Concurrent Use of Stimulants and Second-Generation Antipsychotics Among Children With ADHD Enrolled in Medicaid

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Objective: This study examined the prevalence of and factors associated with concurrent use of long-acting stimulants (LAS) and second-generation antipsychotic agents among children and adolescents with attention-deficit hyperactivity disorder (ADHD).

Methods: The study involved retrospective longitudinal analysis of 2003–2007 Medicaid data from four states for children and adolescents between the ages of six and 17 years who were diagnosed as having ADHD and initiated LAS treatment. Concurrent use of LAS and second-generation antipsychotic medications was defined as simultaneous receipt of both medications for at least 14 days. On the basis of the conceptual framework of the Andersen behavioral model, multivariable logistic regression analysis was used to examine predisposing, enabling, and need factors associated with concurrent use.

Results: Among the 61,793 children who initiated LAS treatment for ADHD, 11,866 (19.2%) received LAS and second-generation antipsychotics concurrently for at least 14 days. Overall, the average length of concurrent use was 130±98 days. Multivariable logistic regression revealed that concurrent use was higher among boys, blacks, and foster care children compared with their respective counterparts. Comorbid psychiatric conditions, including disorders that are not approved indications for second-generation antipsychotic use, were associated with concurrent use of LAS and second-generation antipsychotics.

Conclusions: Almost one in five children and adolescents who initiated LAS also received second-generation antipsychotics concurrently for at least 14 days. Approved and nonapproved indications of second-generation antipsychotics influenced concurrent use in pediatric ADHD.

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Attention-deficit hyperactivity disorder (ADHD) is the most common neurobehavioral disorder among children and is mainly characterized by a persistent and developmentally inappropriate pattern of inattention, hyperactivity and impulsivity, or both (1,2). In 2011, the estimated U.S. prevalence of ADHD among children ages 4 to 17 years was 11%, and nearly 69% of children with ADHD received treatment (3). The national prevalence of ADHD increased significantly by 42% from 2003 to 2011, with an annual increase of approximately 5% among children and adolescents (4). Because 30% to 50% of children who are diagnosed as having ADHD continue to have symptoms in adulthood, ADHD is considered a chronic disorder (4,5). The increasing prevalence of ADHD poses a growing burden on the U.S. health care system.

Central nervous system stimulants, such as methylphenidate, amphetamine, and dextroamphetamine, are the mainstay of treatment for ADHD (6,7). These medications act as dopamine agonists in the dopaminergic system (6,7). Research has consistently shown the effectiveness of these medications in reducing the core symptoms of ADHD, such as hyperactivity, impulsivity, and inattentiveness (6–11). Second-generation antipsychotics, such as risperidone, olanzapine, and quetiapine, are commonly used to treat children with psychiatric disorders, including ADHD (12–17). These medications act as dopamine antagonists and also exert serotonergic properties, effects that are associated with improvements across diseases (12). Second-generation antipsychotics are approved by the U.S. Food and Drug Administration (FDA) for the treatment of schizophrenia, major depressive disorder, mixed or manic bipolar episodes, and behavioral symptoms in autism. Research suggests that visits involving use of antipsychotics for off-label indications increased from 4.4 million in 1995 to nine million in 2008. In 2008, the estimated cost associated with off-label use of antipsychotics was $6 billion (18).

Adverse events associated with use of antipsychotics among children and adolescents are increasingly recognized as a major clinical concern. The results of clinical trials and case reports indicate that among children, the use of second-generation

antipsychotics is associated with higher rates of adverse events, such as extrapyramidal symptoms, seizures, sedation, obesity, type II diabetes mellitus, hyperprolactinemia, gynecomastia, and cerebrovascular or cardiovascular events (19–21). A report by the Agency for Healthcare Research and Quality (AHRQ) found limited evidence from existing trials about the effectiveness of second-generation antipsychotics in the treatment of ADHD (22). There is also a lack of sufficient evidence of effectiveness on the basis of long-term studies involving second-generation antipsychotics in the treatment of ADHD symptoms.

