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REVIEW ARTICLE

Extent, reasons and consequences of off-labeled and unlicensed drug prescription in hospitalized children: a narrative review

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Abstract

Background Off-label and unlicensed prescriptions pose a severe safety concern among the pediatric population. We aimed to summarize the up-to-date evidence on the extent, reasons, and consequences of off-label and unlicensed drugs in hospitalized pediatric patients.

Methods We systematically searched PubMed, EMBASE, SCOPUS, Web of Science and Google Scholar between 1990 and 2020 in which the last search was conducted on 12 February 2021. We included studies with the following inclusion criteria: (1) observational studies in design; (2) target population was hospitalized pediatric patients whether admitted in the intensive care unit or in the general ward; (3) study reporting the prevalence of off-label, unlicensed prescriptions or both; and (4) published in English.

Results A total of 47 studies were eligible for inclusion. The proportion of off-label and unlicensed prescriptions ranged from 7.4% to 99.5% and 0.1% to 74.4%, respectively. The most frequent category of off-label prescriptions was prescription outside the age range, with the most commonly reported reason for off-label prescriptions being the lack of information specifically for pediatrics on the drug information leaflets. The consequences of off-label and unlicensed prescriptions ranged from minor and bearable skin reactions to debilitating renal failure, risking deaths.

Conclusions Off-label and unlicensed prescriptions are extensive and require progressively meditative interventions. However, the pediatric population is currently a "therapeutic orphan". Unless adequate pediatric clinical trials and licensed drugs become available, off-label and unlicensed drug prescription should not entirely be banned but rather promoted in an organized manner.

Keywords Licensed medicines · Off-label prescribing · Pediatrics · Unlicensed prescribing

Introduction

In the 1960s several of today's drugs, which are considered essential human drugs, were readily available over the counter without prescription. Essential drugs herein refers to medicines that satisfy the priority health care needs of the population [1]. Moreover, drugs could be utilized in humans based on experiments exclusively conducted on experimental animals [2]. Following a reported link to congenital disabilities caused by then over-the-counter available thalidomide in the early 1960s, governments and international organizations began introducing strict human drug regulations and monitoring to ensure patients' safety, drug quality, and effectiveness. Many countries today have dedicated drug regulation authorities [1, 2].

To ensure safety, quality and effectiveness, drug regulatory authorities assess drugs presented by pharmaceutical companies through preclinical testing, clinical trial phases involving volunteering human subjects, and review of results before granting a marketing license for public human consumption, as a licensed drug [3]. However, regarding pediatrics, the number of clinical trials used to enable the authorization of adequate pediatric-use licensed drugs as compared to adult population trials is limited [4, 5]. This limitation was attributed to several reasons, including the smaller pediatric population as compared to the adult population. Apparently, to ensure a legitimate consenting process for participating in clinical trials, the pediatric population is subject to a

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number of obstacles [6]. One of the issues is the ethical scheme. This is crucial for consenting people to participate in clinical trials. Another obstacle could be that the pediatric population has different pharmacokinetics. This means their absorption, distribution, metabolism and elimination of drugs is not as robust due to their delicate body physiology as compared to adults [7, 8]. The overall effect is to limit the number of pediatric licensed drugs, which is the main reason behind the current storm of unlicensed and off-label prescriptions in the pediatric population [9, 10].

Unlicensed drug is defined as prescription of a medicinal product for human use, with no granted marketing authorization by the countries' licensing authority. The extent of unlicensed prescriptions has been reported to range from 0.3 to 35%, which severely affects the pediatric population compared to other age groups [11, 12]. Despite the variety of categorization based on an individual country's criteria, as a whole the prescription of an unlicensed drug is not deemed illegal [13]. Moreover, a licensed drug could also be used outside its authorized age group of use, indication, dosage, route of administration, or frequency; this practice is referred to as off-label prescription and is also a legal act with a global reported prevalence ranging from 36.3 to 97.0% [14].

