

# Drug related problems and *off-label* drug treatment in children as seen at a drug information centre

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**Abstract** The aim of this work was to analyse the characteristics of *Questions and Answers* (Q&As) at a drug information centre (DIC) regarding drug related problems and *off-label* drug treatment in children. All questions concerning children 15 years or younger at a DIC in Stockholm, Sweden during the years 1995–2004 were analysed with respect to the main drug related problem, drug/s and drug group/s, whether the drugs were licensed or not, pediatric labelling of the drug/s and age and sex of the patient. Q&As were classified as whether or not they included evaluated literature information, adding to the labelling of the drugs. We identified 249 Q&As concerning pediatric drug treatment. Each question addressed an average of 1.5 drugs. More than two-thirds of the Q&As concerned adverse drug reactions and pediatric drug choice or dosing. Every second question was classified as *off-label*, psychotropic drugs being the most common. In half of all *off-label* Q&As, pediatric documentation on drug efficacy and safety outside the Swedish catalogue of medical products was found. Most Q&As concerned newborns and infants. However, the *off-label* proportion

among questions was highest in adolescence as well as the evaluated literature information, adding to the labelling of the drugs. It was thus found that *off-label* drug treatment is common among pediatric questions at a DIC. This service can provide additional literature based information contributing to a safer use of drugs in children. There is still, however, a substantial need for clinical documentation of drug use in children.

**Keywords** Drug labelling · Child · Drug therapy · Drug information services · Adverse drug reactions

## Introduction

Children, and especially small children, receive considerable amounts of drugs [16, 21, 24, 27] and several studies indicate that drug related problems in children are of great clinical relevance and that many of them are preventable [7, 12, 25].

Drug prescribing in children has been reported to frequently be carried out in an *off-label* and/or unlicensed manner, both in hospitals and in primary health care [20, 26, 27]. The term *off-label* in these studies is defined as the use of a drug outside the terms of the product license for children and *unlicensed* drugs are drugs that do not have a product license.

The licensing procedure is mainly based on clinical trials in adults and aims at ensuring the safety, efficacy and quality of drugs. However, children differ from adults regarding pharmacokinetics and pharmacodynamics [30]. The lack of clinical trials in children results in non-existing pediatric labelling of many drugs and *off-label* pediatric drug use. Attempts have been made by the medical regulatory agencies to stimulate the drug industry to

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perform pediatric clinical trials [6]. However, an investigation of the license status of drugs approved after these initiatives were implemented shows that the majority of the drugs still lack pediatric labelling [11]. *Off-label* drug treatment has been associated with an increased frequency of ADRs compared with licensed pediatric drug treatment [13, 28].

Since readily available information concerning pediatric drug treatment from clinical trials and drug producers are scarce, other sources of information, such as what might be found at drug information centres (DICs), are needed.

The first DIC in Sweden was established in 1974, through a co-operation of clinical pharmacologists and information pharmacists [2]. Today, there is a regional network of DICs in Swedish university hospitals [18]. The DICs in Sweden offer evidence based drug information, comparable to clinical consultations, to drug prescribing health professionals [2, 18]. There are several DICs established in other European countries with similar working methods [18, 22].

We have found no published study on pediatric drug treatment based on data from a DIC. However, three studies concerning drug use in pregnancy or breast-feeding based on data from DICs concluded that the DIC is an important source of evidence based information [1, 9, 14].

The aim of this study was to analyse the characteristics of *Questions and Answers* (Q&As) at a drug information centre regarding *drug related problems* and *off-label drug treatment* in children and also to analyse how often the DIC could provide evaluated information concerning pediatric drug use, in addition to the information available in the Swedish catalogue of medical products.

