CLINICAL

Impact of Atypical Antipsychotic Use Among Adolescents With Attention-Deficit/Hyperactivity Disorder

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Atypical antipsychotics (AAPs) are one of the most common and costly classes of prescription drugs, with annual expenditures exceeding $13 billion, representing nearly 5% of all drug expenditures in the US.[1,2] AAPs are approved by the FDA for the treatment of schizophrenia, behavioral symptoms in autism, and mixed or manic bipolar disorder, and the benefits and risks of AAPs are well documented for these indications.[3] However, AAP use for off-label indications has rapidly increased, and now accounts for the majority of AAP utilization.[4,5] A recent study found that AAP use in children grew by 62% from 2002 to 2007.[6] Due to the potential side effects of AAP use and limited clinical evidence regarding the efficacy and safety of such off-label uses, the utilization of atypical antipsychotics for off-label indications is controversial.[5,7-9] Among studies of off-label AAP use, heightened attention has been paid to attention-deficit/hyperactivity disorder (ADHD), as almost a third of off-label AAP use is related to this condition.[7-9]

ADHD can pose a significant barrier to personal development and cause substantial psychological difficulties for patients and their families if left untreated.[10] There are many pharmacologic treatment options for ADHD, including stimulants and non-stimulants, which have well-established efficacy and safety profiles.[11] Conversely, the risks and benefits of AAP use in current clinical practice for ADHD are largely unknown.[12] The few clinical studies that investigated AAP use in ADHD patients are confounded by patient comorbidities for which AAPs may be appropriate, and are therefore difficult to interpret.[13-16] However, the pediatric population appears to be at higher risk than adults for AAP-induced adverse events including weight gain, elevation in prolactin levels, extrapyramidal symptoms, sedation, and cardiac events.[17-19] Additionally, there is limited evidence regarding the real-world economic outcomes of AAP use for ADHD, and recent literature has called for further investiga-

ABSTRACT

Objectives

To compare treatment patterns, resource utilization, and costs to US third-party payers of stimulant-treated adolescent attention-deficit/hyperactivity disorder (ADHD) patients who switched to or augmented with atypical antipsychotics (AAPs; not FDA-indicated for ADHD) with those who switched to or augmented with non-antipsychotic medications.

Study Design

Retrospective cohort study conducted using a US commercial medical/pharmacy claims database.

Methods

Adolescent patients with an ADHD diagnosis and ≥1 stimulant medication claim between January 2005 and December 2009 were identified. Patients were classified into the AAP or non-antipsychotic cohorts based on subsequent claims for AAPs or non-antipsychotic medications, respectively. Patients with psychiatric diagnoses for which AAPs are often prescribed were excluded. Patients were matched 1:1 from the AAP to the non-antipsychotic cohort using propensity score matching. Treatment patterns, resource utilization, and costs in the 12 months after AAP or non-antipsychotic initiation were compared using Cox models, Poisson regression, and Wilcoxon signed-rank tests, respectively.

Results

After propensity score matching, a total of 849 adolescents were included in each of the matched cohorts. Patients in the AAP cohort had a significantly higher rate of medication augmentation (27.7% vs 15.5%; hazard ratio = 2.56; 95% confidence interval [CI], 1.90-3.46; *P* <.001) than patients in the non-antipsychotic cohort. The AAP cohort also had significantly higher incidences of inpatient admissions (0.13 vs 0.05; incidence rate ratio [IRR] = 2.45; 95% CI, 1.73-3.48; *P* <.001), emergency department visits (0.39 vs 0.31; IRR = 1.27; 95% CI, 1.08-1.49; *P* = .004), and outpatient visits (14.82 vs 13.19; IRR = 1.12; 95% CI, 1.10-1.15; *P* <.001), and incurred significantly higher mean annual medical ($3622 vs $3311; *P* = .002), drug ($4314 vs $2884; *P* <.001), and total healthcare ($7936 vs $6195; *P* <.001) costs.

Conclusions

Stimulant-treated adolescents with ADHD who switched to or augmented with AAPs had significantly greater drug augmentation, healthcare resource utilization, and costs compared with the non-antipsychotic cohort.

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Take-Away Points

■ This study was the first to examine the treatment patterns and economic outcomes associated with off-label atypical antipsychotic (AAP) use in the treatment of adolescent attention-deficit/hyperactivity disorder using real-world data.

■ After controlling for potential confounding variables using a propensity score match, treatment with AAPs was associated with significantly greater subsequent drug augmentation; higher rates of inpatient, emergency department, and outpatient visits; and higher all-cause medical, prescription drug, total healthcare, and mental health–related costs, compared with treatment with non-antipsychotic medications.

tion of the health outcomes in pediatric populations.[6] A companion study examined this effect in children aged 6 to 12 years with ADHD, finding that patients who utilized AAPs had higher rates of drug switching and augmentation, greater medical resource utilization, and higher total healthcare costs compared with patients who used non-antipsychotic therapies.[20] However, no peer-reviewed publications have investigated the economic costs of AAP use specifically in adolescents with ADHD. There is evidence that both the rates of ADHD diagnosis and AAP prescription for ADHD can vary by age category, which indicates the need for specific attention to the adolescent subpopulation.[5,7,9,21]

Therefore, the purpose of this study was to compare, from a US third-party payer perspective, treatment patterns, resource utilization, and healthcare costs of stimulant-treated adolescents with ADHD who switched to or augmented their stimulant treatment with AAPs, versus those who did the same with non-antipsychotic medications.

