Original Investigation

Injury Prevention by Medication Among Children With Attention-Deficit/Hyperactivity Disorder
A Case-Only Study

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IMPORTANCE Children and adolescents with attention-deficit/hyperactivity disorder (ADHD) have an increased risk of injuries. Attention-deficit/hyperactivity disorder is often treated with medication, but the evidence regarding prevention of injuries is inconclusive.

OBJECTIVE To determine via a case-only design whether the use of methylphenidate hydrochloride or atomoxetine hydrochloride reduces the risk of injuries among children and adolescents with ADHD.

DESIGN, SETTING, AND PARTICIPANTS We used the German Pharmacoepidemiological Research Database, which includes records from about 17 million insureds (approximately 20% of the population) from 4 statutory health insurance providers in Germany to identify children aged 3 to 17 years with new diagnoses of ADHD in 2005 and 2006. We identified 37 650 children with ADHD based on inpatient and outpatient diagnostic codes (F90.0, F90.1, and F90.9) from the German modification of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision. Among them, we identified those with an inpatient injury diagnosis during follow-up until 2009. A total of 2128 children with any injury diagnosis at hospitalization, 821 of whom had a brain injury diagnosis, were included in the analysis. We applied the self-controlled case series design to control for time-invariant characteristics of the patients and time trends in the exposure.

EXPOSURES Treatment with methylphenidate or atomoxetine based on prescription data.

MAIN OUTCOMES AND MEASURES Hospitalization because of any injury or brain injury according to the injury mortality diagnosis matrix.

RESULTS Incidence rate ratios for the periods with medication compared with nonmedicated periods were 0.87 (95% CI, 0.74-1.02) for hospitalization with any injuries and 0.66 (95% CI, 0.48-0.91) for brain injuries only in the full sample. These estimates remained stable in sensitivity analyses restricting the sample to a narrower age range or to patients with a single hospitalization. There was no indication that medication prescriptions are increased after hospitalizations.

CONCLUSIONS AND RELEVANCE No significant risk reduction for hospitalizations with injury diagnoses was observed during periods of ADHD medication, but there was a preventive effect on the risk of brain injuries (34% risk reduction). The effects were controlled for time-invariant characteristics of the patients by the study design.
Attention-deficit/hyperactivity disorder (ADHD), the most common neurobiological disorder in children and adolescents, is characterized by the core symptoms of inattention, motor hyperactivity, and impulsivity.1 For both children and adults, studies have shown a positive association between ADHD and a higher risk of injuries, including motor vehicle crashes, fractures, head injuries, burns, and poisoning.2–20 Risk of injury to children and adolescents with ADHD might be mediated by several factors, such as impairment of motor functions,11 developmental coordination disorders,20 or other core symptoms.13 For the treatment of ADHD, methylphenidate hydrochloride and atomoxetine hydrochloride are considered the most effective pharmacologic treatment options and are frequently prescribed in Western countries.14–17 The benefits of ADHD treatment on the prevention of injuries were demonstrated using proxy outcomes in experimental studies with driving simulators, self-reported driving, or a second observer’s impression.18–21 In addition, the effect was evaluated in epidemiologic observational studies, which provided inconsistent results.5,7,22–24 However, most observational studies are complicated by the fact that medication might also be an indicator of individual characteristics of the study participants, such as more severe disease, resulting in confounding by indication and a possible underestimation of the preventive effect. In contrast, self-controlled studies allow accounting for individual characteristics of the participants that are stable over time. We aimed to assess possible risk reduction during periods of medication use among children and adolescents with ADHD using a large German health care database.

**Methods**

**Data Source**

We used data for 2004 through 2009 from the German Pharmacoepidemiological Research Database, which is described elsewhere.25,26 In brief, the database consists of data from 4 statutory health insurance providers, including records of about 17 million people (approximately 20% of the population) from all regions of Germany. The German Pharmacoepidemiological Research Database comprises information on hospital diagnoses and procedures, outpatient diagnoses, and prescriptions. All diagnoses are coded according to the German modification of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10-GM). Information on drug prescriptions is recorded for all outpatient dispensations that are reimbursable by the statutory health insurance provider and includes the date of the prescription, the date of the dispensing, and the central pharmaceutical number. Via linkage of the central pharmaceutical number to a pharmaceutical reference database, information is available on the prescribed quantity, strength, formulation, and the defined daily dose. The database contains data starting in 2004, the year in which statutory health insurance providers in Germany began collecting individual data for diagnoses and treatments in the ambulatory sector. According to German law, the use of these routinely collected pseudonymized data does not require ethical committee review or informed consent of the insured individuals but does require approval by the statutory health insurance providers, the responsible data protection authorities, and the overseeing governmental authorities. The required approvals were obtained for this study.

**Identification of ADHD Cases**

We selected all children and adolescents aged 3 to 17 years at the time of a new ADHD diagnosis in 2005 and 2006, excluding those with a prior ADHD diagnosis or drug treatment for ADHD in the preceding 12 months. Cases of ADHD were identified based on a conservative algorithm used in previous analyses17,27,28: patients had to have at least 1 inpatient diagnosis of ADHD (ICD-10-GM code F90.0 or F90.1), at least 2 outpatient diagnoses of ADHD (ICD-10-GM code F90.0 or F90.1) or at least 1 outpatient diagnosis of ADHD (ICD-10-GM code F90.0 or F90.1) and at least 1 outpatient diagnosis with the unspecific ICD-10-GM code F90.9, or at least 1 outpatient diagnosis of ADHD (ICD-10-GM code F90.0 or F90.1) and at least 1 prescription of methylphenidate or atomoxetine within 365 days. Such a conservative algorithm was necessary as single ADHD diagnoses might indicate outpatient visits in which this diagnosis was excluded. Excluded diagnoses should have a specific qualifier in the database, but this system did not work reliably in 2004 and 2005. The earliest diagnosis or prescription was used as the date of the new ADHD diagnosis.

**Ascertainment of Injuries**

For the ascertainment of injuries, we used the injury mortality diagnosis matrix.27 The injury mortality diagnosis matrix is designed with 2 axes: 1 representing the body region and 1 representing the nature of the injury. We modified the matrix according to the ICD-10-GM and included, for example, some T00 codes that were not in the US version of the ICD-10 and therefore not applied in the original injury mortality diagnosis matrix.29 As outpatient diagnoses of injuries were considered unreliable, we based the outcome definition on injury diagnoses from hospital admissions only. We analyzed the total follow-up of ADHD cases from 2005 to 2009 depending on the availability of data from the respective statutory health insurance providers.

**Ascertainment of Drug Treatment**

We identified prescriptions of methylphenidate and atomoxetine comprising all preparations licensed for the treatment of ADHD in Germany. For each prescription, we calculated the number of days covered by the prescription, assuming 1 tablet per day. Based on this information, we defined the exposure status during follow-up for each patient. Each new prescription initiated a new calculation of days covered by medication; tablets potentially remaining from a previous prescription were discarded.

**Statistical Analysis**

First, we described the study population in terms of age and sex distribution and displayed the distribution of hospitalizations with injuries by age. Then, we applied the self-controlled case series design (SCCSD)30,31 to assess a possible
risk reduction during the periods of medication use. The SCCSD is based on time with medication vs time without medication within the same person and was developed to reduce confounding by individual characteristics. Cohort time was restricted to periods after the initial diagnosis of ADHD. We calculated incidence rate ratios for hospitalization with any injury and hospitalization with brain injuries only.\textsuperscript{31} To control for potential seasonal patterns of injuries, we adjusted for calendar quarters in the analysis. We also conducted a sensitivity analysis without accounting for seasonality. Since some children experienced multiple injuries during the follow-up, we conducted a further sensitivity analysis restricting the sample to children with a single hospitalization to assess the effects of potential intraindividual correlation. Initially, we conducted the analyses using the whole age range, adjusting for changing risk of hospitalization with relation to age. Given that the follow-up period of up to 5 years was substantially shorter than the age spectrum (3-17 years), the age segments were contributed by different persons. To obtain estimation from a more homogeneous sample of persons followed up across the complete time and age range, we conducted sensitivity analyses for stepwise-restricted age ranges. In those analyses, only the follow-up time in the specified age range was included. We repeated these steps in a further analysis restricted to brain injury events only (ICD-10-GM code S06).

