REVIEW

The occurrence of adverse drug reactions reported for attention deficit hyperactivity disorder (ADHD) medications in the pediatric population: a qualitative review of empirical studies

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Background: To review empirical studies of adverse drug reactions (ADRs) reported to be associated with the use of medications generally licensed for treatment of attention deficit hyperactivity disorder (ADHD) symptoms in the pediatric population.

Methods: PubMed, Embase, and PsycINFO® databases were searched from origin until June 2011. Studies reporting ADRs from amphetamine derivates, atomoxetine, methylphenidate, and modafinil in children from birth to age 17 were included. Information about ADR reporting rates, age and gender of the child, type, and seriousness of ADRs, setting, study design, ADR assessors, authors, and funding sources were extracted.

Results: The review identified 43 studies reporting ADRs associated with medicines for treatment of ADHD in clinical studies covering approximately 7000 children, the majority of 6- to 12-year-old boys, and particularly in the United States of America (USA). The most frequently reported ADRs were decrease in appetite, gastrointestinal pain, and headache. There were wide variations in reported ADR occurrence between studies of similar design, setting, included population, and type of medication. Reported ADRs were primarily assessed by the children/their parents, and very few ADRs were rated as being serious. A large number of children dropped out of studies due to serious ADRs, and therefore, the actual number of serious ADRs from use of psychostimulants is probably higher. A large number of studies were conducted by the same groups of authors and sponsored by the pharmaceutical companies manufacturing the respective medications.

Conclusion: Reported ADRs from use of psychostimulants in children were found in clinical trials of short duration. Since ADHD medications are prescribed for long-term treatment, there is a need for long-term safety studies. The pharmaceutical companies should make all information about ADRs reported for these medications accessible to the public, and further studies are needed on the impact of the link between researchers and the manufacturers of the respective products.

Keywords: adverse drug reactions, attention deficit hyperactivity disorder, children, pharmacovigilance

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Introduction

Psychostimulants, such as amphetamine derivates, methylphenidate, and modafinil, as well as the nonstimulant medication atomoxetine, are considered first-line medication treatment of attention deficit hyperactivity disorder (ADHD) symptoms in the pediatric population.[1] Case reports on serious cardiovascular adverse drug reactions (ADRs), sudden death, and psychiatric disorders led regulatory agencies to warn against the use

of methylphenidate in the pediatric population in 2006 and 2007.[2,3] In 2006, warnings were also linked to atomoxetine use due to reports of hepatotoxicity and suicidal thoughts in children.[4] Concern has been raised about ADRs from long-term treatment with ADHD medications, such as psychosis, sensitization, dependency, and withdrawal reactions.[1] The issue of appropriate warnings about possible ADRs to the use of methylphenidate and other ADHD medications is ever more important as usage continues to increase rapidly in many countries: an increase in the number of treated patients has been observed, as well as an increase in the average dispensed daily dose of psychostimulants.[5]

The use of psychostimulants, particularly methylphenidate, to treat ADHD symptoms in children has increased rapidly since the 1990s. Studies have shown that the prevalence of psychostimulant use in children in the Netherlands increased eight times from 1996 to 2006,[6] and in Germany, prescription rates of methylphenidate increased by 96% from 2000 to 2007.[7] From 1994 to 2004, the prevalence of psychostimulant use in Norwegian children increased five times,[8] while the prevalence of stimulant medication increased ten times in American children from 1987 to 1996.[9] Previous meta-analyses and reviews that evaluated the short-term efficacy of psychostimulants on ADHD symptoms in children concluded that psychostimulants are more effective than placebo with respect to treating disturbed attention and impulsivity.[1,10] Several articles have reported information about the safety of methylphenidate and other psychostimulants in clinical studies,[11] but to the current reviewers' knowledge no articles have systematically reviewed the occurrence of ADRs following the use of ADHD medications in the pediatric population.

The objective of this study is to review published empirical studies on the occurrence of adverse drug reactions (ADRs) associated with the use of medications generally licensed for treatment of ADHD symptoms in the pediatric population.

Methods
Literature search
A literature search was performed in PubMed, Embase, and PsycINFO® (whole databases without language restriction) using the search terms "atomoxetine" (ATC group N06BA09), "methylphenidate" (ATC group N06BA04), "modafinil" (ATC group N06BA07), "amphetamine" (ATC group N06BA02), "psychostimulants," and "nonstimulants" combined with any of the following: "adverse drug reaction," "side effect," and "adverse event." Reference

lists of identified articles were also screened for additional potentially relevant articles. For further details of the search strategy, please see Appendix 1. Literature searches were updated until September 2011.

Study selection
Using article titles as the selection basis, the first author retrieved and screened the abstracts to identify studies relevant to the study objective. Potentially relevant articles were retrieved in full text and screened for inclusion. To be considered relevant for this review, articles had to be peer reviewed and report ADRs in children in the age group 0–17 years of age associated with the use of psychostimulants.

Psychostimulants were specified as amphetamine derivates, methylphenidate, and modafinil, and nonstimulants as atomoxetine. Articles reporting ADRs from psychostimulants in mixed populations of children and adults were excluded if age-related ADR occurrence was not specified. Articles were excluded if they did not report data on ADR occurrence that made it possible to calculate rates. Hence, case reports, letters, commentaries, interim analyses, meta-analyses, and review articles were excluded. Further, articles reporting unintended events not classified as ADRs and articles on misuse were excluded, although reference lists of these studies were searched for relevant studies.

Data extraction
Data from included articles were extracted using a standard form, one for each article. The following information was recorded: authors, publication year, country, study design, dosage, comparator, monitoring period (weeks), size of study population, age and gender of included population, and ADR reporting rates in percentage. ADR reporting rates were indicated as reported in the original papers. In placebo-controlled studies, information about ADR reporting rates for placebo was also extracted. Information about who had assessed the ADRs, reported ADRs classified as being serious by the respective authors, and funding sources were also recorded. The first author extracted data, while the second author controlled and verified all cases.

Results
A total of 137 potentially relevant references were identified during the database searches and reference screenings. An overview of the review process and reasons for exclusion are displayed in Figure 1. Sixty-eight studies were excluded after screening abstracts. Sixty-nine studies were retrieved for full text review. Of these studies, four were later excluded as they reported mixed
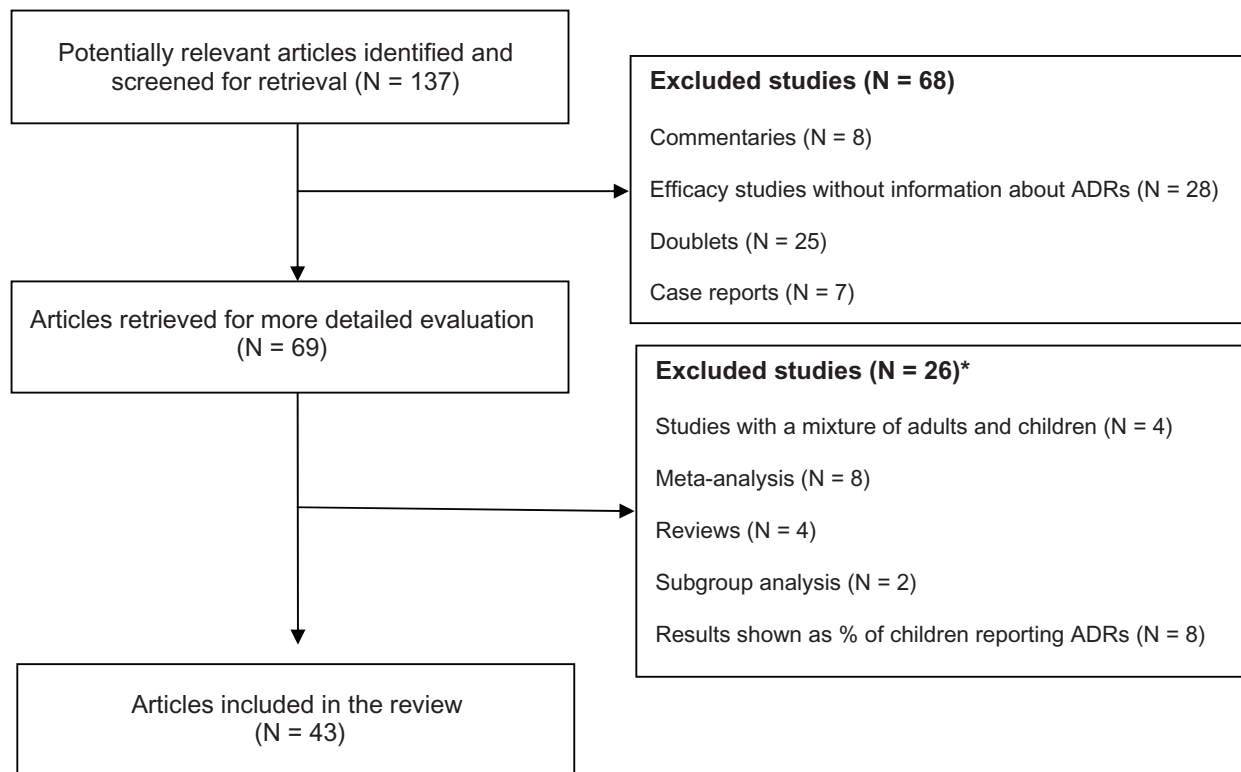
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┌─────────────────────────────────────┐
│ Potentially relevant articles        │
│ identified and screened for          │
│ retrieval (N = 137)                  │
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Excluded studies (N = 68)

