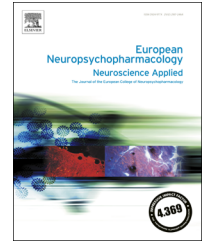




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Trends in ADHD medication use in children and adolescents in five western countries, 2005–2012

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Abstract

Over the last two decades, the use of ADHD medication in US youth has markedly increased. However, less is known about ADHD medication use among European children and adolescents. A repeated cross-sectional design was applied to national or regional data extracts from Denmark, Germany, the Netherlands, the United Kingdom (UK) and the United States (US) for calendar years 2005/2006–2012. The prevalence of ADHD medication use was assessed, stratified by age and sex. Furthermore, the most commonly prescribed ADHD medications were assessed. ADHD medication use prevalence increased from 1.8% to 3.9% in the Netherlands cohort (relative increase: +111.9%), from 3.3% to 3.7% in the US cohort (+10.7%), from 1.3% to 2.2% in the German cohort (+62.4%), from 0.4% to 1.5% in the Danish cohort (+302.7%), and

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from 0.3% to 0.5% in the UK cohort (+56.6%). ADHD medication use was highest in 10-14-year olds, peaking in the Netherlands (7.1%) and the US (8.8%). Methylphenidate use predominated in Europe, whereas in the US amphetamines were nearly as common as methylphenidate. Although there was a substantially greater use of ADHD medications in the US cohort, there was a relatively greater increase in ADHD medication use in youth in the four European countries. ADHD medication use patterns in the US differed markedly from those in western European countries.

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1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a psychiatric disorder with a male preponderance and a worldwide prevalence estimate of 3.4% in childhood and adolescence (Polanczyk et al., 2015), with European studies reporting lower prevalences (Döpfner et al., 2008; Green et al., 2005; Kvist et al., 2013; Meltzer et al., 2000; Russell et al., 2014) and US studies reporting higher prevalences (8.7%-10.6% (Visser et al., 2014; Wolraich et al., 2014)). Generally, studies employing DSM-IV ADHD criteria yield higher prevalences than those based on ICD-10 criteria (Döpfner et al., 2008; Ford et al., 2003). This is due to the fact that the ICD-10 equivalent of ADHD, the so-called “hyperkinetic disorder”, is a narrower and more severe subtype of the DSM-IV “attention-deficit/hyperactivity disorder”. For the sake of brevity, in the following text both disorders will be subsumed under the term “ADHD”.

In school-age children, most international clinical guidelines on the management of ADHD recommend a stepwise approach to treatment, starting with non-pharmacological interventions (Thapar and Cooper, 2016) and, if this is not successful, pharmacological treatment should be initiated. In contrast, US guidelines recommend an individual treatment plan that can include pharmacotherapy, behavioral therapy and/or psychosocial interventions, but which is not designed in a stepwise fashion (Pliszka, 2007). In preschool children with ADHD, parent training should be given priority, and - with the exception of the US (Pliszka, 2007) - prescription of ADHD medication is not encouraged (National Institute for Health and Care Excellence, 2008).

In recent years, the prevalence of ADHD medication use has increased in several countries (Burcu et al., 2016; Dalsgaard et al., 2013; Visser et al., 2014). These increases have been seen across all age groups, from young children to adolescents, and the use is increasingly continued into adulthood (Dalsgaard et al., 2013; Johansen et al., 2015).

For decades, methylphenidate has been the most commonly prescribed drug for treatment of ADHD symptoms, however, use of other drugs for the treatment of ADHD (e.g. atomoxetine, lisdexamfetamine) is increasing (Health and Social Care Information Centre, 2015). According to international treatment guidelines, methylphenidate or dexamfetamine are recommended as first-line pharmacological treatment and atomoxetine as second line in both children and adolescents (Thapar and Cooper, 2016). Long-term effectiveness and safety data are lacking, and there are concerns about safety aspects of prescribing ADHD

medication in the pediatric population (Zito and Burcu, 2016). Despite largely similar treatment guidelines, the use of medication and psychosocial treatment for ADHD varies significantly between countries (Hinshaw et al., 2011; Setyawan et al., 2015). Therefore, an international comparison of medication trends is useful in order to compare medication use patterns.