METHODS

Data

This retrospective cohort study was conducted utilizing data from the Truven Health MarketScan Commercial Claims and Encounters database. These data include commercial health insurance claims and enrollment data from large employers and health plans across the United States. Such plans provide private healthcare coverage for more than 45 million employees and their spouses and dependents. This administrative claims database includes a variety of fee-for-service, preferred provider organization, and capitated health plans.

Sample Selection

Patients were required to have at least 1 medical claim associated with a primary diagnosis of ADHD (*Interna-*

tional Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 314.00 and 314.01) and 1 pharmacy claim for a stimulant (**eAppendix** available at **www.ajmc.com**) during the period of January 1, 2005, to December 31, 2009, to be included in the study sample. The date of the first stimulant claim during this period was defined as the initial stimulant date.

Patients with a pharmacy claim for an AAP (Appendix) after the initial stimulant date were selected into the AAP cohort. The date of the first AAP pharmacy claim after the initial stimulant date was defined as the index date, and the AAP filled was defined as the index drug. Patients with no pharmacy claims for AAPs after the initial stimulant date, but at least 1 claim for atomoxetine, guanfacine immediate-release (IR), clonidine IR, or a stimulant of a different class than the initial stimulant were selected into the non-antipsychotic cohort. For patients who had pharmacy claims for more than 1 non-antipsychotic medication after the initial stimulant date (eg, having claims for both atomoxetine and clonidine IR after the initial stimulant), the index drug was randomly selected from the eligible non-antipsychotic medications. This random selection method was employed to match the treatment history of the AAP cohort (which may have one or more non-antipsychotic medications prior to the index date) in an unbiased manner.

Patients in both cohorts were required to be aged 13 to 17 years on the index date. Individuals were included in the study if they had at least 30 days of supply of a stimulant before the index date and at least 18 months (6 months pre- and 12 months post index date) of continuous eligibility for their health plan. Furthermore, patients were required to have at least one primary diagnosis of ADHD during this 18-month period. Patients were only included if they switched from the initial stimulant to the index drug or augmented a stimulant with the index drug. Patients were considered to have switched if they initiated the index drug within a period defined as beginning 30 days before and ending 30 days after the last day with stimulant supply. Patients were considered to have augmented with the index drug if they had at least 30 consecutive days of overlap between the stimulant and the index drug.

To increase the likelihood that patients' pharmacy claims were for the treatment of ADHD and not for other comorbid conditions that are often treated with AAPs,

patients were excluded if they had a medical claim associated with any of the following diagnoses during the 18-month study period: bipolar disorder, delusions/hallucinations, paranoia, psychosis, tics, or dementia. These conditions were identified by group of medical experts as indications for which AAPs are approved by the FDA or commonly prescribed.

To control for observable confounding factors, propensity score matching was used to match patients in the non-antipsychotic cohort 1-to-1 with patients in the AAP cohort. The propensity score was estimated using an unconditional logistic regression including patient characteristics during the 6-month pre-index period. In addition, patients were exactly matched on whether the patient switched to or augmented with the index drug.

Outcomes

All outcomes were measured during the 12-month period following the index date. Outcome categories included treatment patterns, healthcare utilization, and costs.

Treatment pattern outcomes included discontinuation, switching, and augmentation. Discontinuation was defined as a gap in the usage of the index therapy greater than 30 days. A switch was defined as the initiation of a new ADHD medication (either an AAP or a non-antipsychotic other than the index therapy and the current stimulant) within 30 days before or after the index therapy discontinuation date. Augmentation was defined as initiation of a new ADHD medication, in which the supply of the newly initiated medication had at least 30 days of supply overlap with the index therapy.

Healthcare utilization outcomes included 3 mutually exclusive categories: inpatient, emergency department (ED), and outpatient services. In each category, both all-cause utilization and mental health (MH)-related utilization (*ICD-9-CM*: codes 290.xx-319.xx) were calculated.

Healthcare costs included medical costs and prescription drug costs. Within each category, both all-cause and MH-related costs were evaluated. Cost analyses were conducted from a third-party payer perspective, where costs were defined as the total amount paid without including out-of-pocket costs to patients. All costs were inflated to 2010 US dollars using the medical component of the Consumer Price Index.[22]

Statistical Analysis

During the 6-month pre-index baseline period, baseline characteristics of patients in the AAP cohort were compared with those of the non-antipsychotic cohort before and after propensity score matching. Comparisons employed χ^2 tests and Wilcoxon rank-sum tests before matching, and McNemar's tests and Wilcoxon signed-rank tests after matching.

Treatment patterns were estimated using the Kaplan-Meier (KM) survival estimator; the corresponding hazard ratios (HRs) were estimated using Cox proportional hazard models. Rates of all-cause and MH-related medical utilization were compared between patients in the 2 matched cohorts using McNemar's test, and the corresponding incidence rate ratios (IRRs) were estimated using Poisson regression. Since cost outcomes are typically not normally distributed and highly skewed to the right, cost comparisons were conducted using Wilcoxon signed-rank tests.

