Physical Health Outcomes in Preschoolers with Prior Authorization for Antipsychotics

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Abstract

Objective: To examine incidence of adverse health outcomes and associated factors among preschoolers (under age 6) who received antipsychotic treatment through the Florida Medicaid Prior Authorization (PA) program.

Methods: Using Florida's PA registry linked to the state's Medicaid claims data, we ascertained incident outcomes during PA-approved antipsychotic use between April 2008 and September 2015 (7.5 years). Six outcomes associated with use of antipsychotics included: diabetes, obesity, hyperlipidemia, hyperprolactinemia, cardiovascular disease (CVD) (including hypertension, ventricular arrhythmia, and other CVDs), and extrapyramidal symptoms (EPS) (including dystonia, akathisia, parkinsonism, and tardive dyskinesia). Outcome-specific incidences were stratified by short-term (≤ 1 year) and long-term (> 1 –7 years) antipsychotic use. We used multivariate modified Poisson regressions to determine factors associated with these outcomes among preschoolers.

Results: The overall crude incidence during PA-approved antipsychotic use was highest for EPS and obesity (57 and 19 cases/1000 children-years, respectively). The rate of these two outcomes differed by duration of antipsychotic use. We observed a higher obesity (23.8 vs. 9.6, $p < 0.001$) and dystonia incidence (7.2 vs. 2.5, $p < 0.05$), but lower akathisia incidence (44.4 vs. 60.6, $p < 0.05$) among long-term antipsychotic users compared with short-term users. Five outcomes—ventricular arrhythmia, other cardiovascular side effects, hyperprolactinemia, parkinsonism, and tardive dyskinesia—occurred rarely ($< 2.0/1000$ children-years). Preschoolers who were younger at baseline (≤ 2 years old vs. 4–5 years old) and Black (vs. White) were at a higher risk of EPS.

Conclusion: Risk for EPS and obesity deserves clinical attention during antipsychotic treatment among preschoolers. Controlled studies that allow interpretation of these incidence rates in the context of background risk and that formally quantify the incremental risk associated with antipsychotic initiation during early childhood are needed.

Keywords: preschoolers, antipsychotics, physical health outcomes, prior authorization

Introduction

CONCERNS ABOUT THE INCREASED USE of antipsychotics have led many states to adopt Prior Authorization (PA) approaches to guard against inappropriate use of these medications during early childhood (Schmid et al. 2015). For example, starting in April 2008, Florida became one of the early adopters of a PA, which requires an independent review of therapeutic plans that include antipsychotics for all Medicaid-insured children under the age of 6 years (Schmid et al. 2015). The review, conducted by board-certified child and adolescent psychiatrists, determines whether children recipients meet specific clinical criteria before approving antipsychotic medi-

cation use. In addition to acting as a gatekeeper for antipsychotic use, the PA system serves as an education function by providing prescribers an opportunity to review another clinician's perspective regarding a child's specific clinical presentation and the appropriateness of the requested antipsychotic medications.

While antipsychotics can be effective in treating mental disorders for children and adolescents, the treatment also comes with undesirable side effects. Evidence on health outcomes associated with antipsychotic is available for patients 7–18 years of age (Laita et al. 2007; De Hert et al. 2011). Reported complications include cardiovascular risk, hyperprolactinemia, extrapyramidal side effects, and metabolic syndrome (e.g., weight gain, hypertension, hyperlipidemia,

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and increased blood sugar) and subsequent onset of diabetes. While dyskinesia is likely a consequence of antipsychotic use, metabolic issues are part of the ongoing obesity and diabetes epidemic that could be due to factors other than antipsychotics. The risk of developing these side effects may also be associated with the duration of antipsychotic use. Compared with children using antipsychotics for <1 month, those with >12 months of drug exposure showed higher risk for weight gain, dyskinesia, and elevated total cholesterol and low-density lipoprotein cholesterol (Laita et al. 2007).

Yet, it remains unclear whether the risk of health outcomes for children and adolescents also applies to very young children under 6 years of age exposed to antipsychotics. This is especially concerning because utilization of antipsychotics in preschoolers has increased by as much as fivefold over the last 15 years (Patel et al. 2002; Zito et al. 2007; Olfson et al. 2010). A study of Florida Medicaid-insured children who initiated antipsychotic treatment before age 6 showed that nearly 30% of preschoolers started antipsychotic treatment at age 4, and 13% started at age under 3 (Constantine et al. 2012). If continuously used for a longer duration, antipsychotics may have great impact on children's development and physical well-being later on in life.

To better understand the risks for health outcomes among preschoolers who used antipsychotics, this project focuses on Medicaid-insured children under age 6 who received and filled prescriptions for an antipsychotic through the PA program in the state of Florida. Specifically, the study aims (1) to estimate the incidence of health outcomes during PA-approved antipsychotic use; and (2) to identify risk factors for these outcomes among preschoolers.

