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

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Running head:
Antidepressant use in children and adolescents

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Key points:

- The annual prevalence of antidepressant prescriptions in minors aged 0-17 years was relatively stable between 2004 and 2011 in Germany (1.7 to 2.1 per 1.000 minors).
- The use of selective serotonin reuptake inhibitors (especially fluoxetine) markedly increased from 2004 to 2011 while the use of tricyclic antidepressants declined.
- Among pediatric antidepressant users, 46.4% received only one single prescription.
- Depression was by far the most frequent diagnosis among all pediatric antidepressant users as well as among subjects with only one single prescription.
- In 2011, 36.3% of all antidepressant prescriptions to children and adolescents were off-label.

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Conflict of interest statement:

C. S., B. K., T. B., and O. R. are working in, until October 2014 M. D. was working in, and, until August 2015, E. G. was head of a department that occasionally performs studies for pharmaceutical industries. These 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, 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 have 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. Funding for this study was provided by the German Federal Institute for Drugs and Medical Devices (BfArM). BfArM reviewed the study protocol and commented on the study report but had no further role in the conduct of the study; collection, management, analysis, and interpretation of data; and preparation, review, or approval of the manuscript.

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Abstract

Purpose

Recent studies on the utilization of antidepressant drugs in minors are scarce, methodologically limited and do not factor in off-label use sufficiently. Beyond that, little is known about the short treatment durations that have been observed for many young antidepressant users. The present study examined antidepressant use in pediatric patients aged 0 to 17 years over time, investigated changes regarding the prescribed drugs, analyzed underlying diagnoses, and assessed the rate of off-label use.

Methods

We used claims data of roughly two million individuals to calculate annual prevalence and incidence rates of antidepressant prescriptions for the years 2004 to 2011. Analyses were stratified by age, sex, and drug type. For antidepressant users, numbers of prescriptions, frequencies of disorders/diseases, and specialties of the prescribing physicians were examined. The share of off-label prescriptions was calculated for each year.

Results

The prescription prevalence of antidepressants ranged between 1.7 and 2.1 per 1,000 minors. The use of tricyclic antidepressants decreased from 0.9 to 0.6 prescriptions per 1,000 minors, while the use of selective serotonin reuptake inhibitors increased from 0.5 to 1.1. Of the patients with an antidepressant prescription, 46.4% only received one prescription. Depression was by far the most frequent diagnosis among all antidepressant users as well as among subjects with only one prescription. In 2011, 36.3% of all prescriptions were off-label.

Conclusions

The high proportion of single prescriptions, even in patients with a diagnosed depression, and the high rate of off-label use are particularly noteworthy and should be further investigated in future studies.

Introduction

Antidepressants (ADs), including selective serotonin reuptake inhibitors (SSRIs), tricyclic ADs (TCAs) and phytotherapeutics like hypericum (St. John's wort), are used for the treatment of depression and other psychiatric disorders like obsessive-compulsive disorder, anxiety disorders and sleep disorders. Concerns about an association between AD use and suicidal behavior in minors resulted in warnings from regulatory authorities in 2004 and led to a decreasing use of ADs.[1, 2] However, this decline was only temporary and studies from different countries observed increasing use in pediatric patients over time.[3-5] A Canadian study, for example, reported increasing annual prevalences of AD prescriptions from 5.9 to 15.4 per 1,000 individuals aged up to 19 years between 1983 and 2007, with increasing SSRI and decreasing TCA prescriptions.[4]

Due to the lack of clinical trials and thus regulatory approvals in the pediatric population, drugs are frequently prescribed off-label to minors, carrying the risk of inadequate dosing and adverse events.[6, 7] Also for ADs, previous studies observed high but strongly varying rates of off-label use.[2, 8-12]

Up to now, studies on pediatric AD use were methodologically limited due to short observation periods,[2, 9-11] small sample sizes,[2, 4, 10] limited age ranges under study,[5, 12] or restrictions to subjects with specific conditions.[12] Most importantly, though urgently needed,[4] prospective data after 2004 are still lacking. In most studies investigating the situation beyond 2004, observation periods ended shortly thereafter.[2, 9-11] So far, only one German study covered a longer observation period including the years 2005 to 2012.[3] The authors observed an increasing prevalence of outpatient AD prescriptions in 0- to 19-year-olds from 3.2 to 4.8 per 1,000 persons, with a growing share of SSRI prescriptions and a declining proportion of TCAs. However, the population examined in this study, though of large size, was based on a single statutory health insurance (SHI), which potentially limits the generalizability of the

