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Medication treatment for attention-deficit/hyperactivity disorder and the risk of acute seizures in individuals with epilepsy

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Abstract

Objective: Attention-deficit/hyperactivity disorder (ADHD) affects 10–30% of patients with epilepsy, yet concerns remain regarding the safety of ADHD-medication treatment in this group. The objective of this study was to examine the risk of acute seizures associated with ADHD medication-treatment in individuals with epilepsy.

Methods: 21,557 individuals with a seizure history born 1987–2003 were identified from Swedish population registers. Within this group, we also identified 6773 youth (<19 years) who meet criteria for epilepsy, and 1605 youth with continuous antiepileptic drug(AED) treatment. ADHD-medication initiation and repeated medication periods were identified from the Prescribed Drug Register between January 1, 2006–December 31, 2013. Acute seizures were identified via unplanned visits to hospital or specialist care with a primary seizure discharge diagnosis in the National Patient Register during the same period. Conditional Poisson regression was used to estimate the seizure rate associated with ADHD-medication initiation, and Cox regression to estimate the seizure rate during ADHD-medication periods. Within-individual designs were used to adjust for unmeasured, time-constant confounding.

Results: Among 995 individuals with ADHD-medication initiation during follow-up, within-individual analyses showed no statistically significant difference in the rate of seizures during the 24 weeks pre-and-post medication initiation, compared to the same period in the previous year. In

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Disclosures

Drs Brikell, Chen, Kuja-Halkola, D'Onofrio, Almqvist, Quinn, Chang, and Mrs. Wiggs have no disclosures to report. Dr H Larsson has served as a speaker for Eli-Lilly and Shire and has received research grants from Shire; all outside the submitted work. Dr P Lichtenstein has served as a speaker for Medice; all outside the submitted work.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

the full cohort 11,754 seizure events occurred during 136,846 person-years and 1855 individuals had at least one ADHD-medication period. ADHD-medication periods were associated with a reduced rate of acute seizures (HR=0.73, 95%CI 0.57–0.94), compared to non-medicated periods within the same individual. Similar associations were found in youth with epilepsy and continuous AED treatment, across sex, age, comorbid neurodevelopmental disorders, and when adjusting for AEDs.

Keywords

Seizures; ADHD; Epilepsy; ADHD Seizures; pharmacoepidemiology; methylphenidate; treatment; neurodevelopmental disorders

Introduction

Epilepsy patients have a 3-to-5-fold increased risk of attention-deficit/hyperactivity disorder (ADHD) diagnosis,^{1–3} and as many as 20–50% of children with epilepsy exhibit subclinical ADHD symptoms.⁴ Untreated, ADHD is associated with severe adverse outcomes,^{5–8} making effective treatment crucial. Yet there are concerns regarding the safety of ADHD medication treatment among individuals with epilepsy; North American and European regulatory agencies caution that stimulants may lower the convulsive threshold and should be discontinued if seizure frequency increases.⁹ However, the empirical evidence for an increased risk of seizures related to ADHD medication is varied and debated, with some studies reporting small risk increases and others reporting null effects, or even potential protective effects, of ADHD treatment on seizure frequency.⁴

At least two small open-label trials, one observational study, and two double-blinded trials have examined the risk of seizures in relation to stimulant ADHD medications, with little evidence for an increased risk in individuals with well-controlled epilepsy.^{10–14} Further, one open-label trial reported that methylphenidates, one of the most commonly used ADHD stimulant medications, were safe for patients with difficult-to-treat epilepsies.¹⁵ Further, one retrospective study reported a decreased seizure frequency associated with methylphenidate treatment in patients with brain injury and active seizures.¹⁶ Other studies have reported inconclusive results due to limited sample size or potential evidence of seizure exacerbation in patients with active epilepsy.^{17–19} One clinical and three observational studies have investigated the association between atomoxetine, a non-stimulant ADHD medication, and seizures, with no evidence of seizure exacerbation.^{20–23} However, many of the previous studies were conducted in small clinical samples,^{12–15; 18–20} focused on seizure free populations,^{17; 22} and/or were not fully able to control for confounding factors that can vary between individuals (e.g., shared liability towards ADHD and epilepsy, disorder severity) and may lead to spurious associations between ADHD medication and seizures. Some of these concerns were addressed in a recent large US healthcare claims study, using a within-individual design to compare the risk of seizures during ADHD medicated and non-medicated periods within the same person. Results suggested that ADHD medicated periods were associated with a reduced risk of seizure in patients with and without seizure history.²⁴ Although well powered, the study was not without limitations; commercial healthcare claims databases are not population representative, information on treatment and seizure history

