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Trends in the Prescribing and Adverse Drug Reactions Patterns of Psychostimulants Among Danish Children and Adolescents

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1. Introduction

The use of psychostimulants, particularly methylphenidate, to treat Attention Deficit/Hyperactivity Disorder (ADHD) symptoms in children and adolescents has increased rapidly since the 1990s (Schubert et al. 2010). In the 2000s serious reports on cardiovascular adverse drug reactions (ADRs), sudden deaths and psychiatric disorders have led the regulatory agencies in Europe and the United States (US) to warn against use of psychostimulants in the paediatric population (Schubert et al., 2010). In July 2007, class labels were implemented in the product information to reflect more specific information about cardiovascular and psychiatric adverse events and long-term suppression of growth (European Medicines Agency, 2007, US Food and Drug Administration, 2007). Despite these warnings, the number of children treated as well as the amount of psychostimulants prescribed per child has steadily increased (Kalverdijk et al., 2008).

Studies have shown that the use of psychostimulants in children in the Netherlands increased 8 times from 1996 to 2006 (Trip et al., 2009) and in Germany with 96% from 2000 to 2007 (Schubert et al., 2010). From 1994 to 2004 the use of psychostimulants in children increased 5 times in Norway (Asheim et al., 2007), and from 1987 to 1996 the use of psychostimulants increased 10 times among US children (Zuvekas et al., 2006).

Information about ADRs from psychostimulants has been reported in several clinical studies of short duration, primarily conducted in 6 to 12-year olds boys, particularly in the US (Bloch et al., 2009). The majority of ADRs reported in these studies were of the type *gastrointestinal disorders* as well as *nervous-* and *psychiatric disorders*, and only few serious ADRs were reported (Bloch et al., 2009). In spite of pharmacological treatment of children with ADHD being common, this practice has been highly debated among health care professionals due to the dilemma of treating children with substances potential for abuse, where information about long-term safety aspects is very limited (Bloch et al., 2009). The

concerns about safety issues from use of psychostimulants in the paediatric population are also due to the many anecdotal reports of serious psychiatric ADRs and sudden deaths that have been submitted to the regulatory agencies over recent years (Pringsheim & Steeves, 2011). Systematic analyses of ADRs reported to national databases are necessary, as these databases constitute an important, though underestimated, source of data, especially about new, serious and rarely occurring ADRs (Hansen, 1992; Aagaard & Hansen, 2009a). We did not locate any studies which systematically have analysed spontaneous reports for psychostimulants submitted to national databases compared to data on medicine use in the paediatric population.

The objective of this chapter was to 1) describe trends in prescribing of psychostimulants in the Danish paediatric population and 2) characterise spontaneous ADR reports submitted to the Danish Medicines Agency (DKMA) over a decade with respect to occurrence, seriousness, type and age and gender of the child, reported for psychostimulants.

2. Methods

2.1 Design

We conducted a retrospective analysis of all spontaneous ADR reports for 0-17-year old children from 2000 to 2009. Data were obtained from the Danish ADR database and placed at the disposal of this study in anonymous form with encrypted person identification. The unit of analysis was one ADR. Data on medicine use from each of the stimulants were extracted on individual level from the national Danish medicines registry as defined daily doses (DDD) per 1000 inhabitants per day and users (number of treated persons per 1000 inhabitants).

2.2 Setting

2.2.1 Danish registry of medicine use

In only a few countries information about medicine use at the individual level is available, Denmark being one of these countries. The Registry of Medicinal Product Statistics is a national database covering all outpatient pharmacy-dispensed prescriptions in Denmark.

The registry was established in 1994 to provide complete statistics on the use of medicines in Denmark. Data on prescriptions are registered for each patient via the civil registration number. Each prescription record contains the date of purchase, the dispensing pharmacy, the prescribing physician and detailed information on the drug dispensed, including product name, anatomical therapeutic classification (ATC) system name, dosage, package size and formulation. Medicine use is recorded in different ways. In this study we apply the defined daily doses (DDD) per 1000 inhabitants and number of users per 1000 inhabitants for our analysis. The DDD is defined at the assumed average maintenance dose per day for a drug used for its main indication in adults (WHO, 2011).

2.2.2 Definition of psychostimulants

A psychostimulant is an agent that causes an increase in functional activity, usually of the central nervous system (Howard et al., 2010). Examples of these kinds of effects may

include enhanced alertness, wakefulness, and locomotion, among others. Due to their effects typically having an "up" quality to them, stimulants are also occasionally referred to as "uppers". Stimulants (analeptics) produce a variety of different kinds of effects by enhancing the activity of the central and peripheral nervous systems (Howard et al, 2010).

