

Use and Safety of Respiratory Medicines in Children

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The work presented in this thesis was conducted at the Department of Medical Informatics of the Erasmus University Medical Center, Rotterdam.

The research reported in this thesis was funded by the European Community's 6th Framework Programme. Project number LSHB-CT-2005-005216: TEDDY: Task force in Europe for Drug Development for the Young.

The contributions of the participating primary care physicians in the IPCI, Pedianet and IMS-DA project are greatly acknowledged.

Financial support for printing this thesis was kindly provided by the department of Medical Informatics – Integrated Primary Care Information (IPCI) project of the Erasmus University Medical Center; and by the J.E. Jurriaanse Stichting in Rotterdam.

Cover: Optima Grafische Communicatie
Printed by: Optima Grafische Communicatie

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Use and Safety of Respiratory medicines in Children
ISBN: 978-94-6169-003-6

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Use and Safety of Respiratory Medicines in Children

Het gebruik en de bijwerkingen van respiratoire medicijnen in kinderen

Proefschrift

Ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

Prof.dr. H.G. Schmidt

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 9 februari 2011 om 13.30 uur

door

Elif Fatma Şen

Geboren te 's Gravenhage

Promotiecommissie

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Chapter 1

General introduction

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The lack of appropriately authorised and formulated medicines for use in the pediatric population is a longstanding problem and cause for concern. As a result, most medicines are prescribed to children on an off-label or an unlicensed basis [1]. Dosing regimens approved for adults are extrapolated to pediatric age groups, for example on the basis of proportionality of weight, without pediatric pharmacokinetic or pharmacodynamic data. Safety and efficacy are presumed to be the same as in adults, but this may not be the case. Evidence-based information in children is often not readily available, and prescribing decisions may have to be based on accepted practice presented in formularies.

On January 26, 2007, the new regulation of the European Union (EU) on medicinal products for pediatric use came into force [2]. The overall aim of the regulation is to improve the health of children in the EU. More specifically the objectives include: increasing the development of medicines for use in children; ensuring that medicines used to treat children are subject to high quality research and appropriately authorised for use in children; improving the information available on the use of medicines in children; and achieving the above objectives without subjecting children to unnecessary clinical trials or delaying the authorisation of medicines in the adult population.

Previously, pharmaceutical industry had been free to restrict a particular medicine's development to the adult population; the development of pediatric medicines was solely at the industry's discretion. The new regulation requires that all applications for marketing authorisation for new medicines, must contain the results of all studies and information required in a previously agreed pediatric investigation plan (PIP) The PIP will contain a full proposal of all the studies (and their timings) necessary to support the pediatric use of an individual product and will cover all pediatric age groups and all necessary age-appropriate formulations. In some case, pharmaceutical companies can obtain a deferral of waiver from a PIP, for example where there is no pediatric therapeutic need or where pediatric use of the product is not appropriate. Unless a deferral or a waiver has been granted, pediatric data must be provided in all applications for the authorisation of new medicinal products.

The regulation also establishes a new type of marketing authorisation, called the pediatric use marketing authorization (PUMA), intended to stimulate the development of off-patent products for use in the pediatric population. Only medicines that are intended solely for use in children will be eligible for a PUMA.

The new legislation obliges the European Medicines Agency to build one European network from the different existing networks and collaborative projects, investigators, and specific Centers of Excellence.

TEDDY

The Task-force in Europe for Drug Development for the Young (TEDDY) Network of Excellence was established in 2005 through funding of the European Community's sixth Framework

Programme to contribute to the promotion of safe and efficacious medicines for children in the context of the impending European Paediatric Regulation that came into force in January 2007 [3, 4]. The overall aim of the TEDDY NoE is to promote the availability of safe and effective medicines for children in Europe by integrating existing expertise and good practices, as well as stimulating pediatric drug development. The work presented in this thesis is a spin-off of the TEDDY activities.

Respiratory medicines

Respiratory medicines contain a wide variety of medicines and are amongst the most frequently used medicines in children [5]. In this thesis we will focus on the use and safety of two groups of respiratory medicines in particular, namely asthma medicines and cough and cold medicines.

Asthma medicines

Asthma is defined as a chronic inflammatory disorder of the airways and is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing [6]. Asthma is the most common chronic disease of childhood and the leading cause of childhood morbidity from chronic disease as measured by school absences, emergency department visits and hospitalizations [7]. As a result, asthma medicines are used widely in the pediatric population. According to the Global Initiative for Asthma (GINA), bronchodilators (inhaled short-acting β_2 -mimetics: SABA; long-acting β_2 -mimetics: LABA; anticholinergics: ACH), inhaled corticosteroids (ICS) and alternative (add-on) treatments such as leukotriene receptor antagonists (LTRA), xanthines and anti-allergics (cromones) all have a place in the treatment of childhood asthma, although at various stages depending on severity of illness [6]. Apart from these respiratory drugs, systemic glucocorticoids are also used in the treatment of asthma. However, due to side effects such as potential adrenal suppression and growth impairment with long term use [6, 8], use of systemic glucocorticoids in asthmatic children is restricted to asthma exacerbations and very severe persistent asthma [6].

Despite the widespread use of these medicines by children very little is known about the long term safety. The Pediatric Committee of the European Medicines Agency has recently published a pediatric needs list, containing drugs that are being used in children and where information on pharmacokinetics, efficacy and safety is urgently needed [9]. This list includes asthma medicines such as salbutamol, fluticasone, montelukast and many others.

The missing information on the pediatric needs list is mostly addressed by through performing clinical trials in children, aimed to obtain a PUMA. However, a TEDDY study has shown that a lot of data on pediatric drug usage is readily available in many healthcare databases throughout Europe [10]. These databases provide an enormous potential to conduct pediatric pharmaco-epidemiological research, without subjecting children to unnecessary clinical trials.

In this thesis, we will demonstrate that data on use and safety of asthma medicines in pediatrics can be obtained by using healthcare databases which are readily available.

Cough and cold medicines

Cough and cold medicines (CCMs) are frequently used to treat upper respiratory tract symptoms in children and have been on the market for many decades. This group of medicines includes expectorants, mucolytics, opium alkaloids (for cough), nasal sympathicomimetics and anti-histamines.

In the past years, safety issues have been raised about the use of these drugs in young children. In the United States poison-control centers have reported more than 750,000 calls of concern related to cough and cold medicines since January 2000 [11]. A report from the Centers for Disease Control and Prevention identified more than 1500 emergency room visits in 2004 and 2005 for children under 2 years of age who had been given cough or cold medicines [12]. A review by the Food and Drug Administration (FDA) identified 123 deaths related to the use of such products in children under six during the past several decades [13]. A growing number of studies associated the use of CCMs to serious adverse events in children, such as cardiac arrhythmias, depressed levels of consciousness and even death [14].

In 2007, a citizen petition was sent to the FDA, urging the agency to review the effects of cough and cold medicines in young children. As a result, the FDA released a recommendation that cough and cold medicines should not be used in children below two years of age [15]. Consequently, Canada and the United Kingdom also posted warnings against the use of CCMs in young children [16, 17].

In this thesis, we studied the effects of these regulatory actions on prescription rates of CCMs. We also investigated the type of adverse effects related to the use of CCMs in children that were reported to the Vigibase database on spontaneous reporting.

Data sources used in this thesis

Although randomized controlled trials (RCTs) are the gold standard to assess the efficacy of a drug, observational studies, using data from large health care databases are ideal to assess the utilization and safety of a drug. [18]. As previously mentioned, a TEDDY study showed that many European healthcare databases are readily available, providing an enormous potential for pediatric pharmacoepidemiological research [10]. The conclusion of that study was that future research should focus on methods to bring data from different databases together to use the full capacity effectively.

In this thesis, we combined data from some of these databases to obtain data on utilization and safety of asthma medicines and cough cold medicines.

Three different types of data sources were used for the studies presented in this thesis: primary care physician databases (IPCI, Pedianet and IMS), the PHARMO Record Linkage System, and the Vigibase database of the WHO-UMC which collects spontaneous reports on adverse drug reactions.

These data sources allowed us to perform large scale pharmacoepidemiologic and pharmaco-vigilance studies, without limitations mostly observed in RCTs, such as small sample sizes and

short duration of follow-up [19]. We demonstrate that an enormous amount of healthcare data is available in databases throughout Europe and that these databases can be used to provide valuable information on use and safety of medicines in children.

Aims and outline of this thesis

In this thesis we aimed to analyse the use and safety of asthma medicines and cough and cold medicines in children through large scale observational studies, by combining readily available healthcare databases. In chapter 2 we describe the utilization of medicines in children and in particular, the utilization of asthma and cough and cold medicines. For these studies we used the IPCI, Pedianet and IMS-DA databases

In chapter 3 safety studies are presented. To get a broader understanding of the adverse drug reactions causes by asthma medicines and CCMs, two studies focus on adverse drug reactions for reported to Vigibase.

In two other studies we assess the association between steroids (both inhaled and oral) and two outcomes: fractures and pancreatitis, by means of case control studies. For these studies we used the IPCI and Pedianet databse and PHARMO RLS.

The meaning and limitations of the studies are discussed in chapter 4 and recommendations are made for future research.

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Chapter 2

Drug utilization

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Chapter 2.1

The TEDDY network: Trends in pediatric drug use in Europe, an epidemiological perspective

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*Published in: European Journal of Hospital Pharmacy Practice, 2007; Nr: 6;
Pages: 22- 24;*

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Summary

Not only do we have limited drug efficacy data for children, but also little is known about the extent, types and safety of drugs that are actually being used in pediatrics. The TEDDY network aims to improve pediatric drug development. To help in prioritizing research the network has started out to describe available datasources for pharmacoepidemiologic research and the actual description of drug utilization in children. This paper describes these TEDYY activities in more detail.

Introduction

The Taskforce in Europe for Drug Development for the Young (TEDDY) is a Network of Excellence funded under the 6th EU Framework (www.teddyoung.org). The overall aim of TEDDY is to promote the availability of safe and effective medicines for children in Europe by integrating existing expertise and good practices, as well as stimulating pediatric drug development. One of the objectives of TEDDY is to set up a harmonised, integrated and reliable European database containing information on the types and extent of drugs used in children. This paper reviews activities related to assessing pediatric drug use. The European Medicines Evaluation Agency (EMA) has drafted lists of drugs in need of pediatric research, however with this list of more than 100 drugs it is necessary to prioritize, since it will be impossible to conduct all requested research in parallel (reference necessary!! EMA site). Using data on which types of drugs are actually used in children may help in choosing for which drugs we should most urgently demonstrate efficacy in children, find adequate formulations and provide data on short and long term safety.

Datasources

Information on drug use in general can be obtained from market research sources, but these do not provide information on age, or other clinical details such as the type of prescriber, indication, dose and off-label use. Pharmacoepidemiology (the study of the utilization and effects of drugs in large populations) relies heavily on health care databases as data source for adult drug use and effects. To understand better whether databases would be suitable for pediatric postmarketing drug research a survey was conducted within the TEDDY NoE to describe the characteristics of existing European healthcare databases and to assess whether the databases can be used for pediatric medicines research [1]. Sixteen healthcare databases from 10 different European countries were identified, together covering a source population of about 9 million children from 0-18 years of age. Almost exclusively these databases covered only out-patient drug use, Ten out of the 17 databases previously published studies specifically addressing the paediatric population, but only three databases (PEDIANET, GPRD, IPIC) were already used to investigate the safety of paediatric drugs. [2-9]. An international collaboration or network of databases as foreseen in the TEDDY project would allow for the extraction of important information from data already available and enhance our knowledge about pediatric drug use and safety of e.g. off-label used drugs.

Outpatient drug use

To demonstrate the possibilities of such an international collaboration and to provide information on pediatric drug use in Europe, TEDDY started describing drug prescription patterns in primary care by using established medical record databases in the UK, Netherlands and Italy. These databases contain information on more than five million paediatric prescriptions during 2.3 million pediatric person years). The prevalence of drug use (number of users per year) could be divided in three categories of use namely high use (>10% of children using the drug at least once in a year), moderate use (1-10% users per year) and low use (<1% of users per year). For all age categories, anti-infectives (ATC J), dermatological (ATC D) and respiratory drugs (ATC R) were in the high use group, whereas cardiovascular and anti-neoplastic drugs were always in the low use group[10] (figure 1).

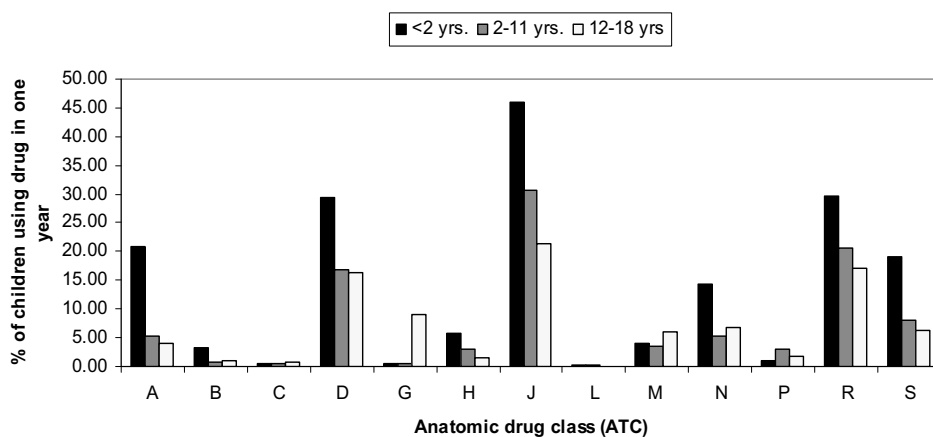


Figure 1: Pediatric drug use in Netherlands, UK and Italy, by age and anatomic class

Legend: ATC A: Alimentary tract, ATC B: Blood and bloodforming organs, ATC C: cardiovascular, ATC D: Dermatological, ATC G: Genitourinary tract, ATC H: Hormones (excl sex), ATC J: Anti-infectives, ATC L: Anti-neoplastic and immunological, ATC M: Musculoskeletal, ATC N: Nervous system, ATC P: Anti-parasitic drugs, ATC R: Respiratory, ATC S: Sensory organs, ATC V: various.

Since the primary care database may miss prescriptions written by specialists we also searched for databases that could provide insight in drug use by type of prescriber. The PHARMO record linkage database in the Netherlands comprises pharmacy dispensing data on more than 360.000 children (www.pharmo.nl). A study on all drugs dispensed in the year 2005 showed that the majority of pediatric drug dispensings (78%) are prescribed by the general practitioners (figure 2). The high volume categories dermatological, respiratory and anti-infective drugs are mostly prescribed by GPs (all less than 15% by specialists). Categories with a relative high percentage of prescribing by specialists are the alimentary tract drugs (ATC A: 49% by specialists), drugs for blood and blood forming organs (ATC B: 46% by specialists), hormones (ATC H: 40% by specialists), antineoplastic and immunomodulating drugs (ATC L: and neuropsychiatric

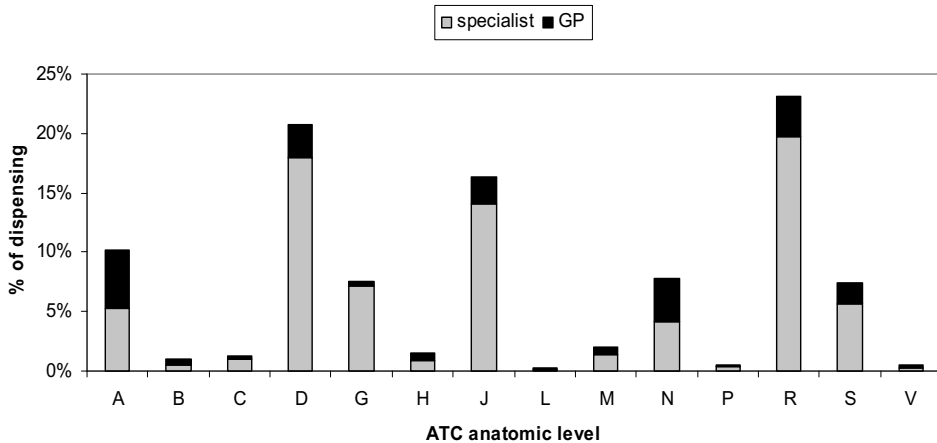


Figure 2: Percentages of pediatric drug dispensings written by specialists or GPs (percentages calculated on the basis of the total number of drug prescriptions)

Legend: ATC A: alimentary tract, ATC B: Blood and bloodforming organs, ATC C: cardiovascular, ATC D: dermatological, ATC G: genitourinary, ATC H: hormones, ATC J: anti-infectives, ATC L: anti-neoplastic and immunological, ATC M: musculoskeletal, ATC N: nervous system, ATC P: anti-parasitic drugs, ATC R: respiratory, ATC S: sensory organs, ATC V: various.

drugs (ATC N: 47%). Within the alimentary drug class, the stomatological preparations group (A01) was responsible for most of the specialist prescriptions, within the ATC B class specialists prescribed mostly antihemorrhagics (B01) and antianemic (B02) drugs, within the class of hormones oral steroids (H02) and thyroid therapy (H03) were mostly prescribed by specialists, within the antineoplastic and immunomodulating class all four groups (antineoplastic drugs, endocrine therapy, immunostimulants and immunosuppressive drugs) were prescribed mostly by specialists, within the neuropsychiatric drugs, antiepileptics (N03), psycholeptics (N05) and psychoanaleptics (N06) were mostly prescribed by specialists (figure 3).

Prescription data from general practices is a reliable source to assess drug exposure in countries where the general practitioner acts as gatekeeper to further care, dispensing data (including outpatient specialists) is available as claims data in countries with a national health system (e.g. Scandinavia, and Italy) but frequently are government owned and more difficult to access.

Apart from some ad hoc studies very little is known about pediatric drug use in the hospital [11], whereas it has been demonstrated that most of the inpatient pediatric drugs are used off-label [12, 13]. There is an urgent need for collaboration between pediatric hospital pharmacies and paediatric researchers to perform quantitative and qualitative studies on this subject. TEDDY is currently looking for partners that can participate in such studies.

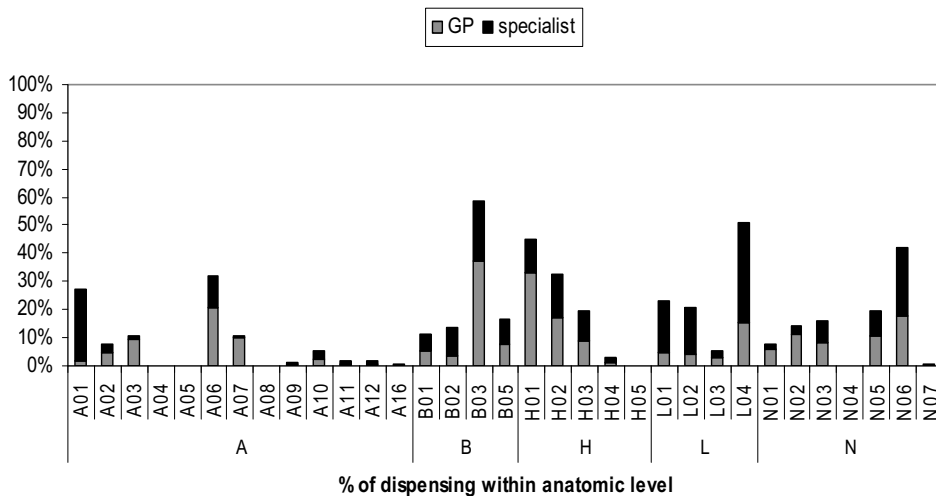


Figure 3: Percentage of pediatric dispensed drug prescriptions written by specialists and GPs, as percentage of total number of prescriptions within anatomic level

Legend: ATC A01: Stomatological preparations, A02: Drugs for acid related disorders, A03: Drugs for functional gastrointestinal disorders, A04: Antiemetics and antinauseants, A05: Bile and liver therapy, A06: Laxatives, A07: Antidiarrheals, intestinal anti-inflammatory/anti-infective agents, A08: Antiobesity preparations, excluding diet products, A09: Digestives, including enzymes, A10: Drugs used in diabetes, A11: Vitamins, A12: Mineral supplements, A16: Other alimentary tract and metabolism products, B01: Antithrombotic agents, B02: Antihemorrhagics, B03: Antianemic preparations, B05: Blood substitutes and perfusion solutions, H01: Pituitary and hypothalamic hormones and analogues, H02: Corticosteroids for systemic use, H03: Thyroid therapy, H04: Pancreatic hormones, H05: Calcium homeostasis, L01: Antineoplastic agents, L02: Endocrine therapy, L03: Immunostimulants, L04: Immunosuppressive agents, N01: Anesthetics, N02: Analgesics, N03: Antiepileptics, N04: Anti-parkinson drugs, N05: Psycholeptics, N06: Psychoanaleptics, N07: Other nervous system drugs.

Unlicensed and off-label

Because of the lack of research on safe and effective drugs in children, unlicensed and off-label drug use in children is widespread [11-14]. Previous investigations have shown that various definitions for “off-label and unlicensed drug use” are used, which makes it difficult to compare data in children. A Delphi method based survey was recently conducted by TEDDY to better define the concepts off-label and unlicensed drug use in children [15]. The definition concluded from the survey has been discussed with the European Agency for the Evaluation of Medicinal Products (EMA) and is agreed by a panel of European experts in the field. Off-label is now defined as all uses of a marketed drug that are not included in the Summary of Product Characteristics (SPC) with reference to indication, dosage, formulation, routine of administration, etc. This definition is adopted by the TEDDY expert group and also endorsed by the EMA.

To quantify the extent of off-label use according to the new definitions, TEDDY is investigating the number of off-label users and percentage of off-label drug use for the drugs prescribed in

primary care in the Netherlands, Italy and the UK according to the new definitions. This scheme can be applied to any type of datasource and demonstrate the areas of greatest pediatric research needs.

Conclusion

To better guide prioritization of pediatric research it is useful to have information about the extent to which various drugs are actually being used in children in both primary care as well as in secondary and tertiary care. Observational databases consisting of drug prescriptions or dispensings are a good resource to describe which specific types and formulations of drugs are actually being used in outpatient settings, TEDDY is providing important information on resources, and outpatient drug use in children. However, resources on in-hospital drug use is lacking and collaboration is being sought to create an international network on in-hospital drug databases. Pharmacists being aware of patient level databases of drug use and diagnoses in their hospital can contact the authors to collaborate in creating a pan-European network of in-hospital data for pediatric drug use.

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Chapter 2.2

Drug utilisation in children -A cohort study in three European countries-

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Published in: British Medical Journal, Clinical research ed. 2008;337:a2245.

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Abstract

Context: The new European legislation concerning paediatric drugs has been conceived in order to stimulate research into children's medicines, but little is known about the patterns of general and chronic drug use in children.

Objective: To provide an overview of drug use in children in three European countries.

Design: A retrospective cohort study covering the years 2000-2005

Setting: Three primary care research databases in the Netherlands (IPCI), United Kingdom (IMS-DA) and Italy (Pedianet)

Patients: All children up to 14 (Italy) or 18 years of age (United Kingdom and The Netherlands).

Main outcome measure. Prevalence of use per year was calculated by drug class (anatomic and therapeutic levels). Within each therapeutic drug level, we estimated the prevalence of "recurrent/chronic" use (≥ 3 prescriptions per year) or "non-recurrent" or "acute" use (< 3 prescriptions per year). Within each anatomic class the top five most frequently used drugs are described and evaluated for off-label status.

Results: Three levels of drug use could be distinguished in the study population of 675,868 children: high (> 10 per year), moderate (1-10 per year) and low (< 1 per year). For all age categories, anti-infectives, dermatological and respiratory drugs were in the high use group, whereas cardiovascular and anti-neoplastic drugs were always in the low use group. Emollients, topical steroids and asthma drugs had the highest prevalence of recurrent use, but low prevalence drugs were relatively more often used recurrently than acutely. In the top five of highest prevalence drugs topical inhaled and systemic steroids, oral contraceptives and topical or systemic antifungals were most frequently off-label

Conclusion: This paper provides an overview of outpatient pediatric prescription patterns in a large European population. As these data are population-based and cover all types of drugs they may support prioritising research needs concerning long-term paediatric drug safety, as well as areas for need of extra efficacy and effectiveness studies in paediatric medicine.

BACKGROUND

Recent years have seen growing concerns about the incompleteness of the evidence relating to the efficacy and safety of the drugs used in children. Almost all of the drugs prescribed to children are the same as those originally developed for adults. They are frequently prescribed to children on an unlicensed or 'off-label' basis (percentages ranging from 11-80)¹ simply by extrapolating adult data, without conducting any paediatric clinical, kinetic, dose-finding or formulation studies. However, childhood diseases may be very different from their adult equivalents, and the processes underlying growth and development may lead to a different effect or an adverse drug reaction unseen in adults (Reye's syndrome is an outstanding example).

In order to provide legitimate and appropriate treatment for children's diseases, new legislation was approved in the US in 2003 and the European Union in 2007². Both the Food and Drug Administration (FDA) and the European Medicines Agency for the Evaluation of Medicinal Products (EMA) now offer license extensions to marketing authorisation holders who provide evidence concerning the efficacy and safety in children of new drugs or 'off-label' drugs³⁻⁶. The World Health Organization underlines the need for these actions and has launched a global campaign in December 2007 to 'make medicines child size' with the purpose to address the need for improved availability and access to safe child-specific medicines for all children⁷

In an attempt to assist public authorities and the research community in specifying the research needs, we investigated the use of paediatric drugs in children in three European countries, using population-based primary care prescription data in order to describe the current patterns of drug prescribing for children by primary care physicians (general practitioners or paediatricians).

METHODS

Setting

The primary care of children is entrusted to general practitioners in the UK and The Netherlands, and to paediatricians in Italy^{8 9}. Access to health care is free in Italy and the UK, and fully covered by healthcare insurance in The Netherlands. In these countries, primary care physicians are the guardians of children's health, which means that all clinical information concerning the patients (including summaries of specialist and hospital care) is kept in their medical records. Since all children need to be registered with a GP in NL and UK, and with a family paediatrician in Italy, the databases are population-based⁹.

Data collection

We used the same protocol to study prescription patterns in Italy (IT), The Netherlands (NL) and the United Kingdom (UK), making use of the Pedianet database (paediatric electronic medical

records from 150 paediatricians since 2000) in Italy¹⁰, the Integrated Primary Care Information (IPCI) database (comprising adult and paediatric electronic medical records from more than 400 doctors since 1996) in The Netherlands^{8 11 12}, and the IMS Disease Analyzer database (IMS-DA: electronic medical records on adults and children from 670 doctors) in the UK¹³. All of these databases include the complete automated medical records of primary care, physicians and have been used and proven valid for pharmacoepidemiological research⁹. The age and gender distribution in the various databases is representative for the country they originate from.

Study population

The dynamic study population in each country consisted of all children aged 0-18 years (0-14 years in Italy) who had a database history of at least six months, or who were born during the study period (1 January 2000 – 31 December 2005), and we calculated the person-time of follow-up of each child, stratified by calendar year and age group. Age was assessed on 1 January of each year and grouped according to the Guidelines of the International Conference of Harmonization (ICH) in <2, 2-11, and 12-18 years of age¹⁴. The <2 year age category could not be further stratified into newborns (<1 month) and infants (1-24 months) as exact dates of birth were not available because of privacy regulations. Each child was followed from the start of the study period or the date of registration with the primary practice (whichever was the latest), until the cancellation of the registration with the practice or the end of the study period. The person-time accumulated in each calendar year was used as denominator for calculation of prevalence rates. Over the study period children could contribute to more than one age category.

Drug prescriptions

All prescribed drugs in children during follow-up were retrieved from the prescription data in the database. The drug prescriptions were grouped on the basis of the WHO's Anatomical Therapeutic Chemical (ATC) classification system which made comparison between countries possible.

Statistical analysis

User prevalence rates (per 1,000 PY) were estimated by counting the number of children using a specific drug in a specific calendaryear. The prevalence rates were calculated by age and country to account for differences in distributions between populations and to allow for direct within stratum comparisons. User prevalence rates should be interpreted as the number of children per 1,000 children who use a specific drug class in one year. Drug use prevalence in Italy was not calculated for children aged 15-18 years because all of the children were censored at the age of 15 years. The use of person-years rather than persons as the denominator was due to the dynamic nature of age and the population.

For each anatomic drug category we assessed the age and country specific user prevalence rates for all individual drugs in 2005. The five drugs with the highest prevalence per anatomic class in each country are reported and were evaluated for off-label status considering age only. A drug was considered to be off-label for age if the child's age at the time of use, was below the lowest approved age as mentioned in the Summary of Product Characteristics of that drug per country¹⁵. Within each therapeutic drug level, we separately estimated the prevalence of children presenting "recurrent/chronic" (≥ 3 prescriptions per year) versus "non-recurrent" or "acute" drug use (< 3 prescriptions per year), and the ratio between them in order to help identify the treatments that are more frequently used for chronic than acute paediatric diseases. Comparisons between user prevalence rates were done by means of the Chi-square test.

RESULTS

Study population

Our population of 675,868 children generated 2,334,673 person-years of follow-up (Table 1); the mean individual follow-up was 3.5 years per child. Most of the children (65%) came from the IMS database in the UK, 19% from Italy and 16% from The Netherlands. The databases recorded more than five million paediatric prescriptions. The prescription rate was highest for the children aged less than two years in all three countries and, in each age group, was significantly higher in the UK and Italy than in The Netherlands (p-values < 0.001), (table 1).

Drug use by anatomically grouped drug classes

The highest prevalence rates among the children aged less than two years were for anti-infectives (ATC code J), respiratory drugs (R) and dermatologicals (D), which were used by 48%, 30% and 30% of the children, respectively (Figure 1). The other frequent prescriptions were for gastrointestinal drugs (A, with a user prevalence of 20%), drugs for the nervous system (N, 14%) and drugs for sensory organs (S, 19%). ATC classes B (blood and blood forming organs), H (hormones) and M (musculoskeletal system) were used by between 1 and 10% of the children, and cardiovascular (C), genitourinary (G), anti-neoplastic (L) and anti-parasitic (P) drugs by less than 1%.

Among the children aged 2-11 years, the prevalence of use of anti-infectives, respiratory drugs and dermatologicals decreased to respectively 30%, 21% and 17%; that of the drugs belonging to ATC classes A, H, M, N, P and S was between 1 and 10%; and that of drugs belonging to class B, C, G and L was less than 1%.

In adolescents (12-18 years of age), anti-infectives, respiratory and dermatologicals were used by more than 10% per year. Most of the other drug classes were used by 1-10%, but the prevalence of use of cardiovascular and anti-neoplastic drugs was less than 1%.

Table 1: Characteristics of the study population

Patient characteristics	Children N	PY N (%)	Rx N	Rx per PY
Italy				
<2 years#	56000	87408 (22)	286597	3.3
2-11 years#	103195	296148 (73)	690688	2.3
12-18 years#*	18154	22599 (6)	35883	1.6
Females	61962	194744 (48)	462580	2.4
Males	67525	211412 (52)	550588	2.6
2000	11188	369 (0)	1150	3.1
2001	73364	45330 (11)	140764	3.1
2002	95712	78850 (19)	220207	2.8
2003	103987	94131 (23)	242261	2.6
2004	106555	96388 (24)	206535	2.1
2005	102911	91086 (22)	202251	2.2
Total	129,487	406,156 (100)	1,013,168	2.5
UK				
<2 years#	95060	106250 (6)	494353	4.7
2-11 years#	262306	855678 (52)	2011153	2.4
12-18 years#*	229959	683900 (42)	1549372	2.3
Females	219669	804646 (49)	2047616	2.5
Males	225153	841182 (51)	2007262	2.4
2000	307884	288450 (18)	659067	2.3
2001	306923	286483 (17)	677373	2.4
2002	305088	285664 (17)	670690	2.3
2003	303594	280085 (17)	679216	2.4
2004	287287	259219 (16)	674389	2.6
2005	265273	245927 (15)	694143	2.8
Total	444,822	1,645,828 (100)	4,054,878	2.5
Netherlands				
<2 years#	25694	36601 (13)	78983	2.2
2-11 years#	62326	159010 (56)	208134	1.3
12-18 years#*	40364	87078 (31)	147250	1.7
Females	49709	138262 (49)	230466	1.7
Males	51850	144427 (51)	203901	1.4
2000	56423	48752 (17)	76319	1.6
2001	53274	46822 (17)	76059	1.6
2002	57998	50219 (18)	81919	1.6
2003	62216	49279 (17)	73462	1.5
2004	60315	50882 (18)	75399	1.5
2005	52252	36735 (13)	51209	1.4
Total	101,559	282,689 (100)	434,367	1.5

PY=person-years; Rx=prescriptions; #The number of children in the various age groups does not add up to the total since one child can contribute to more than one age category. * for Italy the age range included only 12-14 years.

