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Use of medication for attention-deficit/hyperactivity disorder and risk of unintentional injuries in children and adolescents with co-occurring neurodevelopmental disorders

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Abstract

Background: Attention-deficit/hyperactivity disorder (ADHD) is often associated with other neurodevelopmental disorders (NDs) and with risky behaviors and adverse health outcomes, including injuries. Treatment with ADHD medication has been associated with reduced risk of injuries. However, it is unknown whether the association is present in individuals with co-occurring NDs. The aim of the present study was to estimate the association between ADHD medication use and unintentional injuries in Sweden in children and adolescents with ADHD, including those with co-occurring NDs.

Methods: Using a linkage of several national registers via the unique personal identification number, we identified individuals with a diagnosis of ADHD and of other NDs, including autism spectrum disorder, intellectual disability, communication disorders, learning disorders and motor disorders. The primary outcome was unintentional injuries. Secondary outcome was traumatic brain injury (TBI). Individuals were followed from January 1st 2006 or their 5th birthday or the date of the first unintentional injury, whichever came last, to December 31st 2013 or their 18th birthday or death, whichever came first. We compared the rate of injuries during periods on-treatment with the rate of injuries during periods off-treatment within the same individual using stratified Cox regression to calculate hazard ratio (HR) with 95% confidence intervals (CIs).

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Conflict of interest statement: see Acknowledgements for full disclosures.

The remaining authors have declared that they have no competing or potential conflicts of interest.

Results: For children and adolescents with ADHD (N=9421) the rate of any unintentional injuries (HR=0.85; 95% CI=0.78–0.92) and TBIs (HR=0.27; 95% CIs=0.20–0.38) during medicated periods was lower than during non-medicated periods. Similar results were found among individuals with co-occurring NDs (N=2986), for unintentional injuries (HR= 0.88; 95% CI=0.77–1.01) and for TBIs (HR=0.27; 95% CI=0.16–0.44).

Conclusions: Beneficial effects of ADHD medication may extend beyond reduction of ADHD core symptoms to prevention of unintentional injuries in children and adolescents, including individuals with co-occurring NDs.

Keywords

ADHD medication; injuries; neurodevelopmental disorders

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder (ND) that affects 3–5% of children worldwide (Polanczyk et al., 2015, Sayal et al., 2018). Similar to other NDs, like autism spectrum disorder (ASD), ADHD symptoms typically have their onset during childhood and tend to persist into adolescence and adulthood (Thapar et al., 2017). In addition, individuals diagnosed with ADHD often present with symptoms or a diagnosis of other NDs, including learning disability (Larson et al., 2011, Koolwijk et al., 2014), language problems (Korrel et al., 2017, Larson et al., 2011), ASD (Larson et al., 2011, Grzadzinski et al., 2016, Zablotzky et al., 2017, Koolwijk et al., 2014), and intellectual disability (ID; Faraone et al., 2017). ADHD is also associated with several risky behaviors and adverse health outcomes (Erskine et al., 2016, Balazs and Keresztesy, 2017, Nigg, 2013, Mohr-Jensen and Steinhausen, 2016), including injuries (Ruiz-Goikoetxea et al., 2018), which represent a leading cause of morbidity and mortality among children (Haagsma et al., 2015, WHO, 2014). The risk of injuries in children with ADHD is 40–50% higher compared with their peers without ADHD (Ruiz-Goikoetxea et al., 2018), and the risk seems to be elevated for severe injuries, including poisoning (Prasad et al., 2018) and head injuries (Merrill et al., 2009, Tai et al., 2013).

A recent meta-analysis of randomized controlled trials (RCTs) supports efficacy of pharmacological treatment for ADHD in reducing core symptoms of the disorder (Cortese et al., 2018). In addition, observational studies have consistently reported an association between ADHD medication use and lower risk of adverse health outcomes (Chang et al., 2014a, Chang et al., 2014b, Chang et al., 2017, Quinn et al., 2017, Lichtenstein et al., 2012), including injuries (Chen et al., 2017, Dalsgaard et al., 2015, Man et al., 2015, Mikolajczyk et al., 2015, Raman et al., 2013). A recent meta-analysis of observational studies from Germany, Denmark, United Kingdom, The Netherlands and Hong-Kong reported a 12% risk reduction of injuries associated with ADHD medication use (Ruiz-Goikoetxea et al., 2018). A more recent study, using information from a large insurance claim database in the United States, has expanded previous findings by showing a negative association between ADHD medication use and unintentional injuries both in children and in adolescents, in males and in females, and for traumatic brain injuries (Ghirardi et al., 2019).

