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OFF-LABEL DRUG TREATMENT AND RELATED PROBLEMS IN CHILDREN

Elin Kimland

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-A register based investigation

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Abstract

Introduction: There is a lack of pediatric documentation concerning efficacy and safety of many drugs, which may contribute to *off-label* drug treatment and increase the risk for adverse drug reactions (ADRs).

Aims: To; (**I**) analyse the frequency and characteristics of pediatric *off-label* prescribing; (**II**) investigate frequency of *off-label* drug prescribing in pediatric ADR reports; (**III**) analyse drug related problems, the extent of *off-label* drug treatment in pediatric questions to a Drug Information Centre (DIC) and pediatric literature information adding to the labelling of the drug in DIC answers.

Methods: Three retrospective register based investigations on drug treatment of children less than 16 years of age were performed. In study **I,** outpatient records of purchased prescriptions were retrieved and analysed. The analysis was restricted to the drugs that account for 90% of the total use (DU90%). In study **II,** a nation-wide survey of ADR reports to the Medical Products Agency in relation to prescriptions among suspected drugs in outpatients was performed. In study **III,** questions and answers (Q&A) to a DIC in Stockholm (1995-2004) were characterised and analysed.

Results: In Stockholm 1.8 prescribed drugs per pediatric outpatient were purchased in the year 2000. Every fifth drug was classified as an *off-label* prescription. The proportion of *off-label* prescription was highest for topical drugs, followed by psychotropic drugs. In the year 2000, 112 pediatric ADR reports corresponding to 158 ADRs in outpatients were reported. The *off-label* proportion in ADR reports was more than 40%. One third of the reports was regarded as serious and these were more often associated with *off-label* drug prescribing. Antiasthmatic drugs were most commonly reported. Psychiatric symptoms were the most commonly reported ADRs. During a 10-year period DIC in Stockholm handled 249 pediatric questions and each question addressed on average 1.5 drugs. The questions mainly concerned drugs licensed in Sweden. Adverse drug reactions (ADRs), drug choice or dosing were the most common drug related problems. Every third question was *off-label* and among these the most common therapeutic group was psychotropic drugs. In every other response to *off-label* questions, pediatric documentation concerning drug efficacy and safety was found. The most common reason for a drug to be classified as *off-label* was lack of pediatric labelling in the Swedish catalogue of medical products.

Conclusion: This thesis has demonstrated substantial *off-label* prescribing in primary health care. *Off-label* prescribing were common in pediatric ADR reports from primary care. We also found literature information adding to the labelling of the drug. There is a great need for evidence based pediatric drug information, which can be retrieved from a DIC. A future challenge is to further diffuse this knowledge to pediatric prescribers through Internet, expert committees and medical journal databases.

Keywords: **Child, drug therapy, drug labelling, *off-label*, drug information services, adverse drug reactions, prescription drugs, drug related problems**

Sammanfattning (Summary in Swedish)

Introduktion: De flesta läkemedel är enbart testade på vuxna, vilket medför att dokumentation om effekt och säkerhet av läkemedel till barn ofta saknas. Avsaknaden av dokumentation resulterar i att barn förskrivs läkemedel *off-label*. Sådan förskrivning kan medföra att barnet utsätts för okända risker i samband med läkemedelsbehandling.

Syfte: Att; (**I**) identifiera hur vanligt förekommande *off-label* förskrivning av läkemedel till barn är; (**II**) analysera frekvensen *off-label* förskrivning bland biverkningsrapporter; (**III**) identifiera läkemedelsbehandling *off-label* och karaktärisera läkemedelsrelaterade problem hos barn bland frågor vid en läkemedelsinformationscentral, samt kartlägga tillgängligheten av dokumentation rörande barn och läkemedelsbehandling utöver befintlig produktinformation.

Metod: Vi har utfört tre registerstudier på läkemedelsbehandling till barn under 16 år. I den första studien (**I**) analyserades expedierade läkemedel i primärvården i Stockholm år 2000. Enbart läkemedel som utgjorde 90% av den totala förskrivningen (DU90%) inkluderades. I den andra studien (**II**) analyserades biverkningsrapporter till läkemedelsverket från primärvården år 2000. I det tredje arbetet (**III**) studerades frågor och svar besvarade vid en läkemedelsinformationscentral i Stockholm under åren 1995-2004.

Resultat: År 2000 expedierades 1.8 läkemedel per barn i Stockholm. Vart femte läkemedel i primärvården förskrevs *off-label* och andelen var störst för topikala läkemedel följt av psykofarmaka. Under 2000 inkom 112 biverkningsrapporter gällande barn från primärvården. Dessa omfattade 158 biverkningar, varav en tredjedel bedömdes vara allvarliga. Andelen läkemedel som hade förskrivits *off-label* var drygt 40% i biverkningsrapporter och dessa förekom oftare i allvarliga rapporter. Psykiatriska biverkningar respektive astmaläkemedel var vanligast bland rapporterna. Läkemedelsinformationscentralen har under en 10-års period handlagt 249 frågor om barn och varje fråga gällde 1.5 läkemedel. Majoriteten av frågorna rörde registrerade läkemedel i Sverige. Två tredjedelar av frågorna gällde läkemedelsbiverkningar, val av läkemedel eller dosering. Var tredje fråga klassificerades som *off-label*, bland vilka psykofarmaka var vanligast. Den vanligaste orsaken till *off-label* klassificering var avsaknad av dokumentation om läkemedels effekt och säkerhet hos barn i den svenska produktinformationen. Dokumentation om läkemedels effekt och säkerhet på barn utöver den svenska produktinformationen återfanns dock i hälften av alla svar till frågor klassade som *off-label*.

Slutsats: Denna avhandling visar att *off-label* förskrivning är relativt frekvent förekommande i primärvården. *Off-label* förskrivning förekom i nästan hälften av alla biverkningsrapporter hos barn. Det finns betydande dokumentation gällande effekt och säkerhet av läkemedelsbehandling till barn utöver svensk produktinformation. Behov av evidensbaserad information rörande läkemedel och barn är betydande. Via läkemedelsinformationscentralen kan förskrivare erhålla evidensbaserad kunskap om läkemedel och barn som saknas i den svenska produktresumén. En framtida utmaning är att finna kanaler för att sprida denna kunskap till fler förskrivare t ex via integrerade journalsystem, expertstöd och Internet för att förbättra underlaget vid pediatrisk förskrivning.

