Int J Clin Pharm
DOI 10.1007/s11096-014-9924-y

REVIEW ARTICLE

Adverse drug reactions associated with asthma medications in children: systematic review of clinical trials

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Received: 29 October 2013 / Accepted: 11 February 2014

Abstract *Background* Respiratory medications are frequently prescribed for use in children. Several studies have reported information on the safety of asthma medications in clinical studies in adults, but information about safety in children is scarce. *Objective* To review published clinical trials on the occurrence and characteristics of adverse drug reactions (ADRs) in children, reported for asthma medications licensed for paediatric use. *Methods* We systematically reviewed the literature following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines. PubMed, Embase, Cochrane Library, PsycINFO, IPA, and CINAHLs databases were searched from origin until July 2013 for studies reporting ADRs for beta2-receptor agonists, inhaled corticosteroids, leukotriene receptor antagonists and combination products in children from birth to age 17. Information on ADR reporting rates, age and gender, type and seriousness of ADRs, design, setting, observation period, type of assessors, and funding sources was extracted from the articles. *Results* Literature searches resulted in 162 potential relevant articles. However only 12 of these studies were included in this review as they reported information about ADR rates from use of salmeterol, formoterol, fluticasone, montelukast, zafirlukast and budesonide/formoterol in children. The total population was approximately 3,000 children; the majority was 6- to 11-year-olds and two thirds of these were boys. The observation period varied from 1 to 22 months. The most frequently reported ADRs were exacerbation of asthma, respiratory tract infection, cough, fever and headache. Only few ADRs were rated as being serious, however a number of children dropped out of the clinical trials due to serious ADRs, and, therefore, the real number of serious ADRs is probably higher. *Conclusions* Few clinical trials reporting ADRs from use of asthma medications in children were identified in the literature. These studies reported only a few types of ADRs, the majority being non-serious.

Keywords Adverse drug reactions · Asthma · Children · Pharmacovigilance · Pediatric indication

Impacts on Practice

- A large number of clinical trials with respiratory medicines conducted in children can be found in the literature, but only few report information about adverse drug reactions (ADRs).
- Studies of spontaneous ADR reports on respiratory medications submitted to national pharmacovigilance databases must be conducted in order to increase knowledge about ADRs occurring in children.
- There is a need for more population-based studies to collect information about possible ADRs in order to

Electronic supplementary material The online version of this article (doi:10.1007/s11096-014-9924-y) contains supplementary material, which is available to authorized users.

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Published online: 23 February 2014

estimate the prevalence of rarely occurring and unexpected ADRs.

Introduction

Respiratory medications (ATC group R) are prescribed frequently for use in children [1]. In a cohort of approximately 48,000 Danish children one in three children below 3 years of age received prescriptions for anti-asthmatics, mainly oral beta-2 agonists [1]. In the 7 to 15-year-old group 6 % of the children were prescribed anti-asthmatics [1]. Studies from other western countries have reported similar results showing that the level of exposure to respiratory medications was highest in early childhood [2]. In a cohort of 374,068 patients in the US aged 6–11-year the majority (42 %) started their treatment with a prescription of a short-acting beta2-agonists. Other common starting medications was inhaled corticosteroids (ICS) (16 %) [3]. Despite the widespread use of these medications, information about safety in children is scarce [2]. Analysis of spontaneous reports submitted to regulatory authorities in Denmark from 1998 to 2007 showed that ADRs reported for respiratory medications constituted 2 % of all ADRs reported in children from birth to age 17 [4]. Analyses of ADR reports submitted to the WHO database VigiBase from 1995 to 2005 showed that 11 % of all ADR reports in children were for respiratory medications compared to 7 % in adults [5]. The VigiBase study did not provide information about type of reported ADRs and suspected medications [5], so the impact of the ADRs is unknown. A study analyzing ADRs reported to the Dutch national ADR database for ICS from 1984 to 2004 in children below 18 years found that the majority of reported ADRs associated with use of ICS were psychiatric symptoms, growth retardation, rash, alopecia and headache [6]. In 2008 the FDA issued safety alerts requiring manufacturers of leukotriene-receptor antagonists to include suicide and neuropsychiatric events as a precaution in the product information for adults. It remains unclear whether these ADRs may occur in children [6]. Clinical guidelines recommend ICS and beta2–receptor agonists as first-line standard treatment in children [2]. As no articles have previously reviewed the ADR patterns following use of these medications in children, we wanted to review ADRs reported in paediatric clinical trials for these therapeutic groups compared to other paediatric medications licensed for treatment of asthma.