Methods

Study design and source

This retrospective, longitudinal study used the Florida PA registry data linked with the state's Medicaid pharmacy and encounter claims data from April 1, 2008, through September 30, 2015 (7.5 years). The PA registry data contain information on dates of PA requests and services provided to children, including assessments on targeting mental/behavioral conditions (e.g., attention-deficit/hyperactivity disorder [ADHD], autism, and disruptive behavior), physical health (e.g., body mass index [BMI] status), and antipsychotic medications prescribed in treating mental conditions. As part of Florida PA process, children's information assessed during doctor visits are then reviewed by Florida board-certified pediatric psychiatrists licensed in Florida. Each PA application was sent to the University of South Florida (USF), Medicaid Drug Therapy Management Program for Behavioral Health (MDTMP) to establish a comprehensive, real-time registry for monitoring and further research activities. The USF linked the registry data to Medicaid billing records and provided the deidentified data to the University of Florida (UF) for analysis. The UF Institutional Review and Privacy Boards approved this study.

Study sample

The study sample included Florida Medicaid-insured children under 6 years of age who had ≥1 approved PA applications for antipsychotic use between April 1, 2008 and September 30, 2015. The sample was further restricted to children who had ≥1 filled antipsychotic prescription to ensure an active engagement in the antipsychotic PA program. Study entry (the "index date") was defined as the date of the first PA-approved antipsychotic

prescription fill as per pharmacy billing records. Eligible children were followed from the index date until the earliest of the following: first outcome event (defined separately for each investigated outcome), death, Medicaid disenrollment, or study end (i.e., September 30, 2015).

To ascertain incidence cases of health outcomes (as detailed in the next paragraph) during the follow-up period, we created separate cohorts for each outcome by excluding prevalent cases who had been previously diagnosed with the outcome of interest within 6 months before the index date (i.e., baseline). Children with no continuous Medicaid enrollment during the 6-month baseline period were excluded.

Health outcomes

Outcomes of interest included metabolic and endocrine diseases (diabetes, obesity, hyperlipidemia, and hyperprolactinemia), cardiovascular diseases (CVDs) (hypertension, ventricular arrhythmia, and other CVDs), and abnormal involuntary movements (extrapyramidal symptoms [EPS]), further stratified into dystonia, akathisia, parkinsonism, and tardive dyskinesia) (see Supplementary Table S1 for the ICD-9 codes; Supplementary Data are available online at www.liebertpub.com/cap). Because there are no validated algorithms for measuring these outcomes among children under 6, we relied on several sources for case identification. Diabetes, obesity, hyperlipidemia, hyperprolactinemia, and CVDs were determined based on the Condition Categories developed by the Centers of Medicare and Medicaid Services ([CMS] 2007) for Medicare and Medicaid beneficiaries (The Centers for Medicare and Medicaid Services [CMS]). For example, to be considered as case with diabetes, patients were required to have ≥1 inpatient or ≥2 outpatient records with ICD-9-CM codes for diabetes, as summarized in the CMS condition category, in any diagnostic position. EPS outcomes were determined by use of relevant diagnostic codes in Medicaid inpatients or outpatients (Abouzaid et al. 2014). We did not use clinical information, such as BMI, documented on the PA forms due to large missing data in most of the clinical variables. For instance, 84% of the first PA application had missing BMI values because the collection of this information was not required until 2012.

Incidence of physical health outcomes

The overall incidence rate was calculated with a denominator of the total person-years at risk and a numerator of cases with outcome events during the at-risk period, as Equation (1).

$$\text{Overall incidence rate} = \frac{\text{Cases}_{\text{during the denominator}}}{\left[\sum (\text{episode days})_{\text{from index date to censoring point}} \right] / 365} \quad (1)$$

The at-risk period was defined as PA-approved antipsychotic exposure days of eligible children who were available for follow-up and had not developed the selected outcome. Antipsychotic exposure period was determined based on days' supply of dispensed prescription fills in Medicaid claims, a source considered more reliable than prescribing data in identifying use of medication (Grégoire and Moisan 2016). For children who took antipsychotics on and off or children who stopped after continuous use, an additional 6-month follow-up was added at the end of each episode to fully capture latent outcomes that may manifest after antipsychotic discontinuation (Howland 2010). Any days beyond this follow-up period without evidence of antipsychotic use were discarded from

the incidence rate calculation. We further calculated incidence rates for short-term [≤ 1 year, Equation (2)], as well as long-term [> 1 –7 years, Equation (3)] use of antipsychotics following the index date.