results. Besides, no information on underlying diagnoses and off-label use were available. Among minors treated with ADs, even in those with a diagnosed depression, previous studies showed high percentages of patients receiving only one single prescription of an AD agent (up to 51%).[11, 12] Although this indicates short treatment durations which are not in accordance with treatment guidelines,[13-15] further analyses examining the used types of drugs and the underlying diagnoses are still missing. The present study closes this research gap. To our knowledge, this is the first study to investigate outpatient AD use in children and adolescents based on representative data from three German SHIs, covering a long observation period after 2004, as well as a wide range of substances. In detail, we examine a) the annual prevalence and incidence rates (IRs) of AD prescriptions in minors aged 0 to 17 years for the years 2004 to 2011, b) changing prescription patterns over time, c) the number of AD prescriptions per patient, d) diagnoses for AD users, and e) off-label use.

Methods

Data source

We used claims data from three German SHIs included in the German Pharmacoepidemiological Research Database (GePaRD). GePaRD consists of data covering about 20 million persons throughout Germany. The database includes information on demographics, hospitalizations, diagnoses, and outpatient prescriptions.[16] Diagnoses are coded according to the 10th Version of the International Classification of Diseases, German Modification (ICD-10-GM). Among others, hospitalization data include admission and discharge diagnoses with corresponding dates. Outpatient care data include diagnoses and prescriptions. Outpatient prescription data contain the Anatomical Therapeutic Chemical (ATC) code, the defined daily dose (DDD), the dates of prescription and dispensation, and information on the prescribing physician's specialty. GePaRD is representative for the

German population regarding age and sex distribution, region of residence, number of hospital admissions, and drug use.[17, 18]

Study design

The study population comprised individuals aged 0 to 17 years, insured in one of the three participating SHIs between 2004 and 2011. A cross-sectional design was used to assess the annual prevalence of outpatient AD prescriptions. All minors with continuous insurance time either a) during the whole respective study year, or b) from birth in the study year until the end of the 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 study year were included.

We used a cohort design to examine annual IRs of AD prescriptions for the years 2005 to 2011. All subjects, apart from newborns, had to have a 12-month preceding time period (baseline period) of continuous insurance time without an AD prescription (or, for the analyses by drug class, without an AD prescription of the specific drug class). Subjects with AD prescription in the year following the baseline period were categorized as incident.

Drug exposure

All ADs with an ATC code starting with N06A were categorized into TCAs, SSRIs, monoamine oxidase inhibitors (MAOs), selective serotonin norepinephrine reuptake inhibitors (SSNRIs), norepinephrine reuptake inhibitors (NRIs), and other ADs like mirtazapine and hypericum. Because of the rarity of prescriptions of some ADs, all ADs except SSRIs and TCAs were grouped as other ADs for the presentation of results.

Diagnoses

Diagnoses were considered in inpatient and outpatient data. In GePaRD, outpatient diagnoses

are related to a quarter of a year (a three-month interval). All diagnoses of patients treated with an AD were examined in the quarter of the AD prescription. The analysis considered all approved indications of the studied drugs and assessed diagnoses of mental and behavioral disorders (ICD-10-GM: F00-F99) and of diseases of the nervous system (G00-G99).

Off-label use

Off-label use was derived from information on the approved indications, the licensed age range, and contraindications of the ADs under study as stated in the Summaries of Product Characteristics (SPCs). Changes in the SPCs during the study period were taken into account. A prescription was off-label if a) the age of the child was below the licensed age of the drug, b) there was no in- or outpatient diagnosis of an approved indication coded in the quarter of the prescription or in the preceding or following quarter, c) any in- or outpatient diagnoses of contraindications were coded in the quarter of the prescription, or d) there was an overlapping prescription of a contraindicated drug.

Statistical analyses

The number of AD users and AD prescriptions in the study population were analyzed stratified by age, sex, drug class, substance, and prescribing physician's specialty. The annual prescription prevalence (per 1,000 individuals) was calculated by dividing the number of subjects with AD prescription in a particular year by the total number of subjects in that year. The annual IR (per 10,000 person-years (py)) was calculated by dividing the total number of incident users in the respective year by the sum of py of the study cohort in that year. 95% confidence intervals (CI) were calculated using the substitution method, 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.

Ethics and consent

The use of SHI data for scientific research is regulated by the Code of Social Law (SGB X) in Germany. 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.

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 is characterized in Table 1, exemplarily for the first and the last year of the study period. The study population comprised between 1,993,994 (in 2004) and 2,160,541 (in 2009) pediatric subjects. In every year, there was a slight preponderance of boys (51.1 to 51.2%). The mean age was between 8.8 (SD=5.1) and 9.0 (SD=5.1) years.