Aim of the study

To review published clinical trials on the occurrence and characteristics of ADRs in children, reported for asthma medications licensed for paediatric use.

Methods

Literature searches

Literature searches were performed in PubMed, Embase, Cochrane Library, IPA, PsycInfo and CINAHL (whole databases from origin without language restriction). Table 1 lists the asthma medications licensed for paediatric use and their approved paediatric indication with respect to age and anatomical classification [ATC] group R. The selected medications were licensed for treatment of asthma according to international treatment guidelines and they had a paediatric indication listed in the official product information issued by the Danish Health and Medicines Authority and/or the European Medicines Agency. Therefore we searched with the terms "adrenergic beta-2-receptor agonists" [MESH], "ICS", "leukotriene receptor antagonists" [MESH]," cholinergic antagonists" [MESH]," and "anti-immunoglobulin-E-antibodies" combined with any of the following: "adverse drug reaction," "side effect" and "adverse event". Further searches were conducted in Pubmed using the key words "adverse drug reaction" plus each of the following: "salbutamol"," levosalbutamol", "terbutaline", "pirbuterol", "fenoterol", "salmeterol", "formoterol", "bambuterol", "budenosid", "fluticasone"," mometason"," beclometason"," montelukast" and "zafirlukast", and "ipratropium". Additionally, the following search terms: "cortisol suppression", "exacerbation rate", "growth retardation rate" and "psychiatric" combined with "asthma medications" were also included in the searches, as such events have often been reported in clinical trials for asthma medicines. Table 2 provides further details of the search strategy, which was constructed based on advice from an information specialist. Reference lists of identified articles were also screened for additional potentially relevant articles. The clinical trials databases www.clinicaltrials.gov and www.ctr.gsk.co.uk were searched for additional studies. Literature searches were updated until June 2013.

Study selection

Both authors independently screened the retrieved abstracts to identify studies relevant for the review. Potentially relevant articles were retrieved in full text and further screened for inclusion. To be considered relevant for this review, articles had to be peer-reviewed and report ADRs associated with the use of asthma medications licensed for paediatric use displayed as ADR rates (%) in children from birth to age 17. We also included studies not reporting ADRs as rates if the provided data allows for ADR rate calculation. Studies located in the US clinical trials database were excluded, as they provided insufficient information about reported ADRs.

Table 1 Medicines with paediatric indication used to treat asthma according to paediatric guidelines

Therapeutic group (s)	ATC group	Medicine (s)	Paediatric indication (age)[a] (months)
Short-acting beta2-agonists	R03AC02	Salbutamol (Ventoline®)	≥18
	R03AC03	Terbutaline (Bricanyl®)	≥3
	R03AC04	Fenoterol (Berotec®)	≥0
Long-acting beta2-agonists (LABAs)	R03AC12	Salmeterol (Serevent®)	≥4
	R03AC13	Formoterol (Foradil®)	≥5
	R03CC12	Bambuterol (Bambec®)	≥2
Corticosteroids	R03BA02	Budesonid (Spirocort®)	≥0
	R03BA05	Fluticason (Flixotide®)	≥1
	R01AD09	Mometason (Asmanex®)	≥12
	R03BA01	Beclometason (Beclomet®)	≥5
Leukotriene receptor antagonists	R03DC03	Montelukast (Singulair®)	≥15
	R03DC01	Zafirlukast (Accolate®)	≥5
Combination products	R03AK03	Ipratropium/Fenoterol (Berodual®)	≥6
	R03AK06	Salmeterol/Fluticason (Seretide®)	≥4
	R03AK07	Budesonid/Formoterol (Symbicort®)	≥12

[a] Product Information available at the website: www.produktinformation.dk

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, observation period (weeks), size of study populations, age and gender of included population, ADR reporting rates in percentage and information about funding. ADR reporting rates were listed as reported in the original articles. In placebo-controlled studies, information was extracted about ADR reporting rates for the placebo populations as well as dropout figures. We also recorded information about who had assessed the ADRs and if reported ADRs were classified as being serious. The first author extracted data, while the second author checked and verified all cases. Reporting was conducted in the form recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and checklist [7] (see appendix 1).

Definition and seriousness of reported ADR

It was not feasible to apply a common definition of ADRs across studies, as only few of the included papers have specified the applied ADR definitions and causality assessment criteria. In Pearlman et al. 2000 [12] reported adverse event data were tabulated using COSTART (coding symbols for thesaurus of ADRs) terminology. Tal et al. [19] stated that reported adverse events were evaluated with respect to intensity and causality. Hoekx et al. [10] defined a serious ADR as one resulting in death, life-threatening, requiring hospitalization or prolongation of

Table 2 Search strategy: complete databases were searched until June 2013

Search term (mesh/free text)
Adrenergic beta-2-receptor agonists AND adverse drug reaction
Adrenergic beta-2-receptor agonists AND side effect
Adrenergic beta-2-receptor agonists AND adverse event
Inhaled corticosteroids AND adverse drug reaction
Inhaled corticosteroids AND side effect
Inhaled corticosteroids AND adverse event
Leukotriene receptor antagonists AND adverse drug reaction
Leukotriene receptor antagonists AND side effect
Leukotriene receptor antagonists AND adverse event
Adverse drug reaction AND salbutamol
Adverse drug reaction AND levosalbutamol
Adverse drug reaction AND terbutaline
Adverse drug reaction AND pirbuterol
Adverse drug reaction AND fenoterol
Adverse drug reaction AND salmeterol
Adverse drug reaction AND formoterol
Adverse drug reaction AND bambuterol
Adverse drug reaction AND budenosid
Adverse drug reaction AND fluticason
Adverse drug reaction AND mometason
Adverse drug reaction AND beclometason
Adverse drug reaction AND montelukast
Adverse drug reaction AND zafirlukast
Cortisol suppression AND asthma medication
Exacerbation rate AND asthma medication
Growth rate retardation AND asthma medication
Psychiatric AND asthma medication

existing hospitalization, resulting in persistent or significant disability/incapacity in the reporter's opinion, a congenital anomaly/birth defect and other medically important conditions. Other reactions were classified as non-serious.

Results

In total, 162 potentially relevant references reporting ADRs from use of the asthma medications listed in Table 1 were identified during the database searches and reference screenings. Figure 1 provides an overview of the review process and reasons for exclusion. Thirteen studies were excluded after the abstracts, and 149 studies were retrieved for full text review. Of these studies, sixteen were later excluded as they reported mixed data on children and adults did not allow for identification of children. Seven meta-analyses and 2 reviews were excluded as they reported information from original studies already included. Also excluded were two studies reporting data from subgroup analyses of already included studies, and 43 studies in which ADRs were reported only as number of children with an ADR. Eventually, 12 articles corresponding to 13 intervention studies were included. Table 3 presents the study characteristics of the included studies. The included studies were multicenter studies conducted in several countries and the pharmaceutical companies producing the respective medications sponsored all studies. Two studies were found for long-acting beta2-agonists [8, 9], one study for corticosteroids [10], eight studies for leukotriene receptor antagonists [11–18] and one study for the combination product budesonide/formoterol [19]. No studies were located that reported ADR occurrence in children for short-acting beta2-agonists, bambuterol (long-acting beta2-agonist) or the combination products ipratropium/fenoterol and salmeterol/fluticasone. Although studies reporting ADRs for budesonide and beclomethasone were identified, these products were not used as intervention medication in the studies but as the comparator drug [13, 15–19].