Incidence in short-term use =

$$\frac{\text{Cases}_{\text{during the denominator}}}{\left[\sum (\text{episode days})_{\leq 365 \text{th day after index date}} + \sum (\text{carried over days})_{\text{from 1st year}} \right] / 365} \quad (2)$$

Incidence in long-term use =

$$\frac{\text{Cases}_{\text{during the denominator}}}{\left[\sum (\text{episode days})_{\geq 366 \text{th day after index date}} \right] / 365} \quad (3)$$

In the calculation of the short-term rate, following the aforementioned rule, each intermittent or discontinued antipsychotic episode in the first year was extended with a 6-month follow-up period to detect latent cases that may be attributable to antipsychotics. Thus, the extended risk period may exceed the 1-year risk window, and for calculation purposes, these days reaching into the second year were included in the denominator of the short-term rate. Cases that manifested during that second-year period were likewise attributed to the long-term incidence rate calculation. When calculating the long-term rate, we excluded patients who had a short-term (< 1 year) antipsychotic exposure and those who were cases in the first year from the numerator, and excluded the entire first 12 months from the denominator.

Risk factors at baseline

Demographic and clinical characteristics measured at baseline included age (categorized as ≤ 2 , 3, 4, and 5 years), gender, race/ethnicity (categorized as White, Black, others including Asian, Hispanic, American Indian, or Alaskan, and unknown race/ethnicity), and mental health comorbidities. Information on children's

mental conditions at baseline was ascertained primarily from PA assessment data.

Data analysis

For each outcome cohort, we calculated the duration of PA-approved antipsychotic use during follow-up based on the total number of days' supply dispensed as documented in Medicaid pharmacy billing records. The overall, short-term and long-term incidence rates of each individual outcome were reported per 1000 children years of antipsychotic use. We presented risk differences (RDs) and their confidence intervals (95% CIs) to compare rates between the long-term and short-term exposure groups (reference). We also identified a subgroup of eligible children who continuously received PA-approved antipsychotics for at least 2 years following the index date and presented a comparison of incidence rates against short-term use.

To provide a comprehensive overview of sample characteristics, we report children's baseline demographics and clinical characteristics in the cohort with the largest sample size. We examined risk factors with the development of EPS and obesity, because these two outcomes had the highest incidence rates and provided sufficient number of cases for the analysis. We used multivariate modified Poisson regression models, along with generalized estimating equation to estimate the relative risks (RRs) of the association of risk factors with both outcomes separately, adjusting for length of the follow-up period and year of index date. In addition, we reported the incidence of obesity and EPS by baseline use of aripiprazole and risperidone, two most commonly used antipsychotics used in the cohorts. All analyses were performed using SAS[®] 9.4 (SAS Institute, Cary, NC). Statistical significance was set at $p < 0.05$ and all tests were two-tailed.

Results

We identified 1794 eligible children under age of 6 years who had ≥ 1 PA-approved antipsychotic filled during the study period

TABLE 1. DURATION OF FOLLOW-UP AND CUMULATIVE YEARS OF PRIOR AUTHORIZATION-APPROVED ANTIPSYCHOTIC USE DURING FOLLOW-UP

Disease cohort	Total sample (n) ^a	Follow-up ^b (years) Mean (SD)	Cumulative years of PA-approved antipsychotic use during follow-up		
			Mean (SD)	Median	Interquartile ranges
Diabetes	1792	2.9 (2.1)	2.2 (2.0)	1.6	0.5–3.5
Obesity	1764	2.8 (2.0)	2.2 (1.9)	1.6	0.5–3.4
HLD	1787	2.8 (2.0)	2.2 (2.0)	1.6	0.5–3.4
HPRL	1794	2.9 (2.1)	2.2 (2.0)	1.6	0.5–3.5
CVD					
Hypertension	1784	2.9 (2.0)	2.1 (1.9)	1.6	0.5–3.5
Ventricular Arrhythmia	1792	2.9 (2.1)	2.2 (2.0)	1.6	0.5–3.5
Other CVDs ^c	1782	2.9 (2.1)	2.2 (2.0)	1.6	0.5–3.5
EPS	1789	2.8 (2.1)	2.2 (2.0)	1.6	0.5–3.5
Dystonia	1792	2.9 (2.1)	2.2 (2.0)	1.6	0.5–3.5
Akathisia	1766	2.8 (2.0)	2.1 (1.9)	1.5	0.5–3.3
Parkinsonism	1794	2.9 (2.1)	2.2 (2.0)	1.6	0.5–3.5
Tardive dyskinesia	1793	2.9 (2.0)	2.2 (2.0)	1.6	0.5–3.5

^aChildren free of the physical outcome of interest at baseline, defined as 6 months before the index date.

^bIndex date until a physical outcome event, death, Medicaid disenrollment, or study end (September 30, 2015), whichever came first.

^cOther CVDs include heart failure, stroke, and acute myocardial infarction.