In this study, we aimed to compare trends in prevalence of ADHD medication use in children and adolescents (0-19 year-olds) in Denmark, Germany, the Netherlands, the United Kingdom (UK), and the United States (US), stratified by sex and age. Additionally, we aimed to assess the most commonly prescribed ADHD medications.

2. Experimental procedures

2.1. Data sources

2.1.1. Denmark

This study was performed using data from the Danish Registry of Medicinal Products Statistics (RMPS). The RMPS constitutes a national prescription database of all outpatient pharmacy-dispensed prescription medications for the 5.5 million Danish inhabitants. Each prescription record contains detailed information on the drug dispensed (including ATC code). The prevalence of ADHD medication use was calculated using an estimation of the underlying population of 0- to 19-year olds as denominator.

2.1.2. Germany

We used administrative data of the BARMER GEK, which is the largest German health insurance company (9.1 million insureds, representing more than 10% of the German population). In comparison to the total German population, the BARMER GEK insures a higher proportion of females, but there are no differences regarding the socioeconomic status (as measured by education level) (Hoffmann and Bachmann, 2014). Each year's cohort consisted of all insureds who were insured at least 1 day in all four quarters. Each prescription record contains detailed information on the drugs dispensed including ATC code.

2.1.3. The Netherlands

We used pharmacy dispensing data from the 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 dispensed prescriptions. The IADB database includes all prescription drug dispensing data from 59 pharmacies since 1997 for about 600,000 persons in the northern and eastern parts of the Netherlands. With the exception of over-the-counter drugs and in-hospital prescriptions, all prescriptions, regardless of prescriber, reimbursement status, or insurance, are covered by the

IADB database. The IADB database is representative of the whole Dutch population (Visser et al., 2013).

2.1.4. United Kingdom

We used UK Health Improvement Network (THIN) data. THIN is a primary care database, covering solely prescriptions made by General Practitioners from all four United Kingdom (UK) countries. 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), resulting in 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 Information Centre, 2011).

2.1.5. United States

We used computerized administrative claims for publicly-insured youth for the calendar years 2006 through 2012. These were analyzed for 0-19 year olds continuously enrolled in the Children's Health Insurance Program (CHIP) in a mid-Atlantic state (eligible population: 105,188). These children and adolescents are eligible for public insurance coverage due to family income [upper limit is three-times the federal poverty level] (The Henry J. Kaiser Family Foundation, 2015). This population is 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 received an encrypted identification number, which was then used to link the enrollment data files to prescription drug claim files.

2.2. Data analysis

We included children and adolescents (0-19 years of age) who were registered continuously for each calendar year from 2005 (2006 for US data) to 2012. We defined the annual prevalence as the proportion of children and young people with one or more dispensings for centrally acting stimulants (ATC group: N06BA). For each of the national databases, we determined overall ADHD medication prevalence per 100 children and adolescents per year, as well as prevalence stratified by sex and age groups [0-4, 5-9, 10-14, and 15-19 year olds] (Zito et al., 2006). In addition, we assessed the most commonly prescribed ADHD medications in 2005/2006 and 2012 separately for each country.

2.3. Ethical approval

2.3.1. United Kingdom

In February 2015, this study was approved by the CSD Medical Research Scientific Review Committee (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. United States

The study related to the United States 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, no ethical approval was necessary for this study.

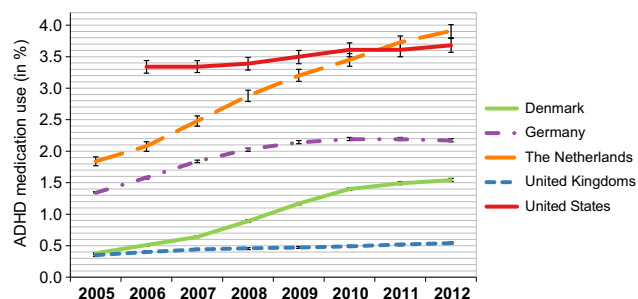


Figure 1 Percent prevalence of ADHD medication use in children and adolescents (0-19 years) in youth cohorts from five countries, 2005/6-2012.

