Office visits</b>					
Patients with a visit (n, %)	286	40.5%	439	30.0%	<b>&lt;.0001</b>
Number of visits (mean, SD) <sup>b</sup>	5.3	4.6	4.4	4.3	<b>.0092</b>
<b>Other outpatient services</b>					
Patients with service (n, %)	377	53.4%	492	33.6%	<b>&lt;.0001</b>
Number of services (mean, SD) <sup>b</sup>	10.4	17.0	7.8	10.7	<b>.0060</b>
Patients with antipsychotic or EPS medication administration (n, %)	21	3.0%	20	1.4%	<b>.0099</b>
Number of antipsychotic or EPS administrations (mean, SD) <sup>b</sup>	4.3	6.4	9.0	6.2	<b>.0235</b>
<b>Antipsychotic or EPS medication outpatient pharmacy</b>					
Patients with a prescription (n, %)	692	98.0%	1080	73.8%	<b>&lt;.0001</b>
Number of prescriptions (mean, SD) <sup>b</sup>	12.9	10.1	7.2	6.7	<b>&lt;.0001</b>
<b>Schizophrenia-related health care costs<sup>b</sup></b>					
Inpatient costs (mean, SD)	\$4896	\$18,134	\$1536	\$8169	<b>&lt;.0001</b>
Outpatient costs (mean, SD)	\$2037	\$5768	\$838	\$3108	<b>&lt;.0001</b>
ED visit costs (mean, SD)	\$189	\$977	\$68	\$471	<b>.0001</b>
Office visit costs (mean, SD)	\$231	\$588	\$169	\$1248	.2086
Other outpatient services costs (mean, SD)	\$1521	\$5096	\$499	\$1923	<b>&lt;.0001</b>
Antipsychotic or EPS medication administration costs (mean, SD)	\$96	\$1536	\$102	\$1242	.9316
Outpatient pharmacy costs (mean, SD)	\$3013	\$5849	\$1861	\$4177	<b>&lt;.0001</b>
Total medical costs (mean, SD)	\$6933	\$20,497	\$2374	\$9094	<b>&lt;.0001</b>
Total costs (mean, SD)	\$9946	\$21,782	\$4235	\$10,223	<b>&lt;.0001</b>

ED, emergency department; EPS, extrapyramidal symptoms; HCRU, health care resource utilization.

<sup>a</sup>Bold cells indicate significant differences between cohorts measured by a  $P < .05$ .

<sup>b</sup>Among patients with at least 1 service/fill.

$P < .01$ ), South/unknown vs Northeast region of residence (OR, 0.81; 95% CI, 0.66-0.98;  $P < .05$ ), higher CCI score (OR, 0.89; 95% CI, 0.83-0.95;  $P < .001$ ), preindex through the index date days' supply of 61 to 90 vs 1 to 30 days (OR, 0.73; 95% CI, 0.55-0.97;  $P < .05$ ), preindex bipolar diagnoses (OR, 0.59; 95% CI, 0.50-0.69;  $P < .0001$ ), and preindex inpatient admission or ED visits (OR, 0.66; 95% CI, 0.52-0.84;  $P < .001$ ).