was limited, and comorbid neurodevelopment disorders (NDDs) were not considered. Polypharmacy may be of particular concern in individuals with NDD multi-morbidity, stressing the need to evaluate ADHD medication safety in this patient group. The observed negative association between ADHD medication and seizures also warrants further investigation. Patients with a seizure history may be more likely to be prescribed ADHD medication in periods of low seizure risk, thus possibly inducing a false protective effect. Further, several recent studies have reported the risk of adverse events, including seizures, to be elevated immediately prior to medication initiation, which could influence the estimated relative risk associated with starting medication treatment.^{25; 26} It is therefore important to further investigate the safety of ADHD medication in samples with more detailed information on seizure history and concurrent antiepileptic drug (AED) treatment, comorbid NDDs, and timing of ADHD medication initiation. To address this, we used nationwide Swedish register data and within-individual comparisons to assess the risk of acute seizures associated with both ADHD medication initiation and repeated ADHD medication periods among individuals with epilepsy with and without comorbid NDDs.

Method

Study population

We identified individuals born between 1987–2003 who were living in Sweden during follow-up and had experienced at least one seizure according to discharge diagnoses from the Swedish National Patient Register (NPR). The NPR has nationwide coverage for inpatient care since 1987 and outpatient care since 2001.²⁷ Diagnoses are coded according to the International Classification of Diseases (ICD) 9th (1987–1996) and 10th revision (1997-onwards). Inclusion criterion was at least one in- or outpatient diagnosis for any seizure event (ICD-9 345; ICD-10 G40&G41). The NPR only includes hospitals and specialist care visits, and is therefore likely to capture more severe seizures. However, individuals with epilepsy treated in primary care may not be detected. We therefore also included information on AED dispensations to define the start of follow-up. AEDs were identified using the Prescribed Drug Register (PDR), which includes all medication dispensations in Sweden since mid-2005 coded according to the Anatomical Therapeutic Chemical (ATC) classification system.²⁸ In line with previous research,^{29–31} AEDs were defined as any drug belonging to ATC class N03A (antiepileptic). In the study population, 12% (N=2584) had at least one AED dispensation in the PDR prior to their first recorded seizure in the NPR. For this reason, individuals were followed from their first seizure diagnosis in NPR or AED dispensation in the PDR (whichever occurred first), 1 January 2006, or their 5th birthday, whichever came last. Follow-up ended on the 31 December 2013 or death, whichever came first. Demographic information was obtained from the Total Population Register, the Migration Register and the Cause of Death Register. Individuals who migrated during follow-up were excluded, resulting in a study population of 21,557 individuals, representing 92% of the study base. From this study population (born 1987–2003), we further defined two sub-cohorts in order to study the risk of seizures associated with ADHD medications in youth who meet criteria for epilepsy according to the current International League against Epilepsy (ILAE) definition (at least two seizures occurring >24 h apart).³² We identified individuals born 1995–2003 who were < 19 years of age at the end of follow-up (31st

December 2013) and had received at least two primary seizure discharge diagnoses in the NPR (N=6773). From this group, we further identified 1605 individuals with continuous AED treatment throughout the follow-up, as ongoing AED treatment can be considered a proxy for active epilepsy.³³ Figure S1 (supplementary materials) shows a flow diagram of the study population selection.

