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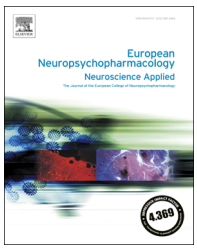

Trends and patterns of antidepressant use in children and adolescents from five western countries, 2005-2012

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Abstract
Following the FDA black box warning in 2004, substantial reductions in antidepressant (ATD) use were observed within 2 years in children and adolescents in several countries. However, whether these reductions were sustained is not known. The objective of this study was to assess more recent trends in ATD use in youth (0—19 years) for the calendar years 2005/6-2012 using data extracted from regional or national databases of Denmark, Germany, the Netherlands, the United Kingdom (UK), and the United States (US). In a repeated cross-sectional design, the

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annual prevalence of ATD use was calculated and stratified by age, sex, and according to subclass and specific drug. Across the years, the prevalence of ATD use increased from 1.3% to 1.6% in the US data (+26.1%); 0.7% to 1.1% in the UK data (+54.4%); 0.6% to 1.0% in Denmark data (+60.5%); 0.5% to 0.6% in the Netherlands data (+17.6%); and 0.3% to 0.5% in Germany data (+49.2%). The relative growth was greatest for 15−19 year olds in Denmark, Germany and UK cohorts, and for 10−14 year olds in Netherlands and US cohorts. While SSRIs were the most commonly used ATDs, particularly in Denmark (81.8% of all ATDs), Germany and the UK still displayed notable proportions of tricyclic antidepressant use (23.0% and 19.5%, respectively). Despite the sudden decline in ATD use in the wake of government warnings, this trend did not persist, and by contrast, in recent years, ATD use in children and adolescents has increased substantially in youth cohorts from five Western countries.

1. Introduction

The safety of selective serotonin reuptake inhibitors (SSRIs) for the treatment of depression in children and adolescents has been a subject of much concern and debate (Brent, 2004; Friedman, 2014). In October 2004, the U.S. Food and Drug Administration (FDA) issued a "black-box", now termed "boxed" warning, indicating an increased risk of suicidal ideation/suicidal behavior in children and adolescents treated with SSRIs (Friedman, 2014). This followed similar action in the United Kingdom by the Medicines and Healthcare Products Regulatory Agency (MHRA), and was soon followed by similar warnings by other regulatory bodies (e.g. European Medicines Agency (EMA) warning against the use of SSRIs in youths < 18 years, August 2005). Within 2 years after these warnings, the use of antidepressants (ATDs) decreased markedly in children and adolescents in Canada, the UK and the USA (Bergen et al., 2009; Busch and Barry, 2009; Katz et al., 2008; Kurian et al., 2007; Olfson et al., 2008). However, such decreases occurred mostly for youth diagnosed with less severe depression while psychotherapy use increased substantially (Valluri et al., 2010). Whether diminished ATD use has persisted is not known.

A decade after government warnings, the controversy continues on the evidence for the risk of suicidal events associated with ATD use in children and adolescents. Notably, the majority of ATDs are not licensed in youth less than 18 years of age, and thus are commonly prescribed "off-label". Considering the broader international context in which there is a significant influence of cultural and health system factors on psychotropic medication use in general (Schomerus et al., 2014; Steinhausen, 2013), information on how ATD use has evolved over recent years in different countries is needed. While there are a few studies assessing multinational patterns of psychotropic medication use in youth (Zito et al., 2006), to date, there is no recent multinational epidemiological data on trends in ATD use in children and adolescents. Single country comparisons (Dörks et al., 2013; Hoffmann et al., 2014; Pottegard et al., 2014; Wijlaars et al., 2012; Zoega et al., 2009) are often hampered by dissimilar study methods (e.g. different timespans or age groups). The objective of this study is to assess more recent trends in ATD use in youth (0−19 years) using data extracted from regional or national databases of Denmark, Germany, the Netherlands, the United Kingdom (UK), and the United States (US). We also assess patterns of antidepressant use according to age group, sex, ATD subclass and entity.

2. Experimental procedures

2.1. Data sources

2.1.1. Denmark

To perform this study we used the Danish Registry of Medicinal Products Statistics (RMPS). The registry is a national prescription database on all outpatient pharmacy-dispensed prescription medications in Denmark (5.53 million inhabitants) and is updated monthly. Each prescription record contains detailed information on the drug dispensed (incl. ATC code). With the use of an estimation of the underlying population (denominator), the prevalence can be calculated.

