

ORIGINAL ARTICLE

Antipsychotic Prescription in Children and Adolescents

An Analysis of Data From a German Statutory Health Insurance Company From 2005 to 2012

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SUMMARY

Background: Despite sparse documentation of their long-term therapeutic effects and side effects, antipsychotic drugs have come to be prescribed more frequently for children and adolescents in recent years, both in the USA and in Europe. No current data are available about antipsychotic prescriptions for this age group in Germany.

Methods: Data from the largest statutory health insurance fund in Germany (BARMER GEK) were studied to identify antipsychotic prescriptions for children and adolescents (age 0–19 years) from 2005 to 2012 and analyze them with respect to age, sex, drug prescribed, prescribing medical specialty, and any observable secular trends.

Results: The percentage of children and adolescents receiving a prescription for an antipsychotic drug rose from 0.23% in 2005 to 0.32% in 2012. In particular, atypical antipsychotic drugs were prescribed more frequently over time (from 0.10% in 2005 to 0.24% in 2012). The rise in antipsychotic prescriptions was particularly marked among 10- to 14-year-olds (from 0.24% to 0.43%) and among 15- to 19-year-olds (from 0.34% to 0.54%). The prescribing physicians were mostly either child and adolescent psychiatrists or pediatricians; the most commonly prescribed drugs were risperidone and pipamperone. Risperidone was most commonly prescribed for patients with hyperkinetic disorders and conduct disorders.

Conclusion: In Germany as in other industrialized countries, antipsychotic drugs have come to be prescribed more frequently for children and adolescents in recent years. The German figures, while still lower than those from North America, are in the middle range of figures from European countries. The causes of the increase should be critically examined; if appropriate, the introduction of prescribing guidelines of a more restrictive nature could be considered.

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Antipsychotic drugs (synonym: neuroleptic drugs) are a heterogeneous group of psychotropic substances that were initially used to treat psychotic disorders such as schizophrenia, states of psychomotor excitation, and sleep disorders.

In many Western industrialized countries, there has been a marked increase in the prescription of antipsychotic drugs, and so-called atypical antipsychotic drugs in particular, in recent years—not just for adults, but for children and adolescents as well (increases of up to 750% from the period 1993–1998 to the period 2005–2009) (1, 2). Part of the increase is due to the prescription of these drugs for disorders for which they are neither indicated nor recommended in the relevant guidelines, e.g., attention-deficit/hyperactivity disorder (ADHD) and anxiety disorders (3, 4).

The prescribing of antipsychotic drugs for children and adolescents is problematic in several respects:

- Only a few antipsychotic drugs have been approved for use in children and adolescents, and off-label prescriptions are common (3). Moreover, the drugs that do carry approval in Germany for use in children and adolescents are approved mainly for the treatment of schizophrenia spectrum disorders and bipolar disorders (Table 1).
- Data on the efficacy of antipsychotic drugs in children and adolescents are sparse (5); long-term studies of their therapeutic effects and side effects are lacking (6, 7, e1).
- There is increasing evidence that atypical antipsychotic drugs, once thought to have a more favorable side-effect profile than classic antipsychotic drugs (which cause extrapyramidal motor manifestations such as early and tardive dyskinesia and akathisia), do in fact have major short- or long-term adverse effects including marked weight gain, hyperlipidemia, and extrapyramidal symptoms (8). These are more common in children and adolescents than in adults (9, 10). Atypical antipsychotic drugs were also once thought more effective than the classic ones; this, too, is questionable (11, e2).

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TABLE 1

Classification of the atypical and classic antipsychotic drugs that were available during the study period and their approval status for use in children and adolescents in Germany

Drug	Patient age	Indication (excerpted or abbreviated in some cases)	On the German market since
Atypical antipsychotic drugs			
Amisulpride		not approved for children or adolescents	1999
Aripiprazole	≥ 13 years ≥ 15 years	bipolar I disorder schizophrenia	2004
Asenapine		not approved for children or adolescents	2010
Clozapine	≥ 16 years	treatment-resistant schizophrenia	1974
Olanzapine		not approved for children or adolescents	1996
Paliperidone		not approved for children or adolescents	2007
Quetiapine		not approved for children or adolescents	2000
Risperidone	≥ 5 years	short-term symptomatic treatment of persistent aggressiveness in conduct disorders accompanied by below-average intellectual ability or intellectual disability	1994
Sertindole		not approved for children or adolescents	1997
Sulpiride	≥ 6 years	acute and chronic schizophrenia; depressive disorder (if treatment with another antidepressant was unsuccessful or not feasible), treatment-resistant vertigo in Ménière's disease	1972
Ziprasidone	≥ 10 years	manic or mixed episodes of up to moderate severity in bipolar disorders	2002
Zotepine		not approved for children or adolescents	1990* ²
Classic antipsychotic drugs			
Benperidol		not approved for children or adolescents	1966
Bromperidol	≥ 12 years	acute, subacute, and chronic schizophrenia	1984
Chlorpromazine	children* ¹	attenuation of psychomotor agitation, vomiting of central origin	1953* ³
Chlorprothixene	≥ 3 years	attenuation of states of psychomotor agitation and excitation in the setting of acute psychotic syndromes; maniform syndromes	1959
Droperidol	≥ 2 years	prevention and treatment of nausea and vomiting after surgery (treatment of second choice)	1963
Flupentixol		not approved for children or adolescents	1966
Fluphenazine	≥ 12 years	acute and chronic schizophrenic psychoses, states of psychomotor excitation	1961
Fluspirilene		not approved for children or adolescents	1972
Haloperidol	≥ 3 years	acute and chronic schizophrenic syndromes, states of psychomotor excitation of psychotic origin, acute manic syndromes, tic disorders, vomiting	1959
Levomepromazine	≥ 16 years	states of psychomotor agitation and excitation in the setting of psychotic syndromes, mild acute psychotic syndromes with delusions, hallucinations, thought disorders and delusions of control, maniform syndromes, combination therapy for pain	1959
Melperone	≥ 12 years	sleep disorders, confusional states, states of psychomotor agitation and excitation	1975
Perazine	≥ 16 years	acute and chronic psychoses, maniform syndromes, states of psychomotor excitation	1958
Perphenazine	children and adolescents* ¹	acute psychotic syndromes, catatonic syndromes, delirium and other exogenous psychotic syndromes, states of psychomotor excitation	1957
Pimozide	children and adolescents* ¹	maintenance therapy for chronic psychosis of schizophrenic type	1971
Pipamperone	children and adolescents* ¹	sleep disorders, states of psychomotor excitation	1961
Promazine	≥ 3 months	states of psychomotor excitation, sleep disorders, combination therapy for pain, neuropathy in childhood	1957* ⁴
Promethazine	≥ 2 years	states of agitation and excitation with underlying psychiatric disease	1950

