Extent and risks of antidepressant off-label use in children and adolescents in Germany between 2004 and 2011

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Extent and risks of antidepressant off-label use in children and adolescents in Germany between 2004 and 2011

Running head:

Risks of antidepressant off-label use in young patients

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Keywords:

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Key points:

- In Germany, the share of pediatric antidepressant users with off-label prescriptions decreased from 58.0% in 2004 to 40.9% in 2011.
- Most off-label prescriptions (29.1 to 43.1%) were off-label by age.
- Hyperkinetic disorder was the most common diagnosis among pediatric patients with antidepressant prescriptions which were off-label by indication.
- In 2011, selective serotonin reuptake inhibitors were more frequently prescribed off-label than tricyclic antidepressants (37.7 vs. 17.5%).
- Adverse events occurred rarely and there were no significant differences between on- and off-label use.

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Conflict of interest statement:

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.

Funding for this study was provided by the 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, the collection, management, analysis, and interpretation of data, and the preparation, review, and approval of the manuscript.

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Abstract

Purpose

So far, only little is known about antidepressant off-label use in pediatric patients. This is the first study examining the prevalence and the risks of off-label antidepressant prescriptions in minors over time in Germany and analyzing patterns with regard to age, sex, drug class, and type of off-label use.

Methods

We used claims data of about two million individuals (<18 years) to calculate the share of off-label antidepressant prescriptions for the years 2004-2011, stratified by age, sex, and drug class. Off-label prescriptions were analyzed regarding underlying diagnoses, the prescribing physician's specialty, and the type of off-label use. Incidence rates of adverse events were calculated for off-label and on-label use and the risk of suicidal events associated with off-label or on-label use was examined in a nested case-control study.

Results

The prevalence of off-label prescriptions decreased from 58.0 to 40.9%. Selective serotonin reuptake inhibitors were more frequently prescribed off-label than tricyclic antidepressants (37.7 vs. 17.5% in 2011). The most common type of off-label use was off-label use by age, followed by off-label use by indication, and off-label use by contraindication. Adverse events were rare with no significant differences between on- and off-label use.

Conclusions

Although off-label antidepressant use in minors decreased over time, it is still common. However, this rather indicates a lack of approved drugs for the treatment of depression in this population than inappropriate medical treatment. This is supported by the fact that off-label use was not associated with a higher risk of adverse events than on-label use.

Introduction

Drugs are frequently prescribed off-label to pediatric patients since agents on the market have often not been studied and approved for this population.[1] This can increase the risk of incorrect dosing and adverse drug events.[2] For antidepressant (AD) compounds, high but varying rates of off-label use (OLU) in pediatric populations have been reported in various countries, including Germany.[3-8]

ADs are prescribed for a variety of indications including depression, sleep disorders, nocturnal enuresis, obsessive-compulsive disorder, anxiety disorders, and chronic pain. Despite the risk of cardiovascular and neurological adverse events, metabolic disorders, and poisoning,[9, 10] and despite worries about an increased risk of suicidal behavior in young patients,[3, 11] increasing pediatric AD use has been observed in several studies from different countries with rates of OLU up to 90.8%.[7, 12-15]

As reported previously,[16] we found a decreasing percentage of off-label prescriptions from 64.2 to 36.3% when examining AD use in minors aged 0-17 years in Germany from 2004-2011. Another German study focusing on the medical treatment of adolescents aged 12-18 years with a diagnosed depression found a share of off-label AD prescriptions of 45.5% in 2009.[8]

However, only very little is known about the risks of AD OLU in young individuals. To close this research gap, we investigate the risks of AD OLU compared to on-label use in a representative sample of minors. To our knowledge, this is the first study providing detailed analyses of changes in the frequency of OLU over time, stratified by age, sex, and drug class. Further, we are looking at the prescribing physicians' specialty and examine, for the first time, whether prescriptions were off-label with regard to the age of the patients, the indications which the ADs were prescribed for, or an underlying contraindication.