In this study we focus on the type of stimulants most frequently prescribed in Denmark, i.e. methylphenidate, atomoxetine, modafinil and amphetamine derivatives in the paediatric population. According to the official summary of product information methylphenidate and atomoxetine are licensed for treatment of ADHD in children and adolescents from 6 and 8 years of age respectively. Modafinil and amphetamine derivatives are not licensed for use in children (Danish Medicines Agency, 2011).

2.2.3 ADR reporting system

The reporting of ADRs has been obligatory in Denmark since 1 May 1968. Initially, only physicians were covered by the obligation; however, in 1972, dentists and veterinary surgeons were also required to report ADRs (Aagaard et al., 2008b). Since 1995, drug manufacturers have been obliged to keep registers of suspected and demonstrated ADRs and to make these available to the regulatory authorities. Since July 2003, consumers and other health care professionals have been able to report ADRs directly to the authorities (Aagaard et al., 2008b). An ADR report is defined by the following four criteria, which must be included in all reports: (i) information about the patient; (ii) the suspected medicine(s); (iii) the presumed ADR(s); and (iv) information about the person making the report. An ADR report may contain one or more ADR terms (Aagaard et al., 2008b).

After receiving the ADR reports, professional staff at the DKMA code and categorize the ADRs by degree of seriousness and type of reaction according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology (Aagaard et al., 2008b).

ADR reports are forwarded electronically to the respective pharmaceutical companies, which periodically assess the ADR reports received. The results of their assessments are reported to the DKMA via periodic safety update reports (PSURs). The Danish ADR database contains all spontaneous ADR reports in Denmark, including those reported directly to the pharmaceutical companies (Aagaard et al., 2008b).

2.2.4 Adverse drug reaction (ADR)

An ADR is defined as "any noxious and unintended response to medicines that occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of diseases" (Volume 9, 2009).

2.2.5 Criteria for seriousness

Severity of reported ADRs was classified according to the criteria defined in volume 9 of the rules governing medicinal products in the European Union guideline (Volume 9, 2009).

Here serious ADRs are divided into: resulting in death, life-threatening, requiring hospitalization or prolongation of existing hospitalization, resulting in persistent or

significant disability/incapacity in the reporter's opinion, a congenital anomaly/birth defect and other medically important conditions (Volume 9, 2009).

Other reactions were classified as being non-serious.

2.2.6 Anatomical therapeutic chemical (ATC) classification groups

The ATC system classifies medicinal products according to the primary constituent, organ or system on which they act and their chemical, pharmacological and therapeutic properties. Medicines are divided into 14 main groups (first level), with one therapeutic subgroup (second level). The third and fourth levels are chemical/pharmacological/therapeutic subgroups and the fifth level is the chemical substance (WHO ATC index, 2011).

The extract from the ADR database only provides information according to the trade name of those medicinal products that have been reported as causing ADRs. Therefore it was necessary to translate manually trade names into generic names at ATC level 5 in the national medicines register, and then run the generic form of the medicine name against the ADRs reported.

2.3 Data extraction

Prescription data were extracted from the Danish registry of dispensed medicine. We extracted information about DDDs per 1000 inhabitants per day and number of persons per 1000 inhabitants prescribed for psychostimulants among children from 0 to 17-years of age. Information about gender was also extracted from the registry. ADR reports submitted to the DKMA were placed at the disposal of this study in anonymous form with encrypted identification of the medicine user. Data were extracted from the ADR database on Microsoft Excel files and the material comprised all ADR reports on children from birth to 17 years of age reported to the Danish Medicines Agency from 2000 to 2009 for the psychostimulants. The unit of analysis was one ADR.

The Danish ADR database defines five categories of persons who may submit data to the database. This article applies this official designation for category of person submitting reports:

- Lawyer: patient injury insurers and/or law firms
- Pharmacist: community or hospital pharmacists
- Physician: general practitioners, physicians and dentists
- Other health care professional: nurses, pharmaceutical companies, social and health care assistants
- Consumers: patients, patients' relatives, other members of the public

Because consumers have had the opportunity to report ADRs in Denmark since 2003, results from this category only cover data from the last 6.5 years of the study period.

3. Results

3.1 Prescribed psychostimulants, 2000-2009

Figure 1 displays the annual number of DDD/1000 inhabitant/day and no. of persons/1000 inhabitants/day for all types of psychostimulants prescribed for children from 0 to 17-years of age.

From 2000 to 2009 the number of prescribed DDDs/1000 inhabitants/day increased with 1629 % (from 10.87 to 187.97 DDD/1000/inhabitants/day) and the number of treated persons/1000 inhabitants/day increased with 775 % (from 21 to 183.67 DDD/1000/inhabitants/day).

