

Incidence of unlicensed and off-label medication prescriptions at the Department of Paediatrics: what has changed after seven years?

Petra Matalová (✉ petra.matalova@fnol.cz)

Lékařská Fakulta Univerzita Palackého v Olomouci: Univerzita Palackého v Olomouci Lekarska fakulta <https://orcid.org/0000-0002-1584-4826>

Lucie Belfínová

Univerzita Palackého v Olomouci Lékařská fakulta: Univerzita Palackého v Olomouci Lekarska fakulta

Kristýna Vrbicová

Univerzita Palackého v Olomouci Lékařská fakulta: Univerzita Palackého v Olomouci Lekarska fakulta

Jana Fůrstová

Lékařská Fakulta Univerzita Palackého v Olomouci: Univerzita Palackého v Olomouci Lekarska fakulta

Martin Wawruch

Univerzita Komenského v Bratislave Lekárska Fakulta: Univerzita Komenskeho v Bratislave Lekarska fakulta

Karel Urbánek

Lékařská Fakulta Univerzita Palackého v Olomouci: Univerzita Palackého v Olomouci Lekarska fakulta

Research

Keywords: Children, Off-label, Paediatrics, Prescriptions, Unlicensed, Comparison

Posted Date: September 30th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-940207/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background

Many common drugs have not been registered for use in children. Therefore, they are sometimes prescribed as unlicensed or off-label. This study, performed at the Department of Paediatrics, University Hospital Olomouc, Czech Republic, evaluated off-label and unlicensed prescriptions. A similar study, conducted in 2013 by the same authors (P. Matalová – maiden name P. Langerová), showed that the number of off-label and unlicensed prescriptions was relatively low, compared to other studies. The goal of this study was to compare the frequency of off-label and unlicensed drug prescriptions, and to assess whether these prescriptions have declined.

Methods

The study evaluated the incidence of unlicensed and off-label prescriptions at the Department of Paediatrics, University Hospital Olomouc during a period of six months. A total of 10,710 prescriptions for 5,243 children were processed.

Results

In our previous study, performed from January to June 2012, a total of 8,559 prescriptions for 4,282 children were processed. Off-label and unlicensed prescriptions were found in 9.01% and 1.26% of all prescriptions, respectively. Unlicensed prescriptions were significantly more common in boys (1.5%) than in girls (1.0%). Seven years later, the same study in the same months was performed to ascertain the development in prescribing practice. In the 2019 study, the total number of prescriptions and patients was higher (18.8% vs. 22.2%, respectively) as was the number of off-label and unlicensed prescriptions (11.1% and 1.7%, respectively).

Conclusions

This study shows that the incidence of unlicensed and off-label drug prescriptions is not high, but paediatricians should avoid exposing children to unnecessary risks as well as depriving them of potentially effective pharmacotherapy. The goal was to highlight the need for clinical trials in paediatrics and to determine in which drugs the demand for also being registered for younger children is highest. The number of off-label and unlicensed prescriptions indicates a gap in registration processes and should provide a clue as to which drugs are candidates for having their SPCs changed.

Introduction

A broad spectrum of drugs has not been registered for use in children or their prescription for children is limited because of age. Sometimes, medicines have to be prescribed as unlicensed (drugs unregistered for children) or off-label. Off-label use refers to prescribing a drug outside the terms of the product licence, for example in an indication, age group, dose or route different from that which is approved by the regulatory authority [1].

In the last twenty years, there has been increased awareness of the lack of medicines documented for use in children. Regulatory actions have been taken to improve the situation by proposing requirements to the pharmaceutical industry to develop new products also suitable for children [2, 3]. The European Union regulatory authorities issued a paediatric regulation, namely the Regulation (EC) No. 1901/2006 of the European Parliament and the Council of 12 December 2006 which came into force in January 2007. This regulation requires clinical trials to be conducted in the paediatric population as well, particularly if children may benefit from a new drug. The regulation permits pharmaceutical companies to modify the Summary of Product Characteristics (SPC) by data acquired from new paediatric trials [4, 5]. In spite of these activities, progress has been slow and paediatricians still have to prescribe drugs without scientific and legal support.