Methods

Data source

We used data from three statutory health insurance (SHI) providers that are part of the German Pharmacoepidemiological Research Database (GePaRD). GePaRD contains information on demographics, outpatient prescriptions, diagnoses, and hospitalizations.[17] Diagnoses are coded according to the International Classification of Diseases, 10th Version, German Modification (ICD-10-GM). Hospitalization data include information on admission and discharge dates with corresponding diagnoses. Outpatient care data cover diagnoses (related to a quarter of a year), prescriptions, and procedures. Outpatient prescription data contain dates of prescription and dispensation, information on the prescribing physician's specialty, the Anatomical Therapeutic Chemical (ATC) code, and the defined daily dose (DDD). GePaRD has been shown to be representative for the German population with regard to region of residence, age and sex distribution, drug use, and number of hospital admissions.[18, 19]

Study design

The study population consisted of minors aged 0-17 years, insured in one of the three SHIs between 2004 and 2011. The study cohort was ascertained in two steps. First, the share of (off-label) AD prescriptions was examined in cross-sectional analyses for each year. All individuals with continuous insurance coverage either (a) during the whole study year, or (b) from birth in the study year until the end of that year, or (c) from birth in the study year until death in that year, or (d) from start of the study year until death in that year were included. Second, a cohort including all minors with at least one AD prescription during the study period who were continuously insured for at least six months before the prescription (baseline period) and who had no simultaneous on- and off-label prescriptions was defined to

investigate the association between AD use and cardio- and cerebrovascular events, suicidal events, and death. Cohort entry was defined as the date of the first AD prescription. Patients were followed until the first of the following events: (a) interruption of insurance time for more than 14 days, (b) December 31st of the year in which the subject turned 17, (c) end of the study period, (d) end of insurance including death, (e) date of occurrence of the outcome. For the outcome with the highest number of events (suicidal events), we were able to additionally conduct a nested case-control study to examine the risk of OLU compared to on-label use. For each case of a suicidal event, up to five controls were matched by age group at index date (0, 1-2, 3-5, 6-11, 12-14, 15-17 years), sex, and SHI, using risk set sampling.

Drug exposure

All ADs (ATC code N06A) were included in the analyses and categorized into tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and other ADs. The duration of drug exposure was calculated based on the prescribed amount and the DDD. Current use was defined as treatment overlapping the date of the event and recent use as treatment ending 1-30 days before the event. Patients with a treatment not classified as current or recent were categorized as past users.

Covariates

In- and outpatient data was used to identify diagnoses. In addition to all approved indications of the prescribed ADs, the analyses considered other diagnoses of mental and behavioral disorders (ICD-10-GM: F00-F99) and of diseases of the nervous system (G00-G99). Additionally, in the nested case-control study, antiepileptics (N03A), antipsychotics (N05A), anxiolytics (N05B), additional ADs (N06A), and psychostimulants (N06B) were considered as co-medications. Covariates and co-medications were ascertained in the baseline period.

Off-label use

Information from the Summaries of Product Characteristics (SPCs) was used to examine OLU. A prescription was off-label by age if the age of the patient was not in accordance with the licensed age of the drug. A prescription was off-label by indication if no diagnosis of an approved indication was coded in the quarter of the prescription or in the preceding or following quarter. A prescription was off-label by contraindication if there were diagnoses of contraindications in the quarter of the prescription or if there was a contraindicated medication overlapping the AD prescription. The lowest age limit was used if SPCs of generic preparations gave inconsistent information or if the licensed age varied by indication. Approved indications and contraindications were assigned to all generic drugs if not all SPCs listed all of them.

Outcome definition

Cardio- and cerebrovascular events (ICD-10-GM: I21, I22, I42, I44, I45, I47-I50, I61, I63, I64, I95.2, R00) were identified by inpatient main discharge diagnoses. Suicidal events, including diagnoses of suicidal ideation (R45.8) and intentional self-harm with a suicidal background (X60-X84), were identified by inpatient main discharge and secondary diagnoses. For all-cause mortality, death was identified using information on the reason for the end of insurance membership and for the end of hospitalization.

Statistical analysis

The prevalence of prescriptions was analyzed stratified by on- and OLU, age, sex, and drug class with 95% confidence intervals (CI) calculated using the substitution method.[20] Off-label prescriptions were further analyzed regarding type of OLU, underlying diagnoses, and

prescribing physician's specialty.

In the cohort study, the all-cause mortality rate and the incidence rate (IR) of cardio- and cerebrovascular and suicidal events were calculated per 10,000 person-years (py) with corresponding 95% CIs, stratified by on- and OLU.

