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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

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

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

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Abstract
Purpose The purpose of the study was to characterize the utilization of medication against attention deficit hyperactivity disorder (ADHD) in Denmark between 1995 and 2011 from a national perspective, by using population-based prescription data.
Methods National data on drug use in Denmark between 1 January 1995 and 30 September 2011 were extracted from the Registry of Medicinal Product Statistics (RMPS). Drug utilization was characterized using descriptive statistics.
Results A total of 1,085,090 prescriptions issued to 54,020 persons were identified. The incidence rate was stable in the last 3 years of the study period, and a slightly decreasing incidence rate and a stabilizing prevalence were observed towards the end of this period. The therapeutic intensity was 6.7 defined daily dose/person/day, with large regional differences that ranged from 64 to 145 % of the national average. Methylphenidate accounted for 92.6 % of DDDs used. The general practitioner (GP) rarely initiated treatment, although treatment initiation based on the GP's advice increased with older age of the patient. Maintenance treatment was found to be distributed roughly equally between prescriber types. For methylphenidate, 1 % of users accounted for 6.1 % of the drug volume and 50 % of users accounted for 84.4 %. The data therefore do not suggest a high proportion of heavy users.
Conclusion The findings of this analysis are mostly reassuring, with the data indicating a seemingly stagnant incidence and prevalence rate and lacking evidence of heavy users. However, the prescriber profile for incident users and the large regional variances raise concerns. It is therefore vital that the use of ADHD drugs is closely monitored.

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

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

A. Pottegård · D. Glintborg · S. I. Moreno
Institute for Rational Pharmacotherapy, Danish Medicines Agency,
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

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

Introduction

Attention deficit hyperactivity disorder (ADHD) is estimated to have a worldwide prevalence of 5 % in children [1] and 3–4 % in adults [1, 2]. The drug treatment of ADHD has received massive international attention in recent years, questioning the rationality of the global increase in use of psychostimulants among children. In Denmark, ADHD drugs are only licensed for treating children and adolescents (6–17 years). In addition, restrictions apply to which prescribers initiate and maintain drug therapy [3]. The rapidly increasing number of children being treated with ADHD drugs has been extensively discussed because of the lack of evidence for long-term efficacy and safety of drug

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treatment [4–9]. Furthermore, the apparent increase in number of adults treated with ADHD drugs is problematic because national treatment guidelines are missing. Finally, the risk of drug abuse, even in children, has become an issue [10]. Although often debated, the knowledge of use patterns of ADHD drugs is sparse. The large increase in the use of ADHD drugs warrants a detailed investigation of whether the increase is ongoing or has stagnated. In addition, evidence is lacking regarding concordance with treatment guidelines and prescriber restrictions. Accordingly, the aim of this study was to characterize use, regional differences, and prescribing patterns of ADHD medication in Denmark between 1995 and 2011 from a national perspective using population-based prescription data. Further analysis, looking into patient-centered data (treatment duration, comedication, development in dosage used, etc.) were also analyzed, but will be presented in a separate paper.

Materials and methods

Data source

National data on drug use in Denmark was extracted from the Registry of Medicinal Product Statistics (RMPS). The database is operated by the Danish Medicines Agency. From 1994 onward, the RMPS has contained individual-level information on all prescription drugs purchased at Danish community pharmacies. Data coverage is, however, incomplete prior to 1 January 1995. For each drug purchase, the database contains information on the following variables relevant for this study: person age and gender, region of residence, date of purchase, Anatomical Therapeutic Chemical (ATC) classification, total defined daily dose (DDD) dispensed, a unique identifier for the prescribing physician, and type of prescriber [general practitioner (GP), practicing specialist, hospital doctor]. In addition, the RMPS contains several other variables not used in this study. As described elsewhere, the registry is deemed to have a high completeness and validity for each data variable [11]. Census data were provided by Statistics Denmark.