Exposure

Dispensations of ADHD medications were identified in the PDR. We considered dispensations for all stimulant (Amphetamine [N06BA01], Dexamphetamine [N06BA02], Methylphenidate [N06BA04], Lisdexamphetamine [N06BA12]), and non-stimulant medications (Atomoxetine [N06BA09]) approved for ADHD treatment in Sweden during the study period. Based on dispensation dates, we identified ADHD medication initiation and repeated ADHD medication periods as follows:

ADHD medication initiation was defined as a dispensation of ADHD medication preceded by at least 18 months without a dispensation. Within the study population born 1987–2003, we identified 995 individuals with an ADHD medication initiation between 1 January, 2007 and 30 June, 2013. This period was chosen to ensure at least 18 months without an ADHD medication dispensation prior to the study period and at least six months follow-up after initiation of medication treatment for ADHD.

In line with previous research,^{5; 34; 35} **repeated ADHD medication periods** were defined by at least two consecutive ADHD medication dispensations no longer than 183 days apart. Each medication period started on the date of the first dispensation and ended on the date of the last dispensation. We identified medication periods between January 1, 2006 and December 31, 2013, taking medication dispensations in the six months pre and post follow-up into account to determine medication status at the start and end of follow-up (the PDR was the only register for which we had information until the end of 2014).

Outcome

Outcome event was acute seizures, defined as a seizure severe enough to lead to an unplanned in- or outpatient visit to hospital or specialist care with a primary discharge diagnosis for seizures according to ICD-10 codes in the NPR. This operationalization was selected to capture seizures that required acute treatment, rather than ongoing medical management (i.e., planned visits).

Covariates

We included concurrent AED treatment periods as a time-varying covariate, identified by any dispensation of drugs in ATC class N03A. AED treatment periods were defined in the same manner as repeated ADHD medication periods (see above). We also identified life-time discharge diagnosis in the NPR for ADHD (ICD-9 314, ICD-10 F90), pervasive and specific developmental disorders including autism (ICD-9 299, 315; ICD-10 F80-F89), intellectual disability (ICD-9 317–319; ICD-10 F70-F79), and tic disorders (ICD-9 307; ICD-10 F95). Finally, we included age at the start of each observation period (5–9, 10–14, and 19–26 years) as a categorical time-varying covariate.

Statistical Analyses

ADHD medication initiation

We compared the incidence rate of seizures during the 24 weeks before and after ADHD medication initiation, with the average incidence rate during the same 48 weeks in the previous year.^{26; 36} Follow-up time was split into 1–12 and 13–24 weeks pre- and post-medication initiation. Incidence rate ratios (IRRs) were estimated using conditional Poisson regression, with each individual as a separate stratum. In this way, analyses are adjusted for confounders that are constant in an individual during follow-up including, but not limited to, sex, age at medication initiation, genetic liability for seizures and ADHD, disorder severity, and early-life risk factors. We included AED treatment as a time-varying covariate; AED treatment status (0/1) was constant within individual during each comparison period (i.e., baseline, 24 weeks pre- and 24 weeks post-ADHD medication initiation), but could vary between the periods. As there were no deaths during the 24 weeks following ADHD medication initiation, all individuals had complete follow-up.

Repeated ADHD medication analyses

To estimate the association between ADHD medication and seizures in the full cohort, including information on all ADHD medication dispensations, we first conducted population-level analyses using Cox proportional hazards regression with time since last seizure as the underlying time-scale and cluster robust standard errors to account for correlated data from the same individual. Next, we performed within-individual analyses using stratified Cox proportional hazards regression, where each individual was entered as a separate stratum. In this model, the within-individual hazard ratio is adjusted for confounding by all unmeasured covariates that are constant within-individual during the follow-up. A detailed description of the statistical method is provided elsewhere.³⁵ We first estimated the population and within-individual level association, adjusted for sex and age as a time-varying covariate (model 1). Concurrent AED medications may confound the association between ADHD medication and seizures, and serve as an index for unmeasured confounders such as increased engagement with health services. We therefore included AED medication treatment periods as a time-varying covariate (model 2), so that AED treatment status (0/1) was constant within each time period, but could vary within individual across the follow-up. Further, we ran analyses stratified by concurrent AED treatment status to estimate the risk of seizures associated with ADHD medication, during periods with and without AED medication (model 3). We stratified analyses by sex (model 4). Finally, we ran the analyses among individuals with a diagnosis of ADHD in the NPR (model 5). In this subgroup, we further stratified analyses by the presence or absence of any additional NDD diagnoses (i.e. pervasive and specific developmental disorders including autism, intellectual disability, and tic disorders) (model 6).