We used conditional logistic regression in the nested case-control analysis to obtain confounder-adjusted odds ratios (ORs) with corresponding 95% CIs. The risk of suicidal events associated with current OLU, simultaneous off- and on-label use, recent use, or past use of any AD was compared to current on-label use (reference group). For covariates, a backward selection (Wald test with $p<0.05$ for staying in the model) was performed.

SAS statistical software version 9.3 was used for all analyses.

Trial registration

The study was registered in the register of studies of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP; No.: EUPAS7034).

Results

Study population

The size of the study population varied between 1,993,994 (in 2004) and 2,160,541 (in 2009) minors with a slight preponderance of boys (about 51%). The mean age was between 8.8 and 9.0 years. Each year, we identified between 3,561 (in 2005) and 4,456 (in 2011) subjects with AD prescriptions.

Extent of off-label use

The number of AD prescriptions increased steadily from 7,908 in 2004 to 12,250 in 2011 with a decreasing share of off-label prescriptions from 64.2 to 36.3%. In 2004, 58.0% of all AD

users had an off-label AD prescription (Figure 1). This proportion decreased to 40.9% in 2011, with 42.4% for males and 39.9% for females. Up to the age of eleven years, there were more individuals with off-label than with on-label prescriptions (Figure 2).

Of the 1,356 TCA users in 2011, 17.5% had off-label TCA prescriptions. Among the 2,340 SSRI users, 37.7% had off-label SSRI prescriptions. Of the 1,134 users of other ADs (hypericum (St. John's wort) had a share of 56.2% in this category), 69.3% had off-label prescriptions.

Throughout the study period, the most common type of OLU was OLU by age, followed by OLU by indication and OLU by contraindication (Figure 1).

Of the 1,298 AD users with a prescription off-label by age in 2011, 80.5% were between 12 and 17 years old, while 2.1% were younger than six years (mean=14.5, SD=3.2, median=16).

Of the 683 AD users with a prescription off-label by indication, 26.6% had a diagnosis of hyperkinetic disorder (ICD-10: F90), 14.6% a diagnosis of reaction to severe stress and adjustment disorder (F43), 11.4% a diagnosis of emotional disorder with onset specific to childhood (F93), 9.5% a diagnosis of conduct disorder (F91), and 9.2% a diagnosis of somatoform disorder (F45) during the quarter of the prescription.

Child and adolescent psychiatrists issued 37.6% of the 12,250 AD prescriptions in 2011, followed by physicians for internal and general medicine (21.1%), pediatricians (11.3%), and (adult) psychiatrists (6.7%). The latter had the highest share of off-label prescriptions (Table 1). The specialty was unknown/not reported for 11.7%. Physicians with various other fields of specialty prescribed the remaining 11.6%.

Risks of off-label use

The AD user cohort included 22,294 individuals (at cohort entry 11,630 on-label users, 10,664 off-label users), of whom 43.1% were male (Table 2). The share of females was

slightly higher in the group of on-label users (58.7 vs. 55.1%). On-label users were also older (mean age: 14.3 vs. 13.4 years). On- and off-label users were similar regarding the prevalence of most comorbidities during the baseline period. Prescriptions of ADs, antiepileptics, antipsychotics, anxiolytics, and psychostimulants during the baseline period occurred at slightly higher rates in the group of off-label users.

In total, we observed 30 subjects with cardio- and cerebrovascular events (IR=7.0 (95% CI: 4.7-10.0) per 10,000 py, on-label users: IR=9.8 (95% CI: 6.0-15.1), off-label users: IR=4.5 (95% CI: 2.1-8.2)) and 121 suicidal events (IR=28.1 (95% CI: 23.3-33.5) per 10,000 py, on-label users: IR=35.2 (95% CI: 27.5-44.3), off-label users: IR=21.7 (95% CI: 16.0-28.6)). With 66 observed deaths in the AD user cohort, the all-cause mortality rate was 15.1 (95% CI: 11.7-19.2) per 10,000 py (on-label users: 10.1 (95% CI: 6.2-15.4), off-label users: 19.6 (95% CI: 14.3-26.3)).

The nested case-control analysis showed no significant differences for the risk of suicidal events between current on-label use and current off-label, current off- and on-label, or recent use of any AD (Table 3). A significantly lower risk was observed for past use of any AD as compared to current on-label use (adjusted OR=0.5 (95% CI: 0.3-0.8). Among the analyzed covariates, a prior suicidal event had the strongest association with suicidal events (adjusted OR=7.3 (95% CI: 3.4-15.8)).