There is evidence that children with ADHD and co-occurring NDs have poorer functioning (Larson et al., 2011) and different treatment patterns (Zablotsky et al., 2017) compared to children with ADHD only. Treatment with stimulants seems to reduce ADHD symptoms in children with tic disorder (Osland et al., 2018) and ID (Aman et al., 2003, Simonoff et al., 2013) or ASD (Sturman et al., 2017), although the evidence is sparse. In fact, RCTs have typically excluded individuals with comorbidities. In addition, it remains unknown whether beneficial effects of treatment may extend to the prevention of adverse health outcomes in these groups of patients. This represents an important knowledge gap because treatment outcomes might be altered in the presence of other disorders (Hodgkins et al., 2011), and treatment course and adverse health events during childhood and adolescence may influence several outcomes later in life.

The aims of the present study were: firstly, to estimate the association between ADHD medication use and injuries in children and adolescents in Sweden; secondly, to explore whether comorbidity with NDs may influence the association between ADHD medication use and risk of injuries (Ruiz-Goikoetxea et al., 2018). This has clinical and public health relevance, considering the strong link between ADHD and other NDs in childhood, with comorbidity rates between 30 and 50% (Larson et al., 2011, Koolwijk et al., 2014, Korrel et al., 2017, Grzadzinski et al., 2016, Faraone et al., 2017, Zablotsky et al., 2017, Ghirardi et al., 2018), and the burden of injuries in this age group (WHO, 2014).

Methods

Study population

We used data from a linkage of several national registers via the unique personal identification number (Ludvigsson et al., 2009). Using the Total Population Register (Ludvigsson et al., 2016), we identified all individuals alive and living in Sweden between January 1st 2006 and December 31st 2013 between age 5 and 18. Using the National Patient Register (Ludvigsson et al., 2011), we identified all individuals with a diagnosis of ADHD at any time during or before the study period according to the International Classification of Diseases, Ninth Revision (ICD-9; 314) or ICD-10 (1997–2013; F90). In Sweden, DSM criteria are used for diagnostic assessment and diagnoses are then recorded in the National Patient Register using the corresponding ICD codes (Giacobini et al., 2018).

Co-occurring disorders

Using the National Patient Register (Ludvigsson et al., 2011), we identified diagnoses of other NDs at any time during or before the study period, using a similar classification as DSM-5. We included: ASD, ID, communication disorders, learning disorders, motor disorders, and other/unspecified NDs. A list of the ICD-9 and ICD-10 codes can be found in Table S1 in the Supporting Information.

Medication usage

We obtained information on the use of ADHD medication from the Prescribed Drug Register (Wettermark et al., 2007). The following stimulant and non-stimulant medications approved in Sweden for the management of ADHD during the study period were included:

methylphenidate [N06BA04], amphetamine [N06BA01], dexamphetamine [N06BA02]) and atomoxetine [N06BA09].

We defined a treatment period as the time between two consecutive medication dispensations that are no longer than 122 days apart (122-days interval), similarly to previous studies (Chen et al., 2014, Lichtenstein et al., 2012, Chang et al., 2014a, Brikell et al., 2019). On-treatment periods started with the first dispensation date and ended with the last dispensation date. The remaining time was defined as off-treatment periods. The rationale behind this was that in Sweden, prescriptions for ADHD medication are usually refilled within 3 months, but, in the case of poor adherence or treatment cessation during holiday, time between dispensations may be longer.

Outcome

The primary outcome was unintentional injuries, analyzed as recurrent events; that is, we counted as events all the injuries occurring after the first injury. We obtained information from the National Patient Register on inpatient and outpatient visits reporting injury as the main diagnosis (ICD-10: S00-T78) and unintentional cause (ICD-10: V01-X59). To minimize the risk to count the same event multiple times due to readmissions for the same injury, we only considered unplanned visits that were more than 14 days apart. Secondary outcome was traumatic brain injury (TBI; ICD-10 codes: S010-S023, S027-S029, S040, S060-S071, S078-S079, S097-S099, T010, T020, T040, T060, T901-T902, T904-T905, T908-T909), as this has been associated with important long-term negative outcomes (Sariaslan et al., 2016). A description of the procedure used to define the outcomes is presented in Table S2.

Follow-up

Individuals were followed from January 1st 2006 or their 5th birthday or the date of the first event (as defined above), whichever came last, to December 31st 2013 or their 18th birthday or death, whichever came first.