Contents

List of original papers

The present licentiate thesis is based on the following publications and manuscripts, which will be referred to in the text by their Roman numerals, **I-III**.

I. Ufer M, Rane A, Karlsson Å, Kimland E, Bergman U. Widespread *off-label* prescribing of topical but not systemic drugs for 350,000 paediatric outpatients in Stockholm. Eur J Clin Pharmacol 2003;**58**:779-783.

II. Ufer M, Kimland E, Bergman U. Adverse drug reactions and *off-label* prescribing for paediatric outpatients a one-year survey of spontaneous reports in Sweden. Pharmacoepidemiol Drug Saf 2004;**13**:147-152.

III. Kimland E, Bergman U, Lindemalm S, Böttiger Y. Drug related problems and *off-label* drug treatment in children at a Regional Drug Information Centre. (Manuscript).

List of abbreviations

ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical classification
DIC	Drug Information Centre
DU 90%	Drug Utilization 90%
DRIC	Drug Research & Information Centre
FASS	The Swedish catalogue of medical products
MPA	Medical Products Agency in Sweden
OTC	Over-The-Counter
SPC	Summary of Product Characteristics
SSRI	Selective Serotonin Reuptake Inhibitors
SWEDIS	SWEdis Drug Information System
WHO	World Health Organization

Terminology

Drug Utilization 90%	The number of drugs accounting for 90% of the total use (in prescriptions or DDDs). (Björn Wettermarks, PhD thesis, Karolinska Institutet 2004).
***Off-label* drug**	A drug that is used outside the terms of the product license.
Over-The Counter	Pharmaceuticals sold without prescription
Pharmacokinetics	The time course, including drug absorption, metabolism and elimination, of a drug and its metabolite in the body.
The Wise Drug List	"Kloka listan", Recommended drugs by the Drug and Therapeutics Committée of the Stockholm County Council, Sweden.
Unlicensed drug	A drug that is not approved by the regulatory authority.

1 Introduction

During recent years, pediatric drug treatment and the lack of documentation in children concerning the efficacy and safety for many drugs has drawn much attention. The licensing procedure, which aims to ensure the efficacy, safety and quality of drugs, and obtain marketing authorisation, is mainly based on clinical trials in adults. Several researchers have demonstrated that pediatric drug prescribing in hospital care frequently is carried out in an *off-label* manner, i.e. drugs are used outside the terms of the product license. This *off-label* drug use means that children receive drug treatment based on less scientific documentation, which may increase the risk of drug related problems. Most drug prescriptions, both to adults and children, are issued in primary health care, where the extent and effects of *off-label* drug treatment is even less studied than in hospital care.

The aim of this thesis was to investigate the extent of *off-label* drug treatment in pediatric outpatients and the frequency of *off-label* drug treatment in adverse drug reactions reports. The problem of pediatric *off-label* drug treatment is further elucidated by a study of the characteristics of questions and answers (Q&A) to a Drug Information Centre (DIC).

1.1 Pharmacokinetics in children

It is well known that pharmacokinetic responses to a drug given to a child may differ substantially from that of an adult, due to several factors. For example, the elimination capacity changes throughout childhood. It can be very low in the newborn, and especially in the preterm neonate, due to immaturity of both the hepatic drug metabolising capacity and the kidney function, whereas the toddler and preschool child have an increased metabolic capacity and may require much higher weight-adjusted doses than adults. Also, the surface area-to-body weight ratio in children can be up to three times higher than in adults, which can lead to a larger proportion of absorption of topically administered drugs (1,2).

1.2 Pediatric drug prescribing

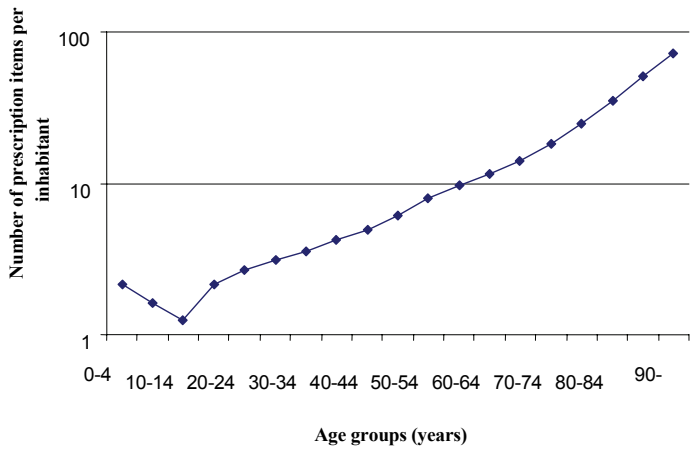
Drug therapy is widely used to treat disease in childhood and several prescription and drug utilization studies have shown that children, especially small children, receive considerable amounts of drugs (3-7).

Two large prescription studies, covering both pediatric in- and outpatients (5,6), and three smaller drug utilization studies in children mainly in primary health care was found in a literature search (3,4,7). The average number of drugs prescribed per child was 1.4 in Sweden (3), and varied in other European countries from 1.2-3.2 drugs per child (3-5,7).

The most commonly prescribed drugs (based on therapeutics groups) in children are antibiotics for systemic use and drugs for the respiratory system (3-5,7).

According to sales statistics from the National Corporation of Swedish Pharmacies infants (0-4 years) receive about 2.2 prescription items per individual, which declines in children and increases again in adolescents (*Figure 1*) (8). Although children receive considerable amounts of drugs, adults and especially the elderly are the large consumers of drugs.

