

# Off-label drug use among hospitalised children: identifying areas with the highest need for research

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Received: 6 August 2007 / Accepted: 9 January 2008  
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**Abstract** *Objective of the study* To analyse the off-label use of drugs on a paediatric ward in Germany, and to identify domains of pharmacotherapy with the highest need for research concerning off-label use in children. *Setting* A prospective observational study was conducted on a paediatric ward in Duesseldorf in Germany between January and June 2006. *Method* Data about patients, diagnoses and prescribed drugs were collected from the prescription records and the discharge letters. Diagnoses were classified in groups by means of the International Classification of Diseases. Drugs were grouped according to the Anatomical Therapeutic Chemical Classification system. We compared the off-label prescriptions with those on the list of paediatric needs and priority list established by the European Medicines Agency (EMA). *Main outcome measure* Off-label use was defined due to age, indication, route of application and dose. *Results* The study included 417 patients. We analysed 1,812 prescriptions representing 211 different drugs. In total, 253 patients (61%) received at least one off-label prescription. Of all analysed prescriptions, 553 (31%) were off-label. The percentage of off-label prescriptions among the five most frequently prescribed drug groups were as follows: 60% cardiovascular drugs (CV: 129/216), 42% anti-infectives (AI: 190/449), 30% drugs for respiratory system (RS: 100/335), 25% drugs for alimentary tract and metabolism (AM: 67/269)

and 3% analgesics and antipyretics (AA: 8/264); with 17 drugs, the cardiovascular drugs also showed the highest number of different off-label prescribed drugs due to age: AI: 14; AM: 11; RS: 5; AA: 1. In addition, there was a nearly complete overlap between the identified off-label prescriptions in cardiovascular drugs and those listed by the EMA to be prioritized for urgent research in Europe. *Conclusion* Cardiovascular drugs are a domain of pharmacotherapy, with a large need for research in paediatrics. The results of our study can guide the researcher to future trials on off-label prescriptions such as cardiovascular drugs, especially due to the fact that the identified off-label prescribed drugs in this group are also mentioned by the EMA to be prioritized for paediatric research.

**Keywords** Off-label use · Cardiovascular drugs · Clinical studies · Children · EMA · Germany

## Impact on practice

- Our results suggest ongoing off-label prescribing among pediatric inpatients in Germany.
- Cardiovascular drugs are the most often off-label prescribed drugs in pediatric inpatients.
- The results of our study can guide the researcher to future trials on the off-label prescribing in cardiovascular diseases.

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## Introduction

Previous studies in Europe and the U.S. had shown that children in hospitals frequently took prescriptions that were either not registered, i.e. unlicensed, or outside the terms of

their license, i.e. off-labeling [1–4]. Many unlicensed drugs are drugs which are not available in a paediatric formulation and have to be modified either to obtain the suitable dose or to make the drugs easier to be swallowed by children. The reason for off-label use among children is that the drug is prescribed at a different dose, for a different indication, by a different route of application or for an age group for which the drug is not licensed [1]. Considerable problems are related to the off-label use in paediatrics: It is not only associated with a higher rate of adverse drug reactions [5, 6], but also with inefficacy of drug treatment in children [7]. Both problems can result from the influence of developmental changes on the pharmacokinetics (PK) [8, 9] and pharmacodynamics (PD) of drugs [7]. Age dependent changes in physiological factors in children and adolescents such as gastric acidity, clearance and drug receptor expression make the data extrapolated from clinical studies in adults inappropriate for children, and demonstrate a large need for paediatric clinical trials and the need to develop appropriate drug formulations for children [10]. Another important aspect concerning off-label use among children necessitates us to urgent research in this field: In contrast to adults [11], the off-label use among children cannot be switched to an authorised alternative drug simply because often there is none. This might be explained by the lack of specific paediatric labelling: Only one third of all drugs authorised by the European Medicines Agency (EMA) between 1995 and 2005 were approved for children [12].

With regard to these facts and ethical reasons, a number of interventions were supported by the EU-parliament and the EMA to increase the number of paediatric studies and the number of licensed drugs for children. The new EU-regulation on paediatric drugs will motivate the pharmaceutical companies to provide paediatric data on newly approved drugs and those still covered by a patent [13]. For the off-patent drugs, i.e. those not covered by a patent or a supplementary protection certificate, the EMA established a list of off-patent drugs and encouraged paediatric studies onto these listed drugs [14].