3. Results

In 2012, the number of children and adolescents who received ADHD medication among eligible youth were as follows: Germany: 30,747/1,414,623; Denmark: 18,585/1,203,817; the Netherlands: 5157/131,954; the United Kingdom: 4489/827,906; and the United States: 3869/105,188. From 2005/6 to 2012, there was an increase in the annual prevalence of ADHD medication use in all included cohorts (Figure 1): Netherlands cohort: 1.8%-3.9%; Germany cohort: 1.3%-2.2%; Denmark cohort: 0.4%-1.5%; UK cohort: 0.3%-0.5%; and US cohort: 3.3%-3.7%. In the US, ADHD medication use was 6.8-fold more extensive than in the UK.

Table 1 shows the prevalence of ADHD medication use by sex, demonstrating a clear male preponderance in all years and all countries. Across the studied countries, the male: female ratio ranged from 2.6 to 6.6 in 2005/6, and from 2.6 to 5.0 in 2012.

The prevalence of ADHD medication use by age group is shown in Table 2, with the highest use in 10-14 year olds in all countries. In 2005/6, age-specific prevalence for 10-14 year olds ranged from 0.7% [95% confidence interval (CI)=0.67-0.73, Denmark] to 8.8% (95% CI=8.45-9.22, US), and in 2012, it ranged from 1.1% (95% CI=1.06-1.15, UK) to 8.8% (95% CI=8.42-9.19, US) in this age group. The prevalence of ADHD medication use was lowest in 0-4 year olds across countries.

Regarding time trends (2005/6-2012) by age group, the greatest increase in ADHD medication use was in 15-19 year olds (up to 6-fold). While the increased use was also observed for 5-14 year olds, in the youngest age group (0-4 years) there were substantial decreases in use across the study years (ranging from -16.5% in Denmark to -67.8% in Germany). For the UK, because of small numbers in the 0-4-year-old group ($N \leq 10$), time trends were not calculated.

There is a distinct utilization pattern for European vs. US data in the proportional distribution of ADHD medication products: Methylphenidate product dispensings predominated in the European countries across study years ranging from 81.3% to 98.9% (Table 3). By contrast, methylphenidate and amphetamine salt products nearly shared the US market in 2012 (52.9% and 42.1%, respectively). Atomoxetine use grew substantially in three of four European countries (2012 prevalence: 3.7%-12.5%) while it dropped in the US from 12% to 5% (Table 3).

4. Discussion

The main results of this study are as follows:

1. From 2005/6 to 2012, the prevalence of ADHD medication use grew markedly in children and adolescents in European countries in contrast to a more modest change in US youth.
2. There were substantial differences between

Table 1 Percent prevalence of ADHD medication use for children and adolescents (0-19 years) in youth cohorts from five countries, by sex, 2005/6-2012 (numbers in brackets=95% confidence interval).