Commentaries (N = 8)

Efficacy studies without information about ADRs (N = 28)

Doublets (N = 25)

Case reports (N = 7)

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│ Articles retrieved for more detailed │
│ evaluation (N = 69)                  │
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Excluded studies (N = 26)*

Studies with a mixture of adults and children (N = 4)

Meta-analysis (N = 8)

Reviews (N = 4)

Subgroup analysis (N = 2)

Results shown as % of children reporting ADRs (N = 8)

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┌─────────────────────────────────────┐
│ Articles included in the review      │
│ (N = 43)                             │
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Figure 1 Decision tree of the review process.
Note: *An overview of excluded studies is shown in Appendix 2.
Abbreviation: ADRs, adverse drug reactions.

data on children and adults that could not be separated. Eight meta-analyses and four reviews of efficacy were excluded as they reported information from studies already included. Also excluded were two studies reporting data from a subgroup analysis of already included studies, and nine studies reporting ADRs as percent of children reporting an ADR.

Eventually 43 articles reporting ADRs from psychostimulants in the pediatric population were included. Table 1 displays an overview of the study characteristics of included articles. The majority of studies were conducted in the United States of America (USA), the remaining in Australia, Canada, Europe, Iran, and Latin America. Atomoxetine studies were published in the period from 2001 to 2009; amphetamine studies from 1997 to 2007; methylphenidate studies from 1997 to 2009; and modafinil studies from 2005 to 2009.

Design and setting
Information about ADRs was reported in clinical studies using different designs, ie, randomized parallel group studies (N = 28);[12–15,17–19,22,23,28,31,32,34–36,40,42–47,48–54] randomized crossover studies (N = 6);[16,23,25,27,30,39] and open-label designs (N = 9).[20,26,29,33,37,38,41,50] The majority of studies were conducted in naturalistic settings at home and at school

(N = 38);[12,13,15–22,24,26,28–30,31–43,44–54] five articles reported ADRs from children participating in laboratory school protocols,[14,23,25,27,30] in which classroom sessions were organized in cycles to include 12 hours of observation. This design consisted of daily schedules of alternating classroom, meals/snacks, recess, and research activities scheduled at specific times during the day. The largest number of studies (N = 21)[31–47] concerned atomoxetine; followed by methylphenidate (N = 14;[17–30] modafinil (N = 7);[48–54] and amphetamine (N = 5).[12–16]

Dosage and comparator
The tested dosages varied from 10 to 70 mg/day in amphetamine studies; from 5 to 72 mg/day in methylphenidate studies; from 10 to 90 mg/day in atomoxetine studies; and from 100 to 425 mg/day in modafinil studies. Placebo was used as a comparator drug in the majority of studies (N = 28), while an active comparator, was administered in nine studies. Seven open-label studies did not include a control group.

Treatment period
Treatment duration varied from 1 to 32 weeks across studies. Treatment duration varied from 2 to 4 weeks in amphetamine

Table 1 Characteristics of included studies by country, design, study population, and funding

Studies (chronological order)	Country	Design	Setting	Dosage (mg/day)	Comparator
Amphetamine					
Biederman et al[12]	USA	R parallel	Naturalistic	30–70	Placebo
Spencer et al[13]	USA	R parallel	Naturalistic	10–40	Placebo
Wigal et al[14]	USA	R parallel	Laboratory	10–30	Atomoxetine
Biederman et al[15]	USA	R parallel	Naturalistic	10–30	Placebo
Efron et al[16]	AU	R crossover	Naturalistic	0.15 mg/kg	MPH
Total/Range					
Methylphenidate					
Arabgol et al[17]	IR	R parallel	Naturalistic	20–50	Reboxetine
Maayan et al[20]	USA	Open label	Naturalistic	10–30	NR
Amiri et al[49]	IR	R parallel	Naturalistic	20–30	Modafinil
Findling et al[18]	USA	R parallel	Naturalistic	10–54	Placebo
Newcorn et al[19]	USA	R parallel	Naturalistic	18–54	Atomoxetine
Findling et al[21]	Various	R parallel	Naturalistic	10–60	Placebo
Greenhill et al[22]	USA	R parallel	Naturalistic	5–30	Placebo
McGough et al[23]	USA	R crossover	Laboratory	10–27	Placebo
Gau et al[24]	TW	R open label	Naturalistic	10–40	None
Silva et al[25]	USA	R crossover	Laboratory	20–40	Placebo
Kemner et al[26]	USA	R open label	Naturalistic	18–72	Atomoxetine
Swanson et al[27]	USA	R crossover	Laboratory	18–60	Placebo
Biederman et al[28]	USA/CA	R parallel	Naturalistic	10–40	Placebo
Kratochvil et al[29]	USA/CA	R open label	Naturalistic	5–60	None
Pelham et al[30]	USA	R crossover	Lab/Nat	5–54	Placebo
Efron et al[16]	AU	R crossover	Naturalistic	0.3 mg/kg	Amphetamine
Total/Range					
Atomoxetine					
Svanborg et al[31]	SE	R parallel	Naturalistic	80	Placebo
Block et al[32]	USA	R parallel	Naturalistic	0.47–1.81 mg/kg	Placebo
Tamayo et al[33]	Various	Open label	Naturalistic	35–120	None
Newcorn et al[19]	USA	R parallel	Naturalistic	0.8–1.8 mg/kg	MPH/Placebo
Bangs et al[34]	US	R parallel	Naturalistic	1.2–1.8 mg/kg	Placebo
Geller et al[35]	USA	R parallel	Naturalistic	0.8–1.8 mg/kg	Placebo
Gau et al[36]	TW	R parallel	Naturalistic	16–99	Placebo
Kratochvil et al[37]	USA	Open label	Naturalistic	0.5–1.8 mg/kg	None
Prasad et al[38]	UK	R open label	Naturalistic	0.5–1.8 mg/kg	SCT
Arnold et al[39]	USA	R cross over	Naturalistic	2.5–40	Placebo
Newcorn et al[40]	USA	R parallel	Naturalistic	1.2–1.8 mg/kg	None
Wigal et al[14]	USA	R parallel	Laboratory	10–60	Amphetamine
Allen et al[42]	USA	R parallel	Naturalistic	0.5–1.5 mg/kg	Placebo
Kemner et al[26]	USA	R open label	Naturalistic	10–80	MPH
Escobar et al[41]	ES	Open label	Naturalistic	0.5–1.8 mg/kg	None
Kelsey et al[43]	USA	R parallel	Naturalistic	0.8–1.2 mg/kg	Placebo
Biederman et al[44]	USA	R parallel	Naturalistic	2 mg/kg	Placebo
Michelson et al[45]	USA	R parallel	Naturalistic	0.5–1.0 mg/kg	Placebo
Kratochvil et al[29]	USA/CA	R open label	Naturalistic	0.2–2.0 mg/kg	None
Spencer et al[46]	USA	R parallel	Naturalistic	90	Placebo
Michelson et al[47]	USA	R parallel	Naturalistic	0.5–1.8 mg/kg	Placebo
Total/Range					
Modafinil					
Kahbazi et al[48]	IR	R parallel	Naturalistic	200–300	Placebo
Amiri et al[49]	IR	R parallel	Naturalistic	200–300	MPH
Boellner et al[50]	USA	Open label	Naturalistic	100–400	None
Wigal et al[51]	USA	R parallel	Naturalistic	170–425	Placebo
Biederman et al[52]	USA	R parallel	Naturalistic	300–400	Placebo
Greenhill et al[53]	USA	R parallel	Naturalistic	170–425	Placebo
Biederman et al[54]	USA	R parallel	Naturalistic	170–425	Placebo
Total/Range					
Total all studies					