Children and adolescents with ADHD commonly use two or more psychotropic medications. Outpatient medical visits involving psychotropic polypharmacy among children significantly increased nationally from 1996 (14.3%) to 2007 (20.2%) (23). Psychiatric visits involving treatment with multiples classes of psychotropic medications among children increased from 22.2% (1996–1999) to 32.2% (2004–2007). There was also a significant increase in the odds of coprescription of ADHD medications and antipsychotic agents (mostly second-generation antipsychotics) versus prescription of only one type of medication (odds ratio [OR]=6.2). An analysis of national survey data from 2000 to 2002 found that nearly 45% of the physician visits by children and adolescents who used antipsychotics involved a prescription for stimulants (24). Polypharmacy involving second-generation antipsychotics and stimulants is a concern because of the drugs' opposing actions on the dopaminergic system and associated adverse effects (25–27).

Limited data exist regarding the factors associated with concurrent use of stimulants and second-generation antipsychotics among children with ADHD. Some studies have found that the presence of psychiatric comorbidities is the single best predictor of polypharmacy and off-label prescribing of psychotropic medications (28). Other studies have shown that publicly insured children have higher odds of receiving second-generation antipsychotics compared with privately insured children (29). Therefore, the objective of this study was to examine the concurrent use of long-acting stimulants (LAS) and second-generation antipsychotic agents and to identify the factors associated with this practice among Medicaid-insured children and adolescents who were diagnosed as having ADHD. The study focused on LAS, given that most (74%) children and adolescents in the Medicaid program who are diagnosed as having ADHD initiate treatment with LAS (30).

METHODS

Data Source

This retrospective cohort study involved the analysis of Medicaid Analytic eXtract (MAX) data from California, Illinois, New York, and Texas for five years (January 2003–December 2007). The MAX files include a personal summary file, an inpatient file, a prescription drug file, and an "other" therapy file. The data elements of these Medicaid data files are described elsewhere in the literature (30). The study cohort was assembled by using the MAX files. The study was approved by the University of Houston Institutional Review Board under the category of exempt studies.

Study Population

The study population involved incident users of LAS, such as methylphenidate, dexmethylphenidate, lisdexamfetamine, amphetamine-dextroamphetamine salts, dextroamphetamine, and pemoline. The LAS were defined on the basis of the American Hospital Formulary Service classification as stimulant preparations with duration of action lasting more than 12 hours. The LAS were identified from the prescription files by using National Drug Codes, generic name, and trade name. The fill date of the first prescription for an LAS was defined as the index date.

Study Design

The study involved a longitudinal, retrospective cohort study design. The incident users were identified as patients with no claim for a stimulant or antipsychotic six months before the index date. Children between the ages of six and 17 years at the index date who had continuous Medicaid eligibility for six months before and 12 months after the index date were included in the final cohort. The diagnosis of ADHD was confirmed by one or more inpatient or outpatient claims for ADHD (*ICD-9-CM* code 314.xx) during the entire study period. Thus the final cohort involved 61,793 continuously eligible ADHD patients who were between the ages of six and 17 at the index date and who initiated ADHD treatment with LAS between July 1, 2003, and December 31, 2006. [A flowchart illustrating the complete study sample selection process is available as an online supplement to this article.]

Concurrent Use

Second-generation antipsychotics, such as clozapine, risperidone, olanzapine, quetiapine, ziprasidone, paliperidone, and aripiprazole, were identified by using National Drug Codes and generic names. Exposure to second-generation agents was defined as a prescription claim for any of the medications listed above at any time during one year after the index date. Concurrent use or polypharmacy involving LAS and second-generation antipsychotics was defined as simultaneous receipt of both medications for at least 14 days (31,32). Sensitivity analyses were conducted by varying the definition of concurrent use as use of both medications for $\geq$30 and $\geq$60 days .

