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Carsten Schröder, Michael Dörks, Bianca Kollhorst, Tilo Blenk, Ralf Dittmann, Edeltraut Garbe, Oliver Riedel

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Corresponding author
Oliver Riedel

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Outpatient antipsychotic drug use in children and adolescents in Germany between 2004 and 2011

Carsten Schröder, MPH[1]; Michael Dörks, PhD[2]; Bianca Kollhorst, Dipl Math[3]; Tilo Blenk, MSC, MD, PhD[1]; Ralf W. Dittmann, MSC, MD, PhD[4]; Edeltraut Garbe, MSC, MD, PhD[1]; Oliver Riedel, PhD[1]

[1] Leibniz Institute for Prevention Research and Epidemiology - BIPS, Department of Clinical Epidemiology, Achterstr. 30, 28359 Bremen, Germany

[2] Carl von Ossietzky University Oldenburg, Department of Health Services Research, Ammerländer Heerstraße 140, 26111 Oldenburg, Germany

[3] Leibniz Institute for Prevention Research and Epidemiology - BIPS, Department of Biometry and Data Management, Achterstr. 30, 28359 Bremen, Germany

[4] University of Heidelberg, Medical Faculty Mannheim, Central Institute of Mental Health, Department of Child and Adolescent Psychiatry and Psychotherapy, Paediatric Psychopharmacology, J 5, 68159 Mannheim, Germany

Corresponding author
PD Dr. rer. nat. Oliver Riedel
Leibniz Institute for Prevention Research and Epidemiology - BIPS
Achterstraße 30
28359 Bremen
Germany
E-Mail: riedel@leibniz-bips.de
Phone: +49 421 218 56883

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Abstract

Studies from different countries showed increasing use of antipsychotics in pediatric patients. However, these studies were methodologically limited and could not assess underlying diagnoses and off-label use sufficiently. This is the first study to examine antipsychotic prescriptions in a representative sample of minors over a long period, looking at changes regarding substances and drug classes, underlying diagnoses, and the rate of off-label use.

Claims data of about two million pediatric subjects were used to calculate annual prevalences and incidence rates of antipsychotic prescriptions for the years 2004 to 2011. Analyses were stratified by sex, age, and drug type. Numbers of prescriptions, frequencies of diseases/disorders, the prescribing physicians' specialties, and the share of off-label prescriptions were examined.

During the study period, the prevalence of antipsychotic prescriptions ranged between 2.0 and 2.6 per 1,000 minors. Antipsychotic prescriptions in children younger than six years decreased from 2.42 per 1,000 subjects in 2004 to 0.48 in 2011. Among antipsychotic users, 47.0% had only one prescription and hyperkinetic disorder was by far the most frequent diagnosis. The annual share of off-label prescriptions varied between 61.0 and 69.5%.

Antipsychotics were mainly prescribed to manage aggressive and impulsive behaviors in hyperkinetic disorder patients. This explains the high share of off-label prescriptions but raises concerns since efficacy and safety of antipsychotics in this indication have not been sufficiently investigated. The decreasing antipsychotic use in younger children and the high proportion of antipsychotic users with one-time prescriptions are striking and should be further investigated in the future.

Keywords

Antipsychotics, Neuroleptics, Children, Adolescents, Off-label use, Epidemiology

Introduction

Antipsychotics (APs) are frequently used for the treatment of mental and behavioral disorders like schizophrenia and bipolar disorder, and especially for treating hallucinations and delusions. Because of their sedative effects, APs are also used to treat sleep disorders, anxiety disorders, and restlessness and agitation. Based on their mechanisms and effects, they can be categorized into typical (first generation/conventional) and atypical (second generation) APs [1].

Typical APs can cause anticholinergic and extrapyramidal side effects, including tardive dyskinesia that can persist for years after therapy discontinuation. These adverse events might also appear under treatment with atypical APs, although to a lesser extent. In addition, atypical APs may cause marked weight gain and hyperlipidemia, possibly resulting in metabolic syndrome [1, 2]. So far, there is only limited knowledge about the safety and effectiveness of AP use in pediatric patients [3, 4]. Some evidence even suggests that children are at higher risk for some adverse events like extrapyramidal and metabolic side effects than adults [5].

Despite that, studies from different countries observed increasing AP use in young patients [6-15]. However, studies so far were methodologically limited because of small sample sizes [7, 9-12, 14-16], short observation periods [13, 15, 16], or restrictions to specific agents [13] or to patients with specific conditions [8]. For Germany, only one recent study investigated pediatric AP use over a longer time period [6]. The authors observed an increase of AP prescriptions in patients aged 0-19 years from 2.3 to 3.2 per 1,000 subjects between 2005 and 2012, with increasing use of atypical and slightly decreasing use of typical APs. However, since this study was based on data from just one statutory health insurance (SHI) provider, known to include individuals with an on average higher socioeconomic status, the results might not be representative [17]. Besides, underlying diagnoses and off-label use were not assessed.