CVD, cardiovascular disease; EPS, extrapyramidal symptoms; HLD, hyperlipidemia; HPRL, hyperprolactinemia; PA, Prior Authorization; SD, standard deviation.

and maintained Medicaid enrollment during the baseline period. From the study sample, 13 cohorts were derived, with each cohort consisting of children free of the specific studied outcome at baseline (ranging from 1764 in the obesity cohort to 1794 in the hyperprolactinemia or parkinsonism cohort) (Table 1). In all disease cohorts, children were available for follow-up for an average of almost 3 years. The average cumulative duration of PA-approved antipsychotic use was 2.1–2.2 years.

Demographic and clinical characteristics of 1794 children without baseline hyperprolactinemia are presented because of its large sample size (Table 2). The mean age of this cohort was 4.3 ± 0.9 years with slightly more than half (52.0%) aged 5 years or older. Males accounted for more than two-third (76.6%) of the

TABLE 2. BASELINE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS OF ELIGIBLE CHILDREN UNDER 6 YEARS OF AGE WHO RECEIVED AN ANTIPSYCHOTIC WITHIN THE PRIOR AUTHORIZATION PROGRAM AND WITHOUT HYPERPROLACTINEMIA AT BASELINE

<i>Baseline^a characteristics</i>	<i>Eligible children in hyperprolactinemia cohort n = 1794 (100%)</i>
Age	
Mean $\pm$ SD (years)	4.3 $\pm$ 0.9
≤2	81 (4.6)
3	242 (13.5)
4	539 (30.0)
5	932 (52.0)
Male	1375 (76.6)
Race/ethnicity	
Whites	432 (24.1)
Blacks	158 (8.8)
Others ^b	235 (13.1)
Unknown	969 (54.0)
Year of first PA-approved antipsychotic use	
2008	410 (22.9)
2009	275 (15.3)
2010	249 (13.9)
2011	244 (13.6)
2012	240 (13.4)
2013	218 (12.2)
2014–2015	155 (8.8)
Mental conditions diagnosed at baseline	
Autism	881 (49.1)
ADHD	801 (44.7)
Mood disorder	180 (10.3)
Bipolar disorder	135 (7.5)
Oppositional defiant disorder	135 (7.5)
Developmental delay, intermittent explosive disorder or behavior disorder	135 (7.5)
Disruptive behavior	113 (6.3)
Tics	36 (2.1)
Other psychotropic medications at baseline	
Any use of ADHD medications	1211 (67.5)
Any use of anticonvulsants	300 (16.7)
Any use of antidepressants	158 (8.8)
Any use of anxiolytic, hypnotics, sedatives	174 (9.7)

^aSix months before the index date that is date of the first PA approval.

^bOthers included Asian, Hispanic, American Indian, or Alaskan. PA, Prior Authorization.

cohort. Nearly one-quarter (24.1%) were White, with more than half (54.0%) having unknown races/ethnicities. Over one-fifth (22.9%) had their first PA application approved in 2008; the number of children who entered the cohort decreased to around 12%–16% of the total cohort between 2009 and 2013, followed by a marked drop to around 9% during 2014–2015, in part, due to implementation of the statewide Medicaid managed care program (Alker and Hoadley 2013). The top three mental health conditions diagnosed at baseline were autism (49.1%), ADHD (44.7%), and mood disorder (10.3%). Two-thirds (67.5%) of the children also used ADHD medications in the 6 months before receiving their first PA-approved antipsychotic medications.

The overall incidence rates during PA-approved antipsychotic use varied by outcome (Table 3). The highest rate was observed for EPS (56.8 children/children years of use), followed by obesity (19.3) and hyperlipidemia (6.5). The high EPS incidence was mainly driven by akathisia (49.9), with little from parkinsonism (0.0) and tardive dyskinesia (1.8). Also, incidence was low for two metabolic/endocrine outcomes (2.7 for diabetes and 1.6 for hyperprolactinemia), as well as CVD outcomes (4.1 for hypertension; <2 for both ventricular arrhythmia and other CVDs). For outcome cohorts with <10 cases, we did not perform further analyses of the short-term and long-term incidence rates.

The overall incidence rates also differed by duration of antipsychotic use. Compared to the short-term users, the long-term users had a significantly higher risk of obesity (RD=14.2, 95% CI=6.7–21.0). Similar results for obesity outcome were also observed in the subgroup who had >2 years of continued antipsychotic use, when compared to children with short-term use. Likewise, a significant risk difference for akathisia (RD=−16.2, 95% CI=−31.3 to −1.8) and dystonia (RD=4.6, 95% CI=0.3–8.3) was found among the short-term and long-term users, although overall EPS incidence did not differ. No significant RD was observed for diabetes, hyperlipidemia, and hypertension between short-term, long-term, and continuous 2-year use of antipsychotics.