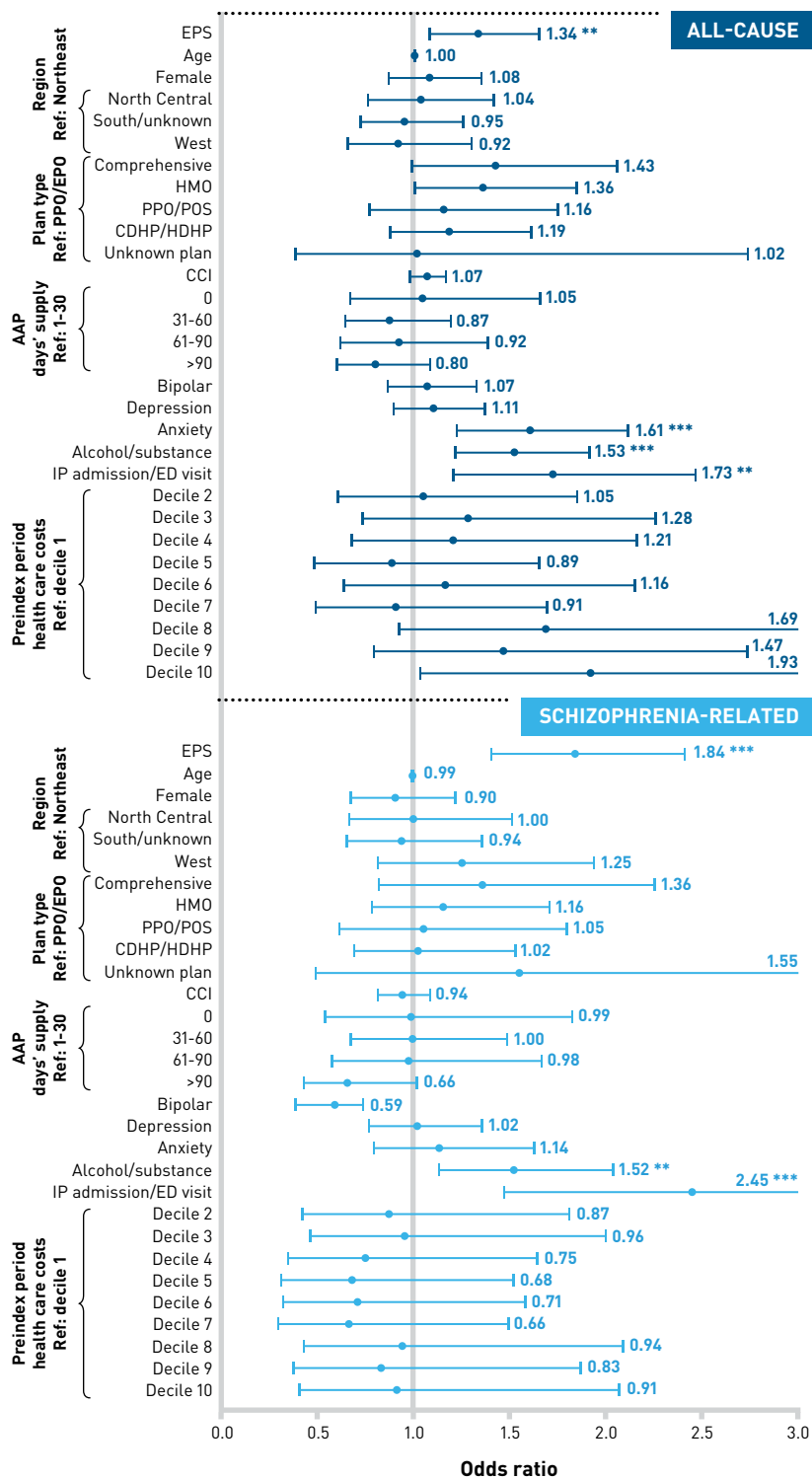
## DISCUSSION

This retrospective analysis examined the incidence and economic burden of EPS in a population of commercially insured patients with schizophrenia. Approximately 1 in 5 patients (22.1%) with

schizophrenia developed EPS in the year following AAP initiation. Patients who developed EPS had 34% increased odds of all-cause inpatient admissions and 84% increased odds of schizophrenia-related inpatient admission over the postindex period compared with patients who did not develop EPS. Consistent with increased HCRU, all-cause adjusted total health care costs were approximately 25% higher (\$26,632 vs \$21,273) for patients with EPS whereas their schizophrenia-related adjusted total health care costs were double those of the non-EPS cohort (\$9018 vs \$4475). Findings from this analysis demonstrate a notable impact of EPS on schizophrenia HCRU and costs.

Our finding that approximately 22% of patients exhibited EPS is reflective of the current literature, which reports EPS in up to

FIGURE 2. Adjusted All-Cause and Schizophrenia-Related Hospitalizations



30% of patients treated with AAPs.<sup>9,10</sup> In our analysis, median time to EPS among affected patients was 21.0 days, indicating rapid onset of symptoms and/or prophylactic prescription of medications, such as anticholinergics, to help mitigate EPS development.<sup>15,16</sup> Our rate of EPS is higher than that reported by Abouzaid et al in one of the few other studies that have used administrative claims to examine the incidence of EPS in schizophrenia; they reported an incidence of EPS of 12.6% in Medicaid patients with schizophrenia over the 90 days following antipsychotic initiation.<sup>14</sup> The shorter period of follow-up in their study, 90 days vs 12 months in our analysis, likely contributes to their lower rate of EPS. Limiting our follow-up to 90 days, we observed an incidence of EPS at 15.1%, which approximates the findings of Abouzaid et al.<sup>14</sup>

Increased HCRU among patients with EPS reported here is consistent with limited, prior work.<sup>14</sup> In our analysis, patients with EPS were significantly more likely to be hospitalized compared with non-EPS patients, with a 34% increased risk of all-cause hospitalization and an 84% increased risk of schizophrenia-related hospitalization. Abouzaid et al also reported increased HCRU and costs among patients with EPS compared with non-EPS patients within a Medicaid sample.<sup>14</sup> In their analysis, they found a 53% increased risk of all-cause hospitalization in patients with EPS compared with non-EPS patients; the risk of schizophrenia-related hospitalization was more than double. Although the ORs for hospitalization risk found by Abouzaid et al were slightly higher than those reported here, their findings are very much aligned with ours.