Sensitivity Analyses

We conducted several sensitivity analyses to examine the robustness of results from the repeated ADHD medication analyses. In line with previous research,^{5; 34; 35} we tested alternative exposure time and outcome definitions to examine the potential influence of misclassification. First, ADHD medication periods were defined as two consecutive

prescriptions within 90 days, rather than 183 days. Second, 90 days was added to the date of last prescription in each medication period. In these analyses, patients with only one ADHD medication dispensation were assumed to be on treatment during 90 days following the dispensation. The 90 days cut-off for sensitivity analyses was chosen as three months is the maximum quantity of drugs allowed at a single dispensation according to Swedish reimbursement regulations.³¹ Third, we used a stricter outcome definition, including only primary seizure discharge diagnosis linked to unplanned emergency care visits, ambulance rides, or inpatient care requiring overnight stay. Discharge diagnoses for status epilepticus (G41), which by definition is an acute seizure, were also included. Fourth, as concerns regarding seizure risk pertain predominantly to stimulant ADHD medication formulations and stimulants and non-stimulants differ in terms of pharmacological mechanism, we also re-estimated models in stimulant only users. There was not sufficient power to estimate the same models in atomoxetine only users.

Data management was done in SAS version 9.4 (SAS Institute, Inc) and analyses were conducted using the R package Generalized Nonlinear Models ('GNM')³⁷ and STATA version 15.0 (StataCorp LLC).

Ethical approval

The study was approved by the regional ethics review board in Stockholm, Sweden, and all personal information from the registers was anonymized by Statistics Sweden. By Swedish law, there is no requirement for informed consent in register-based research.

Results

ADHD medication initiation analyses

Among the 995 individuals who initiated ADHD medication treatment between January 1, 2007 and June 31, 2013, a total of 83 seizure events occurred in 57 persons during the 24 weeks pre- and post-medication initiation, and 82 seizure events occurred in 60 persons during baseline (i.e., the same 48 week period in previous year). During the study period 487 (49%) individuals were continually treated with AEDs, 407 (41%) untreated, 67 (6%) switched treatment status between baseline and the 24 weeks pre- and post ADHD medication initiation, and 37 (4%) switched AED treatment status between the 24 weeks pre- and post ADHD medication initiation; of these, eight persons went from AED treatment to no treatment. The seizure rate per 1000-person weeks during the 24 weeks pre- and post-medication initiation periods are presented in Figure 1. A total of 41 seizure events occurred during the 24 weeks pre-medication initiation; there was no evidence of increased risk of seizures during 24 to 13 weeks prior to medication (Table 1). The estimated IRR showed a small albeit not statistically significant risk increase in the 12 weeks pre-medication initiation, compared to baseline (IRR 1.16, 95%CI 0.74–1.83). A total of 42 seizure events occurred during the 24 weeks post-medication initiation, with no evidence of an increased seizure risk compared to baseline during the first 12 weeks (IRR 0.95, 95%CI 0.60–1.56) or the 13–24 weeks post-medication initiation (IRR 1.05, 95%CI 0.65–1.68). Reported IRRs are adjusted for concurrent AED treatment; adjustment had little effect on the results.

Confidence intervals for all estimated IRRs were wide and included 1, suggesting the analyses were underpowered.

Repeated ADHD medication analyses

In the full study cohort born 1987–2003, a total of 11,754 seizure events occurred in 21,557 individuals with a seizure history during 136,846 person years of follow-up. Among the 1855 (9%) individuals who received ADHD medications during follow-up, there was a total of 3556 ADHD medication periods. In individuals with at least one medication period, 1661 (90%) also had at least one non-medication period. Table 2 shows baseline characteristics of the study population separately for individuals with and without ADHD medication. Table 3 shows further details on ADHD medicated periods, and AED treatment and seizures around the time of ADHD treatment periods.