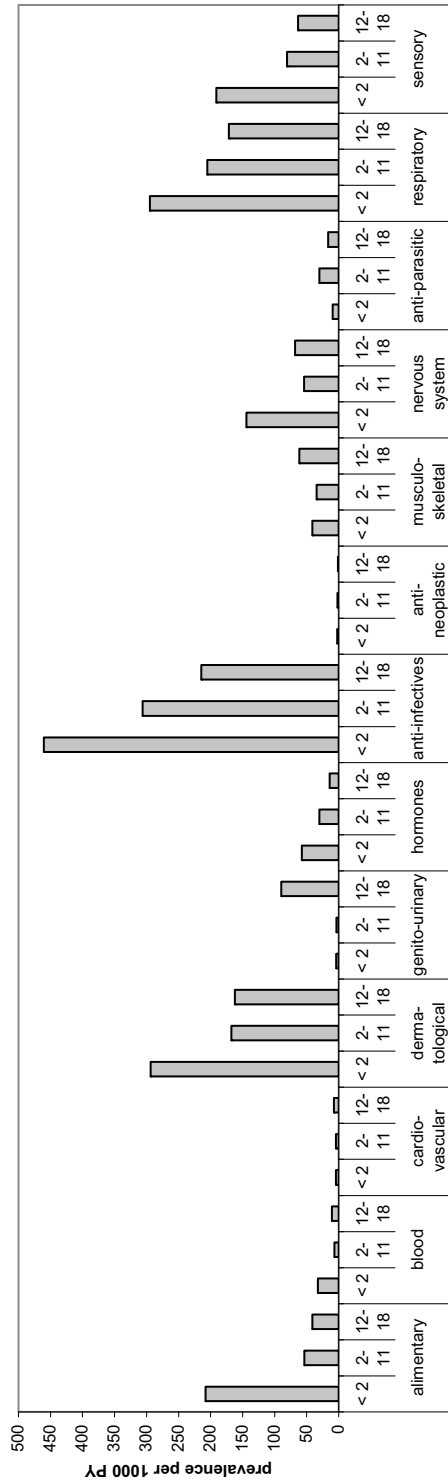


Figure 1: One-year prevalence of drug prescriptions by age (<2, 2-11 12-18 years), and anatomic drug class (X-axis)

Regarding gender differences, in the youngest age groups, most of the drugs were equally prescribed to both genders or more frequently prescribed to boys than girls (rate ratio (RR) <1), particularly anti-infectives and respiratory drugs. This pattern reversed in adolescence, when user prevalence for almost all drug classes (except non-sex hormones) was higher among girls than boys. This gender pattern, which was consistent across countries, was most pronounced for genitourinary drugs (G), whose user prevalence was more than 60-fold higher in girls because they include oral contraceptives, which accounted for 95% of the girls' use of G drugs. The use of drugs for blood and blood forming organs (mainly iron preparations) was also markedly higher among adolescent girls.

The age trend of prevalence of use was consistent across countries, although there were some variations in the age-specific rates (Figure 2). In particular, the UK showed the highest prevalence of alimentary drug use (class A) in children aged less than two years, and the prevalence of prescriptions of dermatological drugs (class D) was 3-4 fold higher in the UK and the NL than in Italy (both p-values <0.001). The prevalence of genitourinary drugs (almost all oral contraceptives) was very high in adolescent girls in the NL (p<0.001). In Italy, the use of hormones (almost all systemic corticosteroids) was 10-fold higher in children aged <2 years (p<0.001) and 5-fold higher in those aged 2-11 years (p<0.001); respiratory drug use was also greater in Italy than in the other two countries (p<0.001). The prevalence of the use of anti-infectives and drugs for musculoskeletal disorders was much lower in the NL; the prescription prevalence of nervous system drugs (including paracetamol that is on prescription in UK) was much higher in the UK; and the use of drugs for the sensory organs was much less in Italy.

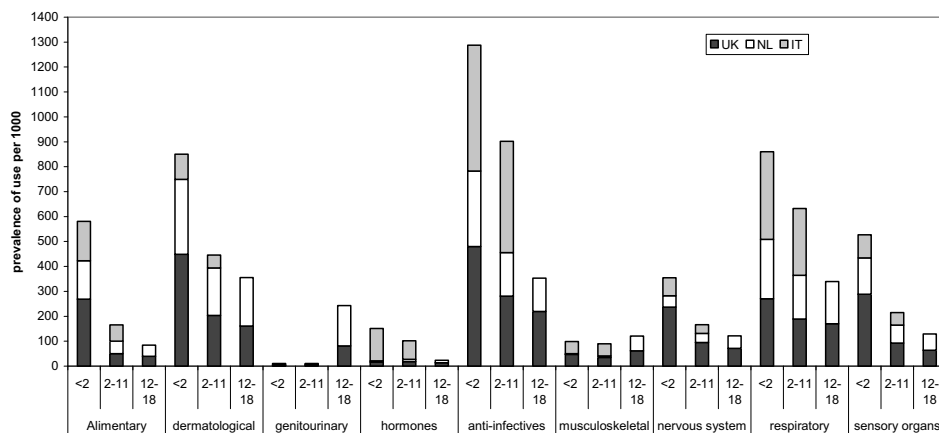


Figure 2: Year prevalence of drug use (per 1000 PY) by age (<2, 2-11, 12-18 years), database (IMS=UK, IPCI= Netherlands, Pedianet=Italy) and anatomic level for the most prevalently used drug classes (PEDIANET data are excluded for the age category 12-18 years)

Prevalence of drug use in therapeutic drug class

Within the most frequently used anatomic drug classes, the therapeutic class of anti-bacterials (J01) accounted for most of the anti-infective drug use; and the therapeutic classes anti-asthmatics (R03), other respiratory products (R07) and nasal preparations (R01) were the most frequently used drugs in the respiratory group (Table 2). Topical corticosteroids (D07) and emollients and protectives (D02) were the therapeutic classes with the highest prevalence of use among the dermatological drugs. Many therapeutic classes in the group of alimentary drugs (laxatives, anti-diarrheals, drugs for acid disorders) had a considerable prevalence of use. The most prescribed drugs in the other classes were anti-anemia medications (ATC class B03), cardiac therapy (ATC class C01, mainly digoxin), sex hormones (ATC class G03), oral corticosteroids (ATC class H02), non-steroidal antiinflammatory drugs (ATC class M01), analgesics (ATC class N02) and ophthalmologicals (ATC class S01).

Ranking of age-specific user prevalence rates of therapeutic classes over the entire range of drugs showed that antibacterials (J01) are the most frequently prescribed drugs in all age groups (table 3), and are at least prescribed to twice as much children as the number two most frequently used drug in each age category. The second most used drug changed by age from ophthalmologicals (S01) (<2 years), drugs for obstructive airway disease (R03) (2-11 years) to sex hormones (G03)(12-18 years).

When the therapeutic classes within each anatomic class were ranked on the basis of the ratio between recurrent (chronic) and non-recurrent(acute), a different pattern was observed (table 2). The drugs with a ratio of >1 (indicating mostly chronic/recurrent use) were often those with a low prevalence of use (except for sex hormones): antidiabetics (A10), digestives (A09), bile and liver therapy (A05), anti-thrombotic agents (B01), agents acting on the renin-angiotensin system (C09), lipid-lowering drugs (C10), sex hormones (G03), thyroid therapeutic agents (H03), immunosuppressive agents (L04), muscle relaxants (M03), anti-epileptics (N03), and psycho-naleptics (N06) (Table 2). In absolute terms, emollients (D02), topical corticosteroids (D07), sex hormones (G03), anti-infectives (J01) and drugs for obstructive airways disease (R03) showed the highest prevalence of recurrent use.

Most frequently used drugs in each anatomic drug class

In the most frequently used anatomic classes (D, J and R), the most frequently used individual dermatological drugs were fusidic acid (except for Italy), topical steroids and topical imidazole/triazole derivatives (table 4). The topical triazoles/imidazoles were off-label in most countries for at least one or more age categories. In the anti-infectives group (J), penicillin derivatives (amoxicillin, amoxicillin+clavulanic acid and phenoxymethylpenicillin) followed by macrolides (erythromycin, clarithromycin) were the most frequently used drugs, cefalexin (UK, < 2 year) was the only off-label drug. Oral acyclovir was one of the top 5 anti-infective drugs in Italy. In the respiratory drug group salbutamol, and inhaled steroids (beclomethasone, fluticasone, flunisolide), antihistaminics (cetirizine, loratidine, clorpheniramine) and xylometazoline were

Table 2: Prevalence of acute use (<3 prescriptions per year) and recurrent use (≥3 prescriptions per year) by age and therapeutic level (prevalence per 1000 PY), ranked by the ratio of recurrent/acute use prevalence.⁴

ATC	Explanation	Acute use prevalence per 1000 PY				Recurrent use prevalence per 1000 PY				Ratio recurrent/acute	Total prevalence
		<2 yrs.	2-11 yrs.	12-18 yrs.	All ages	<2 yrs.	2-11 yrs.	12-18 yrs.	All ages		
A Alimentary tract											
A10	Drugs used in diabetes	0.0	0.2	0.3	0.2	0.0	0.9	2.5	1.3	7.0	1.5
A09	Digestives, including enzymes	0.1	0.0	0.0	0.0	0.1	0.2	0.2	0.2	4.9	0.2
A05	Bile and liver therapy	0.1	0.0	0.0	0.0	0.1	0.1	0.1	0.1	1.7	0.1
A12	Mineral supplements	1.1	0.8	0.5	0.7	0.2	0.3	0.2	0.2	0.3	1.0
A06	Laxatives	24.7	13.3	6.2	12.0	3.3	4.7	1.8	3.6	0.3	15.6
A02	Drugs for acid-related disorders	27.0	3.5	9.6	7.9	12.6	0.8	1.7	2.3	0.3	10.1
A11	Vitamins	24.2	3.6	1.4	4.9	3.5	0.7	0.5	0.9	0.2	5.8
A04	Anti-emetics and anti-nauseants	1.4	0.6	3.7	1.8	0.7	0.1	0.2	0.2	0.1	2.0
A03	Drugs for functional gastrointestinal disorders	25.9	10.6	9.7	11.8	1.4	0.4	0.9	0.6	0.1	12.4
A01	Stomatological preparations	56.3	6.6	4.2	10.7	3.2	0.2	0.2	0.5	0.0	11.2
A07	Antidiarrheals	64.9	11.6	3.2	14.0	1.9	0.3	0.6	0.5	0.0	14.5
B Blood and blood forming organs											
B01	Anti-thrombotic agents	0.2	0.2	0.3	0.3	0.2	0.3	0.3	0.3	1.1	0.5
B03	Anti-anemic preparations	20.8	3.6	6.8	6.4	2.9	0.5	1.2	1.0	0.2	7.4
B02	Anti-hemorrhagics	5.5	1.0	1.6	1.6	0.2	0.1	0.2	0.1	0.1	1.8
C Cardiovascular system											
C09	Agents acting on the rennin-angiotensin system	0.1	0.1	0.1	0.1	0.1	0.2	0.3	0.2	2.5	0.3
C10	Lipid modifying agents	0.0	0.0	0.1	0.0	0.0	0.1	0.1	0.1	1.7	0.1
C03	Diuretics	0.6	0.1	0.1	0.2	0.6	0.1	0.2	0.2	1.2	0.4
C08	Calcium channel blockers	0.0	0.0	0.2	0.1	0.0	0.0	0.2	0.1	0.8	0.2
C07	Beta blocking agents	0.1	0.2	2.2	0.8	0.1	0.2	0.7	0.3	0.4	1.2
C01	Cardiac therapy	1.3	2.2	1.6	1.9	0.2	0.3	0.3	0.3	0.2	2.2
D Dermatologicals											
D10	Anti-acne preparations	0.3	1.0	31.2	11.2	0.0	0.1	15.0	5.2	0.5	16.3
D02	Emollients and protectives	98.8	45.1	25.6	43.8	48.5	21.8	8.1	19.8	0.5	63.6
D05	Anti-psoriatics	3.9	3.1	4.8	3.7	0.2	0.5	2.0	1.0	0.3	4.7
D07	Corticosteroids, dermatological preparations	140.4	74.1	55.9	74.4	24.4	11.9	8.7	12.0	0.2	86.5

Table 2: Continue

ATC	Explanation	Acute use prevalence per 1000 PY				Recurrent use prevalence per 1000 PY				Ratio re-current/acute	Total prevalence
		<2 yrs.	2-11 yrs.	12-18 yrs.	All ages	<2 yrs.	2-11 yrs.	12-18 yrs.	All ages		
D03	Preparations for treatment of wounds and ulcers	1.1	0.7	1.0	0.8	0.0	0.1	0.1	0.1	0.1	0.9
D08	Antiseptics and disinfectants	3.9	2.4	2.8	2.7	0.1	0.1	0.2	0.1	0.1	2.8
D01	Anti-fungals for dermatological use	50.8	18.4	19.6	22.0	1.6	0.6	1.5	1.0	0.0	23.0
D06	Antibiotics and chemotherapeutics	43.6	36.4	23.6	32.8	0.8	0.9	0.9	0.9	0.0	33.7
D11	Other dermatological preparations	5.3	8.9	9.8	8.9	0.2	0.1	0.4	0.2	0.0	9.1
G	Genito-urinary system and sex hormones										
G03	Sex hormones, modulators of the genital system	1.7	0.4	32.3	11.3	0.3	0.1	49.7	17.0	1.5	28.3
G04	Urologicals	0.5	1.1	1.8	1.3	0.1	0.6	0.6	0.5	0.4	1.8
G01	Gynecological anti-infectives and antiseptics	1.1	1.3	9.2	4.0	0.0	0.0	0.5	0.2	0.0	4.2
H	Systemic hormonal preparations, excluding sex hormones and insulins										
H03	Thyroid therapy	0.3	0.2	0.3	0.2	0.4	0.5	1.1	0.7	3.1	0.9
H01	Pituitary and hypothalamic hormones	0.1	2.2	1.5	1.7	0.0	1.3	1.4	1.2	0.7	3.0
H02	Corticosteroids for systemic use	51.0	23.2	8.0	20.7	6.0	2.2	1.0	2.2	0.1	22.9
H04	Pancreatic hormones	0.0	0.3	0.7	0.4	0.0	0.0	0.1	0.0	0.1	0.4
J	Anti-infectives for systemic use										
J01	Anti-bacterials for systemic use	340.0	241.4	166.3	225.6	95.2	47.0	27.6	45.2	0.2	270.7
J04	Anti-mycobacterials	0.5	0.5	0.3	0.4	0.1	0.0	0.0	0.0	0.1	0.5
J07	Vaccines (exc. routine childhood vaccinations)	11.8	10.6	14.3	12.0	0.8	0.4	1.0	0.6	0.1	12.6
J02	Antimycotics for systemic use	1.1	0.6	3.7	1.7	0.0	0.0	0.2	0.1	0.0	1.8
J05	Antivirals for systemic use	9.8	4.2	1.7	3.9	0.1	0.0	0.1	0.1	0.0	4.0

Table 2: Continue

ATC	Explanation	Acute use prevalence per 1000 PY				Recurrent use prevalence per 1000 PY				Ratio re-current/acute	Total prevalence
		<2 yrs.	2-11 yrs.	12-18 yrs.	All ages	<2 yrs.	2-11 yrs.	12-18 yrs.	All ages		
L	Anti-neoplastic and immunomodulating drugs										
L04	Immunosuppressive agents	0.0	0.0	0.1	0.1	0.0	0.1	0.4	0.2	3.8	0.3
L01	Anti-neoplastic agents	0.0	0.1	0.1	0.1	0.0	0.1	0.1	0.1	0.9	0.2
M	Musculoskeletal system										
M03	Muscle relaxants	0.1	0.1	0.2	0.1	0.0	0.1	0.2	0.2	1.7	0.2
M01	Anti-inflammatory and anti-rheumatic products	38.8	32.0	53.6	40.0	1.2	1.2	3.0	1.8	0.0	41.8
N	Nervous system										
N03	Anti-epileptics	0.7	0.7	0.8	0.7	1.1	2.6	3.6	2.8	3.9	3.5
N06	Psychoanaleptics	0.1	1.1	6.8	2.9	0.0	1.7	6.8	3.3	1.1	6.2
N04	Anti-parkinson drugs	0.0	0.0	0.1	0.0	0.0	0.0	0.1	0.0	1.1	0.1
N05	Psycholeptics	7.3	2.2	5.0	3.6	0.4	0.4	1.6	0.8	0.2	4.5
N07	Other nervous system drugs	0.1	0.2	2.0	0.8	0.0	0.0	0.4	0.2	0.2	1.0
N02	Analgesics	109.9	55.0	38.7	54.9	24.2	8.5	5.6	9.0	0.2	63.9
N01	Anaesthetics	2.1	4.2	4.2	4.0	0.1	0.1	0.2	0.1	0.0	4.1
P	Antiparasitic products										
P03	Ectoparasiticides	2.9	14.9	10.6	12.2	0.1	1.5	0.8	1.1	0.1	13.4
P01	Anti-protozoals	1.8	1.7	2.2	1.9	0.0	0.0	0.0	0.0	0.0	1.9
P02	Ant-helminthics	4.4	12.2	3.1	8.4	0.1	0.2	0.0	0.1	0.0	8.5
R	Respiratory system										
R03	Drugs for obstructive airway diseases	126.3	69.3	39.2	64.7	34.8	39.1	31.8	36.2	0.6	100.9
R07	Other respiratory system products	45.4	55.1	53.0	53.4	2.8	8.1	14.1	9.6	0.2	63.0
R06	Anti-histamines for systemic use	50.4	29.1	17.4	27.3	3.5	2.1	2.6	2.4	0.1	29.7
R01	Nasal preparations	79.1	36.2	43.7	43.0	3.9	2.1	4.4	3.1	0.1	46.1
R05	Cough and cold preparations	4.1	2.2	1.7	2.2	0.2	0.1	0.0	0.1	0.0	2.3
R02	Throat preparations	1.1	1.4	4.0	2.3	0.0	0.0	0.1	0.0	0.0	2.3
S	Sensory system										
S01	Ophthalmologicals	164.9	60.7	42.9	64.9	10.3	3.1	4.0	4.1	0.1	69.0
S03	Ophthalmological and otological preparations	3.2	3.5	4.0	3.7	0.1	0.2	0.1	0.1	0.0	3.8
S02	Otologicals	15.7	15.0	13.5	14.6	0.4	0.5	0.6	0.5	0.0	15.1

All ATC therapeutic levels with prevalence of both acute and recurrent use below 0.1 per 1000 PY have been excluded.

Table 3: Top ten of most frequently used therapeutic classes in various age categories

< 2 years		
Therapeutic class		users per 1000 PY
J01	Antibacterials for systemic use	435
S01	Ophthalmologicals	175
D07	Corticosteroids, dermatological preparations	165
R03	Drugs for obstructive airway diseases	161
D02	Emollients and protectives	147
N02	Analgesics	134
R01	Nasal preparations	83
A07	Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	67
A01	Stomatological preparations	59
H02	Corticosteroids for systemic use	57
2-11 years		
Therapeutic class		users per 1000 PY
J01	Antibacterials for systemic use	288
R03	Drugs for obstructive airway diseases	108
D07	Corticosteroids, dermatological preparations	86
D02	Emollients and protectives	67
S01	Ophthalmologicals	64
N02	Analgesics	63
R07	Other respiratory system products	63
R01	Nasal preparations	38
D06	Antibiotics and chemotherapeutics	37
M01	Anti-inflammatory and antirheumatic products	33
12-18 years		
Therapeutic class		users per 1000 PY
J01	Antibacterials for systemic use	194
G03	Sex hormones and modulators of the genital system	82
R03	Drugs for obstructive airway diseases	71
R07	Other respiratory system products	67
D07	Corticosteroids, dermatological preparations	65
M01	Anti-inflammatory and antirheumatic products	57
R01	Nasal preparations	48
S01	Ophthalmologicals	47
D10	Anti-acne preparations	46
N02	Analgesics	44

most frequently prescribed. Beclomethasone, xylometazoline and cetirizine were off-label in the youngest children (< 2 years) in either UK or NL.

In the moderately used drugs (anatomic groups A, G, N, S), the most frequently prescribed alimentary tract drugs (A) were laxatives (lactulose), nystatin, domperidone, mebeverine or ranitidine. Only ranitidine and laurilsulfate were off-label in children < 2 years of age. For the genito-urinary drugs, oral contraceptives and topical anti-fungals (miconazole) determined the top five in NL and UK, whereas Italy (only until age 12) had estrogens, drugs for treatment of incontinence and antiseptics as most frequently prescribed drugs. The percentage of off-label

Dermatological (D)	194	100	1013	100	311	100	1518	Hydrocortisone	2425	0	7311	0	2574	0	12310	Betamethasone/ antibiotics	205	0	431	0	636
Fusidic acid	284	100	734	100	269	100	1287	Fusidic acid	880	0	3936	0	1457	0	6273	Mometasone	240	0	362	0	602
Hydrocortisone	273	0	337	0	204	0	814	Clobetasone	232	0	1888	0	1080	0	3200	Mupirocin	90	0	313	0	403
Miconazole	36	100	360	100	292	100	688	Clotrimazole	828	100	1617	0	627	0	3073	Clotrimazole	175	100	118	100	293
Triamcinolone	48	100	168	100	139	100	355	Betamethasone	74	0	967	0	1360	0	2401	Econazole	90	100	83	100	173
Ketoconazole																					
Genito urinary system and sex hormones (G)																					
Levonorgestrel/ estrogen	1	100	3	100	1034	100	1038	Clotrimazole	61	100	182	100	801	0	1046	Conjugated estrogens	57	0	26	0	83
Cyproterone/ estrogen	0	Na	4	100	321	100	325	Norethisterone	0	Na	4	100	1019	100	1025	Oxybutynin	0	Na	37	0	37
Norethisterone	0	Na	2	100	98	100	100	Levonorgestrel	0	Na	0	0	946	0	946	Benzylamine	2	100	19	100	21
Miconazole	4	100	14	100	58	100	76	Medroxy prog/ estrogen	0	Na	1	100	693	0	695	Povidone-iodine	1	100	14	100	15
Lynestrenol	0	Na	4	100	57	100	61	Desogestrel	1	100	0	100	268	100	272	Estriol	9	100	5	100	14

Table 4 cont'd

Drug name	NL				UK				IT				total users									
	< 2 years	2-11 years	≥12 years	Total users	< 2 years	2-11 years	≥12 years	Total users	< 2 years	2-11 years	≥12 years	Total users										
	#	%	#	%	#	%	#	%	#	%	#	%	#									
	OL	OL	OL	OL	OL	OL	OL	OL	OL	OL	OL	OL	OL									
Systemic hormonal preparations (H)																						
Desmopressin	0	Na	94	0	49	0	143	0	Na	467	0	312	0	779	Betamethasone	1430	0	2064	0	3494		
Prednisolone	14	100	41	100	31	100	86	0	89	0	159	0	267	0	245	Prednisone	5	0	240	0	245	
Levothyroxine sodium	1	0	13	0	16	0	30	0	Na	77	0	108	0	185	Desmopressin	0	Na	120	0	120		
Prednisone	0	Na	11	100	7	100	18	0	100	44	0	8	0	72	Dexamethasone	18	0	6	0	24		
Dexamethasone sodium	4	0	6	0	2	0	12	0	Na	28	0	26	0	54	Levothyroxine sodium	5	0	17	0	22		
Antinfectives for systemic use (J)																						
Amoxicillin	763	0	1870	0	302	0	2935	0	6057	0	5710	0	12285	0	6176	Amoxicillin	2573	0	3603	0	6176	
Amoxicillin / clavulanic	133	0	657	0	155	0	945	0	897	0	4223	0	11163	0	5970	Amoxicillin / clavulanic	1760	0	4210	0	5970	
Clarithromycin	131	0	489	0	137	0	757	0	5265	0	3386	0	9938	0	3282	Azithromycin	666	0	2616	0	3282	
Azithromycin	47	0	246	0	111	0	404	0	351	0	2122	0	5096	0	3068	Clarithromycin	683	0	2385	0	3068	
Pheneticillin	22	0	211	0	161	0	394	0	345	100	1597	0	3041	0	1048	Aciclovir	309	0	739	0	1048	
Antineoplastic and immunomodulating agents (L)																						
Fluorouracil	0	Na	6	100	3	100	9	0	Na	16	0	65	0	81	0	91	Pidotimod	11	0	80	0	91
Azathioprine	0	Na	0	0	3	0	3	0	Na	10	0	24	0	34	0	7	Leuporelin	0	na	7	100	7
Triptorelin	0	Na	2	100	0	100	2	0	Na	13	100	8	0	22	0	6	Triptorelin	0	na	6	100	6
Methotrexate	0	Na	1	0	0	0	1	0	Na	5	0	9	0	14	0	5	Methotrexate	0	na	5	100	5
Ciclosporin	0	Na	1	0	0	0	1	0	Na	2	100	2	100	6	0	3	Ciclosporin	0	na	3	100	3
Musculo-skeletal system (M)																						
Diclofenac	0	Na	29	0	233	0	262	0	1085	0	4251	0	10740	0	1907	Ibuprofen	508	100	1399	100	1907	
Naproxen	0	Na	10	0	171	0	181	0	2	0	1247	0	1290	0	564	Morniflumate	118	100	446	100	564	

Ibuprofen	0	Na	29	0	131	0	160	Mefenamic acid	0	Na	11	0	1278	0	1289	Ketoprofen	8	0	354	0	362
Diclofenac, combinations	0	Na	2	100	12	100	14	Naproxen	0	Na	4	0	143	0	147	Flurbiprofen	19	0	220	0	239
Bufexamac	3	100	8	100	3	100	14	Ketoprofen	0	Na	15	100	70	0	86	Niflumic acid	62	0	168	0	232
Nervous system (N)																					
Methyphenidate	0	Na	125	0	140	0	265	Paracetamol	4292	0	11085	0	2832	0	18209	Paracetamol	603	0	491	0	1094
Paracetamol	38	0	99	0	32	0	169	Methyphenidate	0	Na	286	0	433	0	719	Paracetamol, combinations	255	0	506	0	761
Lidocaine/ prilocaine	3	0	110	0	14	0	127	Pizotifen	0	Na	207	0	430	0	637	Niaprazine	158	0	39	0	197
Carbasalate calcium	0	Na	27	0	79	0	106	Fluoxetine	0	Na	6	0	0	0	404	Diazepam	41	0	85	0	126
Diazepam	8	100	39	100	34	0	81	Diazepam	4	0	124	0	266	0	394	Valproic acid	4	0	39	0	43

Table 4 cont'd

Drug name	UK						IT														
	<2 years	2-11 years	≥12 years	Total users	Drug name	Total users	<2 years	2-11 years	≥12 years	Total users	Drug name	<2 years	2-11 years	total users							
	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#						
	OL	OL	OL	OL	OL	OL	OL	OL	OL	OL	OL	OL	OL	OL	OL						
Antiparasitic drugs, insecticides and repellents (P)																					
Mebendazole	1	0	87	0	14	0	102	Mebendazole	24	100	1695	0	349	0	2069	Mebendazole	38	0	479	0	517
Metronidazole	2	100	21	0	20	0	43	Phenothrin	3	0	201	0	53	0	257	Pyrantel	11	0	145	0	156
Pruganil, combinations	0	Na	4	0	10	0	14	Permethrin	35	0	845	0	400	0	1280	Mefloquine	8	0	16	0	24
Permethrin	1	0	8	0	3	0	12	Malathion	40	0	1088	0	372	0	1500	Albendazole	1	0	22	0	23
																Permethrin	0	na	13	0	13
Respiratory system (R)																					
Salbutamol	311	0	1053	0	448	0	1813	Salbutamol	1309	100	12403	0	8321	0	22034	Beclometasone	1584	0	2849	0	4433
Fluticasone	159	0	702	0	201	0	1062	Beclometasone	256	100	6332	0	3963	0	10552	Salbutamol	1202	0	1932	0	3134
Desloratadine	14	0	447	0	366	0	827	Cetirizine	24	100	3382	0	4145	0	7552	Flunisolide	615	0	1256	0	1871
Xylometazoline	154	100	356	0	143	0	654	Chlorphenamine	578	0	3945	0	959	0	5482	Cetirizine	234	0	1435	0	1669
Levocetirizine	0	Na	177	0	302	0	479	Loratadine	1	0	1992	0	2261	0	4254	Salbutamol combinations	537	0	725	0	1262
Sensory organs (S)																					
Fusidic acid	342	100	441	100	263	100	1049	Chloramphenicol	4155	100	7161	0	2192	0	13509	Tobramycin	441	0	515	0	956
Levocabastine	2	100	130	100	156	100	291	Cromoglicic acid	53	100	1875	0	2630	0	4559	Antifungives, combinations	117	0	256	0	373
Hydrocortisone /antifungives	12	0	129	0	70	0	211	Fusidic acid	1316	0	1951	0	540	0	3807	Dexamethasone and antiinfectives	42	100	229	100	271
Lidocaine	33	100	135	0	16	0	185	Nedocromil	0	Na	265	0	465	0	730	Nedocromil	43	0	156	0	199
								Hydrocortisone	101	100	236	0	57	0	395	Combinations of different antibiotics	90	0	75	0	165

Na=not assessable ; OL= off-label for age

use of oral contraceptives and antifungals was high in NL and UK. In the group of nervous system drugs paracetamol is clearly the most used (but underestimated due to high OTC use in NL and IT) drug, methylphenidate (NL and UK), lidocaine (NL), pizotifen (UK), fluoxetine (UK) diazepam, niaprazine (IT) and valproic acid (IT) were also in the top 5 of at least one country. None of them was off label, except diazepam < 12 years of age in NL. In the group of sensory organ drugs many different drugs were used in the various countries, the most frequently prescribed drugs in NL (fusidic acid, levocabastine) and UK (chloramphenicol) were off label. The low prevalence drugs comprised many classes (groups B, C, H, L, M, P). In the blood forming organs group (B), phytomenadione, iron, tranexamic acid, platelet inhibitors and vitamin K antagonists were most frequently prescribed. Salicylic acid derivatives were off-label. In the cardiovascular drug group topical steroids (anti-hemorrhoidal crèmes), topical anesthetics (lidocaine, oxetacaine), B-blockers (propranolol, atenolol), furosemide, disopyramide, epinephrine and enalapril were most frequently prescribed. Furosemide, B-blockers, epinephrine and topical (antihemorrhoidal) steroids were off-label in at least one country. For the non-sex hormones (H) desmopressin, oral steroids, (dexamethasone, prednisolone and prednisone), levothyroxine and glucagons) were the most frequently prescribed drugs. Only the oral steroids were off-label (NL and UK only). The most frequently prescribed anti-neoplastic and immunomodulating drugs (L) differed substantially between countries but were almost always off-label. In the musculoskeletal drug group (M) NSAIDs were the most frequently prescribed drugs, with important sequence differences between countries but little off-label use except in Italy where the number one and two drugs (ibuprofen and morniflumate) were off-label. The number one anti-protozoal drug (P) was mebendazole in all countries, there was very little off-label drug use.

DISCUSSION

This study describes age-specific paediatric drug prescribing in three different European countries from a very high aggregation level of anatomic classes to the level of individual drugs. This information could facilitate the prioritisation of paediatric research by regulatory authorities.

Prioritisation of drug safety research in paediatrics

Prioritising the research needs in medicines for children has currently been done mostly on the basis of one component, whereas we recommend two important assessments: The first is public health assessment¹⁶ comprising the severity and prevalence of disease and the availability of treatment alternatives. In addition to the public health assessment a second assessment should be done which is utilisation assessment. Utilisation assessment may comprise the frequency or volume of use and the licensing/labelling status of medicines for children. The use of off-label and unlicensed medicines implies that there are no proper labelling and dosing

recommendations, which can potentially be harmful to children^{17 18 19 20}. Therefore off-label and unlicensed medicines should be of higher priority for research than licensed/on-label medications, especially if no data on safety, efficacy in children is available. Our study focused on assessing the volume and labelling status in order to provide knowledge to experts and facilitate research prioritisation that includes both the public health as well as the utilisation assessment.

The utilisation data from this study underline the conclusions of the recently published EMEA consensus/expert derived list of research priorities concerning off-patent medicinal products¹⁶, which emphasized the need for paediatric studies of the safety of topical, systemic and inhaled steroids. Steroids are associated with impairment of growth²¹, abnormalities in the metabolism of glucose²² and adrenal suppression^{23 24}. Of these adverse effects, growth retardation is the most common and is of particular concern in children. The extent of growth suppression varies with the method of administration (e.g., inhaled or oral) and the duration of treatment as well as with the type and dose of glucocorticoid used^{21 25}. Topical and systemic antifungals (imidazoles/triazoles), acid-reducing drugs and antineoplastic drugs are also listed as research priorities by EMEA. Our utilization data found that these drugs are frequently or recurrently used and are mostly off-label. Many other drugs that are listed on the priority list of EMEA did not appear as frequently used drugs in this study, and would not be considered priorities on the basis of frequency of use in primary care alone, but apparently were considered priorities for other reasons. On the other hand sex hormones are not listed on the priority list of the EMEA, whereas they are frequently and recurrently prescribed, and mostly off-label. Few long term safety studies on the use of sex hormones in adolescents are available and to our knowledge no RCTs on the safety and efficacy of sex hormones in adolescents have been conducted. The use of oral contraceptives in adolescents has been associated with an increased risk of lower bone mineral density, higher serum cholesterol and triglyceridemia²⁶⁻²⁸. Similar to adults, the use of oral contraceptives by teenagers has also been associated with an increased risk of cardiovascular events (eg myocardial infarction, stroke) as well as an increased risk of venous thrombo-embolism²⁹⁻³³. As the use of sex hormones in young adolescents is relatively high, implying a long duration of use, further studies on the efficacy and long term safety effects of these drugs when used by youngsters are warranted.

Although drug use patterns and labeling status can inform decisions on prioritization of research, these data inform us also about suboptimal use and even may demonstrate undesirable prescribing practices. For example fusidic acid and chloramphenicol are frequently used and often off-label (table 4). Fusidic acid is known to be prescribed for the treatment of conjunctivitis in the Netherlands similarly to chloramphenicol which is used in the UK. However, the beneficial effect of antibiotics in the treatment of this condition is not convincingly proven^{34 35}. Indeed the literature shows that acute bacterial conjunctivitis is frequently a self-limiting condition and topical antibiotic use offers only marginal benefit in improving clinical outcomes; hence the emphasis should be on educating clinicians not to prescribe such treatment rather than a

call for more research^{36 37}. Another example underlining the need for education rather than research is the cough and cold medications. These drugs are not only available over the counter but are also frequently prescribed which should be strongly discouraged due to reports of death and lack of efficacy³⁸.