It follows that off-label and unlicensed prescriptions in the pediatric population could be beneficial because there are currently limited authorized drugs for this population. On the other hand, the practice could pose a big concern regarding patients' safety. Therefore, we aimed to explore the extent, reasons, and consequences of off-label and unlicensed drugs in hospitalized pediatric patients, by conducting a narrative review of the literature.

Methods

This review was written based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) but was designed to be a narrative review of the literature. The aim was to determine the extent, reasons, and consequences of off-label and unlicensed drugs in hospitalized pediatric patients including admitted children in a neonatal intensive care unit (NICU) or pediatric intensive care unit (PICU) and in the general pediatric ward.

Search strategies

We systematically searched PubMed, EMBASE, SCOPUS, Web of Science and Google scholar from between 1990 and 2020 in which the last search was conducted on 5 February 2021. We performed advanced search in all the databases using medical subject headings (MeSH) and key term depending on the database. In PubMed database, the search strategy: ["off-label use" (Mesh) AND "prevalence" (Mesh)] AND "child" (Mesh) was built using keys like off label use AND prevalence AND child with Boolean operators. The search strategies used in the other databases are as follows: ("prevalence"/mj AND "off label drug use"/mj OR "unlicensed drug use"/mj) AND "child"/mj for EMBASE, prevalence AND off AND label AND drug AND use OR unlicensed AND child OR pediatrics AND treatment OR therapy for SCOPUS, (TI = prevalence AND TI = off label drug use OR TI = unlicensed AND TI = child) AND language: (English) AND document types: (article) for Web of Science and prevalence AND off label drug use OR unlicensed AND child fo*r* Google search.

Eligibility criteria

We included studies with the following inclusion criteria: (1) observational studies in design; (2) target population was hospitalized pediatric patients whether admitted in the intensive care unit or general ward; (3) study reporting the prevalence of off-label, unlicensed prescriptions or both; and (4) published in English.

Exclusion criteria

We excluded studies with the following criteria: (1) review articles; (2) duplicate publications; (3) articles not in full text; (4) articles not written in English; (5) studies based on mixed participants; (6) study participants not children; and (7) studies outside of study setting.

Results

A total of 822 articles were identified using electronic search engines and strategies. Among these articles, 131 were dropped as duplicates and 691 articles remained for further screening. The evaluation of title, full text and abstract screening resulted in the exclusion of an additional 602 articles. Therefore, a balance of 89 full-texts of studies was screened for eligibility criteria and other parameters that are not compatible with the review objectives. The full texts of 89 studies were reviewed for eligibility, and 11 studies were excluded from the analysis for not being English studies and nine studies were excluded for not reporting on the prevalence of the outcome (unlicensed and off-label prescriptions). In addition, seven studies were participants not children, nine studies were reviews, and six studies included mixed participants (adult and children). Therefore, a total of 47 studies were included in this review (Fig. 1).

This review summarized the most common off-labelled and unlicensed drugs prescribed in the selected studies (Table 1). Our review consisted of 25 studies from the Pediatric ward (Table 2). When comparing the PICU and NICU