Off-label use of drugs, which is associated with an increased risk of inadequate dosing and adverse events [18, 19], is common in pediatric patients due to lacking regulatory approvals for this population. So far, little is known about the extent of off-label AP use in minors. Previous studies, which showed strongly varying rates of off-label use between 36 and 93%, were often limited by small sample sizes or did not factor in all types of off-label use but were restricted to off-label use by age and/or off-label use by indication but did not consider off-label use by contraindication [20].

To our knowledge, this is the first study examining pediatric AP use in a representative sample of minors over a long observation period, covering a wide range of substances and investigating off-label use. In detail, we assess a) annual prevalence and incidence rates (IR) of AP prescriptions in subjects aged 0-17 years from 2004 to 2011, stratified by age, sex, and type of drug, b) the number of prescriptions per patient, c) diagnoses of AP users, and

d) the extent of off-label use.

Methods

Data source

Data from three SHI providers which are part of the German Pharmacoepidemiological Research Database (GePaRD) were used for this study. GePaRD contains information on demographics, hospitalizations, diagnoses, and outpatient prescriptions [21]. Diagnoses are coded according to the International Classification of Diseases, 10th Version, German Modification (ICD-10-GM). Hospitalization data include admission and discharge dates with corresponding diagnoses. Outpatient care data include drug prescriptions and diagnoses. Outpatient prescription data contain the defined daily dose and the Anatomical Therapeutic Chemical (ATC) code of the drugs, information on the prescribing physician's specialty, and the dates of prescription and pharmacy dispensation. GePaRD is representative for the German population regarding age, sex, region of residence, drug use, and number of hospital admissions [22, 23].

Study Design

The study population included individuals aged 0-17 years between 2004 and 2011 (all years for which data were available at the time of the study). We used a cross-sectional design to examine the annual prevalence of outpatient AP prescriptions. Minors with continuous insurance time a) during the whole respective study year, or b) from birth in the study year until the end of the study year, or c) from birth in the study year until death in the same year, or d) from the start of the study year until death in the same year, were included.

A cohort design was used to examine annual IRs of AP prescriptions for the years 2005 to 2011. Before January 1 of the respective study year, all individuals except newborns had to have 12 months of continuous insurance coverage without AP prescriptions (or without prescriptions of the specific drug class for the analyses stratified by drug class). Subjects with an AP prescription in the year after this baseline period were categorized as incident. Individuals entered the cohort on January 1 of the respective study year (newborns on their first day of insurance) and were followed until either the first dispensation of an AP, December 31 of that year, or the end of insurance coverage.

Drug exposure

All APs with an ATC code starting with N05A and the code N05CM22 (promethazine) were considered and categorized into typical and atypical APs.

Diagnoses

Diagnoses were identified in inpatient and outpatient data. Outpatient diagnoses do not have an exact date but are related to a three-month interval (quarter of a year) in GePaRD. All approved indications of the drugs under study and other diagnoses of diseases of the nervous system (ICD-10-GM: G00-G99) and of mental and behavioral disorders (F00-F99) were considered.

Off-label use

We used information on the licensed age range, the approved indications, and contraindications of the APs under study as stated in the Summaries of Product Characteristics (SPCs). A prescription was regarded off-label if the subject was younger than the licensed age, or had no diagnosis of an approved indication in the quarter of the prescription or in the preceding or following quarter, or had a diagnosis of a contraindication in the quarter of the prescription, or a simultaneous prescription of a contraindicated drug. Approved indications were assumed for all generic drugs if SPCs of same-substance preparations gave divergent information. If the licensed age varied by indication or if SPCs of generic preparations gave inconsistent information, the lowest age limit was used.

Statistical analyses

The numbers of AP users and AP prescriptions were assessed stratified by sex, age group, drug class, substance, and prescribing physician's specialty. Annual prescription prevalences (per 1,000 subjects) were calculated by dividing the number of individuals with AP prescription in a particular year by the total number of individuals in that year. Annual IRs (per 10,000 person-years (py)) were calculated by dividing the total number of incident AP users in the respective year by the sum of py of the cohort in that particular year. The substitution method was used to calculate 95% confidence intervals (CI), assuming a Poisson distributed number of events and a fixed person-time without sampling variation. SAS statistical software version 9.3 was used for all analyses.

Trial Registration

This study is registered in the register of studies of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (http://encepp.eu/encepp/viewResource.htm?id=9854).

Results

Study population

The study population included a minimum of 1,993,994 (in 2004) and a maximum of 2,160,541 (in 2009) subjects. Table 1 shows the characteristics of the study population exemplarily for the last year of the study period. There were only small variations regarding sex and age distribution. In each year, the share of boys (51.1 to 51.2%) was slightly higher than that of girls. The mean age varied between 8.8 and 9.0 years.