Drug use patterns

We show that the prevalence of the most frequently prescribed drugs in primary care is highest in children aged less than two years, that the most frequently used drugs (anti-infectives, dermatologicals and respiratory drugs) are the same in all three age categories, and that almost all other drugs are used by less than 10% of children per year. In general, three groups can be distinguished: drugs used by more than 10% of children per year, those used by 1-10%, and those by less than 1%. The use of the high prevalence drug classes decreases with increasing age but remains high, whereas the use of the lowest prevalence drug groups increases to a moderate prevalence rate in adolescence except in the case of cardiovascular and anti-neoplastic agents. Only a few therapeutic drug classes accounted for the majority of use in a specific anatomic drug class: anti-bacterials, topical corticosteroids, anti-asthma and anti-anemia medications, cardiac drugs, sex hormones, oral corticosteroids, non-steroidal anti-inflammatory drugs, analgesics and ophthalmologicals. The high prevalence drugs were relatively more often used for acute use. Only 12 drug classes (anti-diabetics, digestives, bile and liver therapy, anti-thrombotic agents, drugs affecting the renin-angiotensin system, lipid-lowering drugs, sex hormones, thyroid therapeutic agents, immunosuppressive agents, muscle relaxants, anti-epileptics and psychoanaleptics) were prescribed more frequently for recurrent than acute use.

An interesting age-related gender reversal was observed: female adolescents had consistently higher drug use prevalence rates than adolescent boys (except in the case of non-sex hormones), whereas the opposite was true in the younger age categories this was in line with a previous Dutch and Danish study^{39 40}.

Interestingly, the percentage of off-label use varied highly between countries and similar drugs differed in off-label status between countries. This confirms that the differences in the Paediatric Status of the drugs, instead of the different prescription habits or medical cultures as postulated by many authors represent the real reason for the variability reported by years and from many European studies and surveys on the off-label use in children.⁴¹

Previous studies

Our study was population-based, had a very large sample size, and covered different European countries. Previous European studies have been country or region specific, and have concentrated on specific conditions except for previous Swedish, Dutch and Danish studies in the late nineties and a recent Italian study covering 2000-2006 data^{40 42-44}. These studies all took all types of drugs into account but the methodologies to calculate prevalence and ranking (on

the basis of number of dispensed boxes or user prevalence) and age ranges vary largely which complicates direct comparisons. The overall results: highest drug use in lowest age category, ranking of the most frequently used drugs (anti-infectives, respiratory and dermatological drugs), and the gender pattern (more prescriptions for girls than boys after the age of 10) are consistent with the findings of our study^{39 45 46}.

Potential of multi-country database studies

Our study shows the potential of studying the primary care prescribing of a wide range of drugs using multiple databases. As all databases include outcome data such as morbidity and mortality data, they can also be used for studies of paediatric drug safety. The country-specific estimates provide insights into prescription differences and allow a search for high prevalence countries regarding drug prescribing.

Limitations

One limitation of this study is the fact that it captured only outpatient, primary care drug prescriptions and no use of over the counter drugs (which has resulted in a substantial underestimation of the use of paracetamol and phytomenadione, and potentially other drugs such as cough and cold medications). At least in the Netherlands, the UK and Italy, most health problems are dealt with in primary care⁸ and, as drug prescriptions by a specialist for a chronic disease are often continued by general practitioners or paediatricians, most of them are picked up. However, hospital medication administration and the monitoring of chemotherapeutic and biological drugs are unlikely to be fully captured by our databases. Despite differences in the absolute prevalence rates of drug prescribing and the types of drugs that were prescribed, age and gender patterns were very consistent in the three countries considered in this study. However, as the UK accounted for 60 percent of the study population, the pooled results are inevitably dominated by UK prescription patterns, therefore stratified analyses were conducted as much as possible. Due to the nature of the databases, we studied drug prescriptions rather than drug intake, and so the prevalence of actual drug exposure may be lower than estimated here.

In brief, this paper provides a unique overview of primary care prescription patterns in a large multinational European paediatric population. The data could be used to improve the prioritisation of research into long-term paediatric drug safety, as well as efficacy and effectiveness studies in paediatric medicine. Off-label use in some of the most frequently and recurrently used drugs is high (e.g. oral contraceptives) and these should be considered for prioritisation.

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Contributors

All authors helped conceive the idea for the study, design the study, and analyze and interpret the data. MCJMS and KMCV drafted the manuscript. AN, EFS revised the manuscript. AC and ICKW supervised the study. MCJMS is guarantor.

Funding

The work presented in this paper was funded by the European Community's 6th Framework Programme. Project number LSHB-CT-2005-005216: TEDDY: Task force in Europe for Drug Development for the Young. The funding agency had no role in the collection of data, the analysis or interpretation of the data nor of the decision to submit.

Competing interests

Miriam CJM Sturkenboom (received various unconditional research grants from pharmaceutical companies (Merck, Pfizer, Johnson&Johnson, Amgen, Roche, Altana, GSK), MCJMS is consultant to Pfizer, Celgene, Servier and Sanofi Aventis, none of issues is related to this topic), Katia MC Verhamme (no conflict of interest), Alfredo Nicolosi (AN has been reimbursed by Pfizer Inc for attending several conferences; Pfizer Inc has funded research to the National Research Council of Italy on sexual and bladder dysfunctions in adults) Macey L. Murray (no conflicts), Antje Neubert (no conflicts), Ian C. Wong (no conflicts), Daan Caudri (no conflicts), Gino Picelli (has conducted research funded by unconditional research grants in pediatrics from Merck USA, and BMS), Elif Fatma Sen (no conflicts), Carlo Giaquinto (Fee for speaking, consulting and research grants were provided by: Sanofi Pasteur, GSK, Abbott, BMS, Gilead, Abbott, Tibotec, Boheringer Ingelheim., GSK-Biologicals) Luigi Cantarutti (as president of SOSETE he has received research grants from GSK, Abbott, Merck and BMS), Paola Baiardi (no conflict), Adriana Ceci (no conflict)

Ethical approval:

Internal review board of the integrated primary care information database. (IPCI)

The use of IMS data for this study has been reviewed by an Independent Scientific and Ethics Committee

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Chapter 2.3

Assessment of Pediatric asthma drug use in three European countries; a TEDDY study

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Published in: European Journal of Pediatrics, 2010 Sep 2. [Epub ahead of print]

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What is already known

- Asthma drugs are among the most prescribed drugs to children
- Most frequently used asthma drugs are short-acting beta2-mimetics and inhaled steroids
- There is a large variability in prescription rates between countries

What this study adds

- Off-label use of asthma drugs in children is low
- Linking multi-country databases makes it possible to study country specific pediatric drug use in a systematic manner without being hampered by methodological differences

Abstract

Asthma drugs are amongst the most frequently used drugs in childhood, but international comparisons on type and indication of use are lacking. The aim of this study was to describe asthma drug use in children with and without asthma in the Netherlands (NL), Italy (IT), and the United Kingdom (UK). We conducted a retrospective analysis of outpatient medical records of children 0-18 years from 1 January 2000 until 31 December 2005. For all children, prescription rates of asthma drugs were studied by country, age, asthma diagnosis and off-label status. One-year prevalence rates were calculated per 100 children per patient year (PY). The cohort consisted of 671,831 children of whom 49,442 had been diagnosed with asthma at any time during follow-up. β 2-mimetics and inhaled steroids were the most frequently prescribed asthma drug classes in NL (4.9 and 4.1/100 PY), the UK (8.7 and 5.3/100 PY) and IT (7.2 and 16.2/100 PY), respectively. Xanthines, anticholinergics, leukotriene receptor antagonists and anti-allergics were prescribed in less than 1 child per 100 per year. In patients without asthma, β 2-mimetics were used most frequently. Country differences were highest for steroids, (Italy highest), and for β 2-mimetics (the UK highest). Off-label use was low, and most pronounced for β 2-mimetics in children < 18 months (IT) and combined β 2-mimetics+anticholinergics in children <6 years (NL).

Conclusion: This study shows that among all asthma drugs, β 2-mimetics and inhaled steroids are most often used, also in children without asthma, and with large variability between countries. Linking multi-country databases allows us to study country specific pediatric drug use in a systematic manner without being hampered by methodological differences. This study underlines the potency of healthcare databases in rapidly providing data on pediatric drug use and possibly safety.

Introduction

Respiratory drugs are amongst the most frequently prescribed drugs in children, and especially asthma drugs are frequently prescribed (36). Prevalence rates of asthma drug use range between 4 and 26 percent, depending on country, age range, and study period (Table 1) (8, 12, 16-18, 20, 22, 23, 25, 26, 41, 43). Asthma is defined as a chronic inflammatory disorder of the airways and is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing (1). In children aged 5 years and younger the clinical symptoms of asthma are variable and non-specific. Furthermore, routine testing for main asthma features is not possible in this age group, which hampers making a diagnosis.

According to the Global Initiative for Asthma (GINA), bronchodilators, (inhaled short-acting β 2-mimetics: SABA; long-acting β 2-mimetics: LABA; anticholinergics: ACH), inhaled corticosteroids (ICS) and alternative (add-on) treatments such as leukotriene receptor antagonists (LTRA), xanthines and anti-allergics (cromones) all have a place in the treatment of childhood asthma, although at various stages depending on severity of illness (1). In pediatrics, asthma is one of the main indications for which these drugs are used.

Apart from these respiratory drugs, systemic glucocorticoids are also used in the treatment of asthma. However, due to side effects such as potential adrenal suppression and growth impairment with long term use (1, 37), use of systemic glucocorticoids in asthmatic children is restricted to asthma exacerbations and very severe persistent asthma (1).

Use of asthma drugs varies largely between countries as observed from the literature (Table 1). Part of this variability may be explained by differences in age distribution and type of data (i.e. surveys, prescriptions, dispensing), which hampers good comparisons between studies. To better explore differences in prescription rates of asthma drug use between countries, we conducted a retrospective cohort study in three European countries: the Netherlands, Italy and United Kingdom, using the same methodology and stratifying by age, sex and asthma diagnosis.

Methods

Data collection

Data were obtained from general practice medical record databases in three countries according to a common protocol. Databases were the Pedianet database in Italy (29), the Integrated Primary Care Information (IPCI) database in the Netherlands (40), and the Mediplus Disease Analyzer-Mediplus database (IMS-DA) in the UK (42). Details are described elsewhere (36). Primary care in children is provided by the GP in the UK and the Netherlands, and by a family pediatrician in Italy. These primary care medical record databases were chosen because they

Table 1: Overview of studies that have investigated the prevalence of asthma-related drug use in children

Author	Type of data	Country	Years studied	# children in study	Age	Prevalence estimate	Study drugs
Bianchi et al (8)	Pharmacy dispensing records (NHS claims data)	Italy	2003	55,242	0-<18	11.9	All asthma drugs (R03)
Bollinger et al (12)	Pharmacy dispensing records (Medicaid claims data)	USA	1997-2000	57,586 – 282,402	0-<18	10.4 – 13.2	β2-mim, ICS, LTRA, xanthines, OS
Clavenna et al (16)	Pharmacy dispensing records (NHS claims data)	Italy	2006	923,353	0-<14	26	All asthma drugs (R03)
Clavenna et al (17)	Pharmacy dispensing records (NHS claims data)	Italy	2000	417,559	0-<14	22.2	All drugs, including ATC R03
Khaled et al (25)	Pharmacy dispensing records (Claims data from administrative databases)	Canada	1999-2000	1,031,731	0-<18	18	β2-mim, ICS, LTRA, xanthines, cromones, ketotifen
Korelitz et al (26)	Pharmacy dispensing records (IL Claims data IL)	USA	2004-2005	4,259,103	0-<18	14.58	β2-mim, ICS, ACH, cromones, xanthines, OS
Goodman et al (22)	Pharmacy dispensing records (GHC)	USA	1984-1993	83,232 (in 93)	0-<18	4.0 – 8.1	β2-mim, ICS, cromones, xanthines, fixed combinations
De Vries et al (18)	Pharmacy dispensing records (IADB)	Netherlands	2002	73,416	0-<15	4.9	β2-mim, ICS, LTRA, ACH, fixed combinations, antihistamines, OA
Furu et al (20)	Pharmacy dispensing records (NPD)	Norway	2004	1,192,841	0-<20	9.1	All asthma drugs (R03)
Joesch et al (23)	Pharmacy dispensing records (MEPS)	USA	1996	6789	0-<18	6.5	β2-mim, ICS, LTRA, ACH, cromones, xanthines

Table 1: Continue

Author	Type of data	Country	Years studied	# children in study	Age	Prevalence estimate	Study drugs
Wang et al (41)	Survey, claims, prescriptions (MEPS)	USA	'96+'98+2000	15,554	5-17	5.2	β2-mim, ICS, LTRA, ACH, cromones, xanthines, OS
Zuidgeest et al (43)	Prescription data (GP)	Netherlands	2001	74,580	0-<18	7.5	β2-mim, ICS, cromones, LTRA

Legend:

Study drugs: β2-mim = β2-mimetics, ICS = inhaled corticosteroids, LTRA = leukotriene-receptor antagonists, ACH = anticholinergics ATC R03 = drugs for obstructive airway diseases, OS = oral steroids, OA = oral adrenergics *Type of data:* NHS = national health service, NPD = Norwegian Prescription Database, GHC = Group Health Cooperative of Puget Sound, MEPS = Medical Expenditure Panel Survey, IL = Ingenix LabRx, IADB = InterAction DataBase

contain detailed information on the population, diagnoses and prescriptions. The geographic location of the databases allowed us to study North and South European differences in drug prescribing.

Study population

The study population consisted of all children aged 0-18 years (0-11 years in Italy) during the study period 1 January 2000– 31 December 2005 (1 January 2001– 31 December 2005 for Italy). All persons needed to have a database history of ≥ 6 months, except for children born during the study period. For each child the person years of follow-up were calculated, stratified by calendar year, age group, sex, and asthma diagnosis. For privacy issues, some databases only contain the year of birth, therefore age was assessed at the 1st of January of each year, and in order to identify infants, preschoolers and adolescents separately. We used modified ICH (the International Conference of Harmonization) age categories to stratify by age (<2, ≥2-≤4, 5-11 and ≥12 years of age) (2). Each child was followed from study start until the patient left practice or end of study period (whichever was earliest).

Assessment of asthma

For each child we assessed whether a diagnosis of asthma was made at anytime in its medical records using the following diagnostic codes: ICPC code R96 in IPCI, ICD-9 code 493 in Pedianet and ICD-10 code J45 in IMS and free text (4, 5, 27). If at any time during the follow-up asthma was diagnosed, the child was considered asthmatic for the entire period.

Classification of prescriptions

Drug prescriptions were categorized based on the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification system (6). All prescriptions for "obstructive airway

Table 2: Population size by country, age, sex and asthma diagnosis

Patient characteristics	NL		Italy [§]		UK		Total
	Children with asthma	Total pop.	Children with asthma	Total pop.	Children with asthma	Total pop.	Children with asthma
	No.# (% of total)		No.# (% of total)		No.# (% of total)		No.# (% of total)
Age							
<2 years	2,165 (8.4)	25,694	2,539 (4.6)	54,999	2,977 (3.8)	79,246	7,681 (5.7)
≥2-≤4 years	2,820 (11.8)	23,902	4,269 (7.3)	58,735	7,610 (7.5)	101,835	14,699 (8.0)
5-≤11 years	5,545 (11.7)	47,435	5,399 (7.5)	72,264	19,856 (12.8)	155,488	30,800 (11.2)
12-≤18 years	3,689 (8.3)	44,636			19,809 (13.3)	149,093	23,498 (12.1)
Sex							
Females	3,940 (7.9)	49,709	2,851 (4.7)	60,089	14,377 (6.5)	219,669	21,167 (6.4)
Males	5,419 (10.5)	51,850	4,730 (7.2)	65,361	18,125 (8.1)	225,153	28,274 (8.3)
Total	9,359 (9.2)	101,559	7,581 (6.0)	125,450	32,502 (7.9)	444,822	49,442 (7.4)

PY=person-years; #The number of children in the various age groups does not add up to the total since one child can contribute to more than one age category during the study period.

§ For Italy the age range included only 0-11 years for the years 2001-2005

diseases" (ATC R03) and "glucocorticosteroids for systemic use" (ATC H02AB) were obtained from the prescription files and further categorized into: β 2-mimetics (either short-acting [SABA] or long-acting [LABA]), inhalation glucocorticosteroids, inhalation anticholinergics, fixed combination of SABA + short-acting anticholinergics, fixed combination of LABA + inhalation glucocorticosteroids, anti-allergic agents (best known as cromones), xanthines and leukotriene receptor antagonists (LTRA). Use of β 2-mimetics+ICS was classified as a non-fixed combination if the child used β 2-mimetics and an ICS in the same year. For each drug class, we calculated prevalence rates for the most frequently prescribed drugs (top 3) by country.

Due to differences in labeling status between countries, off-label use was assessed per country. A drug was classified as being "off-label" if the child receiving the prescription had an age below the minimum age as specified in the summary product characteristics (SPC) or the drug was given for a different indication than specified in the SPC. This is in line with the new definition of pediatric off-label use provided by the Task Force in Europe for Drug development for Young (31).

Statistical analysis

Annual prevalence rates (per 1000 PY or per 100 PY) of asthma drug use were calculated by counting the number of children using each drug or drug class by calendar year, age, sex, asthma status and country and dividing this number by the number of person years attributed by the different strata. User prevalence rates can be interpreted as the number of children per 1,000 children that uses a specific drug (class) during one year. If expressed per 100 PY it can be freely translated as the percentage of children using these drugs in one year. The fact that we used annual prevalence rates means that a child who uses one drug (class) multiple times in one year, will be counted only once for that year. The use of person-years rather than persons in

the denominator was necessary due to the dynamic nature of the cohort where persons could have variable durations of follow-up.

Differences in prescription rates between countries were tested by means of the χ^2 -test.

Results

Patient characteristics

Our population consisted of 671,831 children (66% UK, 19% IT, 15% NL) of whom 49,442 (7.4%) had asthma at any point during follow-up.

Asthma drug classes

The user prevalence rate of any asthma drug was highest in young children and decreased with age (Figure 1), it was highest in Italy for each age category. The difference between NL, the UK and IT is largest for the youngest age categories with user prevalence rates of 25-30/100 PY in Italy, rates of 12 in the UK, and 10/100 PY in NL (Figure 3-4). In the youngest age groups, prescription rates were higher for boys. This pattern switched in adolescence (between the ages 14 to 16), where user prevalence rates for almost all drug classes were higher in girls (Figure 1). β_2 -mimetics and ICS were each used by 1-10 children/100 PY in all age categories in each country (Figure 2). In Italy, prevalence of use of ICS was higher than use of β_2 -mimetics and even exceeded 10 /100 PY in the youngest age group. The fixed combinations of anticholinergics+SABA were frequently used in the Netherlands and Italy but not in the UK,

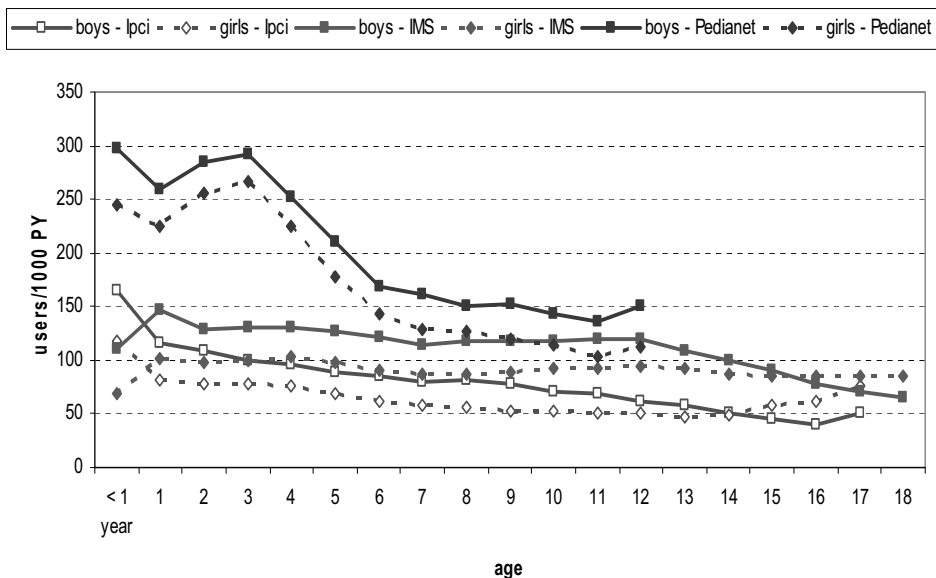


Figure 1: Age, country and sex specific user prevalence rates of asthma drugs (all ATC R03)

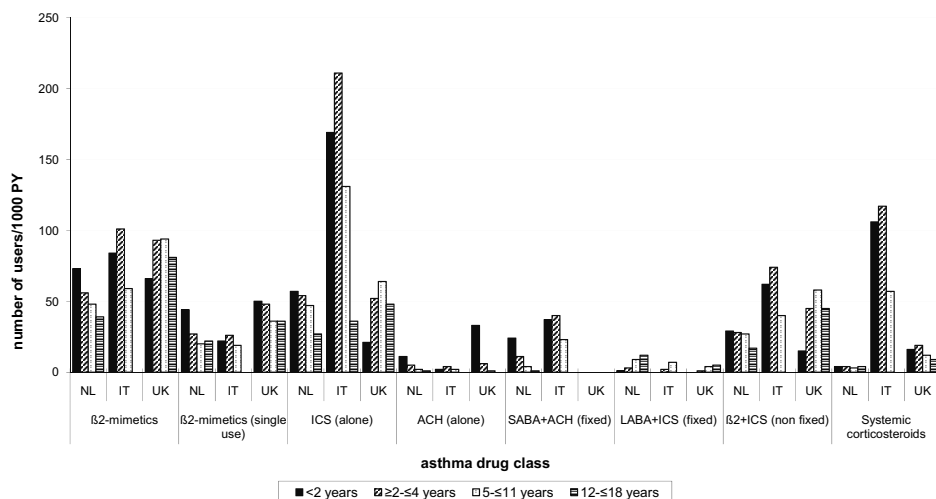


Figure 2: Annual user prevalence rates of the most frequently prescribed respiratory drugs
 NL: the Netherlands, IT: Italy, UK: the United Kingdom, β 2-mimetics: inhaled β 2-mimetics (this can be single or non-fixed combination use), ICS: inhalation corticosteroids, ACH: anticholinergics, SABA+ACH: fixed combinations of short-acting β 2-mimetics+anticholinergics, LABA+ICS: fixed combinations of long-acting β 2-mimetics+inhalation corticosteroids, β 2+ICS(non fixed): non-fixed combination of β 2-mimetics (LABA or SABA)+inhalation corticosteroids

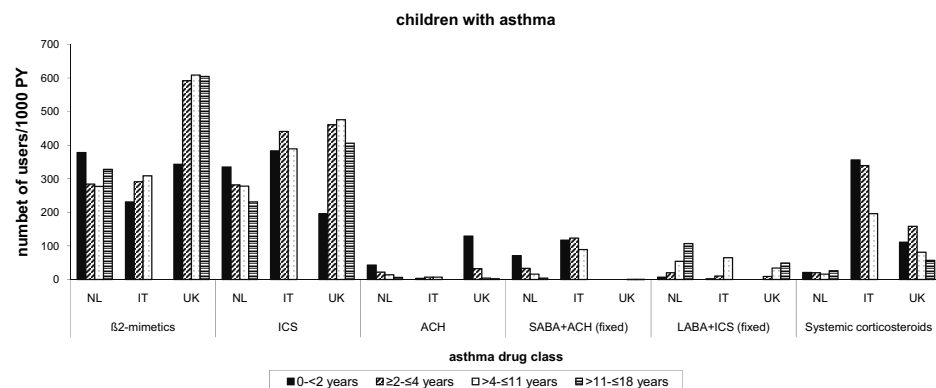


Figure 3: Prevalence of respiratory drug use by age category and country in children with asthma
 b2-mim= β 2-mimetics; ics=inhalation corticosteroids; ach=anticholinergics; saba+ach= fixed combination of short-acting β 2-mimetics+anticholinergics; laba+ics= fixed combination of long-acting β 2-mimetics+inhalation corticosteroids; scort=systemic corticosteroids

where mostly anticholinergics were used as single compound. Leukotriene receptor antagonists, anti-allergics and xanthines were used by less than 1 child/100 PY in each country and each age category, which is in concordance with protocols concerning asthma treatment. Fixed combinations of ICS+LABA were infrequently used in young children but exceeded 1/100 PY in adolescents in the Netherlands. Systemic use of steroids was very heterogeneous between

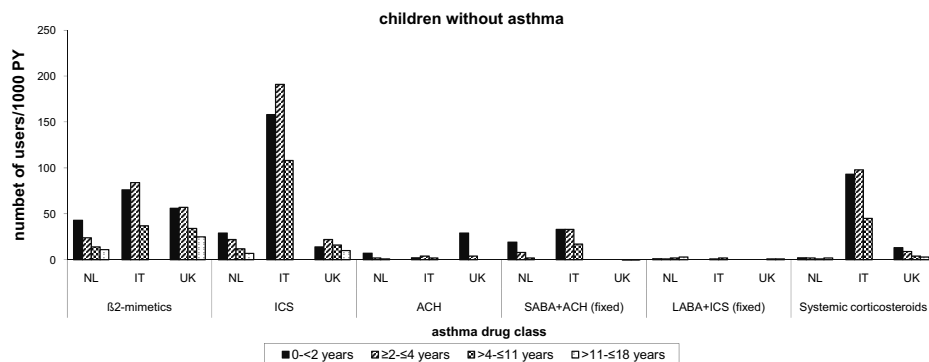


Figure 4: Prevalence of respiratory drug use by age category and country in children without asthma
 b2-mim= β 2-mimetics; ics=inhalation corticosteroids; ach=anticholinergics; saba+ach= fixed combination of short-acting β 2-mimetics+anticholinergics; laba+ics= fixed combination of long-acting β 2-mimetics+inhalation corticosteroids; scort=systemic corticosteroids

countries. User rates exceeding 10/100 PY were observed in Italy, especially in the youngest children, whereas user rates were 5-8 folds lower in the UK and almost 20 fold lower in the Netherlands.

User prevalence rates for individual drugs

The prevalence of SABA use in children with asthma was similar in the Netherlands and Italy but much higher in the UK (30 vs. 60/100 PY). In children without asthma diagnosis the prevalence was between 1 and 8/100 PY. The most frequently prescribed SABAs were salbutamol and terbutaline in NL and the UK, whereas terbutaline was not frequently used in Italy (Table 3). User rates of LABA (this can be combined or single use) were very low (< 1/100 PY), but strongly increased with age in children with asthma. Most frequently used drugs were salmeterol and formoterol. In children without asthma, use of LABA was negligible (Table 3 and Figure 3). Single use of β 2-mimetics (without a prescription for ICS in the same year) was highest in the UK (195/1000 PY in children with asthma and 23 in children without). In NL and IT prevalence rates were 127 and 75/1000 PY in children with asthma and 12 and 18/1000 PY in children without an asthma diagnosis. In both countries prevalence rates decreased gradually with increasing age. ICS were most frequently prescribed in Italy, especially in children < 2 years of age. In children with asthma, ICS use was highest in the UK. The choice of drug differed; fluticasone was most often prescribed in NL and beclomethasone in the UK and Italy. Among the children with asthma who used β 2-mimetics, 42% were not prescribed ICS in that year in NL, 26% in Italy, and 33% in the UK. In children without asthma, ICS use was low in NL and the UK but reached rates of more than 10/100 PY in Italy.

Oral corticosteroid use was highest in Italy, with prescription rates of 26/100 PY in children with asthma and 7/100 PY in children without asthma. Rates were especially high in the younger age categories. In the other countries, prescription rates in children with asthma were much

Table 3: Prevalence of respiratory drug use per country by treatment class and asthma diagnosis

	Netherlands		Italy			United Kingdom		
	asthma	no asthma	asthma	no asthma	asthma	no asthma		
SABA								
Salbutamol	276	19	Salbutamol	283	59	Salbutamol	519	32
Terbutaline	39	2	Terbutaline	1.4	0.1	Terbutaline	88	2.8
<i>Overall</i>	293	17		284	59		596	35
LABA								
Salmeterol	14	0.4	Salmeterol	13	0.5	Salmeterol	40	0.6
Formoterol	7.6	0.2	Formoterol	1.6	0.1	Formoterol	2.5	0.02
<i>Overall</i>	21	0.6		15	0.6		42	0.6
ICS								
Fluticasone	162	8	Beclomethasone	239	98	Beclomethasone	313	11
Budesonide	68	4	Fluticasone	122	10	Budesonide	72	1.9
Beclomethasone	50	2	Flunisolide	76	32	Fluticasone	63	1.5
<i>Overall</i>	271	14		404	143		437	14
LTRA								
Montelukast	5.5	0.1	Montelukast	37	1.7	Montelukast	15	0.3
			Zafirlukast	0.0	0.0	Zafirlukast	0.2	0.02
<i>Overall</i>	5.5	0.1		38	1.7		15	0.3
Short-acting anticholinergics								
Ipratropium bromide	15.7	1.6	Ipratropium	6.2	2.4	Ipratropium	9.1	2.7
			Oxitropium	0.3	0.1	Oxitropium	0.04	0
<i>Overall</i>	16	1.6		6.4	2.5		9.1	2.7
β2-agonists+ICS (non fixed)								
	177	5		217	42		404	12
SABA+SACH (fixed)								
Fenoterol+ Ipratropium	19	4.1	Salbutamol+ Ipratropium	104	25	Salbutamol+ Ipratropium	0.7	0.06
Salbutamol+ Ipratropium	0.9	0.9	Fenoterol+ Ipratropium	0.1	0.0	Fenoterol+ Ipratropium	0.05	0
<i>Overall</i>	20	4.4		104	25		0.07	0
LABA+ICS (fixed)								
Salmeterol+ Fluticasone	33	1.3	Salmeterol+ Fluticasone	37	1.3	Salmeterol+ Fluticasone	31	0.5
Formoterol+ Budesonide	6.8	0.3	Formoterol+ Budesonide	2.1	0.1	Formoterol+ Budesonide	6.1	0.07
<i>overall</i>	60	2.3		38	1.4		37	0.6

Asthma = prevalence in children with asthma; no asthma = prevalence in children without asthma; SABA= short-acting β2-mimetics; LABA= long-acting β2-mimetics; ICS=inhalation corticosteroids; LTRA= leukotriene-receptor antagonists; β2-agonists+ICS (non fixed) = non-fixed combination of β2-mimetics+inhalation corticosteroids; SABA+SACH (fixed) = fixed combination of short-acting β2-mimetics+short-acting anticholinergics; LABA+ICS (fixed) = fixed combination of long-acting β2-mimetics+inhalation corticosteroids. * Could either be the combination of LABA+ICS are SABA+ICS but always a loose combination (more than 1 device)

lower in each age category, both in children with and without asthma. The most frequently prescribed drugs were betamethasone in Italy and prednisolone in NL and the UK.

Combination preparations

Use of the fixed combinations of short acting SABA+ACH was low overall, but most frequent in Italy. Prescription rates decreased with age.

For the fixed combinations of ICS+LABA, use was highest in NL with 6/100 PY in children with asthma. A clear increase of prescription rates with age was seen in all 3 countries.

Use of the loose combination of β 2-mimetics+ICS was highest in IT (55/1000 PY), followed by the UK (48/1000 PY) and NL (24/1000 PY). In children with asthma prevalence rates were highest in the UK (404/1000 PY), followed by IT (217) and NL (177)

Off-label use

Off-label use defined by use below the minimum age as specified in the SPC was investigated in Italy and NL. In Italy, salbutamol is indicated for use in children from the age of 18 months onwards, however user rates were 22.7 /100 PY in children with asthma and 7.5 in children without asthma diagnosis below 18 months. In NL off-label use was observed for the fixed combinations of β 2-mimetics+anticholinergics. The minimum age for use of these drugs is 6 years in NL, however, prescription rates in children <6 years were 0.5-3.5 /100 PY in NL (data not shown).

Off-label use defined as use for other indications than specified in the SPC (for drugs that only had asthma or COPD as indication) in children without recorded asthma diagnosis was observed in all 3 countries for several drugs (Table 4). In Italy budesonide had the highest off-label prescription rate, in NL salbutamol, and in the UK beclomathesone.

Discussion

This paper provides detailed information on asthma drug use in three European countries, and clearly demonstrates the similarities and differences in prescription rates.

Whereas short-acting β 2-mimetics are the most frequently used drugs for treatment of asthma in the Netherlands and the UK, inhaled and systemic corticosteroids are most frequently used in Italy, especially in the youngest age groups. Long-acting products, anticholinergics, xanthines, and LTRAs were in general infrequently prescribed in all countries.

Our data are in line with previous studies on asthma drug use in children, which also demonstrated that short-acting β 2-mimetics and inhaled corticosteroids were prescribed most, but these studies often considered only one country or a region (20, 21), whereas our study captures multiple countries in different European regions. Our data also confirm findings of a recent survey showing high use of inhaled β 2-mimetics in northern Europe and high usage

Table 4: Off-label use defined as use for other indications than specified in the Summary of Product Characteristics

Drug	Netherlands			Italy			United Kingdom		
	% off-label	Prescription Rate*	Drug	% off-label	Prescription Rate*	Drug	% off-label	Prescription Rate*	Drug
Salbutamol	32.8	15	Budesonide	80.0	14.8	Terbutaline	23.5	2.7	
Terbutaline	30.7	2.1	Salmeterol+Fluticasone	31.6	1.3	Salmeterol	12.1	0.6	
Salmeterol	19.0	0.4	Formoterol+Budesonide	29.1	0.1	Beclomethasone	25.8	11	
Formoterol	16.4	0.2	Cromoglicic acid	51.3	0.3	Budesonide	21.0	1.9	
Beclomethasone	27.2	2.3	Nedocromil	54.5	2.1	Fluticasone	18.7	1.5	
Fenoterol+Ipratropium	63.0	4.1	Montelukast	36.1	1.7	Ipratropium	74.2	2.7	
Salbutamol+Ipratropium	72.5	0.3				Salbutamol+Ipratropium	45.5	0.1	
Salmeterol+Fluticasone	24.4	1.3				Formoterol+Budesonide	10.8	0.1	
Formoterol+Budesonide	28.4	0.3				Cromoglicic acid	34.7	0.2	
Cromoglicic acid	26.3	0.1							
Montelukast	16.0	0.1							

-% off-label = the percentage of off-label use of the specific drug

-*prescription rate = the prescription rate of the drug /1000 PY in children without asthma

-e.g.: 80% of the children receiving Budesonide in Italy do not have a diagnosis asthma

-all study drugs were checked for off-label status. Only those with off-label use are listed in the table

of corticosteroids in southern Europe (11). The north south gradient that we observed in the prescription of asthma drugs can not be explained by country specific differences in asthma treatment protocols, as the protocols in the Netherlands; the UK and Italy are all based on the GINA guidelines.

There are various prescribing behaviors which deserve specific attention since they may be associated with a differential risk of adverse drug reactions. First of all, SABA use is high in the lower age categories which may at least partly be explained by the fact that they are recommended on an as-needed basis for acute wheezing in preschool children (13). However, paradoxical responses like deterioration of asthma with use of these drugs have been reported in infants (38).

Secondly, prescription rates for long-acting β_2 -mimetics were low for all 3 countries, which is in line with guidelines and recommendable since a black box warning was issued by the FDA due to safety issues in children, especially in mono-use (19). Thirdly, in children with asthma the percentage of children using β_2 -mimetics without ICS as controller was substantial, especially in the UK and Netherlands. A possible explanation could be that these children were intermittently treated with SABA's on an as-needed basis as defined in the 1st step of the guidelines (1). However, chronic use of β_2 -mimetics without ICS is contraindicated in children with asthma because it may lead to increased airway inflammation and worsening of asthma control, and is in severe cases even associated with death (28, 33).

Fourth, use of ICS was very high in children under the age of 5 in Italy; this level of use certainly raises a question about potential overprescription, especially in children without asthma. However, a recent survey among children 1-5 years of age showed that southern Europe had the highest rate of wheezing symptoms (48%) compared with northern Europe (29%), which may explain some of the high use of ICS (11). Although there is some evidence supporting the effectiveness of regular inhaled corticosteroids in preschool wheeze (9) its use remains controversial (13, 24). Long term use of steroids (inhaled and specifically oral) might cause side effects such as temporary growth retardation and adrenal suppression (1, 7). Less severe but more frequent and relevant side effects in children treated with ICS are oropharyngeal candidiasis, dysphonia, reflex cough and pharyngitis (14).

Fifth, systemic corticosteroids are not the first choice of treatment in asthma and should only be used for exacerbations. A recent study showed that oral prednisolon and placebo did not differ in duration of hospitalization in children with mild to moderate wheezing associated with a viral infection (32). Although the high use of oral steroids in Italy is consistent with previous study findings (1, 8, 15), it may be slightly overestimated. Betamethasone (dispensed as capsules) is often administered via a nebulizer meaning that the actual oral use will be lower than reported, unfortunately we could not distinguish between these modes of administration. Fixed combination therapies of an ICS+LABA are relatively new in the treatment of childhood asthma and their long term safety is not well known. Use was highest in NL, similar to a recently reported increase in use of the fixed combination of ICS+LABA in Denmark (10). Although fixed

combination products of ICS+LABA are only licensed for use in children over 4 years, these drugs were also prescribed to children <2 years in the Netherlands. We found only 1 small retrospective study investigating the effect of a fixed combination of ICS+LABA in children <4 years, reporting a reduction in morbidity and an acceptable safety profile (34). So far, the safety and efficacy data of the fixed combination of ICS+LABA in children <2 years is too scarce to justify prescribing these drugs in young children.

In general, off-label use of asthma drugs defined as use below the minimum age as reported in the SPCs was low except for the fixed combination of β 2-mimetics+anticholinergics in children <6 years in the Netherlands and the use of SABA in children <18 months in Italy. Prescription rates for asthma drugs in children without an asthma diagnosis are much lower than in children diagnosed with asthma but still surprisingly high, especially for ICS and SABA. These drugs may have been used to treat wheezy young children with other respiratory conditions, such as respiratory tract infections (e.g. bronchiolitis) or first symptoms of undiagnosed asthma in young preschool children, but still, overuse cannot be excluded.

Use of asthma drugs is high, although very few long-term safety studies are available for children. The Pediatric Committee of the European Medicines Agency has recently published a pediatric needs list, containing drugs that are being used in children and where information on pharmacokinetics, efficacy and safety is urgently needed (3). This list includes frequently used respiratory drugs such as salbutamol, fluticasone, montelukast and many others. Although RCTs are the gold standard for efficacy assessment, safety studies are more effectively conducted through large scale postmarketing observational studies (35). Clinical trials are often small and too short for safety assessment. Pharmacoepidemiological studies are a valid tool for assessing safety under real life circumstances and often rely on secondary use of routine care data from claims databases and medical records. This study, as well as a previous inventory on databases with pediatric data, shows that exposure and outcome information is available on a large pediatric population (30, 36). Pharmacoepidemiological studies should be promoted to improve the safety assessment of pediatric drugs since RCTs are hampered by methodological difficulties, especially in the pediatric subpopulation, and consequently, results may not be prompt and sufficient enough for safety assessment.

As for all observational research, our data has some limitations. First of all, as we used primary care data, we may not capture all specialist prescriptions in the UK and the Netherlands. This will minimally influence our results since asthma is a condition often dealt with in primary care, and asthma drugs originally prescribed by a specialist are often continued or prescribed by general practitioners (39). Also, the health care provider in the studied countries differed: GP data from the UK and NL and family pediatrician data from IT. However, we do not believe that this would hinder comparability between databases as the nature of the databases is the same. If there are differences between countries, this reflects differences in primary care prescribing behavior and not in the type of data.

Furthermore, it is not possible to diagnose asthma in young pre-school children and the diagnosis of asthma is often made at a later age, which could lead to misclassification of the indication in young children. However, to minimize the possibility of misclassification, we searched the entire medical record of a child for the diagnosis of asthma. If the diagnosis was made at a later age, the child was counted as having asthma during the whole study period.

To conclude, our results show high use of SABA and ICS, although not always combined, and low use of other asthma drugs. Safety data on specific asthma drugs are needed according to the European Medicines Agency (3). This study underlines the potency of healthcare databases in rapidly providing data on pediatric drug use and possibly safety.

Acknowledgements: We would like to thank Peter Stephens of IMS Health for providing the IMS-DA database. We thank all of the physicians contributing data to the PEDIANET, IPCI and IMS-DA databases.

None of the authors has a conflict of interest. The principal investigator had full access to all of the data in the study and takes responsibility for their integrity and the accuracy of the data analysis.

Funding: Funded by the European Community's 6th Framework Programme. Project number LSHB-CT-2005-005216: TEDDY: Task force in Europe for Drug Development for the Young.

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Chapter 2.4

Effects of safety warnings on prescription rates of cough and cold medicines in children below 2 years of age

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Accepted for publication in: British Journal of Clinical Pharmacology

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What is already known

- Cough and cold medicines are frequently used in children to treat upper respiratory tract infections without solid proof of benefits.
- Safety issues have been raised about the use of these drugs in young children
- In 2007 international warnings have been issued advising against use of these drugs in young children

What this study adds

- Cough and cold medicines prescribing by primary care physicians has not really been influenced by international warnings in the Netherlands, where no additional national warnings were made and only partially in Italy.
- A concerted action should be taken in Europe to strongly advise against the OTC use and prescription of cough and cold medicines in young children.

Abstract

Aim: To assess the influence of national and international warnings on the prescription rates of cough and cold medicines (CCMs) in the youngest children (<2 years) in the Netherlands (NL) and Italy (IT) countries.

Methods: Analysis of outpatient electronic medical records of children <2 years in IT and NL. Age and country specific prescription prevalence rates were calculated for the period 2005-2008. Comparisons of prescription rates in 2005 (pre) and 2008 (post) were done by means of a Chi-square test.

Results: The cohort consisted of 99,176 children < 2 years of age. After international warnings, overall prescription rates for CCMs decreased slightly from 83 to 77/1000 person years ($p=0.05$) in Italy and increased in NL from 74 to 92/1000 children per year. Despite the international warnings, prescription rates for nasal sympathomimetics and opium alkaloids increased in NL ($p<0.01$). In Italy a significant decrease of the rates of opium alkaloids and other cough suppressants ($p<0.01$) was observed, and also a significant reduction in use of combinations of nasal sympathomimetics.

Conclusion: Despite the international safety warnings and negative benefit-risk profiles, prescription rates of cough and cold medicines remain substantial and were hardly affected by the warnings, especially in the Netherlands where no warning was issued. The hazards of use of these medicines in young children should be explicitly stipulated by European Medicines Agency and all national agencies, in order to increase awareness amongst physicians and caretakers and reduce heterogeneity across the EU.

Introduction

Cough and Cold Medicines (CCMs) are frequently used to treat upper respiratory tract symptoms in children. This group of medicines includes expectorants, mucolytics, opium alkaloids (for cough), nasal sympathomimetics and anti-histamines. CCMs carry a risk of serious and potentially life-threatening adverse events, such as cardiac arrhythmias, depressed levels of consciousness, and encephalopathy, and should be avoided in the very young [1].

As a result of these safety issues, in 2007 various regulatory actions have been taken in many countries: in the United States, the Food and Drug Administration (FDA) has issued a recommendation advising parents and caregivers not to use these drugs in children younger than 2 [2]; in the United Kingdom, the Medicine and Healthcare Products Regulatory Agency (MHRA) is advising against the use of many CCMs in children under the age of 6 [3], and Health Canada is requiring manufacturers to re-label certain over-the-counter (OTC) CCMs to indicate that these should not be used in children under the age of 6 [4]. In Italy a warning was issued in September 2007 only regarding the use of nasal sympathomimetics in children <12 years. However in the Netherlands and many other countries, no national warning was issued. The safety concerns on the use of CCMs in young children, and the regulatory actions, also received a lot of attention by the scientific community. Sharfstein et al published an important paper in the *New England Journal of Medicine* which was followed by publications in many lay press journals and media attention in most countries [1].

Most of the utilization data that have been published focus on OTC use of CCMs, as this is the major market in the USA [5-10]. Although CCMs can be bought as OTC in many countries, they are also regularly prescribed by physicians, especially when they would be reimbursed. Previous studies have shown that prescription rates of e.g. antidepressants and antipsychotics drop after regulatory warnings. However, to our knowledge, no studies have been performed that evaluated the effect of regulatory warnings on CCMs prescription rates [11-13]. We aimed to investigate the extent of use and to study the effects of the warnings on the prescription rates of CCMs to children under the age of two (since this is the group included in all international warnings) in the Netherlands and Italy, two countries with different types of direct national warnings (NL none, and Italy only on nasal sympathomimetics).

Methods

Data collection

Data were obtained from general practice medical record databases in two countries and were extracted and elaborated according to a common protocol. Databases comprised the Pedianet database in Italy [14] and the Integrated Primary Care Information (IPCI) database in the Netherlands [15]. These databases include complete automated medical records of primary care physicians. The patient population in each database is representative of the respective Dutch and Italian population regarding age and gender. The electronic records contain anonymous and coded information on patient demographics, symptoms and diagnoses, referrals, clinical findings, laboratory assessments, drug prescriptions, and hospitalisations. Details of these databases regarding their pediatric data are described elsewhere [16].

Study population

The study period was from 1 January 2005 to 31 December 2008. The study population in each country consisted of all children aged 0-2 year (up to 24 months) Each patient was followed from start of the study period or date of registration with the primary care practice (whichever was latest), until the patient left the practice or end of the study period (whichever was earliest).

Classification of prescriptions

Cough and cold medicines of interest comprised the following medicines: expectorants (ATC R05CA: althea root, thyme, combinations containing promethazine, oxmemazine, terpenes, guaiacol, and eucalyptus), mucolytics (ATC R05CB: ambroxol, bromhexine, acetylcysteine, carbocisteine, sobrerol, erdosteine, dornase alpha), opium alkaloids and derivatives (ATC R05DA: codeine, dextromethorphan, dihydrocodeine, noscapine, and opium combinations containing pentetrazol, pseudoephedrine, triprolidine, or codeine), other cough suppressants (ATC R05DB: pentoxyverine, levodropropizine, clobutinol, butarimate, dropropizine, cloperastine, and combinations containing pentoxyverine, terpenes, or thyme), nasal sympathomimetics (ATC R01AA: xylometazoline, oxymetazoline, phenylephrine, naphazoline) and combinations of nasal sympathomimetics (ATC R01AB). These drug classes were extracted from the databases using the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification system [17].

Statistical analysis

Annual prescription rates (users per 1000 person years [PY]) of CCMs were estimated by counting the number of children being prescribed each drug or drug class divided by the number of person years attributed, categorized by calendar year, age, and country. Prescription rates can be interpreted as the number of children per 1,000 children who get a specific drug (class) prescribed in one year. Because we used annual prescription rates, a child that uses one drug

(class) multiple times in one year will be counted only once for that year. To inspect seasonal variability monthly rates were calculated by dividing the number of users per month by the person months attributed.

To study the effect of the international warnings in 2007 on prescription rates, we compared prescription rates between 2005 and 2008 for each individual drug and drug class by a Chi-square test. P-values below 0.05 were considered to be significant.

Results

Patient characteristics

Our population of 99,176 children under the age of 2 generated 110,169 person years of follow-up (Table 1). The overall distribution of children per country was fairly equal, 52% of the patients were from Italy (IT) and 48% from the Netherlands (NL).

Table 1: Number of children in the study population and persontime by gender and calendar year

Patient characteristics	Italy			NL		
	Children#	PY	GP practices*	Children#	PY	GP practices*
Females	24532 (48%)	33862		23406(49%)	19741	
Males	26890 (52%)	37002		24348 (51%)	19564	
2005	19070	16338	158	11331	8422	134
2006	19424	18780	176	12189	8340	136
2007	18611	18234	160	13128	10845	138
2008	17596	17512	170	13219	11698	138
Total	51422	70864		47754	39305	

PY=person-years;

*= the number of contributing general practitioner's databases to the study population

#The number of children in various years does not add up to the total since one child can contribute in more than one year during the study period.

Prescription rates of cough and cold medicines

In the Netherlands CCMs prescription rates increased significantly between 2005 and 2008 from 74 to 92/1000 PY ($p<0.01$), but decreased slightly from 83 to 77/1000 PY ($p=0.05$) in Italy (figure 1). In both countries a strong seasonal prescription pattern could be observed, with peaks during winter time (figure 2). The seasonal patterns of CCMs prescription rates were similar before and after the international warnings in Italy and the Netherlands.

When looking at classes of CCMs, different patterns were observed, both in terms of preferred medicines between countries and changes in annual prescription rates. Expectorants were mostly prescribed in NL, and rates decreased significantly from 10.8 to 4.3/1000 PY ($p<0.01$) (table 2), mostly because of a decrease in prescription of both thyme syrup ($p<0.01$) and

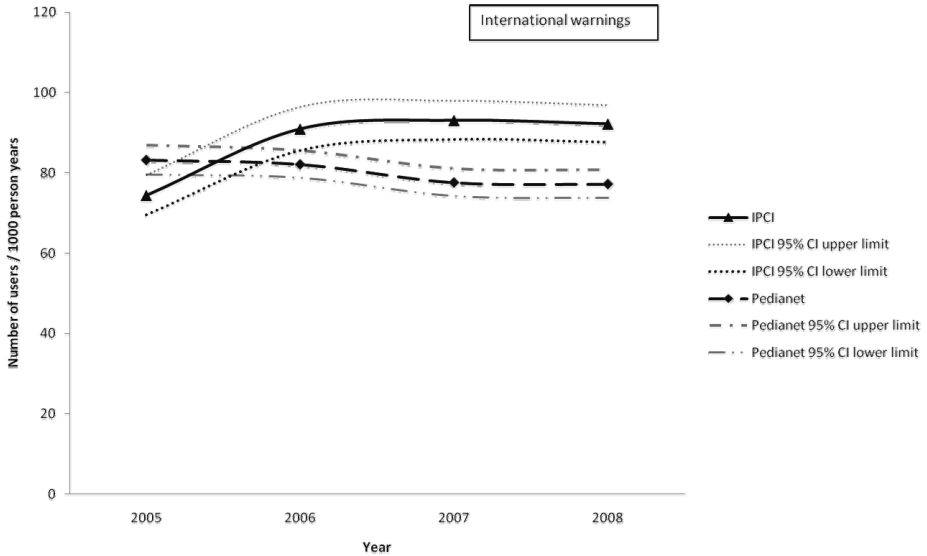


Figure 1: Prescription rates of cough and cold medicines by database and year with 95% confidence intervals
 IPCI= Dutch database
 Pedianet = Italian database

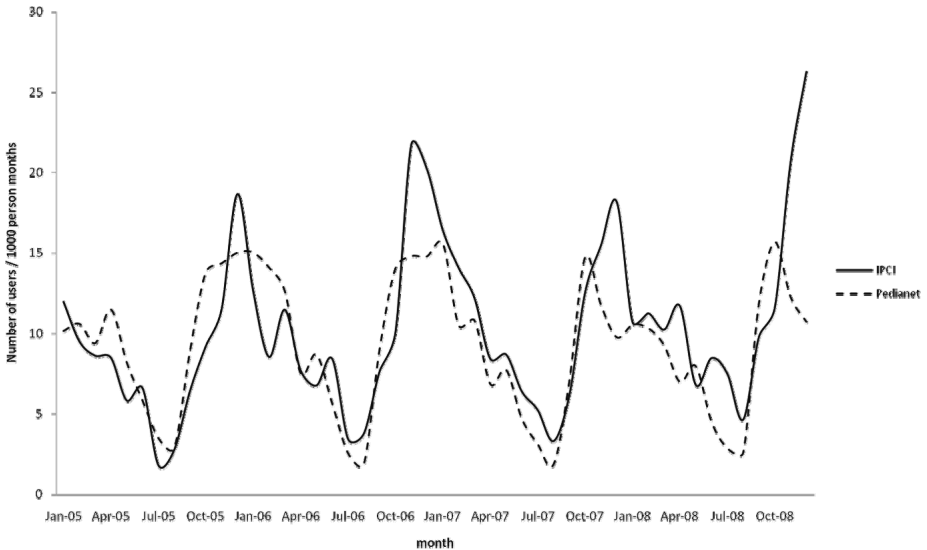


Figure 2: Prescription rates of cough and cold medicines by database and calendar month
 IPCI= Dutch database
 Pedianet = Italian database

combination products ($p < 0.01$) (Table 3). In Italy the only expectorants prescribed were combination products, and prescription rates for these increased slightly.

Table 2: Prescription rates of cough and cold medicines per 1000 person years by year and country

Year	CCMs		Cough relievers				Cough suppressants				Nasal decongestants			
	Overall		Expectorants		Mucolytics		Opium alkaloids and derivatives		Other		Sympathomimetics		Sympathomimetic Combinations	
	NL	IT	NL	IT	NL	IT	NL	IT	NL	IT	NL	IT	NL	IT
2005	74	83	10.8	4.1	6.6	54	4.2	7.4	7.7	21	51	0.9	-	7.3
2006	91	82	9.4	5.6	7.1	56	6.4	5.4	7.2	22	67	1.1	-	4.6
2007	93	78	6.8	5.2	8.6	58	10.9	3.6	9.7	17	70	0.3	-	1.4
2008	92	77	4.3	5.0	5.2	58	13.4	3.6	6.2	16	73	0.1	-	0.3
Overall	88*	79	7.1*	5.0	6.8	57	9.3*	5.0*	7.7	19*	66*	0.6*	-	3.3*

NL: the Netherlands, IT: Italy,

- = not available in NL

* = significant change between 2005 and 2008 ($p < 0.05$)**Table 3:** Pre- and post-warning prescription rates per 1000 person years of individual cough and cold medicines

Class of CCM	Netherlands			Italy				
	2005	2008	p-value	2005	2008	p-value		
Expectorants	Combinations*	4.3	1.7	<0.01	Combinations#	4.1	5.0	0.24
	Thyme syrup	14.8	0.8	<0.01				
	Althea root	0	0.08	0.40				
Mucolytics	Bromhexine	4.4	3.2	0.16	Ambroxol	17.6	19.8	0.13
	Acetylcysteine	2.0	2.0	0.93	Sobrerol	16.0	20.2	<0.01
	Carbocisteine	0.2	0	0.47	Carbocisteine	13.4	14.0	0.65
	Dornase alpha	0	.08	0.40	Bromhexine	9.7	8.2	0.14
Opium alkaloids and Derivatives	Noscapine	3.7	14.1	<0.01	Dextromethorphan	3.8	1.8	<0.01
	Codeine	0.8	0.4	0.88	Codeine	2.3	0.9	<0.01
					Combinations##	0.7	0.2	0.01
Other cough suppressants	Pentoxyverine	7.4	6.2	0.30	Levodropropizine	14.8	10.8	<0.01
	Combinations**	0.6	0	0.28	Cloperastine	5.6	5.0	0.40
					Clobutinol	0.2	0	0.42
Nasal Sympathomimetics	Xylometazoline	51	73	<0.01	Phenylephrine	0.8	0.1	<0.01
	Oxymetazoline	0.1	0.4	0.21	Naphazoline	0.1	0	0.48
Combinations of nasal sympathomimetics	-				Ephedrine based	4.6	0.2	<0.01
					Tuaminoheptane based	2.9	0.1	<0.01

- = not available in NL

* combinations containing: promethazine, oxomemazine, guaiaicol, ipecacuanha

** combinations containing: pentoxyverine, terpenes, thyme

combinations containing: terpenes, eucalyptus, guaiaicol, thyme

combinations containing: pentetrazol, dihydrocodeine, codeine, dextromethorphan, pseudoephedrine, triprolidine

Mucolytics were ten times more often prescribed in Italy than in NL. In both countries, overall rates did not change before and after the warning, but small changes occurred in prescription

of individual products. Especially prescription rates of sobrerol increased in Italy and dornase alpha in NL (tables 2 and 3).

Opium alkaloids and derivatives for cough suppression were most frequently prescribed in NL and prescription rates even tripled between 2005 and 2008 from 4.2 to 13.4/1000 PY ($p < 0.01$). This increase was due to a substantial rise in prescription rates of noscapine. In contrast, in Italy prescription rates of opium alkaloids dropped by half from 7.4 in 2005 to 3.6/1000 PY in 2008 ($p < 0.01$). This decrease was seen for all products in this class (Tables 2 and 3). Prescription rates for other (non-opioid) cough suppressants were highest in Italy, and this was mostly accounted for by levodropropizine. Rates decreased by one third after the warning ($p < 0.01$ (Table 2 and 3)). In NL, use of other cough suppressants did not change significantly.

Single product nasal sympathomimetics (mostly xylometazoline) were primarily prescribed in NL, and prescription rates increased significantly from 51 in 2005 to 73/1000 PY in 2008, mostly due to use of xylometazoline ($p < 0.01$) (Table 2). In IT, xylometazoline was hardly prescribed even before the warning, and prescription rates decreased to almost 0 in 2008. On the other hand, combinations of nasal sympathomimetics were only prescribed in IT, and a strong effect of the warning was seen on their prescription rates (from 7.3 in 2005 to 0.3/1000 PY in 2008, $p < 0.01$). Medicines prescribed in this class were combinations with ephedrine or tuaminoheptane.

Discussion

The formal regulatory review of OTC drugs, including CCMs, started in 1972 in the United States [18]. At that time, most OTC CCMs were generally recognized as safe and effective. Until recently CCMs received little attention regarding their safety and efficacy in children. In 2007, this changed dramatically by a citizen petition submitted to the FDA, raising significant concerns about the safety and efficacy of CCMs in children under the age of 6 years. This petition resulted in a public health advisory by the FDA, recommending that CCMs should not be used in children under 2 years of age because of the risk of serious and life-threatening effects [19]. The FDA warning was followed by other countries issuing warnings and several literature publications. This paper provides information on the effects of national and international warnings on rates of prescriptions of contra-indicated drugs in a country with and a country without additional national warnings. Despite the international warnings and important publications in high impact journals and lay press advising against the use of CCMs in young children, overall prescription rates for CCMs increased in the Netherlands, where no national warning was issued. Use of opium alkaloids and nasal sympathomimetics increased significantly, although these drugs are contraindicated in young children [20]. In Italy, where a specific warning was issued by the Agenzia Italiana del Farmaco only against the use of nasal sympathomimetics, a significant reduction in use of nasal sympathomimetics was seen and also a decrease in use of cough suppressants (opioids and non-opioids).

Although the warnings did not show a considerable impact on the overall prescription rates in the Netherlands, there were shifts regarding use of individual medicines. Rates for expectorant combinations decreased (comprising of promethazine and oxomemazine), whereas the prescription rates for noscapine, an opium alkaloid, increased substantially. Substantial evidence of adverse events related to the use of promethazine and oxomemazine in children exists [1, 21]. There are no studies evaluating the safety of noscapine in children, and no safety issues have been raised so far on the use of these drugs in young children. The Dutch GP society recommends noscapine for the symptomatic treatment of cough in young children [22]. This change from expectorant combinations to noscapine may be seen as a favourable trend although safety of noscapine in these young children should be further investigated. The observed increase in prescription rates of nasal sympathomimetics in the Netherlands is of high concern, since these drugs may cause serious adverse events such as lethargy, tachycardia, convulsions, and even coma [23-27]. Furthermore, a recent Cochrane review concluded that insufficient data are available on safety and efficacy of many nasal decongestants in children, which are therefore not recommended for use in children <12 years of age [28]. In Italy, safety warnings were issued in September 2007 advising not to use nasal sympathomimetics in children <12 years. Prescription rates of these drugs reduced significantly after the warning.

Our data show that CCMs are still prescribed to very young children, and prescription rates were hardly influenced by the international safety warnings, especially in the Netherlands where no national regulatory action was taken. In Italy we could observe positive effects from the safety warnings in some drug classes. Overall however, more action should be taken since use of these drugs in the very young may raise safety issues, and there is no evidence of efficacy [21, 29-31]. The few studies that evaluated the efficacy of CCMs in children with cough and cold found no significant benefit in symptomatic relief when compared to placebo [32-36]. Beside a lack of efficacy, CCMs are more prone to dosing errors. Variations in liquid CCMs dosing with spoons can be as much as 20%, leading to a higher risk of adverse events [37]. A recent study investigating therapeutic errors in children found that 23% of the dosing errors were related to use of CCMs [38]. Another study exploring pediatric fatalities associated with OTC CCMs use concluded that 85% of the fatalities were associated with an overdose of CCMs, mainly in children under the age of 2 [39].

Not only the country specific differences of the international warnings on the prescription rates of CCMs are of interest but also the differences in the types of CCMs that are prescribed. In Italy sympathomimetics are hardly used but very commonly prescribed in the Netherlands, whereas in the Netherlands use of mucolytics is very low, but frequently prescribed in Italy. This is probably due to country specific guidelines on the symptomatic relief of cough and cold.

Many of the CCMs, which are still prescribed as seen in this study, are contraindicated in children younger than 6 years in the United Kingdom and Canada, and younger than 2 in the US [2, 3, 40]. This makes prescription by primary care physicians to young children even more alarming. To minimize the use of CCMs in children, these drugs should no longer be available as OTC; and

caregiver and physician education about the self-limiting nature of coughs and colds, the lack of efficacy and the risk associated with these drugs is needed [1, 41].

As for all observational research, our data has limitations. First of all, since we used primary care prescription data, we did not capture OTC use of these drugs, nor had data on actual intake. However, our aim was to analyse prescription rates of CCMs by primary care physicians as these health professionals are approached directly by regulators/inspectorates. Furthermore, we could not compare our results with pre- and post warning prescription rates in countries where more extensive warnings have been given, since there is no published data about this subject. A major strength of our study is the fact that we capture a large number of children in two different databases across Europe, resulting in a high generalisability of the study population. To conclude, our results show that despite international warnings, a negative safety profile and lack of efficacy data, CCMs are still prescribed to young children in primary care in Italy and the Netherlands, and in the latter country rates even increased. Also, CCMs were prescribed that contain specific active ingredients proven to be most harmful in young children. Two lessons can be learned from this study. First of all, primary care physicians should be more aware of the harm and lack of efficacy of these drugs and should not prescribe them to young children. Secondly, there is heterogeneity in warnings across countries in the EU, which creates inequality. In order to increase awareness among physicians and caretakers and to allow for consistent warnings, the hazards of use of these medicines have to be explicitly stipulated by European Medicines Agency. A concerted action is needed in Europe to advice against the use and prescription of cough and cold medicines to young children.

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Acknowledgements: We thank all of the physicians contributing data to the PEDIANET, and IPCI databases.

None of the authors has a conflict of interest. The principal investigator had full access to all of the data in the study and takes responsibility for their integrity and the accuracy of the data analysis.

Funding: Funded by the European Community's 6th Framework Programme. Project number LSHB-CT-2005-005216: TEDDY: Task force in Europe for Drug Development for the Young.

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Chapter 3

Drug safety

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Chapter 3.1

Use of Asthma medicines and reported adverse drug reactions in children: Results from the WHO adverse events database

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Abstract

Objective: To provide an overview of the paediatric adverse drug reactions (ADR), related to the use of asthma drugs in children, that have been reported to the WHO adverse events reporting database. In addition, we want to identify new ADRs associated with use of asthma medicines in children.

Design: case non-case study

Setting: worldwide spontaneous reporting database: Vigibase

Participants: children aged 0-≤18 years

Main outcome measure: association between asthma medicines and suspected ADRs using the reporting odds ratio (ROR) as a measure of disproportionality while adjusting for gender, continent and reporter. To reduce confounding, vaccine-related records were excluded from the analysis.

Results: Records for asthma drug related ADRs comprised 3.5% of the non-vaccine related records (10,259 records). The majority of the records were for children aged 2-≤11 years (60%) and most records concerned short-acting β 2-agonists (SABAs) and inhaled corticosteroids. Known ADRs such as Churg -Strauss syndrome, paradoxical bronchospasm and adrenal insufficiency were amongst the ADRs with the highest RORs. The majority of the identified asthma medicines-ADR associations are already described in the literature. New, potential signals that we found were intestinal gangrene (ROR 38.2, 95% CI [17-267]) and perforated gastric ulcer (ROR 55.3, 95% CI [21-148]) both associated with use of SABAs, and tooth discoloration with the use of anticholinergics (ROR 21.4, 95% CI [8-59]).

Conclusion: this systematic assessment of pediatric ADRs for asthma medicines in children shows that the majority of ADRs reported to Vigibase are already described in the literature. Some potentially new ADRs were identified, which require further exploration.

Introduction

Respiratory medicines are amongst the most frequently prescribed drugs in children, and especially asthma medicines are frequently prescribed [1]. Prevalence rates of asthma medicines use range between 4 and 26 percent, depending on country, age range, and study period [1-3].

According to the Global Initiative for Asthma (GINA), bronchodilators, (inhaled short-acting β_2 -agonists, long-acting β_2 -agonists, anticholinergics, inhaled corticosteroids and alternative (add-on) treatments such as leukotriene receptor antagonists (LTRA), xanthines and anti-allergics (cromones) all have a place in the treatment of childhood asthma, although at various stages depending on severity of illness [4]. As asthma is the most common chronic disease of childhood, most of these medicines is used for a long term and for some of them, safety concerns exist with long duration of use [5]. For example, increased risk of death with single use of long-acting beta-agonists in adults, and adrenal suppression and growth retardation with use of inhaled steroids in children [6, 7]. However, overall the risk-benefit profile of these medicines has been well studied in randomized controlled trials (RCTs), and is considered to be favorable [4, 7]. However, the majority of these studies have been performed in children older than 5 years and studies in younger children are lacking. Furthermore, RCTs have small sample sizes and relatively short follow-up, which makes it difficult to detect adverse drug reactions (ADRs) which are rare or those that occur after long-term treatment. The missing data on safety and efficacy information regarding these medicines has been a reason for the European Medicines Agency (EMA) to put many asthma medicines on the pediatric needs list. This list, drafted by Pediatric Committee of the EMA, contains medicines for which information on pharmacokinetics, efficacy and safety is urgently needed [8].

Large spontaneous adverse event reporting databases, such as the Vigibase database of the WHO-UMC (Uppsala Monitoring Centre), is a well-recognized source for monitoring the potential risks of drugs, however there has been no systematic approach to investigate safety signals in children. To get a broader understanding of the adverse drug reactions associated with asthma medicines use, which is one of the most frequently used drug group in children, we analysed the adverse drug reactions in relation to asthma medicines reported to the Vigibase database of the WHO-UMC [1].

Methods

WHO-UMC database

We used data from the Vigibase database of suspected ADRs. This global individual case safety report (ICSR) database system, established by the World Health Organisation (WHO) in 1968, holds more than 3.7 million ICSRs as of June 2006. It is maintained on behalf of the WHO Programme by the Uppsala Monitoring Centre (UMC). More than 80 countries participate in the WHO International Drug Monitoring program, and another 17 countries are associate members, not yet actively contributing data. ICSRs are submitted through the national pharmacovigilance centers. WHO Programme member countries submit ICSRs to the UMC on a regular basis; preferably once per month, but at least every quarter.[9].

At the time of the data extraction in 2006, all ADRs within Vigibase were coded using preferred terms of the WHO-Adverse Reaction Terminology (WHO-ART) coding dictionary. Reported drugs were re-coded using the WHO Drug dictionary, and the Anatomical Therapeutic Chemical (ATC) classification system of the WHO Collaborating Centre for Drug Statistics Methodology [10]. Assigned ATC codes of asthma medicines were verified for accuracy in this study. For the purpose of this study drugs were further categorized as: short-acting β -agonists (SABA, ATC codes R03AC02, R03AC03 or R03AC04), long-acting β -agonists (LABA, ATC codes R03AC excluding SABA), inhaled glucocorticoids (ICS, ATC R03BA), anticholinergics (ACH, ATC R03BB), anti-allergic agents (anti-allergics, ATC R03BC), xanthines (ATC R03DA), leukotriene receptor antagonists (LTRA, ATC R03DC), fixed combinations of β -agonists+ICS (β 2+ICS, ATC R03AK06 or R03AK07) and fixed combinations of β -agonists+ACH (β 2+ACH, R03AK03 or R03AK04).