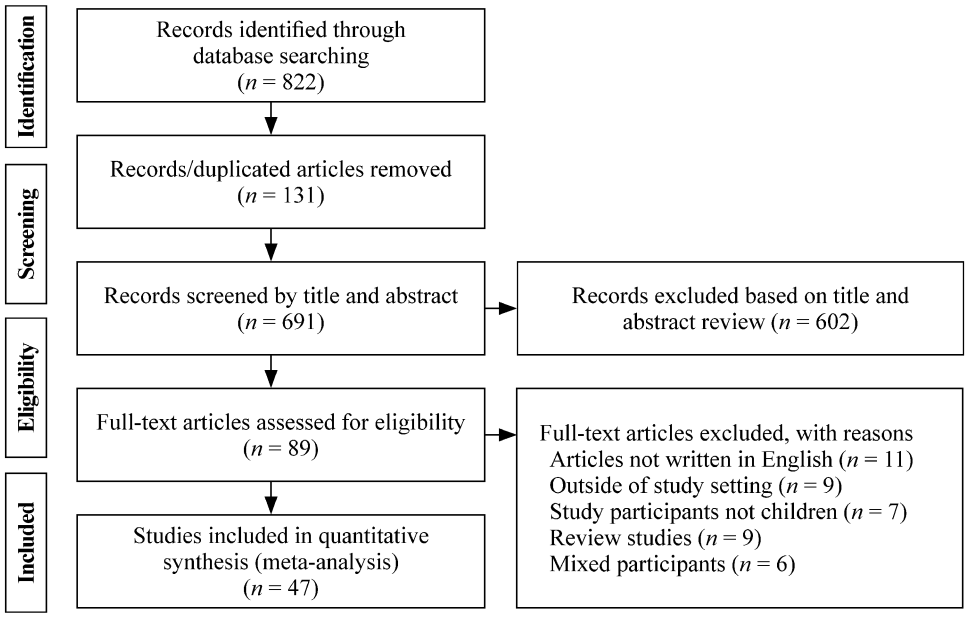

Fig. 1 PRISMA flow diagram summarizing the study selection process of included studies. *PRISMA* preferred reporting items for systematic reviews and meta-analysis

in our review, 13 studies were included in NICU (Table 3) and only five studies in PICU (Table 4). In Tables 3 and 4, the majority (90%) used prospective studies as study designed. We were able to include only four studies [23, 38, 57, 58] on the neonatology ward category. Of these studies, only one was conducted in Saudi Arabia; the rest were conducted in Europe (Slovak Republic, France and Estonia). While two studies were cross sectional, the other two were prospective studies (Table 5).

The extent of off-label and unlicensed drugs among hospitalized children

The proportion of off-label prescriptions ranged from 7.4% (Italy) to 99.5% (Brazil). [32, 47]. The proportion of unlicensed prescriptions ranged from 0.1% (Estonia) to 72.4% (Pakistan) [26, 57]. Moreover, the combined proportions of off-label and unlicensed prescriptions comprises four studies. These ranged from 44.5% (Malta) to 87.7% (Germany), Turkey 62.3% and Korea Republic 84.6% [20, 33, 34, 51].

One study [24] compared the extent of off-label and unlicensed prescription between countries (China and USA). A study [33] compared the proportions in China and USA. Regarding off-label prescriptions, a percentage of 15.87% and 46.5% were recorded in China and the USA, respectively, whereas the proportions of unlicensed drugs were seemingly higher in China with 74.1% compared to 22.0% recorded in the counterpart. Another study considered analysis on seasonal variation of the extent of these sorts of drug usage. During the winter season (August), 27% of prescriptions were classified as unlicensed and 44.6% as off-label; during summer season (January), 29.6% as unlicensed and 45.1% as off-label [9].

Regarding pediatric patients in the intensive care unit, a study from Israel [22], reported a seemingly higher proportion of prescriptions in neonatal population compared to 43.8% in the pediatric population for both off-label prescriptions (64.8% versus 43.8%) and unlicensed prescriptions (5.9% versus 3.4%).

Among the 38 included studies that provided information on the categories of off-label prescription, outside age range prescription (41.2%) was the most frequent category, followed by indication (26.5%) and dosage (20.6%) (Fig. 2). The pediatric population is, therefore, at an increased risk of consequences from off-label prescription, urging prompt global attention and response. The response should involve fostering clinical trials for pediatric population by pharmaceutical companies. Figure 3 illustrates the proportions of studies included in our review that reported mostly prescribed categories of drugs according to anatomical therapeutic chemical classification [59]. The majority (34.2%) of off-label prescription drugs were not effective for systemic use. Moreover, drugs belonging to the nervous system category were mostly (21.1%) prescribed as unlicensed.