From 2000 to 2004 the level of prescribing was rather constant, however from 2005 and onwards large increases in the prescribing of psychostimulants were observed.

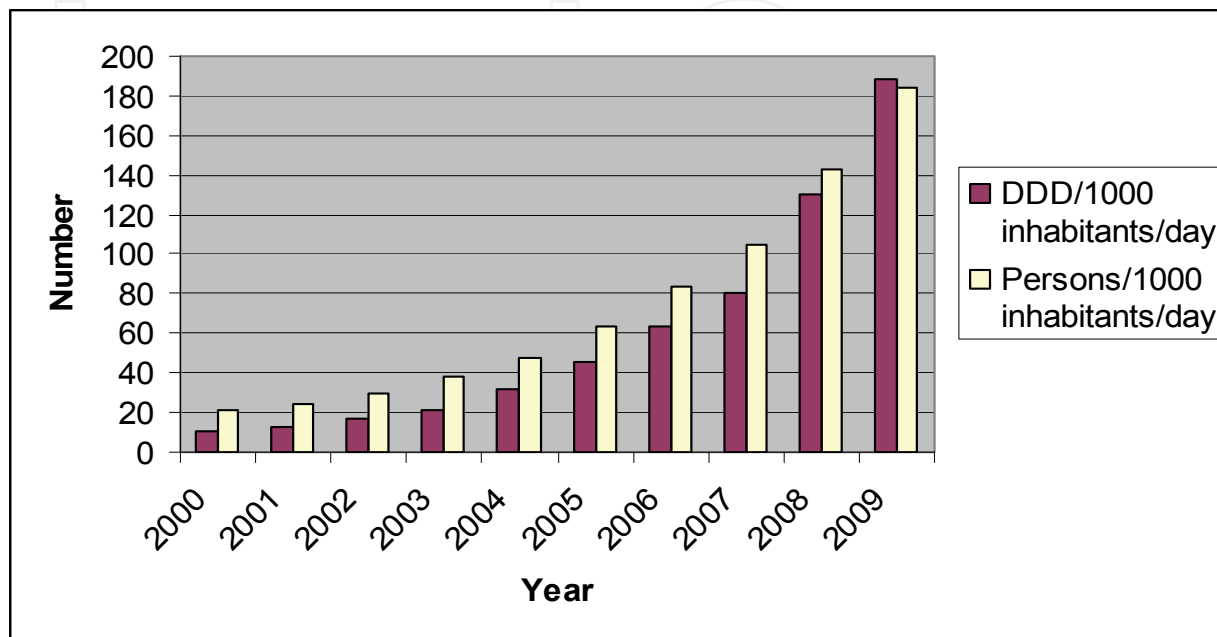


Fig. 1. Annual number of DDDs/1000 inhabitants/day and number of persons/1000 inhabitants/day for psychostimulants for children from 0 to 17-years of age, (2000-2009)

Table 1 displays DDDs per 1000 inhabitant/year per category of psychostimulant medications from 2000 to 2009. Methylphenidate was the dominant prescribed psychostimulant followed by atomoxetine. Only few children and adolescents were prescribed products containing amphetamine derivatives and modafinil.

From 2000 to 2009 the number of prescribed DDDs/1000 inhabitants/day increased with 1557% for methylphenidate (from 10.69 to 177.16 DDD/1000/inhabitants/day), and for atomoxetine an increase in DDDs of 1274% was observed (from 0.74 to 10.17 DDD/1000/inhabitants/day).

Year	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Amphetamine derivatives	0.17	0.18	0.15	0.18	0.3	0.3	0.36	0.44	0.41	0.3
Atomoxetine	0	0	0	0	0	0	0.74	4.03	7.17	10.17
Methylphenidate	10.69	12.79	16.73	20.79	31.09	44.89	61.97	75.77	122.46	177.16
Modafinil	0	0.06	0.22	0.32	0.33	0.25	0.18	0.24	0.31	0.25

Table 1. Annual number of DDD/1000 inhabitants/day by psychostimulants for children from 0 to 17-years of age, (2000-2009)

Figure 2 displays the annual distribution of prescribed DDDs/1000 inhabitants/day for methylphenidate by gender. The majority, 80% of DDDs were prescribed in boys.

From 2000 to 2009 the use of psychostimulants in boys increased with a factor 16 (from 18.92 to 294.45) and in girls with a factor 32 (from 2.39 to 76.03 DDD/1000 inhabitants/day).

