Concurrent Stimulant and Atypical Antipsychotic Drug Use in Children and Adolescents Diagnosed with Attention Deficit/Hyperactivity Disorder (ADHD)

DISSERTATION

by

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Concurrent Stimulant and Atypical Antipsychotic Drug Use in Children and Adolescents Diagnosed with Attention Deficit/Hyperactivity Disorder (ADHD)

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DEDICATION

I dedicate this dissertation work to my family, especially…….

to my mother Sushila Kamble for instilling importance of hard work and education;

to my wife Sanjyot for her patience and understanding.

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DISSERTATION SUMMARY

Objectives

The goals of this study were 1) to examine the prevalence of and factors associated with concurrent use of long acting stimulant (LAS) and atypical antipsychotic agents, 2) to examine the impact of addition of atypical antipsychotic agents on the persistence of LAS treatment, and 3) to examine the risk of cardiovascular adverse events due to addition of the atypical antipsychotic agents already on the regimen of LAS in children and adolescents diagnosed with ADHD.

Methods

The study involved retrospective longitudinal analysis of 2003-2007 Medicaid Analytical eXtract (MAX) data of four US states. The study mainly focused on children and adolescents aged 6 to 17 years who were diagnosed with ADHD and initiated ADHD treatment by using long acting stimulant (LAS) medications from July 2003 to December 2006. The continuous eligibility 6 months before and 12 months after the index LAS date was ensured for the study cohort. The study cohort was uniformly followed for one year after the initiation of LAS. Concurrent use of LAS and atypical antipsychotic medications were defined as receipt of both medications together at least for 14 days. The persistence of LAS was defined as number of days to discontinuation of index LAS treatment. The cardiovascular events were identified by using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes from inpatient and outpatient files. Descriptive analysis was performed to examine the utilization of LAS and atypical antipsychotic agents and compare the study groups. Multiple logistic regression analysis within the conceptual framework of Andersen behavioral model was used to examine the factors associated with concurrent use with LAS use only as reference group. Multivariate analysis was conducted by using accelerated failure time regression to examine the determinants of persistence of LAS. In order to examine cardiovascular safety typical

antipsychotic use was further classified as current use (active atypical antipsychotic use), former use (days after the periods of current use), and nonuse (time before the first atypical antipsychotic use including the follow up of patients who were never exposed to atypical antipsychotics). The cardiovascular risks were compared among the study groups using time dependent Cox regression analysis.

Results

Among the 61, 793 children and adolescents who were diagnosed with ADHD and initiated their ADHD treatment with LAS 11, 866 (19.20%) received LAS and atypical antipsychotic concurrently at least for 14 days. Risperidone was highly used concurrently and clozapine was least used (0.03%) among atypical antipsychotic users. The results of multiple logistic regression revealed that children and adolescents with male gender, black race, and foster care benefit recipients were more likely to receive LAS and atypical antipsychotic agents concurrently than their counterparts. Moreover, FDA approved indications such as schizophrenia, bipolar disorder, and psychosis and FDA non-approved indications such as oppositional defiant disorder, pervasive developmental disorder, tic disorder, and personality disorder determined the concurrent use of LAS and atypical antipsychotic agents. The mean duration of LAS treatment was longer (200 days; 95% Confidence Interval (CI), 197.6-202.9 days) among concurrent LAS and atypical antipsychotic recipients than only LAS users (143 days; 95% CI, 141.8-144 days). The accelerated failure time regression analysis found that concurrent users of LAS and atypical antipsychotic agents had 45% longer (Survival Time Ratio (STR), 1.45; 95% CI, 1.41-1.49) LAS treatment persistence than only LAS recipients. Similarly, adolescents and non-whites had shorter LAS treatment persistence than their counterparts. The numbers of cardiac events were 840, 202, and 45 during periods of atypical non-use, current use and former use, respectively. After controlling for demographic, service related, and clinical characteristics, the study found that current users and former users of atypical antipsychotics among the LAS users were not associated with cardiovascular events compared to no atypical

users (Current use: (Hazard ratio (HR), 1.17; 95% CI, 0.98-1.40; Former use: HR, 1.24; 95% CI, 0.91-1.69). Patient characteristics obesity (HR, 1.63; 95% CI, 1.21-2.20), diabetes (HR, 1.94; 95% CI, 1.27-2.96) and receipt of mood stabilizers increased the risk of cardiovascular events (HR, 1.87; 95% CI, 1.08-3.24) in the study population.

Conclusions

This study found that almost 1 in 5 children and adolescents received LAS and atypical antipsychotics concurrently. In addition to FDA approved indications such as schizophrenia, bipolar disorder, and psychosis, FDA non-approved indications such as oppositional defiant disorder, pervasive developmental disorder, tic disorder, and personality disorder determined the concurrent use of LAS and atypical antipsychotics. The recipients of LAS and atypical antipsychotic agents concurrently had longer LAS treatment continuity than recipients of only LAS. The study did not find any increased cardiovascular risk with addition of the atypical antipsychotics to LAS regimen in children and adolescents diagnosed with ADHD. The addition of the atypical antipsychotic agents along with LAS in ADHD patients may be beneficial in controlling ADHD symptoms. There is need to conduct head to head clinical trials of the 2 treatment groups in order to examine the efficacy of atypical antipsychotic agents and mechanism in the treatment of ADHD. Therefore there is urgent need of conducting head to head long term trials in order to examine the safety and efficacy of concurrent use of LAS and atypical antipsychotic agents in children and adolescents with ADHD and several other psychiatric disorders. Future studies with long term follow up are required to evaluate the long term effects of concurrent use of long acting stimulants and atypical antipsychotic agents.

SPECIFIC AIMS

Attention deficit/hyperactivity disorder (ADHD) is the most prevalent neurobehavioral disorder[1,2] in school aged children with the estimated prevalence of 9.5% in the United States and estimated 4.8% (2.7 million) of all children aged 4 to 17 years take medications for ADHD.[3] Central nervous system stimulants such as methylphenidate, amphetamine and mixed amphetamine salts, and pemoline are considered as the first line treatment for ADHD. The stimulants work as dopamine agonist by increasing the availability of synaptic dopamine and thereby reduce ADHD associated behaviors.[4-6] Although stimulants are mainstay of ADHD treatment, concurrent use of multiple psychotropic medications or psychotropic polypharmacy such as stimulants and atypical antipsychotics is common in children. A recent study found that multiclass polypharmacy increased from 14.3% in 1996 to 20.2% in 2007, odds ratio for trend was 1.89.[7] The trend for concurrent use of stimulants and antipsychotics was more than three times the general polypharmacy trend with odds ratio 6.22.

Antipsychotics such as risperidone, olanzapine, quetiapine are increasingly being used off-label to manage behavioral symptoms of ADHD although evidence base to support such use is limited. Based on short term clinical trial data several pediatric associations have recommended the concomitant use of stimulants and antipsychotics in ADHD patients.[8] However, stimulants and atypical antipsychotic agents have potentially opposing mechanism of action raising concern about “dopamine dilemma”.[9,10] Stimulant acts as a dopamine agonist increasing level of dopamine in neurons[4-6] and antipsychotics work by blocking their effects at dopamine receptors.[11] Some clinical researchers have suggested that concurrent use of stimulants and antipsychotics may actually be more effective at treating ADHD than use of stimulants alone.[8] This may be attributed to the potential benefits of the antagonism by increasing the tolerability and reducing the adverse events of stimulants.

Previous research[12] involving multi-year multi-state Medicaid data revealed that 73% of new stimulant users aged between 6 to 19 years initiated treatment with long-acting stimulant and remaining patients initiated with short or intermediate-acting stimulants. The goal of the research is to generate strong evidence base for concomitant use of stimulants and atypical antipsychotics to promote more effective and safe medication practices in children with ADHD. The study used five year, four state Medicaid data involving cohorts of children with 6 to 17 years of age in order to achieve following objectives.

Specific Aim 1: To examine the utilization pattern of concurrent use of long acting stimulant and atypical antipsychotic agents and predictors of concurrent use in children and adolescent with ADHD

Limited data exists regarding extent of antipsychotic use among new stimulant users and even little is known about predictors of concurrent use. This objective will characterize prevalence and predictors of concurrent use in order to provide a strong understanding of concurrent use patterns among children with ADHD.

Hypothesis 1: Various predisposing, enabling, and need characteristics in the conceptual framework of Andersen behavioral model will be associated with concurrent use of the long acting stimulant and atypical antipsychotic use.

Specific Aim 2: To assess the impact of concurrent use on persistence of long acting stimulants among children and adolescents with ADHD

The opposing action of stimulants and antipsychotic agents on dopaminergic system is likely to help to increase the tolerability and thereby increase the persistence of stimulant regimen.

Hypothesis 2: The persistence of long-acting stimulants will be longer among the concurrent users of the long acting stimulant and atypical antipsychotic agents than only long acting stimulant users.

Specific Aim 3: To evaluate the cardiovascular safety of concurrent long acting stimulant and atypical antipsychotic use

Both stimulants and antipsychotic agents have been linked to cardiovascular adverse events in various experimental and quasi experimental studies.[13-24]

Hypothesis 3: This aim will test the hypothesis that the concurrent use of long acting stimulants and atypical antipsychotic agents will be associated with lower cardiovascular adverse events than long acting stimulants alone.

BACKGROUND, SIGNIFICANCE, AND RATIONALE

Attention-deficit/hyperactivity disorder (ADHD) is characterized by a persistent and developmentally inappropriate pattern of inattention, hyperactivity, and/or impulsivity.[1,2] ADHD is the most prevalent neurobehavioral disorder in the United States with estimated prevalence of 9.5% (5.4 million) among children and adolescents aged between 4 to 17 years in 2007 and about 2.7 million of them received treatment.[3] The national prevalence of ADHD increased significantly by 21.8% just within four years from 2003 to 2007 with annual increase of 5.5% in children and adolescents.[3,13] It is a chronic disorder with 30 to 50% of those individuals diagnosed in childhood continuing to have symptoms in adulthood. Pediatric ADHD is very serious public health concern which leads to overwhelming effect not only on individual but also on their families and overall social system in terms of morbidity and healthcare burden.

Central nervous system (CNS) stimulants such as methylphenidate, amphetamine, dextroamphetamine, and pemoline are the first line treatment for ADHD in children and adolescents. Methylphenidate accounts for more than 90% stimulant use in ADHD in the United States.[14] The psychostimulant properties of these medications result from its binding to a site on the dopamine transporter as dopamine agonist resulting in inhibition of dopamine reuptake and enhanced levels of synaptic dopamine.[4] Various randomized clinical trials (RCTs) have shown the effectiveness of these medications in terms of reducing the core symptoms of the ADHD such as hyperactivity, impulsivity, and inattentiveness.[5,6]

Effectiveness of stimulants in clinical care is realized only if an individual is persistent with the stimulant therapy. Once the pharmacological treatment is discontinued, the treatment benefits also disappear. Poor persistence with stimulants leads to suboptimal symptom management

and has also been suggested as a precursor for negative long-term outcomes.[15,16] Persistence variation has been attributed to behavioral factors and drug-related effects.

Some concerns have been raised regarding safety of stimulants in children. Most importantly, clinical evidence from placebo controlled trials have demonstrated an increase in blood pressure and heart rate[17-23] and many case reports reported to FDA Adverse Events Reporting System (AERS) have linked CNS stimulants to stroke, myocardial infarction, and sudden death.[23] Recently, Winterstein and colleagues analyzed Florida Medicaid data from 1994 to 2002 and found a small but statistically significant association between stimulant exposure and physician visits for cardiac symptoms and circulatory diseases (Hazard ratio [HR] =1.2; 95% Confidence interval [CI]: 1.0–1.4).[24]

Psychotropic polypharmacy is increasingly common in pediatric population. Prescriptions for at least two psychotropic classes of medications for children and adolescents during outpatient visits increased significantly from 14.3% to 20.2% between the years 1996 and 2007, according to a new national study.[7] In terms of medical visits in which a current mental disorder was diagnosed, the percentage with multiclass psychotropic treatment increased from 22.2% (1996-1999) to 32.2% (2004-2007).[7] There were also specific increases in co-prescription of ADHD medications and antipsychotic medications (Adjusted Odds Ratio (AOR)) =6.22, 95% CI, 2.82-13.70). Atypical antipsychotic (AP) medications include risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, and asenapine. Atypical antipsychotics too act on the dopamine receptors but on D_2 in addition to $5HT_{1A}$ and $5HT_{2A}$ receptors which state its atypicality.[11] The use of atypical antipsychotics for non-FDA-approved indications accounts for most treatment and has been growing faster.[25] Extant clinical trial studies and case reports indicate that the use of atypical antipsychotics in children is associated with higher rates of adverse events, such as: extrapyramidal symptoms (EPS), seizures, somnolence/sedation,

weight gain/obesity, Type II diabetes mellitus, increased prolactin levels, and cerebrovascular or cardiovascular events (e.g. arrhythmias, ischemic events, orthostasis, and exacerbation of hypertension).[26-28] The analysis of the South Carolina Medicaid data from 1996-2005 by Jerrell and colleagues found increased risk of obesity/excessive weight gain, Type II diabetes and dyslipidemia, digestive/urogenital problems, cardiovascular and neurological /sensory symptoms.[14,15] Mcintyre and colleagues found that odds of developing cardiovascular events due to antipsychotics were 1.9 times greater in patients with type II diabetes mellitus and dyslipidemia and 2.1 times higher in those with incident type II diabetes mellitus and dyslipidemia.

Psychopharmacology research clearly suggests that stimulant and antipsychotic medications have opposing mechanisms of action. The psychostimulant properties of stimulants result from dopamine agonism, resulting in inhibition of dopamine reuptake and enhanced levels of synaptic dopamine.[4] But atypical antipsychotics acts on D_2 in addition to $5HT_{1A}$ and $5HT_{2A}$ receptors.[11] The concurrent use of CNS stimulants and antipsychotics leads to the dopamine antagonism and related dopamine dilemma.[9,10] An examination of dopamine pathways and receptors suggests that concerns regarding interactions between these two classes are justified and relevant. Concurrent stimulant-antipsychotic use has been rationalized by suggesting that they likely interact with different receptor subtypes and do so in different pathways of the brain.

Significance and Innovation

Stimulants and antipsychotic medications are commonly used together despite their potentially opposing mechanisms in dopaminergic system, often referred to as “Dopamine Dilemma” due to the opposing action.[9,10] Some clinical researchers have suggested that concurrent use of stimulants and antipsychotics may actually be more effective at treating ADHD than use of stimulants alone.[8] No study to date has examined tolerability and safety of concurrent stimulant and antipsychotic use. The current study examined the persistence and cardiovascular safety of

polypharmacy of stimulant and atypical antipsychotic medications in children and adolescents in real world practice. The results of the study will help clinicians and other decision makers to make the better decisions about the treatment strategy in the vulnerable patient population.

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The next three sections provide study design details, results, conclusions in the form of manuscript drafts for each of the specific aims

Manuscript 1: Specific Aim 1

Manuscript 2: Specific Aim 2

Manuscript 3: Specific Aim 3

MANUSCRIPT 1

Concurrent Stimulant and Atypical Antipsychotic Use among Medicaid Children and Adolescents diagnosed with ADHD

Abstract

Background

Multiple psychotropic drug use is highly prevalent in children and adolescents despite the lack of sufficient safety and efficacy data for such use. Moreover there is no study available in current literature examining the concurrent use of stimulant and atypical antipsychotic agents and its determinants in children and adolescents diagnosed with ADHD.

Objective

The goal of this study was to examine the prevalence of and factors associated with concurrent use of long acting stimulant and atypical antipsychotic agents among children and adolescents who initiated ADHD treatment by using long acting stimulant medications.

Methods

A retrospective longitudinal analysis was conducted by using Medicaid Analytical eXtract data of four states from 2003-2007. The study mainly focused on children and adolescents aged 6 to 17 years who were diagnosed with ADHD and initiated ADHD treatment by using long acting stimulant (LAS) medications from July 2003 to December 2006. Concurrent use of LAS and atypical antipsychotic medications were defined as receipt of both medications together at least for 14 days. The study cohort was uniformly followed for one year after the initiation of LAS medications in order to examine the concurrent use. Descriptive analysis was performed to examine the utilization of LAS and atypical antipsychotic agents. Multiple logistic regression analysis within the conceptual framework of Andersen behavioral model was used to examine the factors associated with concurrent use.

Results

Among the 61, 793 children and adolescents who were diagnosed with ADHD and initiated their ADHD treatment with LAS 11, 866 (19.20%) received LAS and atypical antipsychotic concurrently at least for 14 days. Children and adolescents who received LAS and atypical antipsychotics concurrently among them 67.37% were aged between 6-12 years, 72.33% were males, 35.44% were whites, and 24.89% received foster care benefits. Almost 77% of concurrent users of LAS and atypical antipsychotic agents had at least one additional psychiatric disorder. The multiple logistic regression revealed that children and adolescents with male gender, black race, and foster care benefits were more likely to receive LAS and atypical antipsychotic agents concurrently than their counterparts. Moreover, FDA approved indications such as schizophrenia, bipolar disorder, and psychosis and FDA non-approved indications such as oppositional defiant disorder, pervasive developmental disorder, tic disorder, and personality disorder determined the concurrent use of LAS and atypical antipsychotics.

Conclusions

This study found that almost 19.20% of children and adolescents received LAS and atypical antipsychotics concurrently. The FDA approved indications such as schizophrenia, bipolar disorder, and psychosis and FDA non-approved indications such as oppositional defiant disorder, pervasive developmental disorder, tic disorder, and personality disorder determined the concurrent use of LAS and atypical antipsychotics along with male gender, black race, and foster care benefits. Therefore there is urgent need of conducting head to head trials in order to examine the safety and efficacy of concurrent use of LAS and atypical antipsychotic agents in in children and adolescents with ADHD and several other psychiatric disorders.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder among children and mainly characterized by a persistent and developmentally inappropriate pattern of inattention, hyperactivity, and/or impulsivity.[1,2] Although the precise etiology of ADHD has not been elucidated, dopaminergic neural transmission particularly in the prefrontal cortex has been implicated in the pathophysiology of this condition.[3-5] Children with ADHD tend to have difficulty in organizing tasks and sustaining attention during schoolwork or play related activities. They may experience various functional problems such as school related difficulties,[6] academic under-achievement, difficult interpersonal relationship with family members and peers,[7,8] and low self esteem. The estimated prevalence of ADHD was 9.5% (5.4 million) among children and adolescent aged between 4 to 17 years in 2007 and about 66.3% (2.7 million) of them received treatment.[9] The national prevalence of ADHD increased significantly by 21.8% just within four years from 2003 to 2007 with annual increase of 5.5% in children and adolescents.[9,10] It is a chronic disorder with 30% to 50% of those individuals diagnosed in childhood continuing to have symptoms in adulthood.[11] Youth with childhood history of ADHD also shows greater impairment in academic functioning, including reading and mathematics achievements and failing a grade;[12] and more problems with parents, siblings, and peers.[13] Pediatric ADHD and its persistence into adulthood is very serious public health concern which leads to overwhelming effect not only on individual but also on their families and overall social system in terms of morbidity and healthcare burden.