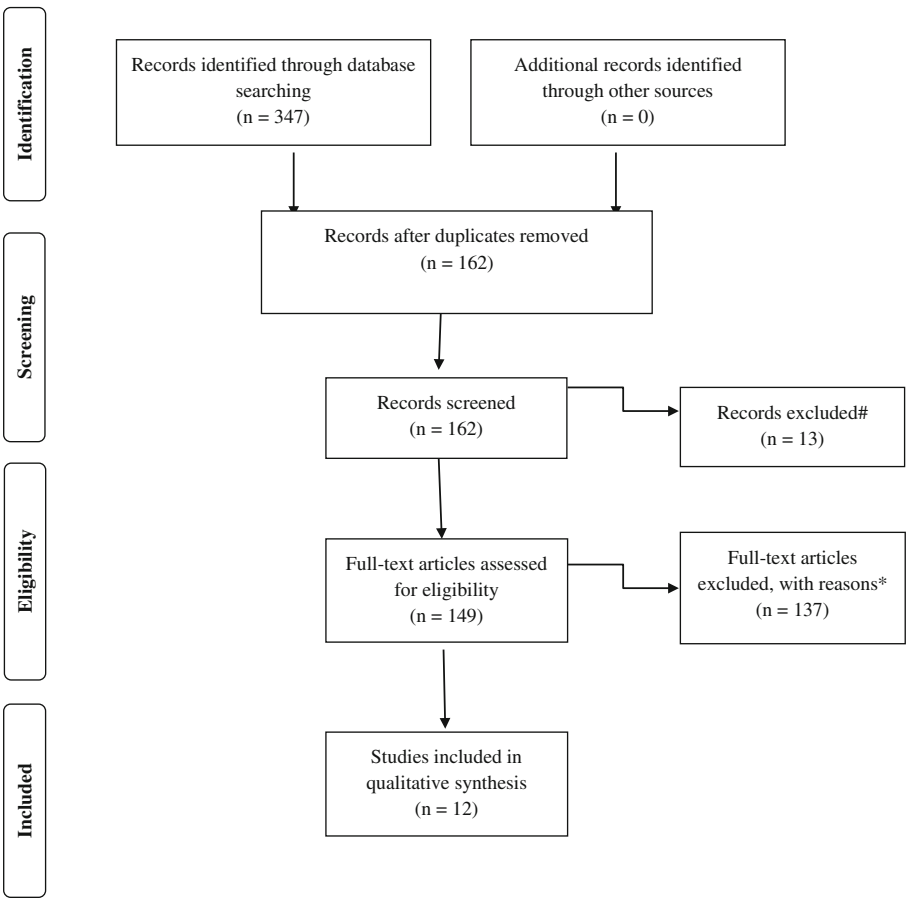

Fig. 1 Decision tree for the review process. # Commentaries/letters to the editor (n = 6), cost-effectiveness studies (n = 2) and quality of life studies (n = 5). *A list of excluded studies is presented in Appendix 2: Meta-analyses (n = 7), efficacy studies (n = 59), non-peer reviewed articles (n = 7), studies with mixed child/adults populations (n = 16), reviews (n = 2), ADRs shown as number of children reporting an ADR (n = 43), subgroup analyses (n = 2), and an article in Chinese language (n = 1)