Reasons and justification of the off-label or unlicensed prescription practice

A total of 28 (59.57%) studies reported various reasons that led to the unavoidable practice of prescribing off-label and unlicensed drugs as shown in Tables 2, 3, 4 and 5. The most common reason was lack of information, specifically for pediatrics on the drug information leaflets. Other reasons included lack of suitable formulation for pediatrics, imported medicines not authorized in

Table 1 The most common off-labelled and unlicensed drugs prescribed

Author, year	Most common off-labelled drugs prescribe	Most common unlicensed drugs prescribe
Tukayo et al., 2020 [15]	Ranitidine, ondansetron, gentamicin and artesunate	Darplex (dihydroartemisinin and piperaquine), cough powder (a combination of ambroxol, guaifenesin, chlorpheniramine maleate and vitamin C), primaquine, cefixime
't Jong et al., 2002 [16]	Acetaminophen, cefotaxime and amoxicillin	Acetaminophen, cefotaxime and amoxicillin
Bavdekar et al., 2009 [17]	Ranitidine, cefotaxime, dopamine	–
Sucasas Alonso et al., 2019 [18]	Fentanyl, vitamin E, cefazolin, ranitidine	Caffeine, spironolactone, phosphate, ranitidine
Landwehr et al., 2019 [11]	Ondansetron, fentanyl, oxycodone and paracetamol	Chlorhexidine and dexamethasone
Kouti et al., 2019 [10]	Ampicillin, gentamicin and caffeine	Furosemide and phenobarbital
Dornelles et al., 2019 [9]	Vitamins A and D, beclomethasone and furosemide	Dipyrone, chloral hydrate, metoclopramide, metronidazole, morphine
Costa et al., 2018 [19]	Fentanyl, gentamicin and aminophylline	Caffeine, furosemide and phenobarbital
Lee et al., 2018 [20]	Dopamine, esomeprazole magnesium trihydrate, ciprofloxacin and ramosetron	Dopamine, esomeprazole magnesium trihydrate, ciprofloxacin and ramosetron
Aamir et al., 2018 [21]	Ampicillin, cefotaxime, phenobarbitone	–
Nir-Neuman et al., 2018 [22]	Vitamin A, furosamide, NaCl, phenobarbital and naloxon	Ampicillin sodium, gentamicin sulfate, aminophylline, phytomenadione and glycerin
Mazhar et al., 2018 [23]	Ranitidine, midazolam, tobramycin, salbutamol and fluconazole	Polystyrene sulfonate and mannitol
Zhu et al., 2018 [24] (antipsychotic only)	Olanzapine, quetiapine and risperidone	Olanzapine and quetiapine
Di Paolo et al., 2006 [25]	Morphine, ondansetron, dopamine and potassium chloride	Sodium chloride, heparin, spironolactone and hydrochlorothiazide
Aamir et al., 2017 [26]	Metronidazole, ranitidine, ranitidine and ceftriaxone	–
't Jong et al., 2001 [27]	Cisapride, caffeine and tobramycin	Cisapride, caffeine and tobramycin
Arocas Casañ et al., 2017 [28]	Ampicillin and gentamicin	Caffeine citrate
Teigen et al., 2017 [29]	Ampicillin powder for injection or infusion, sodium chloride 9 mg/mL solution for infusion and salbutamol solution for inhalation	Racemic adrenaline solution for inhalation, caffeine oral solution, ibuprofen suppositories and vitamin K oral drops
Santos et al., 2008 [30]	Ceftriaxone, benzylpenicillin and mebendazole	Captopril, nifedipine and ursodeoxycholic acid
García-López et al., 2017 [31]	Atropine, etomidate, dipyrone and ranitidine	Spironolactone, sildenafil, acetazolamide and hydrochlorothiazide
de Souza et al., 2016 [32]	Heparin, fentanyl and multivitamins without minerals	Tricalcium phosphate, alprostadil, biotin, L-carnitine, riboflavin, and thiamine
Cuzzolin et al., 2016 [33]	Ampicillin, fluconazole, gentamicin and fentanyl	Folinic acid and caffeine
Ellul et al., 2015 [34]	–	–
Jobanputra et al., 2015 [35]	Adrenaline, nor-adrenaline, oseltamavir and frusemide	Isoniazid, ethambutol, pyrizinamide, oseltamivir and fluconazole
Bajcetic et al., 2005 [36]	Furosemide, lincomycin, digoxin and amoxicillin	Acetylsalicylic acid and carvedilol
Joret-Descout et al., 2015 [37]	Pantoprazole, folic acid, esomeprazole and ondansetron	Urosdesoxycholic acid
Schweigertova et al., 2016 [38]	Ketoconazole, anti-diarrheal microorganisms, folic acid and clotrimazole	Caffeine and phenobarbital
Czarniak et al., 2015 [39]	Ondansetron, painstop day, salbutamol, oxycodone and paracetamol	Cephazolin and dilacaine eye drops, dexamethasone, azathioprine, propranolol, tinidazole, gonadorelin and tocilizumab
Riou et al., 2015 [40]	Calcium folinate, amikacin sulphate, ferrous fumaratem, rifamycin sodium and sodium chloride 10%	Glucose monohydrate 10%, norepinephrine, ketamine hydrochloride, glucose phosphate disodique and pentobarbital
Palmaro et al., 2015 [41]	Tixocortol, mequitazine, desloratadine and tuaminoheptane	Physiologic serum and oral rehydration solution
Mohamad et al., 2015 [42]	Diphenhydramine, budesonide and loratadine	–