Selection of ICSRs

From Vigibase, all ICSRs in children (age 0 - \leq 18 years) with onset date between January 2000 and December 2006 were extracted. Only spontaneously reported ICSRs and those with a suspected causal relationship between ADR and drug were included. ICSRs for which information on the reported drug or reported ADR was missing were excluded.

Record definition

One ICSR can contain more than one suspected drug, and more than one ADR. We defined a record as a unique combination of a drug and an ADR. Hence, an ICSR containing two ADRs with one suspected drug counted for two records, and an ICSR containing two ADRs with two suspected drugs counted for four records. (In Sandra's paper kreeg ze vragen over deze keuze van selectie van data – kan je evtl verwijzen naar paper van WHO waar ze ook deze method aanhouden?) Information on each record include country of origin, reporter, age at onset, year of onset, gender, reported drug, reported ADR, starting and stopping date of the drug, starting and stopping date of the ADR, dosing regimen of the drug, administration route, and causality assessment.

Statistical analysis

All analyses were conducted on a record basis, thus using unique drug-ADR combinations. Disproportionality was assessed by calculation of the reporting odds ratio (ROR), which is analogous to an odds ratio [11]. RORs with 95% confidence intervals (95% CI) were calculated for the different subgroups of cough and cold medicines.

The ROR was only calculated if at least 3 records of the drug-ADR combination of interest were available. A ROR of ≥ 2 with a 95% confidence interval not including 1 is considered a signal. Since this method is purely hypothesis generating it must be emphasized that a significant signal does not imply causality.

To study the effect of age; the ROR was calculated within predefined age-categories. In line with the guidelines of the International Conference of Harmonization (ICH), age at the time of the event was categorized into the following age categories: 0 - < 2 years, 2 - ≤ 11 years and 12 - ≤ 18 years [12].

Since vaccines represent a substantial part of the drugs used in children and may confound the RORs of other drug-ADR combinations, vaccine related records were excluded. Additional logistic regression analyses using SPSS version 15.0 for Windows (SPSS, Inc., Chicago, Illinois) was performed to correct for gender, continent and type of reporter.

Results

In the period between January 2000 and December 2006 221,508 suspected (thus potentially causally related) spontaneous ICSRs in children aged ≤ 18 years were included in the WHO-Vigibase translating in a total of 845,090 records. After exclusion of records that were vaccine related ($n= 517,642$) and for which information on the reported drug or reported ADR was missing ($n= 32,675$), the total number of drug-ADR combinations in the analysis was 294,773. The database comprised 10,259 asthma medicines related records (3.5% of all non-vaccine related records). Compared to all non-vaccine related records, records of asthma medicines related ADRs involved more boys, were more often reported by a general practitioner, and involved younger children (mean age difference of 1.3 years) (table 1). ADRs were most frequently reported for SABA (24.1%) ICS (23.6%) and LTRAs (20.8%) (table 2).

Drug-ADR combinations with the highest RORs

Table 3 shows the top ten of strongest associations. The number one was Churg-Strauss syndrome (ROR 365, 95% CI 48-2802) followed by paradoxical bronchospasm (ROR 77 95% CI 21-284) (Table 3) and cortisol decreased. Most of the associations were not seen in the youngest children, apart from decreased levels of cortisol and tenosynovitis.

Table 1: Characteristics of all non-vaccine and asthma medicines related ADR records

	All non-vaccine related records	% of total number of records	Asthma medicines related records	% of all records (row)
N	294,773		10,259	
Male gender	153,708	52.1	5,787	3.8
Notifier				
General practitioner	53,790	18.2	2,438	4.5
Physician	50,300	17.1	1,368	2.7
Hospital	38,795	13.2	349	0.9
Other	151,888	51.5	5,834	3.8
Country of origin				
United States	181,126	61.4	6,367	3.5
France	18,820	6.4	374	2.0
Thailand	16,464	5.6	182	1.1
Other//				
Age				
Mean / SD (years)	9.7	6.0	8.4	
Median (years)	10.0		8.0	
0 - < 2 years	45,209	15.3	1,023	2.3
2 - ≤ 11 years	114,704	38.9	6,199	5.4
12 - ≤ 18 years	134,860	45.8	3,037	2.3

Table 2: Distribution of asthma drugs related records by drug class and age category

Drug class	0-2 years		2-11 years		11-18 years		Total	
	N	%*	N	%*	N	%*	N	%*
SABA	427	41.7	1,235	19.9	806	26.5	2,468	24.1
LABA	6	0.6	270	4.4	302	9.9	578	5.6
ICS	238	23.3	1,698	27.4	480	15.8	2,416	23.6
ACH	30	2.9	90	1.5	10	0.3	130	1.3
Anti-allergics	27	2.6	203	3.3	54	1.8	284	2.8
Xanthines	110	10.8	211	3.4	154	5.1	475	4.6
LTRA	76	7.4	1,505	24.3	557	18.3	2,138	20.8
β-agonists+ICS	10	1.0	747	12.1	440	14.5	1,197	11.7
β-agonists+ACH	12	1.2	17	0.3	8	0.3	37	0.4
Other asthma drugs	87	8.5	223	3.6	226	7.4	536	5.2
Total	1,023	100	6,199	100	3,037	100	10,259	100

* = % of total within this age category

SABA=short-acting beta-agonists, LABA=long-acting beta-agonists, ICS = inhaled corticosteroids, ACH=anticholinergics, LTRA = leukotriene receptor antagonists

Analyses by type of asthma medicines showed that for SABAs paradoxical bronchospasm, intestinal gangrene and perforated gastric ulcer were associated with the highest RORs (table 4). In

Table 3: Ten highest reporting odds ratios (RORs) for ADRs associated with asthma drugs stratified by age

Adverse drug reaction	Associated with asthma drugs N	Associated with any other drug N	All age categories		Stratified by age category		
			ROR crude (95% CI)	ROR* (95% CI)	ROR* (95% CI) 0-2 yr	ROR* (95% CI) 2-≤11 yr	ROR* (95% CI) 12-≤18 yr
Churg Strauss syndrome	13	1	352.6 (46-2696)	365.8 (48-2802)	-	Infinity	244.1 (29-2031)
Bronchospasm paradoxical	10	3	90.4 (25-328)	77.7 (21-284)	-	23.3 (5-99)	Infinity
Cortisol decreased	30	10	81.5 (40-167)	73.8 (36-151)	-	71.8 (21-251)	105.8 (41-271)
Adrenal Insufficiency	84	34	67.5 (45-101)	63.1 (42-94)	19.9 (6-62)	96.7 (52-79)	17.5 (7-46)
Intestinal gangrene	5	4	33.9 (9-126)	28.4 (8-107)	-	-	49.1 (11-210)
Nasal septum perforation	7	6	31.6 (11-94)	24.1 (8-72)	-	32.7 (3-323)	30.4 (8-114)
Anisocoria	4	4	27.1 (7-108)	23.3 (6-94)	-	29.0 (5-161)	-
Tenosynovitis	4	4	27.1 (7-108)	24.9 (6-100)	Infinity	-	-
Bronchospasm aggravated	16	18	24.1 (12-47)	25.4 (13-50)	-	24.6 (8-76)	23.2 (9-62)
Osteoporosis	36	45	21.7 (14-34)	20.6 (13-32)	-	30.3 (14-65)	21.7 (12-39)

* = adjusted for gender, continent and type of reporter

- = number drug-ADR combination with ≥ 3 records

age-specific analyses the highest RORs were for psychosis in children aged 0-2 years, bronchiectasis in children 2-≤11 years and intestinal gangrene in the oldest age category.

No LABA related ADRs were reported for children aged 0-2 years, which is not indicated below age 5. In children aged 2-≤11 years the highest RORs were for tooth disorders and hemiplegia. In children aged 12-≤18 years, sudden death was amongst the ADRs with the third highest ROR within this drug group (table 4)

In all 3 three age categories, disorders of the adrenal gland (adrenal insufficiency and decreased levels of cortisol) were ADRs with the highest ROR for ICS. Perforation of the nasal septum was also among the ADRs with the highest ROR in this drug group in children aged 2-≤11 and 12-≤18 years. (table 4) Other ADRs with the highest ROR for ICS were hypertrichosis and varicella in children <2 years and osteoporosis in children aged 12-≤18 years.

For anticholinergics respiratory acidosis was strongly associated. When stratifying by age categories, drug-ADR combinations with ≥ 3 records for anticholinergics were only observed in children aged 2-≤11. The three highest RORs in this category were found for tooth discoloration, mydriasis and constipation. (table 4)

Table 4: Three highest significant RORs by drug class and age category

Drug class	0-2 years				2-11 years				12-18 years						
	ADR	# cases	# no cases	ROR*	Described in literature or SPC	ADR	# cases	# no cases	ROR*	Described in literature or SPC	ADR	# cases	# no cases	ROR*	Described in literature or SPC
SABA	Psychosis	3	2	139	[34]	Bronchiectasis	3	13	19	Conf. [35]	Intestinal gangrene	4	4	76	No
	Vasodilatation	3	14	22	[36]	Myocardial ischaemia	4	19	18	[36]	Perforated gastric ulcer	6	11	72	No
	Hypokalemia	4	23	19	[36]	Heart valve disorders	3	16	15	No	Asthma	52	214	40	Conf./Tr. fail.
LABA						Tooth disorder	3	35	30	No	Asthma	14	252	24	Conf./Tr. fail.
						Hemiplegia	3	37	31	No	Taste perversion	4	82	20	[24]
						Asthma	11	336	12	Conf./Tr. fail.	Sudden death	3	73	16	[37]
ICS	Adrenal insufficiency	5	8	59	[15]	Cortisol decreased	14	3	258	[15]	Cortisol decreased	14	8	395	[15]
	Hypertrichosis	5	9	80	[38]	Adrenal insufficiency	69	16	252	[15]	Nasal septum perforation	4	5	171	[25]
	Varicella	3	13	27	[39]	Nasal septum perforation	3	1	109	No	Osteoporosis	17	31	133	[15]
ACH						Tooth discolouration	4	292	18	No	Tooth discolouration	4	292	18	No
						Mydriasis	4	303	15	[24]	Mydriasis	4	303	15	[24]
						Constipation	3	274	11	[24]	Constipation	3	274	11	[24]

Table 4: Continue

Pneumonia	3	1054	6	[27]	Rhinitis	8	241	17	Conf.	3	234	26	Conf.
Antiallergics					Rhinitis	3	113	14	No	3	575	11	[40]
					Photosensitivity reaction	3	113	14	No	3	575	11	[40]
					Myalgia	3	196	8	[40]	8	1,732	12	Conf./Tr. fail. [28]
Drug level decreased	10	32	18	No	Hypokinesia	4	108	22	No	9	231	24	
Xanthines					Acidosis	5	186	15	[28]	5	156	25	[29]
	8	292	11	[29]	Palpitation	3	157	10	[29]	3	105	25	[29]
Jaundice neonatal	3	117	16	Hepatitis in adults	Churg strauss syndrome	7	-	Infinity	[30]	5	2	654	[30]
Allergic reaction	3	181	10	[30]	Monocytosis	3	9	19	No	4	6	137	No
Premature birth	3	596	3	[41]	Airway obstruction	3	10	21	other drugs	4	77	8.3	[30]
β -agonists+					Medical device complication	3	18	18		5	34	70	No
ICS	-	-	-	-	Enanthema	4	29	21	[42]	8	69	34	[42]
					Asthma	32	315	13	Conf./Tr. fail.	22	244	24	Conf./Tr. fail.
β -agonists+ ACH	-	-	-	-	Coughing	4	625	57	[33]	-	-	-	-

* = adjusted for gender, continent and type of notifier

- = number of drug-ADR combination with ≥ 3 recordsSABA=short-acting beta-agonists, LABA=long-acting beta-agonists, ICS = inhaled glucocorticoids, ACH=anticholinergics, LTRA = leukotriene receptor-antagonists
Conf./Tr. fail. = confounding/treatment failure

Antiallergics were strongly associated with rhinitis in children aged 2-≤11 and 12-≤18 years. In children <2 years, the only ADR with ≥3 records for antiallergics was pneumonia.

For xanthines, heart rhythm disorders related ADRs (tachycardia, palpitation, extrasystoles) were amongst the ADRs with highest RORs in all age categories. (table 4) Acidosis had the highest ROR in children aged 2-≤11 and 12-≤18 years. (table 4)

In children < 2 years, the highest RORs for LTRAs were calculated for neonatal jaundice, allergic reactions and premature birth. Churg Strauss syndrome had the highest ROR in children aged 2-≤11 and 12-≤18 years. In children aged 2-≤11 years LTRAs were the only group for which Churg Strauss syndrome was reported as an ADR.

In the overall analysis, leg cramps were most strongly associated with β2+ICS combinations. Within the age categories, drug-ADR combinations with ≥ 3 records for β2+ICS were only observed in children aged 2-≤11 and 12-≤18 years. The highest ROR in children 2-≤11 years were observed for medical device complications and for increased levels of glucocorticoids in children aged 12-≤18 years.

Flushing and coughing were the ADRs with the highest RORs for β2+ACH in the overall analysis. Within the age categories, the only drug-ADR combination with ≥ 3 records was coughing in children aged 2-≤11 years.

Discussion

This is the first study that analysed pediatric ADRs reported for asthma medicines in the Vigibase WHO-UMC database. There are several important findings in our study.

First, asthma drugs related ADRs were infrequently reported (3.5% of the non-vaccine related records) although drug utilization studies have shown that 4-26% of children use an asthma medicine per year [1, 2]. The low reporting rate could be due to the fact that most asthma drugs are on the market for many years, and are thought to have a good safety profile. Second, most asthma medicines related ADRs were reported for children aged 2-≤11 and 12-18 years of age although utilization studies have shown that prevalence of use of asthma medicines is highest in younger children [1, 3]. There thus seems to be a discrepancy between the percentage of asthma medicines use in children <2 and the proportion of ADRs reported for this age group. A possible explanation could be that ADRs are not recognized in very young children. Third, most asthma medicines related ADRs concerned SABAs and ICS, drugs for which utilization studies have shown that these are the mostly used asthma medicines in pediatrics [3].

The majority of ADRs with the highest ROR that we found in this study are also described in literature and SPCs (e.g. paradoxical bronchospasm, adrenal insufficiency and Churg Strauss syndrome) [13-16]. For example, adrenal insufficiency is a well-known side-effect of steroids (both inhaled and oral) [15]. Another example is the increased risk of serious adverse drug reactions when using single LABA. A Cochrane review found that serious adverse events were

significantly higher in children using LABA [17]. In 2006, the SMART study showed an excess risk of asthma-related deaths in adult patients using LABA [6]. As a result, the Food and Drug Administration (FDA) issued a 'black box' warning for LABA, warning patients about a fatal outcome and recommending never to use LABAs as monotherapy but always to combine it with ICS. Recently, the FDA added further safety requirements to the use of LABAs [18]. For children and adolescent, the FDA requires that when LABA use is required, this should only be a combination product containing both an inhaled corticosteroid and a LABA, to ensure compliance with both medications.

ADRs that were not yet described in literature nor mentioned in the SPC were the following: intestinal gangrene, gastric ulcer perforation, heart valve disorders, hemiplegia, tooth disorder, hypokinesia and iritis.

Intestinal gangrene, gastric ulcer perforation and heart valve disorders were reported for children using SABAs; hemiplegia and tooth disorders for LABAs, hypokinesia for xanthines and iritis for LTRAs. Most of these ADRs are serious, and in light of the widespread use of asthma medicines in children with asthma, more research is needed to confirm our findings eventually by means of large observational safety studies.

As for all observational research, our data has limitations. First of all, we used data from spontaneous reporting systems, which suffer from bias such as under- and overreporting. [19-21]. Furthermore, it has to be underlined that a signal with a high ROR does not prove that the drug and ADR are causally related. The observed signals are purely hypothesis generating and further research is needed to assess these signals in an appropriate setting [22]. Also, some of the found ADRs are most likely caused by the underlying condition and treatment failure rather than the investigated drugs. This is most probably the case for asthma being reported as an ADR, since all analysed medicines are indicated for use in asthma. Also respiratory acidosis reported for ACH is most probably caused by confounding or treatment failure. Studies have shown that metabolic acidosis occurs in patients with severe acute asthma attacks [18]. Similar explanations hold for rhinitis as ADR for antiallergics, since antiallergics are also used to treat rhinitis [23].

Due to the nature of the database, information on indication is missing, and therefore it is not possible to identify the underlying condition.

The strength of this study is the large number of pediatric ADRs that was available for analysis. To our knowledge, this is the first study to systematically analyse the spontaneous reports from the Vigibase database for associations between asthma medicines and ADRs in children. It is reassuring to see that the majority of strongly associated ADRs are known already and have described in literature and included in the SPC. On the other hand we found some new signals regarding events that have not yet been described in literature and more research to explore the potential causality is needed.

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Chapter 3.2

Cough and cold medicines related adverse drug reactions in children: Results from the WHO adverse events database

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Abstract

Objective: To provide an overview of pediatric adverse drug reactions (ADR) associated with the use of cough and cold medicines (CCMs) reported to the WHO adverse events reporting database and possibly identify new ADRs associated with CCMs use.

Design: case non-case study

Setting: worldwide spontaneous reporting database: Vigibase

Participants: children aged 0-18 years

Main outcome measure: association between cough and cold medicines and suspected ADRs using the reporting odds ratio (ROR) as a measure of disproportionality while adjusting for gender, continent and reporter. To reduce confounding, vaccine-related records were excluded from analysis.

Results: Records for CCMs related ADRs comprised 1.2% of the non-vaccine related records (3,467 records). The majority of the reports were for children aged 2-18 years (80%) and most reports concerned mucolytics and opium alkaloids. Severe ADRs such as subarachnoid haemorrhage, myocardial infarction and cerebrovascular disorders were amongst the ADRs with the highest RORs. Most of the found CCMs-ADR associations are described in literature (such as dosing errors, neurologic ADRs associated with opioids use). However, we found some new CCMs-ADR associations such as chronic renal failure associated with use of expectorants (ROR 22.9, 95% CI [7.2-72]) and cerebral infarction associated with the use of opium alkaloids+expectorants (ROR 50.4, 95% CI [23-109]).

Conclusion: this overview of pediatric ADRs associated with CCMs use shows that severe and potentially life-threatening ADRs occur in children of all ages. We underline the advice not to use CCMs in young children, and recommend that CCMs, in view of their poor benefit-risk profile should not be given to children over all.

Introduction

Cough and cold medicines (CCMs) are frequently used to treat upper respiratory tract infections in children. In the past years, safety issues have been raised concerning the use of these drugs in young children. A growing number of studies associated the use of CCMs to serious adverse drug reactions (ADRs) in children, such as cardiac arrhythmias, depressed levels of consciousness and even death [1]. As a result, some countries undertook regulatory actions against over-the-counter use of CCMs in young children [2-4].

Most of the published data on the safety of CCMs deal with children <2 years, however concerns also exist about the safety of these drugs in older children. Because of these concerns, the safety monitoring of CCMs in older children is ongoing [3]. It is difficult to assess the safety of CCMs via randomized controlled trial first of all because very few RCTs have been done in children and the available RCTs have small sample sizes and short follow-up. Spontaneous adverse event reporting databases, such as the Vigibase database of the WHO-UMC (Uppsala Monitoring Centre), can be a source get a better insight in the potential risks of these drugs.

To get a broader understanding of the adverse drug reactions associated with CCMs use in children, we analysed the pediatric adverse drug reactions in relation to CCMs reported to the Vigibase database of the WHO-UMC.

Our objective was to analyse and describe: 1) pediatric ADRs with the highest reporting odds ratios related to CCMs and 2) possibly identify new safety signals (CCMs-ADR combinations that have not yet been described in literature or the summary of product characteristics)

Methods

WHO-UMC database

We used data from the Vigibase database of suspected ADRs. This global individual case safety report (ICSR) database system, established by the World Health Organisation (WHO) in 1968, holds more than 3.7 million ICSRs as of June 2006. It is maintained on behalf of the WHO Programme by the Uppsala Monitoring Centre (UMC). More than 80 countries participate in the WHO International Drug Monitoring program, and another 17 countries are associate members, not yet actively contributing data. ICSRs are submitted through the national pharmacovigilance centers. WHO Programme member countries submit ICSRs to the UMC on a regular basis; preferably once per month, but at least every quarter.[5].

At the time of the data extraction in 2006, all ADRs within Vigibase were coded using preferred terms of the WHO-Adverse Reaction Terminology (WHO-ART) coding dictionary. Reported drugs were recoded using the WHO Drug dictionary.

Drugs were additionally coded using the Anatomical Therapeutic Chemical (ATC) classification system of the WHO Collaborating Centre for Drug Statistics Methodology [6]. ATC codes of cough and cold medicines were manually checked for accuracy allocated to the following subgroups: expectorants (e.g. guaifenesin, althea root etc.), mucolytics (e.g. acetylcysteine, ambroxol etc.), opium alkaloids and derivatives (e.g. codeine, dextrometorphan), other cough suppressants (e.g. pentoxyverine, levodropropizine), combination products of opium alkaloids and expectorants, combinations products of other cough suppressants and expectorants, other cold combination preparations, combination products of opium alkaloids and antihistamines (e.g. dextrometorphan+chlorphenamine), combination products of opium alkaloids and sympathomimetics (e.g. dextrometorphan+pseudoephedrine), combination products of other cough suppressants and antihistamines (e.g. guaifenesin+diphenhydramine), combinations products of other cough suppressants and sympathomimetics (e.g. phenobarbital+ephedrine).

Selection of ICSRs

From Vigibase all ICSRs in children (age 0 - ≤18 years) received or with onset date between January 2000 and December 2006 were extracted. Only spontaneously reported ICSRs and those with a suspected causal relationship between ADR and drug were included. In addition, those ICSRs where information on the reported drug or reported ADR was missing were excluded.

Record definition:

An ICSR can contain more than one suspected drug, and more than one ADR. We defined a record as a unique combination of a drug and an ADR. Hence, an ICSR containing two ADRs with one suspected drug counted for two records, and an ICSR containing two ADRs with two suspected drugs counted for four records. Information on these records include country of origin, reporter, age at onset, year of onset, gender, reported drug, reported ADR, starting and stopping date of the drug, starting and stopping date of the ADR, dosing regimen of the drug, administration route, and causality assessment.

Statistical analysis:

All analyses were conducted on a record basis, thus using unique drug-ADR combinations. Disproportionality was assessed via the calculation of the reporting odds ratio (ROR), which is calculated analogous to and odds ratio [7]. RORs with 95% confidence intervals (95% CI) were calculated for the different subgroups of cough and cold medicines.

The ROR was only calculated if at least 3 records of the drug-ADR combination of interest were available. A ROR of ≥ 2 with a 95% confidence interval not including 1 is considered significant. Since this method is purely hypothesis generating it must be emphasized that a significant signal does not imply causality.

To study the effects of age; the ROR was calculated within predefined age-categories. In line with the guidelines of the International Conference of Harmonization (ICH), age at the time

of the event was categorized into the following age categories: 0 - < 2 years, 2 - ≤11 years and 12 - ≤18 years [8].

Since vaccines represent a substantial part of the drugs used in children and may bias the RORs of other drug-ADR combinations, vaccine related records were excluded. Additional logistic regression analysis using SPSS version 15.0 for Windows (SPSS, Inc., Chicago, Illinois) was performed to correct for gender, continent and type of reporter.

Results

In the period between January 2000 and December 2006 221,508 suspected (thus potentially causally related) spontaneous ICSRs in children aged ≤18 years were reported to the WHO-UMC, containing a total of 845,090 records. After exclusion of records that were vaccine related (n= 517,642) and for which information on the reported drug or reported ADR was missing (n= 32,675), the total number of drug-ADR combinations in the analysis was 294,773.

General characteristics of all records and ATC R05 related records are presented in table 1. The database comprised 3,467 CCMs related records (1.2% of total records). Compared to all drugs (including records of CCMs), records of CCMs related ADRs involved more females, were more often reported by a physician, were less likely to originate from the United States and involved younger children (mean age difference of 1 year).

Table 1: Characteristics of all records and cough and cold medicines (CCM) related records

	All records	%	CCM related records	%
N	294,773		3,467	
Gender; male	153,708	52.1	1,628	47.0
Notifier				
<i>General practitioner</i>	53,790	18.2	456	13.2
<i>Physician</i>	50,300	17.1	759	21.9
<i>Hospital</i>	38,795	13.2	456	13.2
<i>Other</i>	151,888	51.5	1,796	51.8
Country of origin				
<i>United States</i>	181,126	61.4	1,470	42.4
<i>France</i>	18,820	6.4	555	16.0
<i>Thailand</i>	16,464	5.6	170	4.9
Age				
Mean / SD	9.7	6.0	8.7	6.3
Median	10.0		8.0	
<i>0 - < 2 years</i>	45,209	15.3	601	17.3
<i>2 - ≤ 11 years</i>	114,704	38.9	1,477	42.6
<i>12 - ≤ 18 years</i>	134,860	45.8	1,389	40.1

Distribution of records by drug class

The distribution of CCMs related records by drug class and age category is given in Table 2. Most ADR records involved children aged 2-≤11 years (43%), followed by 12-≤18 years (40%) and children aged <2 years (17%). ADRs were most frequently reported for mucolytics (30.3%) and opium alkaloids and derivatives (20.5%).

Table 2: Distribution of cough and cold preparations related records by drug class and age category

Drug class	0-2 years		2-11 years		11-18 years		Total	
	N	%*	N	%*	N	%*	N	%*
Expectorants	40	6.7	103	7.0	48	3.5	191 [#]	7.9
Mucolytics	179	29.8	474	32.1	397	28.6	1,050 [#]	30.3
Opium alkaloids and derivatives	92	15.3	259	17.5	359	25.8	710 [#]	20.5
Other cough suppressants	47	7.8	126	8.5	103	7.4	276 [#]	8
Combinations of opium alkaloids and expectorants	15	2.5	104	7.0	156	11.2	275 [#]	7.9
Combinations of other cough suppressants and expectorants	0	0.0	12	0.8	0	0.0	12 [#]	0.3
Combinations of opium alkaloids and antihistamines	112	18.6	166	11.2	110	7.9	388 [#]	11.2
Combinations of opium alkaloids and sympathicomimetics	80	13.3	149	10.1	160	11.5	389 [#]	11.2
Combinations of other cough suppressants and antihistamines	0	0.0	1	0.1	0	0.0	1	0
Combinations of other cough suppressants and sympathicomimetics	2	0.3	2	0.1	0	0.0	4	0.1
Other cold combination preparations	34	5.7	81	5.5	56	4.0	171 [#]	2.6
Total	601	100	1,477	100	1,389	100	3,467	100

* = % of total within this age category

= statistically significant difference (p<0.05) between number of records in the age categories for that drug class

Drug-ADR combinations with the highest RORs

The highest ROR between CCMs as a group and specific events were found for cystic fibrosis (ROR 64.0, 95% CI 20-203) and hepatic haemorrhage (ROR (54.2, 95% CI 18-167)) both mainly in children aged 12-≤18 years (table 3). Severe ADRs such as subarachnoid haemorrhage and cerebral infarction were also among the ADRs with the highest RORs. Subarachnoid haemorrhage was only reported in children aged 12-≤18 years, and cerebral infarction in both children aged 2-≤11 and 12-≤18 years (table 3).

Expectorants:

Analyses by type of CCM showed that for expectorants the most disproportionately reported ADRs were subarachnoid haemorrhage, chronic renal failure and cerebrovascular disorder (table 4 and 5). When stratifying by age category, ROR for expectorants was the highest for apnoea in children aged 0-2 years, chronic renal failure in children 2-≤11 years and cerebrovascular ADRs (subarachnoid haemorrhage and cerebrovascular disorder) in the oldest age category.

Table 3: Ten highest reporting odds ratios (RORs) for ADRs associated with cough and cold preparations (CCM) stratified by age

Adverse drug reaction	Associated with CCM N	Associated with any other drug N	All age categories		Stratified by age category		
			ROR crude (95% CI)	ROR* (95% CI)	ROR* (95% CI) 0-2 yr	ROR* (95% CI) 2-≤11 yr	ROR* (95% CI) 12-≤18 yr
Cystic Fibrosis	5	7	60.1 (19-189)	64.0 (20-203)	-	-	2981x10 ³ (0-infinity)
Hepatic Haemorrhage	5	8	52.6 (17-161)	54.2 (18-167)	-	-	65.2 (21-206)
Infusion site reaction	3	12	21.0 (5.9-75)	21.0 (5.9-75)	-	-	35.6 (9.4-135)
Haemoptysis	11	70	13.2 (7.0-25)	13.3 (7.0-25)	-	23.3 (7.5-72)	12.3 (5.6-27)
Subarachnoid Haemorrhage	6	39	12.9 (5.5-31)	13.7 (5.8-32)	-	-	29.5 (9.7-90)
Incorrect drug administration dosage	3	21	12.0 (3.5-40)	12.4 (3.7-42)	12.2 (3.6-42)	-	-
Cerebral infarction	13	130	8.4 (4.8-15)	8.6 (4.9-15)	-	4.1 (1.3-13)	16.2 (8.3-32)
Cerebrovascular Disorder	28	284	8.3 (5.7-12)	8.7 (5.9-13)	14.4 (6.0-35)	8.0 (4.2-15)	8.0 (4.4-14)
Pleurisy	3	33	7.6 (2.3-25)	6.3 (1.9-21)	-	-	-
Hypernatraemia	5	62	6.8 (2.7-17)	6.9 (2.8-17)	-	-	21.4 (7.2-64)

* = adjusted for gender, continent and type of reporter

- = number drug-ADR combination with ≥ 3 records

Mucolytics:

Mucolytics were strongly associated with an aggravation of the condition, involuntary muscle contractions and angioedema in the children 0-2 years. In older children, haemoptysis, urticaria, meningitis and infusion site reaction were the ADRs with the highest RORs.

Opium alkaloids and derivatives

Opium alkaloids and derivatives were associated with neurological ADRs in children younger than 12 years namely stupor in children < 2 years and ataxia, neurologic disorder and mydriasis in children aged 2-11 years. In children 12-18 years, pulmonary problems were most strongly associated with opium alkaloids.

Other cough suppressants (e.g. pentoxyverine)

The therapeutic class "other cough suppressants" was most strongly associated with coma in children < 2 years. In the category 2-≤11 years, psychiatric ADRs (delirium and hallucination) and in children 12-≤18 years increased sweating, coma and increased levels of SGOT were most strongly associated.

Table 4: Three highest reporting odds ratios (RORs) by drug class

Drug class	ADR	Number of ADRs associated with drug of interest	Number of ADRs associated with other drugs	ROR* (95%CI)	Described in literature
<i>Expectorants</i>	Subarachnoid Haemorrhage	4	41	138.6 (49-393)	Yes [24]
	Chronic Renal Failure	3	217	22.9 (7.2-72)	No
	Cerebrovascular Disorder	5	307	22.8 (9.3-56)	Yes [24]
<i>Mucolytics</i>	Cystic Fibrosis	5	7	216.1 (66-706)	Confounding by indication
	Infusion site reaction	3	12	74.8 (-20-275)	Yes [25]
	Haemoptysis	10	71	39.3 (20-77)	Confounding by indication
<i>Opium alkaloids and derivatives</i>	Pulmonary Congestion	6	133	16.1 (6.6-39)	Yes [11]
	Drug Dependence	5	250	9.5 (3.9-23)	Yes [11]
	Ataxia	20	525	9.0 (5.1-16)	Yes [11]
<i>Other cough suppressants</i>	Delirium	3	206	13.9 (4.4-44)	Yes [26]
	Oedema cerebral	3	231	13.6 (4.3-43)	Yes [27]
	Arrhythmia	3	411	7.3 (2.3-23)	Yes [28]
<i>Combinations of opium alkaloids and expectorants</i>	Cerebral infarction	7	136	50.4 (23-109)	No
	Myocardial Infarction	5	115	43.2 (17-107)	Yes [24, 29]
	Cerebrovascular Disorder	11	301	32.6 (18-60)	Yes [24, 30]
<i>Combinations of opium alkaloids and antihistamines</i>	Incorrect drug administration dosage	3	21	121.6 (36-411)	Yes [31, 32]
	Bleeding time increased	3	42	56.9 (18-185)	Yes [33]
	Hepatic Necrosis	3	106	22.9 (7.2-73)	Yes [34, 35]
<i>Combinations of opium alkaloids and sympathomimetics</i>	Faeces Discoloured	3	87	25.0 (7.9-80)	No
	Heart Disorder	4	132	19.8 (7.3-54)	Yes [3, 36]
	Allergy	3	119	21.4 (6.8-68)	Yes [37, 38]
<i>Other cold combination products</i>	Angioedema	3	1324	6.3 (2.0-20)	Yes [39, 40]
	Urticaria	10	7443	5.2 (2.6-10)	Yes [39, 40]
	Face Oedema	3	2156	5.2 (1.7-17)	Yes [40]

* = adjusted for gender, continent and type of reporter

Combination products

Combination products of opium alkaloids and expectorants were strongly associated with neurological disorders in each age category within the children. In the category 2-≤11 years allergic reaction, and in children 12-≤18 heart disorders and myocardial infarction were strongly associated as well.

Combinations of opium alkaloids and antihistamines were mostly associated with liver injury related ADRs in children <2 years, such as an increased bleeding time, hyperammonaemia and

hepatic necrosis. In children aged 2-≤11 years, neurologic disorder were amongst the most strongly associated ADRs (hypertonia, mydriasis). In the older age category, mainly psychiatric and neurologic ADRs were found to have the highest RORs (paranoid reaction, apathy and abnormal thinking).