Analytical Framework

The Andersen behavioral model (ABM) of health services was used to examine the predisposing, enabling, and need factors associated with concurrent use of LAS and second-generation antipsychotics among children and adolescents diagnosed as having ADHD (33). The ABM has been employed previously in other studies to examine the determinants of medication use (34–37). Predisposing, enabling, and need factors were selected from the literature and their availability in the Medicaid data. Predisposing factors, including age, gender,

TABLE 1. Use of long-acting stimulants among 61,793 children and adolescents with ADHD

Long-acting stimulant	N	%
Amphetamine-dextroamphetamine	20,862	33.8
Dexmethylphenidate	3,210	5.2
Methylphenidate	37,604	60.9
Pemoline	117	.2

race, cohort entry year, and season of index stimulant prescription, were identified from eligibility and claims files. Enabling characteristics included service-related characteristics, such as state of residence, receipt of foster care child benefits, receipt of Temporary Assistance for Needy Families (TANF), and participation in the State Children's Health Insurance Program (SCHIP) at the time of index LAS prescription. The predisposing and enabling characteristics were identified during the six months before the index date. Because of the effect of seasonality on ADHD use, especially during summer months, the study included season of ADHD treatment initiation (38). Previous studies have found high rates of psychotropic polypharmacy among foster care children (39,40); therefore, the study included foster care as an enabling factor.

The need characteristics included mainly psychiatric comorbidities and previous mental health–related hospitalization. Patients with a psychiatric comorbidity were identified by the presence of a medical claim in the inpatient, outpatient, and the other therapy files with an *ICD-9-CM* diagnosis code during the study period (41,42). These psychiatric comorbidities included mainly anxiety disorder, bipolar disorder, conduct disorder, depression, developmental disorder, oppositional defiant disorder, personality disorder, pervasive developmental disorder, psychosis, schizophrenia, sleep disorder, and substance use disorder. Recent mental health–related hospitalization was used as a proxy measure for severity of the mental disorder; it was defined as an inpatient claim during 180 days before the index date with an *ICD-9-CM* code for any designated mental disorder (290.xx–319.xx) (30).

Statistical Analysis

Descriptive statistics were used to examine the extent of LAS and second-generation antipsychotic utilization and characteristics of users of such drugs. Multivariable logistic regression was used to identify the predisposing, enabling, and need characteristics associated with concurrent use of LAS and second-generation antipsychotic agents. For the purpose of analysis, the dependent variable, concurrent use of LAS and second-generation antipsychotics, was coded as 1 if both medications were received simultaneously for at least 14 days and as 0 for shorter periods of concurrent use or no concurrent use. The independent variables were predisposing, enabling, and need factors. Any variable whose univariable test had a p value $<.25$ was selected as a candidate for the multivariable model (43). All statistical analyses were performed by using SAS, version 9.3, with an a priori significance level of .05 (44).

TABLE 2. Use of second-generation antipsychotics among 13,939 children and adolescents who received long-acting stimulants for ADHD

Antipsychotic	N[a]	%
Risperidone	8,593	61.6
Quetiapine	3,741	26.8
Olanzapine	1,155	8.3
Aripiprazole	3,030	21.7
Ziprasidone	896	6.4
Paliperidone	21	1.5
Clozapine	5	0

[a] Numbers may not add up to the total number of children and adolescents because >1 antipsychotic may be reported per patient.

RESULTS

In the study population, most of the children were ages 6–12 years (N=45,193, 73.1%), males (N=44,334, 71.8%), and whites (N=24,379, 39.5%). Among the study population, 15.3% (N=9,448) received foster care, 15.5% (N=9,550) received TANF, and 2.1% (N=1,297) received SCHIP benefits. Almost 60.9% (N=37,604) of children and adolescents initiated treatment for ADHD with long-acting preparations of methylphenidate (Table 1). A total of 13,939 (22.6%) received second-generation antipsychotics; risperidone was used by 61.6%, quetiapine by 26.8%, and aripiprazole by 21.7% (Table 2).

The concurrent use (≥14 days) of LAS and second-generation antipsychotic agents was found among 11,866 (19.2%) patients. The prevalence of concurrent use for ≥30 and ≥60 days was 17.8% and 13.8%, respectively. Overall, the average length of concurrent use was 130±98 days.