Prevalence of AD prescriptions and off-label use

The one-year prevalence of AD prescriptions ranged between 1.65 (95% CI: 1.60-1.71) per 1,000 minors in 2005 and 2.13 (95% CI: 2.07-2.20) in 2011 (Figure 1). Throughout the study period, prescriptions of TCAs decreased from 0.86 (95% CI: 0.82-0.90) to 0.65 (95% CI: 0.62-0.68), while prescriptions of SSRIs increased from 0.50 (95% CI: 0.47-0.53) to 1.12 (95% CI: 1.08-1.17) per 1,000 minors. The prevalence of hypericum prescriptions decreased

from 0.64 (95% CI: 0.60-0.67) to 0.30 (95% CI: 0.28-0.33). The prevalence of all other ADs combined was less than 0.3 per 1,000 minors throughout the study period.

These trends are corroborated by the most frequently prescribed AD agents in 2004 and 2011 (Table 2). Hypericum was the most commonly prescribed AD in 2004, with 32.0% of all pediatric AD users receiving a hypericum prescription. By 2011, this number had decreased by more than half. Simultaneously, prescriptions of the TCAs imipramine and opipramol decreased substantially, while prescriptions of the SSRI fluoxetine almost quadrupled. These tendencies can also be observed looking at different age groups. The percentage of hypericum prescriptions decreased among children aged up to 11 years (from 47.2 to 28.9%) as well as among adolescents aged 12 to 17 years (from 25.5 to 13.3%), while prescriptions of the most frequently prescribed SSRI fluoxetine increased from 2.1 to 15.8% and from 10.2 to 27.4%, respectively. In children younger than twelve years, imipramine was the most commonly prescribed TCA with a share of 34.3% in 2004 and 20.9% in 2011. In the group of 12- to 17-year-olds, opipramol was the most frequently prescribed TCA with a proportion of 13.6% in 2004 and 9.8% in 2011.

In 2011, the prevalence of AD prescriptions was higher in girls (2.61 (95% CI: 2.52-2.72) per 1,000) than in boys (1.67 (95% CI: 1.59-1.75)). Between the age of 6 to 14 years, ADs were slightly more frequently prescribed in boys (1.48 (95% CI: 1.39-1.59) vs. 1.21 (95% CI: 1.12-1.31)) while among 15- to 17-year-olds, the prevalence was more than twice as high in females (10.97 (95% CI: 10.50-11.45) vs. 5.01 (95% CI: 4.70-5.34)). There were only very few prescriptions in children younger than six years (0.04 (95% CI: 0.03-0.06) per 1,000).

In 2011, most ADs were prescribed by child and adolescent psychiatrists (37.6%) and physicians for internal and general medicine (21.1%). Pediatricians prescribed 11.3% and (adult) psychiatrists 6.7% of all ADs. The specialty was unknown/not reported for 11.7% of

AD prescriptions. The remaining 11.6% were prescribed by physicians with other fields of specialty.

The most common diagnoses among pediatric AD users were depression (with an increasing prevalence from 28.1% in 2004 to 47.4% in 2011), restlessness & agitation (18.9 to 24.8%), other anxiety disorders (11.5 to 18%), headache and migraine (15.0 to 17.5%), and hyperkinetic disorders (13.2 to 17.0%). In 2011, the majority of patients (60.4%) had two or more different diagnoses (Table 3). Restricting the analysis to children younger than twelve years, hyperkinetic disorder (32.9%) was the most frequent diagnosis, followed by emotional disorders with onset specific to childhood (22.7%), and other behavioral and emotional disorders (20.5%). In the group of other behavioral and emotional disorders, most diagnoses (50.9%) accounted for nonorganic enuresis.

Looking at the diagnoses for pediatric patients treated with different AD agents, we found that depression was the most common diagnosis for users of hypericum and most SSRIs (Table 2). For users of imipramine, the most frequent diagnosis was other behavioral and emotional disorder, while users of amitriptyline were most frequently diagnosed with headache and migraine.

Regarding the number of AD prescriptions per patient between 2004 and 2011, we observed differences between users of any AD (one prescription: 46.4%, 2-5 prescriptions: 36.7%, five or more: 16.8%, Q1=1, median=2, Q3=4), users of TCAs (57.3%, 32.0%, and 10.8%, Q1=1, median=1, Q=3), and users of SSRIs (30.6%, 44.8%, and 24.7%, Q1=1, median=3, Q3=5). Among subjects with a diagnosis of depression and any AD usage, 34.9% had one prescription, 44.3% had two to five, and 20.7% had five or more (Q1=1, median=2, Q3=5). In subjects with any TCA usage, these shares were 50.5%, 37.3%, and 12.3% (Q1=1, median=1, Q3=3) and 27.2%, 50.0%, and 22.8% (Q1=1, median=3, Q3=5) in patients with any SSRI prescription, respectively.