Table 3 Study characteristics of included studies by study population

Studiess in chronological order for each ATC group	Country	Design	Dosage (μg/day)	Intervention	Comparator	Rescue medication	Observation period months (n)	Intervention patient included (n)	Intervention patients completed (n)	Comparator patients included (n)	Comparator patients completed (n)	Age (year)	% Male
Beta2-agonists													
Von Berg et al. [8]	Multicountry	R, DB, P	2 × 50	Salmeterol	Placebo	Yes	12	220	212	206	200	6–15	63
Von Berg et al. [9]	Multicountry	R, DB, P	2 × 4.5/9	Formoterol	Placebo	Yes	3	164	113	84	84	6–17	54
Corticosteroids													
Hoekx et al. [10]	Multicountry	R, DB, P	400	Fluticasone	Budesonide	Yes	2	119	100	110	91	4–13	68
Leukotrine receptor antagonists													
Knorr et al. [11]	CA, US	R, DB, P	5 mg	Montelukast	Placebo	Yes	2	201	189	135	125	6–14	67
Pearlman et al. et al. [12]	Multicountry	R, DB, P	5–40 mg	Zafirlukast	Placebo	Yes	1.5	508	475	206	185	5–12	60
Storms et al. [13]	Multicountry	R, DB, P	5 mg	Montelukast	Placebo	Yes	2	201	193	135	132	6–15	67
Storms et al. [13]	Multicountry	R, O	5 mg	Montelukast	Beclomethasone	Yes	22	207	198	38	38	6–15	67
Knorr et al. [14]	Multicountry	R, DB, P	4 mg	Montelukast	Placebo	Yes	3	461	416	228	202	2–5	59
Maspero et al. [15]	Multicountry	R, O	5 mg	Montelukast	Beclomethasone	Yes	6	83	78	41	38	6–11	64
Bukstein et al. [16]	US	R, C, O	5 mg	Montelukast	Cromolyn	Yes	1	168	149	165	143	6–11	64
Garcia et al. [17]	Multicountry	R, DB, P	5 mg	Montelukast	Fluticasone	Yes	12	495	459	499	466	6–14	65
Von Adelsberg et al. [18]	Multicountry	R, DB, P	4 mg	Montelukast	Placebo	Yes	1.5	175	169	81	74	0.5–2	66
Combination products													
Tal et al. [19]	Multicountry	R, DB, P	160/9	Budesonide/formoterol	Budesonide	Yes	3	148	139	138	129	4–17	61
Total all studies/range							1–22	3,150	2,890	2,038	1,880	0.5–17	54–81

DB double blind, *R* randomized, *P* parallel, *O* open label, *C* cross-over, *NA* no information

Table 4 Reported ADRs for asthma medications leading to patient dropouts from clinical trials

Studies (chronological order for each ATC groups)	Intervention adverse drug reaction (s)	Comparator adverse drug reaction (s)
Beta2-agonists		
Von Berg et al. [8]	Asthma exacerbations, headache, tremor, cough	Asthma exacerbations, headache, tremor, cough
Von Berg et al. [9]	Asthma deterioration, lack of efficacy	Asthma deterioration, lack of efficacy
Corticosteroids		
Hoekx et al. et al. [10]	Asthma exacerbations	Asthma exacerbations, allergic skin reaction
Leukotrine receptor antagonists		
Knorr et al. [11]	Asthma exacerbations, pneumonia, dehydration, upper respiratory tract infection	Asthma exacerbations, urticaria
Pearlman et al. [12]	Asthma exacerbations	Asthma exacerbations
Storms et al. [13]	Yes, reactions not specified	Yes, reactions not specified
Storms et al. [13]	Yes, reactions not specified	Yes, reactions not specified
Knorr et al. [14]	Asthma exacerbations, drug overdose, rash, paraesthesia, reflux, varicella	None
Maspero et al. [15]	Abdominal pain	None
Bukstein et al. [16]	Asthma exacerbations	Asthma exacerbations
Garcia et al. [17]	Yes, reactions not specified	Yes, reactions not specified
Von Adelsberg et al. [18]	None	None
Combination products		
Tal et al. [19]	Asthma deterioration	Asthma deterioration

Population

A total of 3150 children were included in the studies, of which 2018 children completed the intervention treatment. The majority of completing children (78 % of total) were treated with montelukast (n = 2,326) and zafirlukast (n = 466). The other treatments were: salmeterol (n = 212); formoterol (n = 157); fluticasone (n = 100); budesonide/formoterol (n = 139). The age of the included children varied from 0.5 to 17 years. The share of male patients was higher than that of female and varied from 51 to 80 %. The reasons given for dropping out of a study were many, with the appearance of ADRs being the most frequently mentioned but generally without specification of which ADRs. Table 4 displays the information available in the articles about ADRs leading to patient dropout. Across studies asthma exacerbation was the most common cause for discontinuation [8–19].