Table. Estimated Risk Reduction Associated With the Use of ADHD Medication\textsuperscript{a}

<table>
<thead>
<tr>
<th>Age Range for the Period at Risk, y</th>
<th>Person-time Exposed to Medication (in 100 000)\textsuperscript{b}</th>
<th>Incidence Rate Ratio (95% CI)</th>
<th>Person-time Exposed To Medication (in 100 000)\textsuperscript{b}</th>
<th>Incidence Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Injuries</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Exposed</td>
<td>29.06</td>
<td>6.47</td>
<td>0.87 (0.74-1.02)</td>
<td>10.85</td>
</tr>
<tr>
<td>Exposed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain Injuries</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Exposed</td>
<td>19.22</td>
<td>4.93</td>
<td>0.84 (0.69-1.01)</td>
<td>7.46</td>
</tr>
<tr>
<td>Exposed</td>
<td>15.11</td>
<td>4.09</td>
<td>0.81 (0.66-1.00)</td>
<td>5.86</td>
</tr>
</tbody>
</table>

Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

\textsuperscript{a} Self-controlled case series analysis accounting for age-specific risk of injuries and additionally adjusted for seasonality (results not adjusted for seasonality are presented in the eTable in the Supplement).

\textsuperscript{b} Only among those with at least 1 prescription for ADHD medication during the follow-up.

Results

We identified 37 650 children and adolescents in the database with a new ADHD diagnosis in 2005 or 2006. Among them, there were 2128 children and adolescents with at least 1 hospitalization with any injury diagnosis in the studied time period; most of these children were aged 6 to 11 years at the first ADHD diagnosis and nearly 80% were boys. The distribution of hospitalizations by age was similar for those with any injury and those with brain injury (Figure). The majority of patients hospitalized for an injury had only 1 hospitalization during follow-up (90.3% for any injury and 95.6% for brain injury). More than half (53.9%) of the children received either methylphenidate or atomoxetine at some point during the follow-up. When counting each single tablet separately, most of the prescribed doses (92.0%) were for methylphenidate, with only 8.0% for atomoxetine.

There was a nonsignificant risk reduction during the periods of medication use. The SCCSD is based on time with medication vs time without medication within the same person and was developed to reduce confounding by individual characteristics. Cohort time was restricted to periods after the initial diagnosis of ADHD. We calculated incidence rate ratios for hospitalization with any injury and hospitalization with brain injuries only.\textsuperscript{31} To control for potential seasonal patterns of injuries, we adjusted for calendar quarters in the analysis. We also conducted a sensitivity analysis without accounting for seasonality. Since some children experienced multiple injuries during the follow-up, we conducted a further sensitivity analysis restricting the sample to children with a single hospitalization to assess the effects of potential intraindividual correlation. Initially, we conducted the analyses using the whole age range, adjusting for changing risk of hospitalization with relation to age. Given that the follow-up period of up to 5 years was substantially shorter than the age spectrum (3-17 years), the age segments were contributed by different persons. To obtain estimation from a more homogeneous sample of persons followed up across the complete time and age range, we conducted sensitivity analyses for stepwise-restricted age ranges. In those analyses, only the follow-up time in the specified age range was included. We repeated these steps in a further analysis restricted to brain injury events only (ICD-10-GM code S06).
seasonality in the hospitalizations provided similar results (eTable in the Supplement). Similarly, although results are not shown in the Table, restricting the sample to children with a single hospitalization did not affect the estimates.

Discussion

We demonstrated a risk reduction for injuries among children with ADHD during periods of medication use; this risk reduction was statistically significant only for brain injuries. Recently, Raman et al22 applied the SCCSD to The Health Improvement Network database and reported a risk reduction for injuries among 328 children with ADHD during periods of medication use. Our study covers a substantially larger sample from Germany. Differences in health care systems might affect both diagnosis and treatment of ADHD. Unlike the study by Raman et al, our analysis was restricted to injuries requiring hospital admissions, representing a selection of more severe injuries (38.6% of them brain injuries). The analysis by Raman et al failed to demonstrate a risk reduction for brain injuries, likely as a consequence of a limited sample size and therefore insufficient power.