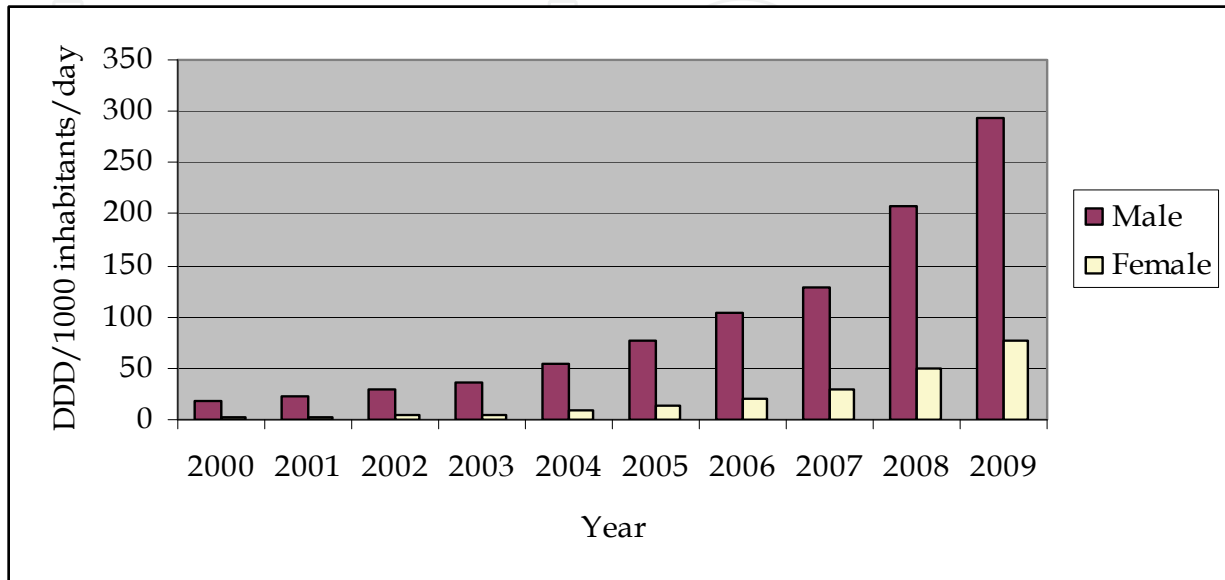


Fig. 2. Annual distribution of DDDs/1000 inhabitants/day for methylphenidate by gender, 2000 - 2009.

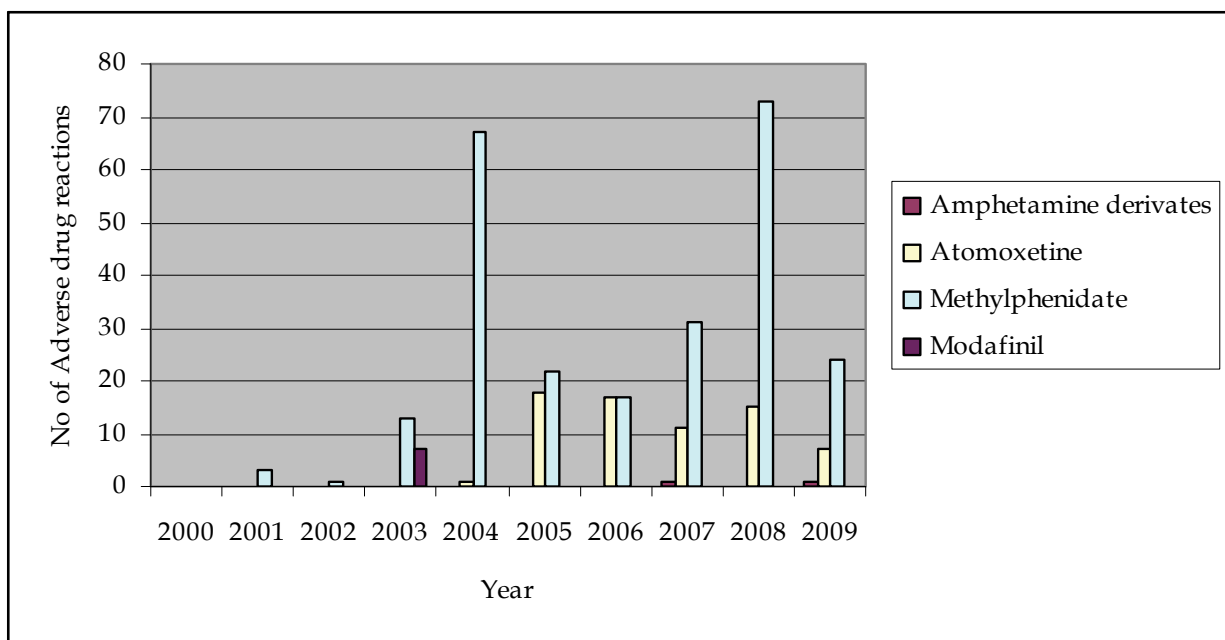


Fig. 3. Annual number of adverse drug reactions (ADRs) reported for psychostimulants in children, 2000 -2009