For the combinations of opium alkaloids and sympathomimetics the highest RORs were found for neurologic ADRs in children <2 years. In children 2-≤11 years, hallucination was most strongly associated to these drugs, whereas in children 12-≤18 years heart disorder was the ADR with the highest ROR.

ADRs for other cold combination products were only reported for the age categories 0-2 and 2-≤11 years. Allergic reactions such as urticaria and angioedema were ADRs with the highest ROR in both children aged 0-2 and 2-≤11 years.

For the drug groups combinations of other cough suppressants and expectorants, combinations of other cough suppressants and antihistamines, and combinations of other cough suppressants and sympathomimetics, no drug-ADR combination with at least 3 records were reported to the database.

Discussion

This is the first study that analysed pediatric ADRs reported for cough and cold medicines (CCMs) in the Vigibase WHO-UMC database. There are several important findings in our study. First, CCMs related ADRs were infrequently reported (1.2% of the non-vaccine related records) although studies have shown that in a given week, 10% of the children use a CCM [9]. The low reporting rate could be due to the fact that most CCMs are sold over the counter and therefore monitoring is lacking.

Second, most CCMs related ADRs were reported for children aged 2-≤11 and 12-18 years of age although utilization studies have shown that prevalence of use of CCMs is highest in younger children and decreases with age [9]. There thus seems to be a discrepancy between the percentage of CCMs use in children <2 and the proportion of ADRs reported for this age group. A possible explanation could be that ADRs are not recognized in very young children. Third, most CCMs related ADRs concerned mucolytics and opium alkaloids, although these are not the most commonly used CCMs in pediatrics [9].

Forth, among the ADRs with the highest RORs, serious and potentially life threatening reactions such as hepatic haemorrhage, subarachnoid haemorrhage and cerebral infarction were reported.

Our results are in line with the existing literature studying CCMs-related ADRs. Most of the ADRs that we found in this study, are also described in literature (Tables 4 & 5). For example, in our analyses, dosing errors are amongst the ADRs with the highest RORs in children aged 0-2 years. A recent study conducted by Dart et al. concluded that 85 % of the pediatric fatalities

Table 5: Three highest RORs by drug class stratified by age category

Drug Class	0-2 years			2-11 years			12-18 years		
	ADR	ROR* (95%CI)	Described in literature	ADR	ROR* (95%CI)	Described in literature	ADR	ROR* (95%CI)	Described in literature
Expectorants	Apnoea	10.0 (3.1-33)	Yes, in animals [41]	Chronic Renal Failure	35.3 (11-114)	No	Subarachnoid Haemorrhage	453.9 (125-1654)	Yes [24]
	Maculopapular Rash	5.2 (1.8-15)	Yes [42]	Pain	9.6 (3.5-26)	Yes [43]	Cerebrovascular Disorder	50.0 (15-163)	Yes [24]
	Erythematous Rash	3.4 (1.01-11)	Yes [42]	Pneumonia	9.7 (3.0-31)	Yes [43]	Asthenia	14.3 (4.4-46)	Yes [43]
Mucolytics	Condition aggravated	36.8 (24-57)	Yes [44]	Haemoptysis	82.6 (25-268)	Confounding by indication	Cystic Fibrosis	1026x10 ⁴ (0-infinity)	Confounding by indication
	Involuntary Muscle Contractions	4.6 (1.4-15)	Yes [45]	Urticaria Acute	10.5 (4.2-26)	Yes [46]	Infusion site reaction	131.2 (33-516)	Yes [25]
	Angioedema	5.9 (1.9-19)	Yes [46]	Meningitis	8.8 (3.2-24)	No (mogelijk confounding, rinosinusitis-> meningitis)	Haemoptysis	35.0 (15-82)	Confounding by indication
Opium alkaloids and derivatives	Stupor	19.9 (6.1-64)	Yes [11]	Ataxia	9.7 (4.5-21)	Yes [11]	Pulmonary Congestion	25.2 (10-63)	Yes [11]
	Somnolence	6.8 (3.3-14)	Yes [11]	Neurologic Disorder NOS	8.7 (2.8-28)	Yes [11]	Medication Error	10.5 (7.0-16)	Yes [31]
	Cyanosis	6.2 (2.3-17)	Yes [11]	Mydriasis	5.7 (2.1-15)	Yes [11]	Pulmonary Oedema	8.6 (3.5-21)	Yes [11]
Other cough suppressants	Coma	15.1 (4.6-49)	Yes [47]	Delirium	32.1 (9.8-105)	Yes [48]	Sweating Increased	8.8 (2.8-28)	No
	Convulsion	8.9 (3.5-23)	Yes [49]	Angioedema	3.5 (1.1-11)	Yes [50]	Coma	8.6 (3.8-20)	Yes [47]
				Hallucination	3.6 (1.3-9.7)	Yes [51]	SGOT Increased	5.1 (1.6-16)	No

Table 5: Continue

Drug Class	0-2 years		2-11 years		12-18 years	
	Neurologic Disorder (33-463)	Yes [11]	Cerebrovascular Disorder Hydrocephalus	Yes [24]	Cerebral Infarction	Yes [24]
Combinations of opium alkaloids and expectorants	124.5 (33-463)	Yes [11]	Cerebrovascular Disorder Hydrocephalus	Yes [24]	Cerebral Infarction	Yes [24]
			Allergic Reaction	Yes [52]	Myocardial Infarction	Yes [24]
	186.2 (44-782)	Yes [33]	Hypertonia	No	Paranoid Reaction	Yes [53]
Combinations of opium alkaloids and antihistamines	95.1 (25- 357)		Acidosis	Yes [54]	Apathy	Yes [11, 53]
	55.9 (16- 199)	Yes [34, 35]	Mydriasis	Yes [11]	Thinking Abnormal	Yes [53]
	17.5 (5.3- 57)	Yes [11]	Hallucination	Yes [55]	Heart Disorder	Yes [36]
Combinations of opium alkaloids and sympathomimetics	10.1 (3.7- 28)	Yes [11]	Therapeutic Response increased	No?	Mydriasis	Yes [11]
	3.2 (1.2- 9.1)	Confounding by indication	Medication Error	Yes [10]	Cardiac Arrest	Yes [36]
	13.7 (4.7- 40)	Yes [56]	Angioedema	Yes [39, 40]		
Other cold combination products	9.7 (2.8- 33)	Yes [39, 40]	Somnolence	Yes [57]		
			Urticaria	Yes [39, 40]		

* = adjusted for gender, continent and type of notifier
 - = number of drug-ADR combination with ≥ 3 records

associated with CCMs use, was due to an overdose of CCMs, mainly in children under the age of 2 [10]. Another example of known ADRs found in this study are the typical (of characteristic) adverse effects associated with the use of opium alkaloids, such as stupor, ataxia and mydriasis [11].

Very few ADRs were not yet described in literature namely chronic renal failure associated with expectorants use, cerebral infarction associated with opium alkaloids+expectorants use and discoloration of the faeces associated with use of opium alkaloids+antihistamines. As Chronic renal failure and cerebral infarction are serious and potentially life-threatening adverse events, more research is needed to confirm our findings eventually by means of large observational safety studies. .

When stratifying by age category, no clear pattern in type of ADR and severity could be observed. For all all age groups, various ADRs of different levels of severity were reported.

Over the counter use of CCMs in children <6 years has been banned in many countries, because of safety concerns [2-4]. Safety issues are probably not only limited to younger children and use of CCMs in this age category is substantial. This explains why the safety of these drugs in older children is currently under review by the FDA [3, 9, 12]. Lookin at our data, we also found several severe ADRs (e.g. subarachnoid haemorrhage, hydrocephalus, hepatic haemorrhage) associated with CCMs both in children aged 2-≤11 and 12-≤18 years. The fact that there is no evidence of efficacy of CCMs in children and our observed findings underline the need for further safety data of CCMs both in young and older children [13-16].

As for all observational research, our data has limitations. First of all, we used data from spontaneous reporting systems, which suffer from bias such as under and overreporting. [20-22]. Furthermore, it has to be underlined that a signal with a high ROR does not prove that the drug and ADR are causally related. The observed signals are purely hypothesis generating and further research is needed to assess these signals in an appropriate setting [23]. Also, some of the found ADRs are most likely caused by the underlying condition, rather than the investigated drugs (confounding by indication).

This is probably the case for the ADRs cystic fibrosis, haemoptysis and meningitis reported with the use of mucolytics. The mucolytic agent dornase alfa is indicated for use in patients with cystic fibrosis [17]. Mucolytics are also used to treat cough, which can cause haemoptysis. Meningitis is most probably a complication of bacterial rhinosinusitis, for which mucolytics could be given. It is described in literature that meningitis can be a severe complication in patients with bacterial rhinosinusitis [18].

Hydrocephalus associated with use of opium alkaloids+expectorants could also be confounding, since the cough for which these drugs are given for, can be the first symptom of hydrocephalus [19]. However, hydrocephalus has also been described as a complication of methadon (an opioid) use. Since opium alkaloids and methadon have the same pharmacological origin, hydrocephalus could be caused by the use of opium alkaloids+expectorants.

Due to the nature of the database, information on indication is missing, and therefore it is not possible to identify the underlying condition.

The strength of this study is the large number of pediatric ADRs available for analysis. To our knowledge, this is the first study analysing the spontaneous reports from the Vigibase database for associations between CCMs and pediatric ADRs. We found some new ADRs associated with some drug groups which have not yet been described in literature and more research to explore the potential causality is needed. .

Our results show that serious ADRs associated with CCMs occur in children of all ages. We underline the advice not to use CCMs in young children, and recommend that CCMs should also not be used in pediatrics at all.

None of the authors has a conflict of interest. The principal investigator had full access to all of the data in the study and takes responsibility for their integrity and the accuracy of the data analysis.

Funding

Funded by the European Community's 6th Framework Programme. Project number LSHB-CT-2005-005216; TEDDY: Task force in Europe for Drug Development for the Young.

Disclaimer:

Data from the WHO Collaborating Centre for International Drug Monitoring was used. The information is not homogeneous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction. The information does not represent the opinion of the WHO.

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Chapter 3.3

Use of corticosteroids in children and risk of fractures: a nested case-control study in two European countries

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Abstract

Background: Asthma medicines, including glucocorticosteroids (inhaled [ICS or oral [OCS] are amongst the most frequently used drugs in childhood. Long term use of these medicines has been associated with several side effects, including fractures

Objective: To estimate the association between use of inhaled and oral steroid and risk of fractures in children

Setting: two primary care information databases in the Europe (IPCI from the Netherlands and Pedianet from Italy)

Methods: We conducted a population-based case-control study during 1996-2008, nested in a cohort of users of asthma medicines. The risk of fractures with steroids use was calculated for current, past and cumulative use of ICS, OCS and ICS+OCS. Each case was matched to the maximum number of controls from the asthma medicines users cohort. Odds ratios (ORs) were estimated through conditional logistic regression analyses.

Results: The adjusted OR for current exposure to ICS+OCS was 0.80, CI [0.6-1.1] and OR 0.97, CI [0.9-1.1] for past use. For cumulative exposure to ICS+OCS the following ORs were observed: OR 0.93, CI [0.8-1.1] for <60 days; OR 1.00, CI [0.8-1.2] for 60-120 days; OR 0.98, CI [0.8-1.3] for 120-180 days; and OR 0.98, CI [0.8-1.2] for >180 days of use. For cumulative exposure to ICS and OCS alone we also did not find an association.

Conclusion: We found no increased risk of fractures for children exposed to ICS alone, OCS alone or combined use of ICS+OCS. Our findings, show that ICS, which are the mainstay of pediatric asthma treatment, can be used in children without fearing for fractures.

Introduction

Asthma is defined as a chronic inflammatory disorder of the airways and is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing [1]. In children, asthma is the most common chronic disease and the leading cause of childhood morbidity from chronic disease as measured by school absences, emergency department visits and hospitalizations [2]. According to the Global Initiative for Asthma (GINA), inhaled (gluco)corticosteroids (ICS) are the first choice therapy in the long-term management of asthma in children [1]. Besides ICS, oral (gluco)corticosteroids (OCS) are recommended for the treatment of very severe persistent asthma and exacerbations. As a result, ICS and OCS are widely used in asthmatic children. Prevalence rates of use ranges between 1 and 50 percent per year for ICS and between 1 and 40 percent for OCS, depending on country, age range and underlying condition [3].

Long term use of ICS in children has been associated with major safety concerns such as adrenal suppression and growth retardation [1]. The association between the use of ICS and the risk of fractures remains controversial and very few studies have been conducted in children. This potential association is difficult to investigate by means of randomized controlled trials (RCTs) as the follow-up in these trials is often too short and the sample size too small.. To our knowledge, there are 2 case-control studies (both in the UK conducted with the general practice research database) evaluating the association between ICS use and risk of fractures in children, and one cross-sectional study [4-6]. In these studies, use of ICS was not associated with an increased risk of fractures. To our knowledge, there are no studies assessing the association between corticosteroids use and risk of fracture in children using combined data other European countries, where the patterns of use may differ, for example Italy where use of steroids, especially oral, is relatively high.

To quantify the risk of fractures associated with the use of corticosteroids in children, we conducted a population based nested case-control study using two primary care databases: the Dutch Integrated Primary Care Information (IPCI) and the Italian Pedianet database, including children 0-18 years of age.

Methods

Setting

Data were obtained from general practice medical record databases in two countries and were extracted and elaborated according to a common protocol. The databases comprised the Pedianet database in Italy [7] and the Integrated Primary Care Information (IPCI) database in the Netherlands [8]. These databases include complete automated medical records of primary care physicians (general practitioner in the Netherlands and family paediatrician in Italy). As in Italy children are registered with a family paediatrician up to the age of 14, the Pedianet database contains data for children aged 0-14 years. The patient population in each database is representative of the respective Dutch and Italian population regarding age and gender. The electronic records contain anonymous and coded information on patient demographics, symptoms and diagnoses, referrals, clinical findings, laboratory assessments, drug prescriptions, and hospitalisations. Details of these databases with regard to their pediatric data are described elsewhere [9].

Source population

The source population consisted of all patients registered in the IPCI and Pedianet database and with at least 365 days of valid history except for newborns who did not require a previous medical history. This meant that the practice had been contributing data to the database for at least 12 months and that the patient had been registered with the primary care physician for at least 12 months. A one year pre-enrollment period was required (except for newborns) in order to be able to characterize the patients in terms of comorbidity and exposure. The study period started on January 1996 and ended in June 2008.

Study cohort

The study cohort included all patients who received a prescription for an asthma drug (ATC code R03) before or at the age of 18 years.

All patients with a prescription for an asthma drug were followed from cohort entry until the occurrence of a fracture, death or end of the study period, whichever came first.

Cases definition and nested case-control analysis

Case patients were all patient with a first ascertained bone fracture. We used a 2-step procedure for case ascertainment. First, we identified all the potential cases of a fracture through an automatic electronic search on coded diagnosis (ICPC codes L72-76, ICD-9 codes 800-829) in combination with a free text search in the two databases. Second, all hits of fractures were manually reviewed by two medically trained experts. Only fractures that were confirmed by an X-ray or medical specialist were included in the analysis. The index date was the date of the first

X-ray or specialist confirmed fracture after study entry. Clavicle fractures occurring during birth were excluded from the analysis.

To each case set we matched a maximum number of controls from the asthma drugs users cohort on index date, gender, year of birth and general practice. Due to this incidence density sampling approach, controls could be re-sampled at different moments in time and their contribution should be considered in person-time (moments) rather than by number of subjects.

Definition of drug exposure

To estimate the association between use of inhaled or oral corticosteroids and fracture, we created exposure categories based on timing and duration of use. We obtained data on corticosteroid use from prescription files and calculated duration of exposure on the basis of the prescribed number of units and the dosing regimen. We grouped exposure to steroids in the following categories: exposure to inhaled corticosteroids (ICS, this included prescriptions for ICS only as well as fixed combinations of ICS+short-acting beta2-agonists), exposure to oral corticosteroids (OCS), and exposure to a combination of inhaled and oral corticosteroids (ICS+OCS).

We defined drug exposure as 'current' if the prescription covered the index date or if the last intake occurred within 30 days prior to the index date and as 'past' if the child had received a prescription anytime before index date and last intake ended more than 30 days prior to the index date.

To analyse the effect of cumulative exposure to corticosteroids and risk of fractures, we used total duration of exposure. Total duration of exposure was defined as the total number of days a child was exposed to corticosteroids from start of follow-up until the index date (e.g. if a child received two prescriptions prior to the index date namely one for 30 days and one for 60 days, the total days of exposure will be 90 days). If the index date fell between the start and stop date of the prescription, only the number of exposed days prior to the index date were taken into account. The effect of cumulative exposure was investigated for ICS+OCS (summing days of exposure for both types), ICS only and OCS only.

Covariates

Age, gender, a previous history of trauma, diabetes mellitus, epilepsy, history of biliary tract disease, hyperthyroidism and hypothyroidism were considered as potential confounders. To control for confounding by indication, we also considered other classes of asthma treatment namely inhaled short-acting and long-acting beta2-agonists (ATC R03AC), inhaled anticholinergics (ATC R03BB), leukotriene receptor-antagonists (ATC R03DC), anti-allergics (ATC R03BC) and xanthines (ATC R03DA)

Current exposure to the following concomitant drug were also taken into account: drugs for gastrointestinal disorders (ATC A03), drugs for acid related disorders (ATC A02), drugs used in diabetes (ATC A10), psychotropics+antidepressants (ATC N05), cardiovascular drugs (ATC C), sex

hormones (ATC G03), anti-epileptics (ATC N03), anti-inflammatory and anti-rheumatic drugs (ATC M01).

Statistical analysis

We compared characteristics of cases and controls by using conditional logistic regression. Covariates that were associated ($P < 0.05$) with fractures were later added to the final adjusted model.

We used conditional logistic regression analysis to assess the matched unadjusted and adjusted estimates of risk for the association between exposure to steroids and the occurrence of a fracture. We estimated odds ratios (ORs) and 95% confidence intervals (95% CI) for current and total exposure to steroids compared to no exposure.

We performed stratified analyses by gender, to observe whether gender modified the risk of steroids on fractures.

We conducted all conditional logistic regression analyses in SPSS/PC, version 13 (SPSS, Chicago, Illinois). The level of significance for all statistical tests was set at P-value less than 0.05.

Results

The study cohort comprised of 75,385 children, being 18 years or younger at cohort entry, which was a prescription for an asthma drug during the study period. Within this cohort, we identified 2,548 cases of incident fractures.

The fracture site in IPCI was as follows: 395 (40.7%) had a fracture of the arm, 215 (22.2%) had a fracture of the hand/fingers/wrist, 145 (14.9%) had a fracture of the foot/toe/ankle, 85 (8.8%) had a fracture of the leg and 122 (12.6%) had a fracture at another location. The fracture site was not available for Pedianet.

The characteristics of case and control patients with regards to age, gender and covariates are displayed in Table 1. The mean age of the cases was 8.8 years (standard deviation 4.7) and 62.8% were males. Cases had a higher prevalence of trauma and current exposure to drugs for functional gastrointestinal disorders, sex hormones and anti-inflammatory and anti-rheumatic drugs increased the risk of a fracture. These covariates were adjusted for in the final model.

Exposure to other asthma drugs is displayed in Table 2. The most commonly used other asthma drugs were short-acting beta2-agonists and anticholinergics. Current and past use of other classes of asthma drugs were not associated with a higher risk of fractures.

Exposure to corticosteroids and the risk of fractures is displayed in Table 3, the adjusted OR for current exposure to ICS+OCS was 0.80, CI [0.6-1.1] and OR 0.97, CI [0.9-1.1] for past use. When considering total days of exposure to ICS+OCS, no association was observed between the cumulative days of exposure and the risk of fractures: OR 0.93, CI [0.8-1.1] for <60 days; OR 1.00, CI [0.8-1.2] for 60-120 days; OR 0.98, CI [0.8-1.3] for 120-180 days; and OR 0.98, CI [0.8-1.2] for

Table 1: Risk of fractures according to patient characteristics. * Values are numbers (%) unless stated otherwise

Characteristics	Cases (n=2,548)	Controls (n=32,778)	Matched OR# (95% CI)	p-value
Age (mean,SD)	8.8 (4.7)	6.9 (3.6)		
Male	1,600 (62.8)	21,270 (64.9)		
Comorbidity				
Trauma	168 (6.6)	203 (0.6)	11.19 (8.85-14.15)	<0.0001
Current use of other drugs (use in month before index date)				
Drugs for functional gastrointestinal disorders (ATC A03)				
Sex hormones (ATC G03)	6 (0.2)	117 (0.4)	1.12 (1.03-1.23)	0.01
Anti-inflammatory and anti-rheumatic drugs (ATC M01)	47 (1.8)	111 (0.3)	1.43 (1.06-1.93)	0.02
	24 (0.9)	269 (0.8)	1.09 (1.01-1.18)	0.03

* Only variables with cell count ≥ 5 and p-value <0.05 are shown

= matched on gender, age, index date and general practice

Table 2: Risk of fractures according to use of respiratory drugs. Values are numbers (%) unless stated otherwise

	Cases (n=2,548)	Controls (n=32,778)	Matched OR# (95% CI)	p-value
Inhaled short-acting beta-agonists				
Never used	1,151 (45.2)	17,940 (54.7)	1 (Reference)	-
Current use	102 (4.0)	446 (1.4)	1.05 (0.80-1.36)	0.74
Past use	1,295 (50.8)	14,392 (43.9)	1.05 (0.95-1.16)	0.31
Inhaled long-acting beta-agonists				
Never used	2,478 (97.3)	32,457 (99.0)	1 (Reference)	-
Current use	6 (0.2)	23 (0.1)	0.68 (0.22-2.06)	0.49
Past use	64 (2.5)	298 (0.9)	1.14 (0.83-1.56)	0.42
Anticholinergics				
Never used	2,437 (95.6)	31,834 (97.1)	1 (Reference)	-
Current use	8 (0.3)	22 (0.1)	1.39 (0.51-3.81)	0.52
Past use	103 (4.0)	922 (2.8)	1.00 (0.77-1.31)	0.99
Anti-allergics				
Never used	2,474 (97.1)	32,066 (97.8)	1 (Reference)	-
Current use	4 (0.2)	24 (0.1)	1.03 (0.29-3.62)	0.96
Past use	70 (2.7)	688 (2.1)	0.85 (0.64-1.14)	0.28
Leukotriene-receptor antagonists				
Never used	2,471 (97.0)	31,652 (96.6)	1 (Reference)	-
Current use	19 (0.7)	206 (0.6)	1.48 (0.89-2.47)	0.13
Past use	58 (2.3)	920 (2.8)	1.15 (0.87-1.53)	0.34
Xanthines				
Never used	2,534 (99.5)	32,392 (98.8)	1 (Reference)	-
Current use	0	1 (0.0)	NA	-
Past use	14 (0.5)	385 (1.2)	1.03 (0.57-1.86)	0.93

NA = not applicable, as no exposed cases

= matched on gender, age, index date and general practice

Table 3: Exposure to steroids (inhaled or oral) and the risk of fracture

	Cases (n=2,548)	Controls (n=32,778)	Matched OR#, Crude (95% CI)	Matched OR#, adjusted* (95% CI)	p-value
Never used steroids (inhaled+oral)	526 (20.6)	4,022 (12.3)	1 (Reference)	1 (Reference)	-
Use of inhaled+oral steroids					
Current	92 (3.6)	573 (1.7)	0.81 (0.62-1.06)	0.80 (0.61-1.05)	0.10
Past	1,930 (75.7)	28,183 (86)	0.97 (0.86-1.10)	0.97 (0.86-1.10)	0.62
Total days of use					
<i>Inhaled+oral steroids</i>					
<60 days	1,381 (54.2)	24,378 (74.4)	0.92 (0.80-1.06)	0.93 (0.80-1.07)	0.28
60-120 days	245 (9.6)	2,180 (6.7)	1.00 (0.84-1.21)	1.00 (0.83-1.20)	0.98
120-180 days	99 (3.9)	704 (2.1)	1.01 (0.78-1.31)	0.98 (0.76-1.27)	0.89
>180 days	297 (11.7)	1,494 (4.6)	0.99 (0.83-1.18)	0.98 (0.82-1.17)	0.80
<i>Inhaled steroids</i>					
<60 days	1,322 (51.9)	23,322 (71.2)	0.93 (0.80-1.07)	0.93 (0.81-1.08)	0.33
60-120 days	231 (9.1)	1,863 (5.7)	0.99 (0.82-1.20)	0.99 (0.82-1.19)	0.88
120-180 days	92 (3.6)	664 (2.0)	0.96 (0.74-1.25)	0.93 (0.71-1.22)	0.61
>180 days	295 (11.6)	1,429 (4.4)	1.00 (0.83-1.19)	0.98 (0.82-1.18)	0.85
<i>Oral steroids</i>					
<7 days	362 (14.2)	6,897 (21.0)	0.96 (0.81-1.13)	0.95 (0.80-1.13)	0.56
7-14 days	120 (4.7)	2,089 (6.4)	1.01 (0.80-1.27)	0.96 (0.76-1.21)	0.73
14-30 days	52 (2.0)	1,204 (3.7)	0.92 (0.67-1.28)	0.86 (0.62-1.20)	0.38
>30 days	26 (1.0)	464 (1.4)	1.18 (0.73-1.89)	1.17 (0.73-1.89)	0.52

= matched on gender, age, index date and general practice

* = adjusted for use of drug for functional gastrointestinal disorders, sex hormones, anti-inflammatory and anti-rheumatic drugs and trauma

>180 days of use. Although almost children had long term exposure to ICS (50% of the children had more than 2 months of ICS exposure, and 11% more than 6 months), no association was observed for cumulative duration of ICS exposure. Cumulative exposure of OCS alone was also not associated (although few children had long term exposure to OCS).

In the stratified analysis by gender, the results were similar to the overall results (Table 4). No association was observed for exposure to steroids (inhaled or oral) and risk of fractures in males and females.

Discussion

In this population based nested case-control study in an Italian and Dutch cohort of pediatric asthma drug users, we found no increased risk of fractures for children exposed to ICS alone, OCS alone or combined use of ICS+OCS.

Exposure to OCS is a known risk factor for developing fractures, both in children and adults [10-12]. However, only few studies have investigated the association between ICS use and the risk of fractures in children. To our knowledge, there are only 3 observational studies that have

Table 4: Exposure to steroids (inhaled or oral) and the risk of fracture stratified by gender

	Males				Females			
	Cases (n=1,600)	Controls (n=21,270)	Matched OR#, adjusted* (95% CI)	p-value	Cases (n=948)	Controls (n=11,508)	Matched OR#, adjusted* (95% CI)	p-value
Never used steroids (inhaled+oral)	319 (19.9)	2,540 (11.9)	1 (Reference)	-	207 (21.8)	1,482 (12.9)	1 (Reference)	-
Use of inhaled+oral steroids								
Current	63 (3.9)	416 (2.0)	0.83 (0.59-1.15)	0.25	29 (3.1)	157 (1.4)	0.73 (0.44-1.20)	0.22
Past	1,218 (76.1)	18,314 (86.1)	0.96 (0.82-1.13)	0.62	712 (75.1)	9,869 (85.8)	0.98 (0.80-1.21)	0.88
Total days of use								
<i>Inhaled+oral steroids</i>								
<60 days	863 (53.9)	15,679 (73.7)	0.91 (0.76-1.09)	0.32	518 (54.6)	8,699 (75.6)	0.95 (0.75-1.19)	0.63
60-120 days	145 (9.1)	1,495 (7.0)	0.90 (0.71-1.14)	0.39	100 (10.5)	685 (6.0)	1.19 (0.75-1.19)	0.26
120-180 days	70 (4.4)	519 (2.4)	1.03 (0.75-1.40)	0.88	29 (3.1)	185 (1.6)	0.87 (0.54-1.41)	0.57
>180 days	203 (12.7)	1,037 (4.9)	1.02 (0.81-1.27)	0.88	94 (9.9)	457 (4.0)	0.89 (0.66-1.22)	0.47
<i>Inhaled steroids</i>								
<60 days	830 (51.9)	15,030 (70.7)	0.93 (0.78-1.11)	0.40	492 (51.9)	8,292 (72.1)	0.94 (0.75-1.20)	0.64
60-120 days	140 (8.8)	1,279 (6.0)	0.92 (0.73-1.17)	0.51	91 (9.6)	584 (5.1)	1.11 (0.81-1.51)	0.52
120-180 days	63 (3.9)	488 (2.3)	0.91 (0.68-1.30)	0.71	29 (3.1)	176 (1.5)	0.89 (0.55-1.45)	0.65
>180 days	201 (12.6)	991 (4.7)	1.02 (0.82-1.28)	0.84	94 (9.9)	438 (3.8)	0.90 (0.66-1.23)	0.50
<i>Oral steroids</i>								
<7 days	233 (14.6)	4,644 (21.8)	0.92 (0.74-1.13)	0.41	129 (13.6)	2,253 (19.6)	1.02 (0.77-1.35)	0.90
7-14 days	79 (4.9)	1,390 (6.5)	0.93 (0.69-1.24)	0.61	41 (4.3)	699 (6.1)	1.03 (0.69-1.52)	0.89
14-30 days	36 (2.3)	835 (3.9)	0.83 (0.56-1.24)	0.36	16 (1.6)	369 (3.2)	0.92 (0.51-1.64)	0.77
>30 days	19 (1.2)	326 (1.5)	1.14 (0.65-2.00)	0.66	7 (0.7)	138 (1.2)	1.25 (0.50-3.12)	0.63

= matched on gender, age, index date and general practice

* = adjusted for use of drug for functional gastrointestinal disorders, sex hormones, anti-inflammatory and anti-rheumatic drugs and trauma

analysed this association. Two of these studies used the General Practice Research Database (GPRD) from the United Kingdom to perform nested case-control studies [4, 5]. In the first study, Schlienger et.al found no increased risk of fractures in children currently exposed to ICS and the risk did not increase for higher number of ICS prescriptions [4]. In the second case-control

study in the same database, Van Staa et al. found a dose-response relationship namely that, children exposed to higher doses of ICS had an increased risk of fractures [5]. This association disappeared however after adjustment for indicators of asthma severity. In a cross-sectional study in Australia, Ma et al. studied risk factors for prevalent fractures in prepubertal children. In this study, exposure to ICS in the year before occurrence of a fracture was not associated with an increased risk of fractures. Van Staa et al. also studied the association between OCS use and fractures in the GPRD in the UK and found that the risk was increased in children receiving more than 3 prescriptions [10]. In contrast to the findings from Van Staa, we did not find an increased risk associated with exposure to OCS. However, this can probably be explained by the fact that, in our study; the majority of the children used OCS for less than 30 days. Indeed, only 1% of the children (both cases and controls) used OCS longer than one month, so our exposure to long term OCS may be too low to find an association. It does show however, that under the general circumstances of use in these two countries, which have quite different user patterns, the attributable risk of fractures due to use of ICS and/or OCS is very low.

Similar to what has been published in literature; we also found that occurrence of fractures was higher in boys than in girls [13-15]. Our results are also in line with other studies regarding the distribution of fracture sites, showing that fractures of the arm and carpal region are the most common [14, 15].

Strengths and limitations of our study

This study has a number of limitations. Due to the nature of the databases, we did not have information on all potential confounders such as the nutritional status of the children, body mass index, bone mineral density, physical activity and smoking status. The inability to completely adjust for confounding normally results in an overestimation of the risk estimate. However, as we did not observe an increased risk of fractures in the matched nor in the fully adjusted analysis, we believe that the issue of remaining confounding is probably limited. Selection bias was unlikely, as all data was obtained from prospectively collected medical records that are maintained for patient care purposes. Information bias by misclassification of the outcome is also unlikely, because all fracture cases were retrieved from medical records and reviewed by two medical experts who were blinded to the exposure. Misclassification of exposure may have occurred, because we used outpatient prescription data and had no information on actual filling of the medications nor on drug intake. Based on the way the data were collected, we believe that this misclassification will probably be non-differential between cases and controls and therefore the actual risk may have been underestimated. Since we used primary care data we may have missed some specialist prescriptions in the Netherlands. However, this will minimally influence our results since asthma is a condition often dealt with in primary care, and asthma drugs originally prescribed by a specialist are often continued or prescribed by general practitioners [16].

A major strength of our study is the fact that we capture a large number of children in two different databases across Europe, resulting in a high generalisability of the study population. Furthermore, we were able to study the effect of total duration of exposure to corticosteroids and the risk of fractures, which has never been studied before.

Our findings, as well as other studies, show that ICS, which are the mainstay of pediatric asthma treatment, can be used in children without fearing for fractures. Also OCS do not seem to increase the risk of fractures in children under the given circumstances of use, we can however not exclude that chronic use will increase the risk since we had few persons exposed to long term use of OCS.

Acknowledgements: We thank all of the physicians contributing data to the PEDIANET and IPCI databases.

None of the authors has a conflict of interest. The principal investigator had full access to all of the data in the study and takes responsibility for their integrity and the accuracy of the data analysis.

Funding: Funded by the European Community's 6th Framework Programme. Project number LSHB-CT-2005-005216: TEDDY: Task force in Europe for Drug Development for the Young.

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Chapter 3.4

Steroid induced pancreatitis in children: results from a population-based case- control study

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Abstract

Background: Pancreatitis is a relatively rare condition in children and has considerable morbidity and mortality. Although drug-induced pancreatitis is rare, a variety of drugs have been associated to pancreatitis (in children and adults), including steroids. So far, no studies have been performed to assess the association between exposure to steroids and pancreatitis in children.

Objective: To estimate the association between use of inhaled and oral steroid and risk of pancreatitis in children aged 0-18 years

Setting: the Dutch PHARMO Record Linkage System

Methods: We conducted a population-based case-control study during 1998-2008. The risk of pancreatitis with steroids use was calculated for current, past and cumulative exposure to inhaled glucocorticosteroids (ICS) and oral glucocorticosteroids (OCS). Up to 20 controls per case were selected, matched on year of birth, gender, and calendar time. Odds ratios (ORs) were estimated through conditional logistic regression analyses.