## Methods

### Settings and subjects

A register of all Q&As handled by the DIC at the Karolinska University Hospital, Huddinge, was used as the information source for this study [2, 18]. When a question is asked, a literature search is performed at the DIC, the available information is evaluated and initially a preliminary answer is given. The most frequent literature sources used are medical databases, e.g. Medline, handbooks, e.g. Martindale, and contacts with relevant authorities, e.g. medical products agency or the manufacturer. After internal review and approval at a weekly staff meeting a written answer with references is sent to the requester [18]. All Q&As are continuously registered in a local database, Dataease, which contains information concerning question date, questioner, demographic data, drug and medical history of the patient, and the drug related problem

in question (adverse reaction, interaction, kinetics, drug choice and/or dosing, or drug formulation and/or administration) and the answer delivered with literature references [2, 18]. The Q&As of general interest are put into an international database, Drugline, that is continually updated by the DICs in Sweden, Odense Denmark and Åbo, Finland [19].

All Q&As concerning children during a ten-year period, from 1995 to 2004, were retrieved and systematically analysed. Out of a total of 6,842 Q&As that were handled at the DIC during this period, 300 (4.4%) concerned children. The further analysis was restricted to Q&As concerning children 15 years or younger. Fifty-one Q&As (17%) were excluded from further analysis since they concerned breast-feeding and/or pregnancy, patients 16 years or older, food, chemicals or doping or accidental ingestion of drugs.

### Classification

The questions were analysed and classified with respect to the main drug related problem, drug/s and drug group/s, pediatric labelling of the drug at the time the question was raised, and age and sex of the patient (if known). Answers relating to *off-label* treatment with drugs licensed in Sweden were analysed with respect to their content of evaluated literature information, adding to the information given in the labelling of the drugs.

The *off-label* assessment was performed by using the Swedish catalogue of medical products (FASS) from the same year as the question [10]. A question was regarded as *off-label* if any of the drugs was explicitly not recommended, or was given for an unproven indication, dose and/or age-group in children. Questions concerning drugs for which no information about the mode of pediatric use in the patient was available, or for which safety and efficacy studies had not been performed in a pediatric population, were also regarded as *off-label*. All drugs that were not listed in FASS were classified as unlicensed, e.g. drugs prescribed on license bases or herbal remedies. The licensed drugs were classified according to the Anatomical Therapeutic Chemical classification system (ATC) up to the 5th level [29]. The register contains no references to patient identity and therefore no ethical approval was needed for the study.

## Results

A total of 249 Q&As concerning children 15 years or younger were identified, most of which originated from hospital care (82%) and related to systemic drug exposure (98%). Each question concerned an average of 1.5 drugs or

**Table 1** Proportion of drug related problems, *off-label* and/or unlicensed drug treatment in all questions ( $n=249$ ), and proportion of evaluated literature information, adding to the labelling of the drugs in *off-label* Q&A ( $n=78$ )

Drug related problem	All ( $n=249$ [100%]) [ $n$ (%)]	Unlicensed ( $n=59$ [24%]) [ $n$ (%)]	<i>Off-label</i> ( $n=78$ [31%]) [ $n$ (%)]	Literature information ( $n=41$ [16%]) [ $n$ (%)]
Adverse drug reactions	91 (37)	10 (17)	21 (27)	8 (20)
Pediatric drug choice and dosing	85 (34)	23 (39)	32 (41)	21 (51)
Drug interactions	31 (12)	10 (17)	14 (18)	6 (15)
Drug formulation and administration	25 (10)	14 (24)	5 (6)	1 (2)
Pediatric drug kinetics	17 (7)	2 (3)	6 (8)	5 (12)

herbal remedies. More than half of the questions concerned use of drugs in an *off-label* (31%) or unlicensed (24%) manner. The most common reason for *off-label* classification of drugs was lack of pediatric labelling (53%), followed by lack of safety and efficacy studies performed in children (23%). As for the answers to questions regarding *off-label* treatment, more than half (53%) were classified as containing evaluated literature information adding to the labelling of the drugs.

Table 1 gives the proportion of drug related problems addressed for all the questions, and also for the groups of questions concerning unlicensed or *off-label* drug use. The last column gives the proportion of answers (to *off-label* questions) containing information not included in the

labelling of the drugs, in relation to the type of drug related problem.

Adverse drug reactions was the most common type of drug related problem referred to in the questions (Table 1). The most common types of adverse reactions were signs and symptoms from the central nervous system (19%, e.g. neuropathy or prolonged anesthesia), hematological reactions (15%, e.g. thrombocytopenia or leucopenia) and skin reactions (11%).