	2005			2006		2007		2008		2009		2010		2011		2012		Difference 2005-2012		
	M	F	M/F ratio	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M/F ratio	Trend	p-Value
Denmark	0.62 [0.60-0.64]	0.13 [0.13-0.14]	4.60	0.81 [0.79-0.83]	0.19 [0.18-0.20]	1.01 [0.98-1.03]	0.26 [0.25-0.28]	1.37 [1.34-1.40]	0.39 [0.37-0.40]	1.75 [1.72-1.79]	0.55 [0.53-0.57]	2.08 [2.05-2.12]	0.68 [0.66-0.70]	2.19 [2.15-2.23]	0.76 [0.74-0.78]	2.22 [2.19-2.26]	0.83 [0.80-0.85]	2.69	+302.7%	<.0001
Germany	2.17 [2.13-2.20]	0.48 [0.46-0.50]	4.51	2.52 [2.48-2.55]	0.60 [0.58-0.62]	2.90 [2.86-2.94]	0.73 [0.71-0.75]	3.18 [3.14-3.22]	0.83 [0.80-0.85]	3.35 [3.31-3.39]	0.89 [0.87-0.91]	3.40 [3.36-3.44]	0.93 [0.91-0.95]	3.39 [3.35-3.43]	0.94 [0.92-0.96]	3.36 [3.32-3.40]	0.93 [0.91-0.96]	3.60	+62.4%	<.0001
Netherlands	2.91 [2.78-3.04]	0.75 [0.69-0.82]	3.87	3.27 [3.14-3.41]	0.86 [0.79-0.94]	3.84 [3.69-3.98]	1.09 [1.01-1.17]	4.43 [4.27-4.59]	1.29 [1.20-1.37]	4.90 [4.74-5.07]	1.45 [1.36-1.55]	5.23 [5.06-5.39]	1.61 [1.52-1.71]	5.63 [5.46-5.81]	1.77 [1.67-1.88]	5.84 [5.67-6.02]	1.92 [1.81-2.03]	3.04	+111.9%	<.0001
UK	0.59 [0.56-0.61]	0.09 [0.08-0.10]	6.55	0.68 [0.65-0.70]	0.11 [0.10-0.12]	0.75 [0.72-0.77]	0.13 [0.11-0.14]	0.77 [0.74-0.79]	0.13 [0.12-0.15]	0.79 [0.77-0.82]	0.14 [0.13-0.15]	0.83 [0.80-0.86]	0.15 [0.14-0.16]	0.86 [0.84-0.89]	0.16 [0.15-0.18]	0.90 [0.88-0.93]	0.18 [0.17-0.19]	5.00	+56.6%	<.0001
US	N/A	N/A	2.57 ^b	4.78 [4.62-4.94]	1.86 [1.75-1.96]	4.69 [4.54-4.85]	1.95 [1.85-2.06]	4.85 [4.69-5.02]	1.87 [1.77-1.98]	5.00 [4.83-5.18]	1.94 [1.83-2.06]	5.12 [4.94-5.31]	2.04 [1.92-2.16]	5.12 [4.94-5.31]	2.04 [1.92-2.17]	5.28 [5.09-5.47]	2.01 [1.90-2.14]	2.63	+10.2%	<.0001

Annotation: F=Females, M=Males, for the US, only data from 2006-2012 were available, ^bratio from 2006 data.

