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Stimulants Do Not Increase the Risk of Seizure-Related Hospitalizations in Children with Epilepsy

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Abstract

Objective: To evaluate the safety of stimulants in children with epilepsy.
Methods: In a retrospective cohort study based on Medicaid Analytic eXtract billing records from 26 U.S. states from 1999 to 2010, we identified incident stimulant use among children with epilepsy through outpatient encounter claims and pharmacy claims. We established a control group of nonusers and used frequency matching to generate index dates. We followed both cohorts for 12 months and calculated hazard ratios [HRs] of current and former use of stimulants versus no use on the outcome of seizure-related hospitalization using multivariate Cox proportional hazard models.
Results: We identified 18,166 stimulant users and 54,197 nonusers in children with epilepsy. The incidence of seizure-related hospitalization in current stimulant users, former users, and nonusers was 3.6, 3.5, and 4.3 per 100 patient-years. After adjustment for confounders, we found current and former use of stimulants did not increase seizure-related hospitalizations (HR 0.95, 95% confidence interval [CI]: 0.83, 1.09 and HR 0.99, 95% CI: 0.85, 1.15). Children with cerebral palsy, congenital nervous system anomalies, or intellectual disability did not have significantly higher HRs than those without the already mentioned comorbidities.
Conclusion: This study has not identified any overall increase in the rate of seizure-related hospitalizations with the use of stimulants in children with epilepsy.

Keywords: epilepsy, ADHD, stimulants, children, safety, Medicaid

Introduction

Epilepsy is one of the most common neurological disorders in children in the United States (Russ et al. 2012), affecting 0.5%–1.0% of children <16 years (Shinnar and Pellock 2002). Based on CDC estimates from the 2007 National Survey of Children's Health, ~470,000 children in the United States have epilepsy (CDC 2014).

Attention-deficit/hyperactivity disorder (ADHD) is the most common psychiatric comorbidity in children with epilepsy. About 23%–40% of children with epilepsy have ADHD (Cohen et al. 2013; Reilly 2014). Stimulants including methylphenidate and mixed amphetamine salts are the first-line therapy for childhood ADHD; however, stimulants may have a potential to lower seizure threshold and increase the risk of uncontrolled or breakthrough seizures (Stevens et al. 2013). The high prevalence of ADHD and the potential proconvulsant effects of stimulants call for studies to evaluate the safety of stimulants in this vulnerable patient population.

This clear need notwithstanding, the evaluation of stimulant safety in children with epilepsy faces several challenges. Clinical trials of stimulants for ADHD treatment, such as the major MTA study, have generally excluded children with epilepsy because of concern about possible risk of seizure exacerbation (MTA Group 1999a, b; Jadad et al. 1999; Pearson et al. 2013; Yatsuga et al. 2014; Shang et al. 2015; Slama et al. 2015; Kang et al. 2016; Ravi and Ickowicz 2016). Clinical trials or observational studies focusing on stimulant treatment for ADHD in children with epilepsy had common limitations of low baseline seizure rates, small sample size, and short observation periods (Torres et al. 2008; Santos et al. 2013; Ravi and Ickowicz 2016; Williams et al. 2016). The statement that stimulants seem safe for ADHD treatment in children with epilepsy needs support from large population-based studies (Ravi and Ickowicz 2016; Williams et al. 2016).

This study aimed to evaluate the safety of stimulants in children with epilepsy using a large administrative database. Because hospitalization in patients with uncontrolled epilepsy is 5.4–6.7 times more likely than those with well-controlled epilepsy (Manjunath et al. 2012), and seizures resulting in hospitalization have been used as an important outcome to measure seizure recurrence (Shcherbakova et al. 2014), we used seizure-related hospitalization

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as the outcome to evaluate the safety of stimulants in children with epilepsy.

Methods

Data source and study population

This is a retrospective cohort study based on Medicaid Analytic eXtract (MAX) files from 26 U.S. states from 1999 to 2010. The study was approved by the University of Florida and Centers for Medicare and Medicaid Services (CMS) Institutional Review and Privacy Boards. Medicaid is a Federal State-funded program of national health assistance that provides healthcare coverage to certain individuals and families with low income and resources in the United States (The National Pharmaceutical Council 2007). As the largest public insurance provider for children and adolescents, Medicaid has the richest healthcare utilization information for children and adolescents. As of 2011, the number of pediatric Medicaid beneficiaries reached 32,662,000 (CMS 2013). MAX provides demographic and enrollment details, diagnoses, and procedures associated with in- and outpatient encounters and pharmacy dispensing billing records. It has been used to provide data to a variety of drug safety concerns including the safety of psychotropic medications (Leonard et al. 2011, 2013; Callahan et al. 2013; Ross et al. 2015).