2.1.2. Germany

We used claims data of the single largest German health insurance company, the BARMER GEK (insuring about 9.1 million persons, representing more than 10% of the German population). Although there are several differences between the statutory insurance system and private insurances, both provide full-coverage health insurance. As compared to the entire German population, the BARMER GEK insures a higher proportion of females, but there are no differences regarding socioeconomic status (as measured by education level) (Hoffmann and Bachmann, 2014). For each year, all insurees who were insured at least 1 day in all four quarters were included. Each prescription record contains detailed information on the drugs dispensed including ATC code.

2.1.3. The Netherlands

This study was performed with pharmacy dispensing data from IADB.nl (Visser et al., 2013). Dutch patients usually register at a single community pharmacy, so a single pharmacy provides an almost complete listing of each subject's prescribed drugs. The database comprises all prescription drug dispensing data from 59 pharmacies since 1994 for about 600,000 persons in the northern and eastern parts of the Netherlands. It includes all prescriptions, regardless of prescriber, reimbursement status, or insurance. Over-the-counter drugs and in-hospital prescriptions are not included. The population in the database is representative of the whole Dutch population (Visser et al., 2013).

2.1.4. United Kingdom

We used The Health Improvement Network (THIN) primary care database, which contains information on prescriptions issued in primary care in all four UK countries. Approximately 98% of the population in the UK is registered with a general practitioner (GP), with GPs issuing 93.4% of all ATD prescriptions dispensed by community pharmacies in the UK (Health and Social Care Information Centre, 2015). THIN is broadly representative of the UK population in terms of demographics and consultation behavior (Blak et al., 2011). We included only practices with good quality data recording (Horsfall et al., 2013; Maguire et al., 2009). We analyzed data from 2005 to 2012 and included 552 practices, covering 6% of the UK population. Prescribing data in THIN has been shown to reflect dispensed prescriptions with a mean practice redemption rate for all prescribing of 98.5% in 2008 (NHS National Information Centre, 2011). The redemption rate for antidepressants was slightly lower (96.7%), although still high.

2.1.5. United States

For the United States (US) data, computerized Medicaid administrative claims for the calendar years 2006 through 2012 were analyzed for a narrowly-defined population of youth (0–19 years) enrolled in Children's Health Insurance Program (CHIP) in a mid-Atlantic state. Such youth are eligible for Medicaid coverage due to family income (upper limit is three-times the federal poverty level; The Henry J Kaiser Family Foundation (2015)) and are similar to privately-insured youth in the US with respect to age distribution, race and family composition, and general health status, with moderately lower parental education, employment, and income (Byck, 2000). Each youth was assigned an encrypted identification number, which was then used to link the enrollment data files to prescription drug claim files. Youth who were not continuously enrolled in the CHIP program in a given year were excluded from the analyses in that year.

2.2. Data analysis

Annual prevalence was defined as the percent of youth (0–19 years) with one or more dispensings for antidepressant medication among continuously enrolled youths in a given calendar year in the 2005/6–2012 period. The data extracted from the above-mentioned databases are presented as total prevalence per 100 youths and stratified according to age groups [0−4, 5−9, 10−14, 15−19 years (Zito et al., 2006)], and gender. In addition, among antidepressant-treated youths, we compared the proportional distribution of antidepressant subclasses [SSRI (e.g. fluoxetine, paroxetine), TCA (e.g. imipramine, amitriptyline), other (e.g. mirtazapine, duloxetine, St John's wort)] between 2005/6 and 2012 separately for each country.

2.3. Ethical approval

2.3.1. United Kingdom

The CSD Medical Research Scientific Review Committee approved this study in February 2015 (reference number 14-086). The scheme for THIN to obtain and provide anonymous patient data to researchers was approved by the National Health Service South-East Multicentre Research Ethics Committee in 2002.

2.3.2. USA

The study related to the US data was reviewed and approved by the Institutional Review Board of the University of Maryland, Baltimore.

2.3.3. Denmark, Germany and The Netherlands

According to the respective national regulations, ethical approval was not necessary for this study.

