

A questionnaire-based study in Calabria on the knowledge of off-label drugs in pediatrics

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ABSTRACT

Off-label use is very common among pediatricians, and the main cause is attributable to the lack of drugs specifically designed and marketed for children in different age groups. In this study, we evaluated, through a questionnaire, the knowledge of off-label drugs in pediatrics. Furthermore, we made a directory of 28 off-label drugs most commonly used by pediatricians in agreement with data obtained from Italian Agency for drugs (AIFA) referred to the law no. 648/1996; 180 pediatricians referred to the Italian Society of Pediatrics Calabrian section were asked to complete an online anonymous questionnaire. Eighty five (47.3%) of these completed the anonymous questionnaire, 40% revealed that they used off-label drugs "sometimes"; generally, drugs were used off-label for age and to treat respiratory diseases. For 75 pediatricians (88%) the information about the risk/benefit of off-label drugs is inadequate and 63 pediatricians (74%) did not have a good knowledge about this practice. In conclusion, the knowledge of off-label drugs is very low in pediatricians; more information about off-label drugs could be useful in order to improve the appropriateness of drugs' prescription and to reduce the development of side effects and improving drug safety.

Key words: Children, off-label drugs, pediatrics, questionnaire

INTRODUCTION

Off-label use is very common among pediatricians, and the main cause is attributable to the lack of drugs specifically designed and marketed for children in different age groups. In pediatrics, drugs are often prescribed using dosage and indications approved for adults, resulting in increased

risk of serious adverse events (including drug therapeutic failure).^[1-4] Moreover, physicians when administering drugs to children are frequently forced to deviate from the established labelling indications, by manipulating drug formulation to obtain a pediatric dose or by changing the indicated route of administration.^[5] Off-label prescribing could be related to several problems such as safety for the patient, costs for the society, and legal risk for the physician; therefore, this practise should be used only when the benefit outweighs the risk.^[6] Italian legislation on the use of off-label drugs is based on law no. 648/1996. Off-label is allowed for drugs included in a specific list, which includes the innovative drugs not yet marketed in Italy, drug still undergoing clinical trials, and medicines administered for a different therapeutic indication not included in the leaflet, in case of absence of therapeutic alternatives and previous written consent of the patient. Italian

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Law no. 94/1998 allows the physician, in individual cases, to off-label use a drug on the basis of efficacy evidence, under his/her direct responsibility, and after obtaining written informed consent by the patient. This law does not allow the widespread off-label use but permits the physicians to prescribe the appropriate therapy based on data published on the international valuable literature and previously documented demonstration of the absence of other therapeutic alternatives.^[6] In this context, the aim of the present study was to evaluate the knowledge of off-label drugs in pediatricians of Calabria region of Italy.

MATERIALS AND METHODS

In agreement with our previous article, we performed a questionnaire study.^[7] This study was prompted on Calabrian pediatricians members of the Italian Society of Pediatrics (SIP) in two phases. The first phase started in December 2012 and finished in March 2013 and was aimed to perform a directory of off-label drugs most commonly used by pediatricians in agreement with data obtained from Italian Agency for drugs (AIFA) referred to the law no. 648/1996. During the second phase, started in April and finished in May 2013, SIP’s pediatricians completed an online anonymous questionnaire with 10 answers [Table 1].

Table 1: Questionnaire completed online by pediatricians

- 1. How often do you prescribe off-label drugs?
☐ Sometimes ☐ Often ☐ Very Often ☐ Rarely ☐ Never
- 2. What are your off-label prescriptions for, in the majority of cases?
☐ Age ☐ Indication ☐ Dosage ☐ Route of Administration ☐ Other
- 3. Which one of the following active ingredients do you prescribe often in off-label form? [Table 2]
- 4. To which category the drugs belong that you most often prescribe in off-label form?
- 5. What is your main personal reason for prescribing off-label drugs?
☐ Lack of Unauthorized Formulations for pediatric Use ☐ Technical Sheet Dosage not Adequate for Clinical Practice
- 6. To what extent does the use of off-label drugs impact negatively on prescriptive appropriateness?
☐ Much ☐ Not Much ☐ Little ☐ Not at All
- 7. What are the risks related to the off-label use of drugs in pediatrics in your experience?
☐ Adverse Reactions ☐ Inefficiency ☐ Improper Formulations ☐ Increase of Therapeutic Errors
- 8. Do you consider your knowledge of the use of off-label prescriptions in pediatrics adequate?
☐ Yes ☐ No
- 9. Do you think that risk/benefit information available on the off-label use of drug is appropriate?
☐ Yes ☐ No
- 10. To what extent does the lack of drugs or specific formulations for pediatric age groups available on the market constrain clinical practice?
☐ Much ☐ Not Much ☐ Little ☐ Not at All

