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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

The use of medication against attention deficit/hyperactivity disorder in Denmark: a drug use study from a patient perspective

Anton Pottegård · Bine Kjøller Bjerregaard · Dorte Glintborg · Lisbeth Sandal Kortegaard · Jesper Hallas · Søren Ilsøe Moreno

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Abstract
Aim Our aim was to characterize utilization patterns for drugs used to treat attention deficit/hyperactivity disorder (ADHD) on the level of the individual patient among Danish users, focusing on treatment duration, doses used, and concurrent use of ADHD and non-ADHD drugs.
Methods Using the Danish Registry of Medicinal Product Statistics, we extracted data on 1,085,099 prescriptions for ADHD drugs issued to a total of 54,024 persons in the study period 1 January 1995 to 30 September 2011. For users in the final year of the study period, we further extracted 315,365 prescriptions for non-ADHD drugs. Drug utilization was characterized using descriptive statistics.
Results The mean duration of ADHD treatment was highest (3.6–4.2 years) for patients initiating therapy at a young age (age<13). Dropout rate after receiving only one prescription was highest among off-label users (age<6 and age >17). All age categories showed an increase in the average daily dosage of methylphenidate used from 2003 to 2010. Concomitant treatment with methylphenidate and atomoxetine was rare, as only 2 % of methylphenidate treatment overlapped with atomoxetine treatment. Nineteen percent of methylphenidate instant-release treatment overlapped with methylphenidate controlled-release treatment. Users of ADHD drugs across all age categories had an increased use of drugs related to the nervous system, especially antipsychotics [standardized morbidity rate (SMR), 6.4–19.5] and antiepileptics (SMR, 4.0–5.5).
Conclusion We found certain traits that warrant further investigation: the apparent increase in average daily doses, the low adherence to treatment among off-label users, and the increased use of other psychotropic medication.

Keywords ADHD · Drug utilization · Denmark · Psychostimulants · Methylphenidate · Atomoxetine

A. Pottegård · J. Hallas
Clinical Pharmacology, Institute of Public Health,
University of Southern Denmark,
Winsløwparken 19, 2,
5000 Odense C, Denmark

A. Pottegård · D. Glintborg · S. I. Moreno
Institute for Rational Pharmacotherapy, Danish Health and Medicines Authority,
Axel Heides Gade 1,
2300 København S, Denmark

B. K. Bjerregaard
Medicines Control Division, Statistics and Analysis,
Danish Medicines Agency,
Axel Heides Gade 1,
2300 København S, Denmark

L. S. Kortegaard
Center for Child and Adolescent Psychiatry,
Aarhus University Hospital,
Harald Selmers Vej 66,
8240 Risskov, Denmark

A. Pottegård (✉)
Clinical Pharmacology, University of Southern Denmark,
JB Winsløwsvej 19, 2,
5000 Odense C, Denmark
e-mail: apottegaard@health.sdu.dk

Introduction

The drug treatment of attention deficit/hyperactivity disorder (ADHD) has received massive international attention in recent years, questioning the rationality of the global increase in the use of ADHD drugs among children, adolescents and adults. Guidelines for initiating ADHD drug therapy in children and adolescents are based on solid evidence from short-term studies, but little is known about long-term use and treatment adherence

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[1–3]. In contrast, in adults, there are no national guidelines that describe diagnosis and recommended treatment, and adult drug treatment is always initiated off-label. Consequently, psychostimulants are prescribed despite uncertainties about the diagnosis and long-term efficacy and safety of this therapy in this age group and a limited knowledge of dosing and treatment duration.

As ADHD patients are known to have multiple co-morbid psychiatric disorders, this patient group is expected to use a high frequency of concurrently prescribed psychotropic drugs [4–6]. However, little is known about this use and the concurrent use of other drug classes. Information on the duration of treatment, doses used and concurrent medication is necessary to ensure a meaningful debate of the increasing use of ADHD drugs over the past years.

In a previous study we characterized the utilization, regional differences and prescribing patterns of ADHD drugs in Denmark between 1995 and 2011 from a national perspective [7]. In the study reported here we further explore utilization from a patient perspective, with the aim of characterizing the use of ADHD drugs according to the duration of treatment, doses used and concurrent use of ADHD and non-ADHD drugs in children, adolescents and adults.

Material and methods

Data source

The prescription datasets used in this paper have been used in previous analysis [7]. In brief, national data on drug use in Denmark were extracted from the Registry of Medicinal Product Statistics (RMPS) [8]. Beginning in 1995, the RMPS contains individual level information on all prescription drugs dispensed at Danish community pharmacies. For each drug dispensed, the database contains information on the age and gender of the individual for whom the prescription was written, the date of purchase, Anatomical Therapeutic Chemical (ATC) classification, the dispensed quantity expressed in defined daily doses (DDD), a unique drug item number (Nordic article number) and several other variables not relevant to this study. The registry has been assessed to have a high level of completeness and validity for each data variable [8].