### Aim of the study

Most of the previous studies on off-label use among children suggested the need to test the off-label prescriptions on children in order to provide more information about off-label use in paediatrics and to increase the number of drugs available for paediatric use [3, 15]. This should help to ensure the efficacy and the safety of drugs prescribed to children. The objective of our study was to analyse the off-label use in a paediatric ward in Germany and to identify domains of pharmacotherapy with the highest need for research concerning the off-label use among children.

### Methods

A prospective observational analysis was performed on the paediatric pneumology and cardiology ward at the University Hospital of Düsseldorf in Germany. Prescription records of all patients admitted between January and June 2006, regardless of their ages, were collected. We used the electronic prescribing system “Theriak<sup>TM</sup>” to archive the patients’ data and their prescriptions. For each patient the following parameters were collected: Date of birth, height, weight and details about the prescriptions such as dose, dose frequency and route of application. The diagnoses were obtained from the discharge letters and classified by means of the International Classification of Diseases (ICD-10 German modification) [16]. We excluded patients whose data lacked discharge letters or those with no information about the age or the weight when weight was required, to calculate the dose of the prescribed drugs. The prescriptions of intravenous nutrition, inhaled 0.9% sodium chloride and subcutaneous or intravenous administered heparin were excluded.

The study population was subdivided according to the EMA age classification: neonates (0–27 days), infants (28 days–23 months), children (2–11 years), adolescents (12–18 years) and adults (>18 years). Drugs were coded by means of the Anatomical Therapeutic Chemical Classification (German ATC-Classification) and grouped in the following: anti-infectives (ATC-Code: J, A07, D01 and S01), respiratory system (R), analgesics and antipyretics (N02 and M01), alimentary tract and metabolism (A without A07), cardiovascular system (ATC-Code: C and B01), systemic hormone preparations (H), blood and blood forming organs (B without B01), dermatologicals (D without D01), nervous system (N without N02), antineoplastic and immunomodulating agents (L) and various (V) [17].

The off-label prescriptions were categorised according to a hierarchy; first, the prescriptions were analysed due to age, i.e. drugs with no paediatric information or prescribed in an age group, for which the drug was not licensed. Afterwards, the residual prescriptions were classified due to indication, then due to route of application, and finally due to dose. An off-label prescribed drug can’t be classified in more than one classification. Drug information was obtained from the Official Summary of Product Characteristics ([www.fachinfo.de](http://www.fachinfo.de)) and the Pharmaceutical Index for Germany (<http://www.rote-liste.de>). We compared our results with the list of paediatric needs and priority list established by the EMA [14, 18].

Like some previous studies [3, 19], we classified the drugs that had no paediatric information as off-label prescriptions due to age. This differs from the classification of other studies, which had classified such prescriptions as unlicensed drugs [20]. Furthermore, our study was not designed to

analyse the unlicensed use of drugs with respect to the modification of formulation.

### Data analysis

Frequencies and percentages were used to summarize categorical variables of patients and prescriptions. The mean (range) was used to summarize the number of prescribed drugs for every patient, whereas the median (range) was used to summarize the age of patients, and the average strength of off-label prescription among the cardiovascular drugs.

### Results

The study included 417 patients. Of these, 237 (57%) were male. Patients' ages ranged from 1 day to 40 years (median 3.6 years). There were 30 (7%) neonates, 142 (34%) infants, 153 (37%) children, 69 (17%) adolescents and 23 (6%) adults. Infections (ICD-10: A00-B99; J00-J22; T80-T88) were the main reason for the admission to hospital in 184 patients (44%), followed by cardiovascular diseases (ICD-10: I00-I99; Q20-Q28) in 68 patients (16%) and oncologic, haematologic and immunologic diseases (ICD-10: C00-C97; D50-D90) in 51 patients (12%).

We analysed 1,812 prescriptions representing 211 different drugs. The mean number of prescriptions was 4.3 per patient (range: 0–23). The five most frequently prescribed drug groups were the following: Anti-infectives, drugs for the respiratory system, drugs for the alimentary tract and metabolism, analgesics and antipyretics, and cardiovascular drugs. The number and percentage of prescriptions for these drug groups are shown in Table 1.

Not a single drug that had no license in Germany was used. We found that 253 out of 417 patients (61%) received at least one off-label prescribed drug. On the level of prescriptions, 553 out of 1,812 prescriptions (31%) were off-label. Of these, 216 (39%), 170 (31%) and 167 (30%) were off-label due to dose, indication and age respectively.

Table 1 illustrates the status of off-label use among the five most frequently prescribed drug groups. The

cardiovascular drugs had the highest percentage of off-label prescriptions, where 34% of these drugs were off-label due to age. Table 1 does not present any off-label prescription due to route of application, since all drugs that were administered by a route of application not included in the license were already considered as off-label prescriptions due to indication. In addition, there was no drug, that was prescribed off-label due to age, and at the same time administered by a route of administration not included in the license.