Design

Information about ADRs was reported in clinical studies using different designs, i.e. randomized, parallel group studies (n = 10) [8–14, 17, 18], randomized open-label design (n = 2) [13, 15], and a randomized crossover study (n = 1) [16]. The tested dosages were within the labeled dosages. Placebo was used as comparator in seven studies [8, 9, 11–14, 18] while an active comparator was administered in six studies [10, 13, 15–17, 19].

Treatment period

Treatment duration varied from 1 to 22 months across studies: between 3 and 12 months in the beta2-agonist studies [8, 9]; 2 months in the fluticasone study [10], between 1 and 22 months in leukotriene receptor antagonist studies [11–18] and 3 months in the budesonide/formoterol study [19].

ADRs by type and occurrence

Tables 5 and 6 show the ADR reporting rates (%) of paediatric patients reported in clinical trials listed in the included studies for each type of asthma medication and its comparator. Information about ADR incidence in the monitored populations was only reported if the incidence was above 2 and/or 5 %; consequently, information about rarely occurring ADRs was not reported in the articles. Overall the same categories were reported for both intervention and control groups. In the single studies no

Table 5 Reporting rates (%) of non-serious paediatric ADRs reported in published clinical trials for asthma medications by type and medication

Adverse drug reaction(s)	Intervention	Comparator
	Salmeterol	Placebo
Asthma exacerbations	47	40
Bronchitis	10	11
Cough	9	11
Fever	8	10
Headache	12	8
Sore throat	11	12
Upper respiratory tract infection	24	23
	Formoterol	Placebo
Accident/injury	4	2
Asthma exacerbations	20	17
Bronchospasm	4	7
Headache	6	8
Pharyngitis	4	5
Respiratory tract infection	28	26
Rhinitis	10	10
Viral infection	5	4
	Fluticasone	Budesonide
Allergic skin reaction	1	5
Asthma exacerbations	24	25
Cough	6	4
Ear problems	7	4
Eye disorders	13	9
Headache	3	7
Influenza	3	5
Pyrexia	4	5
Respiratory tract infection	12	15
Rhinitis	11	12
Sore throat	4	5
	Budesonide/ formoterol	Budesonide
Asthma exacerbations	5	3
Cough	5	5
Headache	6	4
Pharyngitis	8	12
Pyrexia	6	2
Respiratory tract infection	8	6
Rhinitis	7	4
Viral infection	7	3

Table 6 Reporting rates (%, range) of non-serious paediatric ADRs reported in published clinical trials for asthma medications by type and medication

Adverse drug reaction(s)	Intervention treatment	Comparator treatment	Placebo
Montelukast			
Abdominal pain	5–11	2–11	9–10
Asthma exacerbations	16–30	1–39	22–38
Bronchitis	5	NA	7
Cough	6–19	13–17	7–11
Diarrhoea	10–11	NA	8–12
Dizziness	3	11	NA
Headache	13–33	1–24	19–22
Infectious gastroenteritis	2–10	5	4
Infectious, viral	6	5	NA
Influenza	9–11	7	4
Nasal congestion	4–11	3	5
Nausea	4	NA	4
Pharyngitis	12–26	4–26	13–15
Pyrexia	8–27	5–7	4–27
Rash	11	8	NA
Respiratory tract infection	15–57	12–50	21–30
Rhinitis	12	12	NA
Rhinorrhoea	1	13	NA
Sinusitis	5–20	16	2
Tonsillitis	8	10	NA
Vomiting	1–16	3	4–20
Wheezing	7	10	NA
Zafirlukast			
Abdominal pain	2	NA	2
Accidental injury	2	NA	3
Asthma exacerbations	4	NA	6
Diarrhoea	2	NA	2
Flu syndrome	2	NA	3
Headache	4	NA	3
Respiratory tract infection	18	NA	28
Sinusitis	3	NA	6
Vomiting	3	NA	2

significant differences in ADR reporting rates were detected between intervention medication and comparator treatment. The following ADRs were the most frequently reported for all tested asthma medications: asthma exacerbation, respiratory tract infection, cough, fever and headache. In the majority of studies the study investigator collected information about ADRs. Two studies did not provide information about assessors [13, 14]. Only sparse information was provided about the scales and classification systems used to detect and assess adverse ADRs reported during the clinical trial.