Treatment weeks (N)	Patients included (N)	Patients completed (N)	Age (y)	% Male	Type of assessor	Funding
4	290	218	6–12	69	Parent	Industry
4	335	308	6–17	69	Parent	Industry
3	102	93	6–12	75	Parent	Industry
3	374	336	6–12	80	Parent	Industry
2	125	121	5–15	91	Teacher/Parent	Nonindustry
2–4	1226	1076	5–17	69–91		
6	16	12	7–16	66	Teacher/Parent	Nonindustry
4	14	11	4–5	82	Self	NR
6	32	30	6–15	80	Teacher/Parent	Nonindustry
7	189	137	6–12	65	Self	Industry
6	220	180	6–16	71	Parent	Industry
3	272	240	6–12	80	Self	Industry
7	53	48	6–17	59	Self	Industry
5	42	41	6–12	73	Self	Industry
4	64	64	6–15	91	Self	Industry
<1	54	53	6–12	70	Parent	Industry
3	891	850	6–12	74	Parent	Industry
NR	184	181	6–12	74	Self/Parent	Industry
2	65	61	6–14	80	Parent	Industry
10	44	25	7–15	100	Parent	Industry
3	70	68	6–12	NR	Teacher/Parent	Industry
2	125	121	5–15	91	Teacher/Parent	Nonindustry
1–10	2303	2092	4–17	59–100		
10	49	49	7–15	80	Self	Industry
6	288	140	6–12	73	Parent	Industry
10–11	1198	947	6–17	76	Self	Industry
6	222	186	6–16	78	Parent	Industry
9	72	71	12–17	72	Self	Industry
12	87	66	8–17	62	Self	Industry
6	72	72	6–16	90	Parent	Industry
8	22	20	5–6	86	Parent	Industry
10	104	78	7–15	89	Self	Industry
12	16	15	5–15	75	Self	Industry
32	229	160	6–16	72	Parent	Industry
3	101	97	6–12	76	Parent	Industry
18	76	74	7–17	92	Self	Industry
3	499	473	6–12	74	Parent	Industry
10	36	36	6–15	89	Parent	Industry
8	133	107	6–12	71	Parent	Industry
9	31	31	7–13	0	Self	Industry
6	85	84	6–16	71	Parent	Industry
10	184	118	7–15	91	Parent	Industry
12	129	127	7–13	76	Parent	Industry
8	213	176	8–17	71	Self	Industry
3–32	3846	3127	5–17	0–91		
6	24	23	6–15	76	Teacher/Parent	Nonindustry
6	32	30	6–15	78	Teacher/Parent	Nonindustry
8	220	166	6–14	72	Parent	Industry
9	423	411	10.2	72	Parent/Self	Industry
4	197	175	6–14	75	Parent	Industry
9	133	100	6–16	73	Parent/Self	Industry
9	164	97	6–17	69	Parent	Industry
4–9	1137	949	6–17	69–75		
	8512	7244	–	–		

Abbreviations: AU, Australia; CA, Canada; IR, Iran; lab, laboratory; MPH, methylphenidate; nat, naturalistic; NR, not reported; R, randomized; ES, Spain; SCT, standard current therapy; SE, Sweden; TW, Taiwan; USA, United States of America.

studies; from 1 to 10 weeks in methylphenidate studies; from 3 to 32 weeks in atomoxetine studies; and from 4 to 9 weeks in modafinil studies.

Population

A total of 8512 children were included in the clinical studies, of which 7244 children completed treatment: amphetamine (1076); methylphenidate (2092); atomoxetine (3127); and modafinil (949). The reasons for noncompletion were many, but lack of efficacy and the appearance of ADRs were the most common. The ages of the included children varied from 4 to 17 years (median 6–12 years), and the share of male patients in the studies varied from 0 to 100% (median 69%).

Type of assessor

Parents rated information about ADRs in 20 studies,[12–15,19,25–28, 32,35–36,40–46,48,50,52] 54 patients in 15 studies,[18,20–24,31,33–35,38–39,42,44,47] and a combination of teacher/parent (five studies),[16–17,30,48–49] and patient/parent (three studies).[27,49,51] The articles specified only limited information about applied ADR scales and the classification systems used.

Funding source

In almost all studies the funding source was the manufacturer of the respective medications, and only four studies were publicly funded. Additionally, a large number of the studies were conducted by the same groups of authors who declared conflicts of interest. The majority of the authors received contributions from the pharmaceutical companies producing the medications in return for activities, such as providing scientific advice and making oral and poster presentations at scientific meetings.

ADRs by type and occurrence

Tables 2–5 display the ADR reporting rates listed in the included studies for each type of psychostimulant. ADRs of similar type and wording were aggregated in a common category in order to clarify data presentation. The aggregated categories were: weight changes (changes in weight, weight decreased, weight increased, decrease in weight); gastrointestinal pain (abdominal pain, upper abdominal pain, gastrointestinal pain); anxiety (anxiety, anxiousness); influenza (influenza, flu syndrome); tics (tics, motor tics, facial tics); blood pressure changes (diastolic blood pressure, changes in blood pressure); sleeping problems (awake during the night, difficulty falling asleep, sleep disturbance, delayed onset of sleep); changes in heart rate (racing heart,

changes in heart rate). Thirty-one categories of ADRs were reported for amphetamine derivates (Table 2); 65 categories for methylphenidate formulations (Table 3); 55 categories for atomoxetine (Table 4); and 38 categories for modafinil (Table 5). The following ADRs were most frequently reported for all four psychostimulants: decrease in appetite, gastrointestinal pain, and headache.

ADRs by seriousness

The majority of reported ADRs were categorized by the authors/investigators as nonserious. Table 6 shows information about the categories of serious ADRs reported in the clinical studies. Serious cases included aggression (amphetamine, methylphenidate);[16] anxiety (amphetamine);[16] emotional disturbances (amphetamine);[14,15] insomnia

Table 2 Adverse drug reaction reporting rates (%) for amphetamine derivates by category and study

Reference number	12	13	14	15	16	Range	Placebo (range)
Adverse drug reaction							
Accidental injury	–	5	–	–	–	5	5
Anorexia	–	25	17	22	–	17–25	2
Anxiety	–	–	–	–	68	68	–
Appetite decrease	39	–	28	–	59	28–59	4–5
Cough	1	–	–	5	–	1–5	5
Crying	–	–	–	–	76	76	–
Daydreams	–	–	–	–	62	62	–
Dizziness	5	–	6	–	32	5–32	–
Dry mouth	5	–	–	–	–	5	–
Emotional disturbance	–	–	–	–	59	59	–
Emotional lability	–	5	–	9	–	5–9	2
Fatigue	–	–	2	–	–	2	–
Fingernail biting	–	–	–	–	40	40	–
Gastrointestinal pain	12	11	19	14	–	11–19	5–10
Headache	12	19	15	18	30	12–30	10–21
Insomnia	19	20	28	17	–	17–28	2–8
Irritability	10	–	7	–	82	7–82	–
Nasal congestion	1	–	–	–	–	1	–
Nasopharyngitis	5	–	–	–	–	5	–
Nausea	6	–	7	5	–	5–7	3
Nervousness	–	6	–	6	–	6	2
Nightmares	–	–	–	–	28	28	–
Pharyngitis	–	7	–	7	–	7	5–20
Sleeping problems	–	–	–	–	70	70	–
Social withdrawal	–	–	–	–	64	64	–
Somnolence	–	–	5	–	–	5	–
Stomachache	–	–	–	–	40	40	–
Tics	–	–	–	–	26	26	–
Unusually happy	–	–	–	–	26	26	–
Vomiting	9	–	5	7	–	5–9	4
Weight changes	9	8	6	–	–	6–9	1

Table 3 Adverse drug reaction reporting rates (%) for methylphendiate by category and study