The children's diagnosed with ADHD often show number of co-occurring psychiatric conditions.[14] In community derived samples, up to 44% of ADHD children have at least one other disorder and 43% have at least two or more additional disorders.[15] As many as 87 % of clinically diagnosed ADHD children may have at least one other psychiatric disorder and 67% have at least two other psychiatric disorders.[16] These psychiatric comorbidities mainly include mood/bipolar disorder, anxiety disorder, oppositional defiant disorder (ODD) , conduct disorder

(CD), antisocial disorder, learning disabilities, developmental disorder, tics, tourette's disorder, and substance use disorder.[17] Between 15% to 75% of the ADHD patients had mood disorder, 25% had anxiety disorder, 30%-50% had ODD/CD in both epidemiological and clinical samples of children and adolescents.[18] Lifetime rates of comorbid depression in children with ADHD increased from 29% at baseline to 45% at an average age of 15 years at 4 year follow up. The presence of ADHD increases the odds of ODD/CD by 10.7 fold (95% Confidence Interval [CI] = 7.7-14.8) in general population studies.[19] Follow up studies of children with ADHD indicate that subgroups of patients with ADHD and comorbid disorder have a poor outcome as supported by significantly greater social, emotional, and psychological difficulties.[17]

Central nervous system (CNS) stimulants such as methylphenidate, amphetamine, dextroamphetamine, and pemoline are the first line treatment for ADHD in children and adolescents. Methylphenidate accounts for more than 90% stimulant use in ADHD in the United States.[20] The psychostimulant properties of these medications result from its binding to a site on the dopamine transporter as dopamine agonist resulting in inhibition of dopamine reuptake and enhanced levels of synaptic dopamine.[21] Various randomized clinical trials (RCTs) have shown the effectiveness of these medications in terms of reducing the core symptoms of the ADHD such as hyperactivity, impulsivity, and inattentiveness.[22, 23] These medications also improve classroom behavior and academic performance; diminish oppositional and aggressive behaviors; promote increased interaction with teachers, family, and others; and increase participation in leisure time activities.[24, 25] Some concerns have been raised regarding safety of stimulants in children. Most importantly, clinical evidence from placebo controlled trials have demonstrated an increase in blood pressure and heart rate[26-32] and many case reports reported to FDA Adverse Events Reporting System (AERS) have linked CNS stimulants to stroke, myocardial infarction, and sudden death.[33] In February 2006, the United States, Food and Drug Administration (FDA) started initiatives about issuing the black box warning due to cardiovascular events based on the known propensity of sympathomimetic agents related

structural relationship and various case reports but later these initiatives were held back due to concern about the discouragement of the only available treatment for ADHD.[34-35] In addition, Adderall XR (long acting amphetamine) was withdrawn temporarily from Canadian market based on 20 international case reports about sudden cardiac death.[36] The American Heart Association (AHA) released a statement on cardiovascular monitoring in children and adolescents who receive stimulant medications in which it recommends electrocardiogram (ECG) monitoring as part of the evaluation. The statement is based on data from studies of various aspects of child health, including causes of sudden cardiac death and ECG screening programs to detect underlying cardiac disease.[37] Apart from this the most common side effects of CNS stimulants are insomnia, decreased appetite and weight loss, stomach ache, headache, and jitteriness.[38-39] The evidence about the safety of the CNS stimulants available until this date is from short term RCTs and there is lack of studies evaluating long term effects in children in their growing age.

Atypical antipsychotic (AP) medications include clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, iloperidone, and asenapine. Atypical antipsychotics act on the dopamine D_2 receptors in addition to serotonergic $5HT_{1A}$ and $5HT_{2A}$ receptors which state its atypicality.[40] During the past decade, there has been a substantial increase in the atypical antipsychotic use in children and adolescents for a variety of psychiatric disorders including attention-deficit/hyperactivity disorder, conduct disorder, depression, and anxiety disorders[41-44] but they are approved only in schizophrenia, behavioral symptoms in autism, Tourette's disorder, major depressive disorder, and mixed or manic bipolar episodes by the FDA. The use of atypical antipsychotics for non-FDA-approved indications accounts for most treatment and has been growing faster.[45] There is 6-fold increase in pediatric visits nationally that included prescriptions for antipsychotic medications, of which 90% were atypical antipsychotics.[46] In children and adolescents, as in adults, antipsychotic drug associated adverse events are increasingly recognized as a major clinical issue and concern not only in

clinical arena but in media too. Extant clinical trial studies and case reports indicate that the use of atypical antipsychotics in children is associated with higher rates of adverse events, such as: extrapyramidal symptoms (EPS), seizures, somnolence/sedation, weight gain/obesity, Type II diabetes mellitus, increased prolactin levels, and cerebrovascular or cardiovascular events (e.g. arrhythmias, ischemic events, orthostasis, and exacerbation of hypertension).[47-49] One placebo controlled trial conducted for 6 weeks shows clinically and statistically significant reduction in both disruptive behavior and hyperactivity subscale score among risperidone treated patients, in comparison to placebo, regardless of concomitant stimulant use.[50] Another open label trial conducted for 9 weeks shows quetiapine addition to methylphenidate was effective in reducing ADHD and aggression among adolescents who did not respond sufficiently to OROS methylphenidate alone at 54 mg/day dose.[51] But the recent evidence report published by the Agency of Healthcare Research and Quality found lack of RCTs examining effectiveness of atypical antipsychotic in ADHD patients. This report also suggests low evidence for effectiveness of atypical agents in the treatment of ADHD from existing trials.[52]

Psychotropic polypharmacy is increasingly common in pediatric population. Prescriptions for at least two psychotropic classes of medications for children and adolescents during outpatient visits increased significantly from 14.3% to 20.2% between the years 1996 and 2007, according to a new national trends survey study.[53] In terms of medical visits in which a current mental disorder was diagnosed, the percentage with multiclass psychotropic treatment increased from 22.2% (1996-1999) to 32.2% (2004-2007).[53] There were also specific increases in co-prescription of ADHD medications and antipsychotic medications (Adjusted Odds Ratio (AOR)) =6.22, 95% CI, 2.82-13.70) of which 90% were atypical antipsychotics. The analysis of National Ambulatory Medical Care Survey data from 2000 to 2002 found 37.8% mental health visit with prescription for antipsychotics had diagnosis of disruptive behavior and 44.2% of the physician visits by children and adolescents also received prescription for stimulants.[54]

The increase in psychotropic medication prescribing has not been matched by solid evidence of safety and efficacy.[55] There is growing concern with psychiatric community mainly due to multiple or concurrent psychotropic prescribing and prescription for medications that do not have FDA approval for particular indication and lack of required safety and efficacy data among children and adolescents.[56-59] Although polypharmacy and off-label use that may involve prescribing with limited evidence it do not inherently represent bad practice or practice without evidence[59] and banning such practice could instead create barrier to quality of care.[60] Off-label use of psychotropic medications can be defined as lack of official approval based on available evidence regarding medications efficacy with a specific age, a psychiatric disorder or problem, or both age and disorder. The risks associated with the off-label use are mainly due to unknown safety and efficacy. The risk may be more evident when a medication is prescribed off-label with respect to age. There are important developmental influences on children's responses to medications that can affect the way a medication is absorbed, distributed, metabolized, and excreted.[61] Psychotropic medications that are safe with adults can have toxic effects in younger children due to the immaturity of the neuro-endocrine system and blood–brain barrier, lowered activity levels of detoxifying enzymes, and changes in the neural circuitry and neurotransmitter systems.[61] Even when a medication may be safe for use in pediatric populations, it still may not be efficacious. Off-label prescribing with respect to problem or disorder may thus mean that an individual is receiving a medication that is not demonstrated efficacious, or perhaps even demonstrated ineffective, for his or her problem.[62,63] Indeed early onset mental disorders that are left untreated or improperly treated are linked to academic failure, childbearing in adolescence, unsteady employment, premature and unstable marriages, and violent behavior[64], as well as increasingly severe disability and comorbidity that becomes progressively more difficult to treat.[65]

The analysis of national survey of child psychiatrist found that psychiatric comorbidities is the single, best fitting predictor of the polypharmacy and off-label prescribing of the

psychotropic medications.[66] Another study shows that publicly insured children receive atypical antipsychotic four times more than privately insured children.[67] Our previous research shows that 74% of the Medicaid children and adolescents diagnosed with ADHD initiate treatment by using long acting stimulant medications.[68] The literature review suggest that there is lack of data on the characteristics promoting concurrent use of stimulant and atypical antipsychotic polypharmacy among children and adolescents from real world data. Therefore this study examined long acting stimulant and atypical antipsychotic drug utilization, concurrent use of long acting stimulant and atypical antipsychotic agents, and predictors of concurrent use of long acting stimulant and atypical antipsychotics among the Medicaid children and adolescents diagnosed with ADHD.

Methods

Study Design Data Source

This retrospective cohort study involved the analysis of five year (January 2003-December 2007) Medicaid Analytic eXtract (MAX) data from four states (California, Illinois, New York, and Texas). The Medicaid Analytic eXtract (MAX) files included Personal Summary File, Inpatient File, Prescription Drug File, Long-term Care File, and Other therapy file. Personal summary file contains demographic and enrollment data for persons enrolled for at least a day during the year. An inpatient file contains complete stay records for enrollees including diagnoses, procedures, and discharge status, length of stay and payment related information. Prescription drug file contains claims data for outpatients and nursing home prescriptions. Long-term care file contains records for services provided by skilled nursing home facilities, intermediate care facilities and psychiatric facilities. Other Therapy File contains claim data for all non-institutional Medicaid services such as physician services, laboratory services, and premium payments. The study cohort was assembled by using personal summary file, inpatient file, other therapy file, and prescription drug file. This study was approved by the institutional review board of the University of Houston.

Study Population

The study population involved only incident users of the long acting stimulant (LAS) medications such as methylphenidate, dexmethylphenidate, lisdexamfetamine, amphetamine-dextroamphetamine salts, dextroamphetamine, and pemoline. The long acting stimulant medications were defined based on the American Hospital Formulary Classification as stimulant preparation with duration of action more than 12 hours. The long acting stimulant medications were identified from the prescription files by using National Drug Code, generic name, and trade name. The prescription fill date of first long acting stimulant was defined as index date. The new users or incident users were identified as patients with no stimulant claim in previous six months of index date. The children and adolescents aged 6 to 17 years at the index date with continuous Medicaid eligibility for 6 months before and 12 months after the index date were included in the final cohort. The diagnosis of ADHD during the study period were confirmed by ≥1 inpatient or outpatient claim for ADHD, defined as International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) Clinical Modification (CM) code 314.xx during the entire study period. Thus the final cohort involved 61,793 continuously eligible ADHD patients, aged 6 to 17 years at index date, who initiated their ADHD treatment newly by using long acting stimulant medications in between July 1, 2003 to December 31, 2006. The complete study sample selection process is outlined in Figure 1.

Concurrent Use or Polypharmacy

Atypical antipsychotic medications such as clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole were identified by using National Drug Codes and generic names from prescription files during one year period after the index date. Concurrent use or polypharmacy of long acting stimulant and atypical antipsychotic medications were defined as receipt of both medications together at least for 14 days. The concurrent use or polypharmacy has been already defined in previous literature by Kortzan and collegues as receipt of second prescription ≥ 14 days before completion of the first prescription.[69]

Demographic, Service, and Clinical Characteristics

The Andersen behavioral model of health services was used to examine the factors associated with concurrent use of LAS and atypical antipsychotic use among children and adolescent diagnosed with ADHD.[70] This model has been previously employed in other studies to examine the determinants of medication use.[71-74] According to the Andersen behavioral model, an individual's use of health services is a function of 3 characteristics: predisposing, enabling, and need factors. Predisposing factors are characteristics of an individual that exist before illness and include demographic characteristics, social structure characteristics, and health beliefs. Enabling factors are those that give the individual the ability to secure the health services, such as income, health insurance, and availability of the service. The need factors represent either a subjective acknowledgment of need such as a patient's symptoms or the need for health care as perceived by the patient or professional judgment.

Predisposing, enabling, and need factors were selected from the literature and the availability of the factors in the Medicaid data. Predisposing factors included demographic characteristics such as age, gender, and race. Age at index date (6 to 12 years, and 13-17 years), gender (male or female), race (whites, blacks, and others) were identified from eligibility and claims file. Enabling characteristics included service related characteristics such as state (California, Illinois, New York, and Texas), cohort entry year (2003, 2004, and 2005), season of index stimulant prescription (autumn, winter, spring, and summer), foster care child benefits, temporary assistance to needy families (TANF), and State Child Health Insurance Program (SCHIP) at the time of index LAS prescription. The need characteristics mainly included psychiatric comorbidities, psychotropic co-medications, and previous mental health related hospitalization.

The psychiatric case mix of the population was characterized by the types and number of co-existing mental health conditions and recent inpatient psychiatric treatment. The presence of a medical claim during the study period from inpatient and other therapy files was used to

identify patients with the psychiatric comorbidity respective to ICD-9-CM diagnoses code for the following mental health disorders: conduct disorder (312.4, 312.8, 312.9, 312.00, 312.01, 312.02, 312.03, 312.10, 312.11, 312.12, 312.13, 312.20, 312.21,312.22, and 312.23), oppositional defiant disorder (313.81), developmental disorder (317, 319, 307.0, 307.9, V401, 315.5, 315.8, 318.0, 318.1, 318.2, 315.1, 315.2, 315.9, V400, 315.4, 315.31, 315.34, 315.39, 315.01, 315.02, 315.09, 315.32, and 315.00), pervasive developmental disorder (299.00, 299.01, 299.10, 299.11, 299.80, 299.81, 299.90, and 299.91), bipolar disorder (296.7, 296.00-296.06, 296.10-296.16, 296.40-296.46, 296.50-296.56, 296.60-296.66, 296.80-296.82, 296.89, 296.99, and 296.99), depression (311, 300.4, 293.83, 296.20-296.26, and 296.30-296.36), personality disorder (301.xx), schizophrenia (295.xx), substance use disorder (292.xx, 303.xx, 304.xx, 305.xx, 265.2, 357.5, 425.5, 291.0-291.5, 291.9, 571.0, 571.2, 571.3, 535.3, 790.3, and 648.30-648.34), psychosis (297.xx, and 298.xx), anxiety disorder (300.xx, 313.0,313.1, 308.1-318.4, 308.9, 293.84, 309.81, 313.21, 313.22, 313.82, and 313.83), sleep disorder (347.xx, 307.4, 780.5, and 307.40-307.49), and enuresis (307.6). Recent mental health hospitalization was used as a proxy measure for the general mental health status of an individual. It was defined as an inpatient claim occurring in the 180 days before or on the index prescription claim date with an ICD-9-CM diagnosis code for any designated mental health disorder (290.xx - 319.xx). The study population was also classified by prescription of other psychotropic medications during 12 month period after the index date, including antidepressants, typical antipsychotics, anxiolytics, sedatives/hypnotics, and mood stabilizers. Mood stabilizers were defined as lithium and anticonvulsants prescribed without a diagnosis of epilepsy (ICD-9 code 345.xx) during the one year after the index date.

Analytic Strategy

Descriptive statistics were used to examine the extent of long acting stimulant and atypical antipsychotic utilization, and to examine the demographic and service related characteristics, psychiatric disorders, and psychotropic medications among those who received

concurrent LAS and atypical antipsychotics and those who received only LAS. Multiple logistic regression was used to identify the demographics, service related characteristics, and psychiatric disorders associated with concurrent use of LAS and atypical antipsychotics. For the purpose of analysis dependent variable concurrent use of long acting stimulant and atypical antipsychotic medication were coded as "1" if patient received both medication together at least for 14 days and "0" if not. The independent variables were demographics, service related characteristics, and psychiatric comorbidities. All statistical analyses were performed by using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina) with a priori significance level of 0.05.

Results

Figure 1 provides the details of cohort development and sample selection. After enforcing all inclusion and exclusion criteria 61, 793 children and adolescents initiated their ADHD treatment with LAS out of which 60.85% initiated their treatment with long acting preparation of methylphenidate (Table 1). Those who initiated ADHD treatment with LAS among them

13, 939 (22.56%) received at least one prescription of atypical antipsychotics. Risperidone was highly used (49.26%) and clozapine was least used (0.03%) among atypical antipsychotic recipients (Table 2). Almost 11, 866 (19.20%) received LAS and atypical antipsychotic concurrently at least for 14 days.

Table 3 provides the demographics, service related, and clinical characteristics of children and adolescents who initiated ADHD treatment by using LAS. Children and adolescents who received LAS and atypical antipsychotics concurrently were significantly different than those who received LAS only except in terms of gender. In terms of demographic characteristics children and adolescents who received LAS and atypical antipsychotics concurrently among them 67.37% were children aged between 6-12 years, 72.33% were males, and 35.44% were whites. In terms of service related characteristics 24.89% received foster care benefits, 14% received TANF benefits, and only 1% received S-CHIP related benefits. In terms of psychiatric

comorbidities 47.54% had at least one psychiatric disorder among who received only LAS. On the contrary 76.63% had at least one psychiatric disorder among LAS and atypical antipsychotic recipients. Among concurrent LAS and atypical antipsychotic users 23.18% had conduct disorder, 21.62% had oppositional defiant disorder, 22.51% had developmental disorder, 4.35% had pervasive developmental disorder, 0.83% had tic disorder, 33.17% had bipolar disorder, 29.40% had depression, 2.51% had personality disorder, 2.71% had schizophrenia, 4.17% had substance use disorder, 7.58% had psychosis, 22.53% had anxiety disorder, and 3.29% had sleep disorder. In terms of co-medications those who received LAS and atypical antipsychotics concurrently also received anxiolytics (6.89%), antidepressants (37%), mood stabilizers (27.47%), sedatives/hypnotics (2.03%), atomoxetine (11.93%), typical antipsychotics (1.26%), short acting stimulants (7.47%), and intermediate acting stimulants (6.82%). Among concurrent users 6.06% had at least one mental health related hospitalization during six months before the initiation of LAS medications.