Drug	Patient age	Indication (excerpted or abbreviated in some cases)	On the German market since
Prothipendyl	children and adolescents* ¹	attenuation of states of psychomotor agitation and excitation with underlying psychiatric disease	1958
Thioridazine	children and adolescents* ¹	chronic forms of schizophrenic and other psychoses	1959
Tiapride	children and adolescents* ¹	Huntington's disease	1978
Zuclopenthixol		not approved for children or adolescents	1981

Approval status was classified by a method analogous to that of Mühlbauer et al. (39): a substance was classified as approved if the pertinent summary of product characteristics and/or the German Red List contained dosage instructions for use in the age group in question for at least one commercial preparation of the substance. According to this scheme, substances with which children and adolescents are supposed to be treated "only in exceptional cases" (e.g., prothipendyl) or "with special attention to the risk–benefit ratio" (e.g., pipamperone) are classified as approved.

*¹ If the relevant documentation does not permit any determination of the age group(s) for which the drug was approved (a particularly common situation for drugs that were approved many years ago), the original wording is reproduced.

*² withdrawn from the market in December 2010

*³ withdrawn from the market in December 2007

*⁴ withdrawn from the market in January 2006

There have been only two publications to date regarding the frequency of antipsychotic prescriptions for children and adolescents in Germany. A cross-sectional study based on data of the Gmünder ErsatzKasse (a statutory health-insurance fund) revealed that, in a population of 356 520 children and adolescents, 0.34% received a prescription for an antipsychotic drug in the year 2000 (12). An analysis of data from AOK Hesse (another statutory health-insurance fund) for the years 2000–2006 revealed, among a population of children and adolescents that rose from 56 169 to 65 866, a rise in the frequency of antipsychotic prescriptions from 0.19% to 0.28% (13). This increase was solely due to the prescription of atypical antipsychotic drugs and was most marked among 10- to 14-year-olds. No more recent data are available.

Therefore, in the present study, we examine the current state and secular trend of antipsychotic prescriptions for children and adolescents in Germany.

Methods

Data from BARMER GEK (2005–2012) served as the basis for this study. The study population consisted of persons aged 0 to 19 years who were insured for at least one day in each quarter of the year in question. Antipsychotic drugs were defined as all substances designated by the Anatomical Therapeutic Chemical (ATC) Code N05A, except lithium. These were classified as classic or atypical (Table 1) according to the scheme of Kalverdiijk et al. (2).

The target variable was the percentage of the study population receiving at least one antipsychotic prescription in each of the years 2005 to 2012. Trends in prescribing behavior were determined for atypical and classic antipsychotic drugs, with stratification by age (0–4, 5–9, 10–14, and 15–19 years), sex, and region (the former West vs. the former East Germany). In addition, the prescribing medical specialties and the underlying medical diagnoses in outpatient care were studied for the year 2011 only. Statistical analyses were performed with SAS 9.2.

Results

Prescribing trends

From 2005 to 2012, the frequency of antipsychotic prescriptions for persons aged 0 to 19 rose from 0.23% (3611/1 595 957) to 0.32% (4518/1 414 623). A slight decrease in prescribing frequency was seen for the classic antipsychotic drugs (from 0.14% to 0.12%), while the prescription of atypical ones rose markedly (from 0.10% to 0.24%) (Figure 1).

Age stratification (Figure 2) reveals that the increase in antipsychotic prescriptions mainly affected older age groups. Such prescriptions actually became less common in children aged 0 to 4 (from 0.15% to 0.01%), while an increase was seen in all other age groups, most prominently in 10- to 14-year-olds (0.24% to 0.43% from 2005 to 2012) and 15- to 19-year-olds (0.34% to 0.54% over the same period).

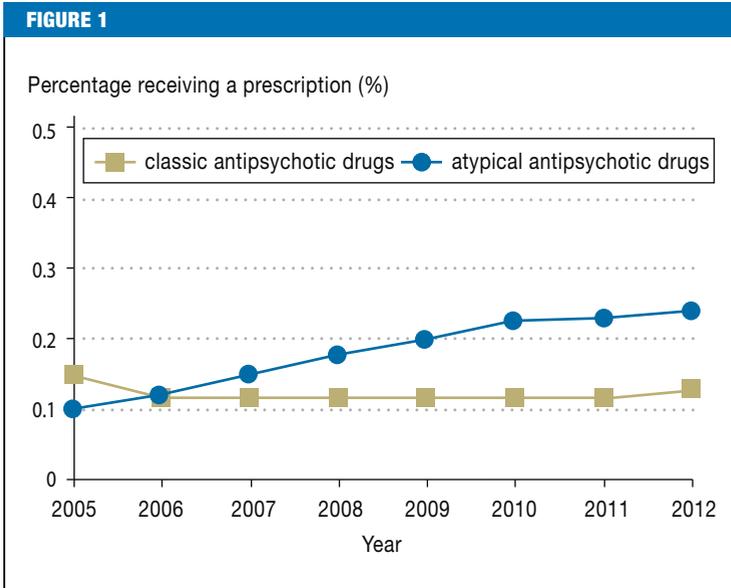
The percentage of girls and young women (up to age 19) receiving antipsychotic prescriptions rose from 0.16% to 0.19% over the time period 2005–2012, while the corresponding figure for boys and young men was 0.29% to 0.44%. The sex ratio (male:female) accordingly rose from 1.85:1 to 2.32:1 from 2005 to 2012.