Discussion

Our results showed a high but decreasing share of OLU, a higher prevalence of off-label prescriptions for SSRIs than for TCAs, and a high proportion of prescriptions that were off-label by age. Adverse events were relatively rare and no significant difference between on- and OLU was detected.

AD OLU decreased markedly during the study period. This can be explained by the growing share of SSRI prescriptions, especially fluoxetine. As reported previously[16], in 2004, fluoxetine accounted for 7.7% of all pediatric AD prescriptions in Germany. In 2006, its regulatory approval was extended to also include the treatment of moderate and severe depressive episodes in children older than eight years. Subsequently, the proportion fluoxetine prescriptions increased to 28.1% in 2011.

Differences in healthcare systems and drug approvals make international comparisons of OLU difficult. Studies from different countries observed proportions of AD OLU in young patients between 42 and 91%.[3-7] Another German study analyzing AD OLU in adolescents for the year 2009 showed a share of off-label prescriptions of 45.5%.[8] That study, however, only assessed OLU by age and solely included patients aged 12-18 years with a diagnosed depression, limiting the comparability.

Most ADs licensed for the treatment of specific disorders in minors are only approved for the treatment of older children and adolescents. Consequently, OLU was less common in older subjects. Imipramine, the most frequently prescribed AD during the study period,[16] is licensed for the treatment of children from the age of five, opipramol and sertraline from the age of six, fluoxetine and fluvoxamine from the age of eight, and hypericum and doxepin from the age of twelve. Citalopram, mirtazapine, and amitriptyline are not licensed for the use in minors at all which explains the high proportion of prescriptions off-label by age. The rather small fraction of prescriptions off-label by contraindication is quite satisfactory from the drug safety perspective as contraindications by definition entail a high risk of adverse events.

Our analyses showed that AD prescriptions off-label by indication were mostly prescribed to minors with a diagnosis of hyperkinetic disorder. ADs are not licensed for this indication; however, it is known that TCAs are efficacious in its treatment.[21] According to the German

guideline, the use of TCAs in pediatric hyperkinetic disorder patients can be indicated, especially if they do not tolerate or respond to treatment with stimulants.[22]

ADs were most frequently prescribed by child and adolescent psychiatrists, indicating that many young AD users are treated by physicians specialized in the therapy of mental and behavioral disorders.

The number of subjects suffering from the analyzed adverse events was small, suggesting that these events do not pose a major problem when treating minors with ADs. However, the small number of cases only allowed us to analyze suicidal events in the nested case-control study. The analysis showed a significantly lower risk of suicidal events for past use compared to current on-label use. One explanation is that current users of ADs are more likely to currently suffer from depression, the strongest risk factor for suicide.[23] The risk of suicidal events was lower for current OLU compared to current on-label use, although the difference was not statistically significant. This can be explained by the fact that the share of patients with a diagnosed depression was lower in the group of off-label users (22 vs. 31%).

Studies from the USA and Canada have shown rates of suicide attempts in young AD users between 24.0 and 29.1 per 1,000 py.[24, 25] Comparing results of different studies on suicidality is difficult due to substantial methodological differences. This includes different study populations, medications used by the subjects, and outcome definitions. In our study, suicidal events were identified by inpatient diagnoses only and did not include completed suicide as this information is not available in GePaRD. This and the fact that not all suicidal events are coded by physicians might have led to an underestimation of this endpoint.[26, 27]

Our analysis showed that a prior suicidal event was the strongest predictor for suicidal events. It is known that people with a history of suicidal behavior have a higher risk of suicide.[28] In our study, a history of schizophrenia/delusion, alcohol/drug abuse, and mood disorders, which are also known to increase the risk of suicide in minors,[23] were associated with a higher risk

of suicidal events as well. Other known risk factors like social isolation, family history of suicide, abuse, and neglect[23] are not covered by the data in GePaRD.

There were no striking differences regarding the share of SSRI and TCA prescriptions between suicidal cases with current on-label and those with current OLU. Previous studies similarly did not detect any difference between SSRIs and TCAs and the risk of suicide.[26, 29]

The size of the used database is a major strength of this study. Our analyses reflect real-world drug utilization patterns in a population representative for the general population in Germany.[18, 19]

Using pharmacy dispensing data to determine drug exposure is considered the gold standard in pharmacoepidemiological research as recall bias cannot occur.[30] Beyond that, it has been shown that drug dispensation data give valid information on drug use in Germany.[19, 31]

GePaRD does not contain information on inpatient drug treatment. Accordingly, we were only able to assess outpatient treatment. Yet, since all examined ADs (except hypericum) are available by prescription only, GePaRD should provide valid and almost complete information on outpatient AD use.