Selection of data

Patients were included in the study if they had redeemed at least one prescription for either methylphenidate (N06BA04) or atomoxetine (N06BA09) within the study period from January 1995 through to September 2011. Prescriptions on modafinil (N06BA07) were only included if the user had previously redeemed prescriptions on either methylphenidate or atomoxetine, as modafinil is only used as third line treatment against ADHD. Throughout this text the term *ADHD drugs* refers to methylphenidate (both instant-release and controlled-release drug formulations), atomoxetine and modafinil as a group.

To perform an analysis of co-medication, we retrieved all non-ADHD drug prescriptions redeemed by persons who redeemed at least one prescription for an ADHD-drug within the last year of our study (dataset C, Table 1). We also calculated the number of users in the background population, i.e. all Danish residents not included in our ADHD cohort. Non-ADHD-drug data only covered prescription drugs dispensed at a community pharmacy and not drugs bought over-the-counter.

ADHD drugs not included in our study

Amphetamine and dexamphetamine can be used as alternatives in ADHD treatment. However, both drugs are only available via magistral prescriptions (produced by a specialized pharmacy) and as such are not routinely reported to the RMPS. Accordingly, the data coverage on the use of the two drugs is unknown, but suspected to be low. These two drugs were therefore excluded from our analysis to ensure consistency and reproducibility.

Data analysis

Data were analyzed by descriptive statistics. The analysis was divided into a series of questions, using different subsets of data and units of analysis for each question. The different subsets of data are characterized in Table 1.

The age categories used were infant (0–1 year), toddler (2–5 years), child (6–12 years), adolescent (13–17 years), young adult (18–24 years), adult (25–49 years) and elderly (50+ years). All drug amounts were measured in DDDs as designated by the World Health Organization [9]. The DDD values for the different drugs are 30 mg for methylphenidate, 80 mg for atomoxetine and 300 mg for modafinil.

Table 1 Description of the four different subsets of data that were used

Dataset	Description	Period	No. of individuals	No. of ADHD prescriptions
A	Full period	1 January 1995 to 30 September 2011	54,024	1,085,099
B	Last 3 years	1 October 2008 to 30 September 2011	44,574	698,485
C	Last year	1 October 2010 to 30 September 2011	35,110	289,090

ADHD, Attention deficit/hyperactivity disorder

All analyses were performed using SAS statistical software ver. 9.1 (SAS Institute, Cary, NC).

The analysis was categorized into the following six questions.

How long do patients adhere to treatment? Using the full dataset (dataset A, Table 1) a Kaplan–Meyer plot of drug-survival was produced. For each patient, duration of treatment was calculated from the day the first prescription was redeemed. Treatment was defined as terminated when 180 days had passed without the individual filing a prescription for any ADHD drug. Switching between ADHD-drugs was not seen as termination of treatment. The long interval allowed between prescriptions was chosen to avoid false termination of treatment for patients who had long intervals between prescriptions. Patients were excluded from this analysis if the treatment episode was initiated in the first half of 1995 (i.e. the first 180 days of our dataset) to ensure that the correct starting date was assigned. Persons were censored upon death or upon the end of the study period (30 September 2011). Only the first treatment episode of each person was included. The analysis was specified by age category (using the age at the time of the first prescription). A sensitivity analysis was performed by extending the interval allowed between prescription fillings to 365 days.

Which dose is used by the single patient and how has this developed over time? This question was answered only for methylphenidate by using all prescriptions for this drug in dataset A (Table 1). Methylphenidate was chosen for this analysis because it is the first-line treatment and has been marketed for our entire study period, allowing us to study time trends. Furthermore, pooling of the different ADHD-drugs is not possible due to the DDD values being defined differently.

The dose used in a period between two prescriptions was calculated as the amount of drug received at the first prescription (measured in DDD) divided by the number of days between the first prescription and the second prescription, thus arriving at the DDD used per day. Each prescription was then designated a 'current dose used', calculated as a moving average of the dose used in the last three periods, weighed by the length of each period. Multiple prescriptions for methylphenidate redeemed the same day by one individual were pooled into one prescription. Only periods starting within 365 days before the given prescription were included in the moving average. If only one or two periods were defined in this interval, i.e. because only two or three prescriptions were redeemed, then the moving average was calculated using only one or two periods. For the same reason, no dose used was calculated if a prescription was the first prescription in a year. For a patient redeeming 20, 40 and 20 DDDs each with a 30-day interval, the 'current dose used' would then be 0.67 DDD at the time of the second prescription and 1.00 DDD at the time of the third prescription.

For each quarter, the current dose used was calculated (as explained above) among all users redeeming a prescription in the given quarter, and the 10, 50 and 90 % percentiles of the doses used were reported, specified by age category.

What proportion of users have atomoxetine prescribed as first-line treatment? To evaluate the use of atomoxetine as first-line treatment we used the last 3 years of data (dataset B, Table 1). The percentage of all incident prescriptions that were for atomoxetine was calculated, specified by quarter. For these incident atomoxetine users, the average age and gender distribution were calculated.