The first 5 questions referred specifically to drugs and their off-label use, while the last 5 asked to general guidelines on both risks and limitations of off-label drugs in clinical practice. The answers were analyzed by a working group composed of pharmacists and pharmacologists of the Center of Documentation and Information on Drugs and the Chair of Pharmacology of the University “Magna Graecia” of Catanzaro.

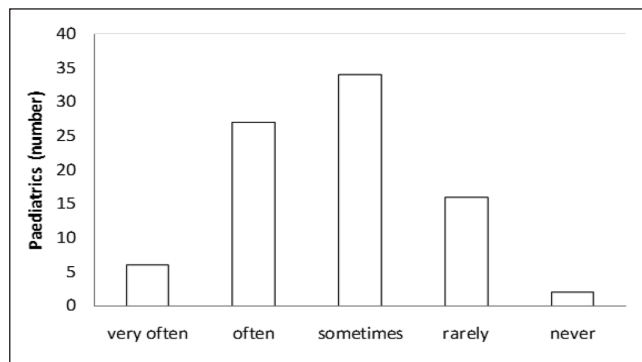
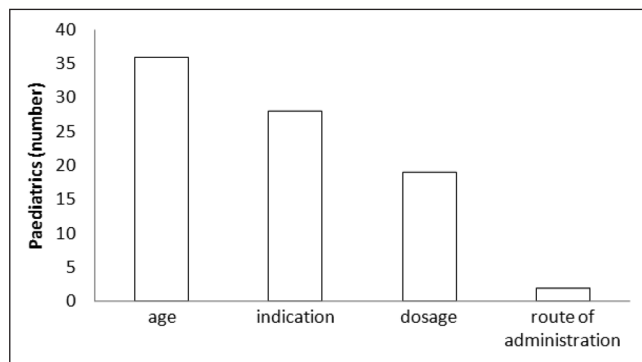
RESULTS

During the first phase, a table of 28 drugs most commonly used as off-label was completed (see Table 2). During the second phase, 180 Calabrian pediatricians SIP’s members were asked to take part at this study and 85 (47.3%) of them completed the anonymous questionnaire. In particular, 35 were Medical Doctor (MD) General Pediatricians (41%), 32 MD Hospital Pediatricians (38%), 10 MD attending the specialty in Pediatrics (12%), and 8 MD Outpatient Pediatricians (9%). MDs prescribed 341 off-label drugs enclosed in 154 categories of diseases.

40% of MDs revealed that they used off-label drugs “sometimes” [Figure 1], and commonly drugs were used off-label for age [Figure 2] and to treat respiratory diseases [Table 3]; beclomethasone was the most widely used drug [Table 4]. Sixty-six MDs used off-label drugs for lack of formulations approved for pediatric use, while 32 revealed that use of off-label drugs have negative effects on prescriptive appropriateness, although their use may be related with the development of adverse reactions [Table 5]. For 75 pediatricians (88%) the information about the risk/benefit of off-label drugs is inadequate and 63 pediatricians (74%) declared not to have a good knowledge about this practice.

Table 2: Most commonly used off-label drugs, in agreement with data of AIFA and list of law no. 648/1996.

Adrenalin	Levofloxacin
Aminophylline	Lorazepam
Atorvastatin	Magnesium hydroxide
Beclomethasone	Mannitol 18%
Clozapine	Metoclopramide hydrochloride
Dalteparina	Metformin
Diclofenac	Midazolam
Esomeprazole	Olanzapine
Enoxaparina	Pantoprazole
Ferrous sulphate	Pravastatin
Glucagon	Salbutamol
Ibuprofen	Simvastatin
Hydrocortisone butyrate	Topiramate
Itraconazole	Warfarin

**Figure 1:** Times of use off-label drugs**Figure 2:** Off-label use in agreement with the leaflet of each drug**Table 3: Categories of off-label drugs most frequently prescribed**