The study cohort was children aged 3–18 years with at least two outpatient encounter claims for epilepsy (ICD-9-CM codes: 345.xx) with at least 30 days apart in 2 years (Reid et al. 2012). The first day of stimulant dispensing after the second diagnosis of epilepsy was set as the index date for stimulant users, before which there should be a minimum of 6 months of continuous Medicaid Fee-for-Service (FFS) enrollment. As nonusers did not have index dates, we used frequency matching to designate index dates for nonusers to ensure the same distribution of intervals between the second epilepsy outpatient diagnosis and index date (Supplementary Appendix S1; Supplementary Data are available online at www.liebertpub.com/cap). All 3- to 18-year-old children with epilepsy were eligible for being selected into the nonuser group. Stimulant prescriptions before the second encounter claim of epilepsy were allowed, as long as there was a 6-month stimulant-free period before the index date.

Children with epilepsy-related hospitalizations (ICD-9-CM codes: 345.xx) during the baseline period for both stimulant users and nonusers were excluded because that was the study outcome. Also excluded were children with brain tumor-related epilepsy (Maschio 2012), central nervous system (CNS) infection-related epilepsy (Singhi 2011), and substance abuse disorder (Koppel et al. 1996; Gordon and Devinsky 2001; Zagnoni and Albano 2002) during the baseline period. Brain tumor and CNS infections were measured based on ICD-9-CM codes for in- and outpatient encounter claims (Supplementary Appendix S2). Substance use disorder was measured based on the methods employed in the Medicaid Substance Abuse Treatment Spending: Findings Report (Bouchery et al. 2012). We excluded patients with brain tumor-related epilepsy because the antitumor treatment regimen complicates seizure control, and this type of epilepsy is often drug resistant (Maschio 2012). We excluded patients with CNS infection-related epilepsy (Singhi 2011) because of different etiology and seizure control in this patient population. We excluded patients with substance abuse disorder because substance abuse, including alcohol, cocaine, marijuana, narcotics, nicotine, and caffeine, may exacerbate seizures in patients with epilepsy in various circumstances (Koppel et al. 1996; Gordon and Devinsky 2001; Zagnoni and Albano 2002).

Measurement of exposure

National Drug Code in pharmacy claims was used to measure stimulant exposure (methylphenidate and amphetamine salts). We grouped methylphenidate and amphetamine salts into stimulants and did not analyze them separately because the study did not have adequate power to do so and their neurochemical mechanisms of action are similar. Total pharmacy dispensed days' supply, including a 10-day extension, was used to measure the duration of treatment. The extension of 10 days accounted for late refills that would erroneously flag treatment interruptions. Treatment was assumed to be continuous as long as the next prescription was filled within the active days' supply (dispensed days' supply with a 10-day extension) of the previous one. Time covered by stimulant fills was defined as current use. Gaps between the last day of a continuous treatment period and the first day of the next treatment period were defined as former use. Because exposure measurement was subjected to misclassification between ''use'' and ''nonuse'' periods for stimulant users, we labeled the nonuse periods in users as ''former use,'' which served as an intermediate state between ''use'' and ''nonuse.'' The examination of former use might also help estimate the magnitude of residual confounding. A significantly increased risk found in former use might indicate not well-uncontrolled confounding.

Study endpoint

We used seizure-related hospitalization (ICD-9-CM codes: 345.xx or 780.39, principal diagnosis) as the study outcome.

Measurement of covariates/confounders

We selected the following covariates as potential confounders based on previous literature. Demographic characteristics (gender, race, and date of birth) were ascertained from enrollment data and adjusted for in the model to control for confounding. State of residence (Shcherbakova et al. 2014) and calendar year for each patient were extracted based on location and time at index date. Enrollment data also provided reasons for Medicaid eligibility, which allowed for the determination of foster care, families receiving cash assistance, with poverty and disability. We measured the comorbidities based on ICD-9-CM codes during the baseline period. Any in- or outpatient claim was sufficient to label the children as having that comorbidity.

We measured epilepsy type and severity based on the epilepsy diagnosis closest to the index date using ICD-9-CM codes as well (Supplementary Appendix S2). Validation studies have shown that ICD-9-CM coding to identify grand mal status (345.3x) and partial epilepsy with complex partial seizures (345.4x) had positive predictive values (PPVs) >75%, but the PPVs for other types of epilepsy are low or unavailable (Jette et al. 2010). Therefore, the misclassification of epilepsy subtypes and severity in claims databases should be considered when interpreting the results.