Data selection

Persons were included in the study if they redeemed at least one prescription for either methylphenidate (N06BA04) or atomoxetine (N06BA09) within the study period from 1 January 1995 through 30 September 2011. Prescriptions for modafinil (N06BA07) were included in the analysis only if the person had previously redeemed a prescription for either methylphenidate or atomoxetine. Modafinil is only registered for narcolepsy in Denmark and is only recommended for ADHD as the third- or fourth-line treatment. If we had included users of modafinil with no prior record of methylphenidate or atomoxetine, then the number of persons would have increased by 5.9 % (40,993 prescriptions for modafinil, 3,202 unique persons with a median age of 47 years). Throughout this text, the term ADHD drugs refers to methylphenidate, atomoxetine, and modafinil as a group.

ADHD drug use not included in our study

Amphetamine and dexamphetamine can be used as alternatives in ADHD treatment. However, as both drugs are only produced by magistral prescriptions, data coverage on their use is unknown but is suspected to be low and highly variable between pharmacies. Therefore, these drugs were excluded from our analysis to ensure consistency and reproducibility. Before the introduction of Strattera® (atomoxetine) and Concerta® (slow-release methylphenidate) in August 2006 and May 2008, up to 669 and 2,124 users, respectively, had a compassionate-use permit, thereby redeeming prescriptions that were not recorded in our database.

Data analysis

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

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); prescribers categories were GP, practicing specialist, hospital doctor, and other. More detailed information dividing specialist prescribers into subspecialties was not available for all prescriptions. Information regarding subspecialties of hospital doctors was not available. All drug amounts were measured in DDD. DDD-values for ADHD drugs are: 30 mg for methylphenidate, 80 mg for atomoxetine, and 300 mg for modafinil. In all analyses, a 2-year run-in period was used when deciding whether a person should be classified as incident (starting new ADHD treatment) or not. For example, a person redeeming one prescription in 2006 and one in 2009 would be counted as incident twice, whereas a person redeeming one in each year from 2006 to 2009 would only be counted as incident once. Unless otherwise specified, each analysis was performed on prescriptions for the three ADHD drugs pooled together. All analyses were performed using SAS statistical software version 9.1 (SAS Institute Inc., Cary, NC, USA).

The analysis was divided into the following questions:

1. What is the incidence rate of treatment with ADHD drugs? Using all ADHD prescriptions (data set A, Table 1), the

Table 1 Description of the four different data subsets used

Data set	Description	Period	No. persons	No. ADHD prescriptions
A	Full period	1 January 1995–30 September 2011	54,020	1,085,090
B	Last three years	1 October 2008–30 September 2011	44,570	698,476
C	The last year	1 October 2010–30 September 2011	35,106	289,081

ADHD attention deficit hyperactivity disorder

number of new (incident) users per quarter was determined, specified by age category and gender. As data was not available prior to 1995, only data from 1997 and forward are shown (allowing for a 2-year run in period). To represent the person-time at risk for each quarter, we used the Danish population in each age category by 1 January in the same year and divided it by four. The incidence rate was calculated by dividing the number of incident users by the estimated person-time at risk. The incidence rate was given per 1,000 person years, specified by age category and gender.

2. What is the prevalence rate of treatment with ADHD drugs?

   This question was answered using all ADHD prescriptions (dataset A, Table 1). For the first day in each quarter, the number of persons currently treated (point prevalence) was estimated by finding the number of unique persons that had redeemed at least one prescription for any ADHD drug during the previous 3 months, specified by age category (using the age at the first prescription in each time window) and gender. From this, the point prevalence rate was calculated by dividing the number of treated persons in each quarter by the size of the population in that age and gender category on 1 January the same year.

   To further illustrate the age and gender distribution of the prevalence rate, the full age spectrum (not grouping age in categories) is shown for the last point prevalence from 1 October, specified by gender.

3. Are there regional differences in the use of ADHD drugs?

   Using the last year of data (dataset C, Table 1), regional incidence rates were estimated using the same template for analysis as in question 1, only this time specifying by region instead of age.