For all incident users who received methylphenidate as a first prescription, we also calculated the percentage of users who by year 1 had received a prescription for atomoxetine or modafinil.

How often is atomoxetine used concomitantly with methylphenidate? To assess the concurrent use of atomoxetine and methylphenidate, we used the last 3 years of data (dataset B, Table 1). First, each prescription was assigned a treatment duration of 90 days from the day of dispensing. A period of 90 days was chosen as most prevalent users were found by exploratory analysis to redeem new prescriptions in intervals of less than 3 months (87, 86 and 63 % for users of methylphenidate, atomoxetine and modafinil, respectively) [10]. For each patient, we then calculated three values: the total number of days treated with methylphenidate, the total number of days treated with atomoxetine and the total number of days treated with both drugs (i.e. days overlapped by both drugs). Lastly, the total number of days in each of these three categories was summed up over all patients, and the percentage of use classified as simultaneous use, as compared to treatment with either atomoxetine or methylphenidate, was calculated.

How often are methylphenidate instant-release and controlled-release drug formulations used concurrently? This question was answered using the same template for analysis as that for the concurrent use of atomoxetine and methylphenidate, only substituting atomoxetine and methylphenidate with methylphenidate instant-release and controlled-release drug formulations, respectively.

Which non-ADHD drug classes are prescribed to ADHD-drug users? To assess the co-medication of ADHD drug users we used the last year of data (dataset C, Table 1), adding all non-ADHD-drug prescriptions redeemed by those included in our ADHD cohort. All drugs were grouped by their ATC code on the second level (e.g. A06, laxatives). We calculated standardized morbidity rates (SMRs), i.e. the ratio between the actual drug use seen in the ADHD cohort and the expected drug use in the ADHD cohort if they had the same use pattern as the background population, standardized by sex and age in 1-year intervals. Exploratory analysis showed very similar patterns

when those aged 2–5, 6–12 and 13–17 years were compared and when those aged 18–24 and 25–49 years were compared. To simplify data representation we therefore pooled these age categories, thus dividing data into three age categories (<18, 18–49 and 50+ years).

The 25 ATC groups with the highest expected number of users, i.e. number of users in the age- and sex-matched background population, were reported.

It was pre-hypothesized that the ADHD cohort would have a high use of drugs in ATC group N (nervous system). We therefore repeated the analysis for ATC group N, only this time grouping drugs at the third ATC level (e.g. N06A, antidepressants). Melatonin (N05CH01) was analyzed separately, as the data coverage of this drug changed in the spring of 2011, when the magistral formulation (not registered in the RMPS) was given a unique drug item number (Nordic article number), allowing its registration in the RMPS. A crude analysis on this drug was performed by taking the percentage of ADHD drug users recorded in the last quarter of our data that in the same quarter redeemed a prescription for melatonin.

Results

The Kaplan-Meyer plot for drug survival (adherence to treatment) is given in Fig. 1. Selected values from the plot are given in Table 2 along with the results from the sensitivity analysis. Those initiating treatment before age 13 years initially show a