All analyses were performed using SAS Version 9.2 (SAS Institute, Cary, North Carolina), and statistical significance was evaluated at the .05 level (2-sided).
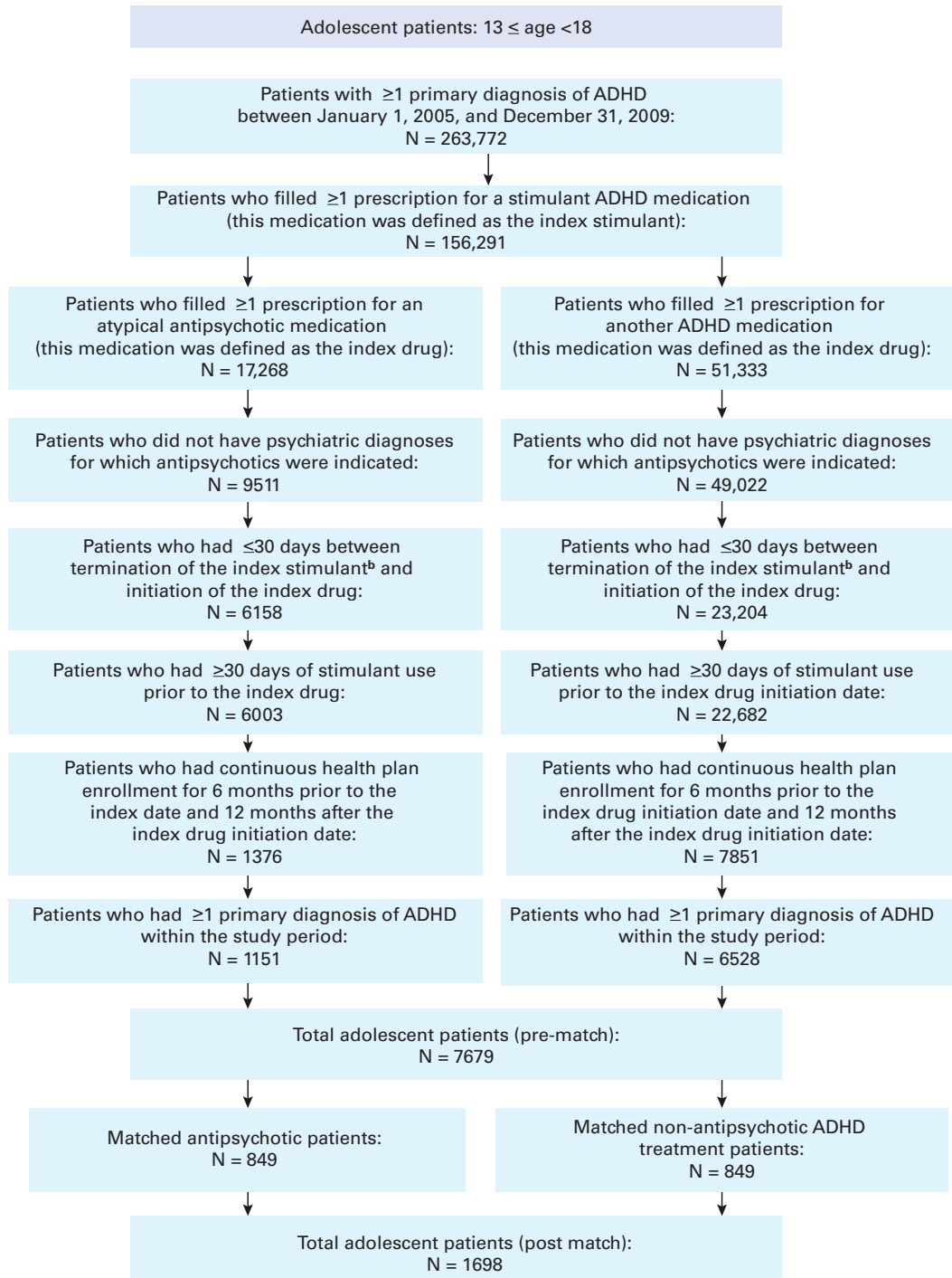
RESULTS

Between January 1, 2005, and December 31, 2009, a total of 263,772 adolescents with at least 1 primary diagnosis of ADHD were identified from the database (**Figure 1**). Of these, 156,291 (59.3%) filled at least 1 prescription for a stimulant medication. Among those with at least 1 stimulant prescription, 17,268 (11.0%) had at least 1 prescription for an AAP medication after the initial stimulant. Similarly, 51,333 (32.8%) had at least 1 prescription for a non-antipsychotic medication (and no fills for an AAP medication) after the initial stimulant date. Among the AAP cohort, 9511 (55.1%) patients did not have any of the psychiatric diagnoses for which AAPs are commonly used. A total of 1151 patients in the AAP cohort and 6528 patients in the non-antipsychotic cohort met all additional eligibility criteria and were included in the study. A total of 1698 patients were included after matching, with 849 patients (187 who switched to the index drug, and 662 who augmented with it) included in each cohort. Inspection of the matched pairs within the propensity score histogram demonstrated that there was sufficient numeric representation and appropriate overlap between the two cohorts across the full range of propensity scores.

Baseline Characteristics

Table 1 compares baseline characteristics between the 2 cohorts before and after matching. Prior to matching, several baseline characteristics were significantly different between the 2 cohorts. After matching, the differences in baseline demographic characteristics, resource utilization,

■ **Figure 1.** Sample Selection Flow Chart

Adolescent patients: 13 ≤ age <18

Patients with ≥1 primary diagnosis of ADHD
between January 1, 2005, and December 31, 2009:
N = 263,772

Patients who filled ≥1 prescription for a stimulant ADHD medication
(this medication was defined as the index stimulant):
N = 156,291

Patients who filled ≥1 prescription for an
atypical antipsychotic medication
(this medication was defined as the index drug):
N = 17,268

Patients who filled ≥1 prescription for
another ADHD medication
(this medication was defined as the index drug):
N = 51,333

Patients who did not have psychiatric diagnoses
for which antipsychotics were indicated:
N = 9511

Patients who did not have psychiatric diagnoses
for which antipsychotics were indicated:
N = 49,022

Patients who had ≤30 days between
termination of the index stimulant[b] and
initiation of the index drug:
N = 6158

Patients who had ≤30 days between
termination of the index stimulant[b] and
initiation of the index drug:
N = 23,204