In Table 2, we present the number of different prescribed drugs and the number of different off-label prescribed drugs due to age among the five most frequently prescribed drug groups. The cardiovascular drugs were associated with the highest number of different off-label prescribed drugs due to age (17 drugs). A list of 21 cardiovascular drugs, which were prescribed in an off-label manner, was established. These drugs were compared with those included in the list of paediatric needs and priority list of the EMEA, and are presented in Table 3. Eight of these 21 cardiovascular drugs were prescribed to at least three different patients and were analysed with regard to the average strength given to the children (Table 4).

### Discussion

Within the study population, the cardiovascular drugs had not only the highest percentage of off-label prescriptions, but also the highest number of different off-label prescribed drugs due to age, compared with the other analysed drug groups. Our study provides for the first time a close analysis of the off-label use of cardiovascular drugs in paediatric inpatients in a western European country. We identified 21 different off-label prescribed drugs among cardiovascular prescriptions, listed in Table 3, including beta blockers, diuretics, calcium-channel blockers, antiarrhythmics, vasodilators and antithrombotic agents. Most of the drugs in our list were also recognised by the EMEA, either in the list of paediatric needs or in the priority list of off-patent drugs, which reaffirm that these off-label prescriptions are not only common in Germany but also in other European countries.

**Table 1** Status of off-label use among the five most frequently prescribed drug groups (number of total prescriptions = 1,812)

	Number of prescriptions (%)	Off-label prescriptions			
		Total number (%)	Due to dose (%)	Due to indication (%)	Due to age (%)
Cardiovascular drugs	216 (12)	129 (60)	19 (9)	38 (17)	72 (34)
Anti-infectives	449 (25)	190 (42)	86 (19)	72 (16)	32 (7)
Respiratory system	335 (19)	100 (30)	75 (22)	16 (5)	9 (3)
Alimentary tract and metabolism	269 (15)	67 (25)	11 (4)	27 (10)	29 (11)
Analgesics and antipyretics	264 (15)	8 (3)	6 (2)	0 (0)	2 (1)

**Table 2** Number of different off-label prescribed drugs due to age among the five most frequently prescribed drug groups

Drug group	Number of different prescribed drugs	Number of different off-label prescribed drugs due to age
Cardiovascular drugs	28	17
Anti-infectives	55	14
Alimentary tract and metabolism	34	11
Respiratory system	20	5
Analgesics and antipyretics	7	1

Focusing on the list of off-label cardiovascular prescriptions, it is obvious that off-label use among children differs markedly from adults and that there is an urgent need to concentrate the clinical research on the use of these drugs. Until now, there is no  $\beta$ -receptor blocker approved for paediatric use on the German market, despite their common administration. Moreover, there is no calcium-channel blocker with exclusively vasodilating properties, for example nifedipine or amlodipine, with a paediatric marketing authorisation in Germany. Studies on some drugs in our list already proved that age dependent changes in physiological factors in children affect the PK and PD and make dosing in children profoundly different from

**Table 3** Off-label prescriptions in cardiovascular drugs in comparison with EMEA-lists [14, 18]

Off-label prescriptions University Düesseldorf	Indication	EMEA Lists	
		Priority off-patent [14] <sup>a</sup>	Paediatric needs [18] <sup>a</sup>
Bisoprolol	Heart failure	+ <sup>b</sup>	–
Carvedilol	Heart failure	+	+
Metoprolol	Angina pectoris	+ <sup>b</sup>	+ <sup>c</sup>
Nebivolol	Heart failure	+ <sup>b</sup>	–
Propranolol	Arrhythmias, heart failure, portal hypertension	+ <sup>b</sup>	+ <sup>c</sup>
Spirolactone	Heart failure	+ <sup>b</sup>	+
Potassium canrenoat	Heart failure	–	–
Furosemide	Forced diuresis	+ <sup>c</sup>	+ <sup>d</sup>
Hydrochlorthiazide	Heart failure	+	+
Nifedipine	Hypertension	+	+
Amlodipine	Hypertension	+	+
Amiodarone	Arrhythmias	+	+
Sotalol	Arrhythmias	+	+
Isosorbide dinitrate	Hypertension	–	–
Glyceril trinitrate	Angina pectoris	+ <sup>b</sup>	–
Sildenafil	Pulmonary hypertension	–	+
Phenoxybenzamine	Hypertension	–	–
Aspirin	Prevention of thrombosis, Kawasaki syndrome	–	+
Phenprocoumon	Prevention and treatment of thrombosis	–	+
Enoxaparin	Prevention and treatment of thrombosis	–	+
Urokinase	Thrombotic events	–	+