ADRs by seriousness

No information about seriousness assessment was presented in the included articles. The majority of reported ADRs were classified as non-serious. Serious ADRs were reported in only few studies. Hoekx et al. [10] reported a serious allergic skin reaction from use of budesonide occurring in one person. For the treatment combination budesonide/formoterol 5 serious cases of "exacerbation of asthma" were reported [19]. In the same study two serious cases of larynx edema and pneumonia were reported [19].

Discussion

As far as we know, this is the first study to review the empirical literature on the occurrence of ADRs reported for asthma medications licensed for use in the paediatric population. Among the 162 potentially relevant studies only 12 studies (7 %) reporting information about ADRs in children were located, the majority for montelukast and zafirlukast. We found information about ADRs in large multicenter clinical studies of short duration, primarily conducted in 6- to 11-year-old boys. Leukotriene receptor antagonists were primarily studied. The most frequently reported ADRs were asthma, upper respiratory tract infection, cough, fever and headache.

Validity of reported ADRs, types and prevalence

Although the review process identified a large number of clinical trials exploring the efficacy of asthma medications in the paediatric population only a few of these reported information about ADR rates occurring in the paediatric population, therefore a large number of published clinical studies were excluded from this review. Many studies were excluded as they reported ADRs as number of children reporting the specific ADRs and not ADR rates (see appendix 2). Others were excluded because too few data about possible ADRs from use of asthma medications were reported. Due to insufficient published information, it was not possible to calculate ADR rates for many of the excluded studies. The exclusion of these studies did not result in reduced information about types of ADRs as no additional ADR categories appeared in the excluded articles. Large variations in ADR reporting rates were observed across studies and therapeutic subgroups. Similar types of ADRs were reported for the different asthma medications, such as fever, rhinitis and diarrhea, and only minor differences between ADR rates for the studied intervention and comparator were observed. These commonly reported ADRs could also be seen as normal symptoms occurring in childhood, and therefore value of ADRs reported in the included clinical trials must be discussed further. In the studies different comparators were used, and the use of rescue medication such as short-acting beta2-agonists was also allowed in the included studies. We do not know the extent to which this practice may have affected the ADR reporting rates for intervention and comparator medication. The drugs most studied, almost 80 %, were leukotriene receptor antagonists (montelukast and zafirlukast) while in daily practice short acting beta2-agonists and ICS are recommend as first choice treatment [2]. There was preponderance in boys of the age of 6–11 years and this is in line with the predominance in asthma symptoms in younger children [20–22]. Whether the outcomes for children in these age groups apply for younger children is not clarified. There were no reports of deaths in the included studies. The SMART study found asthma-related deaths among patients >12 years treated with long acting beta 2-agonists (LABAs) and this prompted black box warnings for all LABAs in the US and restrictions in guidelines [23]. None of the ADRs commonly reported in signal detection studies such as psychiatric events and dental discoloration reported for ICS were reported in the clinical trials analyzed in the present study [6]. The reason for this discrepancy could be that the Dutch study included spontaneous ADR reports collected over a longer period of time, thus increasing the probability of detecting rarely occurring ADRs [6]. It may also be that there is no tradition for systematically observing this kind of ADRs in clinical studies of respiratory medications.

Treatment period

Although in real life children are treated for long periods of time, even years, the duration of most of the analysed studies was shorter than 6 months. This is understandable because of the high financial burden of long lasting studies. However, long-term safety is an important item for patients, parents and health care workers. As clinical trials in the paediatric population are scarce, clinicians and health authorities must rely on spontaneous reports as the main source of information about previously unknown ADRs [24]. For that aim, information from spontaneous reports to national and international databases such as the World Health Organization' VigiBase and the European Medicines Agency EudraVigilance is essential as these databases constitute a critical source of important data, especially information about new, unlabeled, serious, and rarely occurring ADRs.