Table 2 Percent prevalence of ADHD medication use from 2005/6-2012, 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 [0.01-0.02]	0.02 [0.01-0.02]	0.02 [0.02-0.03]	0.02 [0.02-0.03]	0.03 [0.02-0.03]	0.03 [0.02-0.03]	0.01 [0.01-0.02]	0.01 [0.01-0.02]	-16.5%
5-9 years	0.47 [0.45-0.50]	0.59 [0.57-0.62]	0.73 [0.70-0.76]	0.94 [0.91-0.98]	1.18 [1.14-1.22]	1.31 [1.27-1.35]	1.24 [1.20-1.28]	1.13 [1.09-1.17]	+139.1%
10-14 years	0.70 [0.67-0.73]	0.91 [0.88-0.95]	1.14 [1.10-1.17]	1.52 [1.48-1.56]	1.91 [1.86-1.96]	2.31 [2.26-2.36]	2.49 [2.44-2.55]	2.57 [2.52-2.63]	+266.6%
15-19 years	0.32 [0.30-0.34]	0.47 [0.44-0.49]	0.65 [0.62-0.68]	1.03 [1.00-1.07]	1.48 [1.44-1.53]	1.88 [1.83-1.93]	2.14 [2.09-2.19]	2.33 [2.28-2.38]	+635.2%
Germany									
0-4 years	0.01 [0.01-0.02]	0.01 [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 [0.01-0.01]	0.00 [0.00-0.01]	-67.8%
5-9 years	1.33 [1.30-1.37]	1.55 [1.52-1.59]	1.80 [1.76-1.84]	1.95 [1.91-1.99]	1.96 [1.91-2.01]	1.87 [1.83-1.92]	1.75 [1.71-1.79]	1.65 [1.60-1.69]	+23.5%
10-14 years	2.91 [2.86-2.96]	3.35 [3.29-3.40]	3.80 [3.74-3.86]	4.10 [4.04-4.16]	4.30 [4.24-4.37]	4.39 [4.32-4.45]	4.39 [4.33-4.46]	4.34 [4.27-4.40]	+49.1%
15-19 years	0.89 [0.87-0.92]	1.09 [1.06-1.12]	1.29 [1.26-1.33]	1.48 [1.45-1.52]	1.62 [1.58-1.66]	1.74 [1.70-1.78]	1.86 [1.81-1.90]	1.96 [1.92-2.01]	+120.1%
Netherlands									
0-4 years	0.18 [0.14-0.23]	0.14 [0.10-0.18]	0.14 [0.10-0.19]	0.12 [0.08-0.16]	0.11 [0.08-0.15]	0.12 [0.08-0.16]	0.11 [0.08-0.15]	0.08 [0.06-0.12]	-53.0%
5-9 years	2.50 [2.33-2.68]	2.74 [2.56-2.92]	3.38 [3.18-3.58]	3.84 [3.63-4.05]	4.03 [3.83-4.25]	4.19 [3.98-4.41]	4.41 [4.19-4.64]	4.16 [3.94-4.39]	+70.2%
10-14 years	3.44 [3.24-3.64]	3.83 [3.62-4.05]	4.37 [4.15-4.60]	5.02 [4.78-5.26]	5.62 [5.38-5.88]	6.08 [5.83-6.35]	6.59 [6.32-7.08]	7.08 [6.81-7.36]	+106.0%
15-19 years	1.38 [1.26-1.51]	1.75 [1.62-1.89]	2.13 [1.99-2.29]	2.60 [2.44-2.77]	2.99 [2.82-3.17]	3.34 [3.17-3.53]	3.64 [3.46-3.84]	3.96 [3.76-4.17]	+186.4%
UK									
0-4 years	0.01 [0.00-0.01]	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 [0.00-0.01]	0.00 [0.00-0.01]	0.00 [0.00-0.01]	N/A ^b
5-9 years	0.40 [0.37-0.42]	0.42 [0.39-0.44]	0.49 [0.46-0.52]	0.49 [0.46-0.52]	0.49 [0.46-0.52]	0.53 [0.49-0.56]	0.52 [0.49-0.56]	0.52 [0.49-0.55]	+31.7%
10-14 years	0.74 [0.71-0.78]	0.87 [0.83-0.91]	0.91 [0.88-0.95]	0.93 [0.89-0.97]	0.92 [0.88-0.96]	0.98 [0.94-1.02]	1.05 [1.01-1.10]	1.11 [1.06-1.15]	+49.1%

Age group	2005	2006	2007	2008	2009	2010	2011	2012	% change
15-19 years	0.20 [0.18-0.22]	0.28 [0.26-0.30]	0.33 [0.31-0.36]	0.38 [0.36-0.40]	0.44 [0.41-0.46]	0.45 [0.42-0.47]	0.47 [0.45-0.50]	0.49 [0.47-0.52]	+144.6%
US ^a									
0-4 years	N/A	0.46 [0.41-0.51]	0.43 [0.38-0.48]	0.35 [0.31-0.39]	0.29 [0.25-0.34]	0.29 [0.24-0.34]	0.19 [0.15-0.23]	0.19 [0.15-0.23]	-58.7%
5-9 years	N/A	6.83 [6.52-7.16]	7.04 [6.73-7.37]	6.47 [6.17-6.78]	6.12 [5.82-6.43]	5.78 [5.48-6.09]	5.32 [5.03-5.62]	5.08 [4.80-5.37]	-25.6%
10-14 years	N/A	8.83 [8.45-9.22]	8.75 [8.37-9.14]	9.36 [8.97-9.76]	9.40 [9.00-9.82]	9.15 [8.75-9.57]	8.91 [8.52-9.31]	8.80 [8.42-9.19]	-0.3%
15-19 years	N/A	4.84 [4.45-5.26]	4.81 [4.43-5.21]	5.41 [5.01-5.83]	5.56 [5.15-6.01]	5.96 [5.52-6.42]	6.21 [5.77-6.68]	6.52 [6.07-6.98]	+34.7%

^aFor the US, only data from 2006-2012 were available.

