ORIGINAL ARTICLE

OFF-LABEL AND UNLICENSED PRESCRIBING IN HOSPITALIZED CHILDREN: PREVALENCE AND REASONS

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Abstract

There is limited information regarding the extent of the unapproved drug use in Romanian hospitalized children. The objective of this study was to identify the prevalence of the off-label and unlicensed recommendations during hospitalization and the reasons of the prescribing physicians in one paediatrics clinic. A total of 70 drugs were recommended to 100 hospitalized children, with an average (± SD) of 4.62 (± 2.65) drugs per patient. 54% of all drugs were involved in 177 instances of off-label prescribing. 89% of infants and toddlers and 85% of children 2 - 11 years old had at least one off-label recommendation. Off-label for dose was the most prevalent category. Previous positive experiences of the prescribing paediatrician and the hospital guidelines were the most frequently expressed reasons. The high prevalence of the off-label prescribing suggests the need for improving the strategies of paediatric drug research and registration.

Rezumat

Sunt puține informații publicate despre amploarea fenomenului de prescriere a unor medicamente neaprobate la copiii spitalizați în România. S-a urmărit identificarea prevalenței recomandărilor *off-label* și neautorizate pe perioada spitalizării, cât și a argumentelor medicilor prescriptori, într-o clinică de pediatrie. 70 de medicamente au fost recomandate celor 100 de pacienți analizați. În medie (± DS), au fost prescrise 4,62 (± 2,65) medicamente/pacient. 54% dintre medicamente au fost prescrise în 177 de situații evaluate ca *off-label*. 89% dintre copiii cu vârsta între 28 zile - 23 luni și 85% dintre cei de 2 - 11 ani au fost expuși cel puțin unei recomandări *off-label*. *Off-label* pentru doză a fost cea mai prevalentă dintre categorii. Cele mai frecvente argumente au fost experiența medicului prescriptor și recomandările ghidurilor adoptate la nivelul clinicii. Prevalența crescută a recomandărilor *off-label* solicită măsuri de optimizare a studierii și a autorizării medicamentelor de uz pediatric.

Keywords: hospitalized children, off-label prescribing, unlicensed prescribing

Introduction

Unapproved drug use in children is considered to be a highly prevalent phenomenon in all environments of paediatric care. One systematic review conducted in hospitalized populations, found that the frequency of off-label prescribing represented 12.2 to 70.6% of all recommendations, while 42.0 to 100% of children were exposed to at least one unapproved prescribed medication [26]. For children treated as outpatients, 37.6% were exposed to ≥ 1 off-label prescription and 6.7% to ≥ 1 unlicensed drug in 46 general practices in southwestern France, while in a US paediatric population, the off-label prevalence was 62% for all prescribing during the paediatric visits [5, 34]. It is not considered an illegal practice assuming the physicians' discretion to prescribe the therapy considered as appropriate, and it often represents the only clinically appropriate option. It can take the form of "off-label use" meaning situations where the medicinal product is deliberately used for a medical indication not following the authorized product information (the Summary of the Product Characteristics, SPC). Alternatively, it can present as an "unlicensed use" meaning all uses of a drug which has not received a marketing authorization as medicinal for human use in either adults or children [14, 30].

Potential lack of safety and several ethical concerns remain the main challenges associated with the unapproved medication use in children, while the efficacy of an off-label prescription is not as rigorously documented as that of an on-label option. Prospective research among paediatric inpatients demonstrated that the administration of unapproved drugs is more likely to be implicated in adverse drug reactions (ADR) [6]. One retrospective analysis proved that up to one-fifth of all ADRs reported over a decade have been associated with off-label

prescribing of medicines, with 60% of them being evaluated as severe [1]. Nevertheless, the studies searching for an association between off-label use and ADR had various designs, an aspect that limits the generalization of their findings. Therefore, the correct identification of the risk factors for ADR has been suggested as a more pragmatic approach to increasing the safety of unapproved drug use in paediatric patients [28].