Reference number	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	49	Range	Placebo (range)
Adverse drug reaction																		
Abnormal behavior	–	–	–	–	–	3	–	–	–	–	1	–	–	5	–	–	1–5	4
Accidental injury	–	–	–	–	–	–	–	–	–	–	–	3	–	13	3	–	3–13	3
Affect lability	–	–	3	–	–	–	4	–	–	–	–	–	–	–	–	–	3–4	–
Aggression	–	–	–	–	–	–	–	–	–	–	1	–	–	–	–	–	1	–
Anorexia	–	–	3	–	–	5	4	3	–	8	–	3	3	15	–	–	3–15	1–2
Anxiety	61	–	–	–	–	–	–	–	25	–	–	–	–	–	–	5	5–61	1
Appetite decrease	56	31	19	17	28	3	30	–	53	9	6	3	–	–	–	31	3–56	5–9
Asthenia	–	–	–	–	–	–	–	–	–	–	–	–	–	3	–	–	3	–
Blood pressure changes	–	–	–	18	–	–	–	3	–	–	–	–	–	–	–	–	3–18	–
Changes in heart rate	–	–	–	12	–	–	–	–	–	–	–	–	–	–	–	–	12	–
Changes in pulse rate	–	–	–	–	–	–	–	–	–	1	–	–	–	–	–	–	1	–
Chest pain	–	6	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6	–
Cough	–	–	–	4	–	2	–	–	–	–	–	–	–	5	–	–	2–5	4
Crying	71	–	–	–	–	–	–	–	38	–	2	–	–	–	–	–	2–71	–
Daydreams	62	–	–	–	–	–	–	–	30	–	–	–	–	–	–	–	30–62	–
Depression	–	–	–	–	–	–	–	–	–	–	–	–	–	5	–	–	5	–
Diarrhea	–	–	–	–	–	4	–	–	–	–	–	–	–	3	2	–	2–4	1–2
Dizziness	30	13	–	–	–	–	–	–	13	–	1	–	–	–	2	–	1–30	4
Dry mouth	–	–	–	–	–	–	–	–	24	–	–	–	–	–	–	12	12–24	–
Dyspepsia	–	–	–	–	–	–	8	–	–	–	–	–	–	5	–	–	5–8	–
Emotional disturbance	56	–	–	–	–	–	–	–	–	–	1	–	–	–	–	–	1–56	–
Emotional lability	–	–	–	–	8	–	–	–	–	–	–	–	–	5	–	7	5–8	–
Euphoria	–	–	–	–	–	–	–	–	9	–	–	–	–	–	–	–	9	–
Eye redness	–	–	–	–	4	–	–	–	–	–	–	–	–	–	–	–	4	–
Eye twitching	–	–	–	–	4	–	–	–	–	–	–	–	–	–	–	–	4	–
Fatigue	–	–	–	2	4	–	4	–	–	4	1	–	–	–	–	–	1–4	4
Fever	–	–	–	–	4	2	–	–	–	–	–	–	–	10	–	–	2–10	7
Fingerrnail biting	45	–	–	–	–	–	–	–	22	–	–	–	–	–	–	–	22–45	–
Gastroenteritis	–	–	–	–	–	–	4	–	–	–	–	5	–	–	–	–	4–5	4
Gastrointestinal pain	–	–	–	10	12	10	19	–	–	6	4	4	–	18	15	8	4–19	2–13
Headache	24	–	–	11	4	16	25	4	28	2	4	3	2	33	14	8	2–33	3–23
Hyperkinesia	–	–	–	–	–	–	–	–	–	–	–	–	–	5	–	–	5	–
Increases in ALT/AST	–	–	–	–	–	–	–	–	–	–	–	5	–	–	–	–	5	–
Infection	–	–	–	–	4	–	–	–	–	–	–	2	–	8	–	–	2–8	1–4
Influenza	–	–	–	–	–	4	–	–	–	–	–	–	–	10	–	–	4–10	–
Insomnia	–	19	8	27	–	4	8	–	44	4	7	2	3	18	–	–	2–44	3–10
Irritability	80	6	–	6	4	3	4	–	16	–	1	1	–	–	–	7	1–80	2–6
Lymphadenopathy	–	–	–	–	–	–	–	3	–	–	–	–	–	–	–	–	3	–
Mood alteration	–	–	–	–	–	–	–	–	34	–	1	7	–	–	–	–	1–34	–
Nasal congestion	–	–	3	–	4	–	–	–	–	–	–	–	–	–	–	–	3–4	1
Nasopharyngitis	–	–	4	–	–	4	9	1	–	–	–	–	–	–	–	–	1–9	2–7
Nausea	–	–	8	6	–	–	11	4	–	–	1	–	–	5	–	5	1–11	2–6
Nervousness	–	–	–	–	–	–	–	–	–	–	–	4	–	10	–	–	4–10	–
Nightmare	21	–	–	–	–	–	–	–	16	–	–	–	–	–	–	–	16–21	–
Otitis media	–	–	–	–	–	4	–	–	–	–	–	–	–	–	–	–	4	2
Pain	–	–	–	–	–	–	–	–	–	–	–	–	–	3	–	–	3	–
Pallor	–	13	–	–	–	–	–	–	–	–	–	–	–	–	–	–	13	–
Palpitation	–	–	–	–	–	–	–	–	–	–	–	–	–	5	–	–	5	–
Pharyngeal pain	–	–	–	–	–	–	–	3	–	–	–	–	–	–	–	–	3	–
Pharyngitis	–	–	–	–	3	–	–	–	–	–	–	–	–	8	2	–	2–8	3
Rash	–	–	–	–	–	–	–	1	–	–	–	–	–	8	–	–	1–8	4
Respiratory tract infection	–	–	–	–	–	3	9	–	–	–	–	–	–	–	4	–	3–9	2–6
Rhinitis	–	–	–	–	–	–	–	3	–	–	–	–	–	20	2	–	2–20	–
Sensitivity	–	–	–	–	4	–	–	–	–	–	–	–	–	–	–	–	4	–
Sleeping problems	64	–	–	–	12	–	–	–	–	–	–	–	–	–	–	9	9–64	–

(*Continued*)

Table 3 (*Continued*)

Reference number	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	49	Range	Placebo (range)
Socially withdrawn	59	–	–	–	–	–	–	–	27	–	–	–	–	–	–	–	27–59	–
Somnolence	–	–	–	2	–	–	–	–	–	–	1	–	–	–	–	–	1–2	–
Stomachache	32	–	–	–	–	–	4	–	28	–	–	–	–	–	–	–	4–32	–
Tachycardia	–	–	–	–	–	–	–	–	–	–	–	–	–	5	–	–	5	–
Tics	28	–	1	–	–	–	–	–	13	–	–	–	–	–	–	–	1–28	4
Twitching	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3	–	3	–
Unusually happy	28	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	28	–
Urinary incontinence	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1	–	1	3
Vomiting	–	–	10	4	4	3	4	–	–	–	1	1	–	–	3	–	1–10	2–5
Weight changes	–	–	8	1	–	–	–	–	–	–	–	–	–	5	–	8	1–8	4

Abbreviation: AST/ALT, aspartate aminotransferase/alanine aminotransferase.

(amphetamine, modafinil);[13,15,37] and attempted suicide (amphetamine).[13]

Discussion

This is the first study to systematically review the empirical literature on the occurrence of ADRs reported for ADHD medications in the pediatric population. Information about ADRs from psychostimulants and the nonstimulant atomoxetine was reported in clinical studies of short duration, primarily conducted in 6- to 12-year-old boys, and particularly in the USA. The most frequently reported ADRs were decrease in appetite, gastrointestinal pain, and headache. A large number of studies were conducted by the same groups of authors and sponsored by the pharmaceutical companies manufacturing the respective medications.

Design and setting

Although the review process found a large number of small clinical trials exploring the efficacy of ADHD medications in the pediatric population, only a minor share of these studies reported information about ADRs. The studies included in this article were similar in design and setting, treatment duration, as well as number, age, and gender of included patients. The reliability of the studies may be questioned as the number of reported ADRs varied widely for identical and similar study designs. Further exploration of these questions would require access to the original study material. Large variations in ADR reporting rates were observed between studies and therapeutic groups, and similar types of ADRs were reported for the individual ADHD medications. It is puzzling that large numbers of specific ADRs are reported in some studies, but few if any in others. These findings question the relevance of the many small clinical trials

conducted on the medications, particularly atomoxetine and methylphenidate, as they are not designed to measure long-term efficacy and safety.[55] Almost all of these clinical trials were sponsored by the pharmaceutical companies producing the subject medications, and therefore, the current reviewers encourage these companies to make information about the ADRs reported in said clinical trials accessible to the public.