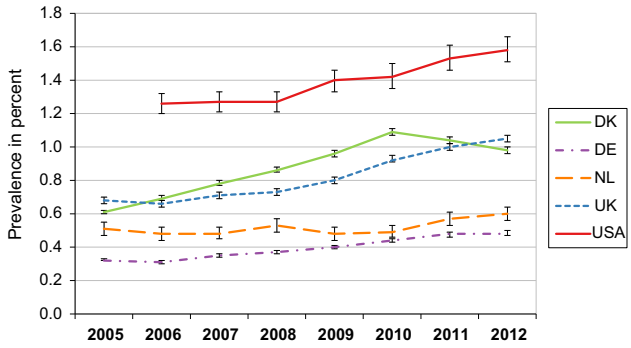

Figure 1 Percent prevalence of antidepressant use in children and adolescents (0–19 years) in youth cohorts from five countries, 2005–2012.
Annotation: DE=Germany, DK=Denmark, NL=Netherlands, UK=United Kingdom, USA=United States of America.

3. Results

In 2012, the number of youths receiving ATD per studied population of youths between 0−19 years were as follows: Germany: 6849/1,414,623, Denmark: 11,774/1,203,817, Netherlands: 790/131,954, United Kingdom: 8680/827,906, and United States: 1667/105,188.

Across seven years from 2005/6 through 2012 (Figure 1), the annual prevalence of ATD use for children and adolescents increased in all studied cohorts as follows: USA cohort: 1.3% to 1.6% (+26.1%), UK cohort: 0.7% to 1.1% (+54.4%), Denmark cohort: 0.6% to 1.0% (+60.5%), Netherlands cohort: 0.5% to 0.6% (+17.6%), and Germany cohort: 0.3% to 0.5% (+49.2%). Cross-national differences in ATD use were up to 2.1-fold in 2005 and up to 3.3-fold in 2012.

The prevalence of ATD use stratified by sex is provided in Table 1, showing a female preponderance in ATD use throughout all years and all countries, with the exception of the USA in 2006. Across countries, female/male ratios in ATD use ranged from 1.7 to 2.3 in 2005 and from 1.1 to 2.4 in 2012.

The ATD use was most common among 15–19 year olds, ranging from 0.8% to 2.4% in 2005/6, and from 1.4% to 6.2% in 2012 (Table 2). There was a consistent linear relation between age and the prevalence of ATD medication use. When looking at the trends in ATD use by age group from 2005/6–2012, ATD use increased most markedly in 15–19 year olds and in 10–14 year olds (Table 2). Time trends in the age group 0–4 years were not calculated, as the number of children in this age group was very small ($N \leq 10$ in most databases in 2012).

Concerning subclasses, both in 2005 and 2012, in most countries, the majority of ATD use was for SSRIs, with Denmark leading in SSRI use (81.8% of all ATD prescriptions in 2012) (Figure 2). The only exception was Germany, where in 2005 tricyclic antidepressant (TCA) prescriptions marginally outnumbered SSRI prescriptions (39.6% vs. 37.7%). In 2012, this trend had inverted, but the percentage of TCA prescriptions to children and adolescents in Germany (23.0%) and also in the UK (19.5%) was still notable.

The entities most frequently prescribed differed markedly between countries (Table 3). While citalopram was first

Table 1 Percent prevalence of antidepressant medication use for children and adolescents (0–19 years) in youth cohorts from five countries, by sex, 2005–2012 (numbers in brackets = 95% confidence interval).