Looking at pediatric AD users with only one prescription of an AD agent in 2011, depression was the most frequent diagnosis (33.7%) (Table 4).

In 2004, 64.2% of all prescribed ADs were prescribed off-label. Over time, this proportion decreased to 49.4% in 2006, 40.6% in 2009 and to 36.3% in 2011. With 29.1% of all pediatric AD users receiving at least one AD prescription off-label by age, this was the most frequent type of off-label use in 2011, followed by off-label use by indication (15.3%) and off-label use by contraindication (3.3%).

Incidence of AD prescriptions

The one-year IR of AD prescriptions was 13.4 (95% CI: 12.9-13.9) per 10,000 py in 2005 and 16.0 (95% CI: 15.5-16.6) in 2011. During this time, the IR of TCA prescriptions varied between 5.3 (95% CI: 4.9-5.6) and 6.3 (95% CI: 6.0-6.7) per 10,000 py, while the IR of SSRI prescriptions increased from 3.5 (95% CI: 3.3-3.8) to 7.9 (95% CI: 7.5-8.3). Throughout the study period, the IR of AD prescriptions was higher for females than for males, with the largest difference in 2011 (females: 20.5 (95% CI: 19.6-21.5); males: 11.7 (95% CI: 11.1-12.4)). In each year, the highest IR was observed in the group of 15- to 17-year-olds (Figure 2).

Discussion

We examined the epidemiology of outpatient AD prescriptions in minors from 2004 to 2011 using claims data of about two million pediatric subjects. Our results showed considerable changes regarding the prescribed substances and high rates of single and off-label prescriptions.

During the study period, the prevalence of TCA prescriptions slightly decreased, while the use of SSRIs markedly grew. This indicates that SSRIs were increasingly used for the

treatment of the most common diagnoses among pediatric AD users, depressive and anxiety disorders, as suggested by German guidelines throughout the study period.[13, 19] SSRIs have a more favorable safety profile than TCAs.[20] Accordingly, an increasing number of SSRI prescriptions over time has also been observed previously.[3, 4, 21, 22] For instance, Hoffmann et al.[3] reported an increase in SSRI prescriptions from 37.7 to 54.4% and a decline of TCAs from 39.6 to 23.0% between 2005 and 2012. Compared to our study, they observed a higher prevalence of AD prescriptions, probably due to the inclusion of 18- and 19-year-olds who have a higher prevalence than younger patients.

The small decrease in the prevalence of SSRI prescriptions which we observed from 2004 to 2005 has also been shown in other studies[23-26] and can possibly be explained by concerns about (self-)aggressive behavior in youths treated with SSRIs, which resulted in warnings from the FDA and the EMA in 2004.[2] Yet, the SSRI fluoxetine became the most frequently prescribed AD in our study. Since July 2006, fluoxetine is the only SSRI licensed for the treatment of major depressive disorder in children older than seven years in Germany. Other SSRIs like citalopram, not approved for the treatment of minors at all, and fluvoxamine, licensed for the treatment of obsessive compulsive disorder in children eight years and older, have been prescribed more commonly as well. The shares of the most frequently prescribed TCAs imipramine, approved for the treatment of depressive syndromes, long-lasting pain, nonorganic enuresis, and sleep terrors in patients older than four years, and opipramol, licensed for the treatment of anxiety and somatoform disorders in children aged six years and older, decreased over time. Hoffmann et al.[3] observed similar trends. Our analysis of the most frequent diagnoses for pediatric patients treated with different AD substances indicates that most agents were primarily prescribed to treat an approved indication but often outside of their approved age range. This was, for example, the case for citalopram, sertraline, and

mirtazapine which are licensed for the treatment of depression but not in individuals younger than 18 years.

Although the prevalence of depression in minors is still understudied, it is known that the risk of depression increases rapidly from the age of 14, with higher prevalences in girls.[27, 28] This is in accordance with our findings of higher prevalences of AD prescriptions in older age groups and in females.

We observed a high proportion of AD users with only one single AD prescription, although depression as the most frequent diagnosis among AD users and also among AD users with only one prescription usually persists for longer time periods. Hoffmann et al.[12] found similar results with 43.7% of adolescents (12-18 years) with a diagnosed depression having only a single prescription. This suggests that the treatment was not in accordance with guidelines, recommending that drug treatment of depression in minors should continue for at least six months after recovery.[13-15] A possible explanation for an early therapy discontinuation is that the prescribed drug was not effective. However, the time span covered by one prescription is usually too short to evaluate treatment success. Besides, if the prescribed drug was not helpful or not well tolerated, the treating physician would probably switch to a different substance instead of terminating the therapy. Another likely explanation is that a substantial proportion of patients (or of their parents) does not follow the prescription after having filled the first one. For Dutch adults, van Geffen et al.[29, 30] found that 23.7% of the patients with a first-time AD prescription filled only a single prescription (22.0% for SSRIs), mostly due to fear of or actual adverse effects.