Drug categories	Numbers	Percentage
Respiratory tract	64	41.55
Gastrointestinal tract and metabolism	33	21.44
General Antimicrobials for systemic use	12	7.8
Sense organs	12	7.8
Musculoskeletal system	11	7.14
Nervous system	9	5.84
Blood and hematopoietic tissues	5	3.24
Antiparasitic agents	3	1.95
Cardiovascular system	2	1.3
Genitourinary system and sex hormones	2	1.3
Other hormones	1	0.64
Total	154	100

DISCUSSION

Less than 15% of all the drugs currently marketed and less than half of those specifically intended for children are used on the basis of clinical trials which demonstrate specific features of risk-benefit balance in children.^[8-10] This study was designed to describe the extent of off-label drug use, to identify drugs most commonly used off-label, and to identify factors associated with off-label drugs use in children and above all what is the opinion of pediatricians relative to this problem and their knowledge about it. The data analysis reveals, in agreement with the

Table 4: Off-label drugs most frequently prescribed

Drugs	n	Percentage
Adrenalin	43	12.6
Aminophylline	8	2.34
Atorvastatin	1	0.3
Beclomethasone	49	14.36
Clozapine	2	0.58
Dalteparina	3	0.9
Diclofenac	8	2.34
Esomeprazole	26	7.62
Enoxaparina	3	0.9
Ferrous sulphate	9	2.63
Glucagon	12	3.51
Ibuprofen	40	11.73
Hydrocortisone butyrate	11	3.22
Itraconazole	2	0.58
Levofloxacin	5	1.5
Lorazepam	3	0.9
Magnesium hydroxide	10	2.93
Mannitol 18%	3	0.9
Metoclopramide hydrochloride	2	0.58
Metformin	9	2.63
Midazolam	16	4.7
Olanzapine	—	—
Pantoprazole	15	4.4
Pravastatin	2	0.58
Salbutamol	41	12.02
Simvastatin	6	1.75
Topiramate	6	1.75
Warfarin	—	—
Others	6	1.75

Table 5: Risks associated with the use of off-label drugs

Risks	Numbers	Percentage
Adverse reactions	34	40
Inefficiency	2	2
Improper formulations	24	28
Increase of therapeutic errors	25	30

data in the literature, that in Pediatrics, off-label prescriptions are very numerous,^[11-13] often driven by the lack of specific formulations on the market for children. The off-label drugs most prescribed are those used for diseases of the respiratory tract and the medication most often used in our studied group is Beclomethasone. Pediatricians demonstrate an awareness of the issues related to the use of off-label drugs, and most importantly, they agree with the data in the literature, indicating an increase in the occurrence of adverse reactions.^[8,9,14-17] The lack of pediatric formulations on the market is considered a major limitation for clinical practice, but not for prescriptive appropriateness. Most compilers did not consider themselves to be sufficiently well prepared in the off-label use of drugs, and specifically, they consider the information relating to the

risks/benefits resulting from such use completely inadequate. In light of all the issues regarding the use of off-label drugs in Pediatrics, the Centre for Documentation and Information on Medicine along with the Chair of Pharmacology at the University “Magna Graecia” in Catanzaro and in collaboration with the regional section of the Italian Society of Pediatrics will begin a drug surveillance project entitled, “*Monitoring, Support and Security regarding Off-Label Prescriptions in Pediatrics within the Calabrian Territory*”. The aim will be to highlight how off-label prescriptions are used within our region, what the issues are relating them and what the possible solutions that could be used.

CONCLUSIONS

Pediatric therapies are often complicated by the shortage of medicines on the market that are designed for children of different ages thus forcing the pediatrician towards a problematic off-label use of adult formulations with the increased possibility of adverse reactions and possible medication errors due to the difficulties in administering the right dosage. It would be desirable to increase the studies and clinical trials to support a greater marketing of specific drugs for the pediatric age. In the meantime, it is important to improve the training of pediatricians on the subject, starting with a course of study, in order to make them more prepared to deal with the problem, but also to increase the information on the risks inherent in the use of off-label drugs, so as to increase the awareness of the prescriber. Our task was brought about in order to make aware a very well known but often forgotten problem. We believe that the contribution of pediatricians is a great help in highlighting some aspects of the problem and especially in seeking a possible resolution.

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