	2005[a]				2006			2007			2008			2009			2010			2011			2012				Difference 2005-2012	
	M	F	F/M ratio	T	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T	M	F	F/M ratio	T	Trend	*p*-Value
Denmark	0.40 [0.38-0.41]	0.83 [0.81-0.86]	2.11	0.61 [0.60-0.62]	0.45 [0.44-0.47]	0.95 [0.92-0.97]	0.69 [0.68-0.71]	0.51 [0.49-0.52]	1.07 [1.05-1.10]	0.78 [0.77-0.80]	0.55 [0.53-0.57]	1.19 [1.17-1.22]	0.86 [0.85-0.88]	0.62 [0.60-0.64]	1.31 [1.28-1.34]	0.96 [0.94-0.98]	0.69 [0.67-0.72]	1.51 [1.48-1.54]	1.09 [1.07-1.11]	0.67 [0.65-0.70]	1.42 [1.39-1.46]	1.04 [1.02-1.06]	0.62 [0.60-0.64]	1.35 [1.32-1.38]	2.17	0.98 [0.96-1.00]	+60.5%	<.0001
Germany	0.24 [0.23-0.25]	0.41 [0.39-0.42]	1.65	0.32 [0.32-0.33]	0.23 [0.22-0.24]	0.39 [0.37-0.40]	0.31 [0.30-0.32]	0.26 [0.25-0.27]	0.43 [0.42-0.45]	0.35 [0.34-0.36]	0.28 [0.27-0.30]	0.47 [0.45-0.49]	0.37 [0.36-0.38]	0.30 [0.29-0.32]	0.49 [0.48-0.51]	0.40 [0.39-0.41]	0.33 [0.32-0.35]	0.55 [0.53-0.57]	0.44 [0.43-0.45]	0.35 [0.34-0.36]	0.61 [0.59-0.63]	0.48 [0.46-0.49]	0.35 [0.34-0.36]	0.63 [0.61-0.64]	1.79	0.48 [0.47-0.50]	+49.2%	<.0001
Netherlands	0.37 [0.33-0.42]	0.65 [0.59-0.72]	1.76	0.51 [0.47-0.55]	0.32 [0.28-0.36]	0.64 [0.58-0.71]	0.48 [0.44-0.52]	0.33 [0.29-0.38]	0.64 [0.58-0.70]	0.48 [0.45-0.52]	0.37 [0.33-0.42]	0.69 [0.63-0.76]	0.53 [0.49-0.57]	0.36 [0.32-0.41]	0.60 [0.54-0.66]	0.48 [0.44-0.52]	0.34 [0.30-0.39]	0.64 [0.59-0.71]	0.49 [0.46-0.53]	0.41 [0.36-0.46]	0.73 [0.66-0.80]	0.57 [0.53-0.61]	0.46 [0.41-0.52]	0.74 [0.67-0.81]	1.59	0.60 [0.56-0.64]	+17.6%	<.0001
UK	0.41 [0.39-0.43]	0.96 [0.93-0.99]	2.34	0.68 [0.66-0.70]	0.40 [0.38-0.42]	0.94 [0.91-0.97]	0.66 [0.64-0.68]	0.42 [0.40-0.44]	1.02 [0.99-1.05]	0.71 [0.69-0.73]	0.43 [0.41-0.45]	1.04 [1.01-1.07]	0.73 [0.71-0.75]	0.47 [0.45-0.49]	1.14 [1.11-1.17]	0.80 [0.78-0.82]	0.54 [0.52-0.57]	1.32 [1.28-1.35]	0.93 [0.91-0.95]	0.59 [0.57-0.61]	1.42 [1.38-1.45]	1.00 [0.98-1.02]	0.63 [0.60-0.65]	1.47 [1.43-1.51]	2.35	1.05 [1.03-1.07]	+54.4%	<.0001
US	N/A	N/A	0.90[b]	N/A	1.32 [1.23-1.41]	1.19 [1.11-1.28]	1.26 [1.20-1.32]	1.34 [1.26-1.43]	1.19 [1.11-1.27]	1.27 [1.21-1.33]	1.26 [1.18-1.35]	1.28 [1.19-1.37]	1.27 [1.21-1.33]	1.41 [1.32-1.51]	1.38 [1.28-1.48]	1.40 [1.33-1.46]	1.40 [1.30-1.50]	1.45 [1.35-1.55]	1.42 [1.35-1.50]	1.52 [1.42-1.63]	1.54 [1.44-1.65]	1.53 [1.46-1.61]	1.52 [1.42-1.62]	1.65 [1.55-1.77]	1.09	1.58 [1.51-1.66]	+26.1%	<.0001

Annotation: F=Females, M=Males, T=Total.

[a]For the US, only data from 2006–2012 were available.

[b]Ratio from 2006 data.

Table 2 Percent prevalence of antidepressant medication use from 2005–2012, by age group in youth cohorts from five countries (numbers in brackets = 95% confidence interval).