3.2 Reported adverse drug reactions for psychostimulants, 2000-2009

From 2000 to 2009 a total of 130 ADR reports including 329 ADRs were reported for psychostimulants for individuals from birth to 17 years of age. One half of ADRs were serious (N = 165), and no fatal cases were reported.

Figure 3 displays the annual number of reported ADRs by type of psychostimulant. The majority of the ADRs were reported for methylphenidate (N = 251) and atomoxetine (N = 69). Only few ADRs were reported for amphetamine derivatives (N = 2) and modafinil (N = 7).

3.2.1 Adverse drug reactions by type of reporter

The distribution of ADRs reported for psychostimulants by seriousness and type of reporter is displayed in table 2.

Seventy-six percent of ADRs were reported by physicians, 13% of ADRs by consumers and 10% of ADRs were reported by other health care professionals.

Type of reporter	Physician	OHCP*	Consumer	Total
Amphetamine derivatives	2(1)	0	0	2(1)
Atomoxetine	68(31)	0	1(0)	69(31)
Methylphenidate	190(71)	31(25)	30(30)	251(126)
Modafinil	7(7)	0	0	7(7)
Total	267(110)	31(25)	31(30)	329(165)

*: OHCP: other health care professionals

Table 2. Total number of adverse drug reactions (ADRs) distributed by type of reporter, medication and criteria of seriousness (in parentheses), 2000-2009

3.2.2 Adverse drug reactions by age and gender

Table 3 shows the distribution of ADRs reported for psychostimulants by age, gender and seriousness in the paediatric population, 2000-2009.

Totally, 80 % of ADRs were reported for boys and 20 % of ADRs for girls.

The largest number of ADRs (N = 75) were reported in 9 to 10-year-olds, followed by 16 to 17-year olds (N = 33) and 15 to 16-year olds (N = 32). Less than one percent of ADRs was reported in children up to 4 years of age.

The largest number of ADRs was reported in 9 to 10-year old boys (N = 68). In 16-17 -year olds girls, a larger number of ADRs (N = 20) were reported than in boys. In the age group a number of ADR reports were submitted without information about gender.

Approximately 50% of ADRs reported for both boys and girls were serious, however large variations were observed within age groups.

Table 4 shows the distribution of reported ADRs by gender and type of psychostimulant.

Age groups (Y)	Boys	Girls	NA*	Total
<1	0	0	0	0
1<2	0	0	0	0
2<3	0	0	0	0
3<4	0	0	0	0
4<5	1(0)	0	0	1(0)
5<6	6(2)	0	0	6(2)
6<7	18(13)	0	0	18(13)
7<8	10(5)	4(0)	3(0)	17(5)
8<9	21(7)	4(3)	0	25(10)
9<10	68(42)	7(0)	0	75(42)
10<11	14(1)	0	0	14(1)
11<12	20(6)	1(0)	0	21(6)
12<13	19(9)	1(0)	0	20(9)
13<14	23(16)	3(0)	0	26(16)
14<15	16(5)	5(3)	0	21(8)
15<16	24(10)	8(6)	0	32(16)
16<17	13(8)	20(15)	0	33(23)
17<18	18(10)	2(0)	0	20(10)
Total	271(134)	55(31)	3(0)	329(165)

*: ADR reports without information about gender.

Table 3. Total number of reported ADRs by age group and gender, serious ADRs in parentheses, 2000 - 2009

Medicines	Boys	Girls	NA	Total
Amphetamine derivatives	1(1)	1	0	2(1)
Atomoxetine	48(22)	21(9)	0	69(31)
Methylphenidate	221(110)	34(23)	3(0)	258(133)
Modafinil	7(7)	0	0	0
Total	271(134)	55(31)	3(0)	329(165)

Table 4. Distribution of total number of reported ADRs (N) by gender and medication (numbers of serious ADRs in parentheses), 2000 - 2009

Approximately 85% of ADRs were reported in boys, the majority for methylphenidate and atomoxetine. All ADRs reported for modafinil occurred in boys and they were all serious. For amphetamine derivatives one out of 2 reported ADRs occurred in boys.

Approximately 45% of ADRs occurring in boys reported for atomoxetine and methylphenidate were serious.