We also observed that adjusted all-cause and schizophrenia-related total health care costs were 25% and more than 200% higher in the EPS cohort compared with the non-EPS cohort, respectively. Abouzaid et al reported lower health care costs than this analysis, consistent with their use of a Medicaid sample. However, like our analysis, they found a greater difference in adjusted schizophrenia-related total costs compared with all-cause total costs, with patients with EPS incurring all-cause and schizophrenia-related total costs that were approximately 23% and 40% higher than those of non-EPS patients, respectively.<sup>14</sup>

AAP, atypical antipsychotic; CCI, Charlson Comorbidity Index; CDHP, consumer-directed health plan; ED, emergency department; EPO, exclusive provider organization; EPS, extrapyramidal symptoms; HDHP, high-deductible health plan; HMO, health maintenance organization; IP, inpatient; POS, point of service; PPO, preferred provider organization; ref, reference.

\**P* < .05; \*\**P* < .01; \*\*\**P* < .001.



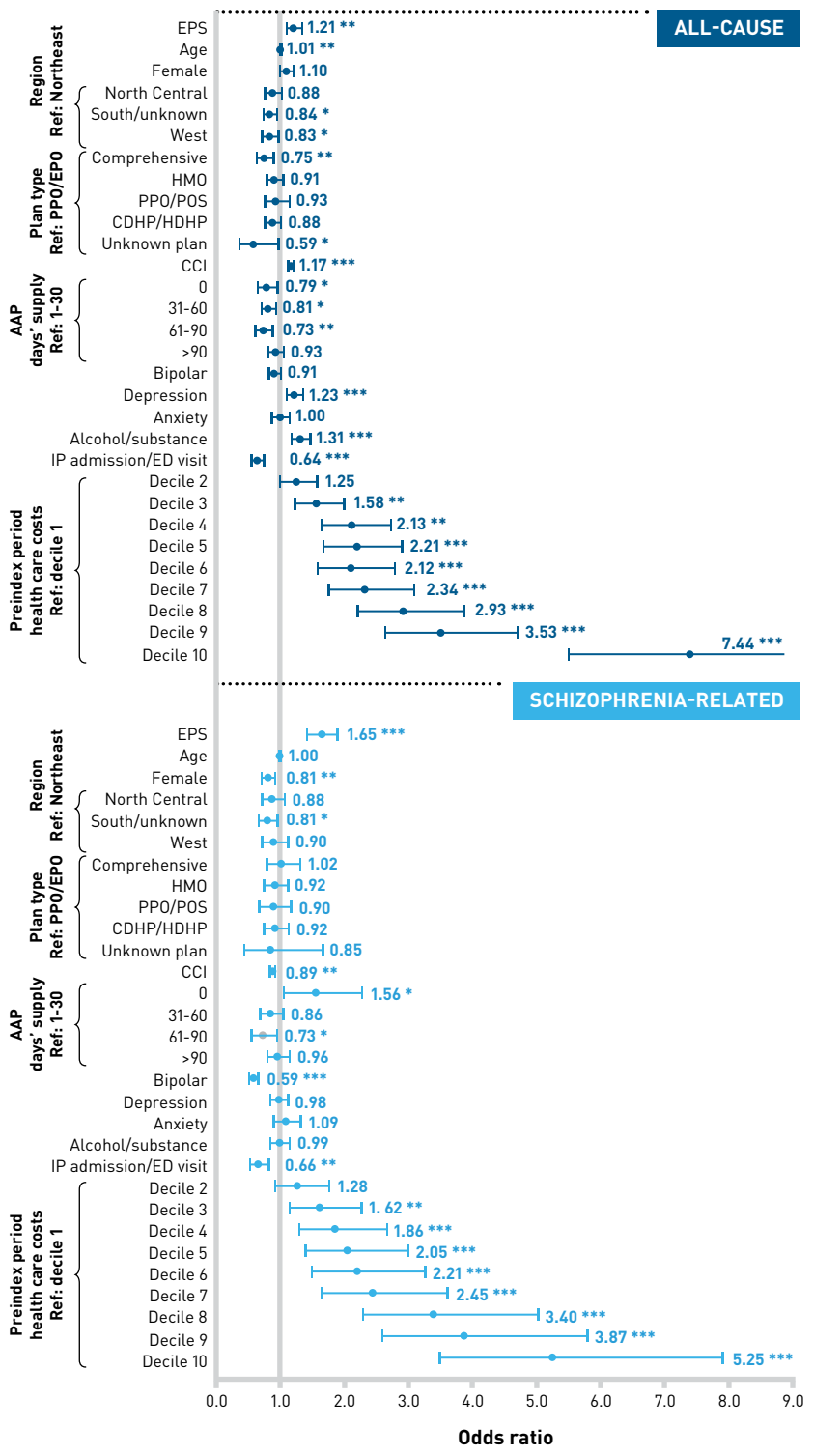
**Limitations**

There are several limitations to this study. First, clinical information was derived from adjudicated claims collected for billing and may be subject to misclassification or miscoding. For example, EPS were defined via diagnosis codes and medication fills/administrations; patients experiencing EPS who did not seek medical intervention would not be identifiable in the database. Similarly, clinician assessments of schizophrenia severity were not available; thus, severity may differ between cohorts. Our sample also included patients with prevalent schizophrenia; therefore, the chronicity of the disorder and prior disease history remain unknown. Individuals with antipsychotic use in the 6-month preindex period were excluded; however, it is possible that patients had earlier, unidentified use of antipsychotics. Multivariate modeling was used to control for differences in baseline demographic and clinical characteristics; however, these adjustments were limited to factors measurable in claims. This analysis was also conducted within a sample of patients with a commercial or Medicare supplemental insurance; findings may not extend to individuals with other types of insurance or the uninsured. Finally, medication utilization was assessed through outpatient pharmacy prescription fills. There is no way to confirm that filled medications were utilized, a point that may be particularly relevant in schizophrenia, in which high levels of nonadherence have been reported.

**CONCLUSIONS**

Our analyses indicate that EPS remain a significant problem in patients with schizophrenia treated with AAPs, with approximately 20% of new AAP users developing EPS within 1 year. The burden of EPS for these individuals carries economic implications, as we observed increased rates of hospitalization and health care costs among patients who developed EPS following AAP treatment. These results underscore the need for the development of new pharmacologic therapies that not only effectively manage the symptoms of schizophrenia but also avoid the burdensome AEs of EPS and associated costs. ■

**FIGURE 3. Adjusted All-Cause and Schizophrenia-Related Total Health Care Costs**



AAP, atypical antipsychotic; CCI, Charlson Comorbidity Index; CDHP, consumer-directed health plan; ED, emergency department; EPO, exclusive provider organization; EPS, extrapyramidal symptoms; HDHP, high-deductible health plan; HMO, health maintenance organization; IP, inpatient; POS, point of service; PPO, preferred provider organization; ref, reference  
 \*P < .05; \*\*P < .01; \*\*\*P < .001.