Seriousness of reported ADRs

Only a small number of serious ADRs were reported. However, in several of the included studies a large number of children withdrew due to experiencing ADRs, and therefore, the actual number of serious ADRs occurring from the use of ADHD medications might be higher, and some types of ADRs may not have been reported. Information about ADR incidence in the monitored population was only reported if the incidence was above 2% and/or 5%; consequently, information about rarely occurring ADRs is not included. Another issue is that information about definitions and scales to define and evaluate events occurring during the clinical trials is not reported in the articles, thus making it impossible to react to this information. Therefore, the regulatory agencies are encouraged to allow access to the original clinical protocols, so that all information reported for ADHD medications can be made public. A previous study has shown that there are large discrepancies between the data reported in clinical trial protocols and data published in scientific journals.[56]

Long-term safety aspects of psychostimulant use

Psychostimulants and other ADHD medications are prescribed for long-term treatment in large populations and

Table 4 Adverse drug reaction reporting rates (%) for atomoxetine by category and study

Reference number	14	19	26	29	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	Range	Placebo (range)
Adverse drug reaction																							
Abnormal behavior	–	–	2	–	–	–	–	–	–	–	19	–	–	–	–	–	–	–	–	–	–	2–19	–
Accidental injury	–	–	–	5	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6	–	3	3–6	5–8
Aggression	–	–	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1	–
Anorexia	9	–	–	19	35	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9–35	5
Appetite decrease	18	14	3	–	6	11	10	13	14	36	50	8	38	15	31	16	18	19	20	22	–	3–50	3–25
Asthenia	–	–	–	8	–	–	–	–	–	10	–	–	–	–	–	–	–	–	11	–	5	5–11	1–5
Blunted effect	–	–	–	–	–	–	–	–	–	–	5	–	–	–	–	–	–	–	–	–	–	5	–
Blood pressure changes	–	18	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	18	16
Changes in heart rate	–	11	–	–	–	–	–	–	–	–	–	–	19	–	–	–	–	–	–	–	–	11–19	12
Constipation	–	–	–	–	–	–	4	–	–	–	–	–	6	–	–	–	–	–	–	–	–	4–6	6
Cough	–	3	–	5	–	–	7	–	5	13	–	6	–	5	–	5	–	16	7	13	10	3–16	5–21
Crying	–	–	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1	–
Depression	–	–	–	3	10	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3–10	4–6
Diarrhea	–	–	–	7	–	–	–	1	–	6	5	–	6	–	–	4	2	3	–	–	5	1–7	5–13
Dilated pupils	–	–	–	–	–	–	–	–	–	–	5	–	–	–	–	–	–	–	–	–	–	5	–
Dizziness	2	–	2	–	–	–	6	13	–	10	–	–	–	–	–	–	–	3	6	–	5	2–13	1–5
Dry mouth	–	–	–	–	–	–	–	–	–	–	–	–	6	–	–	–	–	–	–	–	–	6	6
Dyspepsia	–	–	–	5	–	–	–	–	–	–	–	–	–	–	–	–	6	–	9	–	–	5–9	–
Emotional disturbance	–	–	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1	–
Emotional lability	–	–	–	6	–	–	–	–	–	–	55	–	–	8	–	–	–	3	7	–	–	3–55	5–14
Fatigue	7	5	3	–	33	–	4	–	–	–	5	–	–	5	–	12	10	–	–	–	–	3–33	1–18
Fever/pyrexia	–	–	–	11	4	–	5	3	–	4	–	–	–	10	–	–	–	10	7	–	5	3–11	4–15
Gastroenteritis	–	–	–	–	–	–	–	–	–	–	–	–	31	–	–	–	–	–	–	–	–	31	–
Gastrointestinal pain	15	11	5	23	47	13	7	8	12	8	27	7	–	12	–	9	15	29	17	31	13	5–47	4–22
Headache	10	18	4	31	39	9	17	17	14	10	14	21	13	21	17	21	7	26	20	30	24	4–39	4–28
Hyperkinesia	–	–	–	2	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2	–
Infection	–	–	–	4	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4	4	1
Influenza	–	–	–	5	–	–	–	4	5	–	–	–	–	5	–	–	–	–	–	–	7	4–5	1–6
Insomnia	7	7	3	9	–	–	5	–	5	11	5	–	19	–	–	–	–	3	–	–	7	3–19	1–13
Irritability	4	6	2	–	12	–	–	6	7	–	–	–	–	10	–	–	–	–	–	–	–	2–12	1–4
Mood alteration	–	–	–	–	–	–	–	–	–	–	–	–	44	–	11	–	–	–	–	–	–	44	31
Nasal congestion	–	–	–	–	–	–	–	–	–	–	–	–	–	6	–	–	–	–	–	–	–	6	–
Nasopharyngitis	–	–	–	–	–	4	5	–	7	–	–	–	–	14	–	–	–	–	–	–	–	4–14	6–8
Nausea	9	4	5	10	29	6	9	22	7	17	5	17	31	5	–	16	12	7	12	10	6	4–31	1–14
Nervousness	–	–	–	16	–	–	–	–	–	–	–	–	–	–	–	–	–	7	–	13	6	6–16	5–7
Oppositional behavior	–	–	–	–	–	–	–	–	–	–	–	–	–	–	11	–	–	–	–	–	–	11	–
Pain	–	–	–	5	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6	5–6	6
Palpitation	–	–	–	2	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2	–
Pharyngeal pain	–	–	–	–	–	–	–	–	–	–	–	–	–	10	–	–	–	–	–	–	–	10	–

(Continued)

Table 4 (*Continued*)

Reference number	14	19	26	29	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	Range	Placebo (range)
Pharyngitis	–	–	–	6	–	–	–	–	–	7	–	–	–	5	17	4	–	19	7	16	10	4–19	9–19
Pruritus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4	4	–
Rash	–	–	–	4	–	–	–	–	–	–	–	–	13	–	–	–	–	–	7	–	7	4–13	4–6
Respiratory tract infection	–	–	–	–	10	3	–	–	–	–	–	–	–	8	–	–	–	–	–	–	–	3–10	4
Restlessness	–	–	–	–	–	–	–	–	–	–	–	–	13	–	–	–	–	–	–	–	–	13	19–21
Rhinitis	–	–	–	18	–	–	–	–	–	8	–	–	–	–	–	–	–	26	17	26	14	8–26	15–38
Sinusitis	–	–	–	–	–	–	–	–	5	–	–	–	–	–	–	–	–	–	–	–	–	5	4
Somnolence	19	6	4	11	–	8	–	–	–	22	36	–	–	5	11	–	15	7	11	9	8	4–36	1–14
Stomachache	–	–	–	–	–	5	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	5	–
Tachycardia	–	–	–	6	–	–	–	–	–	–	–	–	–	–	14	–	–	–	–	–	–	6–14	–
Thirst	–	–	–	–	–	–	–	–	–	–	14	–	–	–	–	–	–	–	–	–	–	14	–
Throat pain	–	–	–	–	–	–	3	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3	–
Tics	–	–	–	–	–	–	–	–	–	–	5	–	–	–	–	–	–	–	–	–	–	5	7
Tired	–	–	–	–	–	–	–	–	–	–	14	–	31	–	–	–	–	–	–	–	–	31	4–13
Vomiting	13	7	2	12	12	12	7	13	10	7	–	9	–	8	11	16	6	19	15	15	8	2–19	1–12
Weight changes	4	–	–	3	–	–	–	9	–	6	–	8	–	–	–	–	–	–	–	–	–	1–9	1–6

there is a need for long-term efficacy and safety studies.[1] The lack of sufficient knowledge about ADRs at the point of licensing of new medicines makes spontaneous ADR reporting an important source of information about medicine safety.[57] As clinical trials in the pediatric population are limited, clinicians and health authorities must rely on spontaneous reports as the main source of information about previously unknown ADRs.[57] However, the current review did not find any studies about ADRs from the use of psychostimulants reported to any national ADR databases. Systematic analyses of ADRs reported to national databases are necessary, as these databases constitute a critical (and underestimated) source of important data, especially information about new, serious, and rarely occurring ADRs. Further studies of data from large databases, ie, the World Health Organization/Uppsala Monitoring Centre VigiBase™ (Uppsala, Sweden) or the European Medicines Agency EudraVigilance (London, United Kingdom [UK]) databases, are recommended in order to increase knowledge about ADRs from the use of ADHD medications.

Strengths and limitations of this review

The included studies were conducted over a period of approximately 20 years in different countries, with a great deal of inconsistency in observing and classifying the type and seriousness of reported ADRs. Information about the seriousness of the reported ADRs was extracted from the included studies, and it was not possible for the review to evaluate these ratings, nor to estimate ADRs in terms of effect sizes, as the review did not have access to the original data material. A major limitation of this study is that it is unknown to what extent the causality of these ADRs can be confirmed, and this has implications for the interpretation of the findings in the review. A large number of published clinical studies were not included in this review because these articles did not report information about ADRs, despite the fact that pharmaceutical companies had a legal obligation to monitor ADRs in clinical trials, and therefore, these data must exist. As the clinical trials were mainly sponsored by the pharmaceutical companies that produce the medications, these companies are urged to make these data accessible to the public.