Prevalence of AP prescriptions and off-label use

The one-year prevalence of AP prescriptions ranged between 2.03 (95% CI: 1.97-2.09) per 1,000 minors in 2006 and 2.61 (95% CI: 2.54-2.68) in 2011 (Figure 1). Over time, the use of typical APs decreased from 1.73 (95% CI: 1.67-1.79) prescriptions per 1,000 subjects to 0.96 (95% CI: 0.92-1.00) while the use of atypical APs increased from 0.82 (95% CI: 0.78-0.86) to 1.85 (95% CI: 1.80-1.91).

These trends can also be found for the most frequently prescribed APs in 2004 and 2011 (Table 2). In 2004, 33.6% of all AP users received a prescription of promethazine. Until 2011, this proportion decreased to 14.1% while risperidone became the most frequently prescribed AP (54.1%).

In 2011, there were only few AP prescriptions in children younger than six years (0.48 per 1,000 subjects (95% CI: 0.43-0.54)), while for 6-17-year-olds the prevalence was 3.53 (95% CI: 3.44-3.63). This differed from 2004 where the prevalences were 2.42 (95% CI: 2.30-2.55) and 2.41 (95% CI: 2.33-2.49) in those age groups. The total number of children aged 0-5 years treated with APs decreased from 1,443 in 2004 to 301 in 2011. In this age group, promethazine was the most frequently prescribed AP with a share between 57.9 and 81.3% throughout the study period, while the proportion of AP users with a prescription of risperidone increased from 1.1 to 13.0%. In subjects older than five years, the total number of treated individuals increased from 3,372 in 2004 to 5,158 in 2011. In this age group, risperidone was most frequently prescribed with an increasing share from 26.8% to 56.5%. The proportion of AP users aged 6-17 years with a prescription of the most frequently prescribed typical AP promethazine more than halved between 2004 and 2011 (from 22.9 to 11.1%).

The prevalence of AP prescriptions was much higher in boys than in girls in each study year. In 2011, the prevalence was 3.67 per 1,000 boys (95% CI: 3.56-3.78) and 1.51 per 1,000 girls (95% CI: 1.43-1.58).

In 2011, pediatricians prescribed 30.1% of all APs, followed by child and adolescent psychiatrists (27.6%), physicians for internal and general medicine (13.3%), and general practitioners (3.9%). For 15.9%, the specialty was unknown/not reported. The remaining 9.2% were issued by physicians with other specialties.

Hyperkinetic disorder was the most prevalent diagnosis among AP users throughout the study period with a steady increase from 21.4% in 2004 to 49.0% in 2011 (Table 3). The prevalence of conduct disorder, the second most frequent diagnosis in 2011, almost doubled since 2004 (from 10.9 to 21.4%), while the prevalence of

restlessness and agitation varied between 17.8% (in 2005) and 20.6% (in 2011). The prevalence of sleep disorder decreased from 16.2 to 7.9%. In 2011, most patients (60.9%) had two or more different diagnoses.

Considering only AP users younger than six years, sleep disorder was the most common diagnosis with a prevalence varying between 28.1% (in 2009) and 32.0% (in 2004), followed by restlessness and agitation (12.1 to 17.1%). In this age group, the share of children with a hyperkinetic disorder diagnosis increased from 4.2 to 12.3%.

Looking at all subjects with a diagnosis of hyperkinetic disorder, we saw that risperidone, pipamperone, and tiapride were the most frequently prescribed APs in all of the study years. In 2004, 40.4% of all young individuals diagnosed with hyperkinetic disorder had at least one prescription of risperidone. This percentage increased to 70.4% in 2011. During the same time, the prevalence of pipamperone and tiapride prescriptions decreased from 29.9 to 15.5% and from 17.7 to 8.0%, respectively.

Regarding the number of prescriptions per patient during the study period, differences were observed between users of any AP, users of typical, and users of atypical APs. Among users of typical APs, 66.6% had 1 prescription, 19.8% had 2-5 prescriptions, and 13.7% had more than 5 prescriptions (mean=3.7, median=1). Among atypical AP users, 21.1% had 1 prescription, 30.5% had 2-5 prescriptions, and 48.4% had more than 5 prescriptions (mean=10.0, median=5) (users of any AP: 1 prescription: 47.0%, 2-5: 23.4%, more than 5: 29.6%, mean=7.1, median=2). The proportion of AP users with one-time prescriptions decreased from 54.3% in 2004 to 29.0% in 2011 (from 68.7 to 53.2% among users of typical APs; from 22.4 to 18.4% among users of atypical APs). Correspondingly, the mean number of prescriptions increased from 3.4 to 4.7 (from 2.4 to 3.2 among users of typical APs; from 4.9 to 5.0 among users of atypical APs).

Among patients with one-time prescriptions, hyperkinetic disorder was the most frequent diagnosis as well (Table 3).