Estimates from the Cox regression analyses are presented in Table 4. In model 1, adjusted for age and sex, there was no difference in the rate of seizures during ADHD medicated and non-medicated periods at the population-level (hazard ratio [HR] 1.00, 95%CI 0.78–1.28). Within-individual estimates showed a statistically significant decreased rate of seizures associated with ADHD medication periods (HR 0.73, 95%CI 0.57–0.94). Further adjusting for AED medication periods as a time-varying covariate did not markedly affect the estimates (Model 2: population-level HR 0.94, 95%CI 0.74–1.20; within-individual HR 0.74, 95%CI 0.57–0.94). In model 3, estimates from population-level and within-individual analyses stratified by concurrent AED medication status showed a decreased rate of seizures associated with ADHD-medication periods across strata, although estimates were not statistically significant with confidence intervals including 1. In model 4, estimates stratified by sex were not statistically significantly different at population-level ($p=0.643$), nor within-individual ($p=0.515$). The association between seizures and ADHD medication was similar among individuals with a clinical diagnosis of ADHD to that observed in the full cohort (model 5), and estimates did not differ statistically significantly by the presence or absence of additional NDDs in this subgroup (model 6: population-level $p=0.087$ / within-individual $p=0.307$).

Sensitivity Analyses

Results from sensitivity analyses conducted in the main analysis cohort born 1987–2003 and results from analyses in the sub-cohorts born 1995–2003 are presented in Table 5. In line with the main results, estimates consistently suggested a lower rate of seizures associated with ADHD medication periods in the within-individual analyses (although 95%CI's generally included 1) and no significant association in the population-level analyses. This pattern of results did not differ by exposure definition, either by using a three month cut-off to redefine medication status or by adding 90 days to the end of each medication period and including single dispensation as treatment periods, or when using a stricter outcome definition. Results were also similar in stimulant medication users only.

Analyses in the cohort born 1995–2003 who meet criteria for epilepsy also showed no evidence of an increased risk of acute seizures at the population-level (HR 0.88, 95%CI 0.71–1.10), and a statistically significant decreased rate of seizures associated with ADHD

medication periods in within-individual analysis (HR 0.62, 95%CI 0.44–0.89). Similar results were found in the sub-cohort of individuals who were continually treated with AEDs (population-level HR 0.71, 95%CI 0.54–0.93; within-individual HR 0.63, 95%CI 0.38–1.03)

Discussion

Results from this nationwide register-based study do not support the hypothesis that ADHD medication increases the frequency of seizures. Rather, ADHD medication periods were generally associated with lower risk of acute seizures when comparing seizures rates across medicated and un-medicated periods within the same person. Similar associations were seen when focusing on children and adolescents under the age of 19 years who meet criteria for (lifetime) epilepsy, and in youth with active epilepsy as indicated by continuous AED treatment. Although concerns of pharmaceutical treatment of ADHD in individuals with epilepsy is not limited to childhood, these findings are of importance as ADHD is typically diagnosed in childhood or adolescence, and clinical decisions about initiating ADHD treatment maybe especially challenging among children with active epilepsy.

Our results provide converging evidence with a number of previous studies, but not all,¹⁹ using varying research designs^{10-15; 24} showing limited support for the hypotheses that ADHD medication in prescribed doses is associated with an increased risk of acute seizures. We were also able to expand the previous literature by studying the risk across varying definitions of seizure history and epilepsy, and by including persons with a wide range of NDDs in addition to ADHD, including autism, intellectual disabilities and tics disorders. We did not find evidence that the association between ADHD medication and the risk of acute seizures differed in epilepsy patients with NDD multi-morbidity. This suggests that that stimulants may be a treatment option even in the presence of NDD multi-morbidity, and that future research in this area should not exclude this important patient group.

Investigation of the seizure rate around ADHD medication initiation suggested relatively stable seizure rates during the 24 weeks pre- and post-medication initiation. Within-individual analyses indicated no significant differences in the rate of seizures during the 24 weeks pre- and post-medication initiation, as compared to the same period in the year prior. These finding do not seem to suggest that ADHD medications are only initiated at periods of significantly lower seizure risk, nor do they support a large increased risk of seizures immediately after ADHD medication initiation. However, these results must be interpreted with caution as all CIs included 1 and analyses was based on a small number of informative individuals (165 events among 97 individuals).