Prescriptions for antipsychotic drugs in the former East Germany actually became slightly less common over the period of the study, while becoming more common in the former West Germany (eTable 1).

Multivariate logistic regression confirmed a significant effect on antipsychotic prescribing for each of the following factors: year of prescription (odds ratio [OR] 1.07/year), male sex (OR 2.37), older age (OR 1.12/year), and residence in the former East Germany (OR: 1.44) (eTable 2).

Antipsychotic drugs

Table 2 provides an overview of the antipsychotic drugs that were most commonly prescribed in 2005 and 2012. Risperidone, an atypical antipsychotic drug, was in first place in both years, and the percentage of risperidone prescriptions among all



The percentage of children and adolescents receiving prescriptions for antipsychotic drugs over the period 2005–2012, by type of drug (classic vs. atypical)

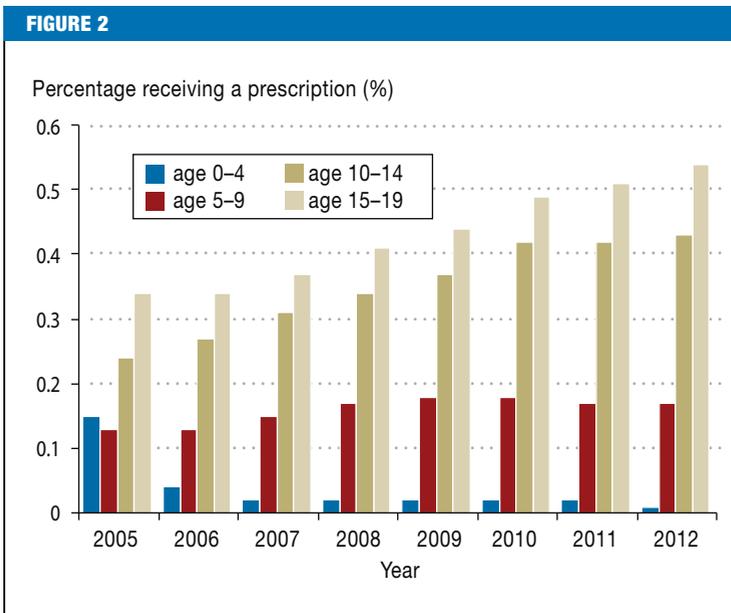
prescriptions of antipsychotic drugs for children and adolescents rose from 30.6% in 2005 to 49.6% in 2012. Pipamperone, a classic antipsychotic drug, took second place in both years. The classic drugs chlorprothixene, melperone, and levomepromazine stayed in the top 10 with only minor changes, while the newly introduced atypical drug aripiprazole, which was first sold in Germany in 2004, was in fifth place by 2012. The percentage of antipsychotic prescriptions accounted for by the classic drugs declined markedly from 52.9% in 2005 to 31.4% in 2012.

Prescribing specialties and diagnoses

In 2011, 24 828 antipsychotic prescriptions were written for a total of 4433 children and adolescents. 27.9% of these prescriptions were written by child and adolescent psychiatrists, 25.4% by pediatricians, and 16.2% by general practitioners. 7.4% of prescriptions were written by neurologists and psychiatrists, and the remaining 23.2% by other physicians who we presume were mainly working in psychiatric hospital outpatient departments.

Age stratification revealed that most prescriptions for children aged 0 to 4 were written by pediatricians (57.3%), while most for older age groups were written by either pediatricians or child/adolescent psychiatrists (age 5–9, 35.6% and 32.1%, respectively; age 10–14, 32.0% and 32.1%, respectively). Most prescriptions for 15- to 19-year-olds were written by child/adolescent psychiatrists (23.5%) or by general practitioners (20.5%).

The coded diagnoses of patients who were given the most commonly prescribed antipsychotic drug, risperidone, are listed in Table 3. 61.5% had hyperkinetic disorders, and 36.5% had conduct disorders.



The percentage of children and adolescents receiving prescriptions for antipsychotic drugs over the period 2005–2012, by age group

Discussion

The findings regarded in a national and international context

Over the period of the study, the percentage of children and adolescents in Germany receiving at least one prescription for an antipsychotic drug rose by 41.2% (this and all other relative increases were calculated on the basis of the unrounded raw data). The rise is clearly due to a marked increase in the rate of prescription of atypical antipsychotic drugs (+129.0%), which was most prominently seen in males and in persons aged 10 to 19. These nationwide comparative figures extend the findings of Schubert and Lehmkuhl (13), who reported a 50.6% rise in antipsychotic prescriptions from 2000 to 2006 that was likewise attributable to atypical antipsychotic drugs and was most prominently seen in 10- to 14-year-olds. A comparison of prescribing trends for antipsychotic drugs with prescribing trends for other types of drugs in the same study population (data not shown) reveals the following: from 2005 to 2012, the percentage of children and adolescents for whom antidepressants were prescribed rose by 49.2% (14), and there was a similar

TABLE 2

The ten antipsychotic drugs that were most commonly prescribed to children and adolescents in 2005 and 2012 (number of prescriptions and percentage of all antipsychotic prescriptions)

2005	Prescriptions	%	2012	Prescriptions	%
Risperidone (AAD)	5611	30.6	Risperidone (AAD)	12 253	49.6
Pipamperone (CAD)	3733	20.4	Pipamperone (CAD)	4079	16.5
Tiapride (CAD)	2174	11.9	Quetiapine (AAD)	2345	9.5
Promazine (CAD)	1226	6.7	Tiapride (CAD)	1471	6.0
Olanzapine (AAD)	1053	5.8	Aripiprazole* (AAD)	1114	4.5
Quetiapine (AAD)	896	4.9	Chlorprothixene (CAD)	769	3.1
Chlorprothixene (CAD)	605	3.3	Melperone (CAD)	604	2.4
Melperone (CAD)	584	3.2	Olanzapine (AAD)	574	2.3
Levomepromazine (CAD)	396	2.2	Levomepromazine (CAD)	366	1.5
Clozapine (AAD)	302	1.7	Sulpiride (AAD)	216	0.9
Other	1730	9.4	Other	932	3.8
Total	18 310	100.0	Total	24 723	100.0

AAD = atypical antipsychotic drug; CAD = classic antipsychotic drug
 *Aripiprazole came onto the German market in 2004

rise in prescriptions for medication to treat ADHD (stimulants/atomoxetine) (+62.4%) (14). This value is lower than the 96.3% increase reported by Schubert et al. for the period 2000–2007 (15).

These German figures are lower than the North American ones (Table 4): A study from the USA revealed an increase in the rate of antipsychotic prescriptions from 0.24% to 1.83% in children, and from 0.78% to 3.76% in adolescents, from the period 1993–1998 to the period 2005–2009 (1). A Canadian study of changes from 2005 to 2009 revealed an increase of the antipsychotic prescription rate from 3.6% to 8.2%, as well as a 121.7% relative increase in prescriptions of atypical antipsychotics (16). A recent Italian study (17) did not reveal any increase at all in antipsychotic prescriptions, but an increase was found in a study from Iceland (18). The frequency of antipsychotic prescriptions was much lower in the Italian study, and higher in the Icelandic one, than in the present study. Steinhausen discusses various possible influences on prescription rates in an international context (e3).

As for sex, the present study—in accordance with others—shows a higher prescribing rate for male patients (3, 19). Peak prescribing rates were found among persons aged 10 to 19; in other studies, peak rates were found in the age groups 7–12, 10–19, 10–14, and 14–20 (1, 2, 20, 21).

The study from the USA revealed an increase in antipsychotic prescriptions for preschool children (22), but no such increase was found in the present study. Indeed, a decrease in such prescriptions for children up to age 4 from 0.15% to 0.01% (2005 vs. 2012) was found, due to the withdrawal of promazine from the German market in early 2006.

TABLE 3

Psychiatric diagnoses in children and adolescents who received at least one prescription for risperidone in 2011 (total number of patients, 2525)

Diagnosis	Percentage of children (%)
Hyperkinetic disorders	61.5
Conduct disorders	36.5
Intellectual disability	23.0
Autism spectrum disorders	17.6
Anxiety disorders and emotional disorders	17.4
Depression	16.4
Specific developmental disorders of scholastic skills	12.6
Tic disorders	7.4
Adjustment disorders	6.0
Elimination disorders	6.0
Somatoform disorders	5.7
Personality disorders	4.6
Mental and behavioural disorders due to psychoactive substance use	3.8
Schizophrenia spectrum disorders	3.6
Obsessive-compulsive disorders	2.4
Eating disorders	1.3
Sleep disorders	0.9
Dissociative disorders	0.9

The diagnoses listed here may appear as a main diagnosis or as a comorbidity (associated diagnosis). Each patient can carry more than one diagnosis. The data do not permit any determination as to which of the coded mental disorders was considered to be an indication for risperidone.

TABLE 4

Overview of recent studies on antipsychotic prescriptions for children and adolescents

Authors	Country	Source of data	Year(s)	Number of subjects	Age (years)	Prevalence (per 1000 persons per year)	Drugs / Drug classes	Secular trends
Bachmann et al., 2013 (present study)	Germany	BARMER GEK	2005–2012	1 414 623–1 595 957* ¹	0–19	2.3 (2005) 3.2 (2012)	CAD: 0.14% → 0.12% AAD: 0.10% → 0.24%	– AP prescriptions overall ↑ (+41.2%) – AAD prescriptions ↑ (+129.0%) – ratio ♂:♀ ↑ from 1.85 to 2.32
Olfson et al., 2012 (1)	USA	National Ambulatory Medical Care Survey	1993–1998 1999–2004 2005–2009	92 370* ²	0–13 (ch) 14–20 (ado)	2.4 (ch) 7.8 (ado) (1993–1998) 18.3 (ch) 37.6 (ado) (2005–2009)	CAD: 1.3% (ch), 1.8% (ado) AAD: RIS > ARI > QUE (ch) ARI > QUE > RIS (ado)	AP prescriptions ↑
Pringsheim et al., 2011 (16)	Canada	IMS Brogan	2005–2009	308 490 (2005) 661 300 (2009)	0–18	36.0 (2005) 82.0 (2009)	CAD: + 25% AAD : + 121% RIS > QUE	AP prescriptions ↑ (+114%)
Alessi-Severini et al., 2012 (3)	Canada* ³ (Manitoba)	Manitoba Health, Statistics Canada	1999–2008	n.d.	0–18	1.9 (1999) 7.4 (2008)	Combination AP + MPH ↑ (13% → 43%)	– AP prescriptions ↑ – ratio ♂:♀ ↑ from 1.9 to 2.7
Clavenna et al., 2011 (17)	Italy* ³ (Verona region)	Verona regional prescription registry	2004–2008	76 000* ¹	0–17	ca. 0.37 (2004) ca. 0.30 (2008)	most common AP: haloperidol (8%)	no change in AP prevalence
Alexander et al., 2011 (23)	USA	IMS Health National Disease and Therapeutic Index	1995–2008	608 000 (CAD) 120 000 (AAD) (1995/96)* ² 31 000 (CAD) 4 216 000 (AAD) (2007/08)* ²	0–17	n.d.	n.d.	Percentage of AAD prescriptions ↑ (2008: 93%), percentage of CAD prescriptions ↓ (1995: 84%)
Schubert & Lehmkühl, 2009 (13)	Germany (Hesse)* ³	AOK Hesse	2000–2006	65 866 (2000)* ¹ 56 169 (2006)* ¹	0–18	1.9 (2000) 2.8 (2006)	AAD: 0.4 CAD: 1.6 (2000) AAD: 1.8 CAD: 1.4 (2006)	AP prescriptions ↑ (+50.6%)
Zoega et al., 2009 (18)	Iceland	National drug registry	2003–2007	78 157 (2003)* ¹ 79 469 (2007)* ¹	0–17	8.7 (2003) 10.6 (2007)	RIS > ARI > QUE	AP prescriptions ↑
Kjosavig et al., 2009 (25)	Norway	Norwegian Prescription Database (NorPD)	2005	n.d.	0–19	♂: 0.6* ⁴ ♀: 0.4	n.d.	n.d.
Acquaviva et al., 2009 (19)	France	two nationwide health insurance funds and data from a nationwide survey	2004	29 393	3–18	♂: 4.1–4.2 ♀: 2.5–2.6 overall: 3.3–3.4	n.d.	– AP prescriptions ↑ in older children/adolescents – prescriptions ♂ > ♀
Rani et al., 2008 (20)	United Kingdom	General Practice Research Database	1992–2005	789 467 (2006)* ¹ 2767* ²	0–18	0.39 (1992) 0.77 (2005)	n.d.	– AAD 60-fold ↑, CAD ↓ – nearly twice as many prescriptions by GPs – rising prevalence mainly due to longer duration of treatment – largest rise in 7-to-12-year-olds

Authors	Country	Source of data	Year(s)	Number of subjects	Age (years)	Prevalence (per 1000 persons per year)	Drugs / Drug classes	Secular trends
Kalverdijk et al., 2008 (2)	Netherlands* ³ (northern and eastern regions)	Inter-Action Database (drug dispensing by pharmacies)	1997–2005	95 158* ¹ (1997) and 119 612* ¹ (2005)	0–19	1997: 3.0 2005: 6.8	n.d.	– rising prevalence mainly due to AAD and longer duration of treatment – highest prevalence at ages 10–14, especially among ♂
Aparasu & Bhatara, 2007 (21)	USA	National Ambulatory Medical Care Survey/National Hospital Ambulatory Medical Care Survey (outpatient department portion)	2003–2004	2.1 million outpatient contacts per year	0–19	1/100 contacts: AP prescription	most common AAD: RIS > QUE > ARI	– AP ↑ in ch/ado over age 9 – AP prescriptions by specialists ↑

AAD = atypical antipsychotic drug; ado = adolescents; AP = antipsychotic drug; ARI = aripiprazole; CAD = classic antipsychotic drug; ch = children; GP = general practitioner; MPH = methylphenidate; n.d. = no data; QUE = quetiapine; RIS = risperidone

*¹ population at risk

*² population with AP prescriptions

*³ regional data

*⁴ data given in defined daily doses (DDD) per 1000 persons

The east-west divide evident in the present study has no clear explanation; in any case, the difference between the two German regions diminished over the course of the study period. Studies in adults have revealed differences in psychiatric morbidity in the former East and West Germany (e4), but there is no such evidence for children and adolescents (e5, e6).

In comparable studies from various countries, off-label prescriptions accounted for 52.0% to 94.5% of the total (1, 18, 23). In view of the coded diagnoses of the patients for whom risperidone was prescribed (Table 3), one may suspect that, in Germany as well, most prescriptions were for externalizing disorders (ADHD, conduct disorders), while only a small fraction were for the approved indication (persistent aggression in a child or adolescent with below-average intellectual ability). A trend toward the use of antipsychotic drugs to treat externalizing disorders has been described in several studies from different countries (3, 16, 21). Further evidence that this is the case comes from the observation of a marked increase in prescriptions for boys aged 10 to 14; the epidemiologic peak incidence of externalizing disorders is found in precisely this group (24).

Among the prescribing medical disciplines, child and adolescent psychiatrists and pediatricians play a central role, together accounting for half of all prescriptions. General practitioners wrote a lower percentage of antipsychotic prescriptions in the present study, in contrast to studies from foreign countries with different health-care systems where general practitioners accounted for more such prescriptions (3, 20, 25), and also in contrast to prescribing patterns for other drugs, e.g., antidepressants (26).

Explanations for the rise in antipsychotic prescriptions

The observed marked increase in antipsychotic prescriptions in Germany in recent years presumably has multiple causes which can be no more than tentatively inferred from the available data.

Increased prevalence of mental disorders—A rise in the prevalence of mental disorders in children and adolescents over the period of the study (if there was such a rise), with a corresponding rise in the need for treatment, might account at least in part for the finding. The currently available data, however, do not support this hypothesis. A meta-analysis of 33 German studies from the years 1953 to 2007 did not reveal any increase in psychiatric morbidity among children and adolescents in recent decades (27). A further study comparing schoolchildren in 1987 and 2008 revealed an increase in the prevalence of somatic symptoms, but no significant increase in internalizing or externalizing psychiatric symptoms (28).

Altered guideline recommendations—There was no change in the relevant therapeutic guidelines of the German Society of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy (Deutsche Gesellschaft für Kinder- und Jugendpsychiatrie, Psychosomatik und Psychotherapie, DGKJP) in the years 2007–2011, so that this potential explanation can rather be discarded.

Altered care situation—Over the course of the study, the two medical specialties that accounted for the largest number of prescriptions saw the following changes in the number of board-certified specialists in practice within the German statutory health-insurance system: pediatrics, +10.5%; child and adolescent psychiatry, +61.5% (authors' calculations

from data of the German Medical Association). A rising number of potential prescribers thus seems a possible cause of the rising number of prescriptions.

Marketing of atypical antipsychotic drugs—The specific rise in the prescription of atypical antipsychotic drugs may also be attributable to intense marketing by drug companies ([29, e7], particularly for the specific encouragement of off-label use: [30]). Among the effects of marketing is that prescribing physicians may believe that atypical antipsychotic drugs have a more favorable risk–benefit profile and therefore prescribe these preferentially.

Drug treatment instead of psychotherapy—A further reason for the increased prescription of antipsychotic drugs may be that drug treatment can be started more rapidly than psychotherapy and, in general, requires a lesser time investment and degree of motivation from the patient and his or her family. Moreover, the findings of an effectiveness study of outpatient treatments for conduct disorders were discouraging (31) despite the fact that for these entities effective psychotherapeutic treatments are principally available (32).

The strengths and weaknesses of this study

This is a longitudinal study based on current data from the largest German statutory health-insurance fund about the prescription of antipsychotic drugs to children and adolescents throughout Germany over an eight-year period. In general, routine insurance data permit the investigation of large, unselected populations without the problems of low participation or recollection error that typically beset studies with primary data collection. On the other hand, the informational value of such studies is lessened by several factors. First, the study population is not necessarily representative, as different health-insurance companies can have differently structured populations of insurees (33). Thus, generalizations from the results can only be made with caution. Second, the use of diagnoses coded by physicians from multiple specialties gives rise to imprecision, especially because no information can be obtained about the diagnostic algorithms, psychological tests, and other diagnosis-confirming techniques that may have been applied. Third, no information is recorded about the patients’ family history, severity and duration of manifestations, ethnic origin (34), living situation (35), or prescribed dose. Finally, not all drugs are actually taken as prescribed.

Comparisons with data from analogous studies in other countries are made more difficult by differences in health-care systems, the composition of study populations, and study duration.

Overview

In Germany as elsewhere in the Western world, prescriptions of antipsychotic drugs for children and adolescents have become more common in recent

years. The numbers are lower than in the USA and Canada, but are in the middle range of figures from European countries. The increase is marked enough to demand attention, particularly in view of the sparse scientific evidence, the high risk of side effects, and above all the fact that many prescriptions are issued to treat disorders (including ADHD) for which antipsychotic drugs are not known to be indicated, and for which effective treatments exist with less severe side effects.

It should also be noted, however, that physicians who treat children and adolescents with serious mental illness are often confronted by a clinical dilemma: only very few effective drugs have been approved for certain indications (see *Table 1*; e.g., haloperidol as the sole approved drug for tic disorders), and some of the older, approved drugs can have major side effects as well.

Thus, until interpretable findings are available from further studies (such as the TOSCA study [e8]), child/adolescent psychiatrists and other specialists treating behavioral disorders in this age group must carefully weigh the indications when considering the initial prescription of an antipsychotic drug. The use of such a drug is justifiable if it seems to be indicated after thorough evaluation and provided that the patient is strictly monitored, while under such treatment, for the occurrence of adverse effects.

The observed discrepancy between the scientific evidence and current prescribing practices points to a pressing need for further studies on the effects of antipsychotic drugs in children and adolescents (e1, e9). In particular, more data are needed on long-term therapeutic effects and side effects, as only data of this type can serve as a solid evidential basis for the determination (or extension) of indications for these drugs in particular groups of patients that are defined by, e.g., an age category or target symptom (5, e1). The Pediatric European Risperidone Studies (www.pers-project.com), under the sponsorship of the European Union, are an exemplary project of this type. Desirable features of future studies would include a naturalistic design (e9) and a multimodal approach (e10, e11).

Furthermore, in the intermediate term, it should be considered whether more explicit framework conditions ought to be set for the prescribing of antipsychotic drugs to children and adolescents (e.g., with respect to the types of physicians allowed to prescribe these medications in this age group) and for the monitoring of adverse effects during drug treatment (see, e.g., [36, 37]). Mere non-binding suggestions can hardly be expected to bring about any change in prescribing practices (38).

Conflict of interest statement

Prof. Bachmann has received lecture fees from Actelion, Novartis, and Ferring as well as payment from BARMER GEK for writing a chapter in a book. He has served as a study physician in clinical trials for Shire and Novartis.

Prof. Glaeske and PD Dr. Hoffmann are active on behalf of a number of statutory health-insurance companies (BARMER GEK, DAK, TK, and various corporate health-insurance funds) in the setting of contracts for third-party payment.

Dr. Lempp states that he has no conflict of interest.

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REFERENCES

1. Olfson M, Blanco C, Liu SM, Wang S, Correll CU: National trends in the office-based treatment of children, adolescents, and adults with antipsychotics. *Arch Gen Psychiatry* 2012; 69: 1247–56.
2. Kalverdijk LJ, Tobi H, van den Berg PB, et al.: Use of antipsychotic drugs among Dutch youths between 1997 and 2005. *Psychiatr Serv* 2008; 59: 554–60.
3. Alessi-Severini S, Biscontri RG, Collins DM, Sareen J, Enns MW: Ten years of antipsychotic prescribing to children: a Canadian population-based study. *Can J Psychiatry* 2012; 57: 52–8.
4. Comer JS, Mojtabai R, Olfson M: National trends in the antipsychotic treatment of psychiatric outpatients with anxiety disorders. *Am J Psychiatry* 2011; 168: 1057–65.
5. Vitiello B, Correll C, van Zwieten-Boot B, Zuddas A, Parellada M, Arango C: Antipsychotics in children and adolescents: increasing use, evidence for efficacy and safety concerns. *Eur Neuropsychopharmacol* 2009; 19: 629–35.
6. Seida JC, Schouten JR, Boylan K, et al.: Antipsychotics for children and young adults: a comparative effectiveness review. *Pediatrics* 2012; 129: e771–84.
7. Ben Amor L: Antipsychotics in pediatric and adolescent patients: a review of comparative safety data. *J Affect Disord* 2012; 138: 22–30.
8. Pringsheim T, Lam D, Ching H, Patten S: Metabolic and neurological complications of second-generation antipsychotic use in children: a systematic review and meta-analysis of randomized controlled trials. *Drug Saf* 2011; 34: 651–68.
9. Cohen D, Bonnot O, Bodeau N, Consoli A, Laurent C: Adverse effects of second-generation antipsychotics in children and adoles-