In 2004, 61.0% of all APs were prescribed off-label. This share increased to 69.0% in 2006, varied between 68.1 and 69.5% in the years 2007 to 2009, and decreased after that to 62.0% in 2011.

Restricting the analysis to subjects with risperidone prescriptions, we observed that between 52.1% (in 2011) and 61.8% (in 2009) of these patients received their risperidone prescription off-label. The most frequent diagnosis among these off-label risperidone users was hyperkinetic disorder with an increasing prevalence from 43.9% in 2004 to 63.8% in 2011, followed by pervasive developmental disorder with a prevalence between 21.9% (in 2008) and 27.0% (in 2011).

Incidence of AP prescriptions

The IR of AP prescriptions was 13.8 (95% CI: 13.2-14.3) per 10,000 py in 2005 and remained relatively constant until 2011 with an IR of 13.2 (95% CI: 12.6-13.7). During the same time, the IR of typical APs decreased from 10.1 (95% CI: 9.7-10.6) to 6.8 (95% CI: 6.4-7.2) per 10,000 py, while the IR of atypical APs increased from 4.8 (95% CI: 4.4-5.1) to 8.2 (95% CI: 7.8-8.6).

The IR was higher for males than for females with the largest difference in 2008 (16.0 (95% CI: 15.2-16.9) vs. 8.6 (95% CI: 8.0-9.2) per 10,000 py).

In every year, except 2005, the highest IR was observed in the group of 15-17-year-olds (Figure 2).

Discussion

We used claims data of more than two million minors to examine patterns of AP prescriptions and the extent of off-label use from 2004 to 2011. We observed considerable changes regarding the prescribed drug classes and substances and high rates of one-time prescriptions and off-label use.

Our results show a marked increase of atypical AP prescriptions over time, while the prevalence of typical APs declined. Similar results have been found in a study which investigated the frequency of AP prescriptions in young patients (0-19 years) based on claims data from one German SHI [6]. In this study, the prevalence of atypical AP prescriptions increased from 1.0 to 2.4 per 1,000 subjects, while the prevalence of typical APs slightly decreased from 1.4 to 1.2 between 2005 and 2012. Recently, similar changes have also been observed in a French study [24]. Although the prevalence of AP use varies between studies, which might be due to methodological and health-political or cultural differences, the trends are quite consistent. The increase of atypical APs is usually thought to result from their more favorable side effect profile in comparison to typical APs [25], even though this is not undisputed [13]. Atypical APs may cause short- or long-term adverse events including marked weight gain and hyperlipidemia and – like conventional APs – they may also cause extrapyramidal symptoms [6], although to a lesser degree. Another explanation for the increasing use of atypical APs and for the decreasing use of typical APs resides in the fact that a growing number of atypical APs have been licensed over recent years. Furthermore, the approved indications of atypical APs have been widened and may now also include indications for children. For example, in 2004, the use of risperidone, introduced to the German market in 1994, was extended to short-term treatment (up to six weeks) of persistent aggression in conduct disorder in patients older than four years with sub-average intellectual functioning or mental retardation.

Between 2004 and 2011, the prevalence of AP prescriptions decreased markedly in younger children (0-5 years) where promethazine was by far the most commonly prescribed AP. Although Olfson et al. [12] recently

observed similar trends in the United States, the reasons for the strong decline of AP use in younger age groups and the increasing prevalence in older age groups remain unclear.

Promethazine is not only licensed for the treatment of restlessness and agitation in an underlying psychiatric disorder but also for the treatment of nausea and vomiting and of sleep disorders in adults. Apart from that, it can also be used as an antihistamine. However, since only the ATC codes for psycholeptic agents were included in our study, it can be assumed that the observed prescriptions were issued for psychiatric indications.

The most frequent diagnoses among AP users show that, in minors, APs are mainly used to manage aggressive and impulsive behaviors. This was different when looking exclusively at children younger than six years where sleep disorder was by far the most common diagnosis. However, considering all age groups, hyperkinetic disorder was by far the most frequent diagnosis which has also been observed in other studies [6, 10, 13]. The higher prevalence of AP prescriptions in boys corresponds to their much higher prevalence of hyperkinetic disorder [26, 27]. One possible explanation for the markedly increasing share of patients with a hyperkinetic disorder diagnosis among children and adolescents treated with APs could be the increasing awareness regarding this disorder and consequently its rising prevalence. For example, Grobe et al. [28] reported an increase in the prevalence of hyperkinetic disorder in individuals aged up to 19 years by 42% between 2006 and 2011 when analyzing outpatient claims data from one large German SHI. The increasing proportion of AP users with a diagnosis of conduct disorder can to some extent be explained by the extension of the approved indications for risperidone in 2004, as mentioned above.