Since GePaRD contains the exact date of dispensation for prescriptions, the potential for misclassification of drug exposure is low. There is, however, no information on patients' adherence to prescriptions. As outpatient diagnoses are only related to a quarter of a year in the database, some misclassification is possible regarding underlying diagnoses for prescriptions. For the same reason, it was not possible to use outpatient diagnoses to identify outcomes in the risk analysis, since it would not have been possible to assure that the outcome followed the exposure. This might have contributed to the small number of identified events.

Using claims data for the investigation of suicidality is difficult as suicide-related events are frequently missed or not reported in clinical assessment and are therefore likely to be underestimated.[26, 27] As information about actual suicides is not available in GePaRD, suicidal

events in our study do not include completed suicide but only suicidal ideation and intentional self-harm with a suicidal background, making an underestimation of suicidal events even more likely.

Conclusions

Despite the decreasing AD OLU in minors during the study period, its extent is still considerable. This does not necessarily indicate inappropriate treatment but rather a lack of clinical trials and subsequently missing approvals in the pediatric population. The low share of ADs prescribed despite the presence of a contraindication and the fact that the risk of adverse events was not higher for off- than for on-label use support this interpretation.

Ethics statement

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

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Table 1. Number of on- and off-label antidepressant prescriptions in 2011 by prescribing physicians' medical specialty (values are expressed as N and %)

Medical specialty	**On-label**	**Off-label**
	7,809 (63.7)	4,441 (36.3)
Child and adolescent psychiatrist	3,170 (68.8)	1,436 (31.2)
Internal and general medicine	1,520 (58.7)	1,070 (41.3)
Pediatrician	863 (62.1)	527 (37.9)
(Adult) psychiatrist	434 (52.9)	387 (47.1)
Unknown / missing	913 (63.8)	517 (36.2)

Table 2. Characteristics of the cohort of antidepressant users including subjects from the years 2004-2011 (values are expressed as N and % unless stated otherwise)

	Total	**On-label users**	**Off-label users**
	22,294 (100)	11,630 (100)	10,664 (100)
Male	9,599 (43.1)	4,809 (41.3)	4,790 (44.9)
Female	12,695 (56.9)	6,821 (58.7)	5,874 (55.1)
Age at cohort entry[a] (in years):			
<1	7 (0.0)	0 (0.0)	7 (0.1)
1-2	102 (0.5)	2 (0.0)	100 (0.9)
3-5	414 (1.9)	113 (1.0)	301 (2.8)
6-11	4,501 (20.2)	1,667 (14.3)	2,834 (26.6)
12-14	4,395 (19.7)	2,666 (22.9)	1,729 (16.2)
15-17	12,875 (57.8)	7,182 (61.8)	5,693 (53.4)
Mean (SD)	13.9 (3.38)	14.3 (2.93)	13.4 (3.75)
Median	15	15	15
Switched exposure group	384 (1.7)	185 (1.6)	199 (1.9)
Follow-up time (in days):			
Mean (SD)	717 (673)	655 (614)	785 (726)
Median	479	444	531
Most frequent diagnoses[b] during baseline period[c]: [d]			
Depression (F20.4, F32, F33)[e]	6.003 (26.9)	3,626 (31.2)	2,377 (22.3)
Restlessness & agitation (F43, R45.0, R45.1, R45.4, R46.3)	4,258 (19.1)	2,315 (19.9)	1,943 (18.2)
Headache & migraine (G43, G44, R51)	4,128 (18.5)	2,611 (22.5)	1,517 (14.2)
Hyperkinetic disorders (F90)	2,989 (13.4)	1,303 (11.2)	1,686 (15.8)
Somatoform disorders (F45)	2.852 (12.8)	1,757 (15.1)	1,095 (10.3)
Other anxiety disorders (F41)	2,611 (11.7)	1,573 (13.5)	1,038 (9.7)
Emotional disorders with onset specific to childhood (F93)	2.369 (10.6)	1,372 (11.8)	997 (9.3)
Other behavioral and emotional disorders (F98)	2,148 (9.6)	1,265 (10.9)	883 (8.3)
Sleep disorders (F51, G47)	1,510 (6.8)	764 (6.6)	746 (7.0)
Mixed disorders of conduct & emotions (F92)	1,291 (5.8)	721 (6.2)	570 (5.3)