	2005	2006	2007	2008	2009	2010	2011	2012	Difference 2005[a]–2012
Denmark									
0-4 years	0.01 [0.00-0.01]	0.00 [0.00-0.01]	0.01 [0.00-0.01]	0.01 [0.00-0.01]	0.01 [0.00-0.01]	0.01 [0.00-0.01]	0.01 [0.00-0.01]	0.01 [0.01-0.01]	N/A[b]
5-9 years	0.05 [0.04-0.05]	0.05 [0.04-0.06]	0.05 [0.04-0.06]	0.05 [0.05-0.06]	0.06 [0.05-0.07]	0.06 [0.05-0.07]	0.06 [0.05-0.07]	0.05 [0.04-0.06]	+4.6%
10-14 years	0.34 [0.32-0.36]	0.38 [0.35-0.40]	0.39 [0.37-0.41]	0.41 [0.39-0.44]	0.44 [0.42-0.46]	0.49 [0.47-0.52]	0.46 [0.44-0.49]	0.46 [0.44-0.49]	+34.9%
15-19 years	2.20 [2.15-2.26]	2.47 [2.41-2.53]	2.77 [2.71-2.83]	2.99 [2.93-3.05]	3.28 [3.21-3.34]	3.67 [3.60-3.73]	3.46 [3.39-3.52]	3.19 [3.13-3.26]	+45.1%
Germany									
0-4 years	0.02 [0.01-0.02]	0.01 [0.01-0.02]	0.01 [0.01-0.01]	0.01 [0.01-0.01]	0.01 [0.00-0.01]	0.01 [0.00-0.01]	0.00 [0.00-0.01]	0.00 [0.00-0.01]	N/A[b]
5-9 years	0.10 [0.09-0.11]	0.10 [0.09-0.11]	0.10 [0.09-0.11]	0.07 [0.06-0.08]	0.07 [0.06-0.07]	0.06 [0.06-0.07]	0.05 [0.04-0.06]	0.04 [0.03-0.05]	−60.6%
10-14 years	0.20 [0.18-0.21]	0.18 [0.17-0.20]	0.20 [0.19-0.22]	0.20 [0.19-0.22]	0.20 [0.19-0.22]	0.19 [0.18-0.21]	0.20 [0.18-0.21]	0.21 [0.19-0.22]	+5.3%
15-19 years	0.83 [0.80-0.85]	0.78 [0.76-0.81]	0.89 [0.87-0.92]	1.01 [0.98-1.04]	1.10 [1.07-1.14]	1.28 [1.24-1.31]	1.40 [1.36-1.41]	1.41 [1.38-1.45]	+71.0%
Netherlands									
0-4 years	0.01 [0.00-0.03]	0.01 [0.00-0.03]	0.01 [0.00-0.03]	0.01 [0.00-0.02]	0.01 [0.00-0.03]	0.02 [0.01-0.04]	0.02 [0.01-0.04]	0.01 [0.00-0.03]	N/A[b]
5-9 years	0.07 [0.05-0.11]	0.05 [0.03-0.08]	0.07 [0.05-0.11]	0.07 [0.04-0.10]	0.05 [0.03-0.08]	0.09 [0.06-0.13]	0.11 [0.08-0.15]	0.09 [0.06-0.13]	+22.8%
10-14 years	0.34 [0.28-0.41]	0.34 [0.28-0.41]	0.26 [0.21-0.32]	0.30 [0.24-0.37]	0.32 [0.26-0.39]	0.33 [0.27-0.40]	0.40 [0.33-0.47]	0.48 [0.41-0.56]	+41.5%
15-19 years	1.59 [1.46-1.72]	1.53 [1.41-1.67]	1.52 [1.40-1.65]	1.65 [1.53-1.79]	1.43 [1.32-1.56]	1.43 [1.32-1.56]	1.62 [1.49-1.75]	1.68 [1.55-1.82]	+5.8%
UK									
0-4 years	0.00 [0.00-0.01]	0.00 [0.00-0.01]	0.00 [0.00-0.01]	0.00 [0.00-0.00]	0.00 [0.00-0.00]	0.00 [0.00-0.00]	0.00 [0.00-0.00]	0.00 [0.00-0.01]	N/A[b]
5-9 years	0.06 [0.05-0.07]	0.05 [0.04-0.06]	0.04 [0.04-0.05]	0.04 [0.04-0.05]	0.05 [0.04-0.06]	0.04 [0.03-0.05]	0.04 [0.03-0.05]	0.03 [0.03-0.04]	−40.5%
10-14 years	0.21 [0.19-0.23]	0.18 [0.16-0.20]	0.19 [0.17-0.21]	0.22 [0.21-0.24]	0.22 [0.20-0.24]	0.22 [0.20-0.24]	0.27 [0.25-0.29]	0.31 [0.29-0.33]	+46.3%
15-19 years	2.37 [2.31-2.44]	2.33 [2.27-2.40]	2.45 [2.38-2.51]	2.45 [2.39-2.51]	2.66 [2.60-2.72]	3.03 [2.96-3.10]	3.19 [3.12-3.26]	3.19 [3.12-3.26]	+34.8%
US[a]									
0-4 years	N/A	0.04 [0.03-0.06]	0.05 [0.04-0.07]	0.04 [0.02-0.05]	0.03 [0.02-0.05]	0.03 [0.02-0.05]	0.01 [0.01-0.03]	0.02 [0.01-0.04]	N/A[b]
5-9 years	N/A	1.20 [1.07-1.35]	1.17 [1.04-1.31]	0.99 [0.87-1.12]	1.05 [0.92-1.19]	0.96 [0.84-1.10]	0.90 [0.78-1.03]	0.88 [0.76-1.01]	−27.1%
10-14 years	N/A	3.49 [3.25-3.75]	3.48 [3.24-3.74]	3.39 [3.15-3.64]	3.57 [3.32-3.84]	3.45 [3.20-3.72]	3.55 [3.30-3.81]	3.50 [3.25-3.75]	+0,0%
15-19 years	N/A	5.35 [4.94-5.79]	5.36 [4.96-5.78]	5.86 [5.44-6.29]	5.93 [5.50-6.38]	5.82 [5.38-6.28]	6.08 [5.64-6.54]	6.24 [5.81-6.70]	+16.7%