In our study, the proportion of single AD prescriptions was much higher for TCAs than for SSRIs (57.3% vs. 30.6%), leading to a higher median number of prescriptions for SSRI users (3 vs. 1). It is unclear to which extent adverse events caused by TCAs, which can lead to an early therapy discontinuation,[31, 32] contributed to this fact. Moreover, in minors, SSRIs are

mainly indicated for longer lasting conditions (e.g. major depression), while TCAs are indicated for disorders like anxiety disorders or sleep disorders.

Over time, the share of individuals with single AD prescriptions decreased from 53.7 to 40.9%, while the median increased from one to two prescriptions per patient, potentially indicating a trend towards longer treatments. This can partially be explained by the increasing SSRI prescriptions during the study period. With a decreasing share of youths up to an age of 19 years with single AD prescriptions and an increase in those with seven or more prescriptions between 1983 and 2007, Meng et al.[4] observed a similar trend.

We found a decreasing share of off-label prescriptions between 2004 and 2011. The most plausible explanation for this trend is the growing share of fluoxetine prescriptions, which is the drug recommended and since 2006 approved for the treatment of depression in patients older than seven years in Germany.[13] Another German study that examined AD off-label use in adolescents also observed a high proportion of off-label prescriptions (45.5%) in the year 2009.[12] However, since that study only included individuals with a diagnosed depression and an age between 12 and 18 years, the results are hardly comparable to our findings. International comparisons of off-label use are difficult due to differences in the licensing of drugs. Accordingly, studies from different countries show a wide range (between 42 and 91%) of off-label AD use in minors.[2, 8, 10, 11, 33]

A major strength of our study is the size of the database, reflecting real-world utilization patterns in a population representative for the German general population.[17, 18] We determined drug exposure based on pharmacy dispensing data which is considered the gold standard in pharmacoepidemiological research as recall bias can be ruled out.[34] Drug dispensation data have been shown to provide valid information on drug use in Germany.[18, 35] This study could only assess outpatient treatment with ADs, as information on inpatient drug treatment is not included in GePaRD. However, since nearly all of the examined AD drugs are available by

prescription only, with the exception of hypericum, the database provides valid and almost complete information on outpatient AD dispensations in pediatric patients. Due to the fact that hypericum is also available over the counter in Germany, its use is underestimated in our study. Since prescription data are available with the exact date of dispensation, the potential for misclassification of drug exposure is low when compared to primary data collections based on interview data, although the patients' adherence to prescriptions is not known. However, some misclassification is possible with regard to the underlying diagnoses for AD prescriptions as outpatient diagnoses in GePaRD are only related to a quarter of a year. Yet, an additional analysis, also using the quarter before and the quarter after the AD prescription to identify diagnoses, showed similar results. Another limitation resides in the fact that there is no way to verify the accuracy and completeness of the diagnoses coded by physicians, which might be relevant when assessing whether a prescription was off-label.

Conclusions

The observed increasing use of SSRIs and decreasing use of TCAs indicate a trend towards medical treatments of mental disorders in minors increasingly in accordance with recommendations of treatment guidelines. There is, however, still a considerable amount of TCA prescriptions. The observed high proportion of single AD prescriptions, even in patients with a diagnosed depression, is remarkable. The reasons for these short treatment durations remain unclear and should be investigated in the future. Another interesting aspect is the high share of off-label prescriptions. Further studies on the reasons for and the risks of off-label AD use in pediatric patients are needed.

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Table 1. Characteristics of the study population (values are expressed as N and %)

Study year	**2004**	**2011**
Study population	1,993,994 (100.0)	2,090,135 (100.0)
Male	1,020,874 (51.2)	1,068,606 (51.1)
Female	973,120 (48.8)	1,021,529 (48.9)
Age (years):		
<1	103,722 (5.2)	112,200 (5.4)
1-2	189,610 (9.5)	212,454 (10.2)
3-5	302,410 (15.2)	304,486 (14.6)
6-11	670,601 (33.6)	683,307 (32.7)
12-14	363,600 (18.2)	405,782 (19.4)
15-17	364,051 (18.3)	371,906 (17.8)
Mean	8.9	8.9
SD	5.2	5.2
Q1	5	4
Median	9	9
Q3	13	13

Table 2. The ten most commonly prescribed antidepressants (with their three most common diagnoses) to minors aged 0-17 years in 2004 and 2011 (values are expressed as N and %)