***Figure 1*: Sales on prescriptions as prescription items per inhabitant in Sweden year 2000.**



1.3 *Off-label* and unlicensed drug treatment in children

Within the present work, the term *off-label* is defined as any drug use outside the terms of the product license, and the term *unlicensed* applies to drugs that are not approved by regulatory authorities, e.g the Swedish Medical Products Agency (MPA).

Drug prescribing in children has been reported to be frequently carried out in an *off-label* or unlicensed manner in hospital health care (9-16), especially in neonatal care units (16-19) (*Table 1*).

Table 1: **Studies of *off-label* and unlicensed drug treatment in hospital health care.**

Settings	Subjects (n)	Drugs (n)	*Off-label* (%)	Unlicensed (%)	Reference
Hospital care	166	862	23	14	9
Hospital care	609	2013	18	6	10
Hospital care	624	2262	39	7	11
Hospital care	132	222	26	8	12
Hospital care	74	237	19	3	13
Hospital care	237	2139	18	48	14
Hospital care	1461	4265	60		15
Hospital /Neonatal care	293	1017	44	28	16
Neonatal care	70	455	10	35	17
Neonatal care	105	525	59	16	18
Neonatal care	97	1442	47	11	19

In hospital or neonatal care studies, the proportion of pediatric *off-label* and unlicensed drug prescriptions varies widely (*Table 1*) (9-19). This variation can partly be explained by varied pediatric hospital care and the size of the study. The main difference though is probably different interpretations of the definition of *off-label* and unlicensed drug therapy, which makes it difficult to compare studies.

All studies (9-19) regarded drugs as unlicensed when they were:
not approved by a regulatory authority

modification to a licensed drug had been performed
drugs that are licensed but the particular formulations is manufactured under a special license

Furthermore, a few studies (10,14,16) regarded licensed drugs as unlicensed when the:
pediatric labelling stated that the drug was not recommended for children
contraindicated for use in children
absence of pediatric documentation was mentioned in the Summary of Product Characteristics (SPC)

The most common therapeutic groups of drugs were antibiotics, analgesics and drugs for the respiratory tract. The main reason for a drug to be classified as *off-label* was that the dose, the frequency of administration, or the age of the patient were not in agreement with the drug labelling (9-16).

In a hospital based study focusing on *off-label* use of analgesics, more than one third of prescribed drugs was regarded as *off-label* (20).

There are limited studies investigating *off-label* drug use among outpatients. The proportion of *off-label* and unlicensed prescriptions varied between 9-29% and 0.3-4%, respectively. These studies had small sample sizes and were restricted to a single general practice or a single study day (21-22).

1.4 Drug related problems in children

A drug related problem has been described as an event or circumstance involving drug therapy that actually or potentially interferes with desired outcomes (23). According to the Pharmaceutical Care Network Europe Foundation (PCNE), drug related problems are divided into 6 categories:

Adverse drug reactions
Drug of choice problems
Dosing problems
Drug use/Administration problems
Interactions
Others

Drug related problems comprise a broad set of clinical situations and can be difficult to analyse and validate. Most studies focuse only on adverse drug reactions (ADRs), and there are only a few studies that do also include other types of drug related problems. Drug related problems were found to be the cause of admittance to hospitals for children in three studies with an incidence between 3.4% to 7.9% (24-26). It has been suggested that at least every second drug related problem is preventable (24,26). Medication errors, e.g. a drug given in an improper or unintended dose or quantity, is another area in pediatric health care that is of great importance (27-29). However, this issue will not be addressed within the present work.

According to the World Health Organisation (WHO), ADRs include any *noxious and unintended drug response that occurred at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function* (30).

A serious ADR is regarded as any untoward medical occurrence that at any dose results in: *death, requires inpatient hospitalisation or prolongation of existing hospitalisation, a life-threatening reaction or persistent, significant disability or incapacity* (30).

Several prospective studies indicate that ADRs in children, especially in hospitalised children, are of great clinical relevance (28,31-36). The overall incidence of ADRs in hospitalised children has been documented to range from 2.3% to 21 %, with severe reactions accounting for about 10-12 % (31-33,35). The overall rate of pediatric hospital admissions due to ADRs varied from 1-7% (28,31,33,36). In hospitalised children, the overall incidence of ADRs varied from 3-18% (31,32). In pediatric outpatient between 1.5-9% suffered from ADR (31,32). Serious reactions occurred in almost 40% of ADRs documented in pediatric hospital admissions (31). It has been suggested that about one fifth of the documented ADRs in these studies could have been avoided by preventing e.g. medication errors or drug interactions (28,36).

The incidence of reported ADRs in children varies, propably partly due to different study settings and different sizes of study populations. However, similar rates of ADRs have been reported in different adult populations (37-41).

1.5 *Off-label* drug treatment and adverse drug reactions (ADRs)

Two prospective hospital-based studies and one community-based survey regarding the association between *off-label* drug use and the risk of ADRs have been published (42-44). In the first study, almost half of the (n=936) patients received at least one unlicensed or *off-label* drug. The incidence of ADRs was 4% among the licensed drugs and 6% among the unlicensed or *off-label* drugs (42). The second study was based on spontaneous ADR reports (n=95) from hospital care, were 25% of the reports were for medicines used *off-label* (43). In the third study, based on 39 participating physicians, nearly 20% of (n=1419) prescriptions to outpatients were regarded as *off-label,* and the incidence of ADRs (a total of 20 non-serious events) was about 1.4% for licensed prescriptions, compared with 2% for unlicensed or *off-label* drug prescriptions (44).

Inadequate labelling of pediatric drugs is often assumed to be due to the lack of scientific documentation in children. However, it has not been investigated to what extent there is available literature information concerning pediatric drug efficacy and safety outside the SPCs.

1.6 The Drug Information Centre

Drug Information Centres (DICs), are established both in Europe and the United States (45-47). In Sweden, the first centre, named the Drug Research & Information Centre (DRIC), was started at Department of Clinical Pharmacology at Huddinge Hospital in Stockholm in 1974, through a cooperation between clinical pharmacologists and information pharmacists (48). The centre is now named Karolic (Karolinska Läkemedelsinformationscentralen), is situated at the Karolinska University Hospital, has two Stockholm offices (one in Huddinge and one in Solna) and is one out of six DICs in Sweden. The DICs in Sweden offer evidence based drug information, comparable to clinical consultations, to health professionals responsible for drug therapy (physicians, midwifes, nurses and dentists). When a question is addressed to the DIC, it is registered in a database (Dataease), a literature search is performed, available information is evaluated, and often a preliminary answer is given. After an internal review and approval at a weekly staff meeting, a written answer with references is sent to the questioner (45). All new, written and approved answers are collected in a database called Drugline, which is continually updated by the DICs in Sweden, Odense Denmark and Åbo Finland (49). Drugline has existed

since the mid 1980's and now contains almost 12500 documents. Karolic-Huddinge receives between 700 and 800 questions per year. The questions mainly concern ADRs, drug interactions, drugs during pregnancy and breast-feeding and drug choice or dosing (45).

No published study on pediatric drug treatment based on data from a DIC has been found, but there are three retrospective DIC-based analyses concerning the use of drugs during pregnancy or breast-feeding (50-52). The first study was a follow-up of documented cases of trimethoprime/sulphamethoxasole use during pregnancy from the DIC at Huddinge Hospital (50). In the second and third study, questions at DICs in Italy concerning drug use during pregnancy and lactation were characterised (51,52). All three studies came to the conclusion that the DIC is an important source of evidence based information for drug treatment during pregnancy and lactation.

2 Aims of the thesis

I. To analyse the frequency and characteristics of *off-label* drug prescribing among pediatric outpatients.

II. To investigate the proportion of *off-label* drug prescribing among ADR reports concerning pediatric outpatients.

III. To investigate pediatric questions and answers (Q&A) at a Drug Information Centre regarding the characteristics of drug related problems, the extent of *off-label* drug treatment, and the prevalence of evaluated literature information in the answers, adding to the pediatric labelling of the drugs.

3 Materials and methods

3.1 Settings and subjects

3.1.1 Study I: *Off-label* drug prescribing to pediatric outpatients

The study is a retrospective analysis of pharmacy-dispensed drugs to children and adolescents less than 16 years of age regarding *off-label* prescriptions in the year 2000.

A computerised population-based prescription database produced by the National Corporation of Swedish Pharmacies encompassing the defined population of more than 1.8 million inhabitants in Stockholm County, of which almost 360 000 were less than 16 years of age, was used. In Sweden no prescription data could be individually linked at the time of the study. Therefore, the data has been analysed on an aggregated level.

The drugs were ranked by purchased volume according to the number of prescribed items. The analysis was restricted to the Drug Utilisation 90% segment (DU90%) containing those drugs that accounted for 90% of the total number of prescriptions and adherence to guidelines in this segment (53). *Off-label* drug prescribing was assessed with respect to age, formulation and route of administration. The *off-label* assessment was validated through the independent analysis of a random sample of 50 different brand names by another researcher, and was found to be identical to the initial assessment.

Furthermore, the guideline used for the adherence assessment was the list of recommended drugs (The Wise Drug List) from the local Drug and Therapeutics Committée (54).

3.1.2 Study II: *Off-label* drug prescribing and ADR reports in children

This study is based on a nation-wide survey of spontaneous ADR reports to the Medical Products Agency (MPA) in Sweden. The extent and characteristics of *off-label* prescribing were assessed among drugs included in the ADR reports. The SWEdish Drug Information System (SWEDIS) produced by the MPA was used to identify all reported ADRs in children or adolescents under the age of 16 during year 2000. In Sweden all prescribers are legally obligated to report any suspected ADRs related to drugs that are newly marketed, as well as serious, uncommon or otherwise unexpected

ADRs for all drugs. Data collection and evaluation of the ADR reports are performed by the six regional pharmacovigilance centres.

An ADR was defined according to the World Health Organization (WHO) (30). *Off-label* drug treatment was assessed on the basis of age, dose, indication, formulation, route and frequency of administration. ADR analysis and *off-label* assessment were independently performed by two researchers and found to be identical. Population and aggregated drug utilization data were obtained from Statistics in Sweden (55) and the National Corporation of Swedish Pharmacies (8), respectively.

A total of 444 ADR reports concerning children and adolescents younger than 16 years in Sweden was identified in the year 2000, 308 reports of which were vaccine related. Vaccines given to children are almost all licensed and labelled for use in the pediatric population and therefore, they were not included in the further analysis. Of the remaining 136 ADR reports, another 24 reports were excluded for the following reasons: *9 reports concerned inpatients, 7 were related to newborns suffering from an ADR due to maternal drug treatment, 7 described ADRs with unclassifiable causality, and 1 concerned an Over-The-Counter (OTC) drug*.

3.1.3 Study III: Drug related problems, *off-label* drug treatment and drug efficacy and safety documentation in pediatric DIC questions

A register of all questions and answers (Q&A) handled by the DIC at Karolinska University Hospital-Huddinge, Sweden was used as the information source for this study. All the questions are continuously registered in a local database, Dataease, which contains information concerning question date, questioner, demographic data, drug and medical history of the patient, kind of drug related problem and given answer with literature sources used.

All Q&A concerning children during a ten-year period, 1995 to 2004 were retrieved and systematically analysed. Out of a total of 6842 questions processed at the DIC from 1995 to 2004, 300 (4.4%) were documented to concern children. Further analysis was restricted to questions concerning children 15 years or younger. In total, 51 (17%) of the questions were excluded from further analysis as the question concerned: *breast-feeding and/or pregnancy, patients 16 years or older, food, chemicals or doping substances, accidental ingestion of drugs, or multiple registration of the same question*.

All questions were classified with regard to the type of drug related problems and *off-label* drug treatment. Answers relative to *off-label* drug treatment questions were analysed with respect to their content of evaluated literature information, adding to the

information given in the labelling of the drugs in the Swedish catalogue of medical products (56).

3.2 Classification

3.2.1 Drugs (Study I-III) and treatment guidelines (Study I)

Licensed drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification to the fifth level (57) and their license status was determined with The Swedish catalogue of medical products (FASS) as the primary reference source in all studies (56). Pharmacy-prepared drugs (Apotekstillverkade läkemedel) (58), contact with the manufacturer or product information provided by the MPA was used as secondary reference sources. In the first (**I**) and second study (**II**) FASS for the year 2000 was used, and in the last study (**III**) FASS corresponding to the year of the questions.

3.2.2 ADRs and other drug related problems (Study II-III)

In study **II**, each reported ADR was classified with respect to causality and seriousness. The level of causality was restricted to certain, probable or possible, using the following WHO definitions (30):

Certain: plausible time relationship to drug exposure; positive de- and rechallenge.
Probable: reasonable time sequence to drug exposure; positive dechallenge
Possible: reasonable time sequence to drug exposure; dechallenge may be lacking.

An ADR was considered serious according to the previously mentioned definition (see 1.4) (30). We also classified each ADR as a type A (pharmacological) or type B (idiosyncratic) reaction. ADR reports concerning OTC drugs or vaccines were excluded.

In study **III**, five different categories of drug related problems were used; *ADR, drug interactions, drug kinetics, drug choice and/or dosing, drug formulation and/or administration,* depending on the main objective of the DIC question (45,48).

3.2.3 *Off-label* drug treatment (Study I-III)

The *off-label* assessment was performed in all three studies by analysing the license information for included drugs with reference sources mentioned above (see 3.2.1). A drug was considered to be *off-label* with respect to age if the drug was explicitly not recommended for a certain age group. Absence of information about use of drugs in pediatric patients was classified as *off-label* with respect to both age and dose. Our *off-label* assessment was in accordance with previously used assessments (10,59). Product information regarding pediatric use in general without any age or dose specification, was considered as labelled for all age groups. If the license information was based on body weight, we transcribed it into age requirements according to FASS (56).

In study **I**, the total proportion of *off-label* drug prescribing, as well as by sex and gender, was assessed. The same assessment was performed for 12 different therapeutic groups of drugs.

In study **II**, drugs that exceeded a recommended dose by more than 20% were regarded as *off-label,* but not drugs given in less than the recommended dose.

All drugs that were not listed in our primary or secondary reference sources mentioned above were regarded as unlicensed.

3.2.4 Documentation for drug efficacy and safety in children (Study III)

The content of evaluated literature information, adding to the labelling of the drugs, was assessed and categorised for all Q&As to the DIC that regarded *off-label* drug treatment. Four different categories of information were used:

Age requirements	Information concerning age requirements for pediatric drug treatment
Dosing	Information concerning pediatric dosing recommendations
ADRs	Information concerning ADRs not mentioned in the labelling of the drug
Drug interactions	Information concerning drug interactions not mentioned in the labelling of the drug

3.2.5 Ethical considerations

None of the registers contained any references to patient identity and therefore no ethical approval was needed for these studies.

4 Results

The results are summarised in this section. For a more complete account see the separate publications **I-III** (appendix).

4.1 Drug treatment, *off-label* assessment and adherence to guidelines (Study I-III)

In the first (**I**) and second (**II**) study, antibacterials for systemic use (phenoxymethylpenicillin) and anti-asthmatics (budesonide, terbutalin) were found to be the most commonly prescribed drugs to outpatients in the year 2000, which is in agreement with previous findings (3-7). In study **III**, the most common drugs in the DIC questions were antibacterials for systemic use (erythromycin, pivmecillinam), followed by antiepileptics (carbamazepine, valproate).

In all three papers, *off-label* drug treatment in children was the main topic of interest. The first study (**I**) showed that children in primary health care in the Stockholm were prescribed about 1.8 drugs per child in the year 2000 (*Table 2*). The average proportion of *off-label* drug prescribing for all age and therapeutic groups was more than 20% within the DU90% segment (*Table 2*).

***Table 2 Off-label* drug use and characteristics of study I-III.**

Study	Subjects (n)	Drugs (n)	*Off-label* (%)
I	357 784	575 526	21 (Based on number of prescriptions, n=575 526)
II	112	125	42 (Based on number of ADRs, n=158)
III	249	298	31 (Based on number of DIC questions, n=249)

In the second study (**II**), more than 40% of reported ADRs were related to drugs prescribed in an *off-label* manner (*Table 2*) and the most common reason for the *off-label* classification was a non-approved age and/or dose. In the third study (**III**), we found that more than every third question to the DIC concerned *off-label* drug treatment (*Table 2*).

The *off-label* proportion was highest among adolescents (10-15 years of age) and very young children (less than one year of age) in the first study (**I**). In study **III**, questions were most frequently asked about young children. However, the *off-label* proportion as well as answer content of evaluated information adding to the labelling of the drugs was highest among adolescents (*Figure 2*).

Figure 2: **Number of Q&A classified as within-label, *off-label* and/or unlicensed with or without answers containing evaluated literature information, adding to the labelling of the drugs. Data was based on 172 questions with known age.**

The *off-label* proportion varied considerably between therapeutic groups of drugs. Topically administered drugs (dermatologics, otologics, ophthalmologics) were prescribed to more than 70% in an *off-label* manner among outpatients in our first paper (**I**) (*Table 3*). Next to topical drugs, psychotropic drugs were found to have the highest extent of *off-label* prescribing, with every third prescription classified as *off-label (Table 3)*.

Table 3 **Number of prescription items in therapeutic group of drugs, according to the Anatomical Therapeutic Chemical (ATC) classification system, most commonly classified as *off-label* prescribing in Study I.**

Therapeutic group	ATC group	Prescription items (n)	*Off-label* (%)
All groups		575 526	21
Dermatologics, otologics, ophalmologics (hydrocortisone, propylene glycol, fusicid acid)	D, S01-03	121 058	76
Psychotropics (risperidone, thioridazine, amphetamine, SSRIs)	N05/06	2544	31
Analgesics (codeine, sumatriptan, dextropropoxyphene)	N02	8330	26
Rhinologicals (natriumcromoglycate, budesonid with nasal administration)	R01	17 626	22

Among the ADR reports in the second study (**II**) and among the DIC questions (**III**) almost all used drugs were systemically administered.