Table 4 provides the characteristics significantly associated with concurrent use of long acting stimulant (LAS) and atypical antipsychotic agents among children and adolescents who initiated ADHD treatment with LAS. The children and adolescents with male gender and black race were 22% and 33.5% more likely to receive concurrent LAS and atypical antipsychotic agents respectively. Those who initiated their treatment in the state of Illinois or Texas or California were less likely to receive LAS and atypical antipsychotics concurrently in comparison to those who initiated treatment in New York. The children who initiated their treatment in the season other than summer were less likely to receive LAS and atypical antipsychotic concurrently in comparison to children who initiated ADHD treatment in summer. Also children and adolescents who received foster care benefits were 83% more likely and those who received S-CHIP related benefits were 32.7% less likely to receive LAS and atypical antipsychotics concurrently in comparison to their counterparts. In terms of psychiatric comorbidities children and adolescents with ODD were 44%, PDD were 2.47 times, tics disorder

were 50%, bipolar disorder were 5.05 times, personality disorder were 44%, schizophrenia were 2.7 times, psychosis were 2.5 times more likely to receive LAS and atypical antipsychotic concurrently than their respective counterparts. While children and adolescents diagnosed with developmental disorders were 20% less likely and substance use disorder were 21.3% less likely to receive LAS and atypical antipsychotic concurrently than their respective counterparts. The children and adolescents who were hospitalized during six months before the initiation of the ADHD treatment with LAS were 43% more likely to receive LAS and atypical antipsychotic concurrently than their counterparts.

Discussion

In this Medicaid population almost 61% of children who initiated ADHD treatment by using LAS received methylphenidate preparations. The previous studies show that methylphenidate is highly used in ADHD treatment than amphetamine and its analogues, and pemoline. Methylphenidate accounts for more than 90% stimulant use in ADHD in the United States.[20] Various randomized clinical trials (RCTs) have shown the effectiveness of these medications in terms of reducing the core symptoms of the ADHD such as hyperactivity, impulsivity, and inattentiveness.[22,23] They also improve classroom behavior and academic performance; diminish oppositional and aggressive behaviors; promote increased interaction with teachers, family, and others; and increase participation in leisure time activities.[24,25] Moreover the study conducted by Barbaresi et al. suggests that methylphenidate is better tolerable than dextroamphetamine.[75] Also overuse of the amphetamine in the treatment of obesity and their misuse in 1960 may have given bad reputation to class of amphetamine which may have led to comparatively higher use of methylphenidate.

In this Medicaid population almost 22.50% of those who initiated ADHD treatment by using LAS also received atypical antipsychotic agents and almost 50% of them received risperidone as an atypical agent. In addition 19.20% of children and adolescents who initiated ADHD treatment with LAS received atypical antipsychotic medications concurrently with LAS at

least for 14 days. The incidence of concurrent use is similar to the concurrent use of multiple psychotropic medications examined from cross sectional studies at national level. [53, 54] The cross sectional nature of the data in previous studies may not have captured exact extent of prevalence of concurrent use or polypharmacy. But the longitudinal analysis of the claims data in this study provides precise extent of concurrent use of LAS and atypical antipsychotic agents. The atypical antipsychotic medications are mainly approved in the treatment of schizophrenia, behavioral symptoms in autism, Tourette's disorder, major depressive disorder, and mixed or manic bipolar episodes. These agents have not been approved in the treatment of ADHD by Food and Drug Administration but risperidone, quetiapine, and aripiprazole has been examined for its efficacy in children and adolescents with various psychiatric disorders. One placebo controlled trial conducted for 6 weeks shows clinically and statistically significant reduction in both disruptive behavior and hyperactivity subscale score among risperidone treated patients, in comparison to placebo, regardless of concomitant stimulant use.[50] The open label study conducted by Biederman et al. to measure improvement in ADHD symptoms in children with bipolar disorder due to risperidone found significant improvement in both hyperactivity/ impulsivity and inattentiveness but improvement was modest, and only 29% of subjects showed a 30% reduction in ADHD rating scale score.[76]

There was no statistically significant difference among boys and girls in terms of receiving LAS and atypical antipsychotics concurrently. These finding are similar to analysis of annual National Ambulatory Medical Survey data from 1996 to 2007 by Comer et al in which they found no difference among boys and girls in terms of receiving multiclass psychotropic medications during office visits.[53] But the analysis of same data from 2000-2002 by Olfson et al. found significant difference among boys and girls in terms of receiving atypical antipsychotic medications during office visits.[54] The analysis of the National of National Health Interview Survey data from 2004-2006 by Pastor et al. suggests that boys are more likely to have diagnosis of ADHD or learning disorder or both in comparison to girls.[77] According to the

National Comorbidity Survey of Adolescents prevalence of the one or two classes of psychiatric disorders among boys and girls were almost similar but the prevalence of three or more classes of psychiatric disorders were higher among girls than boys.[78] The extent of concurrent use of LAS and atypical antipsychotics were higher among children aged 6-12 years than adolescents aged 13-17 years. On the contrary Comer et al. found that extent of receiving multiclass psychotropic medication during office visits were higher among adolescents than children[53] and Olfson et al found that extent of receiving antipsychotic agents were higher among adolescents than children.[54] Also those who received foster care related benefits among them almost 25% of the children and adolescents received LAS and atypical antipsychotics concurrently. This can be identified with disproportionately high prevalence of mental health disorders among children in foster care. Several studies show that about 50 to 80 percent of children in foster care have moderate to severe mental health related problems.[79, 80] Moreover, almost 38% of the foster care children aged 0 to 19 years enrolled in Texas Medicaid program received psychotropic medications during September 2003 to August 2004.[81] The analysis of the Texas Medicaid data from July 2004 found that foster care children who received psychotropic medications among them 41.3% received more than 3 classes of drugs and almost 16% received more than 4 classes of drugs.[82] The most frequently used medications among these children were antidepressants (56.8%), ADHD medications (55.9%), and antipsychotic medications (53.2%). Thus high prevalence of the mental health disorders among foster care children may be leading to higher prevalence of multiple psychotropic medications among children.[82]

Interestingly, concurrent users of LAS and atypical antipsychotic agents had higher prevalence of psychiatric disorders than LAS recipients only. Similarly, concurrent users of LAS and atypical antipsychotic agents received significantly more other psychotropic medications than LAS recipients only. Furthermore, concurrent users had higher extent of mental health related hospitalization than only LAS users during 6 months before initiation of ADHD treatment. Thus higher prevalence of psychiatric comorbidities and its severity may necessitates use of the

atypical antipsychotic medications along with ADHD medications such as stimulants. The analysis of national survey of child psychiatrist found that psychiatric comorbidities is the single, best fitting predictor of the polypharmacy and off-label prescribing of the psychotropic medications.[66] But the recent evidence report published by the Agency of Healthcare Research and Quality found lack of RCTs examining effectiveness of atypical antipsychotic in ADHD patients. This report suggests low evidence or very low evidence only for efficacy of risperidone in the treatment of ADHD in children without any other psychiatric disorder and no evidence at all for the efficacy for any atypical antipsychotic agent in the treatment of ADHD children with bipolar disorder.[52] Thus prevalence of multiple psychiatric comorbidities may be leading to the use of atypical antipsychotic medications but there is not enough safety and efficacy data to support such use.

In terms of demographics the likelihood of receiving LAS and atypical agents concurrently increased with having male gender and black race. Children and adolescents with male gender were 2.3 times more likely to receive atypical antipsychotics than female gender during office based physician visits during 2002-2004.[54] Although ADHD is common disorder among boys and girls, ADHD is 4 to 9 times more prevalent in boys than girls.[83] The possibility of over-identification of ADHD and its symptomatology may be the reason behind higher likelihood of receiving LAS and atypical antipsychotics among boys. Interesting this study found that black children and adolescents who initiated their ADHD treatment by using LAS were almost 34% more likely to receive LAS and atypical antipsychotics concurrently than white children and adolescents. But the analysis of National Ambulatory Medical Survey data from 2000-2002 did not find any statistically significant difference among whites and minorities in terms of receiving atypical antipsychotics during physician office visits.[54]

Those who initiated ADHD treatment by using LAS during seasons other than summer were less likely to receive LAS and atypical antipsychotic agents concurrently than those initiated ADHD treatment during summer. These seasonal differences are congruent with

previous findings in which ADHD medications are commonly started or stopped by patients or their parents in relation to school year.[84] The analysis of Verispan's Vector One National Data (VONA) from January 2003 to October 2007 suggests that total monthly prescription volume dropping between 22 and 29 percent between May and July depending on year among children aged 0 to 17 years.[84] The children who received foster care related benefits were 83% more likely to receive LAS and atypical antipsychotics concurrently than their counterpart after controlling for demographic, service related characteristics, and psychiatric comorbidities and co-medications. At the same time The children who received S-CHIP related benefits were 33% less likely to receive LAS and atypical antipsychotics concurrently than their counterpart after controlling for demographic, service related characteristics, and psychiatric comorbidities and co-medications. The diagnoses of the multiple psychiatric disorders are most common in Medicaid foster care children which may require multiple psychotropic drug use.[82]

The children and adolescents diagnosed with bipolar disorder, schizophrenia, and psychosis were 5 times, 2.7 times, 2.5 times respectively more likely to receive LAS and atypical antipsychotics concurrently than their respective counterparts after controlling for demographics, service related characteristics, and psychiatric comorbidities and co-medications. In addition, children and adolescents diagnosed with ODD, PDD, tic disorder, personality disorder were 1.44 times, 2.5 times, 1.5 times, 1.44 times respectively more likely to receive LAS and atypical antipsychotics concurrently than their respective counterparts after controlling for demographics, service related characteristics, and psychiatric comorbidities and co-medications. But children with developmental disorder and substance use disorder were almost 20% less likely to receive LAS and atypical antipsychotics concurrently than their respective counterparts. The children and adolescents who were hospitalized due to mental health disorder 6 months prior to the initiation of ADHD treatment with LAS were 43% more likely to receive LAS and atypical antipsychotics concurrently than those were not had mental health related hospitalization. Atypical antipsychotic medications are approved by FDA only in

the treatment of schizophrenia, behavioral symptoms in autism, Tourette's disorder, major depressive disorder, and mixed or manic bipolar episodes, and psychosis. These medications have not been approved in indications such as ODD, PDD, tic disorder, personality disorder. Thus the study findings suggest that atypical antipsychotics at some extent are being used off-label in children and adolescents. Literature suggests that all the atypical antipsychotics were used off-label (without FAD approved indication, or dose, or an age group) in youth in 2004.[85] In children and adolescents, as in adults, antipsychotic drug associated adverse events are increasingly recognized as a major clinical issue and concern not only in clinical arena but in media too. Extant clinical trial studies and case reports indicate that the use of atypical antipsychotics in children is associated with higher rates of adverse events, such as: extrapyramidal symptoms (EPS), seizures, somnolence/sedation, weight gain/obesity, Type II diabetes mellitus, increased prolactin levels, and cerebrovascular or cardiovascular events (e.g. arrhythmias, ischemic events, orthostasis, and exacerbation of hypertension).[47-49] Therefore there is need to monitor the use of these medications in the light of safety and efficacy in vulnerable patient population such as children and adolescents.

Administrative healthcare claims databases offer several advantages such as large and diverse sample sizes, long follow-up, and availability of real-world clinical practice data. They are powerful tools for measuring treatment patterns. However, retrospective analyses of these databases are also associated with certain inherent limitations, as they are not primarily designed to address particular research questions.[86] One such limitation that the database lacks certain key variables associated with the treatment regimen, such as severity of, and changes in, ADHD symptoms and other psychiatric comorbidities. Hence, unmeasured clinical and physician factors may have confounded the propensity of receipt of LAS and atypical antipsychotic medication concurrently. However, several demographic and clinical factors were adjusted for the variation in multivariable logistic regression model. The study assumes that the medications that are dispensed are actually consumed by patients as prescribed and that the

patients received no other psychotropic medication besides those available in the claims data. The definition of the concurrent use of LAS and atypical agents is limited to overlap of both therapies for at least 14 days. The study did not account for the concurrent use less than 14 days. The study also limited to the Medicaid beneficiaries from four states and prescribing practices of Medicaid providers may also not be representative of those providers contracted under other types of health insurance programs. So, the results may not be generalized to the whole ADHD population or specifically to the privately insured or uninsured patient populations. Finally, diagnoses of ADHD and co-morbid mental disorders were identified based on diagnostic codes, and claim forms limit the number of diagnoses that can be documented.

Conclusions

This study found that almost 19.20% of children and adolescents aged between 6 to 17 years who initiated ADHD treatment with long acting stimulant (LAS) medications received LAS and atypical antipsychotics concurrently. These findings are consistent with the available prevalence of multiclass psychotropic drug utilization from national level cross sectional data. The concurrent users were mainly children aged between 6-12 years, males, and had at least one psychiatric comorbidity. The FDA approved indications such as schizophrenia, bipolar disorder, and psychosis and FDA non-approved indications such as oppositional defiant disorder, pervasive developmental disorder, tic disorder, and personality disorder determined the concurrent use of LAS and atypical antipsychotics along with male gender, black race, and foster care benefits.

Clinical Significance

Multiple psychotropic drug use in children and adolescents is major public health concern mainly due to the lack of sufficient safety and efficacy data. This is the first study which has examined concurrent use of long acting stimulant and atypical antipsychotic agents by using longitudinal data. This study found that concurrent use of atypical antipsychotic agents was driven by FDA non-approved psychiatric comorbidities along with approved ones. If not the non-

approved psychiatric disorders then atypical antipsychotics may have been used to treat symptomatology of ADHD. Atypical antipsychotics have been linked to several adverse events in children and adolescents therefore there is need to practice caution by prescribers while prescribing these medication in developmentally vulnerable population such as children and adolescents. Early onset of multiple mental health disorders if left untreated or improperly treated leads to failure at personal and social level, as well as increasingly severe disability and comorbidity that becomes progressively more difficult to treat. Therefore there is urgent need of conducting head to head trials in order to examine the safety and efficacy of not only atypical antipsychotic agents but also multiple psychotropic use in several psychiatric disorders in children and adolescents.

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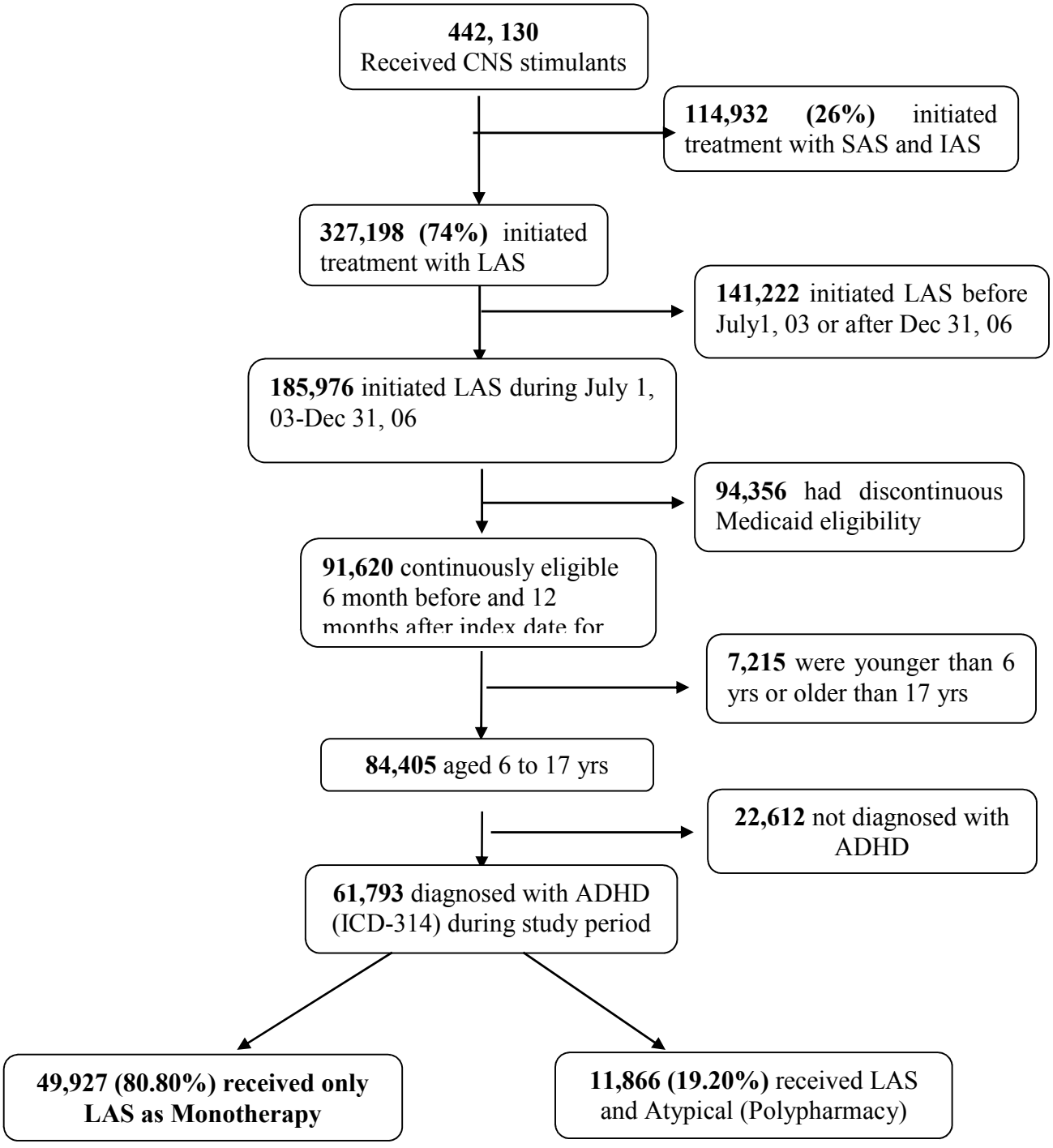
Figure 1: Flow-chart of Study Sample Selection and Study Cohort Development



Abbreviations: ADHD – Attention Deficit/Hyperactivity Disorder; SAS – Short-Acting Stimulants; IAS – Intermediate-Acting Stimulants; LAS - Long-Acting Stimulants

Table 1: Long Acting Stimulant (LAS) Initiation among Children and Adolescents with ADHD (N=61,793)			
LAS	**LAS Brand**	**Frequency (N)**	**Percentage (%)**
Amphetamine-Dextroamphetamine	Adderall XR	20,862	33.76
Dexmethylphenidate	Focalin XR	3,210	5.19
Methylphenidate	Concerta	30,936	60.85
	Daytrana	389	
	Metadate CD	3,245	
	Ritalin LA	3,034	
Pemoline	Cylert	12	0.19
	Pemoline	105	

Table 2: Atypical Antipsychotic Utilization among Children and Adolescents who initiated ADHD Treatment with LAS (N=13,939)		
Atypical Antipsychotic Agents	**Frequency**	**Percentage**
Risperidone	8593	49.26
Quetiapine	3741	21.44
Olanzapine	1155	6.62
Aripiprazole	3030	17.37
Ziprasidone	896	5.14
Paliperidone	21	0.12
Clozapine	5	0.03

Table 3: Characteristics of Children and Adolescents Diagnosed with ADHD (N=61,793)			
Characteristics	**LAS and Atypical Antipsychotic Polypharmacy (n=11,866)**	**LAS Monotherapy (n=11,866) (n=49,927)**	**P-value**
Demographics			
Age (yrs)			
6-12	7,994 (67.37)	37,199 (74.51)	<0.0001
13-17	3,872 (32.63)	12,728 (25.49)	
Gender			
Female	3,283 (27.67)	14,176 (28.39)	0.1143
Male	8,583 (72.33)	35,751 (71.61)	
Race/ethnicity			
White	4,205 (35.44)	20,174 (40.41)	<0.0001
Black	3,314 (27.93)	11,214 (22.46)	
Others	4,347 (36.63)	18,539 (37.13)	
Service			
States			
New York	2,931 (24.70)	10,396 (20.82)	<0.0001
Illinois	2,025 (17.07)	11,393 (22.82)	
Texas	4,645 (39.15)	17,034 (34.12)	
California	2,265 (19.09)	11,104 (22.24)	
Season			
Summer (6-8)	2,720 (22.92)	9,951 (19.93)	<0.0001
Autumn (9-11)	3,995 (33.67)	18,020 (36.09)	
Winter (12-2)	2,762 (23.28)	11,993 (24.02)	
Spring (3-5)	2,389 (20.13)	9,963 (19.96)	
Cohort Entry Year			
2003	2,043 (17.22)	8,647 (17.32)	<0.0001
2004	3,855 (32.49)	18,087 (36.23)	
2005	2,882 (24.29)	11,568 (23.17)	
2006	3,086 (26.01)	11,625 (23.28)	
Foster Care			
No	8,912 (75.11)	43,433 (86.99)	<0.0001
Yes	2,954 (24.89)	6,494 (13.01)	
TANF			
No	10,203 (85.99)	42,040 (68.03)	<0.0001
Yes	1,663 (14.01)	7,887 (12.76)	
S-CHIP			
No	11,739 (98.93)	48,757 (97.66)	<0.0001
Yes	127 (1.07)	1,170 (2.34)	
Psychiatric Comorbidities			
Conduct Disorder			
No	9116 (76.82)	43703 (87.53)	<0.0001
Yes	2750 (23.18)	6224 (12.47)	
Oppositional Defiant Disorder			
No	9300 (78.38)	45798 (91.73)	<0.0001

Yes	2566 (21.62)	4129 (8.27)	
Developmental Disorder			
No	9195 (77.49)	40608 (81.33)	<0.0001
Yes	2671 (22.51)	9319 (18.67)	
Pervasive Developmental Disorder			
No	11,350 (95.65)	49253 (98.65)	<0.0001
Yes	516 (4.35)	674 (1.35)	
Tic Disorder			
No	11768 (99.17)	49707 (99.56)	<0.0001
Yes	98 (0.83)	220 (0.44)	
Bipolar Disorder			
No	7930 (66.83)	47423 (94.98)	<0.0001
Yes	3936 (33.17)	2504 (5.02)	
Depression			
No	8377 (70.60)	43666 (87.46)	<0.0001
Yes	3489 (29.40)	6261 (12.54)	
Personality Disorder			
No	11568 (97.49)	49665 (99.48)	<0.0001
Yes	298 (2.51)	262 (0.52)	
Schizophrenia			
No	11545 (97.29)	49772 (99.69)	<0.0001
Yes	321 (2.71)	155 (0.31)	
Substance Use Disorder			
No	11371 (95.83)	48924 (97.99)	<0.0001
Yes	495 (4.17)	1003 (2.01)	
Psychosis			
No	10967 (92.42)	49361 (98.87)	<0.0001
Yes	899 (7.58)	566 (1.13)	
Anxiety			
No	9193 (77.47)	44233 (88.60)	<0.0001
Yes	2673 (22.53)	5694 (11.40)	
Sleep Disorder			
No	11476 (96.71)	48581 (97.30)	<0.0005
Yes	390 (3.29)	1346 (2.70)	
Co-medications			
Anxiolytics			
No	11048 (93.11)	47903 (95.95)	<0.0001
Yes	818 (6.89)	2024 (4.05)	
Antidepressants			
No	7475 (63.00)	42004 (84.13)	<0.0001
Yes	4391 (37.00)	7923 (15.87)	
Mood stabilizers			
No	8606 (72.53)	47286 (94.71)	<0.0001
Yes	3260 (27.47)	2641 (5.29)	
Sedative/Hypnotics			
No	11626 (97.97)	49665 (89.11)	<0.001
Yes	240 (2.03)	262 (10.89)	
Atomoxetine			
No	10450 (88.07)	44491 (89.11)	<0.0001

Yes	1416 (11.93)	5436 (10.89)	
Typical Antipsychotics			
No	11716 (98.74)	49764 (99.67)	<0.001
Yes	150 (1.26)	163 (0.33)	
SAS			
No	10980 (92.53)	46580 (93.30)	<0.0001
Yes	886 (7.47)	3347 (6.70)	
IAS			
No	11057 (93.18)	47001 (94.14)	<0.0001
Yes	809 (6.82)	2926 (5.86)	
Severity			
Mental Health Hospitalization			
No	11147 (93.94)	49337 (98.82)	<0.0001
Yes	719 (6.06)	590 (1.18)	
No. Psychiatric Comorbidities			
0	2773 (23.37)	26191 (52.46)	<0.0001
1	3208 (27.04)	14371 (28.78)	
2	2571 (21.67)	5961 (11.94)	
3	1677 (14.13)	2144 (4.29)	
4	885 (7.46)	843 (1.69)	
5 and >5	752 (6.34)	417 (0.84)	

Table 4: Characteristics Significantly Associated with Concurrent use of Long acting stimulant (LAS) and Atypical Antipsychotic agents among Children and Adolescents who initiated ADHD treatment with LAS			
Characteristics*‡	**Unadjusted Odds Ratio**	**Adjusted Odds Ratio**	**95% CI**
Demographics			
Age (yrs)			
6-12	1.00	1.00	
13-17	1.416	0.996	0.946-1.048
Gender			
Female	1.00	1.00	
Male	1.036	1.224	1.164-1.288
Race/ethnicity			
White	1.00	1.00	
Black	1.418	1.335	1.259-1.414
Others	1.125	0.995	0.942-1.051
Service			
States			
New York	1.00	1.00	
Illinois	0.631	0.501	0.466-0.539
Texas	0.967	0.843	0.794-0.896
California	0.723	0.727	0.679-0.779
Season			
Summer (6-8)	1.00	1.00	
Autumn (9-11)	0.811	0.847	0.797-0.900
Winter (12-2)	0.843	0.882	0.826-0.943
Spring (3-5)	0.877	0.879	0.819-0.842
Cohort Entry Year			
2003	1.00	1.00	
2004	0.902	0.912	0.851-0.977
2005	1.054	0.997	0.928-1.072
2006	1.124	1.066	0.993-1.145
Foster Care			
No	1.00	1.00	
Yes	2.217	1.828	1.724-1.940
SCHIP			
No	1.00	1.00	
Yes	0.451	0.673	0.550-0.823
Psychiatric Comorbidities			
Oppositional Defiant Disorder			
No	1.00	1.00	
Yes	3.060	1.440	1.280-1.620
Developmental Disorder			
No	1.00	1.00	
Yes	1.266	0.801	0.714-0.900
Pervasive Developmental Disorder			
No	1.00	1.00	
Yes	3.323	2.467	2.092-2.910

Tic Disorder			
No	1.00	1.00	
Yes	1.882	1.503	1.139-1.985
Bipolar Disorder			
No	1.00	1.00	
Yes	9.400	5.055	4.488-5.695
Personality Disorder			
No	1.00	1.00	
Yes	4.883	1.442	1.164-1.787
Schizophrenia			
No	1.00	1.00	
Yes	8.928	2.689	2.119-3.414
Substance Use Disorder			
No	1.00	1.00	
Yes	2.123	0.787	0.670-0.925
Psychosis			
No	1.00	1.00	
Yes	7.149	2.501	2.139-2.925
Severity			
Mental Health Hospitalization			
No	1.00		
Yes	5.393	1.427	1.248-1.632

*Significance level, P<0.05; Model Statistics, χ^2<0..1; C statistics, 0.761;ǂ OR, Odds Ratio; CI, Confidence Interval; ǂ Model Adjusted for predisposing characteristics (age), enabling characteristics (state, season, cohort entry year, and TANF), and need characteristics (comorbidities: conduct disorder, depression, and anxiety).

MANUSCRIPT 2

Impact of Atypical Antipsychotic Agents on the Persistence of the Stimulant Treatment in Children and Adolescents with Attention Deficit/hyperactivity Disorder (ADHD)

Abstract

Background

The treatment non-persistence is measure problem in ADHD children and adolescents. Also multiple psychotropic drug use is highly prevalent in children and adolescents. There is no study available in current literature examining the concurrent use of stimulant and atypical antipsychotic agents and its impact on stimulant treatment persistence.

Objective

The goal of this study was to examine the impact of addition of atypical antipsychotic agents on the persistence of long acting simulant (LAS) treatment in children and adolescents diagnosed with ADHD.

Methods

A retrospective longitudinal analysis was conducted by using Medicaid Analytical eXtract data of four states from 2003-2007. The study mainly focused on children and adolescents aged 6 to 17 years who were diagnosed with ADHD and initiated ADHD treatment by using long acting stimulant (LAS) medications from July 2003 to December 2006. Concurrent use of LAS and atypical antipsychotic medications were defined as receipt of both medications together at least for 14 days. The persistence of LAS was defined as number of days to discontinuation of index LAS treatment from the initiation. The study cohort was uniformly followed for one year after the initiation of LAS medications in order to examine the concurrent use and persistence. Descriptive analysis was performed to compare the demographic, service related, and clinical characteristics of concurrent users and non-users. Multivariate analysis was conducted by using accelerated failure time regression to examine the determinants of persistence of LAS.

Results

Among the 61, 793 children and adolescents who were diagnosed with ADHD and initiated their ADHD treatment with LAS 9, 902 (16.03%) received LAS and atypical antipsychotic concurrently at least for 14 days before the discontinuation of LAS. Most of the children and adolescents who received LAS and atypical antipsychotics concurrently were aged between 6-12 years, males, and white race. The mean duration of LAS treatment was longer (200 days, 95% CI, 197.6-202.9 days) among concurrent LAS and atypical antipsychotic recipients than only LAS users (143 days, 95% CI, 141.8-144 days). The children aged 6-17 years and whites had longer mean LAS treatment duration in both study groups than their counterparts. The accelerated regression analysis found that recipients of LAS and atypical antipsychotic agents had 45% longer (STR, 1.45; 95% CI, 1.41-1.49) LAS treatment persistence than only LAS recipients. Similarly, adolescents and non-whites had shorter LAS treatment persistence than their counterparts.

Conclusions

The study found that recipients of LAS and atypical antipsychotic agents concurrently had longer LAS treatment continuity than recipients of only LAS. The addition of the atypical antipsychotic agents along with LAS in ADHD patients may be beneficial in controlling ADHD symptoms. There is need to conduct head to head clinical trials in order to examine the efficacy of atypical antipsychotic agents and mechanism in the treatment of ADHD.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder among children and mainly characterized by a persistent and developmentally inappropriate pattern of inattention, hyperactivity, and/or impulsivity.[1,2] Children with ADHD tend to have difficulty in organizing tasks and sustaining attention during schoolwork or play related activities. They may experience various functional problems such as school related difficulties,[3] academic under-achievement, difficult interpersonal relationship with family members and peers,[4,5] and low self-esteem. The estimated prevalence of ADHD was 9.5% (5.4 million) among children and adolescent aged between 4 to 17 years in 2007 and about 66.3% (2.7 million) of them received treatment.[6] The national prevalence of ADHD increased significantly by 21.8% just within four years from 2003 to 2007 with annual increase of 5.5% in children and adolescents.[6,7]

Central nervous system (CNS) stimulants such as methylphenidate, amphetamine, dextroamphetamine, and pemoline are the mainstay of treatment for ADHD in children and adolescents. The psychostimulant properties of these medications result from its binding to a site on the dopamine transporter as dopamine agonist resulting in inhibition of dopamine reuptake and enhanced levels of synaptic dopamine.[8] The experimental evidence supports the efficacy, safety, and dosing of these medications in young people for the treatment of ADHD.[9-11] Among stimulants methylphenidate accounts for more than 90% use in ADHD in the United States.[11]

ADHD is one of the chronic disorders with up to 80% of those individuals diagnosed in their childhood continuing to have symptoms in adulthood.[12-14] The benefits of medications are short term and disappear after the treatment discontinuation[15] further disposing to young adults to even poorer outcomes including high number of driving accidents, job turnovers, and divorce.[16-19] The early stimulant discontinuation is highly prevalent in the community care of ADHD.[20,21] In clinical research studies, stimulant persistence rates ranged from 53% to 81%

after one year;[22,23] 21%–70% at the end of three years;[24-26]and 36% after 5 years.[18] The retrospective, population-based studies reported much lower persistence rates: 59% continued medication until month 4, which fell to less than 50% in the next 2–6 months;[27-28] and only 12%–43% persisted with the treatment for at least 1 year.[29-31] The persistence of ADHD symptoms in adulthood underscores the long term continuity of ADHD treatment.

Moreover up to 87 % of clinically diagnosed ADHD children have at least one other psychiatric disorder and 67% have at least two other psychiatric disorders[32] mainly mood/bipolar disorder, anxiety disorder, oppositional defiant disorder (ODD) , conduct disorder (CD), antisocial disorder, learning disabilities, developmental disorder, tics, Tourette's disorder, and substance use disorder. Follow up studies of children with ADHD indicate that subgroups of patients with ADHD and comorbid disorder have a poor outcome as supported by significantly greater social, emotional, and psychological difficulties.[33] The occurrence of psychiatric comorbidities in ADHD patients underscores the concurrent use of other psychotropic medications.

Atypical antipsychotic (AP) medications include clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, iloperidone, and asenapine. Atypical antipsychotics act on the dopamine D_2 receptors in addition to serotonergic $5HT_{1A}$ and $5HT_{2A}$ receptors which state its atypicality.[34] During the past decade, there has been a substantial increase in the atypical antipsychotic use in children and adolescents for a variety of psychiatric disorders including attention-deficit/hyperactivity disorder, conduct disorder, depression, and anxiety disorders[35-38] but they are approved only in schizophrenia, behavioral symptoms in autism, Tourette's disorder, major depressive disorder, and mixed or manic bipolar episodes by the Food and Drug Administration (FDA). The use of atypical antipsychotics for non-FDA-approved indications accounts for most treatment and has been growing faster.[39] There is 6-fold increase in pediatric visits nationally that included prescriptions for antipsychotic medications, of

which 90% were atypical antipsychotics.[40] Another study shows that publicly insured children receive atypical antipsychotic four times more than privately insured children.[41]

Psychotropic polypharmacy is increasingly common in pediatric population. Prescriptions for at least two psychotropic classes of medications for children and adolescents during outpatient visits increased significantly from 14.3% to 20.2% between the years 1996 and 2007 according to a new national trends survey study.[42] In terms of medical visits in which a current mental disorder was diagnosed, the percentage with multiclass psychotropic treatment increased from 22.2% (1996-1999) to 32.2% (2004-2007).[42] There were also specific increases in co-prescription of ADHD medications and antipsychotic medications (Adjusted Odds Ratio (AOR)) =6.22, 95% CI, 2.82-13.70) of which 90% were atypical antipsychotics. The analysis of National Ambulatory Medical Care Survey data from 2000 to 2002 found 37.8% mental health visit with prescription for antipsychotics had diagnosis of disruptive behavior and 44.2% of the physician visits by children and adolescents also received prescription for stimulants.[43] One placebo controlled trial conducted for 6 weeks shows clinically and statistically significant reduction in both disruptive behavior and hyperactivity subscale score among risperidone treated patients, in comparison to placebo, regardless of concomitant stimulant use.[44] Another open label trial conducted for 9 weeks shows quetiapine addition to methylphenidate was effective in reducing ADHD and aggression among adolescents who did not respond sufficiently to OROS methylphenidate alone at 54 mg/day dose.[45] But the recent evidence report published by the Agency of Healthcare Research and Quality found lack of RCTs examining effectiveness of atypical antipsychotic in ADHD patients. This report also suggests low evidence for effectiveness of atypical agents in the treatment of ADHD from existing trials.[46] Although polypharmacy and off-label use that may involve prescribing with limited evidence, it do not inherently represent bad practice or practice without evidence[48] and banning such practice could instead create barrier to quality of care.[47]

Our previous research shows that 74% of the Medicaid children and adolescents diagnosed with ADHD initiate treatment by using long acting stimulant medications. In the current study we evaluate the impact of addition of atypical antipsychotic agents on the persistence of long acting simulant (LAS) treatment in children and adolescents diagnosed with ADHD. This study examines claims of the Medicaid beneficiaries who initiated ADHD treatment with long acting stimulant to compare the persistence of LAS among those who received atypical agents concurrently at least for 14 days and those who did not receive the atypical antipsychotic agents.

Methods

Study Design Data Source

This retrospective cohort study involved the analysis of five year (January 2003-December 2007) Medicaid Analytic eXtract (MAX) data from four states (California, Illinois, New York, and Texas). The Medicaid Analytic eXtract (MAX) files included Personal Summary File, Inpatient File, Prescription Drug File, Long-term Care File, and Other therapy file. Personal summary file contains demographic and enrollment data for persons enrolled for at least a day during the year. An inpatient file contains complete stay records for enrollees including diagnoses, procedures, and discharge status, length of stay and payment related information. Prescription drug file contains claims data for outpatients and nursing home prescriptions. Long-term care file contains records for services provided by skilled nursing home facilities, intermediate care facilities and psychiatric facilities. Other Therapy File contains claim data for all non-institutional Medicaid services such as physician services, laboratory services, and premium payments. The study cohort was assembled by using personal summary file, inpatient file, other therapy file, and prescription drug file. This study was approved by the institutional review board of the University of Houston.