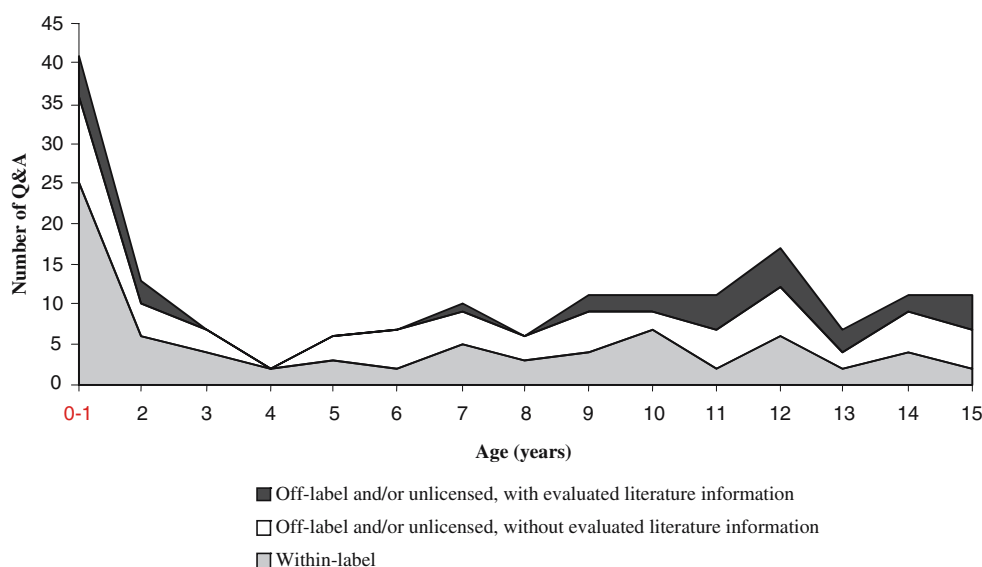
The majority of drugs (298 out of 372) included in the questions were licensed in Sweden. The most common therapeutic groups were antibacterial drugs for systemic use, antiepileptics, antidepressants, vaccines, and neuroleptics and sedatives (Table 2).

**Table 2** Proportion of drugs, occurring five times or more in questions, classified as *off-label* in different ATC groups

Therapeutic group	ATC Group	Licensed (100%) [ $n$ ]	<i>Off-label</i> (32%) [ $n$ ]
Antibacterial drugs for systemic use	J01	44	2
Antiepileptics	N03	28	1
Neuroleptics and sedatives	N05	23	14
Vaccines	J07	18	0
Antidepressive agents	N06A	16	13
Immunosuppressive agents	L04	15	7
Drugs for obstructive airway diseases	R03	14	0
Anesthetics	N01	10	2
NSAID	M01A	10	7
Corticosteroids for systemic use	H02A	9	5
Antihistamines for systemic use	R06A	9	1
Drugs for acid related disorders	A02	7	2
Analgesics	N02	8	4
Antidiarrheals, intestinal antiinflammatory/antiinfective agents	A07	6	3
Antiprotozoals	P01	6	1
Antithrombotic agents	B01A	5	5
Antimycotics for systemic use	J02	5	2
Antimycobacterials	J04	5	2
Antivirals for systemic use	J05	5	2
Pituitary, hypothalamic hormones and analogues	H01	5	2
Diuretics	C03	4	2
Beta blocking agents	C07	4	3
Calcium channel blockers	C08	4	3

The total number of licensed drugs was 298 among 249 enquiries. All data is not shown.

**Fig. 1** Number of Q&A classified as within label, *off-label* or unlicensed with or without answers resulted in evaluated literature information adding to the labelling of the drugs among 172 questions with known age



Psychotropic drugs, immunosuppressive agents and anti-inflammatory/antirheumatic agents were the drug groups most frequently associated with *off-label* questions (Table 2). Warfarin, risperidone, omeprazole, and different selective serotonin reuptake inhibitors (all 3%) were the most common drugs associated with *off-label* questions.