2004 (N=3,984)		**2011** (N=4,456)	
Hypericum (Other)[a]	**1,276 (32.0)**	**Fluoxetine (SSRI)**	**1,254 (28.1)**
Depression	305 (23.9)	Depression	782 (62.4)
Restlessness & Agitation	233 (18.3)	Restlessness & Agitation	336 (26.8)
Headache & migraine	152 (11.9)	Emotional disorders w/ onset specific to childhood	267 (21.3)
Imipramine (TCA)	**596 (15.0)**	**Hypericum (Other)**[a]	**638 (14.3)**
Other behavioral and emotional disorders	257 (43.1)	Depression	288 (45.1)
Hyperkinetic disorders	106 (17.8)	Restlessness & Agitation	126 (19.7)
Restlessness & Agitation	54 (9.1)	Emotional disorders w/ onset specific to childhood	107 (16.8)
Opipramol (TCA)	**412 (10.3)**	**Citalopram (SSRI)**	**555 (12.5)**
Depression	124 (30.1)	Depression	345 (62.2)
Somatoform disorders	101 (24.5)	Restlessness & Agitation	142 (25.6)
Restlessness & Agitation	87 (21.1)	Other anxiety disorders	118 (21.3)
Fluoxetine (SSRI)	**308 (7.7)**	**Amitriptyline (TCA)**	**441 (9.9)**
Depression	138 (44.8)	Headache & migraine	259 (58.7)
Restlessness & Agitation	59 (19.2)	Depression	105 (23.8)
Hyperkinetic disorders	55 (17.9)	Somatoform disorders	89 (20.2)
Amitriptyline (TCA)	**284 (7.1)**	**Opipramol (TCA)**	**351 (7.9)**
Headache & migraine	128 (45.1)	Other anxiety disorders	116 (33.0)
Depression	81 (28.5)	Depression	111 (31.6)
Somatoform disorders	52 (18.3)	Restlessness & Agitation	99 (28.2)
Citalopram (SSRI)	**250 (6.3)**	**Mirtazapine (Other)**	**314 (7.0)**
Depression	117 (46.8)	Depression	202 (64.3)
Restlessness & Agitation	60 (24.0)	Restlessness & Agitation	98 (31.2)
Other anxiety disorders	38 (15.2)	Other anxiety disorders	61 (19.4)

Sertraline (SSRI)	**200 (5.0)**	**Fluvoxamine (SSRI)**	**309 (6.9)**
Depression	91 (45.5)	Obsessive compulsive disorder	161 (52.1)
Hyperkinetic disorders	40 (20.0)	Depression	103 (33.3)
Restlessness & Agitation	40 (20.0)	Emotional disorders w/ onset specific to childhood	70 (22.7)
Doxepin (TCA)	**173 (4.3)**	**Imipramine (TCA)**	**196 (4.4)**
Depression	60 (34.7)	Other behavioral and emotional disorders	78 (39.8)
Restlessness & Agitation	48 (27.7)	Hyperkinetic disorders	66 (33.7)
Somatoform disorders	37 (21.4)	Depression	35 (17.9)
Clomipramine (TCA)	**147 (3.7)**	**Doxepin (TCA)**	**187 (4.2)**
Obsessive compulsive disorder	54 (36.7)	Depression	85 (45.5)
Depression	37 (25.2)	Restlessness & Agitation	52 (27.8)
Hyperkinetic disorders	30 (20.4)	Headache & migraine	48 (25.7)
Fluvoxamine (SSRI)	**134 (3.4)**	**Sertraline (SSRI)**	**163 (3.7)**
Obsessive compulsive disorder	55 (41.0)	Depression	93 (57.1)
Depression	45 (33.6)	Restlessness & Agitation	41 (25.2)
Emotional disorders w/ onset specific to childhood	26 (19.4)	Hyperkinetic disorders	35 (21.5)

Columns may add up to more than 100% because one patient can contribute to more than one line.

Abbreviations: SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

[a] This does not include over the counter hypericum use.