We also measured antiepileptic drugs (AEDs), the number of unique AEDs, AED medication possession ratio, and drugs that may have an independent risk for seizures at baseline (Supplementary Appendix S3).

Statistical analysis

We had performed a power analysis before the study was conducted. To detect a hazard ratio (HR) of 1.2 in stimulant users and nonusers (sample size ratio = 1:3) with type I error of 0.05 and

Table 1. Demographic, Clinical, and Drug Use Characteristics of Study Population

	Stimulant users	*Stimulant nonusers*
Number of patients	18,166	54,917
Gender		
Male (%)	67.0	54.5
Race/ethnicity		
White (%)	52.1	45.1
Black (%)	24.9	26.6
Other (%)	23.0	28.3
Age		
≤5 (%)	8.2	12.2
6–9 (%)	41.0	25.7
10–14 (%)	35.0	32.0
15–18 (%)	15.8	30.1
Medicaid eligibility category		
Foster care (%)	12.4	7.3
Cash assistance (%)	61.4	64.2
Poverty (%)	30.3	25.7
Disability (%)	53.9	62.6
Comorbidities at baseline		
Cerebral palsy (%)	15.7	36.2
Congenital nervous system anomalies (%)	11.2	19.8
Intellectual disability (ID) (%)	29.8	39.7
Head trauma (%)	2.0	1.3
ADHD/adjustment disorders (%)	58.5	10.9
Anxiety (%)	6.4	2.8
Autism (%)	21.9	14.2
Bipolar disorder (%)	6.6	2.0
Depression (%)	6.9	3.1
Oppositional defiant disorder/conduct disorder (%)	20.6	6.3
Schizophrenia (%)	2.1	1.1
Sleep disorder (%)	4.8	2.7
Epilepsy types at baseline		
Generalized nonconvulsive (%)	12.9	10.3
Generalized convulsive (%)	21.5	25.1
Focal (%)	33.9	29.2
Other (%)	31.8	35.4
Epilepsy severity at baseline		
Intractable (%)	16.3	17.4
Nonintractable (%)	75.6	73.0
Unknown (%)	8.1	9.6
Number of AEDs at baseline		
Mean (standard deviation)	1.2 (1.1)	1.3 (1.1)
AED medication possession ratio at baseline		
0 (%)	30.2	27.2
0.80–1.00 (%)	41.4	50.3
0.01–0.79 (%)	28.4	22.6
AED at baseline (>0.5%)		
Carbamazepine (%)	17.2	18.6
Clonazepam (%)	3.0	5.5
Diazepam (%)	6.1	9.6
Divalproex (%)	28.0	23.9
Ethosuximide (%)	1.7	1.5
Felbamate (%)	0.5	0.9
Gabapentin (%)	2.3	2.4
Lamotrigine (%)	9.3	9.6
Levetiracetam (%)	6.3	9.4
Lorazepam (%)	1.6	2.4
Oxcarbazepine (%)	10.8	8.4
Phenobarbital (%)	2.8	10.0
Phenytoin (%)	2.9	4.9
Topiramate (%)	8.6	10.5
Zonisamide (%)	2.8	3.5
Drugs that may increase the seizure risk (prevalence ≥1%)		
Amoxicillin (%)	26.5	26.0
Ciprofloxacin (%)	3.0	3.8
Desmopressin (%)	2.7	1.0
Ofloxacin (%)	1.9	2.3
Non-AED psychotropic drugs at baseline		
Selective serotonin reuptake inhibitors (SSRIs) (%)	8.9	4.3
Non-SSRI antidepressants (%)	7.0	3.3
Atypical antipsychotics (AAPs) (%)	19.0	8.0
Other antipsychotics (non-AAPs) (%)	1.3	0.9

ADHD, attention-deficit/hyperactivity disorder; AED, antiepileptic drug.

type II error 0.20 accepted, we would need 1259 events (seizure-related hospitalizations) for this study (UCSF, 2017).

We followed the patients until seizure-related hospitalization, 1 year after the index date, the end of the study period, the end of enrollment in Medicaid FFS, their 19th birthday, hospitalization >30 days due to other reasons, or death, whichever came first. A maximum follow-up time of 1 year was set based on previous literature, in which the follow-up period varies from 4 weeks to 1 year (Ravi and Ickowicz 2016). We did not extend our follow-up period beyond 1 year because we speculate seizure-related hospitalization may be less likely to be caused by stimulant after 1-year use. As stimulant users may have less severe seizures and lower risk of seizure-related hospitalization than nonusers, seizure severity is an important confounder to consider. We did a sensitivity analysis with varied seizure severity in stimulant users and nonusers to examine the robustness of the results.