Results from the analyses of repeated ADHD medication periods replicate findings from a recent large-scale US study²⁴ and one small clinical study¹⁵ showing reduced rates of seizures associated with ADHD medication periods, even after adjusting for concurrent AED medications. Convergent results across countries with different health care systems and ADHD medication prescription practices (US and Sweden), and across different types of data sources indicate that this effect is unlikely to be merely a methodological artefact. However, there are many potential explanations for an observed lowered risk of seizures during ADHD medication periods. Treatment of ADHD may improve adherence to AED

medications or reduce exposure to factors that can trigger seizures, such as stress and alcohol use. It is also possible that the observed protective effect partly relates to improved medical management of seizures.

Strengths and Limitations

This study has several strengths, including the use of nationally representative data, long follow-up time, consideration of underlying seizure risk as well as active epilepsy indicated by ongoing AED treatment, the inclusion of patients with comorbid NDDs, and the use of within-individual analyses to adjust for time-constant confounders that vary between individuals. There are also important study limitations. First, as this is a register-based study, we do not have access to neurological assessments, nor to EEG or other neuroimaging to confirm epilepsy. Nonetheless, two previous studies have shown that majority of individuals with epilepsy in Sweden are included in the NPR^{38; 39} and the positive predictive validity of epilepsy diagnosis in the Swedish Inpatient Register (a large part of the NPR) has been estimated at 79%.³⁹ Further, we did not have sufficient power and discriminative validity to study the association across different epilepsy subtypes,⁴⁰ or to distinguish patients with well controlled from not controlled seizures. Second, current clinical guidelines caution against the use of ADHD medication among individuals with seizures. It is therefore possible that our results are biased due medical professionals' reluctance of prescribing in this population, as only individuals who received medication contributed to the risk estimates for ADHD medication. In our study population of individuals aged between 10–26 years at the end of follow-up, 64% of those diagnosed with ADHD also received ADHD medication treatment during follow-up. This is somewhat lower than Swedish prescription levels following ADHD diagnosis among children (75%) but similar to levels among adults (55–60%),⁴¹ suggesting this is unlikely to entirely explain our findings. Third, the definition of medication periods was based on a sequence of dispensed prescriptions that might inaccurately reflect the actual consumption of medication. However, different medication period definitions did not substantially impact the main results, indicating that exposure time misclassification is unlikely to fully account for our findings. Further, we did not include information on dosages as correctly identifying reliable and valid indexes of medication doses from prescription register data is very challenging, particularly across different types of stimulants. Fourth, our outcome definition only captures seizure events severe enough to warrant a hospital or specialist care visit. As patients with epilepsy are unlikely to seek medical treatment for minor or routine seizures, we cannot exclude that ADHD medication may still exacerbate seizures that do not require acute medical attention. Finally, as this is an observational study we cannot rule out that other unmeasured time-varying factors could still confound the results.

Conclusion

We found no evidence for an overall increased rate of seizures severe enough to warrant medical attention associated with ADHD-medication periods in individuals with epilepsy. In fact, our findings suggest a possible reduced rate of acute seizures associated with ADHD medication periods. These results were robust in individuals with a seizure history, in youth who meet criteria for a lifetime diagnosis of epilepsy, and among children and adolescents with active epilepsy. Despite longstanding concerns regarding the safety of stimulant

medication use in patients with epilepsy, our results add to a growing body of research showing limited evidence for an exacerbated seizure risk associated with ADHD medications. Since ADHD can have a significant adverse impact on academic, social, and cognitive functioning, effective treatment of ADHD is crucial.^{19; 42} Our findings suggest that epilepsy should not automatically preclude patients from pharmacological treatment for ADHD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Significance:

We found no evidence for an overall increased rate of acute seizures associated with ADHD-medication treatment among individuals with epilepsy. These results suggest that epilepsy should not automatically preclude patients from receiving ADHD-medications.