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**Authorship Information:** Concept and design (AK, BLB, CD, GRW, JMK); acquisition of data (AK); analysis and interpretation of data (AK, BLB, CD, GRW, JMK); drafting of the manuscript (BLB, CD, GRW, JMK); critical revision of the manuscript for important intellectual content (AK, BLB, CD, GRW, JMK); obtaining funding (CD); administrative, technical, or logistic support (AK, CD); and supervision (CD, JMK).

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## REFERENCES

- Patel KR, Cherian J, Gohil K, Atkinson D. Schizophrenia: overview and treatment options. *P T*. 2014;39(9):638-645.
- McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiol Rev*. 2008;30:67-76. doi:10.1093/epirev/mxn001
- Correll CU, Rubio JM, Kane JM. What is the risk-benefit ratio of long-term antipsychotic treatment in people with schizophrenia? *World Psychiatry*. 2018;17(2):149-160. doi:10.1002/wps.20516
- Keepers GA, Fochtmann LJ, Anzia JM, et al. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. *Am J Psychiatry*. 2020;177(9):868-872. doi:10.1176/appi.ajp.2020.177901
- Lally J, MacCabe JH. Antipsychotic medication in schizophrenia: a review. *Br Med Bull*. 2015;114(1):169-179. doi:10.1093/bmb/dv017
- El Abdellati K, De Picker L, Morrens M. Antipsychotic treatment failure: a systematic review on risk factors and interventions for treatment adherence in psychosis. *Front Neurosci*. 2020;14:531763. doi:10.3389/fnins.2020.531763
- D'Souza RS, Hooten WM. Extrapyramidal symptoms. StatPearls. Updated August 3, 2021. Accessed June 8, 2021. <https://www.ncbi.nlm.nih.gov/books/NBK534115/>
- Honer WG, Kopala LC, Rabinowitz J. Extrapyramidal symptoms and signs in first-episode, antipsychotic exposed and non-exposed patients with schizophrenia or related psychotic illness. *J Psychopharmacol*. 2005;19(3):277-285. doi:10.1177/0269881105051539
- Divac N, Prostran M, Jakovcevski I, Cerovac N. Second-generation antipsychotics and extrapyramidal adverse effects. *Biomed Res Int*. 2014;2014:656370. doi:10.1155/2014/656370
- Haddad PM, Das A, Keyhani S, Chaudhry IB. Antipsychotic drugs and extrapyramidal side effects in first episode psychosis: a systematic review of head-head comparisons. *J Psychopharmacol*. 2012;26(5 suppl):S15-S26. doi:10.1177/026988111424929
- Musco S, Ruekert L, Myers J, Anderson D, Welling M, Cunningham EA. Characteristics of patients experiencing extrapyramidal symptoms or other movement disorders related to dopamine receptor blocking agent therapy. *J Clin Psychopharmacol*. 2019;39(4):336-343. doi:10.1097/JCP.0000000000001061
- Roberto P, Brandt N, Onukwugha E, Peretto E, Powers C, Stuart B. Adherence to antipsychotic therapy: association with hospitalization and Medicare spending among Part D enrollees with schizophrenia. *Psychiatr Serv*. 2017;68(11):1185-1188. doi:10.1176/appi.ps.201600434
- Boloc D, Gortat A, Cheng-Zhang JO, et al. Improving pharmacogenetic prediction of extrapyramidal symptoms induced by antipsychotics. *Transl Psychiatry*. 2018;8(1):276. doi:10.1038/s41398-018-0330-4
- Abouzaid S, Tian H, Zhou H, Kahler KH, Harris M, Kim E. Economic burden associated with extrapyramidal symptoms in a Medicaid population with schizophrenia. *Community Ment Health J*. 2014;50(1):51-58. doi:10.1007/s10597-012-9561-7
- Dhaval HS, Pinto C, Dass J, et al. Prophylaxis of antipsychotic-induced extrapyramidal side effects in east Indians: cultural practice or biological necessity? *J Psychiatr Pract*. 2004;10(3):200-202. doi:10.1097/00131746-200405000-00011
- Desmarais JE, Beaudclair L, Margolese HC. Anticholinergics in the era of atypical antipsychotics: short-term or long-term treatment? *J Psychopharmacol*. 2012;26(9):1167-1174. doi:10.1177/0269881112447988