Table 1 (continued)

Author, year	Most common off-labelled drugs prescribe	Most common unlicensed drugs prescribe
Langerová et al., 2014 [43]	Desloratadine and cetirizine	Ramipril and enalapril
Kieran et al., 2014 [44]	Gentamicin, benzylpenicillin, morphine sulphate, chlorhexidine 2% solution and cyclopentolate	Caffeine citrate
Lindell-Osuagwu et al., 2014 [45]	Fentanyl, paracetamol, salbutamol and midazolam	–
Lee et al., 2013 [46]	–	–
Laforgia et al., 2014 [47]	Furosemide, phenobarbital, theophylline and ranitidine	Caffeine and parenteral nutrition solutions
Kimland et al., 2012 [48]	Antifungals, fusidic acid, steroids and isotretinoin	–
de Abreu Ferreira et al., 2012 [49]	Ranitidine, fentanyl, dipyrone and ampicillin	Caffeine citrate
Palčevski et al., 2012 [50]	Pantoprazole, esomeprazole, ranitidin, oxymetazoline and granisetron	Nystatin, kaptopril, iron, trivalent, macrogol and valproic acid
Oguz et al., 2012 [51]	–	–
Dos Santos et al., 2012 [52]	Metoclopramide, omeprazole and salbutamol	Dipyrone, biperidene, tizanidine, ursodeoxycholic acid
Lass et al., 2011 [53]	Gentamicin, ampicillin and heparin	Furosemide, heparin and dobutamine
Khdour et al., 2011 [54]	Salbutamol, adrenaline, paracetamol and dexamethasone	Captopril, furosemide, diclofenac sodium, beclomethasone and hydroxytryptophan
Conroy et al., 2000 [55]	Cyclizin, salbutamol, budesonide, beclometasone and heparin	Beclometasone
van den Berg et al., 2011 [56]	–	Prednisolone, heparin, ethanol and vancomycin
Lass et al., 2011 [57]	Amoxicillin/clavulanic acid, hydrocortisone, chlorhexidine cetirizine drops and salbutamol	–
Nguyen et al., 2011 [58]	Ferrous fumarate, sodium chloride 10%, benzylpenicillin, amikacin, domperidone and sodium alginