Predictors of Concomitant Use of Antipsychotics and Stimulants and Its Impact on Stimulant Persistence in Pediatric Attention Deficit Hyperactivity Disorder

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ABSTRACT

BACKGROUND: Concomitant use of stimulants and atypical antipsychotics is common in pediatric attention deficit hyperactivity disorder (ADHD). However, little is known about the determinants of concomitant use and its utility in the management of pediatric ADHD.

OBJECTIVES: To (a) examine predictors of concomitant stimulant and atypical antipsychotic use and (b) evaluate the impact of concomitant atypical antipsychotic use on the persistence of stimulants in children and adolescents diagnosed with ADHD.

METHODS: The retrospective cohort study was conducted using 4 years (January 2004-December 2007) of IMS LifeLink claims data. The study population included children and adolescents aged 6-16 years with a diagnosis of ADHD and those who initiated long-acting stimulants (LAS) from July 2004 to December 2006. Patients were followed for 1 year after index stimulant use. Concomitant use was defined as the concurrent prescription for LAS and atypical antipsychotic agents with at least 14 days overlap after the index LAS claim. Persistence was measured by summing the total number of days a patient remained on the index LAS from the index prescription date with an allowable gap of no more than 30 days. Multiple logistic regression within the conceptual framework of the Andersen Behavioral Model was performed to determine the predictors of concomitant stimulant and atypical antipsychotic use. Multivariate Cox proportional hazards regression within the conceptual framework of the Andersen Behavioral Model was used to examine the impact of concomitant atypical antipsychotic use on persistence of stimulants.

RESULTS: The study cohort consisted of 39,981 children who initiated LAS treatment. Most (96.10%) received LAS monotherapy, and 3.90% received LAS and atypical antipsychotic concomitantly. The multiple logistic regression analysis found that gender, health insurance, region, year of cohort entry, season, physician specialty, coexisting mental health conditions, and general mental health status influenced the concomitant use of LAS and atypical antipsychotic agents. Bivariate analyses revealed that concomitant users had longer persistence (by 71 days) than the stimulant-alone users. Cox proportional hazards regression revealed that concomitant atypical antipsychotic was associated with improvement in LAS persistence by 15% (HR = 0.85, 95% CI = 0.76-0.94) in comparison with the LAS recipients who did not use atypical antipsychotic concomitantly. Other factors such as age, region, season, coexisting mental health conditions, use of comedications, and general mental health status influenced the LAS treatment persistence among children and adolescents.

CONCLUSIONS: Various predisposing, enabling, and need factors were associated with the concomitant stimulant and atypical antipsychotic use. Concomitant use of atypical antipsychotics was associated with improved LAS treatment persistence in children and adolescents with ADHD.

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What is already known about this subject

- Children and adolescents with attention deficit hyperactivity disorder (ADHD) are frequently prescribed antipsychotics to control behavioral symptoms of ADHD or comorbid psychiatric disorders.
- Psychiatric polypharmacy involving antipsychotics and stimulants has increased in recent years.

What this study adds

- Among children and adolescents with ADHD, 3.90% concomitantly received LAS and atypical antipsychotics for at least 14 days.
- Various predisposing, enabling, and need factors were associated with the concomitant stimulant and atypical antipsychotic use in pediatric ADHD.
- Addition of atypical antipsychotics to the LAS regimen was associated with improvement in LAS persistence by 15% among the pediatric ADHD population after controlling for other factors.

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurobehavioral disorders among children and adolescents, with prevalence rates varying from 2%-10% in the United States.[1-3] Central nervous system stimulants are the first line of therapy to treat the core symptoms of ADHD—hyperactivity, impulsivity, and inattentiveness—by acting as dopamine agonists in the dopaminergic system.[4-6] Although nonstimulant alternatives such as atomoxetine are also used in the treatment of ADHD, stimulants, especially long-acting stimulants (LAS), are often used for management of ADHD symptoms due to ease of administration, better adherence, persistence, tolerability, fewer switching and side effects with the treatment, and lesser use of health care services than with the use of intermediate-acting stimulants (IAS) and short-acting stimulants (SAS).[7-13] The classification of short, intermediate, or long acting is based on half-life of medication and duration of action.[14,15] The use of other stimulants, such as short or intermediate acting, is influenced by patient needs, costs, and clinical judgment.

Other psychotropic medications, such as antipsychotics, are concomitantly used with stimulants to control ADHD symptoms or its associated comorbidities.[16,17] Antipsychotics act as dopamine antagonists and show serotonergic

properties.[6,18] They are approved by the U.S. Food and Drug Administration (FDA) in children for the treatment of bipolar I disorder (mania or mixed), schizophrenia, and irritability associated with autistic disorder.[19-21] However, children are being prescribed antipsychotics to control behavioral symptoms of ADHD or comorbid aggression and for other nonapproved indications.[6,22,23] In addition, psychiatric polypharmacy involving antipsychotics and stimulants has increased in recent years. Cooper et al. (2004) found over a 3-fold increase in the proportion of children who were prescribed antipsychotics for ADHD or conduct disorders from 1996-2001 in the TennCare program.[22] Fullerton et al. (2012) found that the percentage of ADHD youths taking antipsychotics increased from 8% in 1996 to 18% in 2005, which was primarily driven by the increased use of atypical antipsychotics (AAPs).[24] An analysis of physician visits made by children and adolescents from 1996-2007 revealed significant increase in concomitant prescription of ADHD and antipsychotic medications (adjusted odds ratio = 6.22, 95% confidence interval [CI] = 2.82-13.70).[16] Another study examining the prescription of antipsychotics during mental health visits found that approximately 30%-54% of these visits by children and adolescents involved coprescription of stimulants.[25] Existing literature suggests increased risk for adverse effects such as extrapyramidal symptoms, seizures, sedation, obesity, type 2 diabetes mellitus, hyperprolactinemia, gynecomastia, and cerebrovascular or cardiovascular morbidity in children and adolescents using AAPs.[6,26-29] A recent literature review by the Agency for Healthcare Research and Quality found limited evidence for the effectiveness of second-generation antipsychotics in the treatment of ADHD.[30]

Although concomitant use of LAS and AAPs is common in pediatric settings, little is known about the prevalence of and factors associated with concomitant use of LAS and AAPs in youth with ADHD. Recently, Betts et al. (2014) examined the prevalence of concomitant psychotropic medication use in commercially insured children and adolescents with ADHD in the United States to find that AAPs were one of the most commonly prescribed concomitant medications (5.8%-6.8%).[31] Sikirica et al. (2013) evaluated psychotropic concomitant medication (PCM) use in ADHD youth in Europe and found that AAPs were the most commonly used PCMs (4.0% overall, 28.8% of PCM users).[32] Additionally, the number of pre-existing comorbidities and high impairment due to the symptom of anger were important predictors of PCM.[32] However, none of the studies have looked at the predictors of concomitant use of LAS and AAPs in children and adolescents with ADHD. It is important to determine prevalence of and factors associated with the concomitant use of LAS and AAPs in privately insured children and adolescents with ADHD.

Current clinical evidence and practice guidelines suggest continued use of stimulants until the symptoms of ADHD persist.[33] Poor persistence with the use of stimulants may lead to suboptimal efficacy, negative long-term outcomes, and increased cost of therapy.[34,35] Several clinical studies found decrease in persistence of stimulant therapy with the increase in the follow-up period. It varied from 53%-81% after 1 year,[36,37] 21%-70% at the end of 3 years,[34,38,39] and 36% after 5 years.[40] In retrospective studies, stimulant persistence ranged from 59% at 4 months to 12%-43% at the end of 1 year.[10,13,41-43] Antipsychotics might help to improve persistence to stimulant treatment through control of psychiatric comorbidities or behavioral symptoms of ADHD. On the other hand, the use of AAPs might lead to reduced efficacy of stimulants due to their opposite mechanism of action on the dopaminergic system.[6,44] A study by Sikirica et al. (2012) looked at the treatment patterns, resource utilization, and costs in ADHD children treated with AAPs when compared with non-antipsychotic medications.[45] This study did not find any difference in the persistence of the index stimulant between ADHD children treated with AAPs and and those treated with non-antipsychotics.[45] However, the impact of the concomitant use of AAPs on the persistence of LAS therapy is largely unknown. This information could help clinicians in improving treatment persistence and subsequent outcomes among ADHD patients. Therefore, the objectives of this study were to (a) determine predictors of concomitant use of LAS and AAPs and (b) examine the impact of concomitant use of AAPs on persistence of LAS treatment regimens in children and adolescents with ADHD.

Methods

Study Design and Data Source

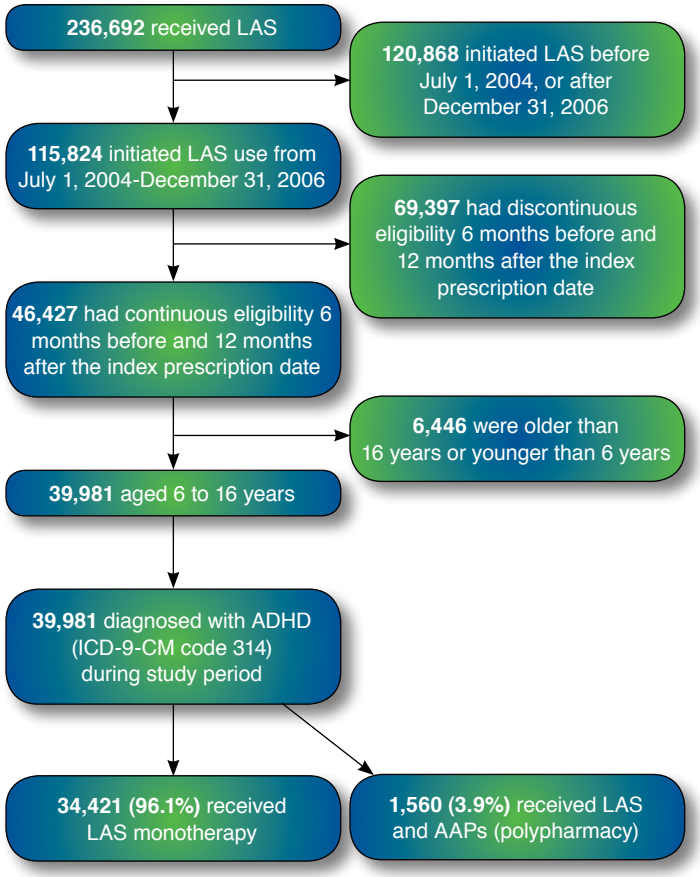
This retrospective study used 4 years of claims data (January 2004-December 2007) from IMS LifeLink to achieve the study objectives. IMS LifeLink provides information about commercially insured populations in the United States. It contains information on more than 61 million patients from more than 98 health plans, including enrollment, pharmacy, medical, and institutional claims. Pharmacy data provide information about the claims field for each prescription drug (coded using the National Drug Code [NDC] number), its date of dispensing, quantity dispensed, and the length of supply. Provider and facility claims have information on date of service, diagnostic codes (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes), and procedure codes (Current Procedural Terminology, 4th edition, and Healthcare Common Procedure Coding System). All claims in the database include a unique encrypted identifier for each patient to link one file to another.

The standard extract from the Health Plan Claims database consists of 2 files: a claims detail file and an eligibility file. The claims file gives detailed information about patients' pharmacy, medical, and institutional claims. The eligibility file provides data about patients' demographics and enrollment. The data are obtained from multiple sources and undergo a series of quality checks to ensure a standardized format, which is helpful in conducting meaningful comparative analyses. The data are longitudinal in nature with an average member enrollment time of 2.5 years.[46] This database abides by all Health Insurance Portability and Accountability Act requirements. This study was approved under the exempt category by the Institutional Review Board for the Protection of Human Subjects at the University of Houston.