Results: 60 cases of pancreatitis (54 acute and 6 chronic) were retrieved from the PHARMO database. Current use of OCS was associated with a higher risk of pancreatitis (OR 21.40, CI [7.1-64.6]). We also found an increased risk for cumulative exposure of >7 days to OCS. Exposure to inhaled steroids was not associated with pancreatitis. In a sensitivity analysis, performed in patients with acute pancreatitis, exposure to OCS and acute pancreatitis remained highly increased: OR 24.0, CI [7.8-73].

Conclusion: We found that the risk of pancreatitis was approximately 20-fold higher in children who were using oral steroids. The use of inhaled steroids was not associated with an increased risk, neither with increased duration of use.

Introduction

Pancreatitis is a relatively rare condition in children and has considerable morbidity and mortality [1]. Pancreatitis mainly occurs in adult life and the mean age of a first pancreatitis attack has been shown to be in the 6th decade of life [2]. The overall incidence of acute pancreatitis varies between 4 and 45/100,000, depending on the country being studied. In adults, the most common causes of acute pancreatitis are gallstones and alcohol abuse [2, 3]. In children, acute pancreatitis has different aetiologies. Reported causes in children include trauma, infection, systemic diseases, toxins, structural anomalies of the pancreaticobiliary tract and idiopathic [4-6]. Drug-induced pancreatitis is considered to be a rare cause of pancreatitis in both children and adults. The available data suggest that between 0.1 and 2% of all acute pancreatitis cases may be drug-induced [7-9]. A variety of drugs have been associated to pancreatitis through spontaneous reports in adults, including glucocorticosteroids [7, 10, 11]. These drugs have also been associated with pancreatitis in children [5, 6, 12]. The pathogenesis of steroid-induced pancreatitis remains to be elucidated. Obstruction of the outflow of pancreatic secretions has been hypothesized as a possible underlying mechanism [13-15]. In contrast, animal studies and a study in humans have reported on the protective effect of steroids on pancreatitis. Experimental studies in rats have shown a protective effect of dexamethason and methylprednisolone on the development and severity of pancreatitis [16, 17]. The real association between exposure to steroids and risk of pancreatitis remains to be elucidated and more studies are needed.

All of the existing data on the association between glucocorticosteroid use and pancreatitis in children has been derived from case reports and case series. Although case reports are a very efficient tool for signal generation, more analytical and epidemiological approaches are necessary to actually quantify the risk. To provide the relative risk of pancreatitis in children using oral or inhaled corticosteroids, we conducted a population-based case-control study. To our knowledge, this is the first study in children analyzing the association between use of glucocorticosteroids and the risk of pancreatitis.

Methods

Source population

Data for this case control study were obtained from the Dutch PHARMO Record Linkage System (RLS). PHARMO RLS (<http://www.pharmo.nl>) includes the pharmacy dispensing histories of more than three million community-dwelling residents in well defined areas in the Netherlands, and these pharmacy records are linked to nationwide hospital discharge records. Pharmacy data include information about the drug dispensed, the date of dispensing, the amount dispensed, the prescribed dosage regimen and the estimated duration of use. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification system [11]. The Hospital Discharge

Register comprises hospitalizations in the Netherlands, including detailed information on the primary and secondary discharge diagnoses; diagnostic, surgical and treatment procedures and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases, 9th edition (ICD-9-CM). Validation studies have shown that the PHARMO RLS has a high level of data completeness and validity [18, 19].

Case and control ascertainment.

Cases were defined as patients 0- ≤18 years old with a first discharge diagnosis of pancreatitis (ICD-9 code 577x) in the period between 1 January 1998 (start of follow-up) until 31 December 2008 (end of follow-up). Pancreatitis was classified as acute (ICD-9 577.0) or chronic (ICD-9 577.1). The index date was the date of hospital admission. For each case, up to 20 controls without a history of pancreatitis during the study period were matched on year of birth, gender, and calendar time (the index date of the corresponding case). Both cases and controls were eligible for inclusion if they had a minimum period of 365 days of history in the PHARMO RLS prior to the index date.

Exposure assessment

Although various drugs have been associated with pancreatitis the main exposure of interest in this study were inhaled (ATC R03BA) and oral glucocorticosteroids (ATC H02AB). Data on exposure were obtained from the dispensing records and categorized by timing and duration of use. We defined drug use as 'current' if the prescribed duration of the drug covered the index date or if the end of it was less than 30 days prior to the index date. Drug exposure was classified as 'past' if the child had received a prescription anytime before the index date but the end of it was more than 30 days prior to the index date.

To analyse the effect of the cumulative use of glucocorticosteroids on the risk of pancreatitis, we calculated the total cumulative duration of exposure from start of follow-up until the index date (e.g. if a child received 2 prescriptions prior to the index date namely one for 4 days and one for 6 days, the total days of use was 10). The total days of use of oral steroids was categorized into the following classes: <7 days, ≥ 7-30 days and ≥ 30 days of use. For inhaled steroids we created two categories for total days of use, namely <1 year and ≥ 1 year. If the indexdate fell between the start and stopdate of the prescription, only the number of days up to the index date was taken into account.

Covariates

As covariates, we considered co-morbidities or use of drugs that have associated with pancreatitis in literature [7, 20]. The following factors were considered: gender and year of birth (matching variables), a previous hospitalization for HIV-infection, gallbladder disorders, cholelithiasis, trauma, cystic fibrosis, lipid disorders, disorders of calcium metabolism, inflammatory bowel disease, malignancies, elevated levels of lipase/amylase and viral diseases.

Current use of the following concomitant drugs were also taken into account: acetaminophen, azathioprine, cimetidine, enalapril, erythromycin, estrogens, furosemide, hydrochlorothiazide, metronidazol, opiates, simvastatin, cotrimoxazol, tetracycline, valproic acid, carbamazepine, doxycycline, famotidine, mesalazine, rifampin, NSAID's, lisinopril, ramipril, losarten, methyl dopa, chlorothiazide, amiodarone, pravastatin, fluvastatin, dapson, nitrofurantoin, clarithromycin, isoniazid, nelfinavir, lamivudine, didanosene, interferon, ribavirin, pentamidine, sodium stibogluconate, meglumine antimonite, omeprazole, mercaptopurine, olsalazine, sulphasalazine, clozapine, clomifene, tamoxifen, thiamazole, carbimazole, ifosfamide, cytarabine, asparaginase, isotretinoin, propofol, cyclopenthiiazide, phenformin, cisplatin, octreotide, alendronate, captopril, ciprofibrate and maprotiline.

Statistical analysis

We used conditional logistic regression analysis to assess the matched unadjusted estimates of risk for the association between exposure to inhaled and oral steroids and the occurrence of a pancreatitis. Adjusted analysis was performed only if more than 5 cases were exposed. For model construction, we first included all covariates that were univariately associated with the outcome ($p < 0.10$). Each risk factor that changed the OR of exposure to glucocorticosteroids by more than 5% was included in the final adjusted model. We estimated odds ratios (ORs) and 95% confidence intervals (95% CI) for current and total use of steroids compared to no use. Sensitivity analyses were conducted in which we excluded patients with chronic pancreatitis. All statistical analysis were conducted using SPSS/PC, version 13 (SPSS, Chicago, Illinois). The level of significance for all statistical tests was set at p-value less than 0.05.

Results

In the PHARMO RLS source population of children 0-18 years of age we identified 68 cases with pancreatitic disorders. Eight cases were excluded because they concerned patients with pancreatic cysts. The case-control study population therefore consisted of 60 patients with pancreatitis (acute or chronic), ≤ 18 years with a first hospitalization for pancreatitis and 6,487 age, sex and time matched controls.

The age distribution of the pancreatitis cases is presented in Figure 1. The number of cases increased with age.

Details on prior hospitalizations and concomitant use of drugs in the cases is presented in Table 1, 54 cases (90%) were hospitalized for acute pancreatitis and 6 for chronic pancreatitis. The median age of the cases was 15.9 (range between 1.2 and 18.9) and the majority of the cases was between 12 and 18 years of age (71.7%), gender was equally distributed.

Only few patients had been hospitalized prior to their pancreatitis, the most frequent reasons were: abdominal pain (n=5), colitis/gastro-enteritis (n=4) and inflammatory bowel disease

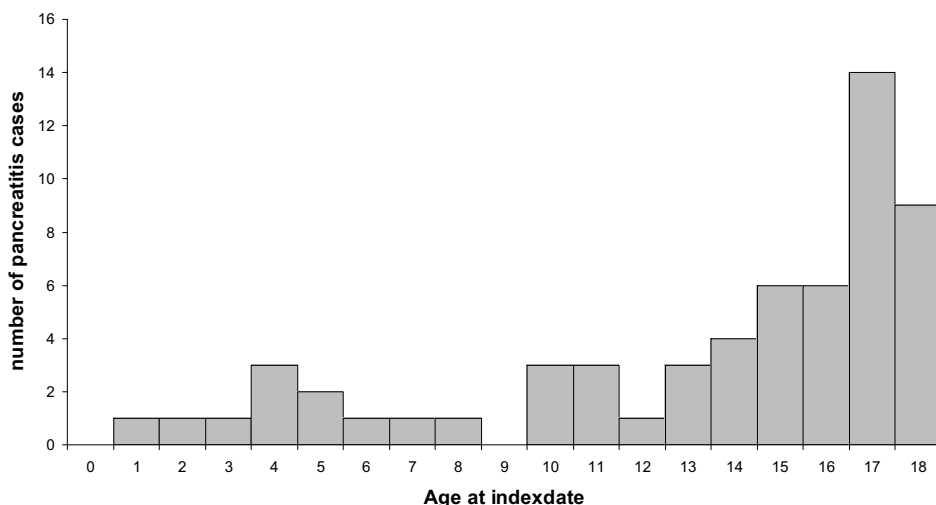


Figure 1: Distribution of pancreatitis cases by age

(n=3). The average duration between hospitalization for abdominal pain and hospitalization for pancreatitis was 6.3 months (range between 4 and 11 months)

The most frequently used drugs in the month before the index date were propulsives (e.g. metoclopramide, cisapride) (n=4), oral contraceptives (n=4), anti-acne preparations (n=3) and azathioprine (n=3), 29 cases (49%) had not any drug dispensed that covered the month before the index date.

A hospitalization for inflammatory bowel disease (OR 41.9, 95% CI [9-188]), gallstones (OR 120.6, 95% CI [11-1368]) and cystic fibrosis (OR 29.5, 95% CI [3-253]) were all associated with pancreatitis although numbers were small (table 2). Also exposure to NSAIDs (OR 4.5, 95% CI [2-13]), azathioprine (OR 37.8, 95% CI [9-154]), mesalazine (OR 69.4, 95% CI [10-466]), metronidazol (OR 69.4, 95% CI [10-466]), opiates (OR 26.9, 95% CI [3-287]) and omeprazole (OR 11.3, 95% CI [1.4-88]) in the month prior to the index date was associated with pancreatitis (Table 2). Four cases were currently exposed to oral steroids and one to inhaled steroids (table 3). Due to the low number of exposed cases, adjustment for concomitant drug use or a history of prior hospitalizations was not possible.

Despite the low power, current use of oral steroids was associated with a higher risk of pancreatitis (OR 21.40, CI[7.1-64.6]). For the total days of oral steroids use we found the following risk estimates: OR 2.37, CI [0.32-17.7] for <7 days; OR 5.90, CI [1.8-19.7] for ≥7-<30 days; and OR 5.34, CI [1.9-15.3] for ≥ 30 days of use (Table 3). Exposure to inhaled steroids was not associated with pancreatitis in any of the exposure categories.

Since steroids may be used to treat pancreatitis, we restricted the analysis to acute pancreatitis, the association between the use of oral steroids and acute pancreatitis remained highly increased: OR 24.0, CI [7.8-73].

Table 1: Characteristics of pancreatitis cases in children (0-18 years)

Pancreatitis cases (n=60)			
Gender: Male	29 (48.3%)		
Age (mean,range)	14.0 (1-18)		
0 - < 2 years	1 (1.7%)		
2 - ≤ 11 years	16 (26.7%)		
12 - ≤ 18 years	43 (71.7%)		
Type of pancreatitis			
Acute	54 (90%)		
Chronic	6 (10%)		
Prior hospitalizations			
Abdominal pain	5	Rheumatoid arthritis	1
Colitis/Gastro-enteritis/proctocolitis	4	Mononucleosis infectiosa	1
Inflammatory bowel disease	3	Obesity	1
Gallstones/cholecystitis	2	Oesophagitis	1
Juvenile Diabetes	2	Paralytic ileus	1
Cystic Fibrosis	1	Pneumonia	1
Hernia inguinalis	1	Viral infection	1
Intestinal disaccharidase deficiency	1		
Concomitants drugs (use in month before index date)			
No use of any drug	29	chloral hydrate	1
Oral contraceptives	4	Codeine	1
prednisolon	4	ciprofloxacin	1
propulsives	4	fenoterol+ipratropium	1
anti-acne preparations	3	ferrous fumarate	1
azathioprine	3	fluticason	1
diclofenac	3	folic acid	1
insulins	2	granisetron	1
mesalazine	2	ibuprofen	1
metronidazole	2	lamotrigine	1
nasal corticosteroids	2	laurilsulfate	1
oxcarbazepine	2	methotrexate	1
proton pump inhibitor	2	methylphenidate	1
short-acting beta-agonists	2	multi-enzymes	1
sodium fluoride	2	Omeprazole	1
acetazolamide	1	Paracetamol	1
anti-androgens+estrogens	1	Somatropin	1
azithromycin	1	Temazepam	1
bisacodyl	1	Tobramycin	1
budesonide, inhaled	1	Tramadol	1
calcium	1	vitamin D	1
ceftazidime	1	vitamin K	1

Table 2: Covariates and their independent risk of pancreatitis in univariate analyses#

Characteristics	Cases n=60 (%)	Controls n=6,487 (%)	Matched OR (95% CI)*	P-value
History of hospitalizations				
Inflammatory bowel disease	3 (5.0)	6 (0.1)	42 (9-188)	<0.001
Gallstones	2 (3.3)	3 (0.04)	121 (11-1368)	<0.001
Cystic fibrosis	1 (1.7)	5 (0.1)	29 (3-253)	0.002
Trauma	1 (1.7)	19 (0.3)	6.3 (0.8-49)	0.08
Viral diseases	1 (1.7)	61 (0.9)	2.2 (0.3-17)	0.44
Concomitant drugs (use in month before index date)				
NSAIDs	4 (6.7)	103 (1.6)	4.5 (2-13)	0.007
Azathioprine	3 (5.0)	8 (0.1)	38 (9-154)	<0.001
Mesalazine	2 (3.3)	3 (0.04)	69 (10-466)	<0.001
Metronidazol	2 (3.3)	3 (0.04)	69 (10-466)	<0.001
Opiates	1 (1.7)	3 (0.04)	26 (3-287)	<0.001
Omeprazole	1 (1.7)	12 (0.2)	11 (1.4-88)	0.021
Paracetamol	1 (1.7)	61 (0.9)	2.2 (0.3-17)	0.44

= only covariates with exposed cases are shown

* = matched on age, gender and index date

Discussion

In this population based case-control study, we found that the risk of pancreatitis was approximately 20-fold higher in children who were using oral steroids. The use of inhaled steroids was not associated with an increased risk, neither with increased duration of use.

The association between use of oral steroids and pancreatitis has been described in some case series and case reports in children [6, 21, 22]. The first case reports on steroid-induced pancreatitis in children were published in 1957 by Barr et al and Marczyńska-Robowska [21, 22], followed by several others in children [6, 23-25]. Although case series and reports provide important information to signal potential adverse drug reactions, they do not provide proof of an association. In some instances, findings from case reports may overestimate the risk of medication-induced pancreatitis. This occurred in adults for postmenopausal hormone replacement therapy, COX-2 inhibitors and anti-lipemics where data from population-based epidemiological studies could not confirm the associations seen in case series [26-28]. However, for oral steroids we consistently find an association in case series and in this population based case control study.

The risk factors we observed in children are in line with those published for pancreatitis in adults. A history of hospitalization for inflammatory bowel disease, gallstones, cystic fibrosis and trauma were all associated with a higher risk of pancreatitis [4, 29, 30]. We also observed a higher risk of pancreatitis for azathioprine, mesalazine, metronidazol, opiates, omeprazole and NSAIDs use, but the prevalence of use was very low, which is usually so in children. All

Table 3: Exposure to steroids (inhaled or oral) and the risk of pancreatitis

	Cases (n=60)	Controls (n=6,847)	Matched OR# (95% CI)	p-value
Never used steroids (inhaled+oral)	46 (76.7)	5,470 (84.3)	1 (Reference)	-
Oral steroids				
Current use	4 (6.7)	24 (0.4)	21.4 (7.1-64.6)	<0.001
Past use	4 (6.7)	226 (3.5)	2.56 (0.9-7.3)	0.079
<i>Total cumulative duration of oral steroids</i>				
<7 days	1 (1.7)	65 (1.0)	2.4 (0.3-17)	0.398
≥7 -<30 days	3 (5.0)	80 (1.2)	5.9 (1.8-19.7)	0.004
≥30 days	4 (6.7)	100 (1.5)	5.3 (1.9-15.3)	0.002
Use of inhaled steroids				
Current	2 (3.3)	201 (3.1)	1.3 (0.6-3.2)	0.54
Past	7 (11.7)	707 (10.9)	1.9 (0.6-6.4)	0.30
<i>Total use</i>				
<1 year	6 (10.0)	641 (9.9)	4.7 (0.6-35.6)	0.13
≥1 year	3 (5.0)	253 (3.9)	1.3 (0.6-2.9)	0.46
Subanalysis excluding patients with chronic pancreatitis				
	Cases (n=54)	Controls (n=5,957)		
Use of oral steroids				
Current	4 (7.4)	22 (0.4)	24.0 (7.8-73.3)	<0.001
Past	3 (5.6)	207 (3.5)	2.22 (0.7-7.4)	0.193
<i>Total use</i>				
<7 days	1 (1.9)	60 (1.0)	2.71 (0.36-20.27)	0.331
≥7 -<30 days	3 (5.6)	74 (1.2)	6.65 (1.97-22.42)	0.002
≥30 days	3 (5.6)	90 (1.5)	4.87 (1.46-16.25)	0.01

= matched on gender, age and index date,

of these drugs have been associated with an increased risk of pancreatitis in adults, although protopathic bias may also occur with the proton pump inhibitors [7, 10, 31].

We did not find an increased risk of pancreatitis for use of inhaled steroids, although power was limited and the upper limit of the confidence interval was 6. If oral steroids are associated with pancreatitis inhaled steroids may do the same since they are also systemically absorbed, especially when inhaled erroneously. We could demonstrate in this study that at least, there is no strong association [32]. In the future larger scale studies are necessary to further assess the association between pancreatitis and inhaled steroids in children, as it is a frequently used drug by children.

The pathogenesis of steroid-induced pancreatitis remains to be elucidated. Obstruction of the outflow of pancreatic secretions has been hypothesized as a possible underlying mechanism [13-15]. Animal studies and postmortem studies in patients treated with steroids demonstrated an increased incidence of focal pancreatic lesions [15, 33-35]. In contrast, animal studies and a

study in humans have also reported on a protective effect of steroids on pancreatitis [16, 17]. A study in humans has demonstrated that the administration of steroids prior to endoscopic retrograde cholangiopancreatography (ERCP) resulted in a decrease in the incidence of post-ERCP pancreatitis [36]. It is clear that more studies have to be performed to understand the mechanism of steroid-induced pancreatitis.

As for all observational studies, our study has limitations, the major one is lack of power due to the rarity of the event in children. This underlines the need for combining large linked health-care databases to study serious but rare drug-safety issues in children adequately. In addition, we may suffer from residual confounding, Body mass index and alcohol intake are important risk factors of pancreatitis in adults. Alcohol consumption, especially in young children may be low, and therefore it may not be a confounding factor in this study. Confounding by indication may also occur: oral steroids might have been initiated to treat pancreatitis, however, the association was most pronounced in persons using steroids for more than 7 days, therefore, this cannot explain the findings. In addition the association remained upon exclusion of 6 cases with chronic hepatitis. Misclassification of the outcome is a potential concern. All potential cases of pancreatitis were selected from The Hospital Discharge Register via an automated search on ICD-9 codes. However, previous studies have shown the validity of The Hospital Admission Register in identifying patients with diseases of interest [37]. Selection bias is unlikely as we conducted a population based case-control study using a large database containing information on more than 3 million inhabitants from the Netherlands. Our study population is representative to the Dutch population so, our data can be extrapolated to the entire pediatric population of the Netherlands. Exposure misclassification is unlikely as the PHARMO database contains pharmacy dispensing data, on prescriptions from both primary and secondary care, ensuring a complete overview of prescription drugs.

The first case reports of steroid-induced pancreatitis in children were published in 1957 [21, 22]. Since then, several case series on this topic have been published, but well-designed observational studies were lacking. We have addressed this gap by performing a population-based case-control study, analyzing the association between steroid use in children and risk of pancreatitis. Our results show that current use and ≥ 7 days of use of oral steroids is associated with an increased risk of pancreatitis in children.

None of the authors has a conflict of interest. The principal investigator had full access to all of the data in the study and takes responsibility for their integrity and the accuracy of the data analysis.

Funding: Funded by the European Community's 6th Framework Programme. Project number LSHB-CT-2005-005216: TEDDY: Task force in Europe for Drug Development for the Young.

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Chapter 4

General Discussion

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In this thesis we present several large scale observational studies on the use and safety of asthma and cough and cold medicines in children. These studies were conducted in the context of the TEDDY Network of Excellence. TEDDY is a 6th Framework Programme funded Network of Excellence aiming to promote the availability of safe and effective medicines for children in Europe by integrating existing expertise and good practices, as well as stimulating pediatric drug development. (www.teddyyoung.org)

The research described in this thesis focuses on the use and the safety of asthma medicines and cough and cold medicines. These medicines belong to the group of respiratory medicines, which have been demonstrated to be amongst the mostly used medicines in children [1].

Asthma is the most common chronic disease of childhood with an estimated prevalence of 10%, and as a result, asthma medicines are used widely in the pediatric population. Despite the widespread use of these medicines by children, very little is known about their long term safety. For this reason, regulatory authorities have implemented guidelines to stimulate research on safe and effective drugs in children, such as the need to get a paediatric investigation plan (PID) for each new regulatory submission and the promotion of the Paediatric Use Marketing Authorisation for off-patent drugs. In addition, the Pediatric Working Party (PEG) (under auspices of the EMA) has generated, by treatment class, a list of drugs with specific needs, in terms of pediatric efficacy and safety. Among these lists, a list on the *“assessment of paediatric needs for asthma and other obstructive chronic lung diseases”* has been compiled stating the need to have information on pharmacokinetics, efficacy and safety data of respiratory drugs [2]. As proof of concept that these needs could be addressed by using observational studies rather than trials we have conducted large observational utilization and safety studies by combining several primary healthcare databases in Europe.

Other drugs; also frequently used in children; and for which safety concerns have been raised are the cough and cold medicines (CCMs) used for the symptomatic treatment of respiratory tract infections. In 2007, the FDA released a recommendation that cough and cold medicines should not be used in children below two years of age because of serious side effects such as cardiac arrhythmias, depressed levels of consciousness and even death [3, 4]. To evaluate the effect of these recommendations and to complete the available literature on ADRs caused by CCMs, we conducted several studies as part of the TEDDY project.

Main Findings

Utilization studies

Use of medicines in children

In chapter 2.1 and 2.2 we present the studies on the utilization of pediatric medicines in the Netherlands, Italy and United Kingdom. In chapter 2.1 we describe utilization patterns of all drugs and in chapter 2.2 we focus on the respiratory drug use in children. Using a retrospective cohort design, the utilization of medicines is described for 675,868 children for the years 2000-2005. The off-label status was checked for the five drugs with the highest prevalence, by anatomic class, in each country. A drug was considered to be 'off-label for age' if the child's age at the time of use was below the lowest approved age as mentioned in the Summary of Product Characteristics (SPC) of that drug in each of the countries of use [5].

The databases recorded more than five million pediatric prescriptions. The main findings were the following: 1) the prescription rate was highest for children aged less than two years in all three countries (average of 3.3 prescriptions/year); 2) In children of all ages, the most commonly used medicines were anti-infectives (antibiotics), respiratory medicines (asthma medicines) and dermatologicals (topical corticosteroids); 3) in the younger age categories, boys had a higher user prevalence rate but this pattern reversed with adolescence, where females had consistently higher drug use prevalence rates; 4) off-label use was mostly observed for topical, inhaled and systemic corticosteroids, oral contraceptives and topical or systemic antifungals.

This was the first study describing pediatric medicines use in different European countries by combining databases using the same methodology. This approach changed the landscape considerably since previous studies were country or region specific with a large heterogeneity between studies, making a comparative evaluation often difficult or incomplete [6]. Since we used the same methodology across the databases, the differences that were observed reflect real prescribing differences. The Pediatric Committee of the European Medicines Agency (EMA) has compiled a pediatric needs list based on expert opinions and consultations. This list provides an overview of drugs for which additional information on use in children is needed. The missing information can go from PK/PD studies in children to the need of long term safety studies. The drugs mentioned on the list of specific needs are also the drugs with the highest user prevalence rates (e.g. inhaled and oral corticosteroids, topical and systemic antifungals). Our findings reinforce the importance of the need of additional data on drugs that are frequently used. However, there are some off-label drugs with high prescription rates that were not mentioned on any of the priority lists of the EMA. One example is the use of sex hormones. Our study revealed high prescription rates and mostly off-label use of these drugs. Similar to adults, the use of oral contraceptives by teenagers has been associated with an increased risk of cardiovascular events (e.g. myocardial infarction, stroke) as well as with an increased risk of venous thrombo-embolism [7-11]. To our knowledge, no RCTs on the safety and efficacy of sex

hormones limited to teenagers only have been conducted. Therefore we would recommend to include sex hormones in the pediatric needs list. This list is used as a tool to enforce pharmaceutical companies to apply for a PUMA (Pediatric Use Marketing Authorizations) for off-patent drugs to be registered for use in children. If authorized, a PUMA will give the pharmaceutical company 10 years of market protection for that specific drug.

The studies presented in chapter 2.1 and 2.2 show that drug utilization studies are important to get a clear understanding of the user prevalence rates in children and the differences by country, gender and age. Information from these studies is important, first of all to prioritize the specific needs but also to be incorporated into the PIPs

Use of asthma medicines

Despite the widespread pediatric use of asthma medicines and the large number of single center or national studies describing user prevalence rates, there have been very few comparative studies on the extent and patterns of use by region. To address this, we assessed the use of asthma medicines in three European countries (Netherlands, Italy and United Kingdom) during 2000-2005 (chapter 2.3) by using a similar methodology. In addition, we checked the off-label use of these drugs per country.

We found that the prevalence of asthma medicines use was highest in young children and decreased with age. The prescription rates were the highest for most asthma medicines in Italy, followed by the UK and the Netherlands. β_2 -mimetics (salbutamol) and inhaled glucocorticoids (fluticasone and beclomethasone) were the most frequently used asthma medicines in all three countries. Overall, off-label use, defined as use below the minimum age as mentioned in the SPC was low, but most pronounced for short-acting β_2 -mimetics in children < 18 months (Italy) and fixed combination of β_2 -mimetics+anticholinergics in children <6 years (Netherlands).

Some of the respiratory drugs are only registered for the treatment of asthma. Off-label use, defined as "use for other indications than asthma", was observed in all 3 countries for several asthma medicines. For some medicines, the percentage of off-label use was considerable (e.g. 80% of the children receiving budesonide in Italy, 74% of the children receiving ipratropium in the UK and 72% of the children receiving salbutamol+ipratropium in the Netherlands do not have a diagnosis of asthma, while these drugs are only licensed for use in asthma).

This high percentage of off-label use of asthma medicines in children can be explained by the fact that in young children it is difficult to make a diagnosis of asthma. This diagnosis is difficult because in young children, it is hard to differentiate between respiratory symptoms related to asthma or respiratory symptoms related to lower respiratory tract infections. Second, in this younger age category, asthma diagnosis by means of spirometry is not possible.

Use of cough and cold medicines

In 2007 the use of CCMs in young children received a lot of attention from regulatory agencies and scientists; and the Food and Drug Administration (FDA) in the United States issued a

recommendation advising parents and caregivers not to use these drugs in children younger than 2 [1]. This recommendation was based on information from ongoing studies reporting on safety concerns (such as cardiac arrhythmias, depressed levels of consciousness, encephalopathy and even death) of CCMs when used in young children [3, 12]. Following the US, warnings were as well issued in Canada, the United Kingdom and a partial warning in Italy on the use of nasal sympathomimetics in children <12 years. In the Netherlands, no national warning advising against the use of these drugs was spread. Although CCMs can be purchased as OTC in many countries, they are also regularly prescribed by primary care physicians, especially when these drugs are being reimbursed.

We assessed the effect of these regulatory warnings on prescription rates of CCMs in children < 2 years in both Italy and the Netherlands (chapter 2.4). We found that, despite the international warnings and important publications in high impact journals and lay press advising against the use of CCMs in young children, overall prescription rates for CCMs increased in the Netherlands. In Italy, where a specific warning was issued against the use of nasal sympathomimetics or combinations, a significant reduction in use of nasal combination products and nasal sympathomimetics was observed as well as a decrease in use of cough suppressants (opioids and non-opioids).

The increase of the prescription of CCMs in the Netherlands is worrisome, especially since there is no evidence of efficacy of these drugs [13]. The few studies that have been conducted in children found no significant improvement in symptomatic relief when compared to placebo [13-17]. Caregiver education and physician reminding on the self-limiting nature of coughs and colds and on the lack of efficacy of these CCMs is needed [3, 18]. We also would advice the European Medicines Agency to explicitly stipulate the hazards of use of CCMs in young children.

Safety studies

Safety studies within Vigibase

Although randomized controlled trials (RCTs) are considered to be the gold standard for performing safety studies, they are often hampered by small sample sizes and short follow-up. Spontaneous adverse event reporting databases, such as the Vigibase database of the WHO-UMC (Uppsala Monitoring Centre), contain the necessary data to elucidate potential safety risks of drugs among all age categories without the need to expose children to unnecessary clinical research.

To our knowledge, Vigibase has not been previously used to describe pediatric adverse drug reactions (ADRs). In this thesis we present the first studies on pediatric ADRs related to asthma medicines and cough and cold medicines using data from the Vigibase.

We analysed all spontaneously reported ADRs for asthma and cough and cold medicines as captured in the Vigibase database of the WHO-UMC during the period 2000-2006. Associations between the use of these medicines and ADRs were assessed by calculating reporting odds

ratio (ROR) as a measure of disproportionality while adjusting for gender, continent and type of notifier.

Asthma medicines related adverse drug reactions in children – data from the Vigibase database

The risk-benefit profile of asthma medicines has been well studied in randomized controlled trials (RCTs), and is considered to be favorable [19]. However, the majority of these studies have been performed in children older than 5 years and studies in younger children are lacking. To get a broader understanding of the adverse drug reactions associated with asthma medicines use in children and to get a better insight in the potential risks of these medicines in children of all age categories, we analysed the spontaneously reported ADRs for asthma medicines in the Vigibase database.

When the records in the VIGIBASE were limited to paediatric data, only 3.5% of the (non-vaccine related) records concerned ADRs related to the use of asthma medicines. This percentage does not correlate with the high prevalence of use of these medicines in children, e.g. 4-26% of children is being prescribed an asthma medicine (depending on country, age range, and study period) [1, 20]. This low reporting rate could be due to the fact that most asthma drugs are on the market for many years and treating physicians do not focus on potential (new) ADRs, because the medicines are thought to be safe. It could as well be that the low percentage of ADRs of asthma medicines, in relation to their high prevalence of use, is a true reflection of the safety of these drugs. This is in contrast to the recent safety concerns on the use of e.g. LABA in children with asthma and the risk of serious asthma related events and/or death [21].

The majority of the associations that were observed are also described in literature and in the SPCs of the drugs of interest (e.g. adrenal insufficiency and use of ICS and Churg Strauss syndrome in relation to LTRA) [22, 23]. We observed very few ADRs with high ROR that were not yet described in literature. New ADRs with high ROR were heart valve disorder, intestinal gangrene and gastric ulcer perforation with use of short-acting beta-agonists, gastric ulcer perforation, hemiplegia and tooth disorder with use of long-acting beta-agonists and hypokinesia with use of xanthines.

Although we did find some new signals, we want to re-emphasize that ADRs from spontaneous reporting databases are purely hypothesis generating and further research is needed to assess these potentially new signals in an appropriate setting [24].

Cough and cold medicines related adverse drug reactions in children - data from the Vigibase database

Because of the high use of CCMs and the concerns on the benefit-risk profile of these drugs in (young) children, we used the Vigibase database to investigate the type of adverse drug reactions and ROR that have been reported for CCMs in children aged 0-18 years.

CCMs related ADRs were infrequently reported (1.2% of the non-vaccine related records), although studies in the USA have shown that in a given week, 10% of the children use a CCM [25]. Actual use is hard to estimate since many CCMs are sold over the counter, this may also have an impact on the reporting rate of spontaneous ADRs, since only few countries allow for direct consumer reporting. Similar to what was observed for the asthma medicines, it could as well be that CCMs are thought to be safe and potential ADRs are not recognized nor reported. Most of the reported ADRs for CCMs concerned mucolytics and opium alkaloids and derivatives. The majority of the observed associations between CCMs and ADRs in the Vigibase were already described in literature and SPCs (e.g. dosing errors and the typical side effects of opium alkaloids) [26, 27]. Two new and potentially life-threatening ADRs were observed namely chronic renal failure associated with the use of expectorants and cerebral infarction associated with the use of the fixed combinations of opium alkaloids and expectorants. We want to re-emphasize that new CCMs-ADRs associations in spontaneous reporting databases are purely hypothesis generating and further research is needed to assess these potentially new signals in an analytical epidemiological approach. Overall, we found that for all age groups, various ADRs of different levels of severity were reported. This shows that CCMs not only cause ADRs in the youngest children, but in children of all ages. We underline the advice not to use CCMs in young children as evidence of their efficacy for the treatment of cough and cold is weak.