- cents: a Bayesian meta-analysis. *J Clin Psychopharmacol* 2012; 32: 309–16.
10. Rani FA, Byrne PJ, Murray ML, Carter P, Wong IC: Paediatric atypical antipsychotic monitoring safety (PAMS) study: pilot study in children and adolescents in secondary- and tertiary-care settings. *Drug Saf* 2009; 32: 325–33.
11. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM: Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet* 2009; 373: 31–41.
12. Zito JM, Safer DJ, de Jong-van den Berg LT, et al.: A three-country comparison of psychotropic medication prevalence in youth. *Child Adolesc Psychiatry Ment Health* 2008; 2: 26.
13. Schubert I, Lehmkuhl G: Increased antipsychotic prescribing to youths in Germany. *Psychiatr Serv* 2009; 60: 269.
14. Bachmann C, Hoffmann F: Ambulante Verordnungen von Antipsychotika bei Kindern und Jugendlichen. In: Glaeske G, Schickel C (eds.): *BARMER GEK Arzneimittelreport 2013. Schriftenreihe zur Gesundheitsanalyse* St. Augustin: Asgard 2013, 243–61.
15. Schubert I, Köster I, Lehmkuhl G: The changing prevalence of attention-deficit/hyperactivity disorder and methylphenidate prescriptions: a study of data from a random sample of insureds of the AOK Health Insurance Company in the German State of Hesse, 2000–2007. *Dtsch Arztebl Int* 2010; 107: 615–21.
16. Pringsheim T, Lam D, Patten SB: The pharmacoepidemiology of antipsychotic medications for Canadian children and adolescents: 2005–2009. *J Child Adolesc Psychopharmacol* 2011; 21: 537–43.
17. Clavenna A, Andretta M, Pilati P, et al.: Antidepressant and antipsychotic use in an Italian pediatric population. *BMC Pediatr* 2011; 11: 40.
18. Zoega H, Baldursson G, Hrafnkelsson B, Almarsdottir AB, Valdimarsdottir U, Halldorsson M: Psychotropic drug use among Icelandic children: a nationwide population-based study. *J Child Adolesc Psychopharmacol* 2009; 19: 757–64.
19. Acquaviva E, Legleye S, Auleley GR, Deligne J, Carel D, Falissard BB: Psychotropic medication in the French child and adolescent population: prevalence estimation from health insurance data and national self-report survey data. *BMC Psychiatry* 2009; 9: 72.
20. Rani F, Murray ML, Byrne PJ, Wong IC: Epidemiologic features of antipsychotic prescribing to children and adolescents in primary care in the United Kingdom. *Pediatrics* 2008; 121: 1002–9.
21. Aparasu RR, Bhatara V: Patterns and determinants of antipsychotic prescribing in children and adolescents, 2003–2004. *Curr Med Res Opin* 2007; 23: 49–56.
22. Constantine RJ, Tandon R, McPherson M, Andel R: Early diagnoses and psychotherapeutic medication treatment experiences of a cohort of children under 6 years old who received antipsychotic treatment in Florida's Medicaid program. *J Child Adolesc Psychopharmacol* 2011; 21: 79–84.
23. Alexander GC, Gallagher SA, Mascola A, Moloney RM, Stafford RS: Increasing off-label use of antipsychotic medications in the United States, 1995–2008. *Pharmacoepidemiol Drug Saf* 2011; 20: 177–84.
24. Garland AF, Hough RL, McCabe KM, Yeh M, Wood PA, Aarons GA: Prevalence of psychiatric disorders in youths across five sectors of care. *J Am Acad Child Adolesc Psychiatry* 2001; 40: 409–18.
25. Kjosavik SR, Ruths S, Hunskaar S: Psychotropic drug use in the Norwegian general population in 2005: data from the Norwegian Prescription Database. *Pharmacoepidemiol Drug Saf* 2009; 18: 572–8.
26. Hoffmann F, Glaeske G, Petermann F, Bachmann CJ: Outpatient treatment in German adolescents with depression: an analysis of nationwide health insurance data. *Pharmacoepidemiol Drug Saf* 2012; 21: 972–9.
27. Barkmann C, Schulte-Markwort M: Prevalence of emotional and behavioural disorders in German children and adolescents: a meta-analysis. *J Epidemiol Community Health* 2012; 66: 194–203.

KEY MESSAGES

- From 2005 to 2012, the percentage of children and adolescents in Germany for whom antipsychotic drugs were prescribed rose from 0.23% to 0.32%.
- Over the same period, prescriptions of atypical antipsychotic drugs rose from 0.10% to 0.24%.
- The greatest rises in the prescription of antipsychotic drugs were seen in male adolescents and in the age group of 10- to 14-year-olds.
- The most commonly prescribed drugs were risperidone, pipamperone, quetiapine, and tiapride.
- The most common diagnoses in persons given risperidone were hyperkinetic disorders, conduct disorders, autism, intellectual disability, anxiety disorders, emotional disorders, and depressive disorders.
- 27.9% of all antipsychotic prescriptions were written by child and adolescent psychiatrists, 25.4% by pediatricians, and 16.2% by general practitioners.