[a] The date of the first prescription of an antidepressant drug

[b] Among the analyzed covariates

[c] The six months before cohort entry

[d] Columns add up to more than 100% because one patient can contribute to more than one line

[e] In brackets: Diagnostic code according to the International Classification of Diseases, 10th Version, German Modification (ICD-10-GM)

Table 3. Risk of suicidal events in the cohort of antidepressant users including subjects from the years 2004-2011 (values are expressed as N and %)

	Cases N=145	**Controls** N=725	**Unadjusted odds ratio**	**Adjusted[b] odds ratio**	**95% CI**
Current on-label use	50 (34.5)	137 (18.9)	1	1	-
Current off-label use[a]	38 (26.2)	168 (23.2)	0.52	0.64	0.37 - 1.12
Current off- and on-label use[a]	4 (2.8)	16 (2.2)	0.50	0.68	0.19 - 2.44
Recent use[a]	12 (8.3)	71 (9.8)	0.41	0.53	0.23 - 1.23
Past use[a]	41 (28.3)	333 (45.9)	0.23	0.46	0.25 - 0.84
Prior[c]					
Suicidal event	24 (16.6)	16 (2.2)	8.23	7.32	3.40 - 15.75
Schizophrenia/delusion	90 (62.1)	260 (35.9)	2.94	2.40	1.55 - 3.73
Eating disorder	20 (13.8)	51 (7.0)	2.02	2.57	1.37 - 4.84
Other development disorder	20 (13.8)	18 (2.5)	7.16	7.27	3.07 - 17.20
Other psychological disorder	48 (33.1)	135 (18.6)	2.30	2.49	1.51 - 4.11
Neurological disorder	34 (23.4)	107 (14.8)	1.75	1.79	1.06 - 3.03
Use of psychostimulants	5 (3.4)	72 (9.9)	0.33	0.29	0.10 - 0.87

[a] Reference group = current on-label use

[b] Adjusted for all statistically significant covariates shown in the table

[c] During the six-month baseline period before the prescription of an antidepressant drug