Patients who had ≥30 days of stimulant use
prior to the index drug:
N = 6003

Patients who had ≥30 days of stimulant use
prior to the index drug initiation date:
N = 22,682

Patients who had continuous health plan
enrollment for 6 months prior to the
index date and 12 months after the
index drug initiation date:
N = 1376

Patients who had continuous health plan
enrollment for 6 months prior to the
index drug initiation date and 12 months
after the index drug initiation date:
N = 7851

Patients who had ≥1 primary diagnosis of ADHD
within the study period:
N = 1151

Patients who had ≥1 primary diagnosis of ADHD
within the study period:
N = 6528

Total adolescent patients (pre-match):
N = 7679

Matched antipsychotic patients:
N = 849

Matched non-antipsychotic ADHD
treatment patients:
N = 849

Total adolescent patients (post match):
N = 1698

ADHD indicates attention-deficit hyeractivity disorder.

and costs (with the exception of drug costs and total costs per patient) were not significantly different, indicating balanced baseline characteristics between the 2 cohorts.

In the post matching AAP cohort, 42.4% used risperidone followed by aripiprazole (27.2%), quetiapine (22.0%), olanzapine (4.7%), ziprasidone (3.3%), and paliperidone (0.4%) as the respective index drug; this distribution was similar to that observed in the pre-matching AAP cohort. In the pre-matching non-antipsychotic cohort, 72.5% of all index drugs were stimulants. After matching, 89.3% of all index drugs were non-stimulants (atomoxetine, 52.2%; clonidine IR, 31.1%; guanfacine IR, 6.0%).

■ **Table 1.** Comparison of Baseline Demographic Characteristics and Comorbidities: Atypical Antipsychotic and Non-Antipsychotic Cohorts (pre- and post matching)

Baseline Characteristics	Pre-Match Sample			Post Match Sample		
	Antipsychotic Users N = 1151	Non-antipsychotic Users N = 6,528	P[a]	Antipsychotic Users N = 849	Non-antipsychotic Users N = 849	P[b]
Demographic characteristics						
Age, mean ± SD	14.80 ± 1.40	14.84 ± 1.39	.431	14.8 ± 1.4	14.8 ± 1.4	.473
Female, n (%)	313 (27.2%)	2137 (32.7%)	<.001	231 (27.2)	227 (26.7)	.828
Index drug switching vs augmenting						
Switching	219 (19.0%)	4151 (63.6%)	<.001	187 (22.0)	187 (22.0)	1.000
Augmenting	932 (81.0%)	2377 (36.4%)	<.001	662 (78.0)	662 (78.0)	1.000
Baseline pharmacologic ADHD treatment						
Number of stimulants, mean ± SD	1.09 ± 0.30	1.76 ± 0.47	<.001	1.1 ± 0.3	1.1 ± 0.3	.609
Duration of stimulants, mean ± SD	86.70 ± 58.39	95.63 ± 54.63	<.001	87.8 ± 57.7	91.6 ± 58.9	.132
Baseline stimulant use, n (%)[c]						
Methylphenidate short acting (MPH SA)	134 (11.6%)	1189 (18.2%)	<.001	104 (12.2)	106 (12.5)	.887
Methylphenidate long acting (MPH LA)	611 (53.1%)	4730 (72.5%)	<.001	462 (54.4)	454 (53.5)	.700
Amphetamine short acting (AMPH SA)	137 (11.9%)	930 (14.2%)	0.034	96 (11.3)	96 (11.3)	1.000
Amphetamine long acting (AMPH LA)	513 (44.6%)	4345 (66.6%)	<.001	376 (44.3)	384 (45.2)	.693
Baseline psychotherapy						
Number of visits, mean ± SD	5.33 ± 7.67	2.14 ± 4.41	<.001	4.1 ± 6.0	4.2 ± 6.3	.958
Number of patients with visit, n (%)	844 (73.3%)	2623 (40.2%)	<.001	559 (65.8)	563 (66.3)	.840
Comorbidity profile, n (%)						
Accidental injury	253 (22.0%)	1289 (19.7%)	.081	177 (20.8)	167 (19.7)	.540
Adjustment reaction	140 (12.2%)	521 (8.0%)	<.001	90 (10.6)	89 (10.5)	.937
Anxiety disorder	111 (9.6%)	300 (4.6%)	<.001	67 (7.9)	74 (8.7)	.544
Asthma	58 (5.0%)	265 (4.1%)	.127	41 (4.8)	37 (4.4)	.651
Conduct disorder	98 (8.5%)	111 (1.7%)	<.001	41 (4.8)	31 (3.7)	.232
Depression	291 (25.3%)	510 (7.8%)	<.001	137 (16.1)	140 (16.5)	.844
Epilepsy	23 (2.0%)	25 (0.4%)	<.001	8 (0.9)	7 (0.8)	.796
Insomnia	14 (1.2%)	45 (0.7%)	.059	12 (1.4)	14 (1.6)	.695
Learning disability	9 (0.8%)	62 (0.9%)	.583	6 (0.7)	9 (1.1)	.439
Neurological disorders	47 (4.1%)	185 (2.8%)	.022	26 (3.1)	31 (3.7)	.500
Obsessive compulsive disorder	32 (2.8%)	38 (0.6%)	<.001	14 (1.6)	12 (1.4)	.683
Oppositional defiant disorder	109 (9.5%)	134 (2.1%)	<.001	39 (4.6)	34 (4.0)	.553
Substance abuse	48 (4.2%)	101 (1.5%)	<.001	24 (2.8)	23 (2.7)	.884
Non-comorbid ADHD[d]	544 (47.3%)	4889 (74.9%)	<.001	503 (59.2)	504 (59.4)	.961
Costs per patient						
Inpatient, mean ± SD	1019.45 ± 4555.84	206.04 ± 2865.05	<.001	543.3 ± 3769.0	484.4 ± 3762.4	.645
Emergency department, mean ± SD	162.19 ± 910.859	2.35 ± 648.19	<.001	103.1 ± 375.5	97.8 ± 371.5	.818
Outpatient, mean ± SD	1784.38 ± 5662.51	1014.14 ± 1820.80	<.001	1312.9 ± 2239.4	1365.9 ± 2528.9	.542
Drug use, mean ± SD	1433.92 ± 2231.04	97.53 ± 1845.11	<.001	1281.7 ± 1989.7	1293.5 ± 2787.7	.047
Total, mean ± SD	4399.93 ± 8584.87	2250.05 ± 4294.47	<.001	3240.9 ± 4989.4	3241.6 ± 6329.6	.018