Study Population

The study population involved only incident users of the long acting stimulant (LAS) medications such as methylphenidate, dexmethylphenidate, lisdexamfetamine, amphetamine-dextroamphetamine salts, dextroamphetamine, and pemoline. The long acting stimulant medications were defined based on the American Hospital Formulary Classification as stimulant preparation with duration of action more than 12 hours. The long acting stimulant medications were identified from the prescription files by using National Drug Code, generic name, and trade name. The prescription fill date of first long acting stimulant was defined as index date. The new users or incident users were identified as patients with no stimulant claim in previous six months of index date. The children and adolescents aged 6 to 17 years at the index date with continuous Medicaid eligibility for 6 months before and 12 months after the index date were included in the final cohort. The diagnosis of ADHD during the study period were confirmed by ≥1 inpatient or outpatient claim for ADHD, defined as International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 314.xx during the entire study period. Thus the final cohort involved 61,793 continuously eligible ADHD patients, aged 6 to 17 years at index date, who initiated their ADHD treatment newly by using long acting stimulant medications in between July 1, 2003 to December 31, 2006. The complete study sample selection process is outlined in Figure 1.

Persistence of long acting stimulant (LAS) medications

Medication persistence can be defined as "the duration of the time from initiation to discontinuation of therapy".[48] 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.[30] When the gap exceeded the permissible limit of 30 days, the treatment episode for the individual was terminated even if the individual 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 stimulant class was allowed, but switching to another class such as short acting stimulants (SAS) or intermediate acting stimulants (IAS) was defined as the discontinuation of the index LAS therapy.

Concurrent Use or Polypharmacy

Atypical antipsychotic medications such as clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole were identified by using National Drug Codes and generic names from prescription files during one year period after the index LAS prescription date. Concurrent use or polypharmacy of LAS and atypical antipsychotic medications were defined as receipt of both medications together at least for 14 days. The concurrent use or polypharmacy has been defined in previous literature by Kortzan and collegues as receipt of second prescription ≥ 14 days before completion of the first prescription.[49]

Demographic, Service, and Clinical Characteristics

The Andersen behavioral model of health services was used to examine the factors associated with discontinuation of index LAS among children and adolescent diagnosed with ADHD.[50] This model has been previously employed in other studies to examine the determinants of medication use.[51-54] According to the Andersen behavioral model, an individual's use of health services is a function of 3 characteristics: predisposing, enabling, and need factors. Predisposing factors are characteristics of an individual that exist before illness and include demographic characteristics, social structure characteristics, and health beliefs. Enabling factors are those that give the individual the ability to secure the health services, such as income, health insurance, and availability of the service. The need factors represent either a subjective acknowledgment of need such as a patient's symptoms or the need for health care as perceived by the patient or professional judgment.

Predisposing, enabling, and need factors were selected from the literature and the availability of the factors in the Medicaid data. Predisposing factors included demographic

characteristics such as age, gender, and race. Age at index date (6 to 12 years, and 13-17 years), gender (male or female), race (whites, blacks, and others) were identified from eligibility and claims file. Enabling characteristics included service related characteristics such as state (California, Illinois, New York, and Texas), cohort entry year (2003, 2004, and 2005), season of index stimulant prescription (autumn, winter, spring, and summer), foster care child benefits, temporary assistance to needy families (TANF), and State Child Health Insurance Program (SCHIP) at the time of index LAS prescription. The need characteristics mainly included psychiatric comorbidities, psychotropic co-medications, and previous mental health related hospitalization.

The psychiatric case mix of the population was characterized by the types and number of co-existing mental health conditions and recent inpatient psychiatric treatment. The presence of a medical claim during the study period from inpatient and other therapy files was used to identify patients with the psychiatric comorbidity respective to ICD-9-CM diagnoses code for the following mental health disorders: conduct disorder (312.4, 312.8, 312.9, 312.00, 312.01, 312.02, 312.03, 312.10, 312.11, 312.12, 312.13, 312.20, 312.21,312.22, and 312.23), oppositional defiant disorder (313.81), developmental disorder (317, 319, 307.0, 307.9, V401, 315.5, 315.8, 318.0, 318.1, 318.2, 315.1, 315.2, 315.9, V400, 315.4, 315.31, 315.34, 315.39, 315.01, 315.02, 315.09, 315.32, and 315.00), pervasive developmental disorder (299.00, 299.01, 299.10, 299.11, 299.80, 299.81, 299.90, and 299.91), bipolar disorder (296.7, 296.00-296.06, 296.10-296.16, 296.40-296.46, 296.50-296.56, 296.60-296.66, 296.80-296.82, 296.89, 296.99, and 296.99), depression (311, 300.4, 293.83, 296.20-296.26, and 296.30-296.36), personality disorder (301.xx), schizophrenia (295.xx), substance use disorder (292.xx, 303.xx, 304.xx, 305.xx, 265.2, 357.5, 425.5, 291.0-291.5, 291.9, 571.0, 571.2, 571.3, 535.3, 790.3, and 648.30-648.34), psychosis (297.xx, and 298.xx), anxiety disorder (300.xx, 313.0,313.1, 308.1-318.4, 308.9, 293.84, 309.81, 313.21, 313.22, 313.82, and 313.83), sleep disorder (347.xx, 307.4, 780.5, and 307.40-307.49), and enuresis (307.6). Recent mental health hospitalization

was used as a proxy measure for the general mental health status of an individual. It was defined as an inpatient claim occurring in the 180 days before or on the index prescription claim date with an ICD-9-CM diagnosis code for any designated mental health disorder (290.xx - 319.xx). The study population was also classified by prescription of other psychotropic medications from index LAS initiation to until discontinuation of index LAS or end of study period mainly antidepressants, typical antipsychotics, anxiolytics, sedatives/hypnotics, and mood stabilizers. Mood stabilizers were defined as lithium and anticonvulsants prescribed without a diagnosis of epilepsy (ICD-9-CM code, 345.xx) during the one year after the index date.

Analytic Strategy

Descriptive statistics were used to compare the patients who received LAS and atypical antipsychotics concurrently and those who received only LAS with respect to demographic and service related characteristics, psychiatric disorders, and psychotropic medications. The patients who received index LAS medication during summer (June-August) in each group were also identified and compared. The comparison between patient groups is presented by using statistical significance level of 0.05.

The mean along with 95% confidence interval and median duration of LAS treatment were calculated for the study groups overall and stratified across age, gender, and race. Accelerated failure time regression using weibull distribution were carried out in order to examine the time to discontinuation of index LAS medications among those who received LAS and atypical antipsychotics concurrently and those who received only LAS monotherapy after controlling for demographic and service related characteristics, and clinical characteristics such as psychiatric comorbidities, psychotropic co-medications, and previous mental health related hospitalization.[30] The dependent variable was time to discontinuation (number of days) of the index LAS treatment. After exponentiating resulting parameter estimates for the drug groups, the regression provides a ratio of the adjusted median time to discontinuation between groups or Survival Time Ratio (STR). Each patient was followed for one year from the index LAS

prescription fill date. The patients were censored at the time of discontinuation of index LAS medications or at the end of study period whichever comes first. For the purpose of analysis primary independent variable concurrent use of long acting stimulant and atypical antipsychotic medication were coded as "1" if patient received both medication together at least for 14 days and "0" if not. All statistical analyses were performed by using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina) with a priori significance level of 0.05.

Results

Demographic and Service related characteristics

Table 1 provides the demographic and service related characteristics of children and adolescents who initiated ADHD treatment by using LAS medications. Approximately 9,902 (16.03%) of the children and adolescents who initiated ADHD treatment by using LAS received atypical antipsychotic agents at least for 14 days concurrently before the discontinuation of LAS treatment or before the end of the study period. Those who received LAS and atypical antipsychotic agents concurrently were significantly more likely to be children aged 6-12 years and whites. There was no difference among boys and girls in terms of receiving LAS and atypical antipsychotics concurrently in comparison to LAS monotherapy. In terms of service related characteristics those who received LAS and atypical antipsychotics concurrently among them 26.63% received foster care benefits, 13.12% received TANF related benefits and 1.1% received S-CHIP related benefits. In terms of mental health related severity those who received LAS and atypical antipsychotics concurrently had greater proportion (6.74% vs. 1.24%) of mental health related hospitalization during 6 months before initiation of ADHD treatment.

Clinical Characteristics

Table 2 provides the clinical characteristics of children and adolescents who initiated ADHD treatment by using LAS medications. Significantly greater proportion of the patient taking LAS and atypical antipsychotics concurrently than LAS only received treatment for mental disorders other than ADHD. The patients who received LAS and atypical antipsychotics mainly

received treatment for bipolar disorder, depression, anxiety, conduct disorder, oppositional defiant disorder, and developmental disorder. The patients who received LAS and atypical antipsychotics concurrently were significantly more likely to receive other psychotropic medications such as anxiolytics, antidepressants, mood stabilizers, sedative/hypnotics, atomoxetine, and short and intermediate acting stimulants.

Persistence of LAS Treatment

Table 3 provides the average along with 95% confidence interval and median LAS treatment persistence among concurrent LAS and atypical users and only LAS users. The average persistence of LAS treatment among concurrent users of LAS and atypical antipsychotic agents were significantly longer (200 days vs. 143 days) than only LAS users. Also children aged 6-12 years, and children and adolescents with white race had longer average LAS persistence than their counterparts in both study groups.

Table 4 provides the survival time ratios (STR) of LAS treatment persistence among children and adolescents with ADHD. In multivariate analysis, several covariates significantly and independently associated with LAS treatment persistence. Specifically, those who received atypical antipsychotics concurrently with index LAS at least for 14 days had 45% (STR, 1.45; 95% CI, 1.41-1.49) longer index LAS persistence than those who received only LAS after adjusting for demographic and service related characteristics, psychiatric comorbidities, psychotropic co-medications, and mental health related hospitalization. Furthermore adolescents aged 13 to 17 years had 31% (STR, 0.69; 95% CI, 0.68-0.70) shorter LAS treatment persistence than children aged 6-12 years. In terms of race/ethnicity children and adolescents with race other than white were 32% to 36% shorter LAS treatment persistence than white children and adolescents after controlling for other demographic, service related, and clinical characteristics.

Figure 2 provides the Kaplan Meier estimates of LAS treatment persistence stratified across LAS and atypical antipsychotic concurrent recipients and only LAS recipients after

adjusting for demographic, service, and clinical characteristics. The group differences become obvious after 30 days after index LAS initiation. However, most of the children and adolescents in both groups discontinued index LAS treatment within one year.

LAS Treatment Persistence during School Years

In order to control for possible confounding due to planned ADHD treatment discontinuation during school summer holidays we examined LAS treatment persistence among children and adolescents who initiated LAS (N=14,390) in September or October. In this subgroup average LAS treatment persistence among LAS and atypical antipsychotic concurrent users were 202 days (95% CI, 197-208 days) and among only LAS users was 150 days (95%CI, 148-153 days). In separate multivariate analysis those who received LAS and atypical antipsychotics concurrently had 40% (STR, 1.40; 95% CI, 1.33-1.50) longer LAS treatment persistence than those who received only LAS treatment after controlling for demographic, service, and clinical characteristics.

Discussion

In this Medicaid population of children and adolescents who initiated ADHD treatment by using LAS 16.03% received atypical antipsychotic agents before the discontinuation of LAS treatment at least for 14 days concurrently. The incidence of concurrent use is similar to the concurrent use of multiple psychotropic medications examined from cross sectional studies at national level. [55, 56] The cross sectional nature of the data in previous studies may not have captured exact extent of prevalence of concurrent use or polypharmacy. But the longitudinal analysis of the claims data in this study provides precise extent of concurrent use of LAS and atypical antipsychotic agents. The atypical antipsychotic medications are mainly approved in the treatment of schizophrenia, behavioral symptoms in autism, Tourette's disorder, major depressive disorder, and mixed or manic bipolar episodes. These agents have not been approved in the treatment of ADHD by Food and Drug Administration but risperidone, quetiapine, and aripiprazole has been examined for its efficacy in children and adolescents with

various psychiatric disorders.[44,57,58] One placebo controlled trial conducted for 6 weeks shows clinically and statistically significant reduction in both disruptive behavior and hyperactivity subscale score among risperidone treated patients, in comparison to placebo, regardless of concomitant stimulant use.[44] The open label study conducted by Biederman et al. to measure improvement in ADHD symptoms in children with bipolar disorder due to risperidone found significant improvement in both hyperactivity/ impulsivity and inattentiveness but improvement was modest, and only 29% of subjects showed a 30% reduction in ADHD rating scale score.[58]

There was no statistically significant difference among boys and girls in terms of receiving LAS and atypical antipsychotics concurrently before the discontinuation of initiated LAS treatment for ADHD. These finding are similar to analysis of annual National Ambulatory Medical Survey data from 1996 to 2007 by Comer et al in which they found no difference among boys and girls in terms of receiving multiclass psychotropic medications during office visits.[55] But the analysis of same data from 2000-2002 by Olfson et al. found significant difference among boys and girls in terms of receiving atypical antipsychotic medications during office visits.[56] The extent of concurrent use of LAS and atypical antipsychotics were higher among children aged 6-12 years than adolescents aged 13-17 years. On the contrary Comer et al. found that extent of receiving multiclass psychotropic medication during office visits were higher among adolescents than children[55] and Olfson et al found that extent of receiving antipsychotic agents were higher among adolescents than children.[56]

Also those who received foster care related benefits among them almost 27% of the children and adolescents received LAS and atypical antipsychotics concurrently before discontinuation of LAS treatment. This can be identified with disproportionately high prevalence of mental health disorders among children in foster care. Several studies show that about 50 to 80 percent of children in foster care have moderate to severe mental health related problems.[59,60] Moreover, almost 38% of the foster care children aged 0 to 19 years enrolled in Texas Medicaid program received psychotropic medications during September 2003 to August

2004.[61] The analysis of the Texas Medicaid data from July 2004 found that foster care children who received psychotropic medications among them 41.3% received more than 3 classes of drugs and almost 16% received more than 4 classes of drugs.[62] The most frequently used medications among these children were antidepressants (56.8%), ADHD medications (55.9%), and antipsychotic medications (53.2%). Thus high prevalence of the mental health disorders among foster care children may be leading to higher prevalence of multiple psychotropic medications among children.[62]

Interestingly, concurrent users of LAS and atypical antipsychotic agents had higher prevalence of psychiatric disorders than LAS recipients only. Similarly, concurrent users of LAS and atypical antipsychotic agents received significantly more other psychotropic medications than LAS recipients only. Furthermore, concurrent users had higher extent of mental health related hospitalization than only LAS users during 6 months before initiation of ADHD treatment. Thus higher prevalence of psychiatric comorbidities and its severity may necessitates use of the atypical antipsychotic medications along with ADHD medications such as stimulants. The analysis of national survey of child psychiatrist found that psychiatric comorbidities is the single, best fitting predictor of the polypharmacy and off-label prescribing of the psychotropic medications.[63] But the recent evidence report published by the Agency of Healthcare Research and Quality found lack of RCTs examining effectiveness of atypical antipsychotic in ADHD patients. This report suggests low evidence or very low evidence only for efficacy of risperidone in the treatment of ADHD in children without any other psychiatric disorder and no evidence for the efficacy for any atypical antipsychotic agent in the treatment of ADHD children with bipolar disorder.[64] Thus prevalence of multiple psychiatric comorbidities may be leading to the use of atypical antipsychotic medications but there is not enough safety and efficacy data to support such use until this time.

In this Medicaid patient population of children and adolescents the average index LAS treatment persistence was longer among those who received atypical antipsychotics

concurrently at least for 14 days. The difference in index LAS treatment persistence was also observed among children and adolescents, and across major racial/ethnic groups. The study found that after controlling for the related background characteristics those who received LAS and atypical antipsychotics at least for 14 days had 45% longer LAS treatment persistence than those who just received LAS. The atypical antipsychotic medications have been studied in very few randomized controlled trials to examine its safety and efficacy in the treatment of ADHD. Although these studies were conducted for very short duration of time they have shown some positive effect of atypical agents in controlling ADHD symptoms. After controlling for the major mental health related problems in the children and adolescents the study found longer persistence among antipsychotic recipients which suggest that antipsychotic medication were added in the treatment of ADHD symptoms. There is possibility that those who received atypical antipsychotics in addition to LAS might have higher severity. Therefore there is need to conduct head to head clinical trials in order to examine the efficacy of atypical antipsychotics in the treatment of ADHD symptoms.

The study also found that after adjusting all background characteristics children's were more likely to LAS treatment adherent than adolescents. These findings are consistent with previous literature. The prospective, three year follow up study of 71 children found that older children were 40% less likely to stimulant treatment adherent than younger ones.[65] The retrospective analysis of Medicaid data by Marcus et al. also found longer extended release methylphenidate and intermediate release methylphenidate treatment continuity among children than adolescents.[30] In terms of racial disparity non-white children and adolescents were less likely to be LAS treatment adherent than white children and adolescents. Similar results were found by Marcus et al. in which African American and Hispanic children and adolescents were more likely to Methylphenidate treatment discontinuation. Therefore, there is need to develop effective intervention strategies to promote the greater continuity of care.

The study has several limitations therefore findings should be interpreted in the context of those limitations. Administrative healthcare claims databases offer several advantages such as large and diverse sample sizes, long follow-up, and availability of real-world clinical practice data. They are powerful tools for measuring treatment patterns. However, they are not primarily designed to address particular research questions.[66] One such limitation that the database lacks certain key variables associated with the treatment regimen, such as severity of, and changes in, ADHD symptoms and other psychiatric comorbidities. Hence, unmeasured clinical and physician factors may have confounded the propensity of receipt of LAS and atypical antipsychotic medication concurrently. However, several demographic and clinical factors were adjusted for the variation in multivariable logistic regression model. The study assumes that the medications that are dispensed are actually consumed by patients as prescribed and that the patients received no other psychotropic medication besides those available in the claims data. The definition of the concurrent use of LAS and atypical agents is limited to overlap of both therapies for at least 14 days. The study did not account for the concurrent use less than 14 days. Also clinically meaningful LAS treatment discontinuation cannot be determined my current study. The study does not have any means to distinguish between clinically meaningful treatment discontinuation from premature treatment continuation. The study also limited to the Medicaid beneficiaries from four states and prescribing practices of Medicaid providers may also not be representative of those providers contracted under other types of health insurance programs. So, the results may not be generalized to the whole ADHD population or specifically to the privately insured or uninsured patient populations. Finally, diagnoses of ADHD and co-morbid mental disorders were identified based on diagnostic codes, and claim forms limit the number of diagnoses that can be documented.