Conclusion

Reported ADRs from the use of psychostimulants in the pediatric population were generally found in clinical trials of short duration. Since ADHD medications are prescribed for long-term treatment there is a need for long-term safety

Table 5 Adverse drug reaction reporting rates (%) for modafinil by category and study

Reference number	48	49	50	51	52	53	54	Range	Placebo (range)
Adverse drug reaction									
Abnormal behavior	–	–	–	–	–	–	–	–	4
Accidental injury	–	–	5	–	–	5	5	5	3–6
Anorexia	–	–	–	–	–	–	–	–	1–2
Anxiety	–	–	–	–	–	–	–	–	1–12
Appetite decrease	35	25	6	16	7	18	16	6–35	2–12
Asthenia	–	–	–	–	–	–	4	4	5
Cough	–	–	5	8	7	9	8	5–9	4–9
Diarrhea	–	–	–	–	–	–	–	–	1–2
Dry mouth	14	14	–	–	–	–	–	14	18
Dyspepsia	–	–	–	–	–	–	–	–	4
Emotional disturbance	–	–	–	–	–	–	–	–	12
Emotional lability	8	4	5	–	–	5	–	5–8	2–6
Fatigue	–	–	–	–	–	–	–	–	4
Fever	–	–	–	5	6	5	5	5–6	2–7
Gastroenteritis	–	–	–	–	–	5	–	5	4
Gastrointestinal pain	8	7	–	10	9	12	7	7–12	2–13
Headache	8	7	10	20	13	22	20	7–22	3–23
Infection	–	–	5	11	6	11	12	5–12	1–15
Influenza	–	–	–	–	–	–	–	–	9
Insomnia	–	–	13	27	12	28	29	12–29	2–10
Irritability	8	7	–	–	–	–	–	7–8	2–6
Nasal congestion	–	–	–	–	–	–	–	–	1
Nasopharyngitis	–	–	–	–	–	–	–	–	2–7
Nausea	4	7	–	5	5	5	–	4–7	2–12
Nervousness	6	7	–	5	–	5	4	4–7	2–6
Otitis media	–	–	–	–	–	–	–	–	2
Pain	–	–	–	–	–	–	5	5	1
Pharyngeal pain	–	–	–	–	–	5	–	5	1–7
Pharyngitis	–	–	–	7	–	8	9	7–9	3–13
Rash	–	–	–	–	–	–	6	6	4
Respiratory tract infection	–	–	–	–	–	–	–	–	2–6
Rhinitis	–	–	5	7	5	8	10	5–10	4–11
Sleeping problems	4	14	–	–	–	–	–	4–14	12
Somnolence	–	–	–	–	–	5	2	2–5	4–5
Tics	–	–	–	–	–	–	–	–	4
Urinary incontinence	–	–	–	–	–	–	–	–	3
Vomiting	–	–	–	5	–	6	6	5–6	2–9
Weight changes	6	7	–	–	–	5	–	5–7	1–6

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Table 6 Serious ADRs reported for ADHD medications in identified studies

Medication (alphabetically)	Reference	Adverse drug reaction(s)
Amphetamine	Spencer et al[13]	Arthrosis
		Hyperkinesia
		Insomnia
		Nervousness
		Pharyngitis
		Suicide attempt
	Wigal et al[14]	Emotional disturbance
		Headache
	Biedermann et al[15]	Anorexia
		Emotional lability
		Insomnia
	Efron et al[16]	Agitation
		Aggression
		Anxiety
Methylphenidate	Efron et al[16]	Aggression
		Headache
		Tearful
	Greenhill et al[22]	Hypersomnia
	Kemner et al[26]	Mania
	Biederman et al[28]	Depression
Atomoxetine	Wigal et al[14]	Upper abdominal pain
	Arnold et al[39]	Aggression
Modafinil	Boellner et al[50]	Insomnia
	Biederman et al[52]	Insomnia
	Wigal et al[51]	Asthma
		Dehydration
		Duodenitis
		Erythema multiforme
		Hypertonia
		Influenza syndrome
		Peptic ulcer
		Stevens–Johnson syndrome

Abbreviations: ADRs, adverse drug reactions; ADHD, attention deficit hyperactivity disorder.

studies. Considering the widespread and increasing use of these medications in children, greater care must be taken when prescribing these medications for long-term use. Further studies of spontaneous reports submitted to national and international databases are recommended in order to increase knowledge about ADRs from the use of psychostimulants in the pediatric population. Pharmaceutical companies should make all information about ADRs reported for ADHD medications accessible to the public. Additionally, the impact of the link between researchers and the manufacturers of the medications needs to be studied.

Acknowledgments

We wish to thank Ditte Sloth-Lisbjerg, MSc (Pharm.), for assistance with parts of the literature search and data extraction.

Authors' contributions

LA and EHH designed the study, analyzed the data, and wrote the final draft of the manuscript. LA conducted the literature search and data extraction. EHH checked all data extractions. Both authors read and approved the final version of the manuscript.

Disclosure

The authors report no conflicts of interest in this work.

References
1. American Academy of Pediatrics. Clinical practice guideline: treatment of the school-aged child with attention-deficit/hyperactivity disorder. *Pediatrics*. 2001;108(4):1033–1044.
2. European Medicines Agency. *Meeting Highlights From the Committee for Medicinal Products for Human Use, 16–19 July 2007*. Doc. Ref. EMEA/431407/2007. London: European Medicines Agency; 2007. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/12/WC500017068.pdf. Accessed October 31, 2011.
3. Novartis Pharmaceuticals Corporation, United States Food and Drug Administration. Ritalin®, Ritalin-SR®. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation; 2007. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/010187s069,018029s040,021284s011lbl.pdf. Accessed October 31, 2011.
4. Mosholder AD. Overview of ADHD and its pharmacotherapy. Gaithersburg, MD: United States Food and Drug Administration, Drug Safety and Risk Management Advisory Committee; February 9, 2006. Available from: http://www.fda.gov/ohrms/dockets/ac/06/slides/2006–4202S1_01_FDA-mosholder.ppt. Accessed July 18, 2011.
5. Nutt DJ, Fone K, Asherson P, et al. Evidence-based guidelines for management of attention-deficit/hyperactivity disorder in adolescents and in adults: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol*. 2007;21(1):10–41.
6. Trip AM, Visser ST, Kalverdijk LJ. Large increase of the use of psychostimulants among youth in The Netherlands between 1996 and 2006. *Br J Clin Pharmacol*. 2009;67(4):466–468.
7. Schubert I, Köster I, Lehmkuhl G. The changing prevalence of attention-deficit/hyperactivity disorder and methylphenidate prescriptions: a study of data from a random sample of insurees of the AOK Health Insurance Company in the German State of Hesse, 2000–2007. *Dtsch Arztebl Int*. 2010;107(36):615–621.
8. Asheim H, Nilsen KB, Johansen K, et al. Forskvivning av sentralstimulerende legemidler ved AD/HD i Nordland [Prescribing of stimulants for ADHD in Nordland County]. *Tidsskr Nor Laegeforen*. 2007;127:2360–2362. Article in Norwegian.
9. Zuvekas SH, Vitiello B, Norquist GS. Recent trends in the stimulant medication use among US children. *Am J Psychiatry*. 2006;163(4):579–585.
10. Bloch MH, Panza KE, Landeros-Weisenberger A, et al. Meta-analysis: treatment of attention-deficit/hyperactivity disorder in children with comorbid tic disorders. *J Am Acad Child Adolesc Psychiatry*. 2009;48(9):884–893.
11. Aagaard L, Thirstrup S, Hansen EH. Opening the white boxes: the licensing documentation of efficacy and safety of psychotropic medicines for children. *Pharmacoepidemiol Drug Saf*. 2009;18(5):401–411.
12. Biederman J, Krishnan S, Zhang Y, et al. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. *Clin Ther*. 2007;29(3):450–463.
13. Spencer TJ, Abikoff HB, Connor DF, et al. Efficacy and safety of mixed amphetamine salts extended release (Adderall XR) in the management of oppositional defiant disorder with or without comorbid attention-deficit/hyperactivity disorder in school-aged children and adolescents: a 4-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled, forced-dose-escalation study. *Clin Ther*. 2006;28:402–418.

14. Wigal SB, McGough JJ, McCracken et al. A laboratory school comparison of mixed amphetamine salts extended release (Adderall XR) and atomoxetine (Strattera) in school-aged children with attention deficit/hyperactivity disorder. *J Atten Disord*. 2005;9(1): 275–289.

15. Biederman J, Lopez FA, Boellner SW, et al. A randomized, double-blind, placebo-controlled, parallel-group study of SLI381 (Adderall XR) in children with attention-deficit/hyperactivity disorder. *Pediatrics*. 2002;110(2):258–266.

16. Efron D, Jarman F, Barker M. Side effects of methylphenidate and dexamphetamine in children with attention deficit hyperactivity disorder: a double-blind, crossover trial. *Pediatrics*. 1997;100(4): 662–666.