Study Population

The study sample selection process is presented in Figure 1. The study cohort was identified using prescription claims for LAS (methylphenidate, dexmethylphenidate, mixed amphetamine salts, pemoline, and lisdexamfetamine dimesylate) and with at least 1 medical claim with a diagnosis of ADHD (ICD-9-CM code 314.xx) during the study period.[8,42,47,48] Index date was defined as the first prescription fill date of the first LAS from July 2004-December 2006. Cohort selection was limited to ADHD patients using LAS only because LAS are more frequently used in children and adolescents with ADHD than the other types of stimulants.[7-11] Index date preceded by a 6-month washout was used to identify new users and avoid selection bias due to prevalent users and also to avoid prevalence bias that might be introduced by pre-exposed cohort members to LAS treatment.[49] New users were those individuals who had no prescription for any stimulant in the 6 months prior to the index date. Inclusion in the cohort required continuous eligibility 6 months before and 1 year after the index date. Selection of the cohort was limited to children and adolescents aged 6-16 years at the index date, since most of the stimulants are indicated for this age group.[23,50] All the patients in the final cohort were followed for 1 year from the index date. The final cohort included 39,981 children and adolescents with ADHD who initiated use of LAS from July 1, 2004, to December 31, 2006.

FIGURE 1 Flowchart of Study Sample Selection and Cohort Development



AAPs = atypical antipsychotics; ADHD = attention deficit hyperactivity disorder; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modifications; LAS = long-acting stimulants.

Medication Use Variables

AAP medications such as clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole were identified by using NDC numbers and generic names during the 1-year period after the index date. Concomitant use of LAS and AAP medications was defined as receipt of both medications together for at least 14 days during the 1-year follow-up period. The concomitant use, or polypharmacy, has been already defined in previous literature as receipt of a second prescription 14 or more days before completion of the first prescription.[51]

Medication persistence can be defined as "the duration of the time from initiation to discontinuation of therapy."[52] Therefore, persistence of index LAS was calculated by summing the number of days the patient remained on index LAS therapy from the index LAS prescription date. The maximum gap of 30 days was allowed between consecutive refills of the index LAS.[42] When the gap exceeded the permissible limit of 30 days, the treatment episode for the patient was terminated even if the patient was persistent with stimulant therapy at a later stage. The objective of the study was to examine the index LAS persistence in terms of time to discontinuation of the index LAS medication. Switching from one type of preparation within the LAS class was allowed, but switching to another class, such as SAS or IAS, was defined as the discontinuation of the index LAS therapy.

Conceptual Framework

The Andersen Behavior Model of Health Services Use was used to examine factors associated with the concomitant use of LAS and AAPs and discontinuation of index LAS among children and adolescent diagnosed with ADHD.[53] This model has been previously used in studies involving medication use.[54-56] According to this model, health care use is a function of predisposing, enabling, and need factors. *Predisposing factors* are the characteristics of an individual that exist before the illness and include demographic characteristics, social structure characteristics, and health beliefs. *Enabling factors* describe the ability of an individual to secure health care services such as income, health insurance, and availability of the service. *Need factors* reflect perceived and actual health status of an individual. Perceived health status refers to the need for care as perceived by the patient and actual health status refers to the need for care as evaluated by the health care professional.

Predisposing, enabling, and need factors were selected from the existing literature and their availability in the IMS data.[16,17,43,57-61] Demographic characteristics such as age and gender were used as predisposing factors. Age at the index date (6-12 years and 13-16 years) and gender (male, female)

TABLE 1 Psychiatric Comorbidities Used in This Study

Psychiatric Comorbidities	ICD-9-CM Codes
Depression	296.2, 296.3, 300.4, 309.0, 309.1, 311.xx
Anxiety	300.0-300.2, 313.0, 308.3
Bipolar disorder	296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.8
Oppositional conduct disorder	300.3
Obsessive compulsive personality disorder	301.xx
Oppositional defiant disorder	313.81
Conduct disorder	312.xx
Learning disorders	315.0-315.3
Psychosis and pervasive developmental disorders	290.xx, 293.xx, 295.xx, 297.xx-299.xx, 296.24, 296.36, 296.44, 296.54, 296.64, 296.76, 296.84
Substance abuse and dependence disorders	291.xx, 292.xx, 303.xx-305.xx
Encopresis	307.6, 788.3
Enuresis	307.7, 787.6
Tics	307.2, 307.3

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

were identified from the eligibility and claims files. Enabling factors included type of health coverage (private, public, and other); physician specialty (pediatrics, psychiatry, and other); year of entry into the cohort (2004, 2005, and 2006), as well the season (winter, spring, summer, and autumn) during which the index LAS was prescribed. Need factors included psychiatric comorbidities, psychotropic comedications, and previous mental health-related hospitalization. Psychiatric comorbidities were determined through the presence of a medical claim during the 6-month washout and 1-year follow-up periods for the first objective and until the time to discontinuation of index LAS for the second objective. These comorbidities were depression, anxiety, bipolar disorder, oppositional conduct disorder, obsessive compulsive personality disorder, oppositional defiant disorder, conduct disorder, learning disorders, psychosis and pervasive developmental disorders, substance abuse and dependence, enuresis, encopresis, and tics. The ICD-9-CM codes for these comorbidities are presented in Table 1.[8,16,60,62] Recent mental health hospitalization was used as a proxy measure for the severity or general mental health status of the patient. It was defined as an inpatient claim occurring within 180 days of the index date with an ICD-9-CM diagnosis code associated with any mental health disorder (290.xx-319.xx).[8,63] This approach has been used in past literature dealing with stimulant persistence in ADHD patients and cardiac safety of stimulants in ADHD patients.[8,48,64] Psychotropic comedications were used as covariates for the second objective only. NDC numbers and generic names were used to identify comedications. Psychiatric comedications were determined through the presence of a prescription claim anytime starting from the index date and until the time to discontinuation of index LAS. Table 2 provides the list of drugs used in this study, which include nonstimulants, alpha 2-agonists, antidepressants, sedatives/hypnotics/anxiolytics, mood stabilizers, and miscellaneous.[16,57,60] The miscellaneous category represents drugs classes such as anticholinergics (e.g., benztropine), and antiparkinsonian agents (e.g., levodopa). The overlapping claim date was shifted to the end date of the previous claim for patients who refilled their drugs before exhausting the previous supply.[65]