28. Eimecke S, Pauschardt J, Remschmidt H, Walter R, Mattejat F: Time Trends in Psychopathology. A 21-year comparison from Germany. *Z Kinder Jugendpsychiatr Psychother* 2011; 39: 187–94.
29. Hebebrand J, Blanz B, Herpertz-Dahlmann B, Lehmkuhl G: Zunahme der Häufigkeit medikamentöser Behandlungen, ethische Prinzipien und Interessenkonflikte in der Kooperation mit der pharmazeutischen Industrie. *Z Kinder Jugendpsychiatr Psychother* 2012; 40: 133–8.
30. Kesselheim AS, Mello MM, Studdert DM: Strategies and practices in off-label marketing of pharmaceuticals: a retrospective analysis of whistleblower complaints. *PLoS Med* 2011; 8: e1000431.
31. Bachmann M, Bachmann CJ, John K, Heinzel-Gutenbrunner M, Remschmidt H, Mattejat F: The effectiveness of child and adolescent psychiatric treatments in a naturalistic outpatient setting. *World Psychiatry* 2010; 9: 111–7.
32. Bachmann C, Lehmkuhl G, Petermann F, Scott S: Evidenzbasierte psychotherapeutische Interventionen für Kinder und Jugendliche mit aggressivem Verhalten. *Kindh Entw* 2010; 19: 245–54.
33. Hoffmann F, Bachmann C: Unterschiede in den soziodemographischen Merkmalen, der Gesundheit und Inanspruchnahme bei Kindern und Jugendlichen nach ihrer Krankenkassenzugehörigkeit. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2013; (in print)
34. Sleath B, Domino ME, Wiley-Exley E, Martin B, Richards S, Carey T: Antidepressant and antipsychotic use and adherence among Medicaid youths: differences by race. *Community Ment Health J* 2010; 46: 265–72.
35. Dosreis S, Yoon Y, Rubin DM, Riddle MA, Noll E, Rothbard A: Antipsychotic treatment among youth in foster care. *Pediatrics* 2011; 128: e1459–66.
36. Pringsheim T, Panagiotopoulos C, Davidson J, Ho J: Evidence-based recommendations for monitoring safety of second generation antipsychotics in children and youth. *J Can Acad Child Adolesc Psychiatry* 2011; 20: 218–33.
37. Gemeinsamer Bundesausschuss (G-BA): Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie: Anlage III Nummer 44. Stimulantien. Vom 16. September 2010. www.g-ba.de/downloads/39-261-1185/2010-09-16_AM-RL3_Stimulantien_BAnz.pdf (last accessed on 29 May 2013)
38. Schulze J, van den Bussche H, Glaeske G, Kaduszkiewicz H, Wiese B, Hoffmann F: Impact of safety warnings on antipsychotic prescriptions in dementia: Nothing has changed but the years and the substances. *Eur Neuropsychopharmacol* 2013; 23: 1034–42.
39. Mühlbauer B, Janhsen K, Pichler J, Schoettler P: Off-label use of prescription drugs in childhood and adolescence: an analysis of prescription patterns in Germany. *Dtsch Arztebl Int* 2009; 106: 25–31.

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 For eReferences please refer to:
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ORIGINAL ARTICLE

Antipsychotic Prescription in Children and Adolescents

An Analysis of Data From a German Statutory Health Insurance Company From 2005 to 2012

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eREFERENCES

- e1. Loy JH, Merry SN, Hetrick SE, Stasiak K: Atypical antipsychotics for disruptive behaviour disorders in children and youths. *Cochrane Database Syst Rev* 2012; 9: CD008559.
- e2. Davies LM, Lewis S, Jones PB, et al.: Cost-effectiveness of first- v. second-generation antipsychotic drugs: results from a randomised controlled trial in schizophrenia responding poorly to previous therapy. *Br J Psychiatry* 2007; 191: 14–22.
- e3. Steinhausen HC: A European perspective on paediatric psychiatric pharmacoepidemiology. *World Psychiatry* 2013; 12: 131.
- e4. Bramesfeld A, Grobe T, Schwartz FW: Prevalence of depression diagnosis and prescription of antidepressants in East and West Germany: An analysis of health insurance data. *Soc Psychiatry Psychiatr Epidemiol* 2010; 45: 329–35.
- e5. Hoffmann F, Petermann F, Glaeske G, Bachmann CJ: Prevalence and comorbidities of adolescent depression in Germany. An analysis of health insurance data. *Z Kinder Jugendpsychiatr Psychother* 2012; 40: 399–404.
- e6. Bachmann CJ, Manthey T, Kamp-Becker I, Glaeske G, Hoffmann F: Psychopharmacological treatment in children and adolescents with autism spectrum disorders in Germany. *Res Dev Disabil* 2013; 34: 2551–63.
- e7. Lieb K, Koch C: Medical students' attitudes to and contact with the pharmaceutical industry—a survey at eight German university hospitals. *Dtsch Arztebl Int* 2013; 110: 584–90.
- e8. Farmer CA, Arnold LE, Bukstein OG, et al.: The treatment of severe child aggression (TOSCA) study: Design challenges. *Child Adolesc Psychiatry Ment Health* 2011; 5: 36.
- e9. Rapoport JL: Pediatric psychopharmacology: too much or too little? *World Psychiatry* 2013; 12: 118–23.
- e10. Remschmidt H: Psychopharmacological treatments in children and adolescents. Adequate use or abuse? *World Psychiatry* 2013; 12: 135–6.
- e11. Arnold LE, Aman MG, Li X, et al.: Research Units of Pediatric Psychopharmacology (RUPP) Autism Network randomized clinical trial of parent training and medication: one-year follow-up. *J Am Acad Child Adolesc Psychiatry* 2012; 51: 1173–84.

eTABLE 1

The percentage of children and adolescents receiving prescriptions for antipsychotic drugs, stratified by region of residence in Germany (in %)

Year	Former West Germany	Former East Germany*	% overall
2005	0.18	0.41	0.23
2006	0.20	0.27	0.21
2007	0.21	0.31	0.23
2008	0.24	0.33	0.26
2009	0.26	0.35	0.28
2010	0.29	0.37	0.31
2011	0.31	0.34	0.31
2012	0.32	0.34	0.32

* including Berlin

eTABLE 2

Multivariate logistic regression for factors associated with the prescription of antipsychotic drugs to children and adolescents in Germany, 2005–2012

Odds ratio (OR) and 95% confidence interval (95% CI)		
Variable	OR	95% CI
Year of prescription (for each additional year)	1.07	1.06–1.07
Age (for each additional year)	1.12	1.12–1.13
Sex (male vs. female)	2.37	2.31–2.43
Region (former East vs. former West Germany)	1.44	1.41–1.48