ADHD indicates attention-deficit hyperactivity disorder.
[a]Wilcoxon rank-sum tests were used to compare continuous variables; χ^2 tests were used to compare dichotomous variables.
[b]Wilcoxon signed-rank tests were used to compare continuous variables. McNemar's tests were used to compare dichotomous variables.
[c]Baseline stimulant use categories are not mutually exclusive, and patients will be included in each category for which they qualify.
[d]Defined as ADHD with the absence of the following diagnoses: adjustment reaction, anxiety disorder, conduct disorder, depression, epilepsy, insomnia, learning disability, neurological disorders, obsessive compulsive disorder, oppositional defiant disorder, and substance abuse.

■ **Figure 2A.** Kaplan-Meier Analysis of Persistence[a]
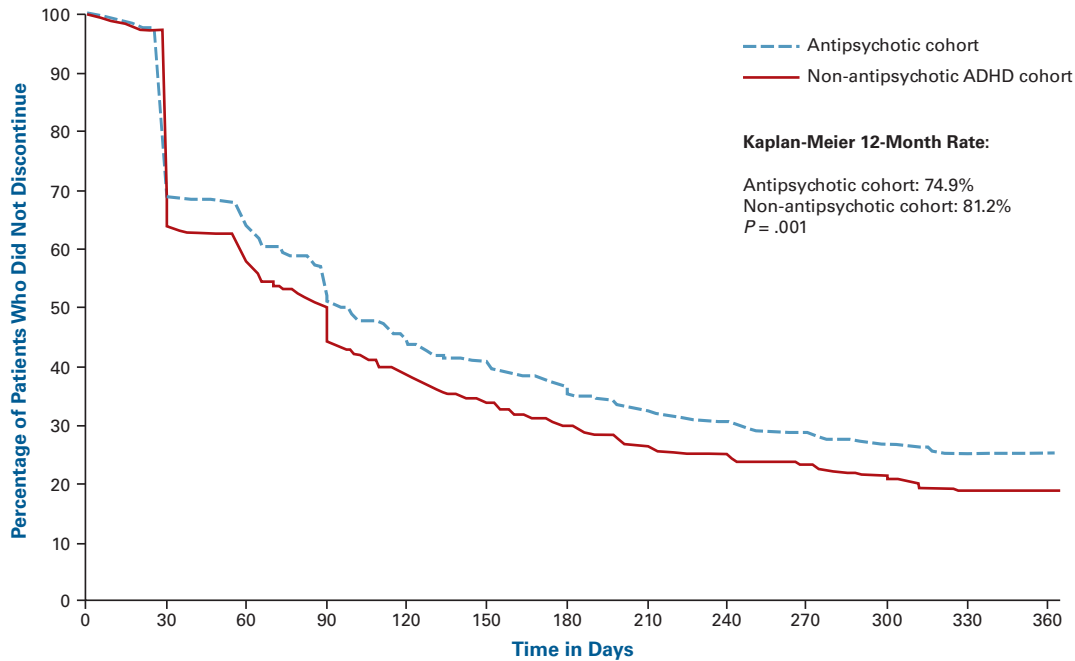
[a]High rates of patient discontinuation at 30 days are due to the frequency of 30-day prescriptions for the index drugs.

Treatment Patterns

During the 12-month period, persistence to the index drug was low in both the AAP and non-antipsychotic cohorts, with the non-antipsychotic cohort being more likely to discontinue the index drug (12-month KM: 74.9% vs 81.2%; HR = 0.85; 95% CI, 0.76-0.94) (**Figure 2A**). Overall, patients were more likely to augment the index drug in the AAP cohort compared with the non-antipsychotic cohort (12-month KM: 27.7% vs 15.5%; HR = 2.56; 95% CI, 1.90-3.46) (**Figure 2B**). The rate of switching was not statistically different between the 2 cohorts (12-month KM: 11.6% vs 9.7%; HR = 1.40; 95% CI, 0.90-2.20) (**Figure 2C**).

Healthcare Utilization

In the 12-month study period, a significantly higher proportion of patients in the AAP cohort had at least 1 inpatient visit compared with the non-antipsychotic cohort (8.6% vs 3.3%, *P* <.001) (**Table 2**). Patients in the AAP cohort experienced an average of 0.13 inpatient visits compared with 0.05 inpatient visits in the non-antipsychotic cohort (IRR = 2.45; 95% CI, 1.73-3.48). The majority of inpatient visits (84.3% in the AAP cohort and 65.9% in the non-antipsychotic cohort) were MH related. Patients in the AAP cohort experienced an average of 0.11 MH-related inpatient visits compared with 0.03 inpatient visits in the non-antipsychotic cohort (IRR = 3.14; 95% CI, 2.07-4.77).