Statistical analyses

To explore the association between ADHD medication use and injuries, we divided the follow-up time into consecutive periods for each patient and compared the rate of injuries during on-treatment periods with the rate of injuries during off-treatment periods within the same individual (within-individual comparison), in contrast with traditional cohort studies where medication users are compared with non-users. We used stratified Cox regression and estimated the hazard ratio (HR) and 95% confidence intervals (CIs) for time to unintentional injury, with robust standard errors accounting for the correlated data from the same patient. The underlying time scale was time since last event, so every time an event occurred, follow-up time was reset to zero at the date of the event.

In stratified Cox regression, each individual is entered as a separate stratum and serves as their own control (Allison, 2009, Allison, 1996). The method allows adjusting for all potential confounders that are constant within each individual during the follow-up. Only individuals with variation in at least one of the time-varying covariates (that is, ADHD

medication status, age, and calendar time) are informative for this analysis. A description of the source population for the samples used in the analyses can be found in Table S3.

In addition, we adjusted for age and seasonal pattern as time-varying covariates, as these may be associated with medication use and risk of injuries. Age was categorized as 5–13 (hereby referred to as children) and 14–17 (hereby referred to as adolescents). Seasonal pattern was accounted for by adding an indicator of school season (September to May) or summer holiday season (June to August).

Separated estimates were obtained for TBIs, children and adolescents, males and females, and individuals with co-occurring NDs and ASD (subsample of the group with co-occurring ND).

Sensitivity analyses

We performed several sensitivity analyses to test if alternative definitions of medication usage, outcome or follow-up would lead to different results. First, we varied the definition of treatment period as the time between two consecutive medication dispensations no longer than 92 days apart (92-days interval), to provide a more conservative definition of the treatment period. Second, we only included stimulant medications, while keeping the treatment period definition used in the main analysis (that is, 122-days interval), to provide estimates comparable with previous studies that included only stimulants. Third, we used a stricter definition of the outcome, including only visits that were longer than 30 days apart. Fourth, we included other psychotropic medications in the model for the whole group and for the groups with co-occurring NDs as a time varying covariate to account for polypharmacy, which may be especially common among those with comorbidities. We included antidepressants [N06A], anxiolytics [N05B] and antipsychotics [N05A]. Medication periods were defined as for ADHD medication.

All analyses were performed using Stata 15 (StataCorp. 2017).

Ethical considerations

The study was approved by the regional ethics review board in Stockholm, Sweden. The requirement for informed consent was waived, because the study was register-based and personal information was anonymized.

Results

Description of the sample

Among all 29,757 individuals with ADHD, 34.6% had at least one event (Table S3). Among those with an additional diagnosis of ND, 32.7% had at least one event, and among the subgroup with ASD, 29.9% had at least one event.

Among the 9421 individuals included in the sample contributing to the main analyses over 30% had an additional diagnosis of ND (N=2986) and the most frequent was ASD (N=1390). Among them, the majority had at least one medication dispensation and one medication switch (Table 1).

ADHD medication use and injuries

The rate of all unintentional injuries (HR=0.85; 95% CI=0.78–0.92) and TBIs (HR=0.27; 95% CI=0.20–0.38) during medicated periods was lower than during non-medicated periods (Table 2). We found negative associations between medication use and rate of unintentional injuries in children (HR=0.66; 95% CI=0.58–0.74) and adolescents (HR=0.85; 95% CI=0.74–0.97), males (HR=0.88; 95% CI=0.80–0.96) and females (HR=0.77; 95% CI=0.67–0.90), and among individuals with co-occurring NDs (HR=0.88; 95% CI=0.77–1.01) and among the subgroup of those with co-occurring ASD (HR=0.77; 95% CI=0.62–0.96; Table 2).

Among individuals with co-occurring NDs, the rate of TBIs during medicated periods was lower than during non-medicated periods (HR=0.27; 95% CI=0.16–0.44). The rate of unintentional injuries during medicated periods was lower than during non-medicated periods in children (HR=0.63; 95% CI=0.51–0.79), but not in adolescents (HR=1.04; 95% CI=0.81–1.34), and in males (HR=0.89; 95% CI=0.75–1.05) and females (HR=0.86; 95% CI=0.67–1.11), although the confidence intervals included one (Table 3).

Among the individuals with co-occurring ASD, the rate of TBIs during medicated periods was lower than during non-medicated periods (HR=0.20; 95% CI=0.10–0.43). The rate of unintentional injuries during medicated periods was lower than during non-medicated periods in children (HR=0.58; 95% CI=0.41–0.82) and adolescents (HR=0.88; 95% CI=0.62–1.24) and in males (HR=0.74; 95% CI=0.57–0.96) and females (HR=0.84; 95% CI=0.57–1.23), although the confidence intervals for the estimates in adolescents and females included one (Table 4).