Table 3. The ten most frequent diagnoses[a] for antidepressant users (aged 0-17 years) in 2011 (values are expressed as N and %)

Diagnosis (ICD-10-GM code)	**Total** (N=4,456)	**Age 0-11 years** (N=556)	**Age 12-17 years** (N=3,900)
Depression (F20.4, F32, F33)	2,112 (47.4)	105 (18.9)	2,007 (51.5)
Restlessness & agitation (F43, R45.0, R45.1, R45.4, R46.3)	1,105 (24.8)	90 (16.2)	1,015 (26.0)
Other anxiety disorders (F41)	803 (18.0)	51 (9.2)	752 (19.3)
Headache & migraine (G43, G44, R51)	781 (17.5)	55 (9.9)	726 (18.6)
Hyperkinetic disorders (F90)	756 (17.0)	183 (32.9)	573 (14.7)
Emotional disorders with onset specific to childhood (F93)	714 (16.0)	126 (22.7)	588 (15.1)
Somatoform disorders (F45)	676 (15.2)	43 (7.7)	633 (16.2)
Obsessive compulsive disorder (F42)	425 (9.5)	42 (7.6)	383 (9.8)
Other behavioral and emotional disorders (F98)	416 (9.3)	114 (20.5)	302 (7.7)
Sleep disorders (F51, G47)	399 (9.0)	49 (8.8)	350 (9.0)
Number of diagnoses[b]:			
One	1,340 (30.1)	146 (26.3)	1,194 (30.6)
Two	1,335 (30.0)	146 (26.3)	1,189 (30.5)
More than two	1,353 (30.4)	169 (30.4)	1,184 (30.4)
None	428 (9.6)	95 (17.1)	333 (8.5)

Columns add up to more than 100% because one patient can contribute to more than one line.

[a] Among the analyzed comorbidities.

[b] Related to the ten most frequent diagnoses.

Table 4. The ten most frequent diagnoses[a] for antidepressant users (aged 0-17 years) with only one single prescription of an antidepressant in 2011 (values are expressed as N and %)

Diagnosis (ICD-10-GM code)	**Total** (N=1,823)	**Age 0-11 years** (N=286)	**Age 12-17 years** (N=1,537)
Depression (F20.4, F32, F33)	615 (33.7)	34 (11.9)	581 (37.8)
Restlessness & agitation (F43, R45.0, R45.1, R45.4, R46.3)	406 (22.3)	36 (12.6)	370 (24.1)
Headache & migraine (G43, G44, R51)	313 (17.2)	30 (10.5)	283 (18.4)
Somatoform disorders (F45)	278 (15.2)	19 (6.6)	259 (16.9)
Other anxiety disorders (F41)	256 (14.0)	17 (5.9)	239 (15.5)
Hyperkinetic disorders (F90)	249 (13.7)	72 (25.2)	177 (11.5)
Emotional disorders with onset specific to childhood (F93)	187 (10.3)	44 (15.4)	143 (9.3)
Sleep disorders (F51, G47)	172 (9.4)	24 (8.4)	148 (9.6)
Other behavioral and emotional disorders (F98)	128 (7.0)	51 (17.8)	77 (5.0)
Mixed disorders of conduct and emotions (F92)	96 (5.3)	14 (4.9)	82 (5.3)

Columns add up to more than 100% because one patient can contribute to more than one line.

[a] Among the analyzed comorbidities.