^bBecause of the small numbers of patients, time trends were not computed for this age group.

countries regarding ADHD medication use. In 2012, while the US youth had nearly seven-fold more extensive use of ADHD medications than in the UK, youth in other European countries, particularly the Netherlands and Denmark, were catching up with the US. 3. ADHD medication prevalence was highest in 10-14 year olds, although the *increase* in use was greatest in 15-19 year olds. 4. Methylphenidate was the most commonly used ADHD medicine in European countries, whereas in the US, amphetamine salt products were nearly as common as methylphenidate products.

4.1. Growth patterns

Across countries, the increase in ADHD medication use was most distinct in Denmark and the Netherlands. The increase in the Netherlands continues the trend observed in earlier data (Schirm et al., 2001). While US data trends have continued to increase across the past 25 years (Zito et al., 2000, 2003), the current data only show a modest growth in ADHD medication use, which might represent a “ceiling effect”. The increase in ADHD medication use found in the UK is in line with recent results from studies based on the UK CPRD primary care database (Beau-Lejdstrom et al., 2016; Renoux et al., 2016). The same holds true for Germany, where Abbas et al. also found a slight increase in stimulant use from 2004 to 2010, which from then on stagnated (Abbas et al., 2016). Dalsgaard et al., who analyzed ADHD medication prescription in Denmark from 2003 to 2010, observed a five-to six-fold increase in ADHD medication use, which is slightly higher than the threefold increase found in our study, and can be explained by the earlier starting point (2003) with lower medication use rates (Dalsgaard et al., 2013).

Age-specific trends show similar growth across countries for 15-19 year olds wherein the largest increases were observed. Increased use in older adolescents and young adults could indicate better recognition of ADHD in this age group, or the persistence of the disorder in patients diagnosed at a younger age. Across countries, there was a reduction in ADHD medication use among 0-4 year olds from 2005/6 to 2012. Also, ADHD medication use increased in 5-14 year olds in the four European countries, but not in the US.

Generally, the growth in ADHD medication use may be explained by different factors, including a higher use of health services and an increased rate of medicated ADHD patients (Steinhausen, 2015), but also an increase in the duration of pharmacological ADHD treatment episodes in children and adolescents (Abbas et al., 2016; Beau-Lejdstrom et al., 2016; van den Ban et al., 2010).

4.2. Extent of ADHD medication use by country

Historically, research has shown the predominance of psychotropic medications for behavioral treatment of children and adolescents in the US (Zito et al., 2008). Our current study shows that the US continues to dominate in the prevalence of use of ADHD medications, but the differences between the US and Denmark, Germany and the UK are shrinking, and the Netherlands now exhibits greater use than in the US data in 2011 and 2012 in terms of overall

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

Rank	Denmark		Germany		Netherlands		UK		US	
	2005 %	2012 %	2005 %	2012 %	2005 %	2012 %	2005 %	2012 %	2006 ^a %	2012 %
1	MPH 98.9	MPH 81.3	MPH 90.3	MPH 91.0	MPH 97.8	MPH 94.2	MPH 90.4	MPH 86.6	MPH 52.3	MPH 52.9
2	AMP 1.1	ATX 17.8	ATX 9.6	ATX 8.6	AMP 2.2	ATX 3.7	ATX 7.9	ATX 12.5	AMP 35.5	AMP 42.1
3	OTH 0.1	AMP 0.7	OTH 0.06	AMP 0.4	-	AMP 2.1	AMP 1.6	AMP 0.8	ATX 12.0	ATX 5.0
4	ATX 0.02	OTH 0.2	-	OTH 0.03	-	-	OTH 0.1	OTH 0.2	OTH 0.2	OTH 0.05

Annotation: AMP=amphetamine salt products (dexamphetamine, lisdexamfetamine), ATX=atomoxetine, MPH=methylphenidate related products (dexmethylphenidate, methylphenidate), OTH=other (armodanafil, modafinil, pemoline).