   Using the same data set, the amount of dispensed ADHD drugs was calculated by taking the sum of DDDs for all ADHD prescriptions dispensed in the period. The calculation was specified by region. The therapeutic intensity was expressed as use in DDD per 1,000 citizens per day.

4. Which kind of ADHD drug is used and to what extent?

   Using the last year of data (dataset C, Table 1), the total amount of dispensed drug was calculated by taking the sum of DDDs for all ADHD prescriptions dispensed, specified by drug type (atomoxetine, methylphenidate or modafinil).

5. Which type of prescriber prescribes ADHD drugs?

   This question was answered using data from the last 3 years (data set B, Table 1), dividing prescriptions into incident and nonincident to assess who initiates treatment and who maintains treatment. An incident prescription was defined as the first one occurring for the user within a 2-year period.

   For incident prescriptions, we recorded which prescriber type had issued the prescription. Specified by age category and each ADHD drug, the percentage of all incident prescriptions attributable to each prescriber type was then calculated. For nonincident prescriptions, the proportion of DDDs attributable to each prescriber type was calculated for each person and each ADHD drug separately. Data are presented for each age category and each prescriber type.

   To assess the specialist prescriber type, we used the last year of data and counted the number of prescriptions attributable to each subspecialty and specified by patient age <18 years or ≥18 years.

6. How are users distributed regarding dose used?

   Using the last year of data (dataset D), a reversed Lorenz curve [12] was produced. The Lorenz curve is an analytical tool to express skewness in drug consumption. First, users were ranked in descending order of total amount of ADHD drug redeemed. Then a graph was produced, displaying which percentile of the total number of users (x axis) accounting for what percentile of the total amount of redeemed DDDs (y axis). From this graph, the Gini coefficient was calculated as a measure of the inequality seen in the Lorenz curve, with a value of 0 expressing total equality and a value of 1 maximal inequality.

   The analysis was done for each ADHD drug separately.

Results

There were 54,020 persons for a total of 1,085,090 redeemed prescriptions for ADHD drugs included in the study (Table 1). The distribution of use between the three ADHD drugs measured in percent of total amounts of DDD was methylphenidate 92.6 %, atomoxetine 6.8 %, and

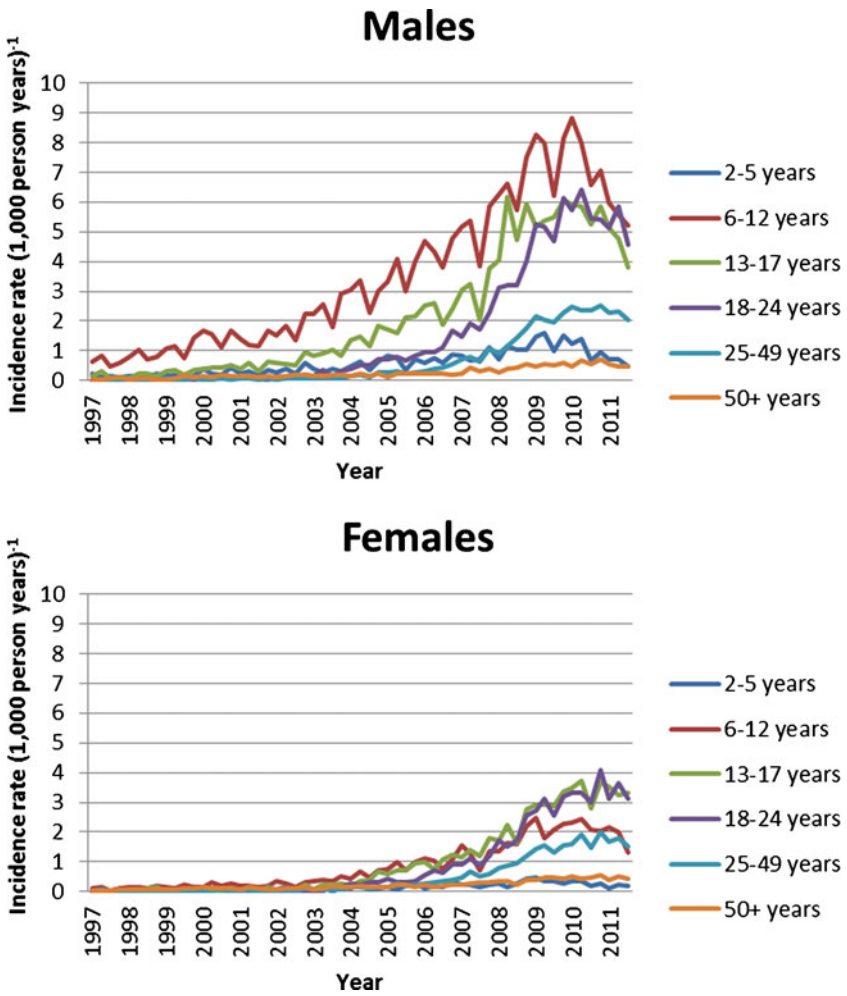

Fig. 1 Incidence rates of persons being treated for attention deficit hyperactivity disorder (ADHD) (incidence per 1,000 person years) per quarter from 1 January 1997 to 30 September 2011, specified by age and gender

modafinil 0.6 %. For the final quarter of our data, the highest incidence rate was observed among boys aged 6–12 years (5.2 per 1,000 citizens). The corresponding prevalence rate was 22.9 per 1,000 citizens (boys 6–12 years). The incidence and prevalence rates specified by age category and gender are given in Figs. 1 and 2. Further details on the age distribution of the last point prevalence are given in Fig. 3. As a sensitivity analysis of the significance of the run-in period for estimating the incidence rate, we changed the 2-year run-in period to 1 year. This generally had little influence on our findings, with the largest differences observed for those aged 18–24, where the incidence rate increased by 22 % among men and 14 % among women.

Large regional variances in incidence rates are observed. For the last year of data the regional incidences given per 1,000 person-years varied from 1.23 (southern Denmark) to 2.41 (central Denmark) (Fig. 4). These differences were reasonably stable over the last 3 years (data not shown). The therapeutic intensity on a national level was 6.7 DDD per 1,000 citizens per day. Large regional variances were observed when comparing regions to national average (index 100 %), ranging from 64 % (southern Denmark) to 145 % (central Denmark) (Fig. 4).

The GP was found to rarely initiate treatment in children <18 years (6–10 % for methylphenidate, Table 2). However, among older users (≥18 years), the GPs share increased to 18–22 %. Maintenance treatment was distributed roughly equally between prescriber types, although shifting toward GPs with increasing patient age (Table 2). The primary prescriber type among children was hospital doctors, who accounted for most treatment initiation and maintenance therapy (Table 2).

Of the 27 % (76,826) prescriptions issued by a specialist, only 66 % contained information allowing identification of prescriber subspecialty. For persons <18 years, distribution between subspecialties was 54 % child and adolescent psychiatrists, 36 % pediatrics, 7 % psychiatrists, and 3 % neurologists. For persons aged ≥18 years, distribution was 94 % psychiatrists, 3 % child and adolescent psychiatrists, 2 % neurologists, and 1.2 % other.

The Lorenz curve for methylphenidate is shown in Fig. 5. The corresponding curves for atomoxetine and modafinil were indistinguishable from the methylphenidate curve and are not shown. The Gini coefficients were 0.49 for methylphenidate,

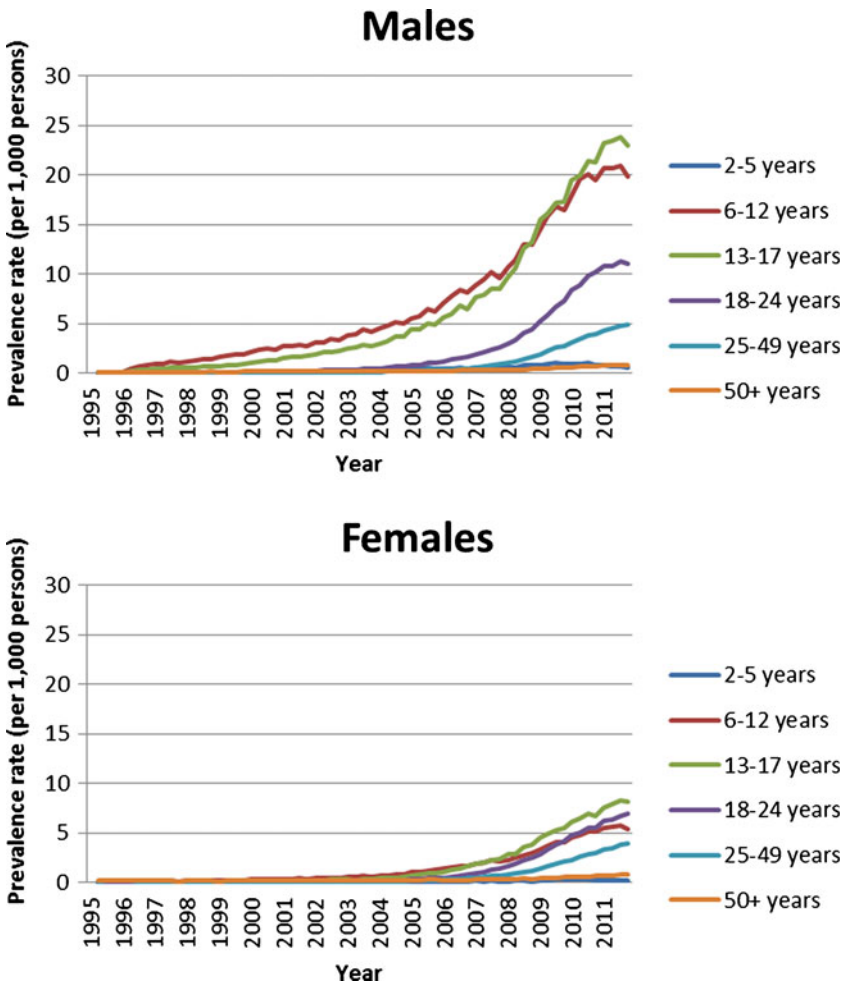

Fig. 2 Prevalence rates of persons being treated for attention deficit hyperactivity disorder (ADHD) (prevalence per 1,000 citizens) per quarter from 1January 1997 to 30 September 2011, specified by age and gender

0.48 for atomoxetine, and 0.53 for modafinil. For methylphenidate, 1 % of users accounted for 6.1 % of the drug volume and 50 % of users accounted for 84.4 %. As a sensitivity analysis, we produced 12 different Lorenz curves specified by age, category, and sex. As expected, this slightly reduced the average Gini coefficient. The least skewness was found among those aged 6–12 (Gini coefficient 0.39 and 0.41 for boys and girls, respectively). Skewness increased with age and was most pronounced among those aged 50+ years (Gini coefficient 0.63 and 0.61 for men and women, respectively).

Discussion

The incidence rate of persons being treated for ADHD was reasonably stable since the beginning of 2009 and seemed to