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**eAppendix Table 1.** All-cause Healthcare Costs – Two Part Model

Factor	Odds Ratio or Cost Ratio	Lower 95% Confidence Interval Limit	Upper 95% Confidence Interval Limit	Z Score	p
<b>Part 1: Odds of any all-cause costs</b>					
Intercept	2.0176	0.6415	6.3454	1.2006	0.2299
EPS Cohort	39.9246	3.9293	405.6648	3.1168	<b>0.0018</b>
Age	1.0333	1.0085	1.0586	2.6478	<b>0.0081</b>
Sex: Female vs. Male	2.9099	1.4013	6.0425	2.8650	<b>0.0042</b>
Region: North Central vs. Northeast	2.1698	0.8830	5.3322	1.6886	0.0913
Region: South/Unknown vs. Northeast	0.9814	0.4715	2.0424	-0.0503	0.9599
Region: West vs. Northeast	1.8205	0.6762	4.9016	1.1856	0.2358
Plan Type: Comprehensive vs. PPO/EPO	0.4209	0.1468	1.2072	-1.6097	0.1075
Plan Type: HMO vs. PPO/EPO	0.9610	0.3820	2.4180	-0.0844	0.9327
Plan Type: POS/POS with Capitation vs. PPO/EPO	1.0107	0.3237	3.1559	0.0183	0.9854
Plan Type: CDHP/HDHP vs. PPO/EPO	0.7823	0.3686	1.6603	-0.6396	0.5225
Plan Type: Unknown vs. PPO/EPO	0.3661	0.0192	6.9766	-0.6682	0.5040
CCI	0.8054	0.5996	1.0819	-1.4372	0.1507
Days' Supply of Antipsychotic Agents: 0 days vs 1-30 days	0.3506	0.1623	0.7571	-2.6684	<b>0.0076</b>
Days' Supply of Antipsychotic Agents: 31-60 days vs 1-30 days	0.5720	0.2433	1.3448	-1.2808	0.2003
Days' Supply of Antipsychotic Agents: 61-90 days vs 1-30 days	6.3778	0.5155	78.9120	1.4436	0.1488
Days' Supply of Antipsychotic Agents: 91+ days vs 1-30 days	4.2669	0.9780	18.6158	1.9304	0.0536
Bipolar	2.3138	1.0810	4.9523	2.1607	<b>0.0307</b>
Depression	0.8802	0.4431	1.7485	-0.3645	0.7155
Anxiety	1.0899	0.3394	3.5002	0.1446	0.8850
Alcohol/Substance Abuse	0.7773	0.3800	1.5897	-0.6902	0.4901
Pre-Index Inpatient Admission or ER Visit	0.7422	0.2652	2.0771	-0.5678	0.5702
Pre-Index Total All-Cause Healthcare Costs: \$875.55-\$2,191.12 vs. \$0-\$875.54	14.1821	2.9569	68.0205	3.3153	<b>0.0009</b>
Pre-Index Total All-Cause Healthcare Costs: \$2,191.13-\$4,530.66 vs. \$0-\$875.54	2.4033	0.8337	6.9285	1.6232	0.1045
Pre-Index Total All-Cause Healthcare Costs: \$4,530.67-\$7,805.35 vs. \$0-\$875.54	3.7503	1.1241	12.5122	2.1502	<b>0.0315</b>
Pre-Index Total All-Cause Healthcare Costs: \$7,805.36-\$11,400.58 vs. \$0-\$875.54	2.9673	0.8081	10.8954	1.6390	0.1012
Pre-Index Total All-Cause Healthcare Costs: \$11,400.59-\$15,036.23 vs. \$0-\$875.54	6.6471	1.3932	31.7129	2.3760	<b>0.0175</b>