During the first decade of life, changes in pharmacokinetics are dynamic and can be non-linear and discordant, making standardized dosing inadequate. During rapid phases of growth/development, drug disposition and response may be altered [6]. Moreover, the safety of patients as well as the therapeutic effect of drugs depend on the experience of the clinician and are not scientifically approved. The use of off-label and unlicensed drugs is widespread and common to all settings, both in primary and hospital care. In addition, off-label and/or unlicensed drugs are frequently prescribed for the youngest and most vulnerable children [7].

The present study evaluates the incidence of off-label and unlicensed prescriptions of proprietary medicinal products in outpatients at the Department of Paediatrics, University Hospital Olomouc, Czech Republic, during a period of six months (January to June 2019), and also includes patients discharged from hospitalization. For the purpose of this study, unlicensed drugs were those not registered for children at all, and drugs prescribed for children younger than those for whom the drug is registered were evaluated as off-label. The goal was to highlight the need for clinical trials in paediatrics and to determine in which drugs the demand for also being registered for younger children is highest.

Methods

Study design and setting, study population

Patients between 0 and 15 years of age attending the outpatient department of the University Hospital in Olomouc from 1 January to 30 June 2019 were included in the study. A total of 10,710 prescriptions for 5,243 children were evaluated. Patients who reached 15 years of age in the follow-up period were included in this study; those older than 15 years were not enrolled. The following characteristics were recorded for each patient: age, sex, and the number of prescriptions. In addition, the incidence of unlicensed and off-label prescriptions and the most commonly prescribed drugs were recorded.

Data processing

According to the Summary of Product Characteristics (available at www.sukl.cz for each registered drug in the Czech Republic), all drugs prescribed in contradiction with the licence information for age were considered off-label. In this study, it meant a drug prescribed for a child younger than the age for which the drug was registered. All drugs that were not registered for children at all were considered unlicensed.

Statistical analysis

All statistical analyses were performed using the R software, version 3.6.3. Frequencies and percentages were used to describe the characteristics of the sample. The differences in proportions were compared with the test of proportions (z-test). The significance level was set at the level of $p < 0.05$ for all statistical significance testing.

Results

The study included 5,243 children under the age of 15 years. A total of 10,710 drugs were prescribed during the six-month follow-up period. The descriptive characteristics of the study cohort are presented in Table 1. Of all prescriptions, unlicensed and off-label prescriptions accounted for 1.7% and 11.1%, respectively. A slight majority (55.5%) of the patients were six years of age or older. The percentage of male patients was significantly higher than that of females (56.5% vs. 43.5%, $p < 0.001$). The number of prescriptions was significantly higher in males as well (57.8% vs. 42.2%, $p < 0.001$).

Table 1
Distribution of the number of patients and prescriptions in different age categories

Age category	Age	Patients	Prescriptions per patient	Females	Prescriptions in females	Males	Prescriptions in males	Prescriptions total
Newborns	0–28 days	25	2.13	15	31	10	19	50
Infants	29–364 days	350	1.76	144	239	206	364	603
Toddlers	1–3 years	747	1.85	308	546	439	828	1374
Preschoolers	3–6 years	1209	2.06	485	938	724	1550	2488
Early school age children	6–11 years	1646	2.07	740	1467	906	1899	3366
School age children	11–15 years	1266	2.23	586	1301	680	1528	2829
Total	0–15 years	5243	2.05	2278	4522	2965	6188	10710

During the study period, there were 178 unlicensed prescriptions of which 61.2% (95% CI: 53.7–68.4) were in boys (1.8% of the total number of prescriptions in males), and 38.8% (95% CI: 31.6–46.3) in girls (1.5% of the total number of prescriptions in females). A similar pattern was seen in off-label prescriptions: they were significantly more frequent in boys (60.6%, 95% CI: 57.7–63.4) than in girls (39.4%, 95% CI: 36.6–42.3). Of the total number of prescriptions, off-label prescriptions accounted for 11.7% and 10.4% in boys and girls, respectively. See Table 2.