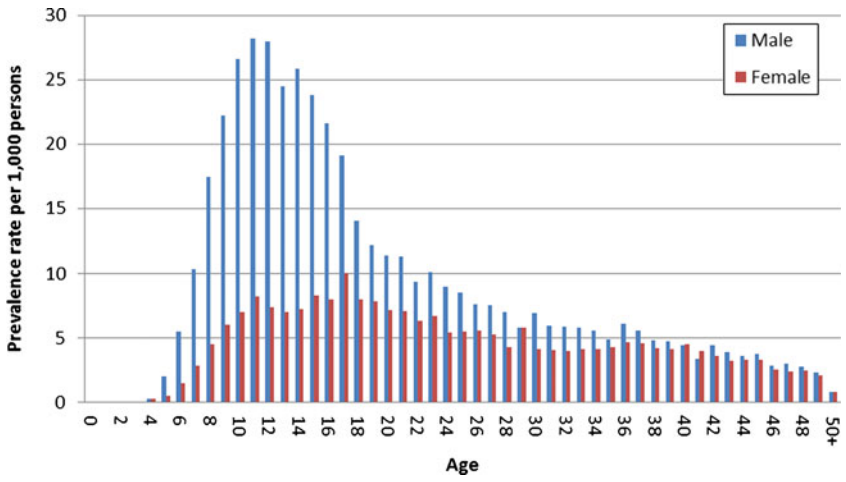

Fig. 3 Prevalence rates of persons being treated for attention deficit hyperactivity disorder (ADHD) for the last quarter of our data (third quarter 2011) specified by age and gender. All persons older than 50 years were pooled together and analyzed as one group

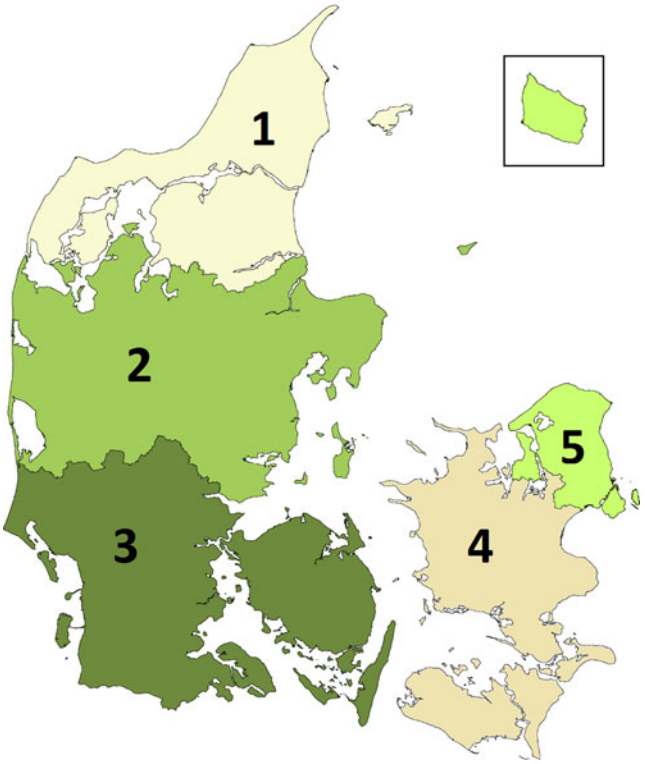

Fig. 4 Overview of the five regions of Denmark. The following values were obtained: region name (incidences of persons being treated for attention deficit hyperactivity disorder (ADHD) per 1,000 person-years/therapeutic intensity of ADHD medication compared with national average). *1* North Denmark(1.88/116 %); *2* central Denmark (2.41/145 %); *3* southern Denmark (1.23/64 %); *4* Sealand (2.24/120 %); *5* capital (1.69; 77 %)

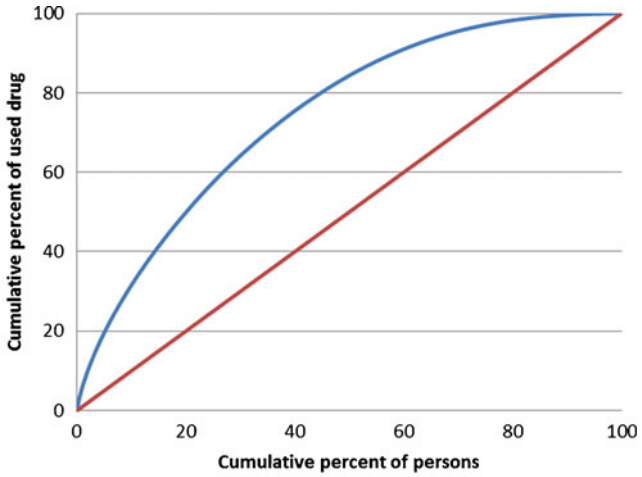

Fig. 5 Lorenz curve for methylphenidate. The *blue line* indicates proportion of drug use accounted for by the proportion of the most intensive users. The *red line* indicates a completely homogenous drug use, with all users taking the same amounts. Study period 1 October 2010–30 September 2011

decrease slightly through 2011. In turn, this led to a stabilizing prevalence. Furthermore, large regional differences and some discrepancies between prescriber patterns and national guidelines were observed.

Our study has several strengths: First, the use of the RMPS allows drug use evaluation of the entire population of Denmark in a 17-year study period. Second, this evaluation was done with very little lag-time, with data up to and including September 2011, allowing us to assess the newest developments in ADHD drug use. Finally, the RMPS has a very high data coverage and data validity for variables used in our study. Our study does, however, have some limitations. First, the registration of prescriber identification in the RMPS is subject to some uncertainty. Often, the ID of the most used prescriber is automatically filled into the electronic dispensing systems at the pharmacies. Consequently, the ID of alternative prescribers needs to be manually corrected by the pharmacy staff, which could potentially lead to misclassifications. The magnitude of this problem is not known, but it would most likely overestimate the proportion of prescriptions attributed to the GP. Second, indication for treatment is not always registered in the RMPS or is unreliable (e.g., methylphenidate for treating

Table 2 Percent distribution of prescriptions between different prescriber types [general practitioner (GP), specialist (SP), hospital doctor (HP)] specified by patient age category, drug, and incident and nonincident prescriptions. Study period: 1 October 2008–30 September 2011

Drug	Patient age category					
	2–5 years	6–12 years	13–17 years	18–24 years	25–49 years	50+ years
Incident prescriptions: percent distribution: GP/SP/HP						
Methylphenidate (*n*)	6/28/66 (539)	7/27/66 (6,338)	10/30/59 (4,231)	18/44/38 (5,243)	20/49/31 (9,767)	22/24/53 (2,864)
Atomoxetine (*n*)	<10	5/27/68 (228)	8/32/60 (371)	15/28/55 (632)	14/35/48 (875)	17/32/50 (96)
Modafinil (*n*)[a]	<10	<10	<10	<10	19/59/22 (27)	42/21/32 (19)
Nonincident prescriptions, weighed by DDD: percent distribution: GP/SP/HP						
Methylphenidate (*n*)	18/25/57 (9,451)	23/24/53 (157,135)	29/24/47 (95,082)	39/33/27 (78,283)	43/38/18 (203,690)	58/23/19 (3,126)
Atomoxetine (*n*)	18/32/51 (565)	10/34/56 (22,985)	13/35/52 (18,211)	21/38/40 (14,520)	22/47/29 (24,007)	24/55/21 (2,201)
Modafinil (*n*)[a]	<10	26/44/27 (75)	27/49/24 (391)	34/50/16 (1,571)	38/50/13 (5,094)	49/35/15 (2,692)

[a] Only persons previously using either methylphenidate or atomoxetine

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 citizens [13], compared with up to 50 per 1,000 for ADHD [1], this is unlikely to have contaminated our findings substantially. Finally, exclusion of amphetamine and dexamphetamine prescriptions from our study, due to the low data coverage, leads to an underestimation of true ADHD treatment prevalence. However, given the suspected limited use of these drugs, it is unlikely to have impacted our findings substantially.

In the US, the rate of psychostimulant use (0–18 years) was reported to be 29 per 1,000 citizens in 2002 [14]. In The Netherlands, the rate (0–19 years) was reported to be 19.5 per 1,000 citizens in 2006 [15] and in Germany (0–18 years) 10.6 per 1,000 citizens in 2007 [16]. Comparisons with our findings are, however, made difficult by differences in methodology. The only previous peer-reviewed study using Danish data is a comparative study of use within the Nordic countries by Zoega et al. [17], indicating that Denmark at the time had a treatment prevalence similar to the average in the Nordic countries, i.e., less than Norway and Iceland, more than Finland, and similar to Sweden. Zoega et al. did, however, only analyze aggregated data and only from 2007. They used a 1-year period prevalence to represent the prevalence rate, whereas our data allowed us to estimate the actual point prevalence. As a result, we found that the prevalence per 1,000 citizens rose from 1.21 on 1 January 2007 to 1.65 on 1 January 2008, as compared with a 1-year prevalence for 2007 of 2.41 found by Zoega et al. [17]. A partial explanation is that Zoega et al. included data on amphetamine, dexamphetamine, and primary users of modafinil, although this did not contribute substantially (for reasons explained above).