3.2.3 Adverse drug reactions by type and seriousness

Table 5 displays the characteristics of ADRs reported for psychostimulants by type, system organ class, seriousness and medication.

The largest share of reported ADRs was of the type “psychiatric disorders” (21 % of total ADRs) followed by the SOCs “general disorders” (19% of total ADRs) and “nervous system disorders” (16% of total ADRs).

For ADRs of the type nervous- and psychiatric disorders the share of serious ADRs ranged from approximately 50 to 70 % of total ADRs. For the medications atomoxetine and methylphenidate approximately 45% of all reported ADRs were serious, and for modafinil all reported ADRs were serious.

System Organ Class (SOC) (alphabetical order)	Amphetamine derivates	Methylphenidate	Atomoxetine	Modafinil	Total
Blood and lymphatic system disorders	0	2(2)	0	0	2(1)
Cardiac disorders	0	11(4)	6(3)	0	17(7)
Congenital, familial and genetic disorders	0	0	1(1)	0	1(1)
Ear and labyrinth disorders	0	1	0	0	1(0)
Endocrine disorders	0	0	2(2)	0	2(2)
Eye disorders	0	6	0	0	6(0)
Gastrointestinal disorders	1	22(12)	10(2)	1(1)	34(15)
General disorders	0	55(15)	5(2)	0	60(17)
Infections and infestations	0	0	1(1)	0	1(1)
Investigations	0	13(10)	7(3)	0	20(13)
Metabolism and nutrition disorders	0	7(1)	3	0	10(1)
Musculoskeletal disorders	0	6(3)	1	0	7(3)
Nervous system disorders	0	48(33)	4(3)	3(3)	55(39)
Psychiatric disorders	1(1)	48(32)	21(12)	3(3)	73(48)
Renal and urinary disorders	0	3(1)	1	0	4(1)
Reproductive system and breast disorders	0	1	0	0	1(0)
Respiratory disorders	0	4(2)	1	0	5(2)
Skin and subcutaneous tissue disorders	0	19(5)	3(1)	0	22(6)
Surgical and medical procedures	0	0	1	0	1(0)
Vascular disorders	0	5(2)	2(1)	0	7(3)
Total	2(1)	251(126)	69(31)	7(7)	329(165)

Table 5. Total number of reported ADRs (N) for children distributed by System Organ Class (SOC), medication (serious ADRs in parentheses), 2000-2009

Table 6 shows characteristics of ADRs reported for the SOC “psychiatric disorders” by type of medication and seriousness.

Adverse drug reaction (ADR) (alphabetical order)	Amphetamine derivates	Methylphenidate	Atomoxetine	Modafinil	Total
Affect lability	0	3(3)	0	0	3(3)
Agitation	0	2(1)	0	0	2(1)
Aggression	0	1	2	1(1)	4(1)
Anger	0	0	2(1)	0	2(1)
Animal phobia	0	1(1)	0	0	1(1)
Anxiety	0	6(2)	2(2)	0	8(4)
Asocial behaviour	0	1	0	0	1
Communication disorder	0	1(1)	0	0	1(1)
Confusional state	0	2(1)	0	0	2(1)
Depression	0	4(3)	4(1)	0	8(4)
Drug abuse	0	2(2)	0	0	2(2)
Emotional disorder	0	1	0	0	1
Euphoric mood	0	2(2)	0	0	2(2)
Food aversion	0	0	1(1)	0	1(1)
Hallucination	0	2(2)	0	1(1)	3(3)
Impulse-control disorder	0	0	1	0	1
Insomnia	0	3(2)	0	0	3(2)
Intentional self-injury	0	0	1(1)	0	1(1)
Mood swings	0	0	1(1)	0	1(1)
Nightmare	0	0	1	1(1)	2(1)
Obsessive thoughts	0	0	1(1)	0	1(1)
Psychotic disorder	1(1)	0	1(1)	0	2(2)
Personality change	0	1(1)	0	0	1(1)
Restlessness	0	1(1)	0	0	1(1)
Sleep disorder	0	7(5)	1(1)	0	8(6)
Social avoidant behaviour	0	3(3)	0	0	3(3)
Suicidal ideation	0	1(1)	3(2)	0	4(3)
Tic	0	2	0	0	2
Total	1(1)	46(33)	21(12)	3(3)	73(48)

Table 6. Total number of reported ADRs of the type “psychiatric disorders” by medication, and seriousness (in parentheses), 2000-2009.

Two-third of ADRs was reported for amphetamine derivates and methylphenidate, and the most frequently reported ADRs were anxiety, depression, and sleep disorders.