Table 4 showed the results of multivariate analyses examining factors associated with the development of EPS and obesity, the top two most frequent outcomes during PA-approved antipsychotic use among preschoolers. After adjustment for follow-up time and time of the first PA-approved antipsychotic use, the results showed an inverse association between age and risk for EPS, with a lower risk in children at 4 and 5 years of age (RR=0.45, 95% CI=0.28–0.72 for age 4 and RR=0.50, 95% CI=0.32–0.79 for age 5), compared with those age 2 or younger at baseline. Children who were Black (RR=1.61, 95% CI=1.05–2.49) or with unknown (RR=1.48, 95% CI=1.07–2.07) races/ethnicity (vs. White) were significantly more likely to develop any EPS. Children with unknown race/ethnicity were significantly more likely to develop obesity (RR=2.03, 95% CI=1.21–3.41, vs. White).

In individual drug analysis, we found that compared with preschoolers who had baseline use of risperidone, children with aripiprazole had higher crude incidence of obesity (23.6 vs. 19.6/1000 children treatment years, $p<0.001$), but lower crude incidence for EPS (56.8 and 59.8/1000 children treatment years, $p<0.001$) (data not shown).

Discussion

Using the Florida PA registry data, this study is the first to provide incidence estimates of potential adverse outcomes associated with antipsychotic use in preschoolers. Our study showed that of the 13 studied outcomes, EPS and obesity were the two most

TABLE 3. INCIDENCE RATES (PER 1000 CHILDREN-YEARS OF ANTIPSYCHOTIC USE) OF DISEASE-SPECIFIC PHYSICAL OUTCOMES, OVERALL AND BY SHORT-TERM, LONG-TERM, AND CONTINUOUS (>2 YEARS) EXPOSURE TO PRIOR AUTHORIZATION-APPROVED ANTIPSYCHOTIC USE

Physical outcomes	Exposure to PA-approved antipsychotic use						
	Overall		Short-term (≤1 year)	Long-term (>1–7 years)	RD ^a (95% CI) ^b	Continuous use of >2 years	RD ^c (95% CI) ^b
	Cases	Incidence	Incidence	Incidence		Incidence	
Metabolic/endocrine outcomes							
Diabetes	14	2.7	0.6	3.7	3.0 (0.0–5.4)	4.4	3.7 (–1.4 to 10.5)
Obesity	96	19.3	9.6	23.8	14.2 (6.7–21.0)***	37.6	28.0 (13.0–44.6)***
HLD	33	6.5	4.4	7.5	3.1 (–1.8 to 7.3)	10.6	6.1 (–2.0 to 16.0)
HPRL	<10 ^d	1.6	— ^e	—	—	—	—
CVD							
Hypertension	21	4.1	3.2	4.6	1.4 (–2.7 to 4.9)	2.9	–0.2 (–5.2 to 6.4)
Ventricular arrhythmia	<10 ^d	0.4	—	—	—	—	—
Other CVDs ^f	<10 ^d	0.8	—	—	—	—	—
EPS							
Any EPS	232	56.8	65.2	52.4	–12.9 (–28.6 to 2.4)	48.5	–16.7 (–39.3 to 8.7)
Dystonia	29	5.7	2.5	7.2	4.6 (0.3–8.3)*	8.9	6.4 (–0.9 to 15.3)
Akathisia	207	49.9	60.6	44.4	–16.2 (–31.3 to –1.8)*	45.7	–15.0 (–36.8 to 9.5)
Parkinsonism	<10 ^d	0.0	—	—	—	—	—
Tardive dyskinesia	<10 ^d	1.8	—	—	—	—	—

^aRD was calculated as the long-term exposure group minus the short-term exposure group.

^bChi-square tests were used for testing statistical significance with * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; for cases <30, Fisher's exact test, along with Agresti–Caffo CIs were calculated.

^cRD was calculated as the 2-year continuous exposure group minus the short-term exposure group.

^dNumbers <10 were not shown to comply with guideline for the release of public data.

^eIncidence rate was not calculated due to excessively small (<10) events.

^fOther CVDs include heart failure, stroke, and acute myocardial infarction.

CI, confidence interval; CVD, cardiovascular disease; EPS, extrapyramidal symptoms; HLD, hyperlipidemia; HPRL, hyperprolactinemia; PA, Prior Authorization; RD, risk difference.

TABLE 4. ASSOCIATION OF DEMOGRAPHIC AND CLINICAL CHARACTERISTICS WITH ANY EXTRAPYRAMIDAL SYMPTOMS AND OBESITY AMONG PRESCHOOLERS RECEIVING ANTIPSYCHOTICS THROUGH THE FLORIDA PRIOR AUTHORIZATION PROGRAM, APRIL 2008–SEPTEMBER 2015