Glucocorticosteroids and risk of fractures

According to the Global Initiative for Asthma (GINA), maintenance treatment with low dose ICS is the treatment of choice for children with persistent asthma [28]. Oral glucocorticoids (OCS) are recommended for the treatment of very severe persistent asthma exacerbations. In accordance with the guidelines, the use of ICS in asthmatic children is high [29]. Long term use of ICS in children has been associated with major safety concerns such as adrenal suppression and growth retardation [28]. Long term use of OCS can cause osteoporosis, diabetes mellitus, adrenal suppression, obesity, skin thinning leading to easy bruising, and muscle weakness [28]. The association between the use of ICS and the risk of fractures remains controversial and very few studies have been conducted in children. All of these studies have focused on one country at the time, and therefore were reduced in size and heterogeneity of exposure was low (United Kingdom and Australia). To our knowledge, there are no studies quantifying the association between corticosteroids use and risk of fracture in children, combining data from different European countries, with different user patterns.

To get a better understanding of the risk of fractures associated with the use of corticosteroids in children, we conducted a population based nested case-control study using two primary care databases (IPCI and Pedianet) with quite different prescription patterns of ICS and OCS in children and including children 0-18 years of age (0-14 for Pedianet). The case-control study was nested in a cohort of users of asthma medicines. We analysed the association between cumulative use of inhaled corticosteroids (ICS), oral corticosteroids (OCS), and use of a combination of

inhaled and oral corticosteroids (ICS+OCS) and the risk of fractures. No association was found between use of ICS or use of OCS and the risk of fractures in any of the exposure categories. None of the previously conducted studies in children found an increased risk of fractures following use of ICS [30-32]. In contrast to the studies from Van Staa et al., we did not find an increased risk of fractures for children using OCS. Van Staa et al. found that the risk of fractures was increased in children receiving more than 3 prescriptions of OCS [33]. In our study, the majority of children used OCS for less than 30 days. Indeed only 1% of the children (both cases and controls) used OCS longer than one month. This duration is probably too short to increase the risk of fractures.

Our findings, as well as data from other studies, show that ICS, which are the mainstay of pediatric asthma treatment, can be used in children without concerns on a higher risk of fractures. We expect that long term use of OCS would increase the risk of fractures. As children are rarely chronically treated with OCS, this could not be studied in our database.

Glucocorticosteroids and risk of pancreatitis

Pancreatitis is a relatively rare condition in children and is associated with considerable morbidity and mortality [34]. Pancreatitis mainly occurs in adult life and the mean age of a first pancreatitis attack has been shown to be in the 6th decade of life [35]. In adults, the most common causes of acute pancreatitis are gallstones and alcohol abuse [35, 36]. In children, acute pancreatitis has different aetiologies such as trauma, infection, systemic diseases, toxins, structural anomalies of the pancreatico-biliary tract and idiopathic [37-39]. Drug-induced pancreatitis is considered to be a rare cause of pancreatitis in both children and adults. Glucocorticosteroids are among the drugs that have been associated with pancreatitis, both in adults and children [38-41]. All of the existing data on this subject is derived from case reports and case series. To quantify the association between the use of glucocorticosteroids (both inhaled and oral) and pancreatitis in children, we conducted a population-based case-control study within the PHARMO record linkage system. In a source population of around half a million children we identified only 54 children with acute pancreatitis, demonstrating the rarity of the condition. Many children with pancreatitis had been previously exposed to some type of drug. Current use of oral glucocorticosteroids increased the risk of pancreatitis with a factor 20 compared to no use (OR 21.40, $p < 0.001$). Use of Inhaled glucocorticosteroids use was not associated with an increased risk.

Our results are in line with case series in children, observing an association between oral glucocorticosteroids use and an increased risk of acute pancreatitis [39, 42, 43]. Similar to what has been described in literature, we confirmed known risk factors of pancreatitis such as a history of inflammatory bowel disease, gallstones, cystic fibrosis and trauma; and concomitant use of azathioprine, mesalazine, metronidazol, opiates, omeprazol and NSAIDs. [37, 44-48].

General consideration regarding the use and safety of respiratory medications in children

In this thesis we demonstrated that respiratory medicines are amongst the most frequently used drugs, particularly the inhaled corticosteroids and bronchodilating agents. These drugs merit their place for the treatment of asthma but in young children, these drugs are often used whereas the diagnosis of asthma could not be confirmed. In some countries (e.g. Italy) use of oral steroids is quite high but often for a short duration of follow-up. We showed that each of the classes of respiratory drugs has ADRs reported to the Vigibase of the WHO-UMC. Most ADRs are already known in the literature or in the SPC, but some potential safety signals for these drugs were observed which require further formal testing. In particular cerebral infarction associated with use of opium alkaloids+expectorants, chronic renal failure associated with expectorants use, intestinal gangrene, heart valve disorders and gastric ulcer perforation with use of short-acting beta-agonists; and hemiplegia and tooth disorders with the use of long-acting beta-agonists need to be further explored, as these are serious events.

We quantified the association for ICS and OCS with two particular (known) side effects (fracture and pancreatitis) in children. Use of ICS and OCS was not associated with an increased risk of fractures, whereas OCS, but not ICS, increased the risk of pancreatitis in children.

In the past; children were deprived of new drugs as, for ethical reasons, they were often excluded from clinical trials and thus efficacy and safety data on use in children were lacking: The pediatric regulation aims to facilitate the development and accessibility of medicinal products for use in the pediatric population. For each dossier of a new drug; being submitted for approval, the law stipulates the need of a pediatric investigation plan (PIP): A PIP is a development plan aimed at ensuring that the necessary data are obtained through studies in children to support the authorisation of the medicine for children. The ultimate goal of the new regulation is to stimulate drug research in children to ensure the safety and efficacy of drugs used in children. The implementation of this new regulation should be closely monitored as the drawback could be that children are exposed to unnecessary clinical trials when crucial data can be collected from other sources. Datasources that can be used for analysis are the electronic health care databases which contain information on the incidence/prevalence of the disease, the standard treatment of the disease and potential safety concerns. These are aspects that are part of the requested information from the PIP [49].

To convince skeptics of the importance and added value of observational databases, collaborative actions should be taken to further improve the quality of observational data. It is known that databases on spontaneous ADRs suffer from underreporting. Indeed, it has been estimated that less than 10% of all serious, and 2-4% of all non-serious ADRs are reported [50]. Reporting of spontaneous ADRs should be stimulated by adequate training and information programs, feed back systems and a facilitation of the reporting procedures. The research on rare side

effects and on long term side effects requires databases of considerable size with long term follow-up. This can be achieved by linking databases from various sources. Further research and development is needed to deal with issues such as database ownership, and transcription to uniform disease or drug coding. In addition, databases should try to capture data on important confounding factors. With regard to the safety and effectiveness of respiratory drugs, factors that need to be captured are asthma phenotypes and asthma severity as they modify treatment response.

In our research on the safety of respiratory drugs, we first checked potential safety signals using spontaneous ADR data from the Vigibase database. In addition, we quantified the association between the use of glucocorticosteroids and the risk of fractures and pancreatitis. We are aware that there are currently other safety concerns in relation to respiratory drugs that were not further elucidated. These concerns are the use of LABA in children and the risk of serious asthma related events and/or cardiovascular events. These safety concerns were not further explored for reasons of low LABA exposure and the very low incidence of cardiovascular events in children.

Methodological considerations

In this thesis we have used several readily available healthcare databases to perform large scale pediatric observational studies. The studies performed in this thesis are part of the TEDDY NoE, which aims to promote the availability of safe and effective medicines for children in Europe by integrating existing expertise and good practices

To our knowledge, we are the first to combine data from health care databases by using a predefined, common protocol. Combining the databases in this manner allowed us to perform large-scale pharmacoepidemiological research in pediatrics to get better knowledge about the safety and potentially benefits of drugs in children, without exposing children to unnecessary RCTs.

Primary care physician databases

For several studies in this thesis we used the the Pedianet database (pediatric electronic medical records from 150 pediatricians since 2000) in Italy [51], the IPCI database (comprising adult and pediatric electronic medical records from more than 400 doctors since 1996) in The Netherlands [52, 53], and the IMS DA database (electronic medical records on adults and children from 670 doctors) in the UK [54]. All of these databases contain the complete automated medical records of primary care physicians and have been used and proven valid for pharmacoepidemiological research [55]. The age and gender distribution in the various databases is representative for the country they originate from.

In these countries, primary care physicians are the guardians of children's health, which means that all clinical information concerning the patients (including summaries of specialist and hospital care) is kept in their medical records. Since all children need to be registered with a GP

in the Netherlands and United Kingdom, and with a family pediatrician in Italy, the databases are population-based [55].

Limitations of these databases in pharmacoepidemiological studies

Exposure, information and selection bias

One limitation of these databases is that they only capture outpatient, primary care prescriptions and no specialist prescriptions nor over the counter drugs (OTC). In addition, as we only had access to prescription data, information on actual refill of the prescriptions was missing meaning that we overestimated the actual exposure. In the studies on medicines use overall and use of CCMs, this may have resulted in underestimation of prevalence of use of medicines which are commonly used OTC (e.g. paracetamol, xylometazoline). In our study on asthma medicines use, this will minimally influence our results since asthma is a condition often dealt with in primary care, and asthma medicines originally prescribed by a specialist are often continued or prescribed by general practitioners [53].

In our case-control study on the use of glucocorticosteroids and the risk of fractures, we do believe that **misclassification of exposure** minimally influenced our exposure rates as asthma is a condition often dealt with in primary care, and asthma medicines originally prescribed by a specialist are often continued or prescribed by general practitioners [53]. If present; this misclassification is probably non-differential between cases and controls, therefore the actual risk may have been underestimated.

Selection bias was unlikely, as all data was obtained from prospectively collected medical records that are maintained for patients care purposes.

Information bias via misclassification of the outcome is also unlikely, because all fracture cases were retrieved from medical records and reviewed by two medical experts who were blinded to the exposure.

Confounding

A confounder is a factor that is both associated with the disease of interest and associated with the exposure but is not part of the common pathway (Figure 1). Due to the presence of the confounder, it is not possible to accurately assess the relationship between the exposure and outcome of interest. Confounding may be accounted for by matching participants by likely confounders (such as age and sex), or controlling the effect of the confounder by stratifying the analysis.

We used IPCI and Pedianet to assess the association between steroid use and risk of fractures. Although we tried to adjust for any potential confounders, due to the nature of the databases, we did not have information on all possible confounders such as the nutritional status of the children, body mass index, bone mineral density, physical activity and smoking status. Residual confounding usually results in an overestimation of the observed risk. However, as we did not observe an increased risk we do not believe that the lack of information on these confounders influences our results.

Strengths

A major strength of these databases is that they capture a large number of children in databases across Europe, resulting in a high generalisability of our findings to the general population. In addition, these databases have detailed information on comorbidity and detailed information on hospital referral and discharge letters. This results in a good quality of case ascertainment. The fact that data on millions of children is available in health care databases should be recognized by researchers and efforts should be made to extract data on pediatric drug use/safety from these databases, instead of performing unnecessary clinical trials.

PHARMO RLS

We used PHARMO RLS to assess the association between the use of glucocorticosteroids and risk of pancreatitis.

Exposure and information bias

In contrast to the IPCI and IMS data, the PHARMO-RLS captures refill data. Still, exposure bias might be present as the database does not capture actual intake of the drug. If present; we do believe that this bias will be non-differential as well, leading to an underestimation of the actual risk.

Information bias by misclassification of the outcome may be an issue using the PHARMO database. All outcomes are coded by ICD-9 codes, and manual validation of potential cases is not possible as it would require the de-anonymisation of hospital data and permission to review the files.

In addition, we may suffer from *protopathic bias* since steroids are also given to treat pancreatitis. This could not be the explanation of our findings since the association was only observed in children using oral steroids for 7 days or more.

Confounding

A major limitation of this study is that, as with each observational retrospective study, the findings were prone to unmeasured confounding as information on body mass index and alcohol intake were missing.

Strength

The Pharmo RLS has as strength that it is a very large database containing information on more than 3 million inhabitants from the Netherlands meaning that our results can be extrapolated to the entire pediatric population of the Netherlands. In addition, as PHARMO contains pharmacy dispensing data, both prescriptions from general practitioners and specialists were captured, ensuring a more complete overview of the drugs used. Although the database is large, pancreatitis is very rare and we thus lacked power. Future studies should use approaches as done in TEDDY: pooling across databases.

Vigibase

Vigibase was used to provide an overview of pediatric ADRs related to asthma and cough and cold medicines. Data from spontaneous reporting databases suffer from bias such as under and overreporting. [56-58]. Furthermore, it has to be underlined that a signal with a high ROR does not prove that the drug and ADR are causally related. The observed signals are purely hypothesis generating and further research is needed to assess these signals in an appropriate setting [24]. Also, some of the found signals are due to confounding by indication, such as cystic fibrosis associated to mucolytics. Due to the nature of the database, information on indication is missing, and therefore it is not possible to identify the underlying condition.

The strength of this database is the large number of pediatric ADRs available for analysis.

Recommendations for future research

The studies in this thesis may help to give direction to further research in the field of pediatric medicines research.

First, primary care physicians should be aware of the harms of CCMs in children. The fact that prescription rates of CCMs in the Netherlands even increased after the international warnings is alarming. We believe that in Europe, this topic did not receive the attention it deserves. We highly recommend that a concerted European action is undertaken to advise against the use and prescription of cough and cold medicines to children.

Second, we have shown the potential of linking multi-country databases to study country specific pediatric drug use and safety in a systematic manner without being hampered by methodological differences. Although RCTs are the gold standard for efficacy assessment, safety studies are more effectively conducted through large scale postmarketing observational studies [59]. Clinical trials are often small and too short for safety assessment

Pharmacoepidemiological studies should be promoted to improve the safety assessment of pediatric drugs since they assess the safety of drugs under real life circumstances. As safety information is lacking on long-term use of controller medication in asthmatic children, health-care databases throughout Europe should be combined to perform large scale safety studies. Also, the ADRs we found within Vigibase, which were not yet described in literature, can be assessed in this manner. Combining several databases will make it possible to also detect rare ADRs.

This thesis shows that exposure and outcome information is available on a large pediatric population within Europe. Researchers should try to work together on linking the available databases within Europe, instead of performing clinical trials on a small scale.

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Summary

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The Task-force in Europe for Drug Development for the Young (TEDDY) Network of Excellence was established in 2005 through funding of the European Community's sixth Framework Programme to contribute to the promotion of safe and efficacious medicines for children in the context of the impending European Paediatric Regulation that came into force in January 2007. The overall aim of the TEDDY NoE is to promote the availability of safe and effective medicines for children in Europe by integrating existing expertise and good practices, as well as stimulating pediatric drug development. The work presented in this thesis is a spin-off of the TEDDY activities.

In this thesis, we aimed to study the use and safety of two mostly used medicine groups in children, namely asthma medicines and cough and cold medicines. We did this through large scale observational studies, by combining readily available healthcare databases within Europe.

In chapter 2 we present several multi-national studies on the utilization of medicines in children. In **chapter 2.1 and 2.2** we present the utilization of medicines in children living in Italy, the Netherlands and the United Kingdom. Children up to 14 (Italy) or 18 years of age (United Kingdom and The Netherlands) from three primary care databases were included in the studies. These were the first studies describing pediatric medicines use in different European countries by combining databases using the same methodology

Prevalence of use per year was calculated by drug class (anatomic and therapeutic levels). A total of 675,868 children were included in the studies. The mostly used medicines were anti-infectives, dermatological and respiratory medicines, whereas cardiovascular and anti-neoplastic medicines had the lowest use.

In **chapter 2.3** we describe the utilization of asthma medicines in children from Italy, the Netherlands and the United Kingdom by combining health care databases. For all children, prescription rates of asthma drugs were studied by country, age, asthma diagnosis and off-label status. The cohort consisted of 671,831 children of whom 49,442 had been diagnosed with asthma at any time during follow-up. β 2-mimetics and inhaled steroids were the most frequently prescribed asthma medicine classes in the studied countries. Xanthines, anticholinergics, leukotriene receptor antagonists and anti-allergics were the least frequently prescribed medicines classes. Off-label use was low, and most pronounced for β 2-mimetics in children < 18 months (Italy) and combined β 2-mimetics+anticholinergics in children <6 years (Netherlands). With this study we showed that linking multi-country databases enables us study country specific pediatric drug use in a systematic manner without being hampered by methodological differences.

In **chapter 2.4** we evaluate the effect of international safety warnings on the prescription rates of cough and cold medicines in children in the Netherlands and Italy. Cough and cold medicines are frequently used in children to treat upper respiratory tract infections without

solid proof of benefits and risk of serious adverse events. In 2007 international warnings have been issued advising against use of these drugs in young children. We analysed outpatient electronic medical records of children <2 years in Italy and the Netherlands and calculated pre- and post-warning prescription rates. The cohort consisted of 99,176 children < 2 years of age. After international warnings, overall prescription rates for cough and cold medicines decreased slightly in Italy and increased in the Netherlands. Despite the international safety warnings and negative benefit-risk profiles, prescription rates of cough and cold medicines remained substantial and were hardly affected by the warnings, especially in the Netherlands.

In chapter 3 we assess the safety of asthma and cough and cold medicines by analysing the adverse drug reactions (ADRs) from the WHO Vigibase database and by performing case-control studies.

Chapters 3.1 and 3.2 give an overview of adverse events related to asthma medicines and cough and cold medicines, reported to Vigibase. Of the non-vaccine related records (294,773), 3.5% comprised of asthma medicines related ADRs and 1.2% of cough and cold medicines. For asthma medicines, the majority of the records were for children aged 2-≤11 years and most records concerned short-acting β 2-agonists (SABAs) and inhaled corticosteroids. For cough and cold medicines, most ADRs were reported for children aged 2-18 years and mostly concerned mucolytics and opium alkaloids. In both studies, the majority of the found drug-ADR combinations were already described in literature. New, potential signals that we found were were intestinal gangrene and perforated gastric ulcer associated with use of SABAs, tooth discoloration with the use of anticholinergics, chronic renal failure associated with use of expectorants and cerebral infarction associated with the use of opium alkaloids+expectorants.

In **chapter 3.3** we describe a study on the association between use of corticosteroids (inhaled [ICS or oral [OCS]) and risk of fractures in children. Long term use of OCS has been associated with an increased risk of fractures both in children and adults; whereas the association between the use of ICS and the risk of fractures remains controversial. To assess the risk of fractures associated with the use of corticosteroids in children, we conducted a case-control study combining data from the Netherlands and Italy. We confirmed known risk factors for fractures, such as trauma and current use of drugs for functional gastrointestinal disorders. For exposure to corticosteroids (ICS or OCS), we found no increased risk of fractures.

In **chapter 3.4** a study on the association between use of corticosteroids (inhaled [ICS or oral [OCS]) and risk of pancreatitis in children is described. Although drug-induced pancreatitis is rare, a variety of drugs have been associated to pancreatitis (in children and adults), including steroids. So far, no studies have been performed to assess the association between exposure to steroids and pancreatitis in children. We conducted a case-control study within a Dutch hospital

discharge registry. Current use of OCS and cumulative use of >7 days OCS was associated with a higher risk of pancreatitis. Use of ICS was not associated with pancreatitis.

Chapter 4 includes a general discussion in which the results and conclusions of studies in this thesis are summarized and interpreted. Furthermore, methodological considerations are discussed and suggestions are given for further research.

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Samenvatting

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Gesubsidieerd door de Europese Commissie's zesde Framework Programma is in 2005 de Task-force in Europe for Drug Development for the Young (TEDDY) Netwerk van Excellentie opgericht om een bijdrage te leveren aan de bevordering van veilige en werkzame medicijnen voor kinderen, in de context van de Europese Pediatrische Wetgeving, welke in Januari 2007 van kracht werd.

Het algemene doel van TEDDY is het bevorderen van de beschikbaarheid van veilige en werkzame medicijnen voor kinderen in Europa, door zowel bestaande expertise samen te brengen als ook medicijn ontwikkeling specifiek gericht op kinderen te stimuleren. De studies die gepresenteerd worden in dit proefschrift zijn het resultaat van TEDDY werkzaamheden.

Het specifieke doel van dit proefschrift was het onderzoeken van het gebruik en de veiligheid van twee veel gebruikte medicijn groepen in kinderen, namelijk astma medicijnen en Verkoudheidsmedicijnen. Dit hebben wij gedaan door medische databasen binnen Europa te combineren en hiermee observationele studies op grote schaal uit te voeren.

In hoofdstuk 2 presenteren we meerdere multinationale studies naar het gebruik van medicijnen in kinderen.

In **hoofdstuk 2.1 en 2.2** beschrijven we het gebruik van medicijnen door kinderen in Italië, Nederland en het Verenigd Koninkrijk. Voor deze studies hebben we gegevens van kinderen uit drie huisarten-databasen gecombineerd.

Deze studies waren de eerste in hun soort, waarin het medicijn gebruik door kinderen uit verschillende Europese landen wordt beschreven door medische databasen uit deze landen op uniforme wijze te combineren.

Het gebruik van medicijnen per jaar werd berekend per medicijn-groep (op anatomisch en therapeutisch niveau). In totaal werden 675,868 kinderen geïncludeerd in deze studies. De meest gebruikte medicijnen waren anti-infectiva, dermatologische preparaten en respiratoire medicijnen. Cardiovasculaire medicijnen en chemotherapeutica werden het minst vaak gebruikt.

In **hoofdstuk 2.3** beschrijven we het gebruik van astma medicijnen door kinderen in Italië, Nederland en het Verenigd Koninkrijk aan de hand van het aantal voorgeschreven recepten. Recepten voor astma medicijnen werden bestudeerd per land, leeftijd, astma diagnose en off-label status. In totaal werden 671,831 geïncludeerd in deze studie, van welke 49,442 waren gediagnosticeerd met astma. β -sympathicomimetica en inhalatiecorticosteroïden waren de meest voorgeschreven astma medicijnen. Xanthines, anticholinergica, leukotriene-receptor antagonisten en anti-allergica werden het minst vaak voorgeschreven. Off-label gebruik van astma medicatie was laag, de middelen die het vaakst off-label werden gebruikt waren: β -sympathicomimetica door kinderen <18 maanden oud (in Italië) en β -sympathicomimetica+ anticholinergica door kinderen <6 jaar (in Nederland).

Met deze studie tonen wij aan dat het combineren van multinationale medische databasen wetenschappers in staat stelt om medicijn gebruik door kinderen te bestuderen, zonder gehinderd te worden door methodologische problemen.

In **hoofdstuk 2.4** wordt het effect van internationale veiligheidswaarschuwingen op het aantal recepten voor verkoudheidsmedicijnen aan kinderen in Nederland en Italië beschreven. Verkoudheidsmedicijnen worden vaak gegeven bij bovenste luchtweginfecties, hoewel hun werkzaamheid in kinderen nooit is bewezen en er een verhoogd risico op ernstige bijwerkingen is. Als gevolg hiervan, zijn er in 2007 internationale waarschuwingen gegeven, waarin werd geadviseerd deze medicijnen niet te geven aan jonge kinderen.

Wij hebben de medische gegevens van kinderen <2 jaar in Italië en Nederland bestudeerd en het aantal voorschriften voor verkoudheidsmedicijnen voor en na de waarschuwingen bekeken. 99,176 kinderen jonger dan 2 jaar werden geïncludeerd in deze studie. Na de internationale waarschuwingen, daalde het aantal voorschriften voor verkoudheidsmiddelen in Italië licht en in Nederland steeg het aantal juist. Ondanks de internationale veiligheidswaarschuwingen én het risico op ernstige bijwerkingen, werden verkoudheidsmiddelen nog aanzienlijk voorgeschreven, vooral in Nederland.

In hoofdstuk 3 bestuderen we de veiligheid van astma medicijnen en verkoudheidsmedicijnen door bijwerkingen in de Vigibase database te bestuderen en door case-controle studies uit te voeren.

In **hoofdstukken 3.2 en 3.2** wordt een overzicht gegeven van de bijwerkingen van astma medicijnen en verkoudheidsmedicijnen, die gemeld zijn aan de Vigibase database. Van alle bijwerkingen die niet aan vaccins waren gerelateerd (294,773), betrof 3.5% astma medicijnen en 1.2% verkoudheidsmedicijnen. De meeste bijwerkingen voor astma medicijnen werden gemeld voor kinderen tussen 2-≤11 jaar en betroffen voornamelijk kortwerkende β -sympathicomimetica en inhalatiecorticosteroiden. Voor verkoudheidsmedicijnen werden de meeste bijwerkingen gemeld voor kinderen tussen 2-18 jaar en betroffen voornamelijk mucolytica en opium alkaloiden. De meeste van de beschreven bijwerkingen-geneesmiddel combinaties in beide studies zijn gekend in de literatuur. Mogelijk nieuwe signalen die wij hebben gevonden zijn de volgende: gangreen van de darmen en perforatie van een maagzweer bij gebruik van kortwerkende β -sympathicomimetica, verkleuring van de tanden bij gebruik van anticholinergica, chronisch nierfalen bij gebruik van expectorantia en hersen-infarct bij gebruik van opium alkaloiden+expectorantia.

In **hoofdstuk 3.3** beschrijven we een studie naar de associatie tussen het gebruik van corticosteroiden (zowel inhalatie als oraal) en fractures. Langdurig gebruik van orale corticosteroiden is in de literatuur geassocieerd met een verhoogd risico op fractures in zowel kinderen als volwassenen, het risico bij inhalatie corticosteroiden is tot op heden twijfelachtig. Om de associatie tussen corticosteroiden en fractures te bestuderen in kinderen, hebben wij een case-controle studie uitgevoerd waarin data uit Nederland en Italië werden gecombineerd. Gekende risicofactoren voor fractures, zoals trauma en het gebruik van medicatie voor gastro-intestinale stoornissen, werden bevestigd in onze studie. Het gebruik van corticosteroiden (zowel inhalatie als oraal) gaf geen verhoogd risico op fractures in kinderen.

Hoofdstuk 3.4 beschrijft een studie naar het gebruik van corticosteroiden (zowel inhalatie als oraal) en het risico op pancreatitis bij kinderen. Hoewel pancreatitis veroorzaakt door medicijnen zeldzaam is, zijn een aantal medicijnen in verband gebracht met pancreatitis (zowel in kinderen als in volwassenen), waaronder steroiden. Tot op heden, zijn er geen studies uitgevoerd om het risico op pancreatitis bij gebruik van steroiden te beschrijven in kinderen. Om dit gat aan informatie te vullen, hebben wij een case-controle studie uitgevoerd, gebruik makend van de Nederlandse Pharmo database. Huidig gebruik van orale corticosteroiden en cumulatief gebruik van > 7 dagen waren geassocieerd met een verhoogd risico op pancreatitis. Het gebruik van inhalatie corticosteroiden gaf geen verhoogd risico.

Hoofdstuk 4 bevat een algemene discussie, waarin de resultaten en conclusies van studies in dit proefschrift worden samengevat en geïnterpreteerd. Daarnaast worden methodologische aspecten besproken en worden suggesties gedaan voor verder onderzoek.

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PhD portfolio

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PhD Portfolio

Research skills

2007-2008 Master of Science in Clinical Epidemiology, Netherlands Institute for Health Sciences, Erasmus University, Rotterdam

International conference presentations

2008 11th Biannual Congress of the European Society for Developmental, Perinatal and Paediatric Pharmacology, Rotterdam, the Netherlands; poster presentation 'Respiratory drug use in children in the Netherlands, Italy and United Kingdom'.

2008 11th Biannual Congress of the European Society for Developmental, Perinatal and Paediatric Pharmacology, Rotterdam, the Netherlands; poster presentation 'Use of cough and cold medications in children in the Netherlands and Italy'.

2008 24th International Conference on Pharmacoepidemiology, Copenhagen, Denmark; poster presentation 'Respiratory drug use in children in the Netherlands, Italy and United Kingdom'.

2008 24th International Conference on Pharmacoepidemiology, Copenhagen, Denmark; poster presentation 'Use of cough and cold medications in children in the Netherlands and Italy'.

2009 PRIOMED matchmaking event, Tallinn, Estonia; poster presentation 'Cough and Cold medicine prescriptions in children'.

Attending international meetings

- 2007 TEDDY Open Conference, London, United Kingdom
- 2008 TEDDY NoE annual meeting, ' European symposium on ethics and paediatric Clinical research in Europe', Marseille, France.
- 2010 TEDDY Final Open Conference ' Paediatric Medicines in Europe. Past, Present and Future', Brussels, Belgium.

Teaching

- 2008-2009 Supervising practicals in Evidence Based Medicine at the Faculty of Medicine, Erasmus MC, Rotterdam
- 2008-2009 Teaching assistant, practicals in (pharmaco-)epidemiology at the Faculty of Medicine, Erasmus MC, Rotterdam

Other

- 2010 Reviewing for the 'British Journal of Clinical Pharmacology', and ' European Journal of Clinical Pharmacology'.

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Dankwoord

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Na meer dan 3 jaar onderzoek is het dan eindelijk tijd voor het dankwoord! Opgelucht en met veel plezier schrijf ik dit laatste onderdeel van m'n boekje. Iedereen die op wat voor manier dan ook heeft bijgedragen aan de totstandkoming van mijn proefschrift wil ik natuurlijk bedanken en een aantal mensen in het bijzonder.

Allereerst wil ik mijn promotor, Miriam Sturkenboom bedanken. Toen ik bijna 4 jaar geleden als nacodeur begon op de afdeling Medische Informatica, had ik nooit durven dromen dat ik een aantal jaar later met mijn eigen proefschrift in m'n handen zou staan! Miriam, heel erg bedankt dat je me die kans hebt gegeven. Jouw begeleiding heb ik al die jaren als zeer plezierig ervaren. Tijdens de wat mindere perioden gaven je enthousiasme en positieve energie mij het nodige zetje om door te gaan.

Vervolgens natuurlijk mijn copromotor, Katia Verhamme. Katia de vele uren samen achter de pc, zwoegend over Foxpro, hebben hun vruchten afgeworpen. Bedankt ook voor je geduld, wanneer ik weer 's in al mijn ongeduld een syntax of paper had afgeraffeld! Je was een soort 'moeder op het werk', zorgzaam en bezorgd om je promovendi.

Ik wil ook graag prof. Den Jongste, prof van den Anker en prof. Ceci hartelijk danken voor hun deelname aan de leescommissie.

Toen ik startte als promovendus, kwam ik in een echte mannenkamer terecht. Gianluca (grote broer), Roelof en Seppe, bedankt voor jullie gezelschap! Ik voelde mij binnen no time thuis op de afdeling.

Natuurlijk ook alle andere (oud-)collega's: Ana, Ann, Carmen, Eva, Inge, Jeanne, Lenonoor, Marissa, Nico, Preci, Rene, Sandra, Silvana, Vera.

Tevens wil ik Desiree, Tineke, Carmen en Sander bedanken voor hun hulp bij de administratieve problemen en Kris, Mees en Marcel voor de soms broodnodige technische hulp.

Mijn vrienden, 'the uni-gang', jullie heel erg bedankt voor de vele uren gezelligheid! Sevilay (paranimf), Gülhan, Hatice, Nazli, Shakib, Musa, Mo en Memo; zonder jullie was het de afgelopen jaren toch maar een saaie boel geweest! Ook al hebben de meesten van ons nu andere verplichtingen, ik hoop dat we toch tijd voor elkaar vrij blijven maken.

Mijn familie, pap en mam in het bijzonder, wil ik bedanken voor alle steun en zorg die ik mijn hele leven van ze heb gekregen. De vele weekenden samen zorgden voor de nodige ontspanning. Zonder jullie was ik nooit zover gekomen.

Mijn zus, tevens mijn paranimf, wil ik in het bijzonder bedanken. Mientje, we hebben samen een hele lange weg afgelegd. Je bent er altijd voor me geweest, no matter what, ook nu met mijn promotie. Ik hoop dat ik hetzelfde voor jou kan doen...

Tot slot mijn man Yavuz. Ook al zijn we nog maar net getrouwd, je hebt de afronding van mijn promotie in al zijn hectiek meegemaakt. Hopelijk komen we nu in wat rustiger vaarwater terecht waarin we meer van elkaar gezelschap kunnen genieten. Op naar de rest van ons leven samen...

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List of publications

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List of Publications

Sen EF, Verhamme KM, Herings R, Neubert A, Felisi M, Sturkenboom MC. THE TEDDY NETWORK: EPIDEMIOLOGICAL TRENDS IN PAEDIATRIC DRUG USE IN EUROPE. *European Journal of Hospital Pharmacy Practice*, 6 (2007), 22–24.

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Hsia Y, Neubert A, Sturkenboom MC, Murray ML, Verhamme KM, Sen F, Giaquinto C, Ceci A, Wong IC; on behalf of the TEDDY Network of Excellence. Comparison of antiepileptic drug prescribing in children in three European countries. *Epilepsia*. 2009 Oct 8. [Epub ahead of print]

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About the author

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About the author

Elif Fatma Şen was born on August 5th, 1983 in The Hague, the Netherlands. In 2001 she finished her gymnasium education at the Atlas College in Rijswijk. She studied Biomedical Sciences at the University of Amsterdam for one year and started medical school in 2002. In 2007 she obtained her Medical Bachelor and started her PhD research at the department of Medical Informatics of the Erasmus MC. There, she performed the research described in this thesis. In 2008 she obtained her Master of Science degree in Clinical Epidemiology at the National Institute for Health Sciences (NIHES).

In 2011 she will start her internship to obtain her medical degree.