We used multivariate Cox proportional hazards models to calculate the HRs of the current user and former use versus no use of stimulants (Supplementary Appendix S4). The statistical significance level of 0.05 was used in the model without any interaction terms. The statistical significance level of 0.01 was used for other interaction tests under Bonferroni correction (0.05/5). The tests were all two tailed.

All analyses were performed with SAS 9.4 (Cary, NY).

Results

We identified 18,166 stimulant users and 54,917 nonusers to evaluate the safety of stimulants in children with epilepsy. The intervals between the second diagnosis of epilepsy and the index date were 827 (standard deviation [SD], 748; median, 611) days and 855 days (SD, 750; median, 631) for stimulant users and nonusers, respectively. The standardized mean difference of the intervals was 3.72% (<10%), indicating a negligible difference (Austin 2011). Among 18,166 stimulant users, 9622 (53.0%) had used amphetamine salts, 11,504 had used methylphenidate (63.3%), and 2961 (16.3%) had used both. Table 1 shows the demographic and clinical risk factor distribution of the study population.

There were 15,445 patients (85.0%) among 18,166 stimulant users who had both current use and former use periods. Table 2 shows the number of hospitalizations due to seizures, total follow-up time, and event rates. Although current use was related to a lower risk of hospitalization in the unadjusted model (3.5/100 vs. 4.3/100), after adjustment for demographic and clinical confounders, stimulants were not associated with an increased risk of seizure-related hospitalization (HR, 0.95, 95% CI 0.83, 1.09). The complete parameter estimates of the model are included in Supplementary Appendix S5.

Table 3 shows the results of testing the interactions between stimulant use and epilepsy type, epilepsy severity, cerebral palsy, congenital nervous system anomalies, or intellectual disability (ID). No significant interaction was detected, except that stimulant users with intractable epilepsy have a slightly higher risk of seizure-related hospitalizations on the significance of 0.05, but not 0.01.

Table 4 shows the results of sensitivity analysis, where we manipulated the proportion of intractable epilepsy in stimulant users and nonusers. To reflect clinical practice and get conservative results for the safety of stimulants, we made the proportion of intractable epilepsy consistently lower in stimulant users than in nonusers. The results showed that even if we assume that the proportion of intractable epilepsy in stimulant users be 5% and in nonusers be 80%, the HR of current use versus never use is still not significantly >1.0 (HR = 1.12, 95% CI 0.95, 1.34). This sensitivity analysis shows the robustness of the study results.

Discussion

We did not observe an increased risk of seizure-related hospitalization in children with epilepsy and psychostimulant use. The HRs were not significantly different among patients with or without cerebral palsy, congenital nervous system anomalies, or ID. Epilepsy type and severity did not have a significant impact on the effect of stimulants either.

Most previous studies suggested that stimulants might be safe in children with epilepsy; however, they have been inconclusive due to small sample size (<100), resulting in problems of underpowering or limited generalizability (Feldman et al. 1989; Wroblewski et al. 1992; Gross-Tsur, et al. 1997; Semrud-Clikeman and Wical 1999; Gucuyener et al. 2003; Yoo et al. 2009; Koneski et al. 2011; Fosi et al. 2013; Santos et al. 2013; Radziuk et al. 2015). One study that found an association between higher doses of stimulants and worsening seizure control was also underpowered ($n = 33$) (Gonzalez-Heydrich et al. 2010).

The raw incidence of seizure-related hospitalization was 4.3/100 patient-years in nonusers and 3.5/100 patient-years in stimulant users, suggesting that stimulant treatment may be channeled to patients with better epilepsy control or with less severe seizures. To address the channeling bias and control for confounding, we adjusted for patient demographic characteristics, epilepsy type and severity, comorbidities, and epilepsy management in the model. After adjustment, the HRs increased to 0.95 (95% CI 0.83, 1.09) and 0.99 (95% CI 0.86, 1.15) for current and former use, respectively. Although there might be residual confounding, it is noteworthy that our adjustment removed the protective effects of stimulants that we observed in the unadjusted model. Residual confounding would need to be so robust that it pushed the HR beyond 1. The sensitivity analysis also shows the robustness of the results. Thus, this study provides some evidence that stimulants, as used in current clinical practice, do not increase the risk of seizure-related hospitalizations.

No significant effect modifiers were detected for the safety of stimulants in children with epilepsy. Our data indicated that physicians prescribed fewer stimulants to children with those three comorbidities, and it remains unknown if this prescribing behavior

Table 2. Unadjusted and Adjusted Hazard Ratios of Current and Former Use of Stimulants Versus No Use on the Outcome of Seizure-Related Hospitalizations

Exposure	*Number of events*	*Event rates (per 100 patient-years)*	*Model*	*Hazard ratio*	*95% CI*
Current use	306	3.5	Unadjusted	0.78	0.69, 0.88
			Adjusted	0.95	0.83, 1.09
Former use	243	3.6	Unadjusted	0.89	0.78, 1.02
			Adjusted	0.99	0.86, 1.15
No use	1946	4.3	Reference	Reference	Reference

CI, confidence interval.

Table 3. Interaction Between Stimulant Use and Cerebral Palsy, Congenital Nervous System Anomalies, and Intellectual Disability on the Outcome of Seizure-Related Hospitalizations

	Exposure			
	Current vs. no use		*Former vs. no use*	
Patient characteristics	*Hazard ratio*	*95% CI*	*Hazard ratio*	*95% CI*
All	0.95	0.83, 1.09	0.99	0.86, 1.15
Cerebral palsy	1.06	0.82, 1.35	1.15	0.90, 1.48
No cerebral palsy	0.91	0.78, 1.06	0.93	0.78, 1.10
Congenital nervous system anomalies	1.12	0.85, 1.47	1.07	0.78, 1.45
No congenital nervous system anomalies	0.91	0.78, 1.05	0.97	0.82, 1.14
ID	1.04	0.86, 1.26	1.12	0.92, 1.37
No ID	0.87	0.73, 1.04	0.88	0.72, 1.08
Generalized nonconvulsive	0.77	0.51, 1.17	1.28	0.87, 1.89
Generalized convulsive	1.06	0.82, 1.36	1.09	0.83, 1.43
Focal	1.00	0.80, 1.24	0.97	0.76, 1.24
Other	0.88	0.71, 1.10	0.86	0.67, 1.10
No intractable epilepsy mentioned	0.86	0.73, 1.01	0.97	0.81, 1.15
Intractable	1.26	1.00, 1.59	1.12	0.86, 1.45
Unspecified severity	0.77	0.48, 1.22	0.84	0.52, 1.35

CI, confidence interval.

Table 4. Sensitivity Analysis by Varying Epilepsy Severity

Sensitivity analysis no.	*Percentage of patients with intractable epilepsy in stimulant users*	*Percentage of patients with intractable epilepsy in nonusers*	*Hazard ratio (95%) of current use of stimulant vs. never use, adjusted*
1	5.0	20.0	0.98 (0.86, 1.13)
2	5.0	40.0	1.01 (0.88, 1.17)
3	5.0	80.0	1.12 (0.95, 1.34)

was due to the theoretical concerns that stimulants may lower seizure threshold and exacerbate seizures. The only concerning HR was that for children with intractable epilepsy (1.26, 95% CI 1.00, 1.59). This finding needs to be re-examined by other studies.

Our study has several strengths. First, we used the Medicaid database from 26 U.S. states to establish a large population-based cohort of children with epilepsy, resulting in an adequate power and significant generalizability in the Medicaid population. Second, a new user design was employed to eliminate prior experiences with the effect of stimulants on seizure control, which may have removed susceptible children from the analysis. Third, our primary outcome was based on an objective measure of hospitalization. Subjectively worsening seizure control could be measured through patient self-report of seizure frequency or severity and proxies of healthcare utilization such as hospitalizations, which are thought to indicate that the seizure is severe and requires extensive intervention per a physician's perception. Also, hospitalizations by nature have public health significance.

Despite the strengths, there were several limitations such as the fact that pharmacy claims still do not reflect actual drug exposure and such exposure misclassification may dilute differences between exposed and unexposed groups and bias the results toward the null. The 6-month baseline period without stimulant use might misclassify prevalent users as new users, and older children were more likely to be prevalent users than younger children even though both met the inclusion criteria. In addition, we were not able to examine methylphenidate and amphetamines separately or compare different doses, which was further complicated by missing information on patients' weight in claims data. Thus, the analyses represent the mean risk of the most commonly used stimulants with the most commonly used doses in clinical practice. Another limitation of this study is that we could not capture mildly or moderately increased seizure activity that did not lead to hospitalization.

Conclusion

Current or former use of stimulants was not associated with an increased risk of seizure-related hospitalization after controlling for demographic and clinical characteristics. Epilepsy type, epilepsy severity, cerebral palsy, congenital nervous system anomalies, ID, epilepsy types, and severity do not modify the risk of seizure-related hospitalizations for stimulants.

Clinical Significance

This study has not identified any overall increase in the rate of seizure-related hospitalizations with the use of stimulants in children with epilepsy.

Disclosure

Findings are part of Dr. X.L.'s doctoral dissertation.

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