Pre-Index Total All-Cause Healthcare Costs: \$15,036.24-\$20,124.79 vs. \$0-\$875.54	4.9885	1.0455	23.8034	2.0157	<b>0.0438</b>
Pre-Index Total All-Cause Healthcare Costs: \$20,124.80-\$27,756.20 vs. \$0-\$875.54	4.5172	0.9387	21.7383	1.8810	0.0600
Pre-Index Total All-Cause Healthcare Costs: \$27,756.20-\$46,604.69 vs. \$0-\$875.54	8.6556	1.3810	54.2521	2.3046	<b>0.0212</b>
Pre-Index Total All-Cause Healthcare Costs: \$46,604.70+ vs. \$0-\$875.54	5.2751	1.0249	27.1505	1.9894	<b>0.0467</b>
<b>Part 2: Association of predictors with all-cause costs among patients with any all-cause costs</b>					
Intercept	8289.6817	6370.5683	10786.9218	67.1582	0.0000
EPS Cohort	1.2148	1.0839	1.3614	3.3461	<b>0.0008</b>
Age	1.0069	1.0030	1.0108	3.4953	<b>0.0005</b>
Sex: Female vs. Male	1.1021	0.9820	1.2370	1.6512	0.0987
Region: North Central vs. Northeast	0.8795	0.7472	1.0352	-1.5439	0.1226
Region: South/Unknown vs. Northeast	0.8379	0.7257	0.9673	-2.4128	<b>0.0158</b>
Region: West vs. Northeast	0.8322	0.6970	0.9936	-2.0307	<b>0.0423</b>
Plan Type: Comprehensive vs. PPO/EPO	0.7537	0.6200	0.9163	-2.8371	<b>0.0046</b>
Plan Type: HMO vs. PPO/EPO	0.9088	0.7740	1.0671	-1.1672	0.2431
Plan Type: POS/POS with Capitation vs. PPO/EPO	0.9311	0.7501	1.1557	-0.6477	0.5172
Plan Type: CDHP/HDHP vs. PPO/EPO	0.8828	0.7532	1.0346	-1.5403	0.1235
Plan Type: Unknown vs. PPO/EPO	0.5863	0.3473	0.9897	-1.9987	<b>0.0456</b>
CCI	1.1728	1.1126	1.2362	5.9311	<b>0.0000</b>
Days' Supply of Antipsychotic Agents: 0 days vs 1-30 days	0.7929	0.6375	0.9861	-2.0853	<b>0.0370</b>
Days' Supply of Antipsychotic Agents: 31-60 days vs 1-30 days	0.8103	0.6872	0.9556	-2.5006	<b>0.0124</b>
Days' Supply of Antipsychotic Agents: 61-90 days vs 1-30 days	0.7346	0.5969	0.9042	-2.9109	<b>0.0036</b>
Days' Supply of Antipsychotic Agents: 91+ days vs 1-30 days	0.9274	0.7986	1.0769	-0.9888	0.3228
Bipolar	0.9126	0.8128	1.0247	-1.5476	0.1217
Depression	1.2272	1.0936	1.3771	3.4821	<b>0.0005</b>
Anxiety	0.9995	0.8545	1.1691	-0.0062	0.9951
Alcohol/Substance Abuse	1.3126	1.1602	1.4850	4.3200	<b>0.0000</b>
Pre-Index Inpatient Admission or ER Visit	0.6384	0.5372	0.7587	-5.0948	<b>0.0000</b>
Pre-Index Total All-Cause Healthcare Costs: \$875.55-\$2,191.12 vs. \$0-\$875.54	1.2533	0.9845	1.5956	1.8330	0.0668
Pre-Index Total All-Cause Healthcare Costs: \$2,191.13-\$4,530.66 vs. \$0-\$875.54	1.5752	1.2241	2.0270	3.5316	<b>0.0004</b>
Pre-Index Total All-Cause Healthcare Costs: \$4,530.67-\$7,805.35 vs. \$0-\$875.54	2.1323	1.6404	2.7717	5.6586	<b>0.0000</b>
Pre-Index Total All-Cause Healthcare Costs: \$7,805.36-\$11,400.58 vs. \$0-\$875.54	2.2132	1.6712	2.9310	5.5431	<b>0.0000</b>
Pre-Index Total All-Cause Healthcare Costs: \$11,400.59-\$15,036.23 vs. \$0-\$875.54	2.1170	1.5902	2.8184	5.1368	<b>0.0000</b>
Pre-Index Total All-Cause Healthcare Costs: \$15,036.24-\$20,124.79 vs. \$0-\$875.54	2.3354	1.7517	3.1136	5.7803	<b>0.0000</b>