Table 7 displays the characteristics of ADRs reported for the SOC “nervous system disorders” by type of medication and seriousness.

Within this SOC approximately 90% of ADRs were reported for methylphenidate, the majority of reactions being dizziness, headache and dyskinesia.

Adverse drug reaction (ADR)	Amphetamine derivatives	Methylphenidate	Atomoxetine	Modafinil	Total
Akathisia	0	1(1)	0	0	1(1)
Atypical benign partial epilepsy	0	0	1(1)	0	1(1)
Burning sensation	0	2	0	0	2
Cataplexy	0	0	0	1(1)	1(1)
Crying	0	2(1)	0	0	1(1)
Demyelination	0	2(2)	0	0	2(2)
Disturbance in attention	0	1(1)	0	0	1(1)
Dizziness	0	8(5)	1(1)	1(1)	10(7)
Dyskinesia	0	2(2)	0	0	2(2)
Dystonia	0	1(1)	0	0	1(1)
Epilepsy	0	2(1)	0	0	2(1)
Headache	0	12(9)	2(1)	0	14(10)
Hemiparesis	0	2(2)	0	0	2(2)
Hypoaesthesia	0	3(2)	0	0	3(2)
Hypotonia	0	0	0	1(1)	1(1)
Loss of consciousness	0	2(1)	0	0	2(1)
Nystagmus	0	1	0	0	1
Psychomotor hyperactivity	0	2(1)	0	0	2(1)
Restless legs syndrome	0	1	0	0	1
Somnolence	0	1(1)	0	0	1(1)
Speech disorder	0	2(2)	0	0	2(2)
Syncope	0	1(1)	0	0	1(1)
Total	0	48(33)	4(3)	3(3)	55(39)

Table 7. Total reported ADRs of the type “nervous system disorders” by medication, and seriousness (in parentheses), 2000-2009.

Table 8 shows the characteristics of ADRs reported for the SOC “general disorders and administration site conditions” by type of medication and seriousness.

Within this SOC almost all ADRs were reported for amphetamine derivatives, and no ADRs were reported for atomoxetine and modafinil. Many ADRs relating to the efficacy of the medications were reported.

A large number of ADRs within the SOC “gastrointestinal disorders” were also reported (see table 5). These reactions were predominantly reported for methylphenidate, and were of the type’s abdominal pain, diarrhoea and dry mouth (data not shown).

4. Discussion

This is the first study from a national ADR database that has examined the characteristics and occurrence of ADRs from use of psychostimulants in the paediatric population. The study showed that over a decade the prescribing of psychostimulants in the Danish paediatric population has increased dramatically, and that methylphenidate was the predominant psychostimulant. Two third of ADRs were reported by physicians, and approximately 80 % of all ADRs were reported for boys from above 5 years of age. The

Adverse drug reaction (ADR)	Amphetamine derivates	Methylphenidate	Atomoxetine	Modafinil	Total
Asthenia	0	2(2)	0	0	2(2)
Chest pain	0	5(2)	0	0	5(2)
Chills	0	1	0	0	1
Drug effect decreased	0	17(1)	0	0	19(1)
Drug effect increased	0	1	0	0	1
Drug ineffective	0	14(2)	0	0	14(2)
Drug interaction	0	1(1)	1(1)	0	2(2)
Face oedema	0	1	0	0	1
Feeling hot	0	1	0	0	1
Fatigue	0	7(6)	3(1)	0	10(7)
Irritability	0	0	1	0	1
Pain	0	1(1)	0	0	1(1)
Pyrexia	0	1	0	0	1
Therapeutic response unexpected with drug substitution	0	3	0	0	3(0)
Total	0	55(15)	5(2)	0	60(17)

Table 8. Total number of reported adverse drug reactions of the type “general disorders and administration site conditions” by medication, and seriousness (in parentheses), 2000-2009.

largest shares of reported ADRs was of the type “general disorders and administration conditions”; “psychiatric and nervous system disorders”.

From 2000 to 2009 large increases in number of prescribed dosages and users were observed, and these findings were in line with results from other countries (Asheim et al. 2007; Kalverdijk et al., 2008; Trip et al., 2009; Schubert et al, 2010; Zuvekas et al., 2006). The majority of users were boys; but we found a large increase in use of psychostimulants among girls, and this pattern was expected (Hodgkins et al, 2011). From 2000 to 2004 the use of psychostimulants were at a stable level, however from 2005 the use has increased dramatically. Explanations of this increase could be the marketing pressure, change in diagnostic criteria and the development of new types of psychostimulants such as atomoxetine and modafinil for treatment of ADHD. In the same period of time the pharmaceutical companies have marketed long-term release formulations of methylphenidate for school use (van den Ban et al, 2010). Use of psychostimulants in Danish children has increased more over the last decade than in other countries; however this may be explained by the fact that use of psychostimulants in Denmark was lower at the beginning of the period than in other countries.