Nowadays, it is recognized that the strategies aiming for the improvement of the unapproved drug use process are complex as they involve diverse ethical, legal and safety-related aspects [23]. Firstly, to compensate for the limited participation of children in clinical research, several European and international regulatory actions have intended to encourage the development of medicines for children and to ensure the availability of high-quality information about such medicines [38]. After five years from the implementation of the Paediatric Regulation, the European Medicines Agency assessed that it already had a positive impact as the paediatric development is increasing [13]. Nevertheless, one recently published literature review conducted on 27 studies, concluded that the initiatives to improve clinical research carried out in children had a marginal effect in decreasing the unlicensed, and off-label drug uses prevalence in Europe [7]. Secondly, spontaneous reporting of ADR from medical professionals involved in paediatric drug use was encouraged, and it proved to be intensive when off-label drugs are being used in children [39]. It also became necessary to clarify the legal liability of the prescribing physician, of the delivering pharmacist and the medicine's manufacturer in situations of unapproved drugs use [21]. Other regulatory strategies like for example, the French ones, allowed for a temporary facilitation of access to unapproved medications in serious or rare diseases lacking alternative authorized choices [2].

For the appropriate implementation of such strategies, a major step is the evaluation of the extent of unapproved medication use and the degree of acknowledgment of such practice by the prescribing physicians. There is limited information regarding the unapproved medication use in Romanian paediatric patients [12].

The objective of this study was to identify the prevalence of off-label and unlicensed medication use in a paediatric teaching hospital and the perspectives of the prescribing physicians on this phenomenon.

Materials and Methods

The first phase of the study had an observational and retrospective design. There were recorded the medical data of the paediatric patients admitted to an urban, teaching hospital, the Paediatrics Clinic 3 (70 beds, 6 paediatric units), Cluj-Napoca, Romania, during a 60 days interval. The diagnostic at admission, age, and therapies recommended during hospitalization were recorded in a data collecting sheet. The off-label and unlicensed drug use was identified by comparing the patient's data with the information available in the SPC as it was available in the electronic version of the Romanian Pharmaceutical Index (http://www.anm.ro/anmdm/).

The second phase of the study included a short encounter with the prescribing physician aiming to identify their reasons for the unapproved drug use, among 5 pre-specified options: prescription according to the clinics' implemented guidelines; lack of a registered drug on the Romanian market; the registered alternative is not available (too expensive or secondary to drug shortages); the experience of the prescribing physician confirms the efficacy and safety of the unapproved use of medication; other reason.

According to published available methodology, a hierarchical approach was adopted for the classification of the drugs prescribed off-label: off-label for age if the drug was recommended to a different age group, including drugs with no paediatric indication or those contraindicated in children; off-label for route of administration; off-label for indication; off-label for dose (which included frequency of administration). A drug prescribed off-label was included in only one category. The classification of unlicensed drugs included: unlicensed formulation of a registered drug (through modification of the pharmaceutical formulation), pharmaceutical compounding formulas, non-pharmacological substance administered as a medicine and unregistered formula (having a marketing authorization in other countries). One patient could have been simultaneously exposed to more than one instance of unapproved medication use [9, 18, 30].

Age definitions set by the European Medicines Agency were used for data analysis: infants and toddlers (28 days to 23 months); children (2 to 11 years); adolescents (12 - 18 years) [11]. The drugs recommended during hospitalization were analysed using the WHO-ATC (Anatomical Therapeutic Chemical) classification. Prescriptions for blood products, oxygen, parenteral nutrition, premedication used before diagnostic and treatment procedures, complementary products and insulin therapy were not included in the analysis. Descriptive statistics (means and standard deviations for continuous variables, frequencies, and percentages for categorical variables) were determined for the analysis of the paediatric prescriptions (Microsoft© Office Excel, 2007). The study was approved by the Ethics Committee at "Iuliu Haţieganu" University of Medicine and Pharmacy (No. 423/ December 17, 2014).

Results and Discussion

The first phase of the study

During a 60 days period (November - December 2014), 100 children were admitted mostly for respiratory diagnoses (Table I). The average (± SD) number of drugs prescribed for each child was 4.62 (± 2.65) drugs. The most frequent reasons for hospitalization were respiratory (bronchiolitis, asthma exacerbations, pneumonia, croup, etc.) and gastro-intestinal (gastroenteritis) disorders.

