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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

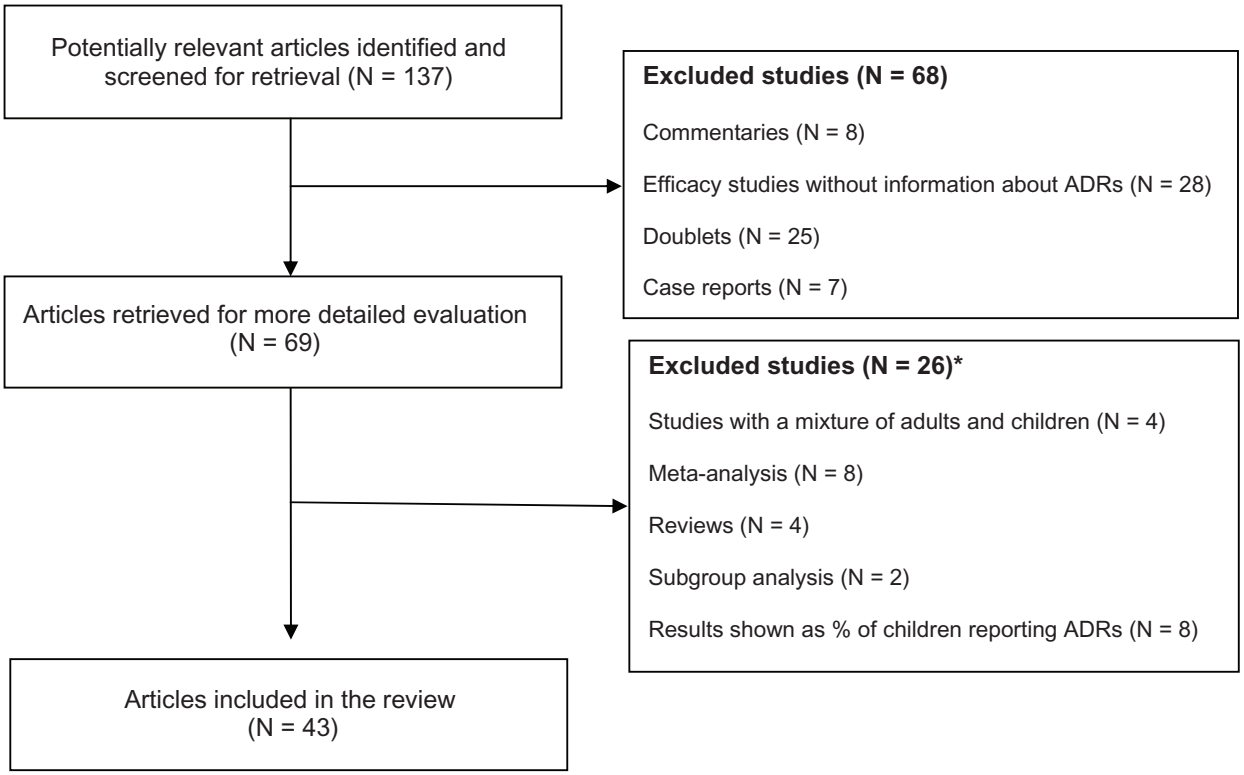


**Figure 1** Decision tree of the review process.
**Note:** *An overview of excluded studies is shown in Appendix 2.
**Abbreviation:** ADRs, adverse drug reactions.

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 pediatic 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 | 13 | – | – | 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 | – | – | – | – | – | – | – | 4–5 | 1–6 |
| Insomnia | 7 | 7 | 3 | 9 | – | – | 5 | – | – | 11 | – | – | 19 | – | – | – | – | 3 | – | – | 7 | 3–19 | 1–13 |
| Irritability | 4 | 6 | 2 | – | 12 | – | – | 6 | 7 | – | – | – | – | 10 | – | – | – | – | – | – | – | 2–12 | 1–4 |
| Mood alteration | – | – | – | – | – | – | – | – | – | – | – | – | 44 | – | – | – | – | – | – | – | – | 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 | – | – | 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 | – | – | – | – | – | – | – | – | – | – | – | – | 31 | – | – | – | – | – | – | – | – | 31 | 4–13 |
| Vomiting | 13 | 7 | 2 | 12 | 12 | 12 | 7 | 13 | 10 | 7 | 14 | 9 | – | 8 | 11 | 16 | 6 | 19 | 15 | 15 | 8 | 2–19 | 1–12 |
| Weight changes | 4 | 1 | – | 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 | – | 4–7 | 2–12 |
| Nervousness | 6 | 7 | – | 5 | – | 5 | 4 | 4–7 | 2–6 |
| Otitis media | – | – | – | – | – | – | – | – | 2 |
| Pain | – | – | – | – | – | – | 5 | 5 | 1 |
| Pharyngeal pain | – | – | – | – | – | – | – | – | 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 |

**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.

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## 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.

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# 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.

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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.

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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.

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