We observed a high proportion of AP users with one-time prescriptions, although disorders like hyperkinetic disorder, conduct disorder, and restlessness and agitation, which were the most frequent diagnoses among all AP users and also among AP users with one-time prescriptions, usually persist for a time period not covered by one prescription. However, over time, the proportion of one-time AP prescriptions decreased, indicating a trend towards longer treatment durations. Evidence for this has also been observed in studies from the Netherlands and the United Kingdom [29, 30].

Our results showed a higher median number of prescriptions for users of atypical than typical APs. Accordingly, the proportion of one-time prescriptions was much higher for typical APs. This can be explained by the fact that atypical APs are usually more frequently prescribed for the treatment of disorders with a more continuous course like pervasive developmental disorders, while the most frequently prescribed typical APs are rather prescribed for the treatment of mania, restlessness and agitation, and sleep disorders [29]. Another explanation is the supposedly higher rate of adverse events, especially extrapyramidal symptoms, caused by typical APs, which can

lead to early therapy discontinuation [25, 29]. With the exception of early manifestations of dyskinesia, these adverse events, however, usually do not occur within a time period covered by one prescription.

The observed high share of off-label prescriptions is not surprising considering that hyperkinetic disorder was the most frequent diagnosis among AP users while no AP has been licensed for the treatment of this disorder so far. Although it cannot be inferred from our results that every AP user with a diagnosis of hyperkinetic disorder received the AP prescription for the treatment of this disorder, the high proportion of off-label AP users with a hyperkinetic disorder diagnosis, who by definition did not have another diagnosis of an approved indication for the AP prescription, make it seem likely that APs were frequently prescribed to treat symptoms of hyperkinetic disorder.

Even though APs are frequently used in combination with psychostimulants in the treatment of hyperkinetic disorder, their efficacy in managing impulsive and aggressive behavior in hyperkinetic disorder patients has not yet been confirmed [31]. Besides, the German guideline only recommends cautious use of APs, since their risks may be greater than their benefit [32]. However, our results show that most APs were prescribed by physicians specialized in the treatment of pediatric patients and patients with psychiatric disorders.

Due to variations in the licensed indications of drugs and also to different treatment standards, international comparisons of the extent of off-label use are difficult. Accordingly, studies from different countries show proportions of AP off-label use in pediatric patients between 36 and 93% [20].

The size of the used database is a major strength of our study. GePaRD contains data representative for the general population in Germany and reflects real-world drug utilization patterns [22, 23]. Drug exposure was determined based on pharmacy dispensing data which is considered the gold standard in pharmacoepidemiological research since recall bias cannot occur [33]. It has been shown that drug dispensation data give valid information on drug use in Germany [23, 34]. Since no information about inpatient drug treatment is available in GePaRD, we were only able to analyze outpatient treatment. However, since all examined APs are available by prescription only, the database provides complete and valid information on outpatient AP dispensations. Misclassification of drug exposure is rather unlikely as drug prescriptions were available with the exact date of dispensation. Yet, outpatient diagnoses were only related to a quarter of a year which makes some misclassification possible regarding underlying diagnoses. Besides, patients' adherence to drug prescriptions is not known.

Conclusions

Our results show that in minors, APs are mainly prescribed to patients diagnosed with hyperkinetic disorder. While this explains the high share of off-label prescriptions, it also raises concerns since the efficacy and safety of APs in managing impulsive and aggressive behavior in hyperkinetic disorder patients have not been sufficiently investigated. The marked decrease of AP use in younger children and the high proportion of AP users with one-time prescriptions are remarkable. The reasons for and the adequacy of the short treatment durations should be examined in future studies.

Ethics and consent

In Germany, the Code of Social Law (SGB X) regulates the use of SHI data for scientific research. All involved SHIs and their governing authorities approved the use of the data for this study. Informed consent and approval by an ethics committee were not needed.

Conflict of interest

C.S., B.K., T.B., and O.R. are working in departments that occasionally perform studies for pharmaceutical industries as indicated below. Until October 2014, M.D. worked at the same institute, and until August 2015, E.G. was head of a department there. The pharmaceutical companies include Bayer, Celgene, GSK, Mundipharma, Novartis, Sanofi, Sanofi Pasteur MSD, and STADA. E.G. has been a consultant to Bayer, Nycomed, Teva, GSK, Schwabe, Astellas, Takeda, and Novartis on issues unrelated to the subject of the study. R.W.D. has received compensation for serving as consultant or speaker, or he or the institution he works for has received research support or royalties from the companies or organizations indicated: EU (FP7 Programme), US National Institute of Mental Health (NIMH), German Federal Ministry of Health/Regulatory Agency (BMG/BfArM), German Federal Ministry of Education and Research (BMBF), German Research Foundation (DFG), Volkswagen Foundation, Boehringer Ingelheim, Ferring, Janssen-Cilag, Lilly, Lundbeck, Otsuka, Servier, Shire, Sunovion/Takeda, and Theravance. R.W.D. owns Eli Lilly stock.