^aFor the US, only data from 2006-2012 were available.

ADHD medication use prevalence [3.91% (95% CI=3.80-4.01) vs. 3.68% (95% CI=3.57-3.79), respectively].

Reviewing the past 30 years, there continues to be a drop in the male: female ratio for ADHD medication treatment (Safer and Zito, 2011). Male: female ratios as high as 12:1 in US middle school-aged children occurred in 1981, but since diagnostic criteria changed in 1988, ratios have continued to reflect the increasing diagnosis of girls with inattentive type ADHD (Safer and Krager, 1988). Our data show strong differences by country. The US has the lowest male: female ratio (2.6), which remained stable across the study years and is consistent with findings from a national survey on US children in the same period (Visser et al., 2014). By contrast, in the four European countries studied the male: female ratio decreased from 2005 to 2012, particularly in Denmark (4.60-2.69), possibly reflecting an increased awareness and/or an expanded treatment of ADHD in females.

The high ADHD medication use rates found in the US cohort might to some extent be due to the nature of the underlying database, which contains insurees with slightly sub-average socio-economic status, which can, but need not necessarily be associated with higher ADHD medication use (Calver et al., 2007; van den Ban et al., 2015). Interestingly, while in 2012 the overall ADHD medication use prevalence in the Netherlands cohort was slightly greater than in the US cohort, the prevalence rates for each age group were lower in the Netherlands cohort than in the US cohort. This seemingly paradoxical finding is due to the age composition of the US cohort, in which the percentage of 0- to 4-year olds is much larger than in the other countries.

4.3. Product preferences

In this study, methylphenidate products predominated in Europe while amphetamine salt products had nearly an equal share with methylphenidate products in the US. In the four European countries, amphetamine salts are rarely used. By contrast, in the US amphetamine salts have grown from 35.5% to 42.1%, partly due to recent expanded use of lisdexamfetamine products (initially approved in the US in 2007). Atomoxetine use has grown in European countries mainly in Denmark (Warrer et al., 2016), but has decreased in the US. Centrally acting alpha-agonists, e.g. clonidine or guanfacine, have not been assessed in this study as they were approved for pediatric use for ADHD only in the US during the studied period.

4.4. Implications of the findings

Several factors potentially contributing to these cross-country variations are discussed below.

4.4.1. DSM vs. ICD criteria

Substantial differences in the identification of childhood ADHD relate to the criteria used to assess the disorder. In the US, the progression of ADHD criteria from DSM-III, DSM-IIIR, DSM-IV and, now, DSM-5 has produced a body of research, which shows an expansion in the community incidence of ADHD. This is probably related to a shift in

the age criterion, i.e. the age before which ADHD symptoms must have appeared, from 5-7 years to 12 years.

An earlier comparison by Baumgaertel et al. showed a 64% increase in the number of German elementary school children who met ADHD criteria when DSM-IV was used compared with DSM-III (Baumgaertel et al., 1995). In addition, by comparison the ICD criteria used in European settings are more restricted requiring hyperactivity as a symptom (Steinhausen, 2015), whereas DSM no longer requires hyperactivity for the diagnosis of ADHD. Finally, recent studies of US youth showed an increasing trend in diagnosing subthreshold (Not Otherwise Specified) and mild psychiatric disorders, which may expand the pool of children with psychiatric diagnoses while they only partially fulfill criteria and may not justify medication use (Paris, 2015; Safer et al., 2015). However, within our data we cannot judge whether medication use is justified, as we have no linked information on the indication or severity of the conditions.

It is unclear whether the general increase in ADHD medication use is a desirable compensation of former under-treatment or whether it is a reason for concern.

Future studies should also evaluate whether altered DSM-5 diagnostic criteria will increase the prevalence of pediatric ADHD diagnoses and related ADHD medication use.