Statistical Analyses

Data were summarized using descriptive statistics. Statistical differences were assessed using Pearson's χ^2 tests for the categorical variables and t-tests for continuous variables. Multiple logistic regression analysis was used to examine factors associated with concomitant use of LAS and AAPs (dichotomized as yes/no). Results were presented as odds ratio (OR) along with 95% CI for the adjusted analysis. Persistence was analyzed as time to discontinuation of the index LAS from the index prescription date. The Cox proportional-hazards regression model was used to examine the effect of independent variables on the persistence of LAS therapy. Primary independent variable of interest was the use of AAPs, which was modeled as a time varying covariate. Other independent variables, such as sociodemographic characteristics, enabling characteristics, comorbidities, and comedications, were used as control variables and modeled as fixed covariates. Patients were censored if the study period ended without occurrence of the event or discontinuation of index LAS. To measure hazards of discontinuation of LAS therapy, hazard ratios (HR) from Cox proportional hazards model were derived. In the multivariate analysis, proportional hazards assumption for the use of AAPs was checked by including an interaction term between the AAPs and log of time in the adjusted model. Results were presented as HRs along with 95% CIs for the adjusted analysis. All the analyses were conducted at a priori 5% alpha level. SAS version 9.2 was used for all the analyses (SAS Institute Inc., Cary, NC).

Results

Figure 1 presents the development process of the study cohort and sample selection—236,692 children and adolescents received LAS from 2004-2007. Of these children and adolescents, 115,824 initiated LAS use from July 1, 2004, to December 31, 2006. After applying the continuous eligibility

TABLE 2 Drug Classes Used in This Study

Drug Class	Medication
Long-acting stimulants	Methylphenidate (Ritalin LA, Metadate CD, Concerta, Daytrana) Dexmethylphenidate (Focalin XR) Mixed amphetamine salts (Adderall XR, Amphetamine-Dextroamphetamine cap SR 24HR) Pemoline (generic, Cylert) Lisdexamfetamine dimesylate (Vyvanse)
Atypical antipsychotics	Ziprasidone, paliperidone, risperidone, olanzapine, aripiprazole, clozapine, quetiapine
Nonstimulants	Atomoxetine
Alpha 2-agonists	Clonidine, guanfacine
Antidepressants	Bupropion, tricyclic antidepressants (e.g., desipramine) Selective serotonin reuptake inhibitors (e.g., fluvoxamine) Selective norepinephrine reuptake inhibitors (e.g., venlafaxine) Others (e.g., isocarboxazid)
Mood stabilizers	Lithium, anticonvulsants (e.g., gabapentine)
Sedatives/hypnotics/anxiolytics	Anxiolytics (e.g., chloral hydrate), beta blockers (e.g., acebutolol), benzodiazepines (e.g., diazepam), antihistamines (e.g., cetirizine)
Miscellaneous	Anticholinergics (e.g., benztropine), antiparkinsonian agents (e.g., levodopa)

criteria of 6 months before and 12 months after the index date, 46,427 patients were obtained. Out of these, 39,981 patients were aged 6-16 years and constituted the study cohort. Among the study cohort, 1,560 (3.9%) concomitantly received LAS and AAPs for at least 14 days, whereas 38,421 patients (96.1%) did not receive LAS and AAPs concomitantly for at least 14 days. Table 3 provides sociodemographic and clinical characteristics of patients who initiated ADHD treatment with LAS. Most of the study population who used LAS and AAPs concomitantly were male (73.0%), aged 6-12 years (60.3%), privately insured (93.3%), and lived in the Midwest region (53.1%). As shown in Table 4, on average, concomitant users had longer persistence (by 71 days) than the users of stimulants alone.

Table 5 presents predictors of concomitant use of LAS and AAPs among children and adolescents who initiated LAS treatment. Boys were 38% more likely to receive LAS and AAPs concomitantly than girls. Odds of concomitant use of LAS and AAPs were 63% lower among publicly insured youth than among others. Geographical variation was present in the concomitant use of LAS and AAPs. ADHD youth residing in the Midwest and West were less likely to receive LAS and AAPs concomitantly than those residing in the East. In addition, there was also variation due to year of cohort entry and season during which index LAS had been started. Children and adolescents with ADHD who entered the cohort in 2005 and 2006 were more likely to be prescribed LAS and AAPs concomitantly compared with those who entered the cohort in 2004. Children initiating LAS use in the summer were more likely to receive LAS and AAPs concomitantly, whereas those initiating LAS use in the spring were less likely to receive LAS and AAPs concomitantly than their counterparts. Diagnosis of various comorbidities such as depression; anxiety; bipolar disorder; obsessive compulsive personality disorder; oppositional defiant disorder; conduct disorder, psychosis; and pervasive developmental disorders, enuresis, tics, and mental health-related hospital visits in the past 6 months were positively associated with the concomitant use of LAS and atypical antipsychotic therapy.

Table 6 presents factors associated with LAS treatment persistence in children and adolescents diagnosed with ADHD. Use of AAPs was associated with improvement in LAS persistence by 15% (HR=0.85, 95% CI=0.76-0.94) when compared with those who used LAS only. Children aged 6-12 years were 26% more likely to be persistent than those aged 13-16 years. Geographic and seasonal variations were present in the LAS treatment persistence. ADHD patients living in the Midwest were 9% more likely to be persistent in the use of LAS than those living in the East. ADHD patients living in the South were 22% less likely to be persistent in the use of LAS than those living in the East. ADHD children initiating LAS use in the winter were 20% more likely to be persistent in the use of LAS, whereas children initiating LAS use in the summer were 20% less likely to be persistent in the use of LAS, when compared with the children initiating LAS use in autumn. ADHD patients seeking care from pediatricians were 4% more likely to use LAS persistently than the others.