References

1. Preston JD., O'Neal JH., Talaga MC. (2013) Handbook of Clinical Psychopharmacology for Therapists. New Harbinger Publications, Oakland
2. Correll CU, Blader JC (2015) Antipsychotic Use in Youth Without Psychosis: A Double-edged Sword. JAMA Psychiatry 72:859-860
3. Ben Amor L (2012) Antipsychotics in pediatric and adolescent patients: a review of comparative safety data. J Affect Disord 138 Suppl:S22-30
4. Seida JC, Schouten JR, Boylan K, Newton AS, Mousavi SS, Beaith A, Vandermeer B, Dryden DM, Carrey N (2012) Antipsychotics for children and young adults: a comparative effectiveness review. Pediatrics 129:e771-784
5. Vitiello B, Correll C, van Zwieten-Boot B, Zuddas A, Parellada M, Arango C (2009) Antipsychotics in children and adolescents: increasing use, evidence for efficacy and safety concerns. Eur Neuropsychopharmacol 19:629-635
6. Bachmann CJ, Lempp T, Glaeske G, Hoffmann F (2014) Antipsychotic prescription in children and adolescents: an analysis of data from a German statutory health insurance company from 2005 to 2012. Dtsch Arztebl Int 111:25-34
7. Schubert I, Lehmkuhl G (2009) Increased antipsychotic prescribing to youths in Germany. Psychiatr Serv 60:269
8. Steinhausen HC, Bisgaard C (2014) Nationwide time trends in dispensed prescriptions of psychotropic medication for children and adolescents in Denmark. Acta Psychiatr Scand 129:221-231
9. Ronsley R, Scott D, Warburton WP, Hamdi RD, Louie DC, Davidson J, Panagiotopoulos C (2013) A population-based study of antipsychotic prescription trends in children and adolescents in British Columbia, from 1996 to 2011. Can J Psychiatry 58:361-369
10. Alessi-Severini S, Biscontri RG, Collins DM, Sareen J, Enns MW (2012) Ten years of antipsychotic prescribing to children: a Canadian population-based study. Can J Psychiatry 57:52-58
11. Olfson M, Blanco C, Liu SM, Wang S, Correll CU (2012) National trends in the office-based treatment of children, adolescents, and adults with antipsychotics. Arch Gen Psychiatry 69:1247-1256
12. Olfson M, King M, Schoenbaum M (2015) Treatment of Young People With Antipsychotic Medications in the United States. JAMA Psychiatry 72:867-874
13. Pringsheim T, Lam D, Patten SB (2011) The pharmacoepidemiology of antipsychotic medications for Canadian children and adolescents: 2005-2009. J Child Adolesc Psychopharmacol 21:537-543
14. Alexander GC, Gallagher SA, Mascola A, Moloney RM, Stafford RS (2011) Increasing off-label use of antipsychotic medications in the United States, 1995-2008. Pharmacoepidemiol Drug Saf 20:177-184
15. Zoega H, Baldursson G, Hrafnkelsson B, Almarsdottir AB, Valdimarsdottir U, Halldorsson M (2009) Psychotropic drug use among Icelandic children: a nationwide population-based study. J Child Adolesc Psychopharmacol 19:757-764
16. Koelch M, Prestel A, Singer H, Keller F, Fegert JM, Schlack R, Hoelling H, Knopf H (2009) Psychotropic medication in children and adolescents in Germany: prevalence, indications, and psychopathological patterns. J Child Adolesc Psychopharmacol 19:765-770