Table 2
Distribution of unlicensed and off-label prescriptions in different age categories

Age category	Prescriptions unlicensed	Prescriptions off-label	Patients unlicensed	Patients off-label	Unlicensed prescr. in females	Unlicensed prescr. in males	Off-label prescr. in females	Off-label prescr. in males	Prescriptions total
Newborns	0	6	0	6	0	0	4	4	50
Infants	4	118	4	87	2	2	49	64	603
Toddlers	18	176	14	141	3	15	66	105	1374
Preschoolers	24	324	21	295	7	18	121	215	2488
Early school age children	53	441	46	359	21	32	172	272	3366
School age children	79	127	66	94	36	42	58	62	2829
Total	178	1192	151	982	69	109	470	722	10710

The proportion of unlicensed medications prescribed in school age children was significantly higher than in any other age group ($p < 0.001$). Namely, the proportion of unlicensed drugs was 2.8% (95% CI: 2.2–3.5) in school age children (11–15 years old), 1.6% (95% CI: 1.2–2.1) for early school age children (7–11 years old), and less than 1.5% in the other age groups. No unlicensed medications were prescribed in newborns.

The highest proportion of off-label prescriptions was found in infants, 19.6% (95% CI: 16.6–22.9). On the contrary, the lowest incidence of off-label medications was observed in school age children (4.5%, 95% CI: 3.8–5.3). In the other age groups, approximately 13% of the prescriptions were off-label drugs. The distribution of unlicensed and off-label prescriptions in different age categories is presented in Table 2.

The drugs most commonly prescribed as off-label and unlicensed are presented in Tables 3 and 4. The most commonly prescribed unlicensed drugs were ramipril and aescin alpha; among off-label drugs, desloratadine and bronchodilators were prescribed most frequently.

Table 3
Drugs most commonly prescribed as off-label

	Prescriptions	Patients	Males	Females
Desloratadine	385	365	221	144
Salbutamol	123	108	61	47
Fluticasone furoate	90	81	57	24
Fluticasone propionate, formoterol fumarate dihydrate	69	56	37	19
Amoxicillin + clavulanate	40	39	15	24
Salmeterol	36	28	11	17
Clarithromycin	36	32	20	12
Macrogol	24	24	16	8
Bilastine	22	18	9	9
Azelastine hydrochloride, fluticasone propionate	21	21	15	6

Table 4
Drugs most commonly prescribed as unlicensed

	prescriptions	patients	males	females
Ramipril	47	41	27	14
Aescin alpha	26	25	19	6
Fluticasone + formoterol inh	10	7	5	2
Acetylsalicylic acid	9	6	2	8
Mesalazine	8	2	4	6
Calcium + vitamin D	8	6	2	8
Cinchocaine	7	7	3	4
Enoxaparin	6	6	4	2
Estradiol	6	6	0	6
Granisetron	5	4	3	1

Discussion

The present study, performed at the Department of Paediatrics in the University Hospital Olomouc, Czech Republic, evaluated off-label and unlicensed prescriptions. A similar study, performed in 2013 by the same authors, showed that the number of off-label and unlicensed prescriptions was relatively low [8], compared to other studies. The goal of this study was to compare the frequency of off-label and unlicensed drug prescriptions, and to assess whether these prescriptions have declined. Many papers have been published showing that off-label and unlicensed prescriptions may vary greatly [9, 10]. One of the reasons is that many studies were performed in neonatal intensive care units [11, 12, 13, 14] or emergency departments [15] where the proportion of off-label prescriptions seems to be the highest.

Another reason may be the ambiguity in the definition of off-label and unlicensed drugs [9]. We evaluated prescriptions of proprietary medicinal products from specialized outpatient departments where the number of prescriptions is the highest. Proprietary medicinal products were chosen because of their availability and their being most likely to be registered for children.