Table I

Demographic data and reason for hospitalization

Data	Number (n = 100)
Number of hospitalized children	100
Median age (range), years	4 (0.17 - 17)
Age distribution	
Infants and toddlers (28 days to 23 months)	35
Children (2 to 11 years)	59
Adolescents (12 to 18 years)	6
Sex distribution	
Male	58
Diagnosis at admission	
Respiratory	59
Gastrointestinal	20
Cardiovascular	4
Dermatologic	4
Other	13

There were 70 drugs prescribed. According to their WHO-ATC category, the largest one prescribed was antiinfectives for systemic use (15 drugs), followed by alimentary tract and metabolism (14 drugs), nervous system, and respiratory system (each with 8 drugs). Patients were most frequently exposed to ibuprofen and paracetamol. Among the most commonly used drugs, three examples were exclusively used off-label for the route of administration: adrenaline injectable solution used by nebulization in acute bronchiolitis, sodium chloride injectable solution and an eye-drops product (an anti-infective and anti-inflammatory combination), both used as nasal drops (Table II).

Table II

The ten drugs most frequently prescribed off-label

Drug	Number of patients exposed	Number (%) of patients receiving an on-label recommendation	Number (%) of patients receiving an off-label recommendation	Off-label subcategory
Ibuprofen	32	10 (32)	22 (69)	age, dose
Paracetamol	30	26 (87)	4 (13)	dose
Salbutamol	29	21 (72)	8 (28)	indication, dose
Fluticasone	28	12 (43)	16 (57)	age, indication, dose
Sodium chloride 0.9% w/v	25	0 (0)	25 (100)	route of administration
Hydrocortisone sodium succinate	16	15 (94)	1 (6)	dose
Cefuroxime sodium	16	14 (87)	2 (12)	dose
Adrenaline 1:1,000 solution for injection	15	0 (0)	15 (100)	route of administration
Montelukast	14	11 (79)	3 (21)	dose
Betabioptal®*	14	0 (0)	14 (100)	route of administration

**Betabioptal®* (Farmila-Thea Farmaceutici S.p.A. - Italy): eye drops, each mL contains 2 mg of betamethasone and 5 mg of chloramphenicol.

For 38 drugs (54% of all those prescribed), 177 instances of off-label prescribing were identified. The most frequent subtypes were off-label for dose and route of administration. The category of drugs off-label for dose mainly included (8 out of 13 drugs) systemic antiinfectives used in different doses than those recommended in the SPC. Another 25 instances of unlicensed use were identified for 11 products (4 registered drugs, 2 chemical substances, and 5 pharmaceutical compounding formulas) (Table III); there was no case of drug prescribed to the hospitalized children, despite being unregistered on the Romanian market.

Table III

Instances of off-label and unlicensed prescribing, according to subcategory

Number of drugs	Category of unapproved prescribing	Number of instances of unapproved prescribing	Subcategory of unapproved prescribing	Number (%) of instances in each subcategory
38	Off-label	177	Age	32 (18.1)
			Route of administration	55 (31.1)
			Indication	22 (12.4)
			Dose	68 (38.4)
11	Unlicensed	25	Unlicensed formulation of a registered drug	8 (32)
			Pharmaceutical compounding formulas	15 (60)
			Non-pharmacological substance administered as a medicine	2 (8)

Acyclovir, furazolidone, prednisone and propranolol tablets needed trituration into an acceptable paediatric formulation, while the pharmaceutical compounding formulas were mainly recommended for topical use (oral mucosa, cutaneous surfaces).

83% of the children were exposed to at least one instance of off-label prescribing during their hospitalization. The youngest age group was the most exposed to both off-label and unlicensed drug use (Table IV).

Table IV

Exposure to off-label and unlicensed medication according to age

Age group	Number of patients	Number (%) of patients exposed to off-label drugs	Number (%) of patients exposed to unlicensed drugs
Infants and toddlers (28 days to 23 months)	35	31 (89)	9 (26)
Children (2 to 11 years)	59	50 (85)	5 (8)
Adolescents (12 to 18 years)	6	2 (33)	1 (17)