Table 3 provides data on the characteristics of children and adolescents by concurrent receipt of second-generation antipsychotics. There were significant differences between children who did or did not use LAS and antipsychotics concurrently in terms of predisposing factors (age, race, season, and year of cohort entry), enabling factors (state of residence and receipt of foster care, TANF, and SCHIP benefits), and need factors (psychiatric comorbidities, mental health–related hospitalization, and number of psychiatric comorbidities).

Table 4 provides the results of multivariable logistic regression analyzing factors associated with concurrent use of LAS and second-generation antipsychotics. In terms of predisposing factors, the odds of concurrent use were higher (OR=1.22) among boys than girls and higher (OR=1.34) among blacks than whites. There was regional and seasonal variation in the odds of concurrent use. Children and adolescents from Illinois (OR=.50), Texas (OR=.84), and California (OR=.73) had lower odds of concurrent use than children from New York. Children and adolescents who initiated ADHD treatment in autumn, winter, or spring had lower odds of receiving LAS and second-generation antipsychotics concurrently than children who initiated treatment in summer. Foster care children had higher odds (OR=1.83) and children who received SCHIP benefits had lower odds (OR=.67) of receiving LAS and second-generation antipsychotics concurrently compared with other children.

Among the need factors, the odds of concurrent use were higher among children with psychiatric comorbidities compared with children without such disorders (bipolar disorder, OR=5.06; oppositional defiant disorder, OR=1.44; personality disorder, OR=1.42; pervasive developmental disorder, OR=2.47; psychosis, OR=2.50; schizophrenia, OR=2.69; and tic disorder, OR=1.50). Mental health–related hospitalization was also associated with higher odds of concurrent use (OR=1.43). Developmental disorder (OR=.80) and substance use disorder (OR=.79) were associated with lower odds of concurrent use. Sensitivity analyses revealed that except for tics, the predictors of concurrent medications remained consistent across the operational definitions (≥30 and ≥60 days) of concurrent use (data not shown).

DISCUSSION

This study found that nearly one in five children and adolescents who initiated ADHD treatment with LAS also received second-generation antipsychotics for at least 14 days. The prevalence of concurrent use for longer overlap periods was lower. Overall, the concurrent use was similar to the findings from cross-sectional studies that examined use of multiple psychotropic medications among children and adolescents by using national survey data (23,24). The current study's findings also revealed that, in general, users of concurrent LAS and antipsychotics had significantly higher rates of psychiatric comorbidities and mental health–related hospitalization compared with users of only LAS. Second-generation antipsychotics are approved for a variety of indications, such as schizophrenia, major depressive disorder, mixed or manic bipolar episodes, and behavioral treatment of autism. A few controlled studies have found some support for use of risperidone to reduce disruptive behavior and to improve hyperactivity and inattention among patients with ADHD (45,46). Therefore, although the concurrent use of LAS and antipsychotics is common in pediatric ADHD, it may be used to treat patients with other psychiatric comorbidities or those with higher disease severity.

The results of multivariable analyses revealed that the odds of receiving LAS and second-generation antipsychotics concurrently were higher among boys than among girls and were higher among blacks than among

TABLE 3. Characteristics of children and adolescents with ADHD who received long-acting stimulants (LAS) and second-generation antipsychotics concurrently or LAS only