The AAP cohort had a significantly higher proportion of patients having at least 1 ED visit—both all-cause (28.2% vs 19.9%, *P* <.001) and MH-related (7.9% vs 4.5%, *P* = .004)—compared with the non-antipsychotic cohort. The average number of all-cause ED events per patient was also significantly higher in the AAP cohort (0.39 vs 0.31, IRR = 1.27; 95% CI, 1.08-1.49). The average number of MH-related ED visits per patient was not statistically different between the 2 cohorts (0.095 vs 0.069, IRR = 1.37; 95% CI, 0.98-1.92).

Almost all patients had at least 1 outpatient visit (98.4% in both cohorts), while the number of patients with at least 1 MH-related outpatient visit was higher in the AAP cohort (94.7% vs 90.8%, *P* = .002). Patients in the AAP cohort also had more outpatient visits during the study period compared with non-antipsychotic patients. (All-cause: 14.82 vs 13.19; IRR = 1.12; 95% CI, 1.10-1.15. MH-related: 9.34 vs 7.51; IRR = 1.24; 95% CI, 1.20-1.29.)

Healthcare Costs

Overall, the AAP cohort had higher mean healthcare costs compared with the non-antipsychotic cohort for both all-cause ($7936 vs $6195, *P* <.001) and MH-related services ($5739 vs $3216, *P* <.001) (**Table 3**). Mean drug costs were significantly higher in the AAP cohort for both all-cause ($4314 vs $2884, *P* <.001) and MH-related ($3856 vs $2016,

Figure 2B. Kaplan-Meier Analysis of Augmentation
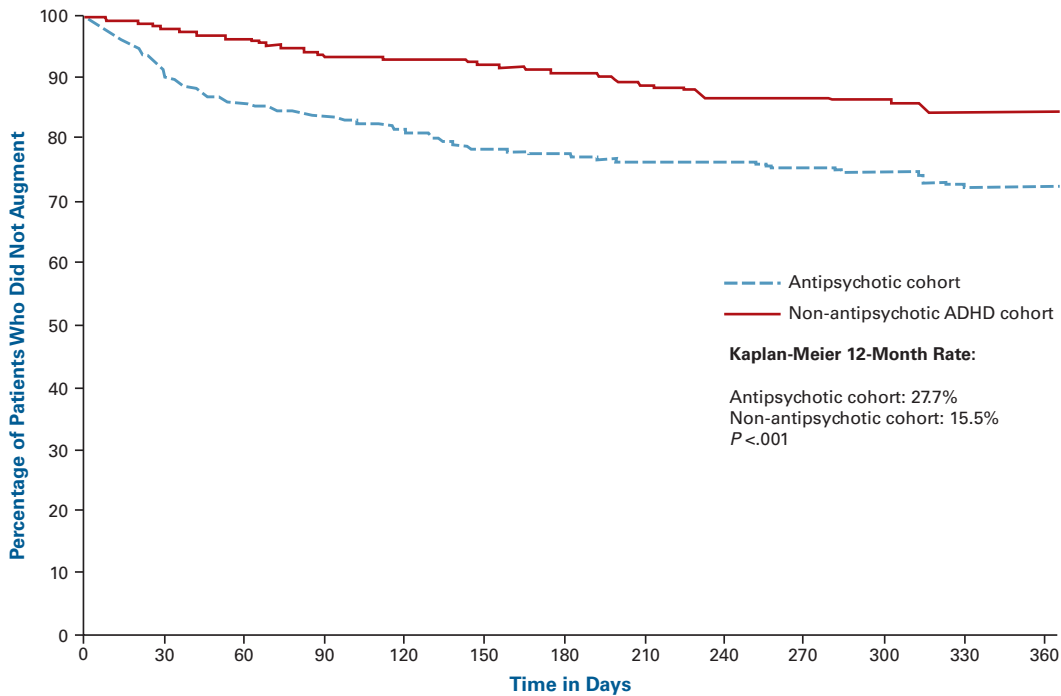
Figure 2C. Kaplan-Meier Analysis of Switching Patterns
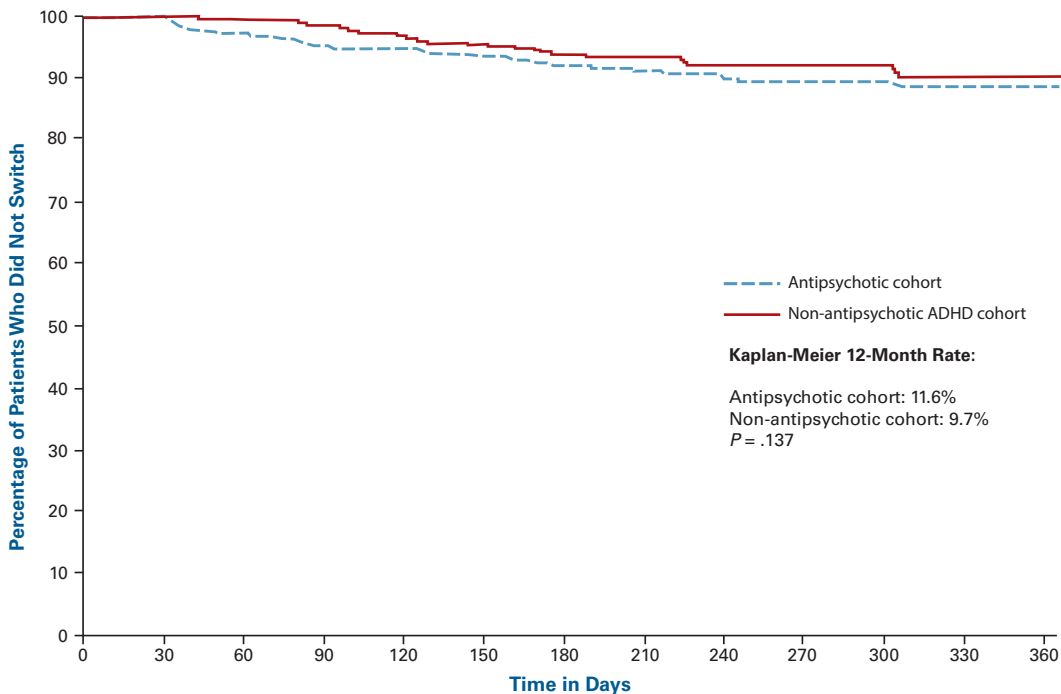
P <.001) pharmacy claims. The total cost for the index drug was also higher in the AAP cohort ($1718 vs $632, P <.001).