The second phase of the study

Ten paediatricians prescribed the therapies that were analysed in this study, and 5 of them were available for explaining 17 instances of the off-label and unlicensed recommendations. The experience of the physician confirmed the efficacy and safety of azithromycin, paracetamol, ceftriaxone, desloratadine, racecadotril, ibuprofen and meropenem that were prescribed off-label for the dose; in the case of antibiotics, higher doses were frequently recommended. In several analysed cases, albendazole, esomeprazole, and drotaverine lacked an approved paediatric alternative for indication or age, but the physician considered that his choice was a safe and effective one. The hospital guidelines sustained the use of erythromycin as prokinetic and the administration of salbutamol and fluticasone by inhalation in acute bronchiolitis. The lack of availability of appropriate approved drugs in the hospital pharmacy were the reasons for the propranolol pharmaceutical compounding into an oral solution recommended in infantile haemangioma and for montelukast use as off-label for age. Unpleasant taste is frequently associated with the administration of liquid formulations of potassium salts supplements and of reconstituted suspension of clarithromycin. To avoid these situations and to ensure adherence to therapy, the paediatrician preferred to change the formulation and to prescribe tablets.

The present study found an increased exposure to off-label medication use, among children younger than 12 years old: 89% of infants and toddlers and 85% of children 2 - 11 years old had at least one such recommendation. The drugs recommended mostly in off-label instances were ibuprofen (69%) and fluticasone (57%). Off-label for dose, mostly for antiinfective drugs, had the highest prevalence in our study and it could easily be explained by the individualization of doses to the severity of the clinical context. According to the European Centre for Disease Prevention and Control, the antibiotic consumption and resistance in Romania are among the highest in Europe and several investigations confirmed these findings even for paediatric patients. For example, Lixandru *et al.* confirmed that in cases of acute otitis media and community-acquired alveolar pneumonia diagnosed in children younger than 5 years old, the *Streptococcus pneumoniae* antibiotic resistance rates were extremely high [25]. On the other hand, our findings are not singular as several other European analyses of antibiotic use in children pointed out that when these medications are used off-label, it is mostly in the off-label for dose subcategory [29, 37]. These results deserve further analysis as, for example, lower antibiotic doses could facilitate the emergence of susceptible strains [33].

Another particularity was the use of several drugs exclusively on a different route of administration than the one authorized in the SPC. One such example was the recommendation of an antibiotic and corticosteroid combination registered as eye-

drops, but prescribed exclusively on the nasal route as treatment for rhinosinusitis. It can be regarded as an approach to limit the exposure to systemic antibiotics or to increase their efficacy, although their therapeutic value in rhinitis or sinusitis is not evidenced [3, 32]. Several safety concerns have been suggested. When used in selected cases of chronic rhinosinusitis, both the active moieties and some preservatives as thiomersal can impair the mucociliary clearance or can present different degrees of systemic absorption [16, 17, 41]. Intranasal irrigations with sodium chloride 0.9% w/v solution are widely used for treating acute and chronic nasal conditions in children and using the parenteral product in this study, was an economically advantageous alternative [27].

Another example in the off-label for the route of administration category was the injectable formulation of adrenaline used by nebulization. For adrenaline, the only commercial formulation available on the Romanian market is the injectable one. The off-label use is justified, considering that using nebulized adrenaline in bronchiolitis, remains an option among the few available that are meant to improve clinical outcomes and to reduce the length of hospitalization [31]. The same context of bronchiolitis explained the off-label for indication administration of nebulized salbutamol and fluticasone, as this indication was not mentioned in their SPC.

Unlicensed formulations were prescribed to 15 (15%) patients. The unavailability of paediatric oral liquid formulations and a long-standing evidence of benefit for some pharmaceutical compounding formulas could explain these findings. Similar studies also identified the youngest age categories as the most exposed to these subtypes of unlicensed use involving the pharmacist intervention [9, 35].

All the tablets that needed an alteration of their pharmaceutical formulation were off-patent drugs, for which, regulatory agencies and producers acknowledged the challenges associated with the production of an appropriate paediatric dosage form; it is, therefore, foreseeable that this type of practice is going to continue as on-label alternatives remain unavailable [40].