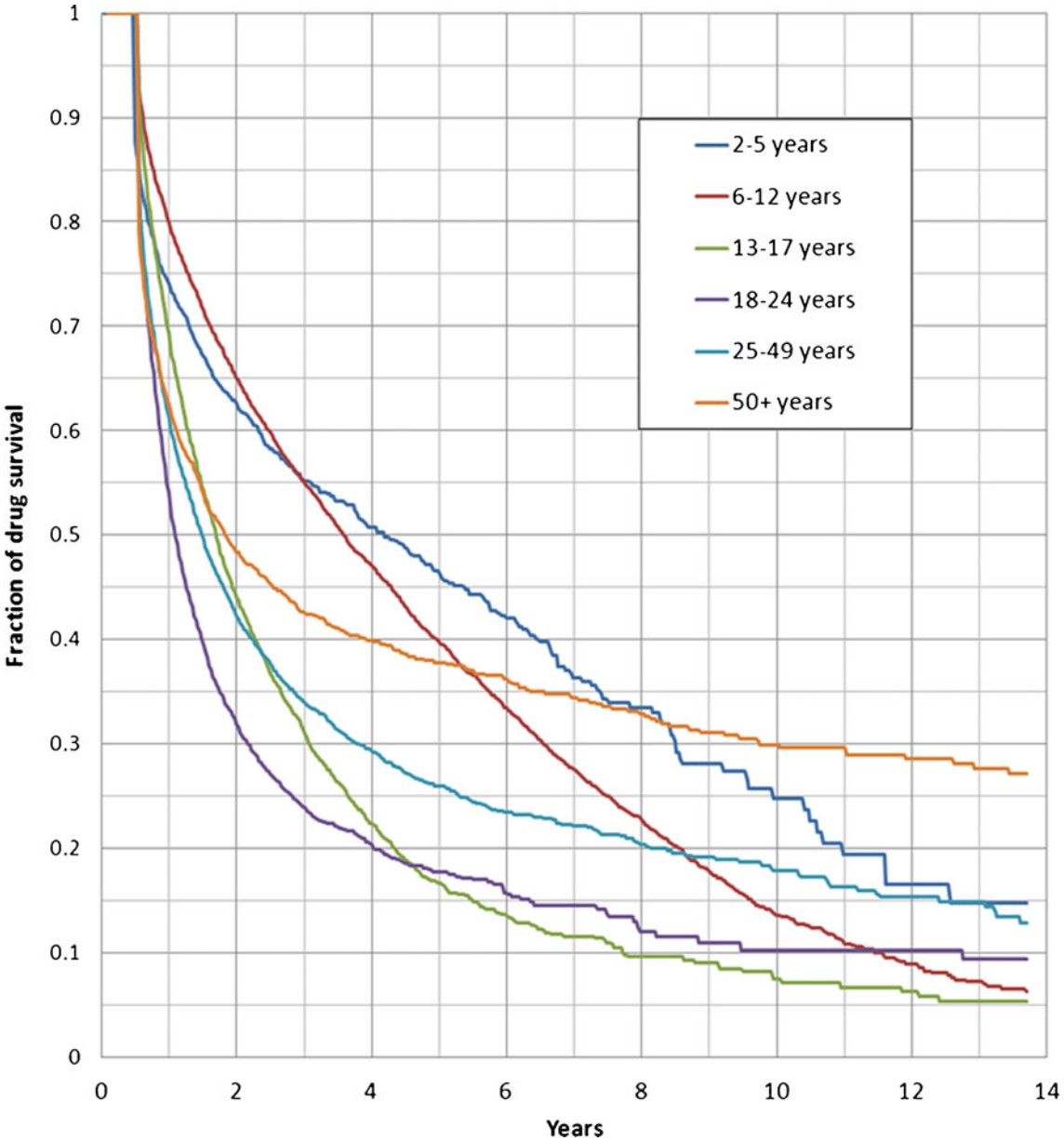

Fig. 1 Kaplan–Meyer plot of drug-survival

Table 2 Selected data from the Kaplan–Meyer plot, specified by age category

Age category	50 % percentile for drug survival (years)		Percentage of users dropping out after only one prescription
	180 days allowed between prescriptions	365 days allowed between prescriptions	
2–5 years	4.2	7.9	11.3
6–12 years	3.6	5.9	6.3
13–17 years	1.7	2.5	7.2
18–24 years	1.1	1.5	13.7
25–49 years	1.5	2.1	14.2
50+ years	1.8	2.2	11.6

higher adherence to treatment, although the difference diminishes over time (Fig. 1). A graphical evaluation of the sensitivity analysis with the allowed interval between prescriptions set to 365 days confirmed the values given in Table 2 (data not shown), i.e. that increasing the allowed interval between prescriptions significantly increased the 50 % percentile for children initiating treatment before age 13 years, but had no significant effect on the remaining age categories. The percentage of users only receiving one prescription varied from 6 to 14 % (Table 2), with a higher drop-out rate in those age categories where treatment is off-label; for example, the drop-out rate was 6–7 % for the 6- to 17-year-old group and 14 % for the 18- to 49-year-old group.

In terms of dose used, all six age categories showed a remarkably similar development, with a stable pattern until 2003, followed by a steady increase. As an example, the data for children aged 6–12 years are shown in Fig. 2. As the other age categories showed a similar trend, the remaining data are presented only as the values for the first quarter of 2002 and the third quarter of 2011 (the last quarter of our data) in Table 3.

The percentage of all ADHD drug first-time users receiving atomoxetine as first-line treatment increased from 4 % in the first quarter of 2009 to 11 % in the third quarter of 2011. The average age and gender distribution of these users were found to be similar to those who receive methylphenidate (data not shown). Of those users receiving methylphenidate as first-line treatment, 11 and 2 % had within 1 year received a prescription for atomoxetine or modafinil, respectively.

A total of 44,364 unique users were included in the analysis on the simultaneous use of atomoxetine and methylphenidate. Of these, 80 % only used methylphenidate and 6 % only used atomoxetine; 9 % of the users had overlapping treatment episodes. Of a total of 19,415,280 days of methylphenidate treatment, 2 % overlapped with atomoxetine treatment; of a total of 2,284,845 days of atomoxetine treatment 15 % were overlapping with methylphenidate treatment.

For the analysis of the simultaneous use of methylphenidate as instant-release or controlled-release drug formulations, a total of 41,888 methylphenidate users were included in the analysis. Of these, 28 % only used methylphenidate instant-release formulations and 20 % only used methylphenidate controlled-release formulations. In all, 36 % of the users had overlapping treatment episodes using both instant-release and controlled-release drug formulations. Of a total of 10,101,945 days of instant-release treatment, 19 % were overlapping with the controlled-release treatment; of a total of 13,877,779 days of controlled-release treatment, 14 % were overlapping with the instant-release treatment.