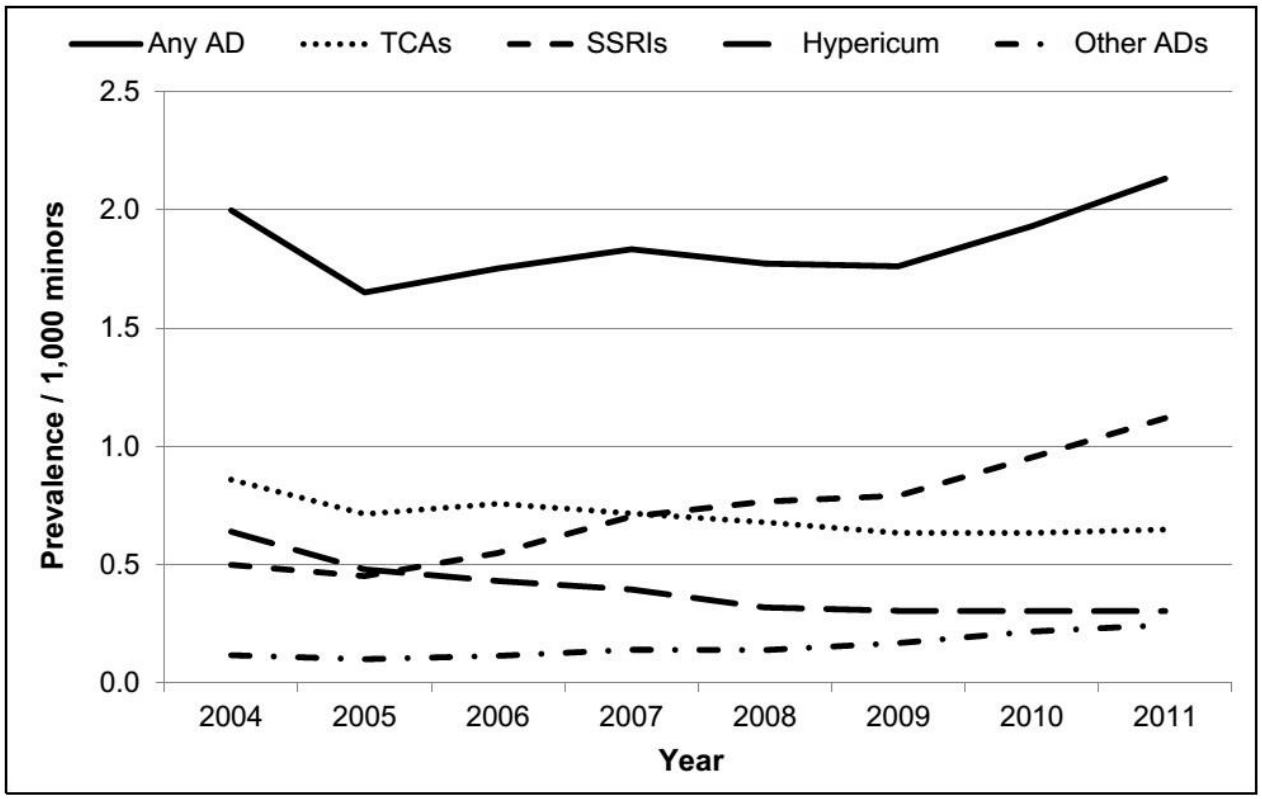

Figure 1. Prevalence of antidepressant prescriptions in minors aged 0-17 years from 2004 to 2011

Abbreviations: AD = antidepressant; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants

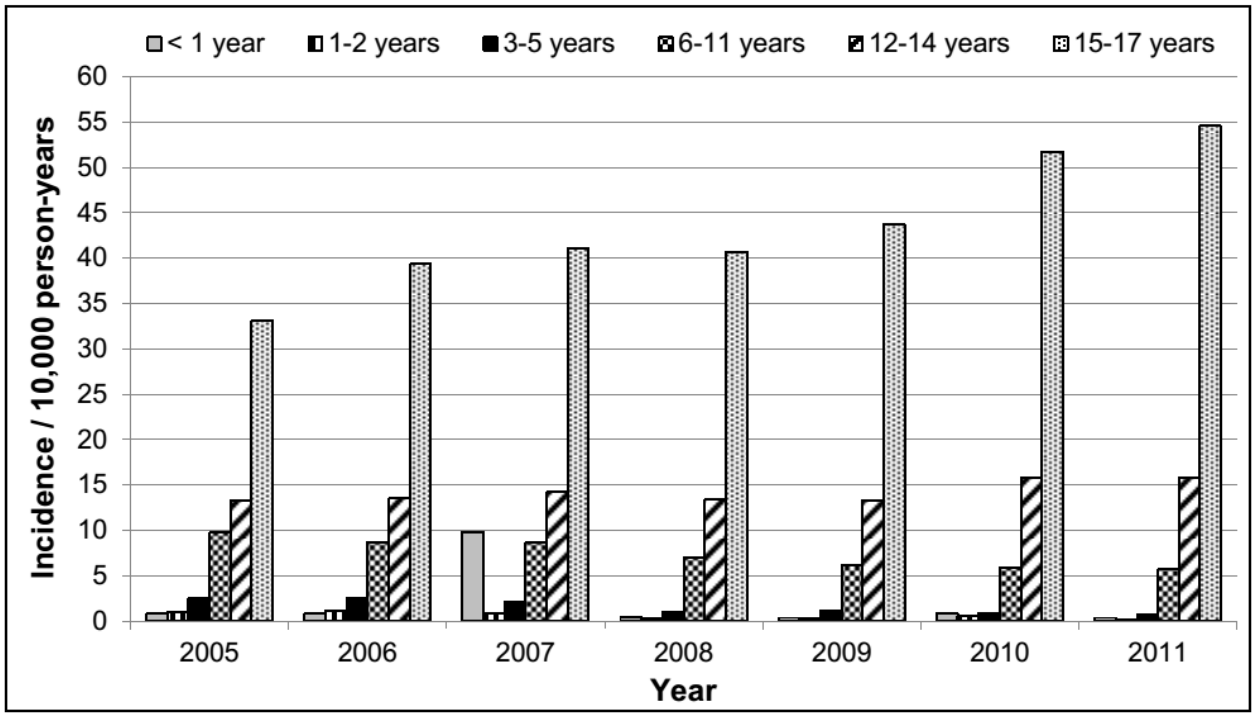

Figure 2. Incidence of antidepressant prescriptions in minors aged 0-17 years from 2005 to 2011 by age group