Conclusion

The study found that recipients of LAS and atypical antipsychotic agents concurrently had longer LAS treatment continuity than recipients of only LAS. The addition of the atypical

antipsychotic agents along with LAS in ADHD patients may be beneficial in controlling ADHD symptoms. There is need to conduct head to head clinical trials in order to examine the efficacy of atypical antipsychotic agents and mechanism in the treatment of ADHD.

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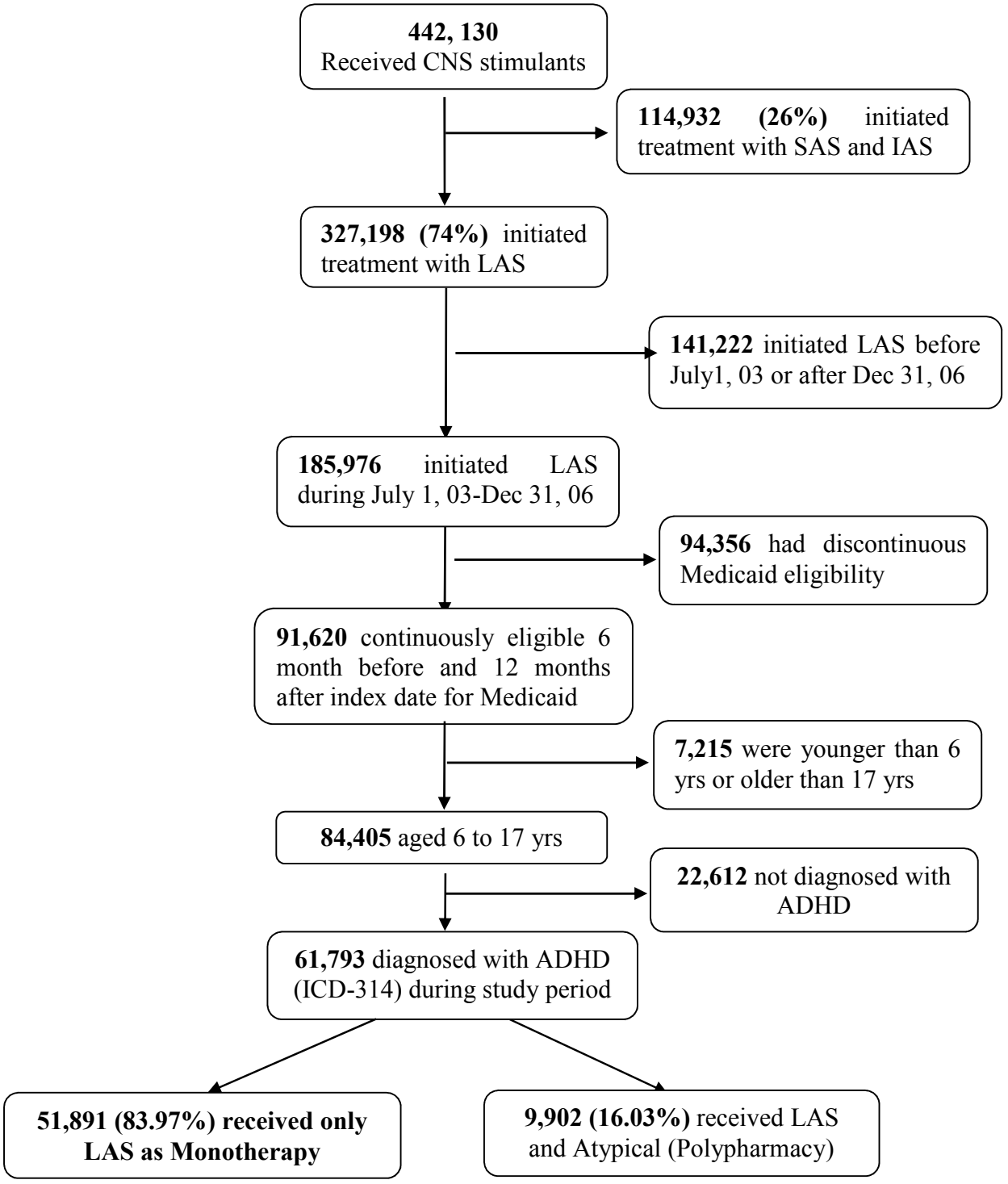
Figure 1: Flow-chart of Study Sample Selection and Study Cohort Development



Abbreviations: ADHD – Attention Deficit/Hyperactivity Disorder; SAS – Short-Acting Stimulants; IAS – Intermediate-Acting Stimulants; LAS - Long-Acting Stimulants

Table 1. Demographic and Service Related Characteristics of Children and Adolescents who received LAS and Atypical Antipsychotics Concurrently (Polypharmacy) and LAS Monotherapy among those who initiated ADHD treatment with LAS			
Characteristics	**LAS and Atypical Antipsychotic Polypharmacy (n=9,902), N(%)**	**LAS Monotherapy (n=51,891) N (%)**	**P Value**
Age (years)			
6-12	6,544 (66.09)	38,649 (74.48)	<0.0001
13-17	3,358 (33.91)	13,242 (25.52)	
Gender			
Female	2,739 (27.66)	14,720 (28.37)	0.153
Male	7,163 (72.34)	37,171 (71.63)	
Race/ethnicity			
White	3,576 (36.11)	20,803 (40.09)	<0.0001
Black	2,711 (27.38)	11,817 (22.77)	
Others	3,615 (36.51)	19,271 (37.14)	
States			
New York	2,517 (25.42)	10,810 (20.83)	<0.0001
Illinois	1,640 (16.56)	11,778 (22.70)	
Texas	3,856 (38.94)	17,823 (34.35)	
California	1,889 (19.08)	11,480 (22.12)	
Season			
Summer (6-8)	2,268 (22.90)	10, 403 (20.05)	<0.0001
Autumn (9-11)	3,347 (33.80)	18,668 (35.98)	
Winter (12-2)	2,231 (23.44)	12,434 (23.96)	
Spring (3-5)	1,966 (19.85)	10,386 (20.02)	
Cohort Entry Year			
2003	1,695 (17.12)	8,995 (17.33)	<0.0001
2004	3,191 (32.23)	18,751 (36.14)	
2005	2,444 (24.68)	12,006 (23.14)	
2006	2,572 (25.97)	12,139 (23.39)	
Foster Care			
No	7,265 (73.37)	45,080 (86.87)	<0.0001
Yes	2,637 (26.63)	6,811 (13.13)	
TANF			
No	8,603 (86.88)	43,640 (84.10)	<0.0001
Yes	1,299 (13.12)	8,251 (15.90)	
SCHIP			
No	9,794 (98.91)	50,702 (97.71)	<0.0001
Yes	108 (1.09)	1,189 (2.29)	
Mental Health Hospitalization			
No	9,253 (93.26)	51,249 (98.76)	<0.0001
Yes	667 (6.74)	642 (1.24)	

Table 2. Clinical Characteristics of Children and Adolescents who received LAS and Atypical Antipsychotics Concurrently (Polypharmacy) and LAS Monotherapy among those who initiated ADHD treatment with LAS			
Characteristics	**LAS and Atypical Antipsychotic Polypharmacy (n=9,902), N(%)**	**LAS Monotherapy (n=51,891), N (%)**	**P Value**
Psychotropic Drugs			
Anxiolytics	434 (4.38)	1,094 (2.11)	<0.0001
Antidepressants	3,101 (31.32)	6,035 (11.63)	<0.0001
Mood stabilizers	2,312 (23.35)	2,008 (3.87)	<0.0001
Sedative/Hypnotics	141 (1.42)	158 (0.30)	<0.0001
Atomoxetine	720 (7.27)	2,620 (5.05)	<0.0001
Typical Antipsychotics	84 (0.85)	73 (0.14)	<0.0001
SAS	472 (4.77)	1,950 (3.76)	<0.0001
IAS	410 (4.14)	1,366 (2.63)	<0.0001
Mental Health Disorders			
Bipolar Disorder	2,888 (29.17)	1,803 (3.47)	<0.0001
Depression	2,544 (25.69)	5,167 (9.96)	<0.0001
Psychosis	648 (6.54)	393 (0.76)	<0.0001
Anxiety	1,950 (19.69)	4,585 (8.84)	<0.0001
Schizophrenia	204 (2.06)	109 (0.21)	<0.0001
Conduct Disorder	1,963 (19.82)	5,346 (10.30)	<0.0001
Oppositional Defiant Disorder	1,846 (18.64)	3,360 (6.48)	<0.0001
Developmental Disorder	1,860 (18.78)	7,686 (14.81)	<0.0001
Pervasive Developmental Disorder	379 (3.83)	569 (1.10)	<0.0001
Tic Disorder	59 (0.60)	172 (0.33)	<0.0001
Personality Disorder	198 (2.00)	185 (0.36)	<0.0001
Substance Use Disorder	316 (3.19)	606 (1.17)	<0.0001

Table 3: Mean and Median LAS Treatment Duration among Children and Adolescents who received Stimulant and Atypical Antipsychotics Concurrently and those who received only LAS				
Characteristics	**LAS and Atypical Antipsychotic Polypharmacy (n=9,902)**		**LAS Monotherapy (n=51,891)**	
	Mean, d(95% CI)	**Median, d**	**Mean, d(95% CI)**	**Median, d**
Total	200 (197.6-202.9)	180	143 (141.8-144)	90
Demographics				
Age (years)				
6-12	210.6 (207.4-213.9)	204	151 (149.6-152.2)	99
13-17	180 (175.6-184.3)	144	120 (117.6-121.4)	73
Gender				
Female	199.7 (194.8-204.7)	179	145.6 (143.6-147.6)	94
Male	200.4 (197.3-203.5)	180	141.8 (140.6-143.1)	90
Race/ethnicity				
White	224 (219.7-228.3)	236	169.1 (167.4-170.9)	123
Black	178.4 (173.4-183.3)	140	122.9 (120.8-125)	74
Others	193.1 (188.8-197.4)	167	126.8 (125.1-128.4)	78

Table 4. Survival Time Ratio (STR) of Index LAS among Children and Adolescent diagnosed with ADHD			
	Survival Time Ratio (STR)		
Characteristics	**Unadjusted STR**	**Adjusted STR**	**95% CI**
Treatment			
LAS only	1.00	1.00	
LAS and Antipsychotics	**1.65**	**1.45**	**1.41-1.49**
Age			
6-12	1.00	1.00	
13-17	**0.75**	**0.69**	**0.68-0.70**
Gender			
Female	1.00	1.00	
Male	**0.98**	**1.04**	**1.02-1.06**
Race			
White	1.00	1.00	
Black	**0.66**	**0.64**	**0.63-0.66**
Others	**0.68**	**0.68**	**0.66-0.69**

Survival time ratio and Hazard ratio adjusted for service related characteristics (state, season, cohort entry year, foster care benefits, temporary assistance to needy families (TANF) benefits, state child health Insurance program (SCHIP) benefits, psychiatric comorbidities, psychotropic medications, and mental health related hospitalization)

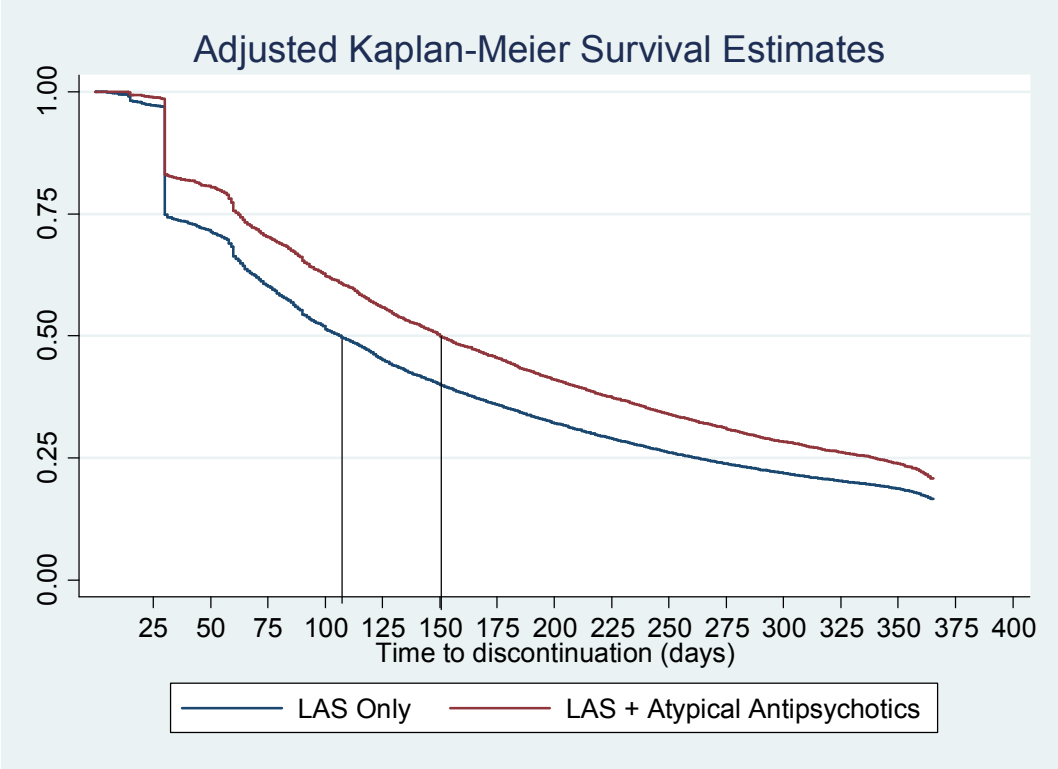


Figure 2. Adjusted (demographic, service related, and clinical characteristics) survival distribution of long acting stimulant (LAS) treatment for attention deficit/hyperactivity disorder among children and adolescents.

MANUSCRIPT 3

Cardiovascular Safety of Concurrent Use of Atypical Antipsychotic Agents and Long Acting Stimulants in Children and Adolescents diagnosed with Attention Deficit/ hyperactivity Disorder (ADHD)

Abstract

Background

Multiple psychotropic drug use is highly prevalent in children and adolescents. The CNS stimulant and atypical antipsychotic agents have been linked independently to cardiovascular adverse events.

Objective

The study examines the risk of cardiovascular adverse events due to addition of the atypical antipsychotic agents in the children and adolescents diagnosed with ADHD and already on the regimen of long acting stimulants.

Methods

This was the retrospective cohort study that used the five year, four states Medicaid claims data. The cohort was composed of the children adolescents aged 6 to 17 years who were newly diagnosed with ADHD (ICD-9-CM Code, 314.XX) and newly initiated treatment by using long acting stimulants (LAS). The continuous eligibility 6 months before and 12 months after the index LAS date were ensured. The atypical antipsychotic use was identified after the initiation of the index LAS treatment and further classified as a daily use in to three categories as current use (active atypical antipsychotic use), former use (days after the periods of current use), and nonuse (time before the first atypical antipsychotic use including the follow up of patients who were never exposed to atypical antipsychotics). The study end point were defined as the first inpatient or outpatient claim due to acute myocardial infarction, stroke, hypertensive disease excluding malignant causes, angina, aortic or thoracic aneurysm, arrhythmias, syncope,

tachycardia, or palpitation. The cardiovascular risks were compared by using time dependent Cox regression analysis adjusting for various cardiac risk factors.

Results

All the study participants were followed for 9,206,873 person-days of observation period and during the period of atypical antipsychotic no-use there were 840 events occurred, during the period of current use there were 202 crude events occurred, during the former use period there were 45 events occurred. In comparison to no use the current use of atypical antipsychotics among the LAS users were not statistically significantly associated with cardiovascular events (HR, 1.17; 95% CI, 0.98-1.40) after controlling for the demographic, service related, and clinical characteristics.. Also former use of atypical antipsychotics were not statistically significantly associated (HR, 1.24; 95% CI, 0.91-1.69) with cardiovascular events in comparison to no-use among LAS users after controlling for the demographic, service related, and clinical characteristics. Those who were diagnosed with obesity and diabetes increased the risk of cardiovascular events by 1.63 times (HR, 1.63; 95% CI, 1.21-2.20) and almost two times (HR, 1.94; 95% CI, 1.27-2.96) in comparison to their counterpart among LAS users. In addition receipt of mood stabilizers increased the cardiovascular risk by 1.87 times (HR, 1.87; 95% CI, 1.08-3.24) in comparison to no use of the mood stabilizers among LAS users.

Conclusions

This study did not find any increased cardiovascular risk due to the addition of the atypical antipsychotic medications in the regimen of the long acting stimulants in children and adolescents diagnosed with ADHD. The diagnosis of the obesity and diabetes and receipt of mood stabilizers determined the cardiovascular risk.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder among children and mainly characterized by a persistent and developmentally inappropriate pattern of inattention, hyperactivity, and/or impulsivity.[1,2] The estimated prevalence of ADHD was 9.5% (5.4 million) among children and adolescent aged between 4 to 17 years in 2007 and about 66.3% (2.7 million) of them received treatment.[3] The national prevalence of ADHD increased significantly by 21.8% just within four years from 2003 to 2007 with annual increase of 5.5% in children and adolescents.[3,4] It is a chronic disorder with 30% to 50% of those individuals diagnosed in childhood continuing to have symptoms in adulthood.[5] Pediatric ADHD and its persistence into adulthood is very serious public health concern which leads to overwhelming effect not only on individual but also on their families and overall social system in terms of morbidity and healthcare burden.