For users in our ADHD cohort in the last study year (dataset C, Table 1), 315,365 prescriptions for non-ADHD drugs were

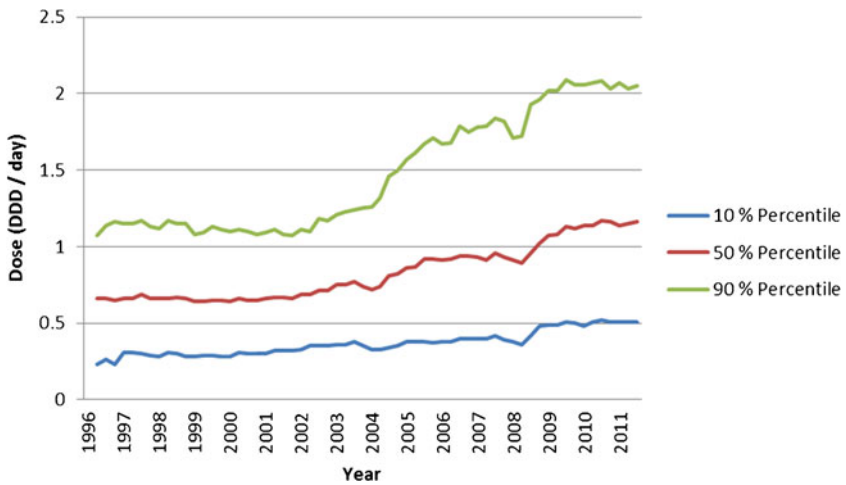

Fig. 2 The development in the dose used in the age category 6–12 years. The five first quarters were excluded as they were based on very few observations. The remaining estimates are based on 95–5,022 observations. *DDD* Defined daily dose

Table 3 The 10, 50 and 90 % percentiles for doses used[a], specified by age, for the first quarter of 2002 and third quarter of 2011 (last quarter of our data)

Age category	Year	Percentiles (DDD/day)		
		10 %	50 %	90 %
2–5 years	2002	0.20	0.45	0.82
	2011	0.36	0.74	1.50
6–12 years	2002	0.33	0.69	1.11
	2011	0.51	1.16	2.05
13–17 years	2002	0.32	0.73	1.38
	2011	0.58	1.39	2.46
18–24 years	2002	0.34	0.90	2.38
	2011	0.38	1.25	2.82
25–49 years	2002	0.24	0.92	1.94
	2011	0.45	1.53	3.78
50+ years	2002	0.11	0.61	1.49
	2011	0.34	1.09	3.17

[a] Percentiles are for defined daily dose (DDD)/day

obtained. The drug classes with the highest number of expected users are given in Table 4. The sub-analysis of ATC group N is shown in Table 5.

The crude analysis for melatonin showed that of the prevalent ADHD drug users in the third quarter of 2011, the percentages also redeeming a prescription for melatonin, according to age category, were 19.6 % (2–5 years), 14.2 % (6–12 years), 8.4 % (13–17 years), 4.3 % (18–24 years), 3.2 % (25–49 years) and 2.3 % (50+ years). However, as the data coverage on melatonin is still expected to be incomplete, the true proportions might be higher.

Discussion

Four main findings can be reported based on the analyses performed within the framework of this study. First, the mean duration of ADHD treatment was longest (3.6–4.2 years) for patients initiating therapy at a young age (<13 years). Second, the drop-out rate after receiving only one prescription was highest among off-label users (<6 years and >17 years). Third, across all age categories, there was a 39 to 90 % increase in the average daily dose of methylphenidate used in the period 2003–2010. Lastly, we found an increased use of drugs related to the nervous system (ACT N), especially antipsychotics and antiepileptics, among users of ADHD drugs.

Our study has several strengths. First, the use of the RMPS allowed us to evaluate the drug use of the entire population of Denmark in a 17-year study period. Secondly, we were able to do so with very little lag-time, including data up to and including September 2011, which allowed us to assess the newest developments in ADHD drug use. Lastly, the RMPS has been found to have very high data coverage and data validity of the variables used in our study [11].

There are also a number of limitations to our study. First, the indication for treatment is not always registered in the RMPS or it is unreliable (e.g. methylphenidate for treating hypocalcemia). Thereby, we might have included some persons who were treated for narcolepsy. However, as the prevalence of narcolepsy is in the order of 0.5 per 1,000 of the Danish general population [12], compared to up to 50 per 1,000 for ADHD [13], this unreliability is unlikely to have substantially biased our findings. Second, the exclusion of amphetamine and dexamphetamine prescriptions from our study leads to an underestimation of the duration of treatment, as people switching to these drugs will appear to have dropped out of treatment. However, given the suspected limited use of these drugs, this exclusion is unlikely to have substantially impacted our findings.

There are some obvious explanations to the finding that adherence to treatment is longest among the youngest users (up to 13 years). Children generally depend on and act according to the decisions made by parents and other caretakers, and they are rarely involved in the decision-making concerning their own health issues. Likewise, the evaluation of effect is primarily based on teacher and parent reports [14]. There is a lack of studies on the child's own perception of the benefits and disadvantages of ADHD medication. Some parents may feel compelled by professionals to keep their child on medication in order to maintain/obtain access to the general education system. Others may experience a sense of relief from guilt feelings when they are told that their child is not misbehaving due to any inadequacy in their approach to child upbringing, but that he/she suffers from 'a chemical imbalance in the brain' that needs drug treatment [15–17].