<sup>a</sup> +, listed by EMEA; –, not listed by EMEA. <sup>b</sup> The mentioned indication is hypertension; <sup>c</sup> Hypertension and heart failure; <sup>d</sup> Hypertension, heart failure and oedema; <sup>e</sup> Hypertension and Arrhythmias

**Table 4** The average single dose for off-label prescriptions among the cardiovascular drugs

Drug	Number of prescriptions	Route of administration	Average single dose (mg) (range)
Spirolactone	20	Oral	7.5 (2.5–100.0)
Aspirin	16	Oral	29.0 (8.0–100.0)
Furosemide	9	Intravenous	20.0 (10.0–60.0)
Phenprocoumon	8	Oral	1.5 (0.5–3.8)
Propranolol	8	Oral	11.3 (1.0–40.0)
Enoxaparin	7	Subcutaneous	30.0 (5.0–50.0)
Amiodaron	5	Oral	150.0 (15.0–200.0)
Sildenafil	4	Oral	3.5 (2.8–8.0)

adult dosing, to be effective and to avoid side effects [21, 22]. The individual drugs listed from the EMEA are a result of a review process from European experts in the field of paediatric pharmacotherapy. Therefore, the nearly complete overlap of substances between the German list from the children's hospital of Duesseldorf and the EMEA list further substantiates the necessity of performing clinical trials on these drugs for the children in Europe.

Concerning the cardiovascular drug group, only one study conducted by Bajcetic et al. in Serbia, has so far investigated the off-label use among paediatric cardiovascular inpatients until now [23]. They showed that 44% of all cardiovascular drugs used in paediatric inpatients were prescribed off-label and that the main reason for off-label use (39% of these prescriptions) was due to dose. In contrast to Bajcetic et al., the majority of off-label use in the present study was not due to dose but due to age, with 34% of all cardiovascular drugs. This difference might reflect differences in the national approval status and prescribing habits.

In the present analysis, 31% of all prescriptions were used off-label. This is in accordance with two German off-label analyses earlier in 2004 and 2000 with 26% and 37% off-label prescriptions respectively [1, 24]. This reflects an ongoing use of off-label prescriptions among paediatric inpatients. Although the off-label use in paediatric outpatients in Germany was recorded lower with 13.2%; more than 50% of the cardiovascular drugs prescribed for the children were off-label [19]. The unlicensed and off-label use of cardiovascular drugs among paediatric outpatients in the Netherlands even reached 74.7% [20]. However, the reason for this high rate is the combined analysis of off-label and unlicensed drug use in this study, particularly with regard to the modification of commercially available formulations. On the one hand, this underlines the necessity for studies on the safety and efficacy of cardiovascular drugs in children, and on the other hand, indicates the need for the development of adequate paediatric formulations of these drugs.

A lot of peroral drugs in our study had to be prepared in the hospital pharmacy in the form of capsules. They were then dispensed or dissolved in water by the nurses directly before the administration. Concerning the list of off-label prescriptions among the cardiovascular drugs, data presented in Table 4 show that a lot of cardiovascular drugs given peroral had to be administered in a very small dose. Therefore, they had to be crushed and divided into capsules with the suitable strength. Crushing the tablets had already proved to result in inaccurate dosage and unknown bioavailability of the drugs [25], demonstrating the need to provide the domain of paediatric cardiology not only with clinical studies about safety and efficacy but also to develop paediatric-appropriate formulation of the drugs.

Despite the clear results of the presented study, there are potential limitations that should be addressed: In addition to the paediatric patients, the study population included 6% adults, which could result in an underestimation of the rate of off-label use due to age. Although we analysed prescriptions covering a wide spectrum of diseases in children, some disease areas, such as diseases of the nervous system and the skin, were not well represented, thus demonstrating the need for further analyses on prescriptions covering other disease areas in children.

## Conclusion

The high rate of off-label use of cardiovascular drugs in both paediatric in- and outpatients in Europe, in addition to the EMEA recommendations clearly reveal the need for prioritising clinical trials in the paediatric area, especially in cardiovascular diseases. We listed 21 off-label prescribed cardiovascular drugs, most of which have no other authorised alternatives currently available for the indications in children. Furthermore, these drugs cover a spectrum of potentially life-threatening diseases in children, such as heart failure, arrhythmias and thrombosis. Therefore, these drugs should have the priority of intensive research in the near future.

**Funding** Financial support for L. H. is provided by the Syrian Ministry of Higher Education.

**Possible conflicts of interests** None.

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