Central nervous system (CNS) stimulants such as methylphenidate, amphetamine, dextroamphetamine, and pemoline are the first line treatment for ADHD in children and adolescents. Methylphenidate accounts for more than 90% stimulant use in ADHD in the United States.[6] Various randomized clinical trials (RCTs) have shown the effectiveness of these medications in terms of reducing the core symptoms of the ADHD such as hyperactivity, impulsivity, and inattentiveness.[7,8] These medications also improve classroom behavior and academic performance; diminish oppositional and aggressive behaviors; promote increased interaction with teachers, family, and others; and increase participation in leisure time activities.[9,10] Most importantly the clinical evidence from placebo controlled trials have demonstrated an increase in blood pressure and heart rate[11-17] and several case reports reported to FDA Adverse Events Reporting System (AERS) have linked CNS stimulants to stroke, myocardial infarction, and sudden death.[18] In February 2006, the United States, Food and Drug Administration (FDA) started initiatives about issuing the black box warning due to cardiovascular events based on the known propensity of sympathomimetic agents related

structural relationship and various case reports but later these initiatives were held back due to concern about the discouragement of the only available treatment for ADHD.[19,20] In addition, Adderall XR (long acting amphetamine) was withdrawn temporarily from Canadian market based on 20 international case reports about sudden cardiac death.[21] Furthermore the American Heart Association (AHA) released a statement on cardiovascular monitoring in children and adolescents who receive stimulant medications in which it recommends electrocardiogram (ECG) monitoring as part of the evaluation. The statement is based on data from studies of various aspects of child health, including causes of sudden cardiac death and ECG screening programs to detect underlying cardiac disease.[22]

The CNS stimulants are used chronically in more than 5% of the American children and rapidly growing numbers in adults.[23] Longitudinal comparisons suggest that both the diagnosis and treatment of childhood ADHD have continued to increase over the last decade and that approximately one third of newly treated children use treatment chronically up to 2 years, and more than 15% continue for more than 5 years according to a recent analysis in this laboratory.[24] Recently Winterstein et al. analyzed Florida Medicaid data from 1994 to 2002, which included 55,383 children and adolescents with a claims diagnosis of ADHD. Of these 55 383 patients, none died of cardiac causes during stimulant exposure. Nonetheless, this study found a small albeit statistically significant association between stimulant exposure and emergency department visits for cardiac symptoms and circulatory disease (hazard ratio [HR] =1.2; 95% confidence interval [CI]: 1.0–1.4).[25] The retrospective analysis of four health plan administrative data by Cooper et al. involving more than 1.2 million children and young adults aged 2 to 24 years did not find any statistically significant increased cardiovascular risk among current and former users of the stimulant medications but upper limits of the 95% confidence interval indicated the doubling of the risk.[26] Another cohort study involving five state Medicaid data and fourteen state commercial health plan data found 1.8 fold increased risk of sudden

death or ventricular arrhythmia due to initiation of methylphenidate among patients aged 18 years and older but lack of dose response relationship couldn't find the causal relationship.[27]

Psychotropic polypharmacy is increasingly common in pediatric population. Prescriptions for at least 2 psychotropic classes of medication for children and adolescents during outpatient visits increased significantly from 14.3% to 20.2% between the years 1996 and 2007, according to a new national trends survey study.[28] Among medical visits in which a current mental disorder was diagnosed, the percentage with multiclass psychotropic treatment increased from 22.2% (1996-1999) to 32.2% (2004-2007). There were also specific increases in co-prescription of ADHD medications and antipsychotic medications (AOR=6.22, 95% CI, 2.82-13.70) and co-prescription of antidepressant and antipsychotic medications (AOR=5.77, 95% CI, 2.88-11.60). Little is known about the safety and efficacy of regimens that involve concomitant use of two or more psychotropic agents in the outpatient mental health care of children and adolescents. Research on this topic has been largely confined to non-controlled, non-blinded, or retrospective reports.[29-37] Case reports,[28-31] case series,[32-34] and retrospective chart reviews[35-37] are limited in the extent to which they can systematically evaluate the safety, tolerability, and efficacy of these complex regimens. The practice of polypharmacy in children and adolescents can be justified due to the various psychiatric comorbidities associated with ADHD.

Atypical antipsychotic (AP) medications which are also called as second generation antipsychotic (SGA) medications include risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, and asenapine. During the past decade, there has been a substantial increase in the prescribing of psychotropic agents especially atypical antipsychotics to children and adolescents for a variety of pediatric psychiatric disorders including schizophrenia, bipolar disorder, attention-deficit/hyperactivity disorder, mood disorders, autism/pervasive developmental disorders, conduct disorder, depression, anxiety disorders, tic disorders, delirium, and eating disorders.[38-41] However, clinical indications approved by the Food and Drug

Administration (FDA) for antipsychotics in young people are limited to schizophrenia, behavioral symptoms in autism, Tourette's disorder, and mixed or manic bipolar episodes. The use of atypical antipsychotics for non-FDA-approved indications now accounts for most treatment and has been growing faster than treatment for FDA-approved indications.[42] Nationally, a 6-fold increase in pediatric visits has been reported that included prescriptions for antipsychotic medication, of which 90% were atypical antipsychotics.[28] Extant clinical trial studies and case reports indicate that the use of atypical antipsychotics in children is associated with higher rates of adverse events, such as: extrapyramidal symptoms (EPS), seizures, somnolence/sedation, weight gain/obesity, Type II diabetes mellitus, increased prolactin levels and the ensuing sexual/reproductive adverse events, and cerebrovascular or cardiovascular events (e.g., arrhythmias, ischemic events, orthostasis, and exacerbation of hypertension).[43-45]

Despite the increased use of atypical antipsychotics, safety and tolerability profile of atypical antipsychotics in children and adolescents is insufficiently documented and the most common cardiovascular adverse effect of the atypical antipsychotic agents is orthostatic hypotension due to their action on the alpha adrenergic receptors while some depress cardiac repolarization due to their effect on the muscarinic receptors and lead to QT prolongation increasing the risk of torsades de pointes which often acts as precursor of the fatal cardiac arrest.[46,47] There is very limited data in terms of observational studies examining the prevalence of various adverse events on the long term basis. The analysis of the South Carolina Medicaid data from 1996-2005 by Jerrell and colleagues found increased risk of obesity/excessive weight gain, Type II diabetes and dyslipidemia, digestive/urogenital problems, cardiovascular and neurological /sensory symptoms.[44,45] Mcintyre and colleagues found that odds of developing cardiovascular events due to antipsychotics were 1.9 times greater in patients with type II diabetes mellitus and dyslipidemia and 2.1 times higher in those with incident type II diabetes mellitus and dyslipidemia. The study sponsored by Pfizer (054) found the greatest effect on the QTc interval compared with drug-free baseline of ziprasidone (80mg twice daily; QTc increased

by 20.3ms above 75ms). Furthermore the US label for ziprasidone contains a warning of the potential for QTc prolongation and sudden death. The highest rates of cardiovascular effects have been reported for clozapine (40%) and quetiapine (13%).[48]

Although polypharmacy and off-label use that may involve prescribing with limited evidence, it do not inherently represent bad practice or practice without evidence[48] and banning such practice could instead create barrier to quality of care.[49] Our previous research shows that 74% of the Medicaid children and adolescents diagnosed with ADHD initiate treatment by using long acting stimulant (LAS) medications. In the current study we evaluate the risk of cardiovascular symptoms due to addition of the atypical antipsychotic agents in children and adolescents diagnosed with ADHD who were already on the regimen of the long acting stimulant (LAS) medications. This study examines claims of the Medicaid beneficiaries who initiated ADHD treatment with long acting stimulants to compare the cardiovascular risk among those who received atypical antipsychotic agents and those who did not receive the atypical antipsychotic agents.

Methods

Study Design Data Source

This retrospective cohort study involved the analysis of five year (January 2003-December 2007) Medicaid Analytic eXtract (MAX) data from four states (California, Illinois, New York, and Texas). The Medicaid Analytic eXtract (MAX) files included Personal Summary File, Inpatient File, Prescription Drug File, Long-term Care File, and Other therapy file. Personal summary file contains demographic and enrollment data for persons enrolled for at least a day during the year. An inpatient file contains complete stay records for enrollees including diagnoses, procedures, discharge status, length of stay, and payment related information. Prescription drug file contains claims data for outpatients and nursing home prescriptions. Long-term care file contains records for services provided by skilled nursing home facilities, intermediate care facilities and psychiatric facilities. Other Therapy File contains claim data for

all non-institutional Medicaid services such as physician services, laboratory services, and premium payments. The study cohort was assembled by using personal summary file, inpatient file, other therapy file, and prescription drug file. This study was approved by the institutional review board of the University of Houston.

Study Population

The study population involved only incident users of the long acting stimulant (LAS) medications such as methylphenidate, dexmethylphenidate, lisdexamfetamine, amphetamine-dextroamphetamine salts, dextroamphetamine, and pemoline. The long acting stimulant medications were defined based on the American Hospital Formulary Classification as stimulant preparation with duration of action more than 12 hours. The long acting stimulant medications were identified from the prescription files by using National Drug Code, generic name, and trade name. The prescription fill date of first long acting stimulant was defined as index date. The new users or incident users were identified as patients with no stimulant claim in previous six months of index date. The children and adolescents aged 6 to 17 years at the index date with continuous Medicaid eligibility for 6 months before and 12 months after the index date were included in the final cohort. The diagnosis of ADHD during the study period were confirmed by ≥1 inpatient or outpatient claim for ADHD, defined as International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) Clinical Modification (CM) code 314.xx during the entire study period. Thus the final cohort involved 61,793 continuously eligible ADHD patients, aged 6 to 17 years at index date, who initiated their ADHD treatment newly by using long acting stimulant medications in between July 1, 2003 to December 31, 2006. The complete study sample selection process is outlined in Figure 1.

Study End Points

The study end point was defined as the incidence of cardiovascular event such as acute myocardial infarction (ICD-9-CM, 410.xx, 411.8x), stroke (430.xx to 436.xx), hypertensive disease (401.xx to 405.xx excluding malignant causes (40x.0x)), angina (413.xx), aortic or

thoracic aneurysm (441.0x, 441.1x), arrhythmias (426.89, 427.xx), syncope (780.2x), tachycardia, or palpitation (785.0x, 785.1x) during physician office visit or hospital visit or emergency department visit whichever comes first. These definitions of the cardiovascular event/symptoms has been previous used in the literature in order to examine the cardiovascular safety of the stimulant medications.[25,26]

Demographic, Service, and Clinical Characteristics

The demographic characteristics such as age, gender, and race were identified from eligibility file. Age at index date (6 to 12 years, and 13-17 years), gender (male or female), race (whites, blacks, and others) were identified from eligibility and claims file. The service related characteristics such as state (California, Illinois, New York, and Texas), cohort entry year (2003, 2004, and 2005), season of index stimulant prescription (autumn, winter, spring, and summer), foster care child benefits, temporary assistance to needy families (TANF), and State Child Health Insurance Program (SCHIP) at the time of index LAS prescription.

The patients with congenital anomalies of the heart and other hereditary diseases which are linked to the adverse event of the circulatory diseases were identified from both inpatient and outpatient claims during entire study period and excluded from the study. These congenital anomalies of the heart and other hereditary diseases mainly included diagnosis of hereditary hemolytic anemia (ICD-9-CM 282.xx), hemophilia (286.0x), anomalies of bulbus cordis and cardiac septal closure (745.xx), other congenital anomalies of the heart (746.xx), congenital anomalies of the circulatory system (747.0x to747.4x), down syndrome (758.0x), gonadal dysgenesis (758.6x), and Fragile X syndrome (759.83). The preexisting heart disease was defined as the presence of any inpatient or outpatient claim within 6 months before the initiation of ADHD treatment by using LAS were identified as the diagnosis of diseases of the circulatory system (390.*xx* to 459.*xx*), syncope (780.2*x*), tachycardia or palpitation (785.0*x*, 785.1*x*), and chest pain (786.50).

To account for the concurrent use of other drugs that have been associated with cardiac effects, we ascertained claims data of non-psychotropic medications such as appetite appetite suppressants and bronchodilators (β- agonists, ipratropium, and theophyline), and psychotropic medications such as antidepressants, typical antipsychotics, anxiolytics, sedatives/hypnotics, and mood stabilizers. Mood stabilizers were defined as lithium and anticonvulsants prescribed without a diagnosis of epilepsy (ICD-9-CM code, 345.xx) during the one year after the index date.

The non-psychiatric comorbidities which are associated with cardiovascular events/symptoms such as diabetes, asthma, obesity, and seizures were identified during the entire study period from inpatient and outpatients claims by using ICD-9-CM codes. The psychiatric case mix of the population was characterized by the types and number of co-existing mental health conditions and recent inpatient psychiatric treatment. The presence of a medical claim during the study period from inpatient and other therapy files was used to identify patients with the psychiatric comorbidity respective to ICD-9-CM diagnoses code for the following mental health disorders: conduct disorder (312.4, 312.8, 312.9, 312.00, 312.01, 312.02, 312.03, 312.10, 312.11, 312.12, 312.13, 312.20, 312.21,312.22, and 312.23), oppositional defiant disorder (313.81), developmental disorder (317, 319, 307.0, 307.9, V401, 315.5, 315.8, 318.0, 318.1, 318.2, 315.1, 315.2, 315.9, V400, 315.4, 315.31, 315.34, 315.39, 315.01, 315.02, 315.09, 315.32, and 315.00), pervasive developmental disorder (299.00, 299.01, 299.10, 299.11, 299.80, 299.81, 299.90, and 299.91), bipolar disorder (296.7, 296.00-296.06, 296.10-296.16, 296.40-296.46, 296.50-296.56, 296.60-296.66, 296.80-296.82, 296.89, 296.99, and 296.99), depression (311, 300.4, 293.83, 296.20-296.26, and 296.30-296.36), personality disorder (301.xx), schizophrenia (295.xx), substance use disorder (292.xx, 303.xx, 304.xx, 305.xx, 265.2, 357.5, 425.5, 291.0-291.5, 291.9, 571.0, 571.2, 571.3, 535.3, 790.3, and 648.30-648.34), psychosis (297.xx, and 298.xx), anxiety disorder (300.xx, 313.0,313.1, 308.1-318.4, 308.9, 293.84, 309.81, 313.21, 313.22, 313.82, and 313.83), sleep disorder (347.xx, 307.4,

780.5, and 307.40-307.49), and enuresis (307.6). Recent mental health hospitalization was used as a proxy measure for the general mental health status of an individual. It was defined as an inpatient claim occurring in the 180 days before or on the index LAS prescription claim date with an ICD-9-CM diagnosis code for any designated mental health disorder (290.xx - 319.xx).

Atypical Antipsychotic Use

Atypical antipsychotic medications such as clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole were identified by using National Drug Codes and generic names from prescription files during one year period after the index LAS prescription date. For each cohort member, each day of follow-up after the initiation of index LAS was classified according to atypical antipsychotic use. The time preceding the first atypical antipsychotic claim, including the follow-up days of all of the subjects who were never exposed to atypical antipsychotics after the initiation of the LAS, was classified as “nonuse.” All of the days where an atypical antipsychotic prescription was active were assigned to the “current use” period. Days after periods of current use were classified as “former use.” Patients were allowed to switch back and forth between former and current use of atypical antipsychotic agents. The category “former use” was established because the characteristics of this group should be similar to those of current use and minimize differences in unmeasured patient characteristics that may be associated with the decision to use stimulants (confounding by indication). These definitions of the no use, concurrent use, and former use have been previous used in the previous literature in order to examine the cardiovascular safety of the stimulant medications among children and adolescents.[25,26]

Analytic Plan

An incident users or new-user design was used where newly treated patients entered the cohort at the first claim for the long acting stimulants (LAS). The first claim of the LAS had to be preceded by a 6-month period of continuous eligibility without any claim of the LAS or atypical antipsychotic agents. The one year continuous eligibility after the index LAS initiation

were ensured and patients were followed for one year until the outcome of first cardiovascular event occurred, the first diagnosis for malignant neoplasm (defined by an inpatient or outpatient claim with ICD-9-CM 140*xx* to 208*xx* or 230*xx* to 234*xx*), or discontinuation of the LAS, or the end of the study period (one year) whichever came first.

Descriptive statistics were used to compare the patients who received LAS and atypical antipsychotics concurrently and those who received only LAS with respect to demographic and service related characteristics, psychiatric and non-psychiatric disorders, and psychotropic and non-psychotropic medications during the follow up period. A time dependent Cox proportional hazard model was used to examine the risk of cardiovascular event among antipsychotic users after controlling for the demographic characteristics, psychiatric and non-psychiatric comorbidities, psychiatric and non-psychiatric co-medications, pre-existing heart diseases, and previous mental health related hospitalization. The age, gender, and race were created as categorical variables. The psychiatric and non-psychiatric co-medications were updated as daily use every day during follow up period. All of the variables were entered in the final multivariate model depending on their independent association with clinical end point of cardiovascular event in univariate analysis. Adjusted incidence rates, defined as first event per patient years of follow-up, were calculated for former use and current use using the crude incidence rate of nonuse multiplied by the respective adjusted hazard ratio (HR). Data management and analysis were conducted with SAS 9.1 (SAS Institute, Cary, NC).

Results

Table 1 provides the demographic, service related, and clinical characteristics of the study cohort. The final cohort consisted of 61,428 patients who initiated ADHD treatment by using LAS and out of them 10,475 (17.05%) used atypical antipsychotic during one year follow up after the LAS initiation. The average age among atypical antipsychotic recipients was 10.58 years while no users was 10.05 years. There was no statistically significant difference among those who received atypical antipsychotics and those did not in terms of gender. The atypical

antipsychotic recipients were more likely to receive foster care benefits psychiatric diagnosis, and psychotropic medications in comparison to non-users. In addition atypical antipsychotic recipients more likely to have baseline cardiovascular disorders and mental health related hospitalization. Also atypical antipsychotics users had 2.39% of cardiovascular events while nonusers had 1.64% events. On an average atypical antipsychotic users were followed for 191 days while non-users were followed for 141 days.

The rates of the cardiovascular events or symptoms are shown in Table 2. All the patients were followed for 9,206,873 person-days of observation, of which no use of atypical antipsychotics contributed for 7,634,169 person-days, current use of atypical antipsychotics were contributed for 1,250,771 person-days, and former use of atypical antipsychotics contributed for 321,933 person-days. During the period of atypical antipsychotic no-use there were 840 events accounting for 40.16 crude cardiovascular events per 1000 person years. During the period of current use there were 202 crude events accounting for 58.95 crude cardiovascular events per 1000 person years while during the former use period there were 45 events accounting for 51.02 cardiovascular events per 1000 person years.

Table 3 shows the results of the time-dependent Cox proportional hazard model. In comparison to no use the current use of atypical antipsychotics among the LAS users were not statistically significantly associated with cardiovascular events (HR, 1.17; 95% CI, 0.98-1.40) after controlling for the demographic, service related, and clinical characteristics.. Also former use of atypical antipsychotics were not statistically significantly associated (HR, 1.24; 95% CI, 0.91-1.69) with cardiovascular events in comparison to no-use among LAS users after controlling for the demographic, service related, and clinical characteristics... Those who were diagnosed with obesity increased the risk of cardiovascular events by 1.63 times (HR, 1.63; 95% CI, 1.21-2.20) in comparison to those did not have obesity among LAS users. Also, those who were diagnosed with diabetes increased the risk of cardiovascular events by almost two times (HR, 1.94; 95% CI, 1.27-2.96) in comparison to those did not have diagnosis of diabetes

among LAS users. In addition receipt of mood stabilizers increased the cardiovascular event related risk by 1.87 times (HR, 1.87; 95% CI,1.08-3.24) in comparison to no use of the mood stabilizers among LAS users. Moreover, those who had cardiovascular disorder or symptoms before the initiation of LAS treatment for ADHD had risk of cardiovascular symptoms after the initiation of LAS more than 5 times (HR, 5.2; 95% CI, 4.29-6.40) in comparison to those who did not have any cardiovascular symptoms before initiation of LAS treatment. The alternative analysis performed after the exclusion of the patients with baseline cardiovascular event did not change the study findings. In the new model only diagnosis of the obesity, diabetes, and receipt of mood stabilizers predicted the cardiovascular event.