Patients in the AAP cohort had higher all-cause and MH-related medical costs compared with the non-antipsychotic cohort (all-cause: $3622 vs $3311, P = .002; MH-related: $1883 vs $1199, P <.001). Medical costs across all categories (inpatient, outpatient, and ED) were higher in the AAP cohort, with the differences in inpatient costs (all-cause: $853 vs $707, P <.001; MH-related: $644 vs $268, P <.001) and ED costs (all-cause: $239 vs $159, P =

■ **Table 2.** Healthcare Utilization: Atypical Antipsychotic and Non-Antipsychotic ADHD Cohorts (among matched patients)

Outcome Measures	Antipsychotic Users N = 849		Non-antipsychotic Users N = 849		Incidence Rate Ratios	
	Patients With Event N (%)	Events per Patient	Patients With Event N (%)	Events per Patient	IRR (95% CI)	P[a]
Hospitalizations	73 (8.60)	0.127	28 (3.30)	0.052	2.45 (1.73-3.48)	<.001
Emergency department visits	239 (28.15)	0.392	169 (19.91)	0.309	1.27 (1.08-1.49)	.004
Outpatient visits	835 (98.35)	14.82	835 (98.35)	13.192	1.12 (1.10-1.15)	<.001
Mental health–related[b]						
Hospitalizations	67 (7.89)	0.107	19 (2.24)	0.0342	3.14 (2.07-4.77)	<.001
Emergency department visits	67 (7.89)	0.095	38 (4.48)	0.069	1.37 (0.98-1.92)	.064
Outpatient visits	804 (94.70)	9.34	771 (90.81)	7.509	1.24 (1.20-1.29)	<.001

[a]*P* values were generated from unadjusted Poisson regression models.
[b]Mental health–related utilization is composed of any claims associated with mental health (*ICD-9*: 290-319)

■ **Table 3.** Cost: Atypical Antipsychotic and Non-Antipsychotic ADHD Cohorts (among matched patients)

Outcome Measures	Antipsychotic Users N = 849 Annual Cost [A] Mean [Median]	Non-antipsychotic Users N = 849 Annual Cost [B] Mean [Median]	Cost Difference [A] - [B] Mean [Median]	P[a]
Total Healthcare Costs	7936 ± 7969 [6091]	6195 ± 12,339 [3839]	1741 [2252]	<.001
Total Medical Costs	3622 ± 6749 [1596]	3311 ± 10,820 [1335]	311 [261]	.002
Inpatient	853 ± 4978 [0]	707 ± 8163 [0]	145 [0]	<.001
Outpatient	2530 ± 3872 [1381]	2444 ± 4802 [1220]	86 [161]	.190
Emergency department	239 ± 854 [0]	159 ± 491 [0]	80 [0]	.001
Total Drug Cost	4314 ± 3813 [3537]	2884 ± 4434 [2084]	430 [1453]	<.001
Index drug	1718 ± 1787 [1139]	632 ± 814 [239]	1086 [900]	<.001
Total Mental Health–Related Costs	539 ± 5688 [4524]	3216 ± 4558 [2519]	2523 [2005]	<.001
Medical	1883 ± 4773 [1596]	1199 ± 4209 [1335]	683 [261]	<.001
Inpatient	644 ± 3812 [0]	268 ± 3617 [0]	376 [0]	<.001
Emergency department	46 ± 201 [0]	25 ± 144 [0]	21 [0]	.010
Outpatient	1193 ± 2136 [522]	907 ± 1892 [359]	286 [164]	<.001
Drug	3856 ± 2923 [3265]	2016 ± 1467 [1669]	1840 [1596]	<.001

[a]Wilcoxon signed-rank tests were used to compare continuous variables.

.001; MH-related: $46 vs $25, *P* = .010) being statistically different. The majority of the medical costs for both cohorts were associated with outpatient visits but only MH-related costs were significantly different (all-cause: $2530 vs $2444, *P* = .190; MH-related: $1193 vs $907, *P* <.001).

DISCUSSION

To our knowledge, this is the first study to evaluate the association between AAP treatment and medical resource utilization and costs for adolescents with ADHD. Our study found that 55% of adolescent ADHD patients with at least 1 prescription for an AAP did not have any psychiatric diagnoses for which AAPs are commonly prescribed. This result is consistent with previous studies of prescribing patterns for ADHD, and highlights the fact that the high prevalence of AAP use in this population warrants a careful assessment of the clinical, medical, and economic impact of such utilization.[9,13-16,20,23,24] This study showed that even after controlling for baseline differences between the 2 treatment cohorts, adolescents with ADHD using AAPs were more likely to have greater resource utilization and healthcare costs compared with those in the non-AAP cohort.