This is a descriptive study, and therefore we cannot conclude whether ADRs are reported more commonly for methylphenidate than the other products, neither whether girls experience more ADRs than boys. The number of ADR reports does not reflect the use of psychostimulants, and the question is where in the lifecycle of medicinal products ADRs are reported. However, since the issue is long-term treatment of children and adolescents ADR signals are extremely important. A high number of reports on decreased drug effect and/or ineffective drugs from use of methylphenidate were reported. Whether this signal is due to problems with the quality of generic products or that real life is different from the testing conditions (Hansen, 1992).

The majority of reports were submitted by physicians, however, we would also have expected a larger number of reports from parents, as they should be concerned about administration

medications to their children, especially medications for long-term use, where information about long-term effects are limited. The explanation of the large number of reports from physicians could be that the parents have become aware of the ADRs, and asked their physician to report them. To increase knowledge about ADRs from long term use of psychostimulants the number of reports submitted to the Danish Medicines Agency and probably other medicines agencies should be increased and the regulatory authorities must focus on increasing ADR reporting rates from both health care professionals and consumers.

An empirical study showed that the licensing material for methylphenidate provided minimal evidence on efficacy and safety in children (Aagaard et al. 2009b), and no information about long-term safety aspects was reported. Spontaneous reports are an important source of information about new and previously unrecognized ADRs, and the value of spontaneous reporting schemes lies in their ability to act as hypothesis-generating signals. Due to the low number of ADRs reported for psychostimulants in Denmark it is necessary to conduct further studies to explore data about rare and serious ADRs in larger databases, such as the EU database EudraVigilance and the international WHO-ADR database Vigibase (Aagaard et al, 2010). These databases contain large amounts of data submitted from European and global populations, and are therefore suitable for studying specific ADRs or new signals.

The strength of our study is that data comprised psychostimulant prescriptions and all ADRs reported in one country over a decade. The purpose was to analyse information reported to the Danish ADR database on ADRs in the paediatric population from use of psychostimulants in the treatment of ADHD, and not to calculate the incidence of ADRs in this population as this is not feasible in material based on spontaneous reporting.

A major limitation to this study is that we do not know to which extent the causality of these ADRs can be confirmed, and this has implications for the interpretation of the results. Spontaneous reporting systems suffer from different barriers, such as incomplete recognition of ADRs, administrative barriers to reporting, and low data quality, all of which may result in the underreporting of important serious and rare events. Nonetheless, the study provides information on reported ADRs, and this information contributes to broadening the knowledge base on psychostimulants safety.

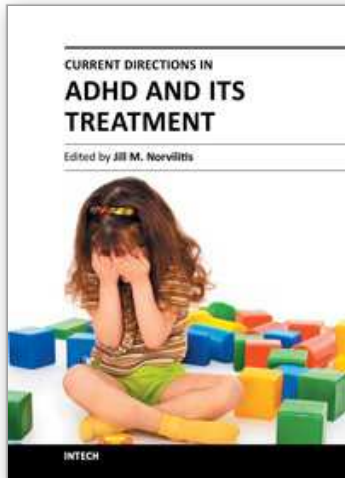
5. Conclusion

In Denmark, a large increase in the use of psychostimulants in the paediatric population has been observed. The large number of serious reported ADRs indicate that psychostimulants should be prescribed with caution of that greater care is needed in relation to prescribing these medications for children. The Danish Medicines Agency should monitor prescribing patterns more tightly to identify potential risks in the paediatric population in relation to the evolving utilisation of use of psychostimulants among children and adolescents and related risks.

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Current Directions in ADHD and Its Treatment

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The treatment of Attention Deficit Hyperactivity Disorder is a matter of ongoing research and debate, with considerable data supporting both psychopharmacological and behavioral approaches. Researchers continue to search for new interventions to be used in conjunction with or in place of the more traditional approaches. These interventions run the gamut from social skills training to cognitive behavioral interventions to meditation to neuropsychologically-based techniques. The goal of this volume is to explore the state-of-the-art in considerations in the treatment of ADHD around the world. This broad survey covers issues related to comorbidity that affect the treatment choices that are made, the effects of psychopharmacology, and non-medication treatments, with a special section devoted to the controversial new treatment, neurofeedback. There is something in this volume for everyone interested in the treatment of ADHD, from students examining the topic for the first time to researchers and practitioners looking for inspiration for new research questions or potential interventions.

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