Characteristics Cohort	Any EPS (yes vs. no) Adjusted RR (95% CI) ^a N = 1616	Obesity (yes vs. no) Adjusted RR (95% CI) ^a N = 1756
Age at baseline		
≤2	1.00 (reference)	1.00 (reference)
3	0.61 (0.38–1.00)	1.13 (0.39–3.31)
4	0.45 (0.28–0.72)**	1.50 (0.55–4.09)
5	0.50 (0.32–0.79)**	1.40 (0.52–3.79)
Male (vs. female)	0.93 (0.70–1.23)	1.35 (0.85–2.13)
Race/ethnicity		
Whites	1.00 (reference)	1.00 (reference)
Blacks	1.61 (1.05–2.49)*	1.84 (0.88–3.83)
Others ^b	1.47 (0.97–2.23)	1.77 (0.91–3.45)
Unknown	1.48 (1.07–2.07)*	2.03 (1.21–3.41)**
Mental comorbidities diagnosed at baseline		
Autism (yes vs. no)	1.21 (0.92–1.58)	1.10 (0.74–1.63)
ADHD (yes vs. no)	0.97 (0.74–1.24)	1.07 (0.72–1.57)
Mood disorder (yes vs. no)	1.00 (0.64–1.56)	0.76 (0.38–1.53)
Bipolar disorder (yes vs. no)	1.05 (0.66–1.67)	1.45 (0.79–2.67)
Oppositional defiant disorder (yes vs. no)	0.58 (0.30–1.13)	1.21 (0.62–2.37)
Disruptive behavior (yes vs. no)	0.88 (0.48–1.60)	1.10 (0.55–2.22)
Developmental delay, Intermittent explosive disorder, Tics or behavior disorder (yes vs. no)	1.08 (0.68–1.71)	0.61 (0.25–1.45)

^aThe model was mutually adjusted for all listed variables and year of first approved PA program and duration of follow-up period.

^bOthers included Asian, Hispanic, American Indian, or Alaskan.

* $p < 0.05$.

** $p < 0.01$.

ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; EPS, extrapyramidal symptoms; PA, Prior Authorization; RR, relative risk.

common conditions, with 57 and 20 children, respectively, diagnosed with these conditions for each 1000 children antipsychotic treatment years. Overall, we observed a low incidence rate ($<4/1000$ children-years) in cardiovascular (hypertension, ventricular arrhythmia, and other CVDs), two metabolic/endocrine (diabetes and hyperprolactinemia), and two EPS (parkinsonism and tardive dyskinesia) outcomes among the preschoolers. Our incidence estimates of health outcomes may serve as useful benchmarks for future work that examines other states' antipsychotic PA policy for children under 6.

To our best knowledge, there is no study examining the incidences of health outcomes related to antipsychotic use in preschoolers. However, incidence data have been reported for Medicaid-insured children/adolescents treated with antipsychotics on metabolic outcomes (obesity, 140; diabetes, 31; dyslipidemia, 30/1000 children-years) and cardiovascular outcomes (any CVD, 90; hypertension, 20/1000 children-years) (De Hert et al. 2011; Rubin et al. 2015). In addition, a meta-analysis showed an incidence of 4 per 1000 children-years for tardive dyskinesia among youths with second-generation antipsychotics (Correll and Kane 2007). Overall, the incidence rates of physical outcomes in children/adolescents seem higher than those in preschoolers observed from our study. It is noted that the prior children/adolescent studies used data before 2007, in which no state had started PA program for antipsychotics. Thus, more studies with consideration of PA policy are warranted to investigate potential age differences in rates of antipsychotic-related adverse outcomes.

The incidences of outcomes may also differ by duration of antipsychotic use. We observed that 10 children developed obesity in the short-term (≤ 1 year) use of antipsychotics, whereas 24 cases in the long-term use ($>1-7$ years) and 38 children in the continuous (>2 year) use for each 1000 children antipsychotic treatment years. The higher rate of obesity in children with longer use of antipsychotic users may be, in part, due to the cumulative metabolic effects of antipsychotic exposure, including impaired lipid metabolism and insulin resistance (Lieberman 2004). However, the definition of long-term use results inevitably in follow-up into higher age ranges, which are independently associated with increased incidence of obesity (Ogden et al. 2014). Our findings warrant further evaluation of the difference in obesity incidence by duration of antipsychotic exposure using larger samples with adjustment of other factors such as chronological age.

For EPS, we observed 65 children experienced this outcome in the short-term antipsychotic use, whereas 53 children in the long-term use and 49 children in the 2-year continuous use. As noted, most of the EPS were related to akathisia. As akathisia occurs primarily in the early phase of treatment with antipsychotics and subsides within a few weeks of treatment, the lower rate of akathisia in long-term users is anticipated (Mathews et al. 2005). Unlike akathisia, which seems to prevail in the short-term use, fewer dystonia cases were observed in the short-term versus long-term use (2.5 vs. 7.2/1000 children years). From our data, it is unclear whether long-term antipsychotic users were exposed to high treatment dose, a major risk factor for the development of dystonia (Mathews et al. 2005). A further investigation on the independent and synergistic effects of dose and duration of antipsychotic may help elucidate the difference in dystonia incidence.