4.4.2. System variables

Payment systems vary across countries. The US lacks a single payer system and there is considerable variation in drug pricing whereas many European countries may set prices at a national level. In addition, direct to consumer prescription drug marketing is permissible in the US and contributes to the promotion of pharmaceuticals (Larkin et al., 2014).

4.4.3. Cultural differences

The medicalization of behavioral health problems is the subject of considerable debate in the US as cultural acceptance of these relatively recent approaches to child development issues has expanded (Conrad, 2007). Interestingly, Steinhausen identifies the growth in psychotropic prescribing by clinicians as an international phenomenon (Steinhausen, 2015), and this is also reflected in a recent international comparison study of pediatric use of antidepressants (Bachmann et al., 2016).

4.4.4. Cardiovascular safety concerns

Concerns about the safety of stimulant use for medical purposes surfaced in 2004 when case reports of death were associated with its use. There are mixed results from nine population-based cardiovascular safety studies in children and adolescents (Zito and Burcu, 2016). Despite the uncertainty of risk of cardiovascular events in stimulant-exposed youth from population-based studies (Dalsgaard et al., 2014; Winterstein et al., 2012), our data suggest that stimulant utilization was not diminished in the current study across countries except among the youngest age group (0-4), consistent with previous studies in the US (Chen et al., 2015; Kornfield et al., 2013). Interestingly, in the present data, there was a plateau in the trends of ADHD medication use beginning in 2008-2010, coinciding with changes in FDA product labeling as well as restricted access

to methylphenidate products by the German regulatory agency (Gemeinsamer Bundesausschuss (G-BA), 2010).

4.5. Limitations

Dispensings of ADHD medications are not equivalent to the actual consumption. Not all datasets had information on important clinical characteristics, e.g., severity, comorbidity, co-medication, off-label use, behavioral interventions, treatment duration and adherence (Garbe et al., 2012; Raman et al., 2015). We also could not explore prescribing physician specialty since some datasets lacked physician specialty information. The databases employed include population cohorts, which are roughly representative of the general populations. However, the US and Netherlands data stem from regional databases, and it is known that ADHD medication use may vary between different geographical regions (Zuvekas and Vitiello, 2012). Unfortunately, we did not have detailed information on the sociodemographic characteristics of the study populations by country. Certainly, the differences in ADHD medication utilization between countries can be affected by the potential differences in socio-economic status (i.e., income and education levels of parents).

To ensure comparability of the prescribed substances, we only included dispensings of centrally acting sympathomimetics (ATC code: N06BA), thus omitting prescriptions of central alpha-agonists, e.g., clonidine or guanfacine, which in some countries constitute additional treatment options for ADHD. Nevertheless, this study provides the most recent international data on pediatric use of ADHD medications.

4.6. Conclusion

Over the past 25 years, the United States has dominated ADHD medication use in community youth populations. However, despite comparatively lower use in the four European countries, this study shows that ADHD medication use has substantially grown in children and adolescents in these European countries in contrast to a modest growth in the US youth cohort from 2005/6 to 2012. In the face of expanded use of ADHD medications, further studies should evaluate outcomes of ADHD care in pediatric community populations.

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No funding was secured for this study.

Contributors

Dr. Bachmann conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. Dr. Burcu acquired, analyzed and interpreted data, revised the manuscript critically, and approved the final manuscript as submitted. Prof. Glaeske acquired, analyzed and interpreted 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. Prof. Hoffmann acquired, analyzed and interpreted data, undertook the statistical analysis, revised the

manuscript critically, and approved the final manuscript as submitted. Dr. Schuiling-Veninga acquired, analyzed and interpreted data, 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. Aagaard 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. All authors mentioned above agree to be accountable for all aspects of the work.

Conflict of interest

Dr. 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. Prof. Glaeske and Prof. 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. Prof. Aagaard has received traveling grants from Pfizer and Swedish Orphan BioVitrum. Dr. 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. Dr. Schuiling-Veninga, Dr. Wijlaars, Prof. Zito and Dr. Burcu declare no conflict of interest.

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