Questions concerning infants 0–1 years were most common ( $n=41$ ), with a proportion of *off-label* or unlicensed treatment of 12%. However, this proportion was highest for questions regarding adolescents (10–15 years) (33% of 68 questions). Literature information, adding to the information given in the labelling of drugs, was mainly found for adolescents (Fig. 1). (Unfortunately, in one third of the questions the age of the child was not specified or was not applicable in questions of a more general character).

## Discussion

This study, analysing pediatric Q&As at a DIC, confirms that a large proportion of children, at least within hospital care, are treated with drugs in a way that is not supported by product labelling. In our data, we found that every second question concerned *off-label* or unlicensed drug treatment. Other hospital based studies have reported frequencies of *off-label* drug treatment between 36 and 92% in pediatric patients [20]. This large variation in the *off-label* frequency is partly explained by varying definitions of the term *off-label* between countries and studies.

The most common reason for a licensed drug in our questions to be classified as *off-label* was a lack of pediatric labelling. Again, this is in accordance with earlier findings [27]. However, the most important, and not previously reported, finding in the present study is the amount of information available through literature searching, that is

apparently relevant to pediatric drug treatment, but that is not included in the product labelling of the drugs. For half of all the questions regarded as *off-label*, additional pediatric documentation was available from scientific publications found mainly in Medline, but also from other drug therapy literature sources, or through contact with the manufacturer. One reason for the large proportion of *off-label* drug treatment can thus be a lack of harmonisation between existing documentation in the literature and drug licenses. How can we make the best use of this information in pediatric health care, to improve the efficacy and safety of pediatric drug treatment? This finding does of course support the importance of a health care facility like the DIC, in providing condensed and evaluated literature information, supporting the treatment of individual patients. It has previously been shown that the DIC has a cost-saving potential in preventing ADRs [15]. The present finding also indicates the need, for example, of local or regional pediatric therapeutic expert groups to regularly survey the literature and distribute relevant new data and findings to all pediatric prescribers. The Internet can be of good use for this purpose, as exemplified by the Swedish webpage Janus (<http://www.janusinfo.se>), which is a non-commercial website, supported by the Stockholm county council, providing drug information to support health care professionals in their every day work.

In this context, it should be noted that a high proportion of *off-label* drug treatment is not necessarily synonymous with unsafe or incorrect pediatric treatment. It has been shown that physicians are well aware of the lack of pediatric labelling [8]. One reason for *off-label* drug use is that pediatricians have clinical experience that supports *off-label* drug use. Therefore, it is of great importance that such experience be documented and published as much as possible.

The present study, in finding that adverse drug reactions was the most common drug related problem, does also emphasize that pediatric adverse drug reactions are of great clinical relevance, in accordance with earlier studies [12, 25]. Adverse drug reactions were also often associated with *off-label* drug treatment, as previously shown [13, 28].

Psychotropic drugs was the most common therapeutic group of drugs in questions classified as *off-label*. This can partly be explained by an increased use of these drugs, e.g. selective serotonin reuptake inhibitors (SSRI), particularly in adolescents [3–5, 17, 23]. Recently, the European Agency for the Evaluation of Medicinal Products (EMA) approved the use of fluoxetine in the treatment of depression in children eight years of age or older, who do not respond to psychotherapy. However, only one question in our material concerned fluoxetine.

We found some therapeutic drug groups that almost totally lacked pediatric labelling, i.e. non-steroidal anti-inflammatory drugs (NSAIDs) and antithrombotic drugs. Especially for NSAIDs, more studies in the pediatric age group is warranted, as these drugs are prescribed to a large number of adult patients and can also be expected to have an impact on pediatric drug treatment. As for antithrombotic agents, these drugs have little use in the pediatric population. Nevertheless, antithrombotic drugs can be of great importance for a concerned group of pediatric patients.

Considering the lack of pediatric labelling for many drugs, we regard the DIC as an important complement to existing sources of drug information. The DICs also have the potential to prevent drug related problems through their pharmacological consultations. A future challenge is to continually spread existing evidence based knowledge regarding pediatric drug treatment to all physicians responsible for treating pediatric patients. Foremost, there is still a large need for increased research concerning pediatric drug treatment.

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