With respect to psychiatric comorbidities, depression, anxiety, oppositional conduct disorder, oppositional defiant disorder, conduct disorder, learning disorder, psychosis, pervasive developmental disorders, substance abuse and dependence disorders, and enuresis were positively associated with LAS treatment persistence in children and adolescents with ADHD. Addition of psychotropic medications such as nonstimulants, alpha 2-agonists, antidepressants, mood stabilizers, sedatives/hypnotics/anxiolytics, and other miscellaneous medications were positively associated with LAS treatment persistence in children and adolescents with ADHD. Recent mental health-related hospitalization was negatively associated with LAS treatment persistence in children and adolescents with ADHD.

Discussion

Little is known about factors associated with concomitant use of LAS and AAPs and its impact on the persistence of LAS use in children and adolescents with ADHD, especially in non-Medicaid populations. In the present study, approximately 4%

TABLE 3 Characteristics of Children and Adolescents Who Initiated ADHD Treatment with LAS

Characteristics	Overall (N = 39,981) n (%)		Polypharmacy (n = 1,560) n (%)		Monotherapy (n = 38,421) n (%)		*P* Value
Predisposing Factors							
Sex							
Male	28,092	(70.3)	1,139	(73.0)	26,953	(70.2)	0.0154
Age (mean = 10.80 ± 3.06)							
6-12	26,931	(67.4)	940	(60.3)	25,991	(67.6)	< 0.0001
13-16	13,050	(32.6)	620	(39.7)	12,430	(32.4)	
Enabling Factors							
Health insurance							
Private	37,512	(93.8)	1,456	(93.3)	36,056	(93.8)	< 0.0001
Public	1,205	(3.0)	30	(1.9)	1,175	(3.1)	
Other/unknown	1,264	(3.2)	74	(4.8)	1,190	(3.1)	
Region							
East	6,780	(17.0)	327	(21.0)	6,543	(16.8)	< 0.0001
Midwest	19,640	(49.1)	828	(53.1)	18,812	(49.0)	
South	8,913	(22.3)	247	(15.8)	8,666	(22.6)	
West	4,648	(11.6)	158	(10.1)	4,490	(11.6)	
Year of entry							
2004	7,949	(19.9)	278	(17.8)	7,671	(19.9)	0.0616
2005	15,708	(39.3)	648	(41.6)	15,060	(39.2)	
2006	16,324	(40.8)	634	(40.6)	15,690	(40.9)	
Season of index prescription							
Winter	10,592	(26.5)	394	(25.3)	10,198	(26.5)	< 0.0001
Spring	7,431	(18.6)	258	(16.5)	7,173	(18.7)	
Summer	7,744	(19.4)	380	(24.4)	7,364	(19.2)	
Autumn	14,214	(35.6)	528	(33.8)	13,686	(35.6)	
Physician specialty							
Pediatrician	16,103	(40.3)	223	(14.3)	15,880	(41.3)	< 0.0001
Psychiatrist	4,993	(12.5)	565	(36.2)	4,428	(11.5)	
Other	18,885	(47.2)	772	(49.5)	18,113	(47.2)	
Need Factors							
Comorbidities							
Depression	5,408	(13.5)	565	(36.2)	4,843	(12.6)	< 0.0001
Anxiety	3,709	(9.3)	345	(22.1)	3,364	(8.8)	< 0.0001
Bipolar disorder	1,223	(3.1)	486	(31.2)	737	(1.9)	< 0.0001
Oppositional conduct disorder	572	(1.4)	78	(5.0)	494	(1.3)	< 0.0001
Obsessive compulsive personality disorder	246	(0.6)	65	(4.2)	181	(0.5)	< 0.0001
Oppositional defiant disorder	3,074	(7.7)	505	(32.4)	2,569	(6.7)	< 0.0001
Conduct disorder	2,959	(7.4)	385	(24.7)	2,574	(6.7)	< 0.0001
Learning disorders	1,706	(4.3)	77	(4.9)	1,629	(4.2)	0.1824
Psychosis and pervasive developmental disorders	1,471	(3.7)	348	(22.3)	1,123	(2.9)	< 0.0001
Substance abuse and dependence disorders	828	(2.1)	101	(6.5)	727	(1.9)	< 0.0001
Enuresis	1,063	(2.7)	78	(5.0)	985	(2.6)	< 0.0001
Encopresis	282	(0.7)	24	(1.5)	258	(0.7)	< 0.0001
Tics	526	(1.3)	60	(3.9)	466	(1.2)	< 0.0001
Comedications							
Nonstimulants	3,127	(7.8)	175	(11.2)	2,952	(7.7)	< 0.0001
Alpha 2-agonists	3,352	(8.4)	440	(28.2)	2,912	(7.6)	< 0.0001
Antidepressants	5,969	(14.9)	736	(47.2)	5,233	(13.6)	< 0.0001
Mood stabilizers	761	(1.9)	222	(14.2)	539	(1.4)	< 0.0001
Sedatives/hypnotics/anxiolytics	5,875	(14.7)	303	(19.4)	5,572	(14.5)	< 0.0001
Miscellaneous	129	(0.3)	33	(2.1)	96	(0.3)	< 0.0001
Recent mental health-related hospitalization	439	(1.1)	158	(10.1)	281	(0.7)	< 0.0001

ADHD = attention deficit hyperactivity disorder; LAS = long-acting stimulants.