Conclusion

In our previous study, performed from January to June 2012, 8,559 prescriptions for 4,282 children were processed. Off-label and unlicensed prescriptions were found in 9.01% and 1.26% of all prescriptions, respectively. Unlicensed prescriptions were significantly more common in boys (1.5%) than in girls (1.0%). Seven years later, the same study in the same months was performed to ascertain the development in prescribing practice. In the 2019 study, the total number of prescriptions and patients was higher (18.8% and 22.2%, respectively) as was the number of off-label and unlicensed prescriptions (11.1% and 1.7%, respectively).

In other words, the number of off-label and unlicensed prescriptions indicates a gap in registration processes and should provide a clue as to which drugs are candidates for having their SPCs changed. Despite numerous initiatives aimed at promoting rational medicine use in children, the prevalence of off-label prescription in outpatient paediatric practice remains high.

Declarations

Acknowledgments

The study was supported by the Palacky University internal grant IGA_LF_2021_013.

Conflicts of Interest

There is no conflict of interest.

References

1. Waller DG. Off-label and unlicensed prescribing for children: have we made any progress? *Br J Clin Pharmacol.* 2007;64(1):1–2.

2. Hoppu K, et al. The status of paediatric medicines initiatives around the world – What has happened and what has not? *Eur J Clin Pharmacol.* 2012;68:1–10.
3. Teigen A, Wang S, Truong BT, Bjerknes K. Offlabel and unlicensed medicines to hospitalised children in Norway. *J Pharm Pharmacol.* 2017;69(4):432–8.
4. The European parliament and the council of the European union. Regulation (EC) no 1901/2006 of the European parliament and of the Council of 12 December 2006 on medicinal products for pediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. *Off J Eur Union* 2006;49:1–19. online at <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32006R1901>.
5. Lindell-Osuagwu L, Korhonen MJ, Saano S, Helin-Tanninen M, Naaranlahti T, Kokki H. Off-label and unlicensed drug prescribing in three paediatric wards in Finland and review of the international literature. *J Clin Pharm Ther.* 2009;34(3):277–87.
6. Matalová P, Urbánek K, Anzenbacher P. Specific features of pharmacokinetics in children. *Drug Metab Rev.* 2016;48(1):70–9.
7. Magalhães J, Rodrigues AT, Roque F, Figueiras A, Falcão A, Herdeiro MT. Use of off-label and unlicensed drugs in hospitalised paediatric patients: a systematic review. *Eur J Clin Pharmacol.* 2015;71(1):1–13.
8. Langerová P, Vrtal J, Urbánek K. Incidence of unlicensed and off-label prescription in children. *Ital J Pediatr.* 2014;40:12.
9. Balan S, Hassali MAA, Mak VSL. Two decades of off-label prescribing in children: a literature review. *World J Pediatr.* 2018;14(6):528–40.
10. Palmaro A, Bissuel R, Renaud N, Durrieu G, Escourrou B, Oustric S, Montastruc JL, Lapeyre-Mestre M. Off-label prescribing in pediatric outpatients. *Pediatrics.* 2015;135(1):49–58.
11. Meles Tekie Gidey. Gebretsadkan YG., Afewerki Gebremeskel Tsadik, Abraham Gebrezgabiher Welie, Brhane Teklebrhan Assefa. Off-label and unlicensed drug use in Ayder comprehensive specialized hospital neonatal intensive care unit. *Ital J Pediatr.* 2020 3;46(1):41.
12. Laforgia N, et al. Off-label and unlicensed drug use among neonatal intensive care units in Southern Italy. *Pediatr Int.* 2014.
13. Suksham Jain SS, Saini D, Chawla P, Kumar S, Dhir. Off-label use of drugs in neonatal intensive care units. *Indian Pediatr.* 2014;51(8):644–6.
14. McD Taylor D, Joffe P, Taylor SE, Jones A, Cheek JA, Craig SS, Gaudins A, Dhir R, Krieser D, Babl FE. Off-label and unlicensed medicine administration to paediatric emergency department patients. *Emerg Med Australas.* 2015;27(5):440–6.
15. Cuzzolin L, et al. Off-label and unlicensed drug treatments in Neonatal Intensive Care Units: an Italian multicentre study. *Eur J Clin Pharmacol.* 2016.