The fact that the prescribing physicians could present their arguments for the off-label recommendations represented an opportunity rarely exploited in similar investigations that showed a high level of awareness among physicians about their off-label prescribing. Other authors found a certain degree of variability around this issue, with specialist care physicians being more familiar with the term "off-label prescribing" compared with the primary care ones [4]. Considering the safety risks implied by the off-label use, it gradually became important to check if these knowledgeable physicians informed the parents that their child was exposed to off-label medication use. Previous research found that although 61% of physicians prescribed off-label, only 49.3% of them informed the parents and only 22.3% noted it in the medical record [36]. Previous positive experiences, either personal or documented by the hospital's guidelines, served as a common explanation and also encouraged the safe and effective off-label administration. Corny *et al.* checked the off-label prescriptions for scientific support in databases that made reference to paediatric drug use. Similar to previous research, they found that only 39.3% of them were evidenced, underlying that in refractory or complex conditions, clinicians often use drugs lacking strong scientific support [8].

It remains difficult to compare the reported prevalence and examples of unapproved drug use in children. The list of registered drugs varies between countries; published studies use variable off-label categories and have variable durations of data collection; investigations are being conducted in different departments of paediatric care, each one having its specific therapeutic armamentarium. Our study found an increased frequency of off-label recommendations as 83% of all children were exposed to this type of prescribing. Kimland *et al.* analysed a large paediatric population from 41 hospitals during a 48 hours interval and found that 60% of the study population was exposed to at least one off-label drug; a substantial off-label use was found for paracetamol, opioids, diclofenac and midazolam [20]. On the other hand, an Italian group analysed the therapy of 4,282 children admitted during 6 months and found a lower frequency of unapproved prescribing: off-label and unlicensed prescriptions were found in 9.01% and 1.26% of all prescriptions, with 15.3% of preschool age children being exposed to off-label drug use [22]. Furthermore, a Finnish investigation compared the frequency of unapproved drugs prescribing in 3 paediatric wards in 2011 versus 2001, and found an amplified trend of this phenomenon (79% *versus* 58% of all admitted patients) with a 100% off-label exposure in the neonatal intensive care unit in 2011. Its authors concluded that the changes in the European legislation had a minor impact on the authorizing status of medicines commonly used in paediatric inpatients in specialized care [24]. In a French analysis conducted on 120 children, 54% of them received at least one off-label or unlicensed medicine, with pantoprazole, folic acid, esomeprazole and ondansetron as the most commonly prescribed off-label medicines, and ursodeoxycholic acid as the most frequently used unlicensed. Moreover, 88% of children hospitalized in the surgery ward *versus* 27% of those on the gastroenterology ward, received an off-label or unlicensed prescription [19]. Furthermore, Czarniak *et al*. confirmed that the first 10 most commonly prescribed off-label drugs

depend on the age group and that significantly more unapproved drugs are prescribed to inpatients compared to outpatients [9].

The high frequency of unapproved prescribing in this population can be viewed as an opportunity for reinforcing practices aiming for a safe and efficacious medication use. The unapproved drug use in paediatrics becomes acceptable regarding its potential risks when a registered alternative is lacking. Checking for the evidence supporting the off-label use is strongly encouraged, together with the accurate evaluation of the clinical severity warranting such therapy. The prescribing physician and the pharmacist delivering the off-label treatment also share the responsibility of informing the children's legal representatives and of obtaining their consent [10, 15].

The main limitation of the present study is that it analysed the medical information of patients admitted to a single paediatric hospital, and the findings cannot be generalized. The information was manually extracted from the patients' medical charts. The electronic version of the Romanian Pharmaceutical Index is continuously updating, and for the interpretation of our results, we used the SPC version available at the moment of the data collection. Not all the prescribing physicians explained their reasons for the unapproved medication use. The potential ADR of the unapproved therapy or the predictors associated with off-label prescribing were not investigated although it would help to better describe the local characteristics of the paediatric prescribing.

Conclusions

The present study identified a high prevalence of off-label prescribing among the youngest Romanian paediatric hospitalised patients. The prescribing physicians were aware of the unapproved status of their recommendations and justified them by previous positive experiences. Further and more extensive research is needed to evaluate the patterns of unapproved drug use corresponding to each paediatric unit or children treated as outpatients. This could help identify national needs and solutions regarding paediatric drug research and registration. Using such prescribing patterns, specific protocols to facilitate interdisciplinary collaboration could also be implemented, as close communication between pharmacists and physicians is needed to increase the effectiveness of the unapproved medication use.

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