17. Arabgol F, Panaghi L, Hebrani P. Reboxetine versus methylphenidate in treatment of children and adolescents with attention deficit-hyperactivity disorder. *Eur Child Adolesc Psychiatry*. 2009;18(1):53–59.

18. Findling RL, Bukstein OG, Melmed RD, et al. A randomized, double-blind, placebo-controlled, parallel-group study of methylphenidate transdermal system in pediatric patients with attention-deficit/hyperactivity disorder. *J Clin Psychiatry*. 2008;69(1):149–159.

19. Newcorn JH, Kratochvil CJ, Allen AJ, et al. Atomoxetine and osmotically released methylphenidate for the treatment of attention deficit hyperactivity disorder: acute comparison and differential response. *Am J Psychiatry*. 2008;165(6):721–730.

20. Maayan L, Paykina N, Fried J, et al. The open-label treatment of attention-deficit/hyperactivity disorder in 4- and 5-year-old children with beaded methylphenidate. *J Child Adolesc Psychopharmacol*. 2009;19(2):147–153.

21. Findling R, Quinn D, Hatch SJ, et al. Comparison of the clinical efficacy of twice-daily Ritalin and once-daily Equasym XL with placebo in children with Attention-Deficit/Hyperactivity Disorder. *Eur Child Adolesc Psychiatry*. 2006;15(8):450–459.

22. Greenhill LL, Muniz R, Ball RR, et al. Efficacy and safety of dexmethylphenidate extended-release capsules in children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2006;45(7):817–823.

23. McGough JJ, Wigal SB, Abikoff H, et al. A randomized, double-blind, placebo-controlled, laboratory classroom assessment of methylphenidate transdermal system in children with ADHD. *J Atten Disord*. 2006;9(3):476–485.

24. Gau SS, Shen HY, Soong WT, et al. An open-label, randomized, active-controlled equivalent trial of osmotic release oral system methylphenidate in children with attention-deficit/hyperactivity disorder in Taiwan. *J Child Adolesc Psychopharmacol*. 2006;16(4):441–455.

25. Silva RR, Muniz R, Pestreich L, et al. Efficacy and duration of effect of extended-release dexmethylphenidate versus placebo in schoolchildren with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2006;16(3):293–251.

26. Kemner JE, Starr HL, Ciccone PE, et al. Outcomes of OROS methylphenidate compared with atomoxetine in children with ADHD: a multicenter, randomized prospective study. *Adv Ther*. 2005;22(5):498–512.

27. Swanson JM, Wigal SB, Wigal T, et al. A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the Comacs Study). *Pediatrics*. 2004;113(3 Pt 1):e206–e216.

28. Biederman J, Quinn D, Weiss M, et al. Efficacy and safety of Ritalin LA, a new, once daily, extended-release dosage form of methylphenidate, in children with attention deficit hyperactivity disorder. *Paediatr Drugs*. 2003;5(12):833–841.

29. Kratochvil CJ, Heiligenstein JH, Dittmann R, et al. Atomoxetine and methylphenidate treatment in children with ADHD: a prospective, randomized, open-label trial. *J Am Acad Child Adolesc Psychiatry*. 2002;41(7):776–784.

30. Pelham WE, Gnagy EM, Burrows-Maclean L, et al. Once-a-day Concerta methylphenidate versus three-times-daily methylphenidate in laboratory and natural settings. *Pediatrics*. 2001;107(6):e105.

31. Svanborg P, Thernlund G, Gustafsson PA, et al. Efficacy and safety if atomoxetine as add-on to psychoeducation in the treatment of attention deficit/hyperactivity disorder: a randomized, double-blind, placebo-controlled study in stimulant-naïve Swedish children and adolescents. *Eur Child Adolesc Psychiatry*. 2009;18(4):240–249.

32. Block SL, Kelsey D, Coury D, et al. Once-daily atomoxetine for treating pediatric attention-deficit/hyperactivity disorder: comparison of morning and evening dosing. *Clin Pediatr (Phila)*. 2009;48(7):723–733.

33. Tamayo JM, Pumariega A, Rothe EM, et al. Latino versus Caucasian response to atomoxetine in attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2008;18(1):44–53.

34. Bangs ME, Emslie GJ, et al, (Atomoxetine ADHD and Comorbid MDD Study Group). Efficacy and safety of atomoxetine in adolescents with attention-deficit/hyperactivity disorder and major depression. *J Child Adolesc Psychopharmacol*. 2007;17(4):407–420.

35. Geller D, Donnelly C, Lopez F, et al. Atomoxetine treatment for pediatric patients with attention-deficit/hyperactivity disorder with comorbid anxiety disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46(9):1119–1127.

36. Gau SF, Huang YS, Soong WT, et al. A randomized, double-blind, placebo-controlled clinical trial on once-daily atomoxetine hydrochloride in Taiwanese children and adolescents with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2007;17:4:447–461.

37. Kratochvil CJ, Vaughan BS, Mayfield-Jorgensen ML, et al. A pilot study of atomoxetine in young children with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2007;17(2):175–185.

38. Prasad S, Harpin V, Poole L, et al. A multi-centre, randomized, open-label study of atomoxetine compared with standard current therapy in UK children and adolescents with attention-deficit/hyperactivity disorder (ADHD). *Curr Med Res Opin*. 2007;23(2):379–394.

39. Arnold LE, Aman MG, Cook AM, et al. Atomoxetine for hyperactivity in autism spectrum disorders: placebo-controlled crossover pilot trial. *J Am Acad Child Adolesc Psychiatry*. 2006;45(10):1196–1205.

40. Newcorn JH, Michelson D, Kratochvil CJ, et al. Low-dose atomoxetine for maintenance treatment of attention-deficit/hyperactivity disorder. *Pediatrics*. 2006;118(6):e1701–e1706.

41. Escobar R, Soutullo C, San Sebastián J, et al. Atomoxetine safety and efficacy in children with attention deficit/hyperactivity disorder (ADHD): initial phase of 10-week treatment in a relapse prevention study with a Spanish sample. *Actas Esp Psiquiatr*. 2004;33(1):26–32. Article in Spanish.

42. Allen AJ, Kurlan RM, Gilbert DL, et al. Atomoxetine treatment in children and adolescents with ADHD and comorbid tic disorders. *Neurology*. 2005;65(12):1941–1949.

43. Kelsey DK, Sumner CR, Casat CD, et al. Once-daily atomoxetine treatment for children with attention-deficit/hyperactivity disorder, including an assessment of evening and morning behavior: a double-blind, placebo-controlled trial. *Pediatrics*. 2004;114(1):e1–e8.

44. Biederman J, Heiligenstein JH, Faries DE, et al. Efficacy of atomoxetine versus placebo in school-aged girls with attention-deficit/hyperactivity disorder. *Pediatrics*. 2002;110(6):e75.

45. Michelson D, Allen AJ, Busner J, et al. Once-daily atomoxetine treatment for children and adolescents with attention deficit hyperactivity disorder: a randomized, placebo-controlled study. *Am J Psychiatry*. 2002;159(11):1896–1901.

46. Spencer T, Heiligenstein JH, Biederman J, et al. Results from 2 proof-of-concept, placebo-controlled studies of atomoxetine in children with attention-deficit/hyperactivity disorder. *J Clin Psychiatry*. 2002;63(12):1140–1147.

47. Michelson D, Faries D, Wernicke J, et al. Atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, dose-response study. *Pediatrics*. 2001;108(5):e83.

48. Kahbazi M, Ghoreishi A, Rahiminejad F, et al. A randomized, double-blind and placebo-controlled trial of modafinil in children and adolescents with attention deficit and hyperactivity disorder. *Psychiatry Res*. 2009;168(3):234–237.

49. Amiri S, Mohammadi MR, Mohamaddi M, et al. Modafinil as treatment for Attention-Deficit/Hyperactivity Disorder in children and adolescents: a double blind, randomized clinical trial. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32(1):145–149.

50. Boellner S, Earl CQ, Arora S. Modafinil in children and adolescents with attention-deficit/hyperactivity disorder: a preliminary 8-week, open-label study. *Curr Med Res Opin*. 2006;22(12):2457–2465.

51. Wigal SB, Biederman J, Swanson JM, et al. Efficacy and safety of modafinil film-coated tablets in children and adolescents with or without prior stimulant treatment for attention-deficit/hyperactivity disorder: pooled analysis of 3 randomized, double-blind, placebo-controlled studies. *Prim Care Companion J Clin Psychiatry*. 2006;8(6):352–360.

52. Biederman J, Swanson JM, Wigal SB, et al. A comparison of once-daily and divided doses of modafinil in children with attention-deficit/hyperactivity disorder: a randomized, double-blind, and placebo-controlled study. *J Clin Psychiatry*. 2006;67(5):727–735.