Studies in other areas of health care, such as diabetes mellitus and human immunodeficiency virus, have revealed that adherence to treatment is a challenge during adolescence [18, 19]. It has been reported that adolescents on average rate the benefit of psychostimulants lower than their parents and teachers [20]. The pattern of adherence to treatment in adolescents closely resembles that of adults, with the exception of those aged 50+ years, with the latter staying longer on medication. There is no obvious explanation for the high persistence in seniors, but one possible explanation could be that the indication for treatment in the oldest group is different from that in the other groups, such as treatment-resistant depression [21].

Early drop-out is higher among adults and pre-schoolers for whom drug treatment is off label. One possible explanation could be uncertainty of the diagnosis and treatment due to the lack of national guidelines. Pre-schoolers often experience intolerable adverse events at a higher rate than older children [22, 23], which may lead to early termination of the treatment. For all age groups, early drop-out from treatment may be accounted for by the lack of treatment efficacy or a change of diagnosis during

Table 4 Analysis of co-medication, including all ATC groups but ATC group N[a] (see Table 5)

ATC category	ATC description	<18 years (*n*=15,660)		19–49 years (*n*=17,057)		50+ years (*n*=2,389)	
		%	SMR[b]	%	SMR[b]	%	SMR[b]
A01	Stomatological preparations	0.5	1.3 [1.0–1.6]	2.0	1.9 [1.7–2.1]	3.9	2.7 [2.2–3.3]
A02	Drugs for acid-related disorders	1.3	1.3 [1.1–1.5]	11.0	2.2 [2.1–2.3]	32.2	2.0 [1.9–2.2]
A03	Drugs for functional gastrointestinal disorders	0.4	1.3 [1.0–1.7]	2.9	2.3 [2.1–2.5]	13.1	5.5 [4.9–6.2]
A06	Laxatives	0.9	2.1 [1.8–2.5]	1.4	2.8 [2.5–3.2]	17.1	5.7 [5.1–6.2]
A07	Antidiarrheal, intestinal, antiinflammatory/antiinfective agents	0.2	1.1 [0.7–1.6]	1.1	1.4 [1.2–1.6]	4.6	2.2 [1.8–2.6]
A08	Antiobesity preparations, excluding diet products	-	(*n*<5)	0.5	2.3 [1.9–2.9]	0.9	3.4 [2.1–5.2]
A12	Mineral supplements	0.1	1.5 [0.8–2.6]	0.7	2.2 [1.8–2.7]	9.4	1.6 [1.4–1.8]
B01	Antithrombotic agents	0.1	2.6 [1.6–4.2]	1.4	1.7 [1.5–1.9]	19.5	1.0 [0.9–1.1]
B03	Antianemic preparations	0.2	1.6 [1.1–2.4]	2.1	1.9 [1.7–2.1]	5.1	1.3 [1.1–1.6]
C01	Cardiac therapy	0.1	0.8 [0.4–1.4]	0.6	2.7 [2.2–3.3]	4.3	1.0 [0.8–1.2]
C03	Diuretics	0.0	1.3 [0.5–2.8]	2.2	2.0 [1.8–2.3]	20.9	1.2 [1.1–1.3]
C05	Vasoprotectives	0.7	1.9 [1.6–2.3]	3.4	1.1 [1.0–1.2]	5.1	1.4 [1.2–1.7]
C08	Calcium channel blockers	0.1	3.9 [2.1–6.7]	1.4	1.5 [1.3–1.7]	11.8	0.8 [0.7–0.9]
C10	Lipid modifying agents	0.0	2.7 [0.9–6.4]	2.2	1.5 [1.4–1.7]	17.4	0.7 [0.7–0.8]
G01	Gynecological antiinfectives and antiseptics	0.2	2.1 [1.4–2.9]	1.3	1.2 [1.0–1.4]	1.0	2.0 [1.3–3.0]
G04	Urologicals	0.1	1.4 [0.9–2.2]	2.5	3.5 [3.2–3.9]	11.6	1.8 [1.6–2.1]
H01	Pituitary, hypothalamic hormones and analogues	1.9	1.5 [1.3–1.6]	0.2	0.9 [0.6–1.2]	0.8	4.5 [2.7–7.0]
H02	Corticosteroids for systemic use	0.3	0.9 [0.7–1.2]	2.7	1.3 [1.2–1.4]	15.3	3.0 [2.7–3.3]
H03	Thyroid therapy	0.3	2.0 [1.4–2.7]	1.3	1.3 [1.2–1.5]	6.3	1.4 [1.2–1.7]
J02	Antimycotics for systemic use	0.7	1.4 [1.2–1.7]	4.5	1.3 [1.2–1.4]	9.0	4.0 [3.5–4.6]
M02	Topical products for joint and muscular pain	0.1	1.0 [0.6–1.7]	0.4	2.5 [2.0–3.2]	0.8	1.8 [1.1–2.8]
M03	Muscle relaxants	0.1	1.5 [0.9–2.5]	1.4	2.1 [1.9–2.4]	3.8	2.9 [2.3–3.5]
P03	Ectoparasiticides, incl scabicides, insecticides and repellants	0.3	1.9 [1.4–2.5]	0.5	3.1 [2.4–3.8]	-	(*n*<5)
R02	Throat preparations	0.2	1.2 [0.8–1.8]	0.4	1.6 [1.2–2.1]	0.7	3.4 [1.9–5.5]
R06	Antihistamines for systemic use	5.1	1.1 [1.0–1.2]	7.4	1.7 [1.6–1.8]	9.3	1.7 [1.5–2.0]