A relatively low incidence rate was observed for other studied outcomes. In particular, five physical outcomes (i.e., ventricular arrhythmia, other CVD side effects, hyperprolactinemia, parkinsonism, and tardive dyskinesia) had an extremely low incidence rate ($<2/1000$ children years). Our findings suggest that these

potential side effects of antipsychotic use may affect a small percentage of children under 6, but sample size was limited to provide precise estimates. Future work with larger sample sizes that would also allow examination of high-risk cohorts are needed to confirm these incidence estimates.

Our study also examined baseline factors associated with the development of EPS and obesity—the two most frequent physical outcomes in these very young antipsychotic users. Our results showed that age and race/ethnicity were significant determinants. Children at relatively older age (3–5 years) tended to have a lower risk of EPS, compared with the youngest age group (≤ 2 years). Reasons for this difference are unclear, but may be due to potential age or mental disease severity that alters an individual's susceptibility to the development of EPS (Ormerod et al. 2008). Black compared with White preschoolers had a higher incidence of EPS, a finding that is consistent with a previous meta-analysis of adults treated with antipsychotics or antidepressants (Ormerod et al. 2008).

The strengths of our study are several. We examined a broad range of physical outcomes that have been linked to antipsychotic use over a long observation period (as long as 7.5 years). We calculated and compared the incidence rate of outcomes by short-term and long-term antipsychotic use to provide preliminary insights regarding RDs that may be attributable to duration of antipsychotic use. Also, exploring factors associated with EPS and obesity may allow identification of and possible interventions for high-risk groups for these two adverse outcomes. Finally, the unique dataset that combines the PA registry data and Medicaid administrative billing records allows us to harness the strengths of both data sources. Children's antipsychotic use was measured based on detailed prescription fill records; their mental conditions were based on clinician assessments in the registry data, which is considered more reliable than diagnostic codes in administrative data (Davis et al. 2016).

While our current study provided an insight into the risk of physical outcomes associated with antipsychotic use, several limitations should be noted. This study is a case series design, and the findings are limited in quantifying the risk attributable to antipsychotic use due to the lack of a comparison group (i.e., nonuser groups), lack of a full range of risk factors that act as potential confounders (e.g., characteristics influencing children's growth, family disease history and environments, and quality of medical care), and a relatively small sample. Importantly, it is necessary to differentiate the impact of antipsychotic exposure and other causes, especially obesity as children advance in age, on the risk of adverse drug events. Future work that uses large-scale and comprehensive data are needed to ensure a sufficient sample to quantify the onset of rare adverse effects in short-term and long-term users of antipsychotics. In addition, this study relied on ICD-9-CM diagnosis codes in Medicaid claims data to ascertain the incidences of physical health outcomes, without using registry data due to missing data on the physical outcomes. Thus, these conditions may be underestimated if not detected/recorded in claims data. In particular, the use of ICD-9-CM codes to detect obesity and akathisia likely leads to underestimates (Hirose 2003; Kuhle et al. 2011). Future work to incorporate clinical measures, such as BMI for physical outcomes is needed to improve case identification. Finally, in November 2010, prescriptions for high-dose antipsychotics among Florida Medicaid preschoolers also require a PA (Florida Medicaid Agency for Healthcare Administration 2011). However, this additional PA requirement had limited impact on our incidence estimates, because few (e.g., 0.3% of the obesity cohort) had gone through high-dose antipsychotic evaluations documented in the PA registry.

Conclusion

EPS and obesity were the most frequent adverse outcomes in preschoolers with PA-approved antipsychotic use, whereas incidence rates for ventricular arrhythmia, other cardiovascular side effects, hyperprolactinemia, parkinsonism, and tardive dyskinesia were extremely rare. Incidence rates of EPS and obesity differed by treatment duration and several risk factors. Our preliminary findings warrant further analysis in large samples, including control groups that allow examination of background risk and more comprehensive consideration of confounding factors. Future controlled studies are necessary to quantify the risk of adverse outcomes associated with antipsychotic exposure and to examine the effect of treatment initiation in the early versus later childhood.

Clinical Significance

When prescribing antipsychotics to preschoolers, pediatricians should closely monitor and assess risks for physical complications, especially EPS and obesity during the course of the treatment.

Disclosures

All authors have no conflicts of interest.