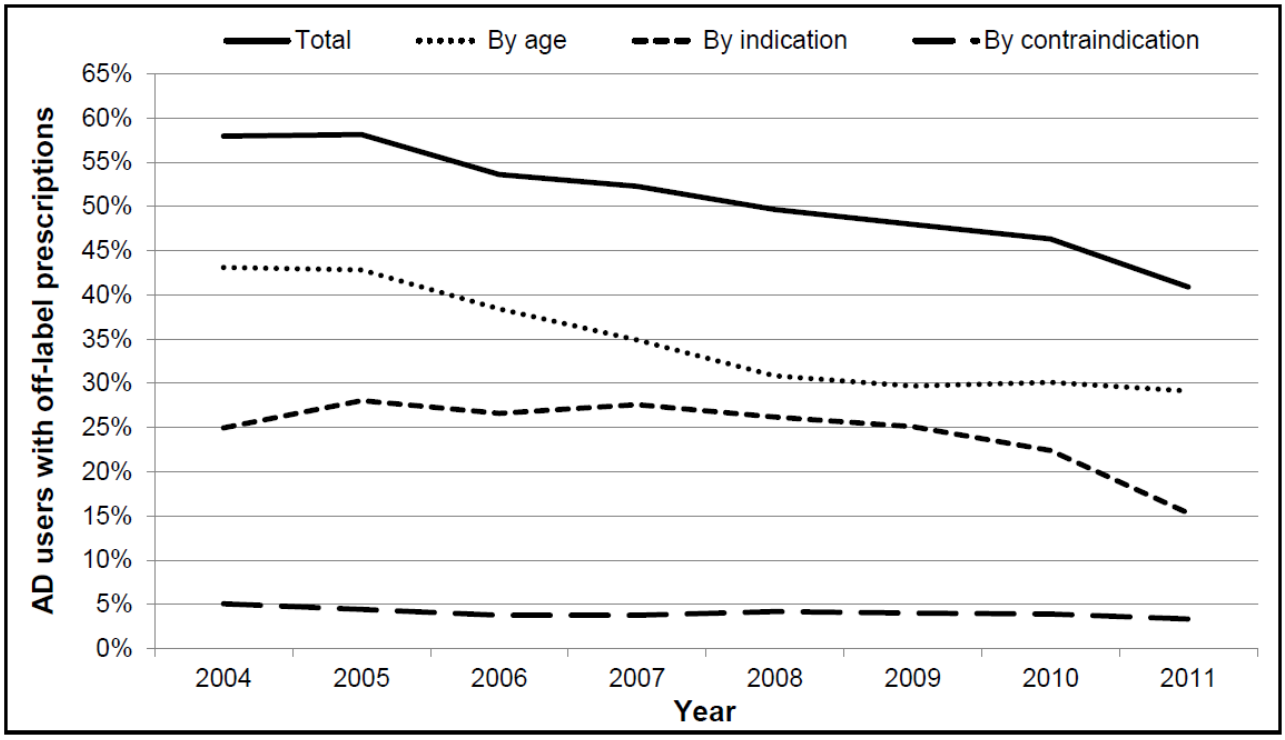

Figure 1. Share of antidepressant users with off-label prescriptions among all pediatric antidepressant users from 2004 (N=3,984) to 2011 (N=4,456)

Note: One patient can contribute to more than one type of off-label use.

Abbreviation: AD = antidepressant

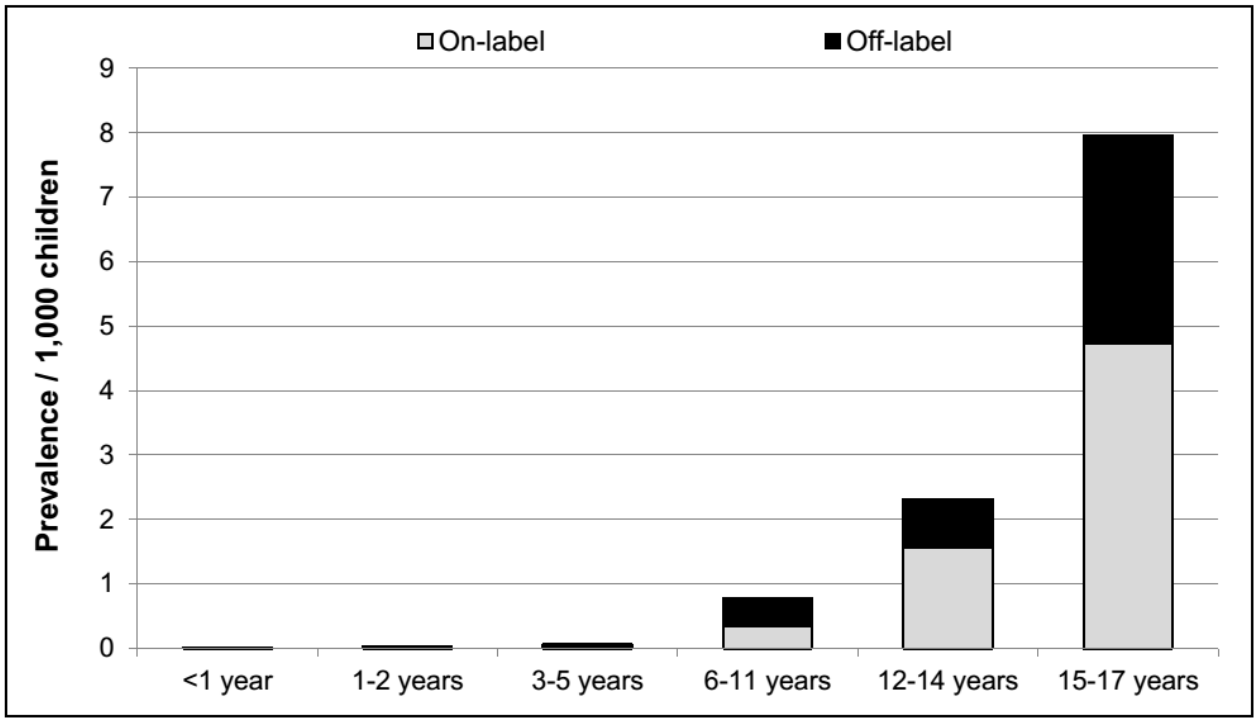

Figure 2. Prevalence of on- and off-label antidepressant prescriptions in 2011 by age group