Characteristic	Concurrent LAS and antipsychotics (N=11,866)		LAS only (N=49,927)		p[a]
	N	%	N	%	
Predisposing factors					
Age					<.001
6–12	7,994	67.4	37,199	74.5	
13–17	3,872	32.6	12,728	25.5	
Gender					ns
Female	3,283	27.7	14,176	28.4	
Male	8,583	72.3	35,751	71.6	
Race					<.01
White	4,205	35.4	20,174	40.4	
Black	3,314	27.9	11,214	22.5	
Other	4,347	36.6	18,539	37.1	
Season					<.01
Summer	2,720	22.9	9,951	19.9	
Autumn	3,995	33.7	18,020	36.1	
Winter	2,762	23.3	11,993	24.0	
Spring	2,389	20.1	9,963	20.0	
Year of cohort entry					<.01
2003	2,043	17.2	8,647	17.3	
2004	3,855	32.5	18,087	36.2	
2005	2,882	24.3	11,568	23.1	
2006	3,086	26.0	11,625	23.3	
Enabling factors					
State					<.01
New York	2,931	24.7	10,396	20.8	
Illinois	2,025	17.1	11,393	22.8	
Texas	4,645	39.2	17,034	34.1	
California	2,265	19.1	11,104	22.2	
Foster care	2,954	24.9	6,494	13.0	<.01
TANF[b]	1,663	14.0	7,887	15.8	<.01
SCHIP[c]	127	1.1	1,170	2.3	<.01
Need factors					
Anxiety	2,673	22.5	5,694	11.4	<.01
Bipolar disorder	3,936	33.2	2,504	5	<.01
Conduct disorder	2,750	23.2	6,224	12.5	<.01
Depression	3,489	29.4	6,261	12.5	<.01
Developmental disorder	2,671	22.5	9,319	18.7	<.01
Oppositional defiant disorder	2,566	21.6	4,129	8.3	<.01
Pervasive developmental disorder	516	4.4	674	1.4	<.01
Psychosis	899	7.6	566	1.0	<.01
Schizophrenia	321	2.7	155	.3	<.01
Sleep disorder	390	3.3	1,346	2.7	<.01
Substance use disorder	495	4.2	1,003	2.0	<.001
Tic disorder	98	.8	220	.4	<.01
Mental health–related hospitalization	719	6.1	590	1.2	<.01
Psychiatric comorbidities					<.01
0	2,773	23.4	26,191	52.5	
1	3,208	27.0	14,371	28.8	
2	2,571	21.7	5,961	12.0	
3	1,677	14.1	2,144	4.3	
4	885	7.5	843	1.7	
≥5	752	6.3	417	.8	

[a] Proportions were compared by chi square test.
[b] Temporary Assistance for Needy Families
[c] State Children's Health Insurance Program

TABLE 4. Factors associated with concurrent use of long-acting stimulants and second-generation antipsychotics among children and adolescents with ADHD[a]

Characteristic	Adjusted OR	95% CI
Predisposing factors		
Gender (reference: female)	1.22	1.16–1.29
Race (reference: white)		
Black	1.34	1.26–1.41
Other	1.00	.94–1.05
Season (reference: summer)		
Autumn	.85	.80–.90
Winter	.88	.83–.94
Spring	.88	.82–.84
Year of cohort entry (reference: 2003)		
2004	.91	.85–.98
2005	1.00	.93–1.07
2006	1.07	.99–1.15
Enabling factors		
State (reference: New York)		
Illinois	.50	.47–.54
Texas	.84	.80–.90
California	.73	.68–.78
Foster care (reference: none)	1.83	1.72–1.94
SCHIP (reference: none)	.67	.55–.82
Need factors (reference: none)		
Bipolar disorder	5.06	4.49–5.70
Developmental disorder	.80	.71–.90
Oppositional defiant disorder	1.44	1.28–1.62
Personality disorder	1.42	1.16–1.79
Pervasive developmental disorder	2.47	2.09–2.91
Psychosis	2.50	2.14–2.93
Schizophrenia	2.69	2.12–3.41
Substance use disorder	.79	.67–.93
Tic disorder	1.50	1.12–1.99
Mental health–related hospitalization	1.43	1.25–1.63

[a] The model adjusted for predisposing characteristics (age), enabling characteristics (Temporary Assistance for Needy Families), and need characteristics (anxiety, depression, and conduct disorder). Model statistics, $\chi^2<.001$, C statistics, .76. All findings are significant ($p<.05$).

whites. A previous study found that boys had 2.3 times higher odds than girls of receiving second-generation antipsychotics during office-based physician visits (24). The high use of second-generation antipsychotics among boys can be attributed to the fact that boys have higher rates of behavioral disorders compared with girls (47). The finding that blacks were more likely to receive concurrent treatment than whites is not consistent with past research. Previous national studies have found that white children were more likely to receive antipsychotics than children from any other race (23,24). The higher odds of concurrent use among blacks than among whites may be attributed to socioeconomic characteristics of the Medicaid study population. However, there is a need to further investigate the issue of racial variation in use of antipsychotic agents among children.