[a]For the US, only data from 2006–2012 were available.
[b]Because of the small numbers of patients, difference in antidepressant use across time was not computed.

choice in Denmark and in the Netherlands, fluoxetine was most frequently prescribed in Germany and in the UK, and sertraline was the top ranking ATD in the US. In 2012, in the UK, Germany and the Netherlands, TCAs (amitriptyline, opipramol) were still among the top five prescribed entities.

4. Discussion

The major findings of this study are as follows: 1) From 2005/6 through 2012, the prevalence of ATD use in children and adolescents increased substantially in cohorts from five Western countries, with both absolute and relative increases being most pronounced in the UK and in Denmark. 2) Regarding age groups, the relative growth was greatest for 15–19 year olds in Denmark, Germany and UK cohorts, and for 10–14 year olds in Netherlands and US cohorts. 3) While SSRIs were the most commonly used antidepressant subclass, youth cohorts from Germany and the UK still displayed notable proportions of tricyclic antidepressant use (23.0% and 19.5%, respectively).

The current trend in ATD use is in line with international prescription trends for other psychotropic classes in children and adolescents, e.g. antipsychotics or ADHD drugs, which show even greater increased rates (Bachmann et al., 2014; Dalsgaard et al., 2013; Olfson et al., 2012; Rapoport, 2013; Ronsley et al., 2013). The reasons for this increase in antidepressant use are not completely clear. An increase of depressive disorders or other conditions demanding treatment with ATDs as a reason for the increase in ATD prescriptions can be largely ruled out, as there is substantial evidence that there has been no significant increase in the rates of children's mental health conditions in Western countries over recent years in studies of German and British youth (Hölling et al., 2014; Sellers et al., 2015). Nevertheless, there is some evidence of an increase in child and adolescent mental health service use, potentially indicating under-treatment in previous years (Breland et al., 2014; Steinhausen and Bisgaard, 2014).

Although there have been no substantial changes in clinical guidelines that would have extended indications for ATD prescriptions, in day-to-day practice there has been a marked trend towards a broadening of indications by prescribers. In terms of psychiatric and behavioral treatments, the growth of comorbidities (Kessler et al., 2009) as well as the increased trend for "not otherwise specified" diagnostic categories, may contribute to expanded medication use (Safer et al., 2015). In the study of Dörks et al. (2013) on ATD utilization in German children and adolescents, more than one third of ATDs were prescribed off-label for indications such as migraine, somatoform disorders, personality disorders, sleeping problems and developmental disorders, and in the US study of Lee et al. (2012), only 9.2% of ATDs were prescribed according to indication. Another potential reason for the increase in ATD use may be the preference for pharmacotherapy because of the limited availability of psychotherapy services or because of patients' and clinicians' expectations of reaching treatment goals faster with ATD use (Correll et al., 2013). Moreover, the increased ATD use may also be related to an increased marketing of ATD by pharmaceutical companies (Kesselheim et al., 2011; Kondro and Sibbald, 2004). Such marketing strategies have been demonstrated to be effective in influencing prescribers' preferences (Larkin et al., 2014). Finally, as Taylor, (2013) argues, the rise in ATD use may be addressing previous under-treatment of child psychiatric disorders. Nevertheless, the findings from this study cannot address questions of overuse or underuse of ATDs in children and adolescents. Further research is warranted on outcomes of community treatment populations to assure effective, appropriate, and quality care.