Estimates from sensitivity analyses were similar to those from the main analyses (Table 5). A negative association between ADHD medication use and unintentional injuries was found with a different definition of medication usage (HR=0.88; 95% CI=0.82–0.95), when only stimulants were considered (HR=0.82; 95% CI=0.76–0.89) and with a different definition of the outcome (HR=0.84; 95% CI=0.78–0.91). Similar estimates were obtained when we adjusted for use other psychotropic medication both in the full sample (HR=0.84; 95% CI=0.77–0.90) and in the groups with co-occurring ND (HR=0.87; 95% CI=0.76–1.00) and ASD (HR=0.76; 95% CI=0.61–0.94).

Discussion

In this study, we wanted to replicate previous findings on the negative association between ADHD medication use and risk of injuries in children and adolescents from other countries, and to test whether such association was similar in those with co-occurring NDs. We found that, in Sweden, ADHD medication use was associated with a reduced rate of unintentional injuries in children and adolescents, in males and females, and in individuals with co-occurring NDs. These results suggest that use of ADHD medication may reduce not only core symptoms of the disorder, but also the risk of adverse health events, such as injuries.

This study adds to the existing literature on the real-world effectiveness of ADHD medication by reporting associations for individuals with co-occurring NDs. No previous

observational study has examined the association between ADHD medication use and injuries in individuals with NDs. Evidence from RCTs is sparse. Simonoff et al. (2013) reported that use of methylphenidate was superior to placebo in reducing ADHD core symptoms in children with co-occurring ID. Other studies have shown that atomoxetine may be effective in reducing ADHD symptoms in children with co-occurring ASD (Harfterkamp et al., 2012, Harfterkamp et al., 2013). Whether beneficial effects of medication among individuals with co-occurring NDs extended beyond core symptoms reduction to prevention of other outcomes was unknown. In this study, we have shown that ADHD medication use is associated with injury risk reduction in children with co-occurring NDs. This has clinical and public health relevance, considering the high rate of comorbidity among NDs (Thapar et al., 2017) and the fact that unintentional injuries are relatively common among children and adolescents (Haagsma et al., 2015, WHO, 2014).

Some of the associations for individuals with co-occurring NDs attenuated. For example, the association in adolescents with co-occurring NDs was null. The confidence intervals for other associations, such as the one in adolescents and in females in the group with co-occurring ASD, became wider and included one. These results suggest that beneficial effects of ADHD medication on the risk of injuries among people with co-occurring NDs may be similar to the larger ADHD group. However, precise estimates and conclusions are limited by the subgroup sample size. More research is needed to replicate these results in other countries and to investigate other outcomes in those with ADHD and co-occurring conditions. Our findings are in line with meta-analytic estimates derived from studies from other countries suggesting a 12% injury risk reduction associated with ADHD medication use (Ruiz-Goikoetxea et al., 2018). In addition, our results suggest that the association may be stronger for TBIs, as previously reported (Mikolajczyk et al., 2015). Our results are consistent with a recent study based on insurance claims in the United States that has found that the association is present in children and adolescents, and in males and females (Ghirardi et al., 2019).

Several study strengths and limitations should be considered. First, by using information from national registers, the estimates are representative of the specialist care of ADHD in Sweden. However, generalization to other countries should be made with caution, considering cross-country differences in administrative prevalence of ADHD and prescription practices (Sayal et al., 2018). At the same time, it is reassuring to notice overall agreement with studies from countries with different ADHD medication utilization and healthcare systems. Second, similar to a previous study (Ghirardi et al., 2019), we only considered unintentional injuries, and excluded intentional self-harm, which may be related to ADHD and ADHD medication use via different mechanisms and, consequently, should be investigated separately. Third, only injuries leading to hospital visits were analyzed. Less severe events not requiring medical attention were not included. While this limits the validity of our results to more severe events only, it is of clear public health relevance to quantify the association between medication use and injuries requiring medical attention. To this purpose, we also provided estimates for TBIs, which may have long-term functional consequences (Sariaslan et al., 2016). Fourth, the source of information on medication prescriptions was the Prescribed Drug Register, which includes information on all prescribed medications dispensed in Sweden (Wettermark et al., 2007), while the source of information

on the outcome was the National Patient Register. These two data sources are independent and not subject to recall bias, since they are routine electronic records. In addition, since in Sweden psychiatry specialists prescribe ADHD medication, the medication prescription and the injury diagnosis and treatment are likely to be given by different practitioners. On the other hand, information on dispensed medications is only a proxy for medication ingestion. Fifth, although we adjusted for within-individual constant confounding by comparing rate of events between on- and off-treatment periods in the same person and for age and seasonal pattern as time-varying confounders, other factors may be associated with treatment initiation and termination and also influence the risk of unintentional injuries, such as non-pharmacological interventions, on which we did not have information. Last, the fact that the main results were similar to results obtained from sensitivity analyses using different definitions of medication usage and outcome supports the robustness of the results.