TABLE 4 Mean and Median Treatment Duration in Children and Adolescents Initiating LAS

	Polypharmacy Users		Monotherapy Users	
	Mean[a] (95% CI)	Median	Mean[a] (95% CI)	Median
Persistence	225.7 ± 132.6 (219.1-232.3)	245.5	154.6 ± 129.1 (153.3-155.9)	105.0

[a]*Significant mean difference in treatment duration between polypharmacy and monotherapy users at P < 0.0001.*

CI = confidence interval; LAS = long-acting stimulants.

of commercially insured children and adolescents with ADHD concurrently received LAS and AAPs. This rate is similar to a recent study that found that 5.8%-6.8% of commercially insured children and adolescents in the United States with ADHD concurrently received AAPs.[31] Another study from Europe found that 4.0% of the ADHD patients using ADHD medications also received AAPs.[32]

This study found that various predisposing, enabling, and need factors were associated with the concomitant stimulant and AAP use and LAS treatment persistence. Among predisposing factors, boys were more likely to receive LAS and AAPs concomitantly than girls. This finding is consistent with the previous literature and could be attributed to behavioral symptoms of ADHD among boys.[7,8,10,42,43,66,67] Various enabling factors such as region, year of cohort entry in the study, season of index LAS prescription, physician specialty, and health insurance coverage were important predictors of concomitant use of LAS and AAPs. When compared with the eastern region, ADHD youth residing in other regions had a lower likelihood of concomitant use of LAS and AAPs. A previous study attributed geographical differences in identification and treatment of ADHD to the number, age, and type of physicians. This could also be due to differences in learning, training, and practice culture among the physicians and patient case mix.[68] Other possible reasons for regional differences in the concomitant use of LAS and AAPs could be the socioeconomic status of the ADHD population, different controlled substance laws in different states, anti-Ritalin campaigns, direct-to-consumer advertising, perceptions, and expectations of caregivers about medication use.[69]

Pediatricians in the present study were less likely to prescribe LAS and AAPs concomitantly, whereas psychiatrists were more likely to prescribe LAS and AAPs concomitantly. Past studies indicate physician specialty to be an important predictor of concomitant psychotropic medication use in children and adolescents.[16,17,70] This is possible because psychiatrists frequently see more treatment-resistant patients who have failed standard treatment and, thus, need concomitant therapy to treat ADHD. Likelihood of concomitant use of LAS and AAPs was 32% higher in 2005 and then decreased to 20% in 2006. In November 2005, the FDA issued a black box warning against the use of AAPs.[71,72] General concerns regarding use of potent antipsychotics in the pediatric population, coupled with the black box warning, might have cautioned physicians against the concomitant use with stimulants in this vulnerable population.

ADHD patients with public health insurance were less likely to receive LAS and AAPs concomitantly. Previous studies have reported a mixed relationship between health insurance and concomitant use of LAS and AAPs. Some studies have found higher rates of receipt of multiclass psychotropic medications among privately insured youth,[16,17,73] whereas another study has found this rate to be higher in publicly insured youth.[19] These mixed findings could be due to the methodological differences in capturing concomitant use, study populations, and study settings. Future research should examine the differential impact of health insurance, if any, on the concurrent use of LAS and AAPs in the pediatric population.

Among need factors, diagnosis of any comorbidity and recent mental health-related hospitalizations were positively associated with concomitant use of LAS and AAPs. In fact, diagnosis of bipolar disorder, psychosis, and pervasive developmental disorders were the main drivers of concomitant use of LAS and AAPs in youth with ADHD. Patients diagnosed with bipolar disorder, psychosis, and pervasive developmental disorders were 3 to 9 times more likely to receive LAS and AAPs concomitantly than patients without these comorbidities. This is consistent with a recently published study that found that number of pre-existing comorbidities was an important predictor of psychotropic concomitant medication use.[32] Treatment of ADHD is challenging due to the complexity of the disease and associated psychiatric comorbidities.[74,75] Treatment of ADHD in the presence of psychiatric comorbidities varies by type of comorbidity.[75,76] Various AAPs are approved by the FDA for the treatment of bipolar I disorder (mania or mixed), schizophrenia, and irritability associated with autistic disorder.[17,19,21] In the present study, among ADHD patients using LAS and AAPs concomitantly, 39.74% of the patients had a diagnosis of bipolar disorder, and 23.66% of the patients were diagnosed with psychosis and pervasive developmental disorders. These are the comorbidities for which use of AAPs is approved in children and adolescents. It is possible that these agents might be used with LAS for better management of ADHD or coexisting psychiatric conditions. However, odds of concomitant use were also high for psychiatric comorbidities, for which AAPs are not approved by the FDA, such as oppositional defiant disorder, personality disorders, and tics. It is possible that AAPs are being used off-label in ADHD patients.[19,23] Given the high risk of metabolic and neurologic adverse effects associated with AAPs in children, there is a greater need for generating safety and efficacy data for concomitant use of LAS and AAPs in children.[77,78] There is a treatment guideline for physicians regarding concomitant use for the treatment of schizophrenia in adolescents and adults.[79] A well-defined guideline for concomitant use in ADHD children and adolescents can help clinicians.[32,75,80]

Mental illness severity has been found to be associated with the use of combination therapy in adults,[63,81] but no such association has been reported in children and adolescents with ADHD. Although the direct relationship between ADHD

TABLE 5 Determinants of Concomitant Use of LAS and AAPs in Children and Adolescents with ADHD