The odds of concurrent use of LAS and second-generation antipsychotics were lower in every season compared with rates of use in summer. This finding suggests that children who initiate ADHD treatment during summer may have more severe ADHD symptomatology that requires management with multiple agents. However, analysis of Verispan's Vector One national data revealed that total monthly ADHD prescription volume drops between 22% and 29% during the summer months (38). Notably, the current study found that foster care children had nearly twice the odds (OR=1.83) of non–foster care children of receiving LAS and second-generation antipsychotics concurrently. A recent Government Accountability Office report highlighted the concerns regarding frequent and long-term use of antipsychotics among children in the foster care system (39). The finding of state-specific variation in concurrent use of LAS and second-generation antipsychotics could be attributed to the differences in Medicaid coverage-related policies and prescribing practices across the states. Similar variations across states regarding the use of second-generation antipsychotics have been found by Rawal and colleagues (48).

The children and adolescents diagnosed as having bipolar disorder, schizophrenia, psychosis, oppositional defiant disorder, pervasive developmental disorder, tics, and personality disorder had significantly higher odds of receiving concurrent LAS and second-generation antipsychotics than their respective counterparts, after controlling for other factors. However, conditions such as oppositional defiant disorder, pervasive developmental disorder, tic disorder, and personality disorder have not been approved by the FDA. These predictors of concurrent use, except tic disorder, remained consistent across the different definitions of concurrent use in the sensitivity analyses. Although off-label use of second-generation antipsychotics among children is common (48,49), there is strong need to develop the evidence base to support such use. A report by the AHRQ about off-label use of second-generation antipsychotics found very limited evidence of effectiveness for several psychiatric disorders and a low level of evidence for effectiveness in the treatment of ADHD (22). Furthermore, several clinical trials, case reports, and observational studies have linked use of second-generation antipsychotic agents to several metabolic, cardiovascular, and cerebrovascular adverse events among children and adults (19–21,25,26). In addition, the concurrent use of stimulants and second-generation antipsychotics is concerning because of their opposing effects on dopamine regulation (27). Therefore, there is an urgent need to evaluate safety and effectiveness of these medications in the children for off-label conditions.

The study had several limitations pertinent to the analysis of retrospective observational claims data (50). One such limitation was that the database lacked certain key variables associated with the treatment regimen, such as severity of, and changes in, ADHD symptoms. Hence, unmeasured clinical and physician factors may have confounded the findings. However, several demographic and clinical factors were

adjusted in the multivariable logistic regression model. The study assumed that patients consumed medications as prescribed and that they received no other psychotropic medication besides those available in the claims data. The definition of concurrent use was based on an overlap of therapies for at least 14 days. Although the prevalence of concurrent use was lower for longer overlap periods, the predictors of concurrent use (except tic disorder) remained consistent across the different definitions of concurrent use. Finally, the study included Medicaid beneficiaries from four states; therefore, the results may not be generalized to the whole ADHD population or, more specifically, to the privately insured or uninsured patient populations.

CONCLUSIONS

This study found that nearly one in five children and adolescents who initiated ADHD treatment with LAS also received second-generation antipsychotics concurrently for at least 14 days. Predisposing and enabling factors influenced concurrent use, as did need factors such as FDA-approved indications (schizophrenia, bipolar disorder, and psychosis) and nonapproved indications (oppositional defiant disorder, pervasive developmental disorder, tic disorder, and personality disorder). In the light of limited evidence, there is an urgent need to examine the safety and effectiveness of concurrent use of LAS and second-generation antipsychotics among children and adolescents with ADHD.

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