Key Points

- ADHD-medication initiation and recurrent ADHD-medication treatment were not associated with an increased risk of acute seizures among individuals with epilepsy in this register-based pharmacoepidemiological study.
- Associations were similar across sex, age, in patients with additional neurodevelopmental disorders, and in individuals with active epilepsy defined by continuous antiepileptic drug treatment during follow-up.
- Results suggest that the presence of epilepsy should not automatically preclude patients from pharmacological treatment for ADHD.

Figure 1.

Incidence rate (IR) of seizures pre and post ADHD medication initiation in 995 individuals with seizure history who initiated ADHD medication treatment between 2007 and 2013. The blue line is the estimated IR per 1000 person-weeks throughout the 24 weeks pre and post ADHD medication initiation, presented with 95% confidence interval. IRs are estimated with natural cubic splines with knots at -24, -12, 0, 12, and 24 weeks.

Table 1.

Within-individual incidence rate ratio (IRR) for acute seizure events in the 24 weeks before and after ADHD medication initiation among 995 with a seizure history

	No of events	Within Individual IRR (95% CI)
Baseline	82	-
24 to 13 weeks Pre-medication	17	0.82 (0.49–1.39)
12 to 0 weeks Pre-medication	24	1.16 (0.74–1.83)
12 to 0 weeks Post-medication	20	0.95 (0.60–1.56)
13 to 24 weeks Post-medication	22	1.05 (0.65–1.68)

Note: Within-individual analyses adjusts for all confounders constant within a person during follow-up. Analyses were further adjusted for concurrent antiepileptic drug treatment as a time-varying covariate. CI, confidence intervals.

Table 2.

Characteristics of study population born 1987–2003, presented by ADHD medication treatment status.

	No ADHD medication (n=19702, 91%)	>= 1 ADHD medication period (n=1855, 9%)
Female, (n, %)	9532 (48%)	649 (35%)
Median (interquartile range) follow-up time, years	8 (5–8)	8 (5–8)
Median (interquartile range) age at start of follow-up, years	13 (9–16)	10 (7–14)
Median (interquartile range) age at first ever seizure in NPR	9 (4–14)	7 (4–11)
Seizure diagnoses in NPR (n individuals, %)		
1 seizure	4446 (23%)	384 (21%)
2–5 seizures	6177 (31%)	483 (26%)
6–10 seizures	4013 (20%)	372 (20%)
> 11 seizures	5066 (26%)	616 (33%)
Total N acute seizure events during follow-up	10692	1062
1 AED medication period (n, %)	12496 (63%)	1289 (70%)
Median (interquartile range) number of AED dispensation	31 (15–62)	35 (16–67)
Median (interquartile range) number of ADHD medication dispensation	na	24 (11–43)
ADHD diagnosis (n, %)	888 (5%)	1593 (86%)
Any NDD (excluding ADHD)	5469 (28%)	1121 (60%)
Pervasive and specific developmental disorders	3549 (18%)	877 (47%)
Intellectual disability	4031 (20%)	578 (31%)
Tic disorders	301 (2%)	129 (7%)

Note: Seizure diagnoses in NPR reflects the number of lifetime seizure discharge diagnoses in the National Patient Register (NPR), which only captures seizures severe enough to warrant a hospital or specialist care visit. These numbers therefore likely underestimate the actual number of seizures. Total N acute seizure events during follow-up reflects the number of seizure event outcomes during follow-up, as defined in the method section.

AED, antiepileptic medication drugs. NDD, neurodevelopmental disorder.

Table 3.

Characteristics of ADHD medication treatment periods, and AED and seizures around the time of ADHD treatment (n treatment periods = 3556, n individuals= 1855)

Characteristic	Frequency (N, %)
Type of ADHD treatment period	
Stimulant	2596 (73%)
Atomoxetine	249 (7%)
Mixed (stimulant and atomoxetine)	711 (20%)
Concurrent AED during ADHD medication period	1778 (50%)
Median (interquartile range) days from first AED treatment to first ADHD treatment, days	805 (244–1458)
Median (interquartile range) days between start of ADHD medication period and subsequent seizure, days	114 (22–398)

Note: Median days from first AED treatment to first ADHD treatment is reported for patients who received AED prior to/at the start of ADHD medication treatment (N= 1077). Median days between start of ADHD medication period and subsequent seizure is reported for acute seizure events that occurred during an ADHD medication treatment period (N periods = 367).