Characteristics	Adjusted OR	95% CI for Adjusted OR
Predisposing Factors		
Sex		
Male	1.38[a]	1.21-1.57
Female	Reference	-
Age		
6-12	0.95	0.84-1.08
13-16	Reference	-
Enabling Factors		
Health insurance		
Private	0.79	0.59-1.04
Public	0.37[a]	0.23-0.60
Other/unknown	Reference	-
Region		
Midwest	0.91[b]	0.78-1.06
South	0.91	0.75-1.10
West	0.70[c]	0.56-0.88
East	Reference	-
Year of entry		
2005	1.32[c]	1.12-1.55
2006	1.20[b]	1.01-1.41
2004	Reference	-
Season of index prescription		
Spring	0.86[b]	0.72-1.03
Summer	1.27[b]	1.08-1.50
Winter	1.04	0.90-1.21
Autumn	Reference	-
Physician specialty		
Pediatrician	0.45[a]	0.38-0.53
Psychiatrist	1.87[a]	1.64-2.13
Other	Reference	-
Need Factors		
Comorbidities		
Depression		
Yes	1.56[c]	1.35-1.79
No	Reference	-
Anxiety		
Yes	1.31[c]	1.13-1.53
No	Reference	-
Bipolar disorder		
Yes	9.08[a]	7.78-10.59
No	Reference	-
Oppositional conduct disorder		
Yes	1.34	0.99-1.81
No	Reference	-
Obsessive compulsive personality disorder		
Yes	1.51	1.02-2.23
No	Reference	-
Oppositional defiant disorder		
Yes	2.56[a]	2.22-2.95
No	Reference	-
Conduct disorder		
Yes	1.86[a]	1.59-2.17
No	Reference	-
Learning disorders		
Yes	0.85	0.65-1.11
No	Reference	-
Psychosis and pervasive developmental disorders		
Yes	3.81[a]	3.23-4.49
No	Reference	-
Substance abuse and dependence disorders		
Yes	0.81	0.60-1.08
No	Reference	-
Enuresis		
Yes	1.62[c]	1.22-2.15
No	Reference	-
Encopresis		
Yes	1.24	0.74-2.06
No	Reference	-
Tics		
Yes	2.20[c]	1.60-3.03
No	Reference	-
Recent mental health-related hospitalization		
Yes	1.83[a]	1.39-2.41
No	Reference	-

[a] *P* < 0.0001.
[b] *P* < 0.05.
[c] *P* < 0.01.
AAPs = atypical antipsychotics; ADHD = attention deficit hyperactivity disorder; CI = confidence interval; LAS = long-acting stimulants; OR = odds ratio.

severity and concomitant use was not estimated, mental health-related hospitalization in the previous 6 months was used as a proxy measure to examine this relationship. Mental health severity was significantly related to concomitant use of LAS and AAPs among ADHD patients. Possibly, LAS alone might not be helpful in controlling the severity of ADHD, and patients might be prescribed AAPs on- or off-label for better management of ADHD and associated comorbidities. Additional research is warranted to explore reasons behind mental illness severity and concomitant use of LAS and AAPs among ADHD patients.

The second objective of this study was to evaluate the impact of AAP use on LAS treatment persistence in children and adolescents diagnosed with ADHD. Patients using LAS and AAPs concomitantly were more persistent to the stimulant treatment than those who used only stimulant. Results from the adjusted

TABLE 6 Determinants of Persistence of Index LAS in Children and Adolescents with ADHD

Characteristics	Adjusted HR	95% CI for Adjusted HR
Atypical antipsychotics		
Yes	0.85[a]	0.76-0.94
No	Reference	-
Sex		
Male	0.98	0.95-1.01
Female	Reference	-
Age		
6-12	0.74[b]	0.72-0.77
13-16	Reference	-
Health insurance		
Private	0.93	0.86-1.01
Public	1.11	0.99-1.24
Other/unknown	Reference	-
Region		
Midwest	0.91[b]	0.87-0.94
South	1.22[b]	1.17-1.28
West	0.99	0.93-1.04
East	Reference	-
Year of entry		
2005	1.00	0.96-1.04
2006	1.01	0.98-1.05
2004	Reference	-
Season of index prescription		
Spring	1.00	0.97-1.04
Summer	1.20[b]	1.15-1.25
Winter	0.80[b]	0.77-0.83
Autumn	Reference	-
Physician specialty		
Pediatrician	0.96[a]	0.94-0.98
Psychiatrist	1.05	1.00-1.10
Other	Reference	-
Comorbidities		
Depression		
Yes	0.90[b]	0.85-0.94
No	Reference	-
Anxiety		
Yes	0.90[a]	0.85-0.96
No	Reference	-
Bipolar disorder		
Yes	0.93	0.82-1.05
No	Reference	-
Oppositional conduct disorder		
Yes	0.76[a]	0.64-0.90
No	Reference	-
Obsessive compulsive personality disorder		
Yes	1.01	0.79-1.29
No	Reference	-
Oppositional defiant disorder		
Yes	0.79[b]	0.73-0.84
No	Reference	-
Conduct disorder		
Yes	0.82[b]	0.77-0.88
No	Reference	-
Learning disorders		
Yes	0.87[c]	0.80-0.94
No	Reference	-
Psychosis and pervasive developmental disorders		
Yes	0.72[b]	0.65-0.80
No	Reference	-
Substance abuse and dependence disorders		
Yes	0.75[b]	0.64-0.86
No	Reference	-
Enuresis		
Yes	0.76[b]	0.68-0.85
No	Reference	-
Encopresis		
Yes	0.84	0.68-1.03
No	Reference	-
Tics		
Yes	1.06	0.91-1.25
No	Reference	-
Comedications		
Nonstimulants		
Yes	0.62[b]	0.57-0.68
No	Reference	-
Alpha 2-agonists		
Yes	0.63[b]	0.58-0.68
No	Reference	-
Antidepressants		
Yes	0.71[b]	0.67-0.75
No	Reference	-
Mood stabilizers		
Yes	0.64[b]	0.55-0.75
No	Reference	-
Sedatives/hypnotics/anxiolytics		
Yes	0.54[b]	0.51-0.58
No	Reference	-
Miscellaneous		
Yes	0.53[a]	0.33-0.84
No	Reference	-
Recent mental health-related hospitalization		
Yes	1.47[b]	1.25-1.72
No	Reference	-

[a] *P* < 0.01.
[b] *P* < 0.0001.
[c] *P* < 0.05.
ADHD = attention deficit hyperactivity disorder; CI = confidence interval; HR = hazard ratio; LAS = long-acting stimulants.