ATC, Anatomical Therapeutic Chemical classification

ATC group N, Nervous system

[b] Standardized morbidity rates, i.e. the ratio between the actual drug use seen in the ADHD cohort and the expected drug use in the ADHD cohort if they had the same use pattern as the background population, standardized by sex and age in 1-year intervals and presented with 95 % confidence intervals (values in square parentheses)

the first weeks of treatment. It is difficult to correctly diagnose ADHD because no objective and age-appropriate test exists that can help clinicians confirming their diagnosis. Consequently, ADHD symptoms may overlap or co-exist with other mental disorders, such as conduct disorder or bipolar disorder. Consequently, new symptoms may appear during the first weeks of treatment that lead to a different diagnosis and subsequently to a change of treatment.

The duration of ADHD therapy remains a point of discussion. There is no solid evidence supporting positive long-term effects of treatment with stimulants on cardinal ADHD symptoms. One recent study has shown that drug-treated versus non-drug-treated ADHD in children did not differ positively or negatively in terms of a number of important outcomes [4]. The large American MTA study came to the same conclusion after 8 years of follow-up [24]. However, long-term stimulant therapy may have beneficial effects on ADHD co-morbidities, with observational studies suggesting that long-term treatment with methylphenidate may reduce the risk of substance abuse disorders related to ADHD [25, 26]. There are also a number of known adverse events that need to be considered when making clinical decisions on the cost/benefit of long-term ADHD treatment, such as psychological adverse events (sadness, anxiety, appetite loss), impact on growth and cardiovascular adverse events [27, 28]. Also, hitherto unknown long-term adverse events need to be taken into consideration. The most serious of these could be permanent changes in brain metabolism leading to sensitization/tolerance/dependence, as seen in animal

Table 5 Sub-analysis of ACT group N

ATC category	ATC description	<18 years (n=15,660)		18–49 years (n=17,057)		50+ years (n=2,389)	
		%	SMR[a]	%	SMR[a]	%	SMR[a]
N01B	Anesthetics, local	0.1	1.3 [0.8–2.0]	0.2	2.4 [1.6–3.5]	0.6	5.0 [2.7–8.4]
N02A	Opioids	0.3	1.1 [0.8–1.4]	10.8	2.7 [2.6–2.8]	35.3	2.9 [2.7–3.1]
N02B	Other analgesics and antipyretics	0.8	2.9 [2.4–3.4]	6.9	3.6 [3.4–3.8]	25.8	2.0 [1.9–2.2]
N02C	Antimigraine preparations	0.6	1.9 [1.5–2.3]	2.7	1.7 [1.6–1.9]	4.5	2.0 [1.7–2.5]
N03A	Antiepileptics	1.9	4.0 [3.6–4.5]	12.1	7.0 [6.7–7.3]	19.6	5.5 [5.0–6.1]
N04A	Anticholinergic agents	0.1	9.3 [4.4–17.0]	0.6	4.8 [3.9–5.9]	0.4	1.5 [0.7–2.7]
N04B	Dopaminergic agents	0.0	9.2 [3.3–19.9]	0.4	4.9 [3.8–6.2]	3.1	3.3 [2.6–4.1]
N05A	Antipsychotics	7.1	19.5 [18.4–20.7]	20.9	11.3 [10.9–11.7]	19.3	6.4 [5.8–7.0]
N05B	Anxiolytics	0.7	3.3 [2.7–4.0]	8.8	5.9 [5.7–6.3]	21.2	3.4 [3.2–3.8]
N05C[b]	Hypnotics and sedatives[b]	0.3	5.3 [3.9–7.0]	8.6	5.3 [5.0–5.6]	22.7	2.9 [2.7–3.2]
N06A	Antidepressants	4.9	7.9 [7.3–8.4]	35.8	5.2 [5.1–5.4]	49.2	4.1 [3.8–4.3]
N07B	Drugs used in addictive disorders	0.1	4.9 [2.6–8.4]	5.2	5.7 [5.3–6.1]	9.9	5.0 [4.4–5.7]
N07X	Other nervous system drugs	0.1	15.5 [6.7–30.5]	0.2	38.4 [25.3–55.9]	0.3	12.8 [5.5–25.3]