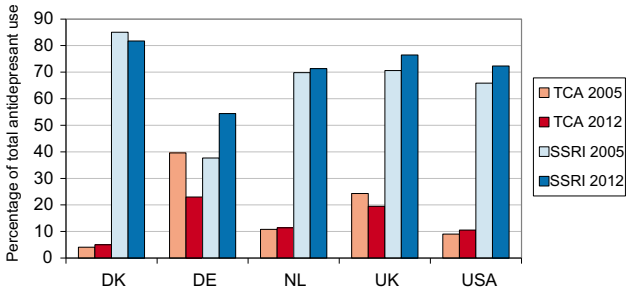

Figure 2 Trends in antidepressant medication use in children and adolescents (0–19 years) in youth cohorts from five countries for tricyclic antidepressants and selective serotonin reuptake inhibitors (2005 vs. 2012).
Annotation: DE=Germany, DK=Denmark, NL=The Netherlands, SSRI=Selective Serotonin Reuptake Inhibitors, TCA=Tricyclic antidepressants, UK=United Kingdom, USA=United States of America.

The greater proportion of ATD use in females compared with males is consistent with prior findings (Zito et al., 2006) and with the gender-specific incidence of depression in youth (Merikangas et al., 2009). Concerning age groups, the current findings show that the proportional growth in ATD use occurred mostly for older youth (10–19 year olds), whereas younger aged children showed minimal changes or sustained drops in ATD use. The marked rise of ATD use in adolescents is a finding consistent with the majority of recent studies on other psychotropic medication use in children and adolescents (Acquaviva et al., 2009; Bachmann et al., 2014; Kalverdijk et al., 2008; Meng et al., 2014; Pottegard et al., 2014; Steinhausen, 2015; Steinhausen and Bisgaard, 2014). In the current study, SSRIs were the most commonly used antidepressant subclass in all five Western countries. However, Germany and the UK displayed notable proportions of tricyclic antidepressant use in 2012. The continuing use of tricyclic antidepressants in youth contrasts with the long-standing negative findings on effectiveness (Hazell and Mirzaie, 2013). Regarding the most commonly prescribed substances, there were several antidepressants among the "top five" which have no approval for use in children or adolescents in the respective country (e.g. amitriptyline in Germany and the Netherlands, bupropion in the UK) or for which no trial evidence on safety or effectiveness in minors is available (e.g. opipramol, St John's worth). These "off-label" prescription practices in minors might reflect an extrapolation of ATD prescription patterns in adults. The true rates of off-label use might even be higher, as our data did not contain information whether licensed ATDs were prescribed for the corresponding indications.

Table 3 The top 5 antidepressant entities in children and adolescents (0-19 years) in youth cohorts from five countries (2005 vs. 2012), as a percentage of total antidepressant use.

Rank	Denmark				Germany				Netherlands				UK				US			
	2005	%	2012	%	2005	%	2012	%	2005	%	2012	%	2005	%	2012	%	2006[a]	%	2012	%
1	CIT	33.5	CIT	40.9	FLX	12.2	FLX	24.3	CIT	28.8	CIT	33.8	FLX	35.2	FLX	31.7	SER	20.6	SER	27.5
2	VEN	11.2	SER	16.8	SJW	11.0	CIT	15.7	PAR	15.6	FLX	16.6	CIT	19.3	CIT	29.2	FLX	20.5	FLX	21.9
3	SER	11.1	VEN	14.7	OPI	10.0	OPI	7.6	VEN	14.6	AMI	8.2	AMI	14.5	AMI	16.4	ESC	14.5	ESC	10.9
4	MIR	10.0	MIR	10.0	CIT	9.4	MIR	7.3	FLX	13.2	ESC	7.1	SER	7.2	SER	14.0	BUP	10.0	CIT	8.9
5	ESC	9.5	ESC	7.9	IMI	8.1	AMI	5.5	FLV	7.0	MIR	6.4	ESC	6.6	MIR	3.1	TRA	9.0	TRA	8.2

Annotation: AMI=Amitriptyline, BUP=Bupropion, CIT=Citalopram, ESC=Escitalopram, FLX=Fluoxetine, FLV=Fluvoxamine, IMI=Imipramine, MIR=Mirtazapine, OPI=Opipramol, PAR=Paroxetine, SER=Sertraline, SJW=St John's Wort, TRA=Trazodone, VEN=Venlafaxine.