Cox model suggest that the use of AAPs had a positive impact on LAS treatment persistence. ADHD patients using AAPs were 15% more likely to be persistent on the index LAS treatment than AAPs nonusers. In contrast to the present finding, Sikirica et al. (2012) did not find any difference in the discontinuation rate of index stimulant between ADHD children treated with AAPs and non-antipsychotics.[45] This could be due to difference in study population and other methodological differences. Concomitant use involving antipsychotic and stimulant medications might be needed to treat comorbid psychiatric and behavioral disorders, such as ADHD and disruptive behavioral disorders.[82] Various international experts, including American Academy of Child & Adolescent Psychiatry (AACP) and Texas Children's Medication Algorithm Project (CMAP),[83] also support the concurrent use of antipsychotics and stimulants to treat ADHD children with comorbidities.[75,80] However, a recently published systematic review found limited evidence regarding safety, efficacy, and tolerability for the concurrent use of AAPs and LAS. Future research is needed to compare benefits and risk of concomitant therapy with stimulant monotherapy.[84]

Consistent with previous literature, children were more likely to be persistent with index LAS treatment than adolescents.[7,8,10,42,43,66,67] This could be due to the careful parental supervision of the administration of ADHD medications in young children. Adolescents, on the other hand, are more likely to make their own treatment decisions and may choose not to take medications.[10,67,85] Additionally, hyperactive/impulsive adolescents might suffer from positive illusory bias, causing them to overrate their capabilities and underrate their problems relative to others.[86] Among enabling factors, lower likelihood of persistence on the index LAS treatment during summer months needs special attention. ADHD youth were 20% less likely to be persistent in the use of index LAS medication during summer months than during autumn months. This observation is similar to the results of Cascade et al. (2008), who found a significant drop in total prescriptions for ADHD in the summer months.[87] This possibly reflects symptomatic treatment of ADHD by physicians. Additionally, parents might not feel the need to medicate their children when they are out of school or on school break and consequently might discontinue the drug therapy during summer school holidays.

Among need factors, comorbidities, comedications, and recent mental health-related hospitalizations were positively associated with index LAS treatment persistence. As discussed already, AAPs might be used with LAS for better management of ADHD and coexisting psychiatric conditions. Optimal control of ADHD and associated comorbidities might translate into improved LAS persistence, as seen in the present study. This is further supported by the fact that there was a 29%-47% increase in index LAS treatment persistence when medications from other psychotropic drug class were added to the index LAS medication. Combination therapy is commonly used in ADHD patients to control ADHD symptoms and related comorbidities, manage improper response from monotherapy, help with sleep, and reduce side effects of a drug.[16,28,88] Recent mental health hospitalization was associated with a higher risk of discontinuing the index LAS medication. This can be attributed to the complexity of these patients requiring constant treatment monitoring or suboptimal treatment effect in severe patients.

Limitations

The present study used a claims database, which offers several advantages, such as large sample size of privately insured patients, long follow-up period, and real-world clinical setting data. Prescription claims databases are valid and reliable sources for gathering medication therapy-related information and for measuring persistence of drug therapy.[89-91] However, this study suffered from certain limitations. A 6-month baseline period without any pharmacy claim for any LAS was used to identify index cases of ADHD, but this criterion might include prevalent ADHD cases with extended drug holidays. Selection bias might be prevalent in the study, since the study population was not randomized to the concomitant use of LAS and AAPs. This study focused on those who initiated LAS only; therefore, the study population might be different from ADHD patients who used LAS along with IAS or SAS. The database used in the current study lacked information on patient characteristics such as race, education, and income. Previous literature suggests racial disparities in the concomitant use and persistence of psychotropic medications in ADHD children.[7,8,43,66,73,92] Information on these variables would have provided a better understanding of the factors affecting concomitant use of LAS and AAPs and persistence of LAS medications. Future studies should investigate this matter using other databases. All the information was obtained from pharmacy and medical claims records, so it was not possible to determine the clinical conditions for which medications or concomitant therapy was used. Therefore, clinically appropriate concomitant therapy could not be distinguished from clinically inappropriate concomitant therapy.

Data on dispensed medication do not reflect that medication was actually taken. Additionally, patients might take medications outside the health insurance through out-of-pocket expenses. The definition of persistence used in the present study allowed a maximum refill gap of 30 days, which does not account for extended drug holidays such as summer school holidays. Thus, results from the present study provide a conservative estimate of LAS persistence in ADHD youth. This study did not distinguish between clinically appropriate treatment discontinuation and premature treatment discontinuation for reasons known to patients and caregivers, such as perceived need and lack of efficacy. It is possible that concomitant users are followed more closely by their prescribers and therefore do better with LAS persistence. Although it was beyond the scope of this study, this information would be helpful for developing interventions aimed at improving persistence of stimulant medications in ADHD children and adolescents. Information was missing on severity of mental health conditions. Although severity of mental illness was controlled by using mental health-related hospitalization, this information is usually underreported in medical claims. Thus, results obtained in

this study provide conservative estimates of the relationship between mental health severity, concomitant use of LAS and AAPs, and persistence. Generalizability of this study might be limited due to use of commercially insured children and adolescents with ADHD, which does not represent all of the children and adolescents with ADHD in the United States. Finally, age of the dataset used might be a limitation. Consequently, there is a need to replicate these study findings in other settings using more recent data.

Conclusions

Various predisposing, enabling, and need factors were associated with the concomitant use of LAS and AAPs and persistence to the index LAS medication. Likelihood of concomitant use of LAS and AAPs was high for approved and nonapproved indications among ADHD patients. Use of AAPs was positively associated with the persistence of index LAS medications. This could be attributed to control of behavioral symptoms of ADHD or comorbid symptomatology. It is possible that concomitant use of AAPs along with stimulants might help in better management of ADHD and its comorbid symptoms. Various randomized controlled trials and national and international organizations support the use of combination therapy for treating ADHD and coexisting comorbidities. However, there is limited evidence to support such use. More empirical evidence is needed for concomitant use of LAS and AAPs to see if the benefits of this practice outweigh the risks in the pediatric ADHD population.

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DISCLOSURES

The authors have no relevant disclosures or conflicts of interest to declare.

Study concept and design were contributed by Bali, Kamble, and Aparasu. Aparasu was primarily responsible for data collection, helped by Bali and Kamble, and analysis was performed primarily by Bali and Aparasu, along with Kamble. The manuscript was written primarily by Bali, along with Aparasu and assisted by Kamble. Revision was performed by Bali and Aparasu, assisted by Kamble.

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