The finding that the incidence rate remained stable for 2–3 years, and even seemed to drop slightly toward the end of the study period (Fig. 1), together with the fact that the prevalence rate has stabilized, is noteworthy; for although we historically see a rapid and massive increase in use, this is the first sign indicating that we have reached a plateau. To our knowledge, no previous studies have found a similar trend, either in the Nordic countries or elsewhere. Although not all patients necessarily require medical treatment, it is also worth emphasizing that the observed treatment prevalence among children (see Fig. 2) is lower than the estimated disease prevalence of 5 % in children [1]. As also found by Zoega et al., our data demonstrate a substantial gender difference in prevalence rate for children and adolescents (Figs. 2 and 3), which decreased with age [17].

The increase in treatment prevalence seen among adults (Fig. 2) is of concern, as no Danish treatment guidelines exist for treating this age group, and knowledge of diagnostics and safety among adults is limited [18]. Consequently, adult treatment is often based on unsystematic treatment reviews. As an example, a narrative Danish review from 2008 on adult treatment of ADHD in primary care advocated an increased need to diagnose ADHD and initiate drug therapy among adults [19]. Such publications may have facilitated the current prevalence patterns. Our findings, that roughly half of all prevalent ADHD drug users is ≥18 years, emphasize the need for developing guidelines for ADHD treatment in adults. However, as seen in children, the observed treatment prevalence among adults (see Table 2) is lower than the estimated disease prevalence of 3–4 % [1, 2].

Values found for the 1- and 50-percentile in the Lorenz curves are not particularly high when compared with an array of other drugs [12]. Consequently, they do not support the notion of ADHD drugs being used in excessive quantities by individual users, at least not through legal channels. Neither does it support the notion of a high level of sporadic use. Another important finding is the large regional differences. One potential explanation could be differences in therapeutic tradition (e.g., prescribing habits and clinical experience of single prescribers). Other potential explanations are differences in the availability of specialists, as they are responsible for most treatment initiations, or regional differences in disease prevalence. The age/gender distribution differs little between regions and thus cannot explain the regional differences in ADHD drug use. Similar large regional differences have been observed in other Nordic countries [20, 21] and between Nordic countries [17].

According to current Danish treatment guidelines [3], treatment with ADHD drugs of children and adolescents should always be initiated by a specialist in either child and adolescent psychiatry or, in some cases, psychiatry, neurology, or pediatrics. Follow-up treatment with methylphenidate (as opposed to atomoxetine and modafinil) can be managed by the GP. From Table 2, it is evident that this guideline is mostly followed among children and adolescents. However, increasing person-age increases the likelihood of treatment being initiated by a GP, with a substantial proportion of those aged ≥18 years being initiated by GPs. Furthermore, it is in clear contrast to treatment guidelines that so many patients have their atomoxetine prescribed by a GP. The division into subspecialties among specialty prescribers confirms that guidelines are followed. However, treatment of children is more scattered among different subspecialties than was to be expected. The validity of this subanalysis is, however, influenced by the low data coverage. As a similar subanalysis could not be performed among hospital doctors, the specialties of hospital doctors remain unknown.

The findings in our analysis are mostly reassuring, i.e., the seemingly stagnant incidence and prevalence rate and the lack of evidence for heavy users. However, the prescriber profile for incident users raises concerns about GPs not following current treatment guidelines. Furthermore, the large regional variances are cause for concern. There are, to our knowledge, no other good examples of drugs that have

been adopted so massively for use in children with so little knowledge about long-term outcomes. It is therefore vital that developments in the use of ADHD drugs are closely monitored and that the rationality for use is evaluated.

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