[a]For the US, only data from 2006-2012 were available.

Among factors that may vary by country are formulary differences, differences in reimbursement, availability of alternative non-pharmacological treatments for emotional and behavioral disorders, clinical guidelines and indications for use, e.g. imipramine for nocturnal enuresis. Cultural attitudes toward the use of psychotropic drugs vary by country. For example, Schomerus et al. (2014) found that US patients embrace psychotropic medications more readily than Germans.

The main limitation of this study is the diversity of the underlying databases in terms of several factors, e.g. representativeness of the full population, prescribing physician specialty (GPs vs. specialists) and socio-economic status (von Soest et al., 2012). These differences in data sources also hamper the inter-country comparability of data. An example for this is the UK database, which contains only GPs' prescriptions. Thus, it lacks prescriptions issued by (child and adolescent) psychiatrists, which might lead to an underestimation of ATD prescription rates. However, as prescriptions are often initiated by psychiatrists and then continued by GPs, GPs' prescribing patterns probably reflect fairly completely ATD prescription trends in children and adolescents originally seen by psychiatrists.

Nevertheless, as the databases also reflect the differences of the respective national health systems (including e.g. prescribing restrictions), the comparability of prescription data between countries will never be completely harmonized. Therefore, the individual countries' relative prescription trends reported in our study are probably a more robust feature than absolute prescription rates.

Moreover, we did not have information on factors that may influence ATD prescribing to children and adolescents such as the underlying indication, co-medication, ethnic background (Wittkampf et al., 2010), foster care status (Fontanella et al., 2011, 2014), adequacy of dosage, duration of pharmacotherapy, adherence, symptom severity and symptom duration. Also, we did not consider medication bought over-the-counter (mainly St John's wort).

In conclusion, despite the sudden decline in ATD use in the wake of government warnings, the trend did not persist, and by contrast, across recent years, ATD use in children and adolescents has increased substantially in youth cohorts in five Western countries. While it is not clear whether this trend reflects overuse or underuse of ATDs in youth, further assessment is warranted. The findings support the need for outcomes research in community-treated populations, and, in the policy arena, for the development of harmonized international clinical guidelines.

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Contributors

Dr. Bachmann conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. Prof. Aagard acquired, analyzed and interpreted data, revised the manuscript critically, and approved the final manuscript as submitted. Mehmet Burcu acquired, analyzed and interpreted data, revised the manuscript critically, and approved the final manuscript as submitted. Prof. Glaeske acquired, analyzed and interpre-

ted data, revised the manuscript critically, and approved the final manuscript as submitted. Dr. Kalverdijk acquired, analyzed and interpreted data, revised the manuscript critically, and approved the final manuscript as submitted. Dr. Petersen acquired, analyzed and interpreted data, revised the manuscript critically, and approved the final manuscript as submitted. Dr. Schuiling-Veninga acquired, analyzed and interpreted data, revised the manuscript critically, and approved the final manuscript as submitted. Dr. Wijlaars acquired, analyzed and interpreted data, revised the manuscript critically, and approved the final manuscript as submitted. Prof. Zito acquired, analyzed and interpreted data, revised the manuscript critically, and approved the final manuscript as submitted. Prof. Hoffmann conceptualized and designed the study, undertook the statistical analysis, drafted the initial manuscript, and approved the final manuscript as submitted. All authors mentioned above agree to be accountable for all aspects of the work.

Conflict of interest

Christian Bachmann has received lecture fees from Actelion, Novartis, and Ferring as well as payment from BARMER GEK and from AOK for writing book chapters. He has served as a study physician in clinical trials for Shire and Novartis. Gerd Glaeske and Falk 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. Lise Aagaard has received traveling grants from Pfizer and Swedish Orphan BioVitrum. Luuk J. Kalverdijk has received lecture fees from Eli-Lilly, Janssen-Cilag and Shire and has served as a study physician in clinical trials of Eli-Lilly. Catharina Schuiling-Veninga, Irene Petersen, Linda Wijlaars, Julie M. Zito and Mehmet Burcu declare no conflict of interest.

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