Validity of 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 experienced ADRs and,

therefore, the actual number of serious ADRs occurring from the use of the respective asthma medications should be expected to be higher/or could be higher. Another issue is that information about definitions and scales to define and evaluate events occurring during the clinical trials was not reported in the articles and, hence, remains unknown. Low quality of reporting ADRs and lack of assessment in randomized clinical trials has been recognized before [25]. Previous studies have shown large discrepancies between the data reported in clinical trial protocols and the data published in scientific journals [25, 26]. Surveys have reported that the fears of children and parents about serious ADRs could lead to poor compliance with prophylactic treatment regimes, resulting in poor control of asthma symptoms, inappropriate use of rescue medication, increased hospitalization, and more frequent visits to general practitioners [27, 28]. This is another reason to report ADRs as accurately as possible. When performing clinical studies researchers should seek ADRs actively and they should not be dependent on spontaneous reports by parents or caregivers. As can be seen in Tables 5 and 6 not much difference between study drug and comparators were found. A statistical comparison between study drugs and comparators was, due to low number, not possible. Although it is tempting to conclude that the number of ADRs is really low, we cannot be sure that this is true, due to the abovementioned reasons.

Publication bias

Previous studies have demonstrated that not all results of clinical trial are published in the literature—especially results of clinical trials conducted in the past for older medications showing negative results with respect to efficacy and safety of the tested medications in vulnerable populations, i.e. children and elderly [28]. Due to the widespread use of beta2-agonists and corticosteroids and the small number of available studies reporting sufficient information about ADRs from use of these medications in children, the publication bias in this specific setting is probably strong, especially since all included clinical trials in the current review were funded by pharmaceutical companies.

Strengths and limitations of this review

The included clinical studies were conducted over a period of approximately 10 years in different countries and observation periods, and with a great deal of inconsistency in observation and classification of type and seriousness of reported ADRs. The variations in the observation periods could have had an impact on the number and type of reported ADRs. However, the clinical studies did not report whether ADR rates were corrected for variations in observation period. Information about the seriousness of the reported ADRs was extracted from the included studies. As we did not have access to the original data material, it was not possible for us to evaluate these assessments, nor to estimate ADRs in terms of effect sizes. A major limitation of this study is lack of information in the clinical trials about causality assessment procedures of the reported ADRs, which has implications for the clinical interpretation of the findings. Another limitation is that we do not know whether "intention-to-treat" or "per-protocol" analysis were used in the clinical trials. Estimates of ADRs may vary substantially within the two types of analysis and may lead to important underreporting bias. The reporting system of ADRs in clinical trials does not represent the gold standard, and the clinical trials have limited duration of time in a selected population in order to collect information about ADRs. This study confirmed, that the included clinical trials did not offer information about new, unexpected, or rare occurring ADRs as expected due to the low number of included children in the trials. Therefore we suggest that further epidemiological studies in this area should be conducted.

Conclusions

Despite the large number of clinical studies on asthma medication in children, only a few studies reporting ADRs from use of asthma medications in children were identified in the literature. This study highlights some very important issues about information on ADRs of asthma medication in clinical studies. Firstly, the patients included are mostly boys in the age of 6–11 years. Information on ADRs in younger children, who are more vulnerable, is scarce. Although in practice salbutamol and ICS are used most frequently, most information on ADRs was on leukotriene receptor antagonists. Only a few serious ADRs were reported, but patients' withdrawal from clinical studies due to ADRs should be investigated more clearly. We believe that giving correct and reliable information on ADRs in asthma medication in clinical trials is a responsibility of researchers, authors, editors of journals, pharmaceutical companies, and regulatory agencies.

Acknowledgments We thank Dr. T.W. de Vries, Paediatric Department, Medisch Centrum Leeuwarden, Netherlands, for commenting on previous drafts of this manuscript. We also thank MSc (pharm) Malene Hammer Krag for assistance with quality assurance of data extractions. Furthermore we also thank the information specialists at the National Library of Denmark and Copenhagen University Library for assistance with the literature searches.

Funding No sources of funding were used to assist in the preparation of this study.

Conflicts of interest None.

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