References

- Abouzaid S, Tian H, Zhou H, Kahler KH, Harris M, Kim E: Economic burden associated with extrapyramidal symptoms in a medicaid population with schizophrenia. *Community Ment Health J* 50:51–58, 2014.
- Alker J, Hoadley J: Medicaid Managed Care in Florida: Federal Waiver Approval and Implementation. 2013. Available from: http://ccf.georgetown.edu/wp-content/uploads/2013/10/Florida-Medicaid-Brief_Fall2013.pdf (accessed April 4, 2017).
- Constantine RJ, Jentz S, Bengtson M, McPherson M, Andel R, Jones MB: Exposure to antipsychotic medications over a 4-year period among children who initiated antipsychotic treatment before their sixth birthday. *Pharmacoepidemiol Drug Saf* 21:152–160, 2012.
- Correll CU, Kane JM: One-year incidence rates of tardive dyskinesia in children and adolescents treated with second-generation antipsychotics: A systematic review. *J Child Adolesc Psychopharmacol* 17:647–656, 2007.
- Davis KA, Sudlow CL, Hotopf M: Can mental health diagnoses in administrative data be used for research? A systematic review of the accuracy of routinely collected diagnoses. *BMC Psychiatry* 16:263, 2016.
- De Hert M, Dobbelaere M, Sheridan EM, Cohen D, Correll CU: Metabolic and endocrine adverse effects of second-generation antipsychotics in children and adolescents: A systematic review of randomized, placebo controlled trials and guidelines for clinical practice. *Eur Psychiatry* 26:144–158, 2011.
- Florida Medicaid Agency for Healthcare Administration: Medicaid Prescribed Drug Program: Spending Control Initiatives. 2011. Available from: www.fdhc.state.fl.us/Medicaid/Prescribed_Drug/pdf/SFY_1011_Q3Q4_FINAL.pdf Accessed April 17, 2017.
- Grégoire J-P, Moisan J: Assessment of adherence to drug treatment in database research. In: B.W. Drug Utilization Research: Methods and Applications. Edited by Elseviers M, Almarsdóttir AB, Andersen M, Benko R, Bennie M, Eriksson I, Godman B, Krska J, Poluzzi E, Taxis K, Vlahović-Palčevski V, Stichele RV. Chichester, UK, John Wiley & Sons, Ltd, 2016.
- Hirose S: The causes of underdiagnosing akathisia. *Schizophr Bull* 29:547–558, 2003.
- Howland RH: Potential adverse effects of discontinuing psychotropic drugs. Part 3: Antipsychotic, dopaminergic, and mood-stabilizing drugs. *J Psychosoc Nurs Ment Health Serv* 48:11–14, 2010.
- Kuhle S, Kirk SF, Ohinmaa A, Veugelers PJ: Comparison of ICD code-based diagnosis of obesity with measured obesity in children and the implications for health care cost estimates. *BMC Med Res Methodol* 11:173, 2011.
- Laita P, Cifuentes A, Doll A, Llorente C, Cortes I, Parellada M, Moreno D, Ruiz-Sancho A, Graell M, Arango C: Antipsychotic-related abnormal involuntary movements and metabolic and endocrine side effects in children and adolescents. *J Child Adolesc Psychopharmacol* 17:487–502, 2007.
- Lieberman JA, 3rd.: Metabolic changes associated with antipsychotic use. *Prim Care Companion J Clin Psychiatry* 6(Suppl 2):8–13, 2004.
- Mathews M, Gratz S, Adetunji B, George V, Basil B: Antipsychotic-induced movement disorders: Evaluation and treatment. *Psychiatry (Edgmont)* 2:36–41, 2005.
- Ogden CL, Carroll MD, Kit BK, Flegal KM: Prevalence of childhood and adult obesity in the United States, 2011–2012. *JAMA* 311:806–814, 2014.
- Olfson M, Crystal S, Huang C, Gerhard T: Trends in antipsychotic drug use by very young, privately insured children. *J Am Acad Child Adolesc Psychiatry* 49:13–23, 2010.
- Ormerod S, McDowell SE, Coleman JJ, Ferner RE: Ethnic differences in the risks of adverse reactions to drugs used in the treatment of psychoses and depression: A systematic review and meta-analysis. *Drug Saf* 31:597–607, 2008.
- Patel NC, Sanchez RJ, Johnsrud MT, Crismon ML: Trends in antipsychotic use in a Texas medicaid population of children and adolescents: 1996 to 2000. *J Child Adolesc Psychopharmacol* 12: 221–229, 2002.
- Rubin DM, Kreider AR, Matone M, Huang YS, Feudtner C, Ross ME, Localio AR: Risk for incident diabetes mellitus following initiation of second-generation antipsychotics among Medicaid-enrolled youths. *JAMA Pediatr* 169:e150285, 2015.
- Schmid I, Burcu M, Zito JM: Medicaid prior authorization policies for pediatric use of antipsychotic medications. *JAMA* 313:966–968, 2015.
- The Centers for Medicare and Medicaid Services (CMS): Chronic Conditions Data Warehouse: Condition Categories. 2007. Available from: www.cdwdata.org/web/guest/condition-categories Accessed May 11, 2016.
- Zito JM, Safer DJ, Valluri S, Gardner JF, Korelitz JJ, Mattison DR: Psychotherapeutic medication prevalence in Medicaid-insured preschoolers. *J Child Adolesc Psychopharmacol* 17:195–203, 2007.

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