17. Hoffmann F, Bachmann CJ (2014) [Differences in sociodemographic characteristics, health, and health service use of children and adolescents according to their health insurance funds]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 57:455-463
18. European Medicines Agency (2007) The European paediatric initiative: History of the Paediatric Regulation. www.ema.europa.eu/docs/en_GB/document_library/Other/2009/09/WC500003693.pdf. Accessed 13 May 2016
19. Turner S, Nunn AJ, Fielding K, Choonara I (1999) Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. Acta Paediatr 88:965-968
20. Carton L, Cottencin O, Lapeyre-Mestre M, Geoffroy PA, Favre J, Simon N, Bordet R, Rolland B (2015) Off-Label Prescribing of Antipsychotics in Adults, Children and Elderly Individuals: A Systematic Review of Recent Prescription Trends. Curr Pharm Des 21:3280-3297
21. Pigeot I, Ahrens W (2008) Establishment of a pharmacoepidemiological database in Germany: methodological potential, scientific value and practical limitations. Pharmacoepidemiol Drug Saf 17:215-223
22. Schink T, Garbe E (2010) Assessment of the representativity of in-patient hospital diagnoses in the German Pharmacoepidemiological Research Database. Gesundheitswesen 72:P10
23. Schink T, Garbe E (2010) Representativity of dispensations of non-steroidal anti-inflammatory drugs (NSAIDs) in the German Pharmacoepidemiological Research Database. Gesundheitswesen 72:V111
24. Verdoux H, Pambrun E, Cortaredona S, Tournier M, Verger P (2015) Antipsychotic prescribing in youths: a French community-based study from 2006 to 2013. Eur Child Adolesc Psychiatry 24:1181-1191
25. Ucok A, Gaebel W (2008) Side effects of atypical antipsychotics: a brief overview. World Psychiatry 7:58-62
26. Schlack R, Holling H, Kurth BM, Huss M (2007) The prevalence of attention-deficit/hyperactivity disorder (ADHD) among children and adolescents in Germany. Initial results from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS). Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 50:827-835
27. Lindemann C, Langner I, Kraut AA, Banaschewski T, Schad-Hansjosten T, Petermann U, Petermann F, Schreyer-Mehlhop I, Garbe E, Mikolajczyk RT (2012) Age-specific prevalence, incidence of new diagnoses, and drug treatment of attention-deficit/hyperactivity disorder in Germany. J Child Adolesc Psychopharmacol 22:307-314
28. Grobe TG, Bitzer EM, Schwartz FW (2013) BARMER GEK Arztreport 2013. http://presse.barmer-gek.de/barmer/web/Portale/Presseportal/Subportal/Presseinformationen/Archiv/2013/130129-Arztreport-2013/PDF-Arztreport-2013.pdf. Accessed 4 August 2016
29. Kalverdijk LJ, Tobi H, van den Berg PB, Buiskool J, Wagenaar L, Minderaa RB, de Jong-van den Berg LT (2008) Use of antipsychotic drugs among Dutch youths between 1997 and 2005. Psychiatr Serv 59:554-560
30. Rani F, Murray ML, Byrne PJ, Wong IC (2008) Epidemiologic features of antipsychotic prescribing to children and adolescents in primary care in the United Kingdom. Pediatrics 121:1002-1009
31. Linton D, Barr AM, Honer WG, Procyshyn RM (2013) Antipsychotic and psychostimulant drug combination therapy in attention deficit/hyperactivity and disruptive behavior disorders: a systematic review of efficacy and tolerability. Curr Psychiatry Rep 15:355

32. German Society of Child and Adolescent Psychiatry Psychosomatics and Psychotherapy (2007) [Guideline hyperkinetic disorders (F90)]. http://www.awmf.org/en/awmf-online-portal-for-scientific-medicine/awmf-news.html. Accessed 13 May 2016
33. Schneeweiss S, Avorn J (2005) A review of uses of health care utilization databases for epidemiologic research on therapeutics. J Clin Epidemiol 58:323-337
34. Hoffmann F, Pfannkuche MS, Glaeske G (2008) Validity of information relevant to research in routine medication claims data from 2000 to 2006. Dtsch Med Wochenschr 133:945-949

Tab. 1 Characteristics of the study population in 2011

	N (%)
Study population	2,090,135 (100.0)
Male	1,068,606 (51.1)
Female	1,021,529 (48.9)
Age (years):	
<1	112,200 (5.4)
1-2	212,454 (10.2)
3-5	304,486 (14.6)
6-11	683,307 (32.7)
12-14	405,782 (19.4)
15-17	371,906 (17.8)
Mean (SD)	8.9 (5.2)
Q1	4
Median	9
Q3	13

Tab. 2 The ten most frequently prescribed antipsychotics to minors aged 0-17 years in 2004 and 2011 (values are expressed as %)

2004 (n=4,815)		**2011** (n=5,459)	
Promethazine (T)	33.6	Risperidone (A)	54.1
Risperidone (A)	19.1	Pipamperone (T)	14.9
Pipamperone (T)	15.0	Promethazine (T)	14.1
Promazine (T)	13.0	Tiapride (A)	7.7
Tiapride (A)	10.6	Quetiapine (A)	5.6
Chlorprothixene (T)	3.5	Chlorprothixene (T)	3.5
Levomepromazine (T)	2.3	Aripiprazole (A)	3.5
Olanzapine (A)	2.3	Melperone (T)	2.4
Melperone (T)	1.9	Levomepromazine (T)	1.8
Sulpiride (A)	1.5	Olanzapine (A)	1.7

Columns may add up to more than 100% because one patient can contribute to more than one line.
Abbreviations: A = Atypical antipsychotic; T = Typical antipsychotic

Tab. 3 The ten most frequent diagnoses[a] for pediatric antipsychotic users in 2011