[a] Standardized morbidity rates, i.e. the ratio between the actual drug use seen in the ADHD cohort and the expected drug use in the ADHD cohort if they had the same use pattern as the background population, standardized by sex and age in 1-year intervals and presented with 95 % confidence intervals (values in square parentheses)

[b] Prescriptions for melatonin (N05CH01) were excluded, see method section

models [29, 30]. A recent study has shown an altered risk of Parkinsonism among users of amphetamine [31]. Even though these studies focused on amphetamine abuse, a similar effect of use at therapeutic doses cannot be ruled out. The uncertainties about long-term effects have led the European Medicines Agency to recommend regular periods of drug treatment-free intervals [32]. To date, however, there have been no reports on the prevalence of the treatment breaks, nor of the criteria to evaluate the outcome of breaks. Abrupt cessation of medication might trigger inattention and hyperkinesia due to abstinence rather than as a manifestation of the ADHD itself.

There are no obvious explanations for the steady rise in daily dose from 2002 onwards, such as major changes in international or national guidelines. No reports showing a similar trend in dose–time escalation have been identified in the literature. The rise in daily dose coincides with the rise in prevalence rate [7]. it is possible that clinicians have become familiarized with the treatment and thereby less reluctant to use larger doses. Another possible explanation for the increase in daily dose could be the development of tolerance. The literature on this topic is scarce, but results from more recent animal model studies do indicate that sensitization to methylphenidate can occur [29].

International guidelines are inconclusive regarding atomoxetine's role as first-line treatment [33, 34], recommending that individual medical circumstances and economic cost/benefits are to be considered. On the other hand, Danish national guidelines recommend stimulants as first-line treatment in children and adolescents [35]. One indication for atomoxetine as first choice is the presence of substance or alcohol abuse patterns in the patient/family. However, as the observed increased use of atomoxetine as first-line treatment does not differ with age, this indication does not seem to be a likely explanation. Another indication is the presence of tic disorder in the patient. It is possible that patients diagnosed with ADHD and tics, who earlier were not considered for medical treatment, are now being offered treatment with atomoxetine [36]. Societal economic interests should be considered, as the price of a DDD of atomoxetine is two to fourfold that of both instant- and controlled-release formulated stimulant treatments. The influence of third parties, such as pharmaceutical companies, also cannot be ruled out. The finding that one out of ten methylphenidate users switch to atomoxetine most probably reflects the fact that 20–30 % of users do not experience a positive effect and or have intolerable adverse events [37].

The literature on the concomitant use of methylphenidate and atomoxetine is scarce. One pilot study showed no positive effect of augmenting atomoxetine with methylphenidate [38]. There is no information available on the reverse combination. One possible explanation for our finding of concomitant use might be the common clinical practice of a stepwise switchover between methylphenidate and atomoxetine [39, 40].

The high prevalence of concomitant use of immediate- and controlled-methylphenidate does not reflect a similar cross-over period. Switching from immediate- to controlled-release drug formulations can be done at once with equivalent doses. It is a common clinical practice to complement controlled-release methylphenidate with immediate-release methylphenidate, either to 'kick start' in the morning or to prolong the effect into

the evening. No studies on the clinical effect of the concomitant use of immediate- and controlled-release methylphenidate are available. One experimental study suggests that immediate-release methylphenidate has a somewhat greater abuse potential when used alone or administered together with controlled-release methylphenidate [41].

The concomitant use of non-ADHD medication showed a small, largely unspecific excess for nearly all therapeutic groups, with ATC-group N as a prominent exception. This is possibly explained by frequent physician contact, as has been observed with other therapeutic groups, such as anti-asthmatics [42]. A trend towards psychotropic medication polypharmacy has been demonstrated in the USA [4, 6], also more specifically regarding ADHD [5]. In our study, we found that especially substances controlling impulsive behavior, such as mood stabilizers and antipsychotics, are used much more frequently in individuals taking ADHD medication. The rationale for using dopaminergic and antidopaminergic medication in the same patient is unclear, and this common practice seems to rest on clinical experience alone. Interactions also need to be taken into consideration. A few case reports are available on the risk of serious adverse events with the concomitant use of stimulants and atypical antipsychotics [43–45] and stimulants and selective serotonin reuptake inhibitors [46].

With respect to the concomitant use of antidepressants, anxiolytics and hypnotics, consideration should be given to the question of whether this use reflects treatment of common adverse events of ADHD medication, or whether it represents the treatment of genuine co-morbid disorders. Sleep disorders are known to be common in patients with ADHD with or without medication [47, 48], but this occurrence cannot solely explain the high prevalence of melatonin users among persons medicated for ADHD. Melatonin is currently regarded to be a relatively safe medication with few adverse events and is preferentially used in children with sleep disorders because children do not tolerate benzodiazepines.

In conclusion, we have demonstrated a pattern of use that is largely consistent with guidelines. However, a few traits warrant further investigation, including the apparent increase in doses and the overuse of other psychotropic medication.

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