In our study, the risk for any type of injury while taking ADHD medication was reduced to a lesser degree compared with the risk of brain injuries, which is consistent with previous studies indicating that children with ADHD are particularly prone to brain injuries.22,33,34 The risk reduction for hospitalizations with any type of injury diagnosis missed statistical significance, but the point estimates were directed toward a risk reduction. While the SCCSD controls intrinsically for time-invariant characteristics of the study participants, it cannot adjust for time-dependent risk factors. For instance, it does not account for changes in the severity of ADHD symptoms over time. However, since patients are also more likely to receive medication during periods of more severe symptoms, the estimate of risk reduction during periods of medication use is rather conservative. While some patients also received atomoxetine, the majority of prescriptions were for methylphenidate; therefore, the observed effects are mainly related to methylphenidate. Since we included only patients with newly diagnosed ADHD, behavioral therapy or changes in diet could have taken place during follow-up, thus confounding the effects of medication. However, this increased attention to a new diagnosis of ADHD would also occur during periods without medication. From our previous analyses,17,27 we know that medication use increased during the first year after diagnosis of ADHD. Therefore, if additional approaches to treat ADHD took place mainly after the initial diagnosis and decreased the risk of injuries, the observed risk reduction during periods of medication use would be biased downward. One could expect that medication prescriptions can increase after a hospitalization with injury diagnosis, but this was not the case in the studied sample.

Using a large administrative database in Germany, we were able to study a large number of injury cases in a cohort of children and adolescents with ADHD and analyze specific and more severe injuries (ie, brain injuries). Applying the SCCSD, we could control for potential time-invariant confounders that could have biased results of previous observational studies.

Our study has some limitations. We restricted the analysis to hospitalizations with injury diagnoses and did not consider injuries treated in the outpatient setting. The main reason for this is that diagnoses of the initial event can be used for reimbursement of the medical follow-up in the outpatient setting. In such cases, the same diagnosis is used repeatedly during a longer period. To distinguish between such diagnoses and the first event, a qualifier of “status post injury” should be used, but these qualifiers were not consistently used in 2004 and 2005. Furthermore, outpatient diagnoses do not have an exact date but are specified only at the level of a quarter of a calendar year and could not be assessed for medication status on a daily level. Therefore, our analysis is restricted to injuries that are likely more severe. It is possible that severe and less severe injuries are not affected in the same way by medication in patients with ADHD, but we cannot address this question in our study. In terms of ADHD diagnosis, we used a conservative algorithm requiring more than a single record of ADHD diagnosis. Also, diagnoses that are only suspected or are a reason for consultation but excluded in the process are documented in the data for reimbursement reasons. Formally, such diagnoses should have a specific qualifier, but, as for injuries, these qualifiers were not used consistently during the early years of the study period. The algorithm identified children diagnosed with ADHD in routine standard of care, which might have a certain level of misclassification. Assuming that patients incorrectly diagnosed with ADHD do not benefit from the medication to the same degree as patients who are correctly diagnosed with ADHD, this would attenuate the true effect of medication. Another limitation is the assessment of medication. Based on the information contained in the database, we could identify the number of prescribed tablets but neither the intake recommendation nor whether the medication was actually used. Thus, particularly in patients receiving immediate-release methylphenidate using 2 or more tablets per day, we might have overestimated the days covered by medication; this would bias the effect toward 1. The database is limited to individuals with statutory health insurance; however, in Germany, approximately 90% of the population is covered by this kind of health insurance. Only the remaining 10% are privately insured.

Conclusions

In a large health care database study, we demonstrated a 34% reduction of the risk of hospital admissions with brain injury during medication periods among children with ADHD. The risk reduction estimate was controlled for time-independent characteristics of the patients by the use of the SCCSD.
Acquisition, analysis, or interpretation of data: All authors
Drafting of the manuscript: Mikolajczyk, Horn, Schmedt, Lindemann, Garbe
Critical revision of the manuscript for important intellectual content: Mikolajczyk, Horn, Schmedt, Langner, Garbe
Statistical analysis: Horn, Langner
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Study supervision: Mikolajczyk

Conflict of Interest Disclosures: Dr Garbe has been a consultant to Bayer-Schering, Nycomed, GlaxoSmithKline, Schwabe, Teva, and Novartis. Dr Garbe runs and Mr Schmedt and Ms Lindemann work for a department that occasionally performs studies for pharmaceutical companies, including Bayer, Celgene, GlaxoSmithKline, Mundipharma, Novartis, Sanofi, Sanofi Pasteur MSD, and STADA. At the time of study, Dr Mikolajczyk, Mr Horn, and Ms Lindemann were employees of this department.

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REFERENCES