Although there are documented differences between children and adolescents in the developmental presentation and trajectory of ADHD, the study findings are consistent with a companion investigation that studied a sample of children (aged 6-12 years) with ADHD. These 2 studies demonstrate that AAPs prescribed for ADHD present a substantial incremental burden to US payers compared with non-antipsychotics.[20] Much of the incremental burden was related to higher MH-related utilization and costs. Although matched to MH-related *ICD-9-CM* codes, the exact reasons for the increased resource utilization and higher medical costs among AAP users cannot be elucidated from the administrative claims data; it is possible that they may be related to inadequate ADHD symptom control, the known side effects of AAPs, or other unknown causes.[2,25-30] Additional research is warranted to determine the specific causes of treatment pattern differences, higher utilization, and higher costs among this population of ADHD patients.

Previous studies have noted gender differences in the presentation and treatment of ADHD, with males being diagnosed at a rate approximately 3 times that of females.[30-32] In the present study, significantly fewer females were treated with AAPs compared with non-antipsychotic treatments before matching (27.2% vs 32.7%, *P* <.001) (Table 1). These differences were controlled for by including gender within the propensity score match. Future analyses may provide more insight into the role gender plays regarding off-label treatment with AAPs for ADHD.

In addition, this study found that a significant number of patients in the pre-match AAP cohort used the index drug to augment their existing drug therapy (81.0% vs 36.4% in the non-antipsychotic cohort, *P* <.001) (Table 1). Recent studies have outlined concerns that arise with such polypharmacy involving stimulants and AAPs, due to potential interactions that may affect dopamine regulation or induce metabolic syndrome and its sequelae.[33-35]

The off-label use of treatments not supported by adequate clinical and economic evidence may pose a substantial economic burden to payers. The need for such evidence is especially pronounced in regard to ADHD, for which several FDA-approved therapies with demonstrated effectiveness exist, including treatments indicated as mono- and combination therapy. A third-party payer could initiate a drug utilization review for off-label treatment of ADHD, which could help managed care organizations better understand the reasons that AAPs are being prescribed, and potentially improve the quality of care for adolescents with ADHD.

LIMITATIONS

There are inherent limitations to using administrative claims data to determine whether AAP prescriptions were used in the treatment of ADHD. Specifically, clinical disease severity measures are not available, and the precise intent of the treating physician cannot be inferred. To minimize these limitations, stringent selection criteria were imposed, and the common indications for the use of AAPs were excluded. However, AAPs may have been used for psychiatric disorders not recorded in the database, possibly due to stigma associated with psychiatric diagnoses or the lack of available codes. Conversely, the stringency of the comorbidities list could have excluded patients with comorbid psychiatric disorders who were prescribed the AAP as a treatment for ADHD (and not their comorbid disorder), which may cause these results to be less generalizable to the entire ADHD population.[36] Additionally, it is possible that AAPs were being prescribed for other off-label indications such as depression, conduct disorders, or oppositional defiant disorder. However, these comorbidities were included in the propensity score matching, and there were no statistically significant differences between the 2 cohorts in the frequency of these diagnoses. While all relevant available variables were included in the propensity score model, potential unobserved confounders may exist that are related to the prescribing of the AAP but are not available in the data set. It is also possible that the decision to prescribe AAPs on-label versus off-label may have been influenced by formulary status or other policies.

Propensity score matching was used to create balanced and comparable cohorts. However, after the propensity score match, differences in drug costs and total costs at baseline remained. The results of the propensity score match are only generalizable to the population included in the match. The final match excluded 302 AAP patients who could not be matched with representative non-antipsychotic patients. These patients had higher rates of medical resource utilization and costs at baseline, thus the results of the current study may underestimate the association between off-label AAP use and medical resource utilization and costs.

Finally, because these analyses covered only the first 12 months following the index date, the results of this investigation cannot be extrapolated to provide insight on the longer-term economic implications of off-label AAP treatment of ADHD. Indeed, the results may understate the actual effect of such treatments, as many of the com-

plications associated with AAPs are chronic and the entirety of their effects on costs and utilization may not be observed within the study period. Future research of the long-term health outcomes and economic implications of off-label AAP use is justified.

CONCLUSION

Compared with adolescent ADHD patients treated with stimulants who switched to or augmented with a non-antipsychotic medication, those who switched to or augmented with an AAP had significantly greater medical resource utilization, and higher total healthcare costs, and they were more likely to augment their treatment in the 12 months after initiating the AAP. These patients may present a greater economic burden to payers. Further outcomes research and/or drug utilization reviews may be necessary to fully evaluate clinical and economic outcomes in adolescents with ADHD who are receiving AAPs.

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■ **eAppendix.** GPI Codes for Atypical Antipsychotics and Non-antipsychotics (stimulants + non-stimulants)

Drug Class	Drug	sGPI code[a]
Atypical Antipsychotics	Aripiprazole	5925001500
	Olanzapine	5915706000 5915706010
	Clozapine	5915202000
	Paliperidone	59070050
	Quetiapine	5915307010
	Risperidone	59070070
	Ziprasidone	59400085
Stimulants	Dexmethylphenidate	61400016
	Methylphenidate	61400020
	Dextroamphetamine	6110002010
	Lisdexamfetamine	6110002510
	Amphetamine-Dextroamphetamine	6110990210
Non-Stimulants	Atomoxetine	6135401510
	Clonidine IR	362010101003
	Guanfacine IR	3620102510

GPI indicates generic product identifier.
[a]The Medi-Span GPI is 14 characters in length; values with fewer than 14 characters indicate that GPI codes beginning with this sequence were included.