AED, antiepileptic medication drugs

Table 4.

Hazard ratios for acute seizure events during ADHD medication treatment periods, compared with non-treatment periods (2006–2013) in cohort born 1987–2003

Analyses	N individuals	N seizure events	Population-level HR (95%CI)	Within-individual HR (95%CI)
Model 1				
<i>Full cohort</i>	21557	11754	1.00 (0.78–1.28)	0.73 (0.57–0.94)
Model 2				
<i>Full cohort, adjusted for concurrent AED medications</i>	21557	11754	0.94 (0.74–1.20)	0.74 (0.57–0.94)
Model 3				
<i>No concurrent AED medications</i>	17269	1929	0.61 (0.41–0.90)	0.57 (0.20–1.60)
<i>Concurrent AED medications</i>	13785	9825	0.98 (0.75–1.27)	0.78 (0.60–1.02)
Model 4				
<i>Males</i>	11376	6054	0.91 (0.65–1.27)	0.79 (0.57–1.08)
<i>Females</i>	10181	5700	1.01 (0.75–1.36)	0.66 (0.45–0.99)
Model 5				
<i>ADHD cases</i>	2481	1558	0.81 (0.63–1.05)	0.70 (0.53–0.91)
Model 6				
<i>ADHD cases with no additional NDDs</i>	971	421	0.58 (0.40–0.82)	0.58 (0.33–1.01)
<i>ADHD cases with additional NDD</i>	1510	1137	0.86 (0.64–1.16)	0.76 (0.55–1.05)

Note: Population-level analyses are adjusted for or stratified by sex. All analyses are adjusted for age at start of each observation periods, coded in four age bins (5–9, 10–14, and 19–26 years). Model 2 and 4–6 are further adjusted for concurrent AED medications. ADHD meds, ADHD medication treatment periods. AED meds, antiepileptic medication periods. CI, 95% confidence interval. HR, hazard ratio. NDD, neurodevelopmental disorder. Main findings are highlighted in bold font.

Model 1 shows the association between ADHD medication and seizures

Model 2 shows the association further adjusted for concurrent AED medications.

Model 3 shows the association stratified by concurrent AED medication. Individuals could contribute data to more than one strata.

Model 4 shows the association stratified by sex

Model 5 shows the association in individuals with an ADHD diagnosis.

Model 6 shows the association in individuals with an ADHD diagnosis, stratified by absence or presence of additional NDDs.

Table 5.

Sensitivity analysis of hazard ratios for acute seizure events during ADHD medication treatment periods compared with non-treatment periods (2006–2013)

	Analysis	No of individuals	No of seizure events	Population-level HR (95%CI)	Within-individual HR (95%CI)
1	ADHD meds 90 day cut-off	21557	11754	0.86 (0.71–1.03)	0.71 (0.55–0.91)
2	ADHD meds + 90 days	21557	11754	1.00 (0.80–1.24)	0.84 (0.67–1.05)
3	Strict outcome definition	21557	5520	0.96 (0.68–1.35)	0.74 (0.51–1.08)
4	Stimulants only	20833	11337	1.10 (0.81–1.49)	0.84 (0.62–1.12)
5	Epilepsy cohort born 1995–2003	6773	4765	0.88 (0.71–1.10)	0.62 (0.44–0.89)
6	Active epilepsy cohort born 1995–2003	1605	2356	0.71 (0.54–0.93)	0.63 (0.38–1.03)

Note: Sensitivity analyses 1–3 were conducted in epilepsy cohort born 1987–2003. Model 4 was conducted among individuals who only ever received stimulant ADHD medications during follow-up. All sensitivity analyses were adjusted for categorical age and concurrent AED medication, apart from analyses 6, which were conducted in an active epilepsy cohort defined by continuous AED treatment during follow-up. Population-level analyses are additionally adjusted for sex. Main findings are highlighted in bold font.

AED meds, antiepileptic medication periods. HR, hazard ratio. CI, 95% confidence interval.