Discussion

The study found that 17.05% of the children and adolescents who initiated ADHD treatment by using LAS medications also received atypical antipsychotics. The prevalence of the atypical antipsychotic can be extrapolated to the prevalence of the several psychiatric comorbidities because those who received atypical antipsychotic agents also had other psychiatric disorders such as bipolar disorder, schizophrenia, psychosis, ODD, CD etc.

This is the first kind of the study examining the cardiovascular safety of the concurrent use of the long acting stimulant and atypical antipsychotic agents in children and adolescents diagnosed with ADHD. The increasing use of the multiple psychotropic medications among young children and adolescents is major public health concern due to the lack of long term safety related data about such use. The both stimulant medications and atypical antipsychotic medications has shown propensity of cardiovascular adverse events among children and adolescents in several randomized controlled trials and observational studies. The current study did not find any statistically significant evidence about the cardiovascular risk related symptoms due to the addition of the atypical antipsychotic agents in the ongoing regimen of long acting stimulants in children and adolescents diagnosed with ADHD. But Mcintyre and colleagues found that odds of developing cardiovascular events due to antipsychotics were 1.9 times

greater in patients with type II diabetes mellitus and dyslipidemia and 2.1 times higher in those with incident type II diabetes mellitus and dyslipidemia in comparison to users.[44,45] The current study did not find any increase in cardiovascular risk after controlling for several demographic, service related, and clinical characteristics which also included diabetes and obesity.

The diagnosis of the obesity and diabetes were independent risk factors of the increased cardiovascular risk or symptoms after controlling for the background characteristics among children and adolescents LAS users. The obesity and diabetes are the independent risk factors for heart diseases and it has been already established in the literature. The study examined the interaction effect of the atypical use and diagnosis of the obesity or the diabetes and found statistically insignificant effect on the cardiovascular effect. Thus there is no effect of the atypical antipsychotic medications according to the presence or the absence of the obesity or diabetes among the users of the LAS.

Furthermore mood stabilizers caused the increased risk of the cardiovascular symptoms among users in comparison to no users. These findings further need to be scrutinized in separate study in order to examine the link between use of mood stabilizers and cardiovascular risk.

The study has several limitations therefore findings should be interpreted in the context of those limitations. Administrative healthcare claims databases offer several advantages such as large and diverse sample sizes, long follow-up, and availability of real-world clinical practice data.. However, they are not primarily designed to address particular research questions.[50] One such limitation that the database lacks certain key variables associated with the treatment regimen, such as severity of, and changes in, ADHD symptoms and other psychiatric comorbidities. The knowledge of the potential cardiac effects of the stimulant or atypical agents may have resulted some office, hospital, or emergency visits. However, several demographic and clinical factors were adjusted for the variation in time dependent Cox proportional model. The study assumes that the medications that are dispensed are actually consumed by patients

as prescribed and that the patients received no other psychotropic medication besides those available in the claims data. The study also limited to the Medicaid beneficiaries from four states and prescribing practices of Medicaid providers may also not be representative of those providers contracted under other types of health insurance programs. So, the results may not be generalized to the whole ADHD population or specifically to the privately insured or uninsured patient populations due to substantial difference in these populations. Finally, diagnoses of ADHD and co-morbid mental disorders, and cardiovascular end point were identified based on diagnostic codes, and claim forms limit the number of diagnoses that can be documented.

Conclusion

This study did not find any statistically significant increased cardiovascular risk due to the addition of the atypical antipsychotic in the ongoing regimen of the long acting stimulants in children and adolescents diagnosed with ADHD. The diagnosis of the obesity and diabetes and use of the mood stabilizers were independent risk factors of the cardiovascular symptoms among patients on long acting stimulant medications.

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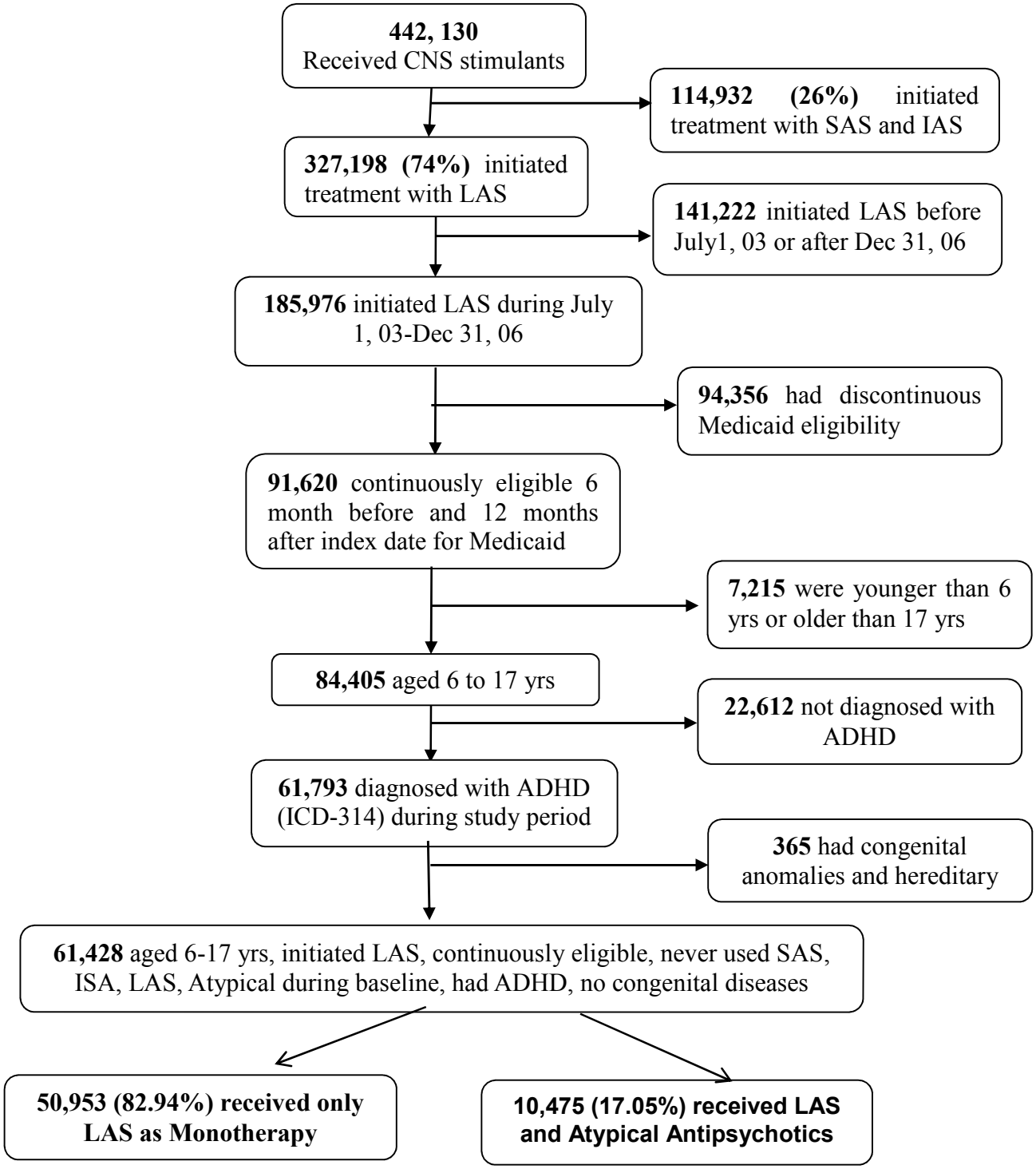
Figure 1: Flow-chart of Study Sample Selection and Study Cohort Development



Abbreviations: ADHD – Attention Deficit/Hyperactivity Disorder; SAS – Short-Acting Stimulants; IAS – Intermediate-Acting Stimulants; LAS - Long-Acting Stimulants

Table 1: Characteristics of Antipsychotic users and non-users among children and adolescents who initiated ADHD treatment with LAS			
Characteristics	Atypical Antipsychotic Use (N=10,475) N (%)	No Atypical Antipsychotic Use (N=50,953) N (%)	P value
CVD Events	250 (2.39)	837 (1.64)	<0.0001
Days of Follow up (mean)	191 days	141 days	<0.0001
Demographics			
Age, years (mean)	10.58	10.05	<0.0001
Gender			
Female	2,901 (27.69)	14,450 (28.36)	<0.168
Male	7,574 (72.31)	36,503 (71.64)	
Race/ethnicity			
White	3,812 (36.39)	29,456 (40.15)	<0.0001
Black	2,843 (27.14)	11,598 (22.76)	
Others	3,820 (36.47)	18,899 (37.09)	
Service Related Characteristics			
States			
New York	2,658 (25.37)	10,588 (20.78)	<0.0001
Illinois	1,766 (16.86)	11,570 (22.71)	
Texas	4,050 (38.66)	17,492 (34.33)	
California	2,001 (19.10)	11,303 (22.18)	
Season			
Summer (6-8)	2,407 (22.98)	10,186 (19.99)	<0.0001
Autumn (9-11)	3,544 (33.83)	18,333 (35.98)	
Winter (12-2)	2,455 (23.44)	12,227 (24.00)	
Spring (3-5)	2,069 (19.75)	10,207 (20.03)	
Cohort Entry Year			
2003	1,808 (17.26)	8,815 (17.30)	<0.0001
2004	3,380 (32.27)	18,425 (36.16)	
2005	2,570 (24.53)	11,800 (23.16)	
2006	2,717 (25.94)	11,913 (23.38)	
Foster Care			
No	7,719 (73.69)	44,305 (86.95)	<0.0001
Yes	2,756 (26.31)	6,648 (13.05)	
TANF			
No	9,094 (86.82)	42,818 (84.03)	<0.0001
Yes	1,381 (13.18)	8,135 (15.97)	
SCHIP			
No	10,367 (98.97)	49,773 (97.68)	<0.0001
Yes	108 (1.03)	1,180 (2.32)	
Co-morbidities			
Conduct Disorder			

No	8,434 (80.52)	45,758 (89.80)	<0.0001
Yes	2,041 (19.48)	5,195 (10.20)	
Oppositional Defiant Disorder			
No	8,463 (80.79)	46,973 (92.19)	<0.0001
Yes	2,012 (19.21)	3,980 (7.81)	
Developmental Disorder			
No	8,552 (81.64)	43,497 (85.37)	<0.0001
Yes	1,923 (18.360	7,456 (14.63)	
Pervasive Developmental Disorder			
No	10,060 (96.04)	50,444 (99.00)	<0.0001
Yes	415 (3.96)	509 (1.00)	
Tic Disorder			
No	10,413 (99.41)	50,788 (99.68)	<0.0001
Yes	62 (0.59)	165 (0.32)	
Bipolar Disorder			
No	7,495 (71.55)	49,328 (96.81)	<0.0001
Yes	2,980 (28.45)	1,625 (3.19)	
Depression			
No	7,813 (74.59)	45,994 (90.27)	<0.0001
Yes	2,662 (25.41)	4,959 (9.73)	
Personality Disorder			
No	10,269 (98.03)	50,786 (99.67)	<0.0001
Yes	206 (1.97)	167 (0.33)	
Schizophrenia			
No	10,271 (98.05)	50,851 (99.80)	<0.0001
Yes	204 (1.95)	102 (0.20)	
Substance Use Disorder			
No	10,163 (97.02)	50,364 (98.84)	<0.0001
Yes	312 (2.98)	589 (1.16)	
Psychosis			
No	9,826 (93.80)	50,588 (99.28)	<0.0001
Yes	649 (6.20)	365 (0.72)	
Anxiety			
No	8,442 (80.59)	46,528 (91.32)	<0.0001
Yes	2,033 (19.41)	4,425 (8.68)	
Asthma			
No	9,193 (87.76)	45,352 (89.01)	<0.0002
Yes	1,282 (12.24)	5,601 (10.99)	
Obesity			
No	10,243 (97.79)	50,090 (98.31)	<0.0002
Yes	232 (0.38)	863 (1.69)	
Diabetes			
No	10,377 (99.06)	50,670 (99.44)	<0.0001
Yes	98 (0.94)	283 (0.56)	
Seizure			

No	10,249 (97.84)	50,106 (98.34)	<0.0004
Yes	226 (0.37)	847 (1.66)	
Baseline CVD			
No	10,136 (96.76)	50,131 (98.39)	<0.0001
Yes	339 (3.24)	822 (1.61)	
Mental Health Hospitalization			
No	9,781 (93.37)	50,391 (98.84)	<0.0001
Yes	694 (6.63)	592 (1.16)	
Co-medication			
Bronchodilators			
No	9,124 (87.10)	45,414 (89.13)	<0.0001
Yes	1,351 (12.90)	5,539 (10.87)	
Anticonvulsants			
No	8,089 (77.22)	48,813 (95.80)	<0.0001
Yes	2,386 (22.78)	2,140 (4.20)	
Antidepressants			
No	7,236 (69.08)	45,188 (88.69)	<0.0001
Yes	3,239 (30.92)	5,765 (11.31)	
Anxiolytics			
No	10,030 (95.75)	49,909 (97.95)	<0.0001
Yes	445 (4.25)	1,044 (2.05)	
Mood stabilizers			
No	10,198 (97.36)	50,887 (99.87)	<0.0001
Yes	277 (2.64)	66 (0.13)	
Typicals			
No	10,388 (99.17)	50, 887 (99.87)	<0.0001
Yes	87 (0.83)	66 (0.13)	
SAS			
No	9,977 (95.25)	49, 082 (96.33)	<0.0001
Yes	498 (4.75)	1,871 (3.67)	
IAS			
No	10,035 (95.99)	49,635 (97.41)	<0.0001
Yes	420 (4.01)	1,318 (2.59)	
Atomoxetine			
No	9,687 (92.48)	48,452 (95.09)	<0.0001
Yes	788 (7.52)	2,501 (4.91)	

Table 2. Adjusted Rates of First Visit (Hospital, Emergency Department, Physician Office) due to Circulatory Diseases and Cardiac Symptoms According to Atypical Antipsychotic Use

Antipsychotic Use	Person Days	Person Years	Events	Crude Events per 1000 patient - years	Adjusted Events (Events per 1000 patient -years)
No Use	7,634,169	20,916	840	40.16	40.16
Current Use	1,250,771	3,427	202	58.95	47.15
Former Use	321,933	882	45	51.02	49.67

Data was adjusted for demographic characteristics (age, gender, race), service related characteristics (state, season, cohort entry year, foster care benefits, temporary assistance to needy families (TANF) benefits, state child health Insurance program (SCHIP) benefits, psychiatric and non-psychiatric comorbidities, psychotropic and non-psychotropic medications, and mental health related hospitalization)

Table 3 : Risk of Cardiovascular Events among children and adolescents who initiated ADHD treatment with Long acting stimulants

Characteristics	Unadjusted HR	Adjusted HR	95% CI
Atypical Antipsychotics			
No Use	1.00	1.00	
Current Use	1.59	1.17	0.98-1.40
Former Use	1.46	1.24	0.91-1.69
Obesity			
No	1.00	1.00	
Yes	2.37	1.63	1.21-2.20
Diabetes			
No	1.00	1.00	
Yes	3.03	1.94	1.27-2.96
Baseline CVD			
No	1.00	1.00	
Yes	7.11	5.2	4.29-6.40
Mood Stabilizer			
No	1.00	1.00	
Yes	2.54	1.87	1.08-3.24

The model was adjusted for demographic characteristics (age, gender, race), service related characteristics (state, season, cohort entry year, foster care benefits, temporary assistance to needy families (TANF) benefits, state child health Insurance program (SCHIP) benefits, psychiatric and non-psychiatric comorbidities, psychotropic and non-psychotropic medications, and mental health related hospitalization)

CONCLUSIONS AND IMPLICATIONS

This study found that almost 19.20% of children and adolescents aged between 6 to 17 years who initiated ADHD treatment with long acting stimulant (LAS) medications received LAS and atypical antipsychotics concurrently. These findings are consistent with the available prevalence of multiclass psychotropic drug utilization from national level cross sectional data. The concurrent users were mainly children aged between 6-12 years, males, and had at least one psychiatric comorbidity. The FDA approved indications such as schizophrenia, bipolar disorder, and psychosis and FDA non-approved indications such as oppositional defiant disorder, pervasive developmental disorder, tic disorder, and personality disorder determined the concurrent use of LAS and atypical antipsychotics along with male gender, black race, and foster care benefits. Therefore there is urgent need of conducting head to head trials in order to examine the safety and efficacy of concurrent use of LAS and atypical antipsychotic agents in in children and adolescents with ADHD and several other psychiatric disorders.

The recipients of LAS and atypical antipsychotic agents concurrently had longer LAS treatment continuity than recipients of only LAS. The accelerated regression analysis found that recipients of LAS and atypical antipsychotic agents had 45% longer (STR, 1.45; 95% CI, 1.41-1.49) LAS treatment persistence than only LAS recipients. The addition of the atypical antipsychotic agents along with LAS in ADHD patients may be beneficial in controlling ADHD symptoms. Altthough the study found improvement in stimulant persistence due to atypical agents, there is need to conduct future research to examine the efficacy and effectiveness of atypical antipsychotic agents in the management of ADHD symptomatology.

This study did not find any statistically significant increased cardiovascular risk due to the addition of the atypical antipsychotic in the ongoing regimen of the long acting stimulants in children and adolescents diagnosed with ADHD. In comparison to no use the current use of atypical antipsychotics among the LAS users were not statistically significantly associated with

cardiovascular events (HR, 1.17; 95% CI, 0.98-1.40) after controlling for the demographic, service related, and clinical characteristics.. Also former use of atypical antipsychotics were not statistically significantly associated (HR, 1.24; 95% CI, 0.91-1.69) with cardiovascular events in comparison to no-use among LAS users. However, the diagnosis of the obesity and diabetes and use of the mood stabilizers were independent risk factors of the cardiovascular symptoms among patients on long acting stimulant medications.