The proportion of *off-label* related ADRs was highest for rhinologicals or antitussives (fluticasone), gastrointestinal (omeprazole) and cardiovascular (clonidine) drugs in study **II**.

In the third study (**III**), psychotropic drugs (e.g. risperidone, SSRI) was the most common drug class among *off-label* questions, followed by Non Steroid Anti-Inflammatory Drugs (NSAIDs) (indomethacin, ketorolac) and immunosuppressive agents (azathioprine, mycophenolic acid). All of these drugs had an *off-label* proportion of about 70% among the DIC questions. We found that certain therapeutic drug groups almost completely lacked pediatric labelling, such as antithrombotic drugs (Study **III**)

The main reasons for *off-label* classification of drugs in all studies (**I-III**) was found to be lack of pediatric labelling, or the absence of drug safety or efficacy studies performed in children, rather than explicit prohibits of pediatric use.

4.2 ADRs and other drug related problems (Study **II-III**)

In the final analysis (Study **II**) 112 ADR reports corresponding to 158 ADRs were included. *Off-label* drug prescribing in study **II** were more often associated with serious (51%) than non-serious (39%) ADR reports. In study **II,** reported ADRs were three times as often classified as type B (idiosyncratic) than type A (pharmacological) reactions.

Adverse drug reactions, drug choice or dosing in children were most common in DIC questions, both those regarded as *off-label* or not (Study **III**) (*Table 4*).

***Table 4*: Proportion of drug related problems, *off-label* drug treatment and evaluated literature information, in addition to the labelling of the drugs, in Q&A to a DIC. Total number of questions during the whole period was 249.**

Drug related problem	All [n (%)]	*Off-label* [n (%)]	Literature information [n (%)]
All	249 (100)	78 (31)	41 (16)
Adverse drug reactions	91 (37)	21 (27)	8 (20)
Pediatric drug choice and dosing	85 (34)	32 (41)	21 (51)
Drug interactions	31 (12)	14 (18)	6 (15)
Drug formulation and administration	25 (10)	5 (6)	1 (2)
Pediatric drug kinetics	17 (7)	6 (8)	5 (12)

Among the most common ADRs, in ADR reports and/or DIC questions, were symptoms from the central nervous system, skin reactions, gastrointestinal, and hematological symptoms (*Table 5*).

***Table 5*: Proportion of the most common different kinds of ADRs in study II and III.**

Adverse drug reactions	**Study II [n (%)]**	**Study III [n (%)]**
All	158 (100)	91 (100)
Central nervous system disorders	54 (34)	17 (19)
(sleeping disorders, aggressiveness, headache, paresthesia)		
Skin reactions	29 (18)	10 (11)
(urticaria, exanthema)		
Gastrointestinal symptoms	19 (12)	3 (3)
(nausea, vomiting, abdominal pain)		
Hematological symptoms	5 (3)	14 (15)
(leucopenia, thrombocytopenia, bleeding complication)		

4.3 Pediatric documentation of drug efficacy and safety (Study **III**)

In the third study (**III**), more than half of the answers to *off-label* Q&A were found to contain evaluated pediatric drug information, in addition to the information available in the Swedish catalogue of medical products (FASS).

Among these questions, the most common drug related problem was pediatric choice of drug or dosing (*Table 4*). Scientific papers from Medline (PubMed), Drugline and medical handbooks were the most common sources for pediatric documentation, which consisted mainly of documentation of treatment concerning pediatric age requirements and dose recommendations. Pediatric documentation concerning drug efficacy and safety adding to FASS was found in several age groups, but mainly in adolescents (*Figure 2*).

Within the DU90% segment, 61% of prescription items in Study **I** corresponded to drugs that were recommended in the local treatment guidelines.

5 Discussion

5.1 Findings and interpretations

5.1.1 *Off-label* drug treatment

Every fifth pediatric prescription in outpatients was classified as *off-label*, which is in between the documented *off-label* proportion in previously published outpatient studies (*Table 6*) (21,22,60-65), but lower than in hospital care (66).

***Table 6*: Studies of *off-label* and unlicensed drug prescription in primary health care.**

Settings	Subjects	Drugs (n)	*Off-label* (%)	Unlicensed (%)	Reference
Outpatients	989	2522	29	4	21
Outpatients	1175	3347	11	0.3	22
Outpatients	455661	1592006	13	Not studied	60
Outpatients	1802	1925	15	<1	61
Outpatients	19283	68019	23	17	62
Outpatients	6141	17453	14	15	63
Outpatients	**357784**	**575526**	**21**	**Not studied**	**Study I**
Outpatients	18043	66222	21	17	64
Outpatients	167865	Not specified	26	Not studied	65

None of the previous *off-label* prescription studies in outpatient studies linked prescription data to any clinical outcome, nor did they evaluate the quality of the prescribing. Also, several of the previously published studies were limited by a small sample size.

Our finding that there was a high proportion of *off-label* drug treatment in ADR reports in outpatients is not necessarily generalised to all children treated with drugs, especially since the spontaneous reporting system is subject to substantial underreporting (67,68). Although there is a known general underreporting of ADRs it is possible that physicians are more prone to report side effects occurring during *off-label* treatment.

The *off-label* proportion in study **II** is nearly twice as high as was previously reported in a hospital setting (43).
A recent publication, including both pediatric in- and outpatients, further supports that drugs used outside the Summary of Product Characteristics (SPC) are possibly more often associated with ADRs than drugs used according to the SPC (69).

Adolescents and/or children less than two years of age were found to be most frequently prescribed *off-label* drugs by us and by other investigators (21,60,63,64).

Topically administered drugs were often classified as *off-label* and made up more than 70% of all prescribed drugs to outpatients in our Study **I**. A high proportion of *off-label* prescribing of topical drugs has also been found by other investigators (21,60,62,63). This highlights an area were there is a need for further clinical studies. The fact that most ADR reports concern systemically administered drugs is probably due to a belief that these drugs have the potential to be more harmful and give rise to more severe ADRs. However, the potential risks of topical drugs in children needs to be further studied.