Pre-Index Total All-Cause Healthcare Costs: \$20,124.80-\$27,756.20 vs. \$0-\$875.54	2.9327	2.1967	3.9152	7.2981	<b>0.0000</b>
Pre-Index Total All-Cause Healthcare Costs: \$27,756.20-\$46,604.69 vs. \$0-\$875.54	3.5344	2.6291	4.7516	8.3622	<b>0.0000</b>
Pre-Index Total All-Cause Healthcare Costs: \$46,604.70+ vs. \$0-\$875.54	7.4390	5.5176	10.0294	13.1634	<b>0.0000</b>

**eAppendix Table 2.** Schizophrenia-related Healthcare Costs – Two Part Model

Factor	Odds Ratio or Cost Ratio	Lower 95% Confidence Interval Limit	Upper 95% Confidence Interval Limit	Z Score	p
<b>Part 1: Odds of any schizophrenia-related costs</b>					
Intercept	6.0981	3.0965	12.0091	5.2289	0.0000
EPS Cohort	17.2519	8.9236	33.3528	8.4673	<b>0.0000</b>
Age	1.0026	0.9919	1.0133	0.4696	0.6386
Sex: Female vs. Male	1.1099	0.8099	1.5209	0.6484	0.5167
Region: North Central vs. Northeast	1.2211	0.7767	1.9197	0.8654	0.3868
Region: South/Unknown vs. Northeast	0.7537	0.5111	1.1113	-1.4274	0.1535
Region: West vs. Northeast	1.2354	0.7492	2.0371	0.8284	0.4075
Plan Type: Comprehensive vs. PPO/EPO	1.1302	0.6695	1.9078	0.4580	0.6469
Plan Type: HMO vs. PPO/EPO	1.5961	0.9808	2.5974	1.8821	0.0598
Plan Type: POS/POS with Capitation vs. PPO/EPO	1.4851	0.8001	2.7566	1.2533	0.2101
Plan Type: CDHP/HDHP vs. PPO/EPO	1.0637	0.7084	1.5973	0.2979	0.7658
Plan Type: Unknown vs. PPO/EPO	2.5929	0.3318	20.2592	0.9083	0.3637
CCI	1.0148	0.8748	1.1771	0.1936	0.8465
Days' Supply of Antipsychotic Agents: 0 days vs 1-30 days	0.0692	0.0434	0.1104	-11.2000	<b>0.0000</b>
Days' Supply of Antipsychotic Agents: 31-60 days vs 1-30 days	0.8059	0.5275	1.2314	-0.9975	0.3185
Days' Supply of Antipsychotic Agents: 61-90 days vs 1-30 days	0.6608	0.3955	1.1042	-1.5815	0.1138
Days' Supply of Antipsychotic Agents: 91+ days vs 1-30 days	3.4649	1.9170	6.2628	4.1148	<b>0.0000</b>
Bipolar	0.6289	0.4577	0.8642	-2.8597	<b>0.0042</b>
Depression	0.7900	0.5778	1.0800	-1.4777	0.1395
Anxiety	1.0543	0.6700	1.6590	0.2286	0.8192
Alcohol/Substance Abuse	0.9143	0.6492	1.2876	-0.5129	0.6080
Pre-Index Inpatient Admission or ER Visit	1.3098	0.8137	2.1084	1.1113	0.2664
Pre-Index Total All-Cause Healthcare Costs: \$875.55-\$2,191.12 vs. \$0-\$875.54	1.3253	0.7259	2.4196	0.9169	0.3592
Pre-Index Total All-Cause Healthcare Costs: \$2,191.13-\$4,530.66 vs. \$0-\$875.54	0.9418	0.4887	1.8151	-0.1791	0.8579
Pre-Index Total All-Cause Healthcare Costs: \$4,530.67-\$7,805.35 vs. \$0-\$875.54	0.5888	0.3039	1.1405	-1.5702	0.1164
Pre-Index Total All-Cause Healthcare Costs: \$7,805.36-\$11,400.58 vs. \$0-\$875.54	0.6849	0.3290	1.4261	-1.0114	0.3118
Pre-Index Total All-Cause Healthcare Costs: \$11,400.59-\$15,036.23 vs. \$0-\$875.54	0.8378	0.3881	1.8086	-0.4507	0.6522