53. Greenhill LL, Biederman J, Boellner SW, et al. A randomized, double-blind, placebo-controlled study of modafinil film-coated tablets in children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2006;45(5):503–511.

54. Biederman J, Swanson JM, Wigal SB, et al. Efficacy and safety of modafinil film-coated tablets in children and adolescents with attention-deficit/hyperactivity disorder: results of a randomized, double-blind, placebo-controlled, flexible-dose study. *Pediatrics*. 2005;116(6):e777–e784.

55. Hansen EH. Technology assessment in a user perspective – experiences with drug technology. *Int J Technol Assess Health Care*. 1992;8(1):150–165.

56. Gøtzsche P, Hróbjartsson A, Johansen HK, et al. Constraints on publication rights in industry-initiated clinical trials. *JAMA*. 2006;295(14):1645–1646.

57. Aagaard L, Hansen EH. Information about ADRs explored by pharmacovigilance approaches: a qualitative review of studies on antibiotics, SSRIs, and NSAIDs. *BMC Clin Pharmacol*. 2009;9:4.

Appendix 1
Search strategy: complete databases were searched until February 2011

Embase
  Adverse event
  Methylphenidate
  Adverse drug reaction AND methylphenidate
  (Adverse event OR adverse drug reaction) AND psychostimulant
  Atomoxetine OR modafinil OR methylphenidate OR amphetamine
  (Atomoxetine OR modafinil OR methylphenidate OR amphetamine) AND adverse event

PubMed
  Adverse event
  Methylphenidate
  Adverse event AND methylphenidate
  Adverse event OR adverse drug reaction
  Psychostimulant
  (Adverse event OR adverse effect) AND psychostimulant
  Atomoxetine OR modafinil OR methylphenidate OR amphetamine
  (Atomoxetine OR modafinil OR methylphenidate OR amphetamine) AND adverse event

PsycINFO®
  Adverse event
  Methylphenidate
  Adverse event AND methylphenidate
  Side effect
  Adverse drug reaction
  Psychostimulant
  (Adverse drug reaction OR side effect) AND psychostimulant
  Adverse drug reaction OR side effect OR adverse event
  Atomoxetine OR modafinil OR methylphenidate OR amphetamine
  (Adverse event OR side effect OR adverse drug reaction) AND (Atomoxetine OR modafinil OR methylphenidate OR amphetamine)

Appendix 2
Excluded studies listed by reason for exclusion, alphabetically by first author

Meta-analyses

Bangs ME, Tauscher-Wisniewski S, Polzer J, et al. Meta-analysis of suicide-related behavior events in patients treated with atomoxetine. *J Am Acad Child Adolesc Psychiatry*. 2008;47(2):209–218.

Greenhill LL, Newcorn JH, Gao H, et al. Effect of two different methods of initiating atomoxetine on the adverse event profile of atomoxetine. *J Am Acad Child Adolesc Psychiatry*. 2007;46(5):566–572.

Kratochvil CJ, Wilens TE, Greenhill LL, et al. Effects of long-term atomoxetine treatment for young children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2006;45(8):919–927.

Kratochvil CJ, Michelson D, Newcorn JH, et al. High-dose atomoxetine treatment of ADHD in youths with limited response to standard doses. *J Am Acad Child Adolesc Psychiatry*. 2007;46(9):1128–1137.

Kratochvil CJ, Milton DR, Vaughan BS, et al. Acute atomoxetine treatment of younger and older children with ADHD: a meta-analysis of tolerability and efficacy. *Child Adolesc Psychiatry Ment Health*. 2008;2(1):25.

Polzer J, Bangs ME, Zhang S, et al. Meta-analysis of aggression or hostility events in randomized, controlled clinical trials of atomoxetine for ADHD. *Biol Psychiatry*. 2007;61(5):713–719.

Schachter HM, Pham B, King J, et al. How efficacious and safe is short-acting methylphenidate for the treatment of attention-deficit disorder in children and adolescents? A meta-analysis. *CMAJ*. 2001;165(11):1475–1488.

Wilens TE, Newcorn JH, Kratochvil CJ, et al. Long-term atomoxetine treatment in adolescents with attention-deficit/hyperactivity disorder. *J Pediatr*. 2006;149(1):112–119.

Review articles

Brams M, Moon E, Pucci M, et al. Duration of effect of oral long-acting stimulant medications for ADHD throughout the day. *Curr Med Res Opin*. 2010;26(8):1809–1825.

Findling RL. Evolution of the treatment of attention-deficit/hyperactivity disorder in children: a review. *Clin Ther*. 2008;30(5):942–957.

Merkel RL Jr, Kuchibhatla A. Safety of stimulant treatment in attention deficit hyperactivity disorder: Part I. *Expert Opinion Drug Saf*. 2009;8(6):655–668.

Wernicke JF, Faries D, Girod D, et al. Cardiovascular effects of atomoxetine in children, adolescents, and adults. *Drug Saf*. 2003;26(10):729–740.

Studies with a mixture of adults and children/adolescents

Bangs ME, Jin L, Zhang S, et al. Hepatic events associated with atomoxetine treatment for attention-deficit hyperactivity disorder. *Drug Saf*. 2008;31(4):345–354.

Maia CR, Matte BC, Ludwig HT, et al. Switching from methylphenidate immediate release to MPH-SODAS in attention-deficit/hyperactivity disorder. *Eur Child Adolesc Psychiatry*. 2008;17(3):133–142.

Paterson R, Douglas C, Hallmayer J, et al. A randomised, double-blind, placebo-controlled trial of dexamphetamine in adults with attention deficit hyperactivity disorder. *Aust N Z J Psychiatry*. 1999;33(4):494–502.

Wernicke JF, Holdridge KC, Jin L, et al. Seizure risk in patients with attention-deficit-hyperactivity disorder treated with atomoxetine. *Dev Med Child Neurol.* 2007;49(7):498–502.

Sub-group analyses of clinical studies

Durell TM, Pumariega AJ, Rothe EM, et al. Effects of open-label atomoxetine on African-American and Caucasian pediatric outpatients with attention-deficit/hyperactivity disorder. *Ann Clin Psychiatry.* 2009;21(1):26–37.

Spencer TJ, Sallee FR, Gilbert DL, et al. Atomoxetine treatment of ADHD in children with comorbid Tourette syndrome. *J Atten Disord.* 2008;11(4):470–481.

ADRs presented as number of children reporting ADRs, assessment of rate not possible

Davari-Ashtiani R, Shahrbabaki ME, Razjouyan K, et al. Buspirone versus methylphenidate in the treatment of attention deficit hyperactivity disorder: a double-blind and randomized trial. *Child Psychiatry Hum Dev.* 2010;41(8):641–648.

Barkley RA, McMurray MB, Edelbrock CS, et al. Side effects of methylphenidate in children with attention deficit hyperactivity disorder: a systemic, placebo-controlled evaluation. *Pediatrics.* 1990;86(2):184–192.

Firestone P, Musten LM, Pisterman S, et al. Short-term side effects of stimulant medication are increased in preschool children with attention-deficit/hyperactivity disorder: a double-blind placebo-controlled study. *J Child Adolesc Psychopharmacol.* 1998;8(1):13–25.

Pelham WE, Gnagy EM, Chronis AM, et al. A comparison of morning-only and morning/late afternoon Adderall to morning-only, twice-daily, and three times-daily methylphenidate in children with attention-deficit/hyperactivity disorder. *Pediatrics.* 1999;104(6):1300–1311.

Pelham WE Jr, Greenslade KE, Vodde-Hamilton M, et al. Relative efficacy of long-acting stimulants on children with attention deficit-hyperactivity disorder: a comparison of standard methylphenidate, sustained-release methylphenidate, sustained-release dextroamphetamine and pemoline. *Pediatrics.* 1990;86(2):226–237.

Pelham WE, Aronoff HR, Midlam JK, et al. A comparison of Ritalin and Adderall: efficacy and time-course in children with attention-deficit/hyperactivity disorder. *Pediatrics.* 1999;103(4):e43.

Rugino TA, Copley TC. Effects of modafinil in children with attention-deficit/hyperactivity disorder: an open-label study. *J Am Acad Child Adolesc Psychiatry.* 2001;40(2):230–235.

Swanson JM, Greenhill LL, Lopez FA, et al. Modafinil film-coated tablets in children and adolescents with attention-deficit/hyperactivity disorder: results of a randomized, double-blind, placebo-controlled, fixed-dose study followed by abrupt discontinuation. *J Clin Psychiatry.* 2006;67(1):137–147.