Excluding topical drugs, the *off-label* proportion of systemically prescribed drugs in outpatients was 6% in Study **I**. Among these, psychotropic drugs had the highest proportion of *off-label* use. Similar results were reported by another investigator (60). Prescription data from an individually linked prescription register, available at the National Board of Health and Welfare in Sweden, indicate that only a small fraction of depressed children or adolescents (5-19 years) received antidepressant medication in 2005 (70). However, psychotropic agents have a potential therapeutic use in the pediatric population, in particular in adolescents, and therefore further studies are warranted.

The Wise Drug List is a general treatment guideline for all patients and lack specific recommendations for pediatric patients. Nevertheless, we found that the adherence to The Wise Drug List was high among pediatric drug prescribers. Several of the recommended drugs, however, were classified as *off-label* for the use in children. Similar therapeutic guidelines are available in e.g. Denmark and England (5,71). In England, therapeutic guidelines recommended 86 drugs for treatment in children, but only half were licensed for use in children (71).

5.1.2 Drug related problems

Considering the fact that about 1.7 million Swedish children or adolescents receive 1.6 prescription items per year, the number of ADR reports (n=112) for pediatric outpatients in the year 2000 was low. In a 15-year survey of ADR reports in Sweden approximately the same annual reporting rate for non-vaccine related reports were documented (72). However, it is well known that the spontaneous reporting system is subject to substantial under-reporting (67,68). O*ff-label* prescribing were more common among serious ADR reports (51%) than non-serious (39%) in the second study (**II**). However, the majority of ADR reports are non-serious reports (87%) (72). Therefore it is difficult, based on our register data, to evaluate whether serious ADRs would occur more often during *off-label* than licensed drug treatment among all treated outpatients. No similar published paper have studied serious ADRs and the relation to *off-label* drug use.

The number of subjects or questions concerning ADRs was too low and perhaps selected in study **II** and **III** to analyse if *off-label* drug use is in fact associated with an increased risk of ADRs or not.

The most frequently reported ADRs (*Table 5*) were in accordance with a recently published paper concerning *off-label* drugs in ADRs reports and the pattern of the overall non-vaccine related ADRs reported in Sweden (69,72).

Drug related problems presented in Q&A from the DIC did not always relate to past events. Sometimes the questioner asked prior to prescribing a drug. The DIC, therefore, has an important role in increasing the scientific basis of *off-label* drug use and thereby hopefully in preventing drug related problems in children. It has also been shown that the DIC has a cost-saving potential in preventing ADRs (73).

5.1.3 Pediatric documentation of drug efficacy and safety

Lack of pediatric labelling and pediatric safety or efficacy studies was noted by us, and by other investigators, as the most common reason for *off-label* drug use (60,62). The o*ff-label* drug treatment has been demonstrated to be substantial, both in primary and

hospital health care. However, in the third study (**III**), we found that in half of all Q&A regarded as *off-label,* additional pediatric documentation outside the Swedish catalogue of medical products (FASS) was available from scientific publications, and from other drug therapy literature sources. One problem with pediatric *off-label* drug treatment is therefore a lack of harmonisation between the existing literature evidence and drug licenses. Published articles concerning pediatric drug treatment in PubMed are of course available. However, it is not feasible for all physicians responsible for pediatric prescribing to conduct a literature search themselves every time they prescribe *off-label* treatment to children. They are in need of readily available, processed, evaluated and continuously updated information concerning pediatric drug treatment. In individual patient cases, this can obviously be provided by the DICs. However, there is also a need for e.g. expert groups devoted to pediatric drug treatment within the organisation of the Drug and Therapeutics Committées, that could continuously process new literature data and convey relevant information to physicians in both hospital and primary health care.

5.2 Methodological considerations

Our three studies are not comparable as to the *off-label* proportion due to the different settings (*Table 2*). However, all three studies demonstrate that *off-label* drug use is of great concern in both primary and hospital health care.

There are no statistical calculations in the included papers. In the first paper (**I**), the prescription data presented include all purchased prescriptions for children in Stockholm County (i.e. the complete population is studied, and not a sample) and therefore no significant calculations are needed. Unfortunately, at the time of the study no linkage of individuals to prescription data was possible, and therefore, incidence or prevalence data could not be provided. In the second (**II**) and third (**III**) papers, the numbers are too small and the data is perhaps not representative of the whole pharmacologically treated pediatric population to allow statistical calculations of the risk for ADRs due to *off-label* treatment or the true frequency of *off-label* drug treatment.

Register based data can have several limitations. All registers used in our studies can be subject to bias such as whether the patient really has ingested their purchased prescription or not or if reported ADR or drug related questions asked to the DIC is

representative for the overall pharmacological treated pediatric population. In register studies there are usually not any controls for the exposure of interest and the data collection can be selected e.g. more *off-label* ADR are reported and more questions are asked to the DIC regarding *off-label* than licensed drug treatment. Therefore these register studies are rather hypothesis or signal generating, and do not allow conclusions as to causal relationships (74).

In our first study (**I**) we focused on those drugs accounting to 90% of the prescription (DU90%) for practical reasons. The remaining 10% of the drugs prescribed are used more rarely and perhaps even more often lack pediatric labelling. Therefore, use of DU90% in this study could have contributed to an underestimation of the *off-label* proportion of outpatient drug prescribing.

It has not yet been established whether *off-label* drug treatment in children increases the risk of ADR or not (75). One area, which is most interesting in pediatric health care, is whether *off-label* drug use is associated with an increased frequency of drug related problems. Here ADRs, as well as drug choice, dosing and formulation will be included. However, drug related problems are more difficult to study compared to ADR.