Conclusion

This study suggests that beneficial effects of ADHD medication extend beyond reduction of core symptomatology of ADHD and may prevent unintentional injuries in children and adolescents, including individuals with co-occurring NDs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

- ADHD medication use has been associated with reduced risk of injuries.
- Despite high comorbidity rates, little is known on the association between ADHD medication and injuries among children with co-occurring NDs.
- In this study, we found that ADHD medication use is associated with reduced risk of injuries in children and adolescents with co-occurring NDs and in the subgroup with ASD.

Table 1.

Description of the samples informative for the main analyses

	All ADHD (<i>N</i> =9421)		Co-occurring NDs (<i>N</i> =2986)		Co-occurring ASD (<i>N</i> =1390)	
	<i>N/Mean</i>	<i>%/StD</i>	<i>N/Mean</i>	<i>%/StD</i>	<i>N/Mean</i>	<i>%/StD</i>
Age at start of the follow-up (years)	10.27	3.33	9.99	3.33	9.68	3.36
Females	2,710	28.77	793	26.56	397	28.56
At least one medication period	7559	80.24	2434	81.51	1118	80.43
At least one medication switch	7419	78.75	2374	79.50	1084	77.99
Starting with medicated period	979	10.39	407	13.63	199	14.32

Abbreviations: N=number; StD=standard deviation; NDs=neurodevelopmental disorders; ASD=autism spectrum disorder.

Table 2.

ADHD medication use and injuries

	N of events	Person-years at risk	HR	95%CI
Overall	16,344	53,069	0.85	(0.78–0.92)
TBIs	1696	9075	0.27	(0.20–0.38)
Age				
Children	7525	23,086	0.66	(0.58–0.74)
Adolescents	6572	13715	0.85	(0.74–0.97)
Sex				
Males	11,472	37,951	0.88	(0.80–0.96)
Females	4872	15,118	0.77	(0.67–0.90)
Co-occurring disorders				
Co-occurring NDs	5212	17,313	0.88	(0.77–1.01)
Co-occurring ASD	2344	8125	0.77	(0.62–0.96)

Abbreviations: N=number; HR=hazard ratio; 95% CI=95% confidence interval; TBIs=traumatic brain injuries; NDs=neurodevelopmental disorders; ASD=autism spectrum disorder.

Table 3.

ADHD medication use and injuries in individuals with co-occurring NDs

	N of events	Person-years at risk	HR	95%CI
TBIs	557	3013	0.27	(0.16–0.44)
Age				
Children	2562	8058	0.63	(0.51–0.79)
Adolescents	1949	3955	1.04	(0.81–1.34)
Sex				
Males	3741	12,790	0.89	(0.75–1.05)
Females	1471	4524	0.86	(0.67–1.11)

Abbreviations: N=number; HR=hazard ratio; 95% CI=95% confidence interval; TBIs=traumatic brain injuries; NDs=neurodevelopmental disorders.

Table 4.

ADHD medication use and injuries in individuals with co-occurring ASD

	N of events	Person-years at risk	HR	95%CI
TBIs	257	1387	0.20	(0.10–0.43)
Age				
Children	1223	3941	0.58	(0.41–0.82)
Adolescents	784	1636	0.88	(0.62–1.24)
Sex				
Males	1623	5837	0.74	(0.57–0.96)
Females	721	2288	0.84	(0.57–1.23)

Abbreviations: N=number; HR=hazard ratio; 95% CI=95% confidence interval; TBIs=traumatic brain injuries; ASD=autism spectrum disorder.

Table 5.

Sensitivity analyses

	N of events	Person-years at risk	HR	95%CI
92-days interval	16,408	53,194	0.88	(0.82–0.95)
Only stimulant medications	16,232	52,699	0.82	(0.76–0.89)
No visits in the previous 30 days =9342	15,834	52,800	0.84	(0.78–0.91)
Adjustment for other psychotropic medication	16,522	53,476	0.84	(0.77–0.90)
Adjustment for other psychotropic medication in individuals with ND	5293	17,511	0.87	(0.76–1.00)
Adjustment for other psychotropic medication in individuals with ASD	2390	8244	0.76	(0.61–0.94)

Abbreviations: N=number; HR=hazard ratio; 95% CI=95% confidence interval.