Diagnosis (ICD-10-GM code)	n (%)
Antipsychotic users	**5,459 (100.0)**
Hyperkinetic disorder (F90) [c]	2,676 (49.0)
Conduct disorder (F91)	1,169 (21.4)
Restlessness & agitation (F43, R45.0, R45.1, R45.4, R46.3)	1,126 (20.6)
Other behavioral and emotional disorder (F98)	883 (16.2)
Mental retardation (F70-F79)	874 (16.0)
Mixed disorder of conduct and emotions (F92)	817 (15.0)
Specific developmental disorder of speech and language (F80) [c]	733 (13.4)
Autism (F84.0, F84.1, F84.5)	699 (12.8)
Emotional disorder with onset specific to childhood (F93)	669 (12.3)
Mixed specific developmental disorder (F83) [c]	655 (12.0)
Number of diagnoses[b]:	
One	1,510 (27.7)
Two	1,717 (31.5)
More than two	1,607 (29.4)
None	625 (11.4)
Antipsychotic users with one single prescription	**1,583 (100.0)**
Hyperkinetic disorder (F90) [c]	506 (32.0)
Restlessness & agitation (F43, R45.0, R45.1, R45.4, R46.3)	275 (17.4)
Conduct disorder (F91)	185 (11.7)
Sleep disorder (F51, G47)	184 (11.6)
Depression (F20.4, F32, F33)	163 (10.3)
Emotional disorder with onset specific to childhood (F93)	152 (9.6)
Mixed disorder of conduct and emotions (F92)	147 (9.3)
Other behavioral and emotional disorder (F98)	138 (8.7)
Mental retardation (F70-F79)	116 (7.3)
Mixed specific developmental disorder (F83) [c]	109 (6.9)

Columns add up to more than 100% because one patient can contribute to more than one line.
[a] Among the analyzed comorbidities during the quarter of the antipsychotic prescription.
[b] Related to the ten most frequent diagnoses.
[c] None of the antipsychotic agents under study was licensed for the treatment of this disorder during the study period.

Figure captions

Fig 1 Prevalence of antipsychotic prescriptions in minors aged 0-17 years from 2004 to 2011

Abbreviations: AP = antipsychotic

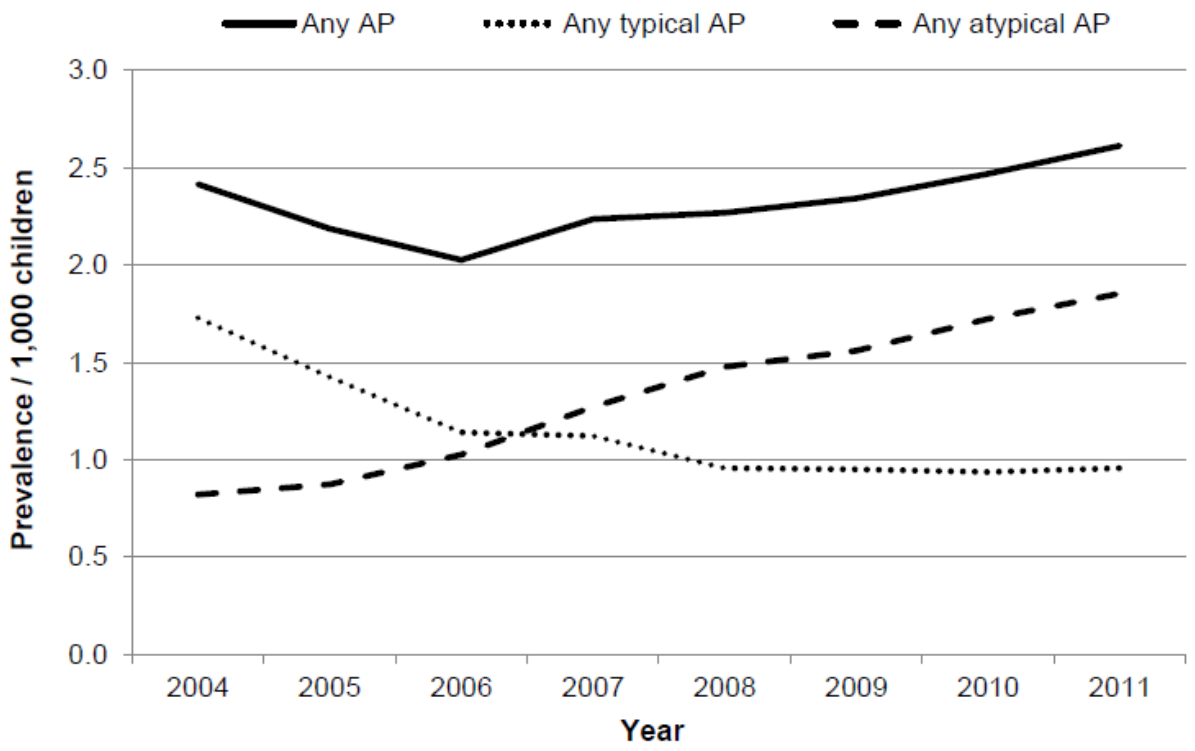

Fig. 2 Incidence of antipsychotic prescriptions in minors aged 0-17 years from 2005 to 2011 by age group