Pre-Index Total All-Cause Healthcare Costs: \$15,036.24-\$20,124.79 vs. \$0-\$875.54	0.6832	0.3172	1.4715	-0.9733	0.3304
Pre-Index Total All-Cause Healthcare Costs: \$20,124.80-\$27,756.20 vs. \$0-\$875.54	0.7490	0.3444	1.6291	-0.7290	0.4660
Pre-Index Total All-Cause Healthcare Costs: \$27,756.20-\$46,604.69 vs. \$0-\$875.54	0.6433	0.2885	1.4342	-1.0784	0.2809
Pre-Index Total All-Cause Healthcare Costs: \$46,604.70+ vs. \$0-\$875.54	0.6521	0.2920	1.4566	-1.0427	0.2971
<b>Part 2: Association of predictors with schizophrenia-related costs among patients with any schizophrenia-related costs</b>					
Intercept	5452.0145	3791.2108	7840.3613	46.4163	0.0000
EPS Cohort	1.6529	1.4219	1.9213	6.5443	<b>0.0000</b>
Age	0.9978	0.9925	1.0030	-0.8305	0.4063
Sex: Female vs. Male	0.8118	0.6940	0.9496	-2.6061	<b>0.0092</b>
Region: North Central vs. Northeast	0.8803	0.7059	1.0978	-1.1318	0.2577
Region: South/Unknown vs. Northeast	0.8058	0.6626	0.9799	-2.1637	<b>0.0305</b>
Region: West vs. Northeast	0.9010	0.7092	1.1447	-0.8536	0.3933
Plan Type: Comprehensive vs. PPO/EPO	1.0204	0.7800	1.3349	0.1475	0.8828
Plan Type: HMO vs. PPO/EPO	0.9199	0.7427	1.1395	-0.7642	0.4448
Plan Type: POS/POS with Capitation vs. PPO/EPO	0.8956	0.6711	1.1953	-0.7485	0.4542
Plan Type: CDHP/HDHP vs. PPO/EPO	0.9233	0.7434	1.1468	-0.7216	0.4706
Plan Type: Unknown vs. PPO/EPO	0.8518	0.4300	1.6876	-0.4597	0.6457
CCI	0.8875	0.8272	0.9521	-3.3263	<b>0.0009</b>
Days' Supply of Antipsychotic Agents: 0 days vs 1-30 days	1.5586	1.0537	2.3053	2.2218	<b>0.0263</b>
Days' Supply of Antipsychotic Agents: 31-60 days vs 1-30 days	0.8559	0.6849	1.0698	-1.3673	0.1715
Days' Supply of Antipsychotic Agents: 61-90 days vs 1-30 days	0.7272	0.5466	0.9676	-2.1860	<b>0.0288</b>
Days' Supply of Antipsychotic Agents: 91+ days vs 1-30 days	0.9632	0.7912	1.1724	-0.3743	0.7082
Bipolar	0.5894	0.5033	0.6902	-6.5614	<b>0.0000</b>
Depression	0.9794	0.8374	1.1455	-0.2607	0.7943
Anxiety	1.0934	0.8865	1.3484	0.8343	0.4041
Alcohol/Substance Abuse	0.9925	0.8405	1.1719	-0.0888	0.9293
Pre-Index Inpatient Admission or ER Visit	0.6610	0.5224	0.8363	-3.4483	<b>0.0006</b>
Pre-Index Total All-Cause Healthcare Costs: \$875.55-\$2,191.12 vs. \$0-\$875.54	1.2784	0.9108	1.7944	1.4198	0.1557
Pre-Index Total All-Cause Healthcare Costs: \$2,191.13-\$4,530.66 vs. \$0-\$875.54	1.6176	1.1424	2.2906	2.7099	<b>0.0067</b>
Pre-Index Total All-Cause Healthcare Costs: \$4,530.67-\$7,805.35 vs. \$0-\$875.54	1.8586	1.2869	2.6843	3.3051	<b>0.0009</b>
Pre-Index Total All-Cause Healthcare Costs: \$7,805.36-\$11,400.58 vs. \$0-\$875.54	2.0530	1.3938	3.0237	3.6408	<b>0.0003</b>
Pre-Index Total All-Cause Healthcare Costs: \$11,400.59-\$15,036.23 vs. \$0-\$875.54	2.2109	1.4889	3.2830	3.9331	<b>0.0001</b>
Pre-Index Total All-Cause Healthcare Costs: \$15,036.24-\$20,124.79 vs. \$0-\$875.54	2.4496	1.6483	3.6404	4.4324	<b>0.0000</b>

Pre-Index Total All-Cause Healthcare Costs: \$20,124.80-\$27,756.20 vs. \$0-\$875.54	3.3967	2.2824	5.0551	6.0281	<b>0.0000</b>
Pre-Index Total All-Cause Healthcare Costs: \$27,756.20-\$46,604.69 vs. \$0-\$875.54	3.8735	2.5782	5.8196	6.5201	<b>0.0000</b>
Pre-Index Total All-Cause Healthcare Costs: \$46,604.70+ vs. \$0-\$875.54	5.2526	3.4790	7.9305	7.8913	<b>0.0000</b>