The proportion of drugs assigned *off-label* status varied between our first two papers (**I,II**) compared with similar studies. In the second paper (**II**), non-approved age/and or dose was the most common *off-label* category, but in other studies indication and drug interactions was most common (44,69). This difference is partly due to different number of *off-label* categories among studies. Every fifth prescription was classified as *off-label* in study **I**, which may not be a high number, particularly if topical drugs are excluded. The use of fewer *off-label* categories probably results in an underestimation of the *off-label* proportion. The reason for using different *off-label* categories is often due to limitations in the available data. E.g. in study **I** and **III**, a dose assessment was not possible, since the dose was not known at all in the first study (**I**) and only in a few questions in the third study (**III**).
If we had been able to analyse the dose in relation to the *off-label* assessment in study **I**, the *off-label* proportion might have been higher due to either too low or too high pediatric doses (76).
Another reason for variation of the *off-label* proportion is the definition of *off-label* and unlicensed status of drugs. Some researchers regarded licensed drugs that had no

information on pediatric use in their SPC as unlicensed instead of *off-label*. This makes it difficult to compare different *off-label* proportions. However, the proportion of *off-label* prescribing to pediatric outpatient in Sweden is probably not less than 20%.

5.3 Future studies and challenges

Although the overall proportion of *off-label* drug treatment is substantial, this is not all together synonymous with unsafe and/or incorrect pediatric treatment. It has been shown that physicians are well aware of the lack of pediatric labelling (77). One reason for treatment with drugs in an *off-label* manner is probably that pediatricians have clinical experience that supports *off-label* drug use. Naturally, it is of great importance that this experience, as far as possible, is documented through clinical studies and scientific reports. Another reason for *off-label* drug use can be that therapeutic guidelines, as e.g. the Wise Drug List, giving recommendations that are based partly on scientific knowledge outside the SPC, are applied in pediatric drug treatment.

To improve the documentation on drug efficacy and safety in children, attempts have been made by medical authorities (US Food and Drug Administration and European Agency for the Evaluation of Medical Products) to stimulate the drug industry to perform pediatric clinical trials and submit pediatric labelling information (78). These attempts have included some economic incentives regarding patent protection (78). However, no major impact on pediatric labelling for drugs approved from these initiatives has been documented (79-81). Furthermore, these initiatives concern new drugs and not drugs that are already on the market, or drugs that do not have a patent. A more efficient and clear legal framework that encourages the pharmaceutical industry to carry out more clinical studied in children on both new and old drugs is highly warranted. Another desirable initiative is that health care and drug regulation authorities provide economic incentives to the medical academia to perform studies on the efficacy and safety of drugs that are of special concern in the pediatric population.

The lack of scientific documentation does also, and perhaps to an even larger degree, apply to OTC drugs and herbal remedies. It has been suggested that children are subject to substantial self-medication by their guardians with these types of pharmaceuticals (25,82). Greater efforts and resources should be devoted to research

in this area, primarily to evaluate the possible hazards of OTC drugs and herbal remedies in children.

In a pilot study on children admitted to a pediatric hospital it was discovered that, in addition to *off-label* treatment, drug use in children was poorly documented in patient medical records (data on file). We plan to expand this pilot study by performing a questionnaire or interview study on children admitted to hospitals, focusing mainly on *off-label* drug treatment, drug related problems and their preventability, and discrepancies between documented pediatric drug treatment in the patient medical records and information given by the parents.

Clinical trials highlighting drug safety can in many cases increase the knowledge about the safety of new or old drug substances. However, clinical trials may have limitations, such as a small and homogenous study population and limited duration and thereby have a low external validity. Clinical trials can also be more difficult to perform in the pediatric population due to ethical concerns. An alternative approach is to perform pharmacoepidemiological studies as a complement in this area, and/or to develop a post-marketing surveillance network for pediatric drug treatment. Children apparently suffer from ADRs in approximately the same degree as do adults. However, ADRs in children may not have the same characteristics or incidence as in adults (83). Untoward effects of drugs can e.g. influence the neurological and/or somatic development of a growing child. ADRs relating to neurodevelopment may not bee apparent for many years and can thus be difficult to detect. These ADRs can preferable be analysed in a pharmacoepidemiological study. The new Swedish individually linked prescription register also makes it possible to perform better pharmacoepidemiological studies regarding e.g *off-label* drug treatment. Another alternative approach is population pharmacokinetics studies, where you can theoretically, through modeling, estimate pediatric doses based on data from clinical trials in adults (84).

One way of increasing the knowledge of pediatric prescribers about drug effects and safety in children is to produce specific pediatric therapeutic guidelines that are updated regularly by pediatric expert groups. Recently, a British National Formula for Children

(BNFC) (www.bnfc.org) was launched, to provide information on pediatric prescribing beyond what is required by the marketing authorisations.

A future challenge is to continuously spread existing knowledge concerning pediatric drug treatment to all physicians responsible for pediatric patients, through for instance pediatric expert groups. Modern information technology and e.g. internet-based services, such as the webpage of the Stockholm Drug and Therapeutics Committée (www.janusinfo.se), can be of good use for this purpose. Nevertheless, there is still a large need for increased evidence from scientific studies in the field of pediatric drug treatment.

6 Conclusions

Off-label drug prescribing, especially of topical drugs, to pediatric patients in primary health care is substantial, and although the proportion of *off-label* prescriptions is smaller than in hospital care, the absolute number can be assumed to be much higher.

Off-label prescribing was a common phenomenon among drugs reported to have caused an ADR in pediatric outpatients, and was more often found in serious than non-serious ADR reports.

Pediatric Q&A to a DIC often concerned *off-label* drug treatment, especially questions about drug choice or dosing. Although pediatric labelling is lacking, documentation retrieved through literature searching concerning pediatric drug efficacy and safety outside the Swedish catalogue of medical products (FASS) was available in more than half of the *off-label* questions.

Since available evidence based information concerning pediatric drug treatment from clinical trials and drug producers are lacking, other sources such as DICs or pediatric therapeutic guidelines for drug treatment are needed. A future challenge is to develop drug surveillance programs in the field of pediatrics to reduce and prevent drug related problems and increase the knowledge of drug efficacy and safety in children.

Off-label pediatric drug prescribing remains a public health concern and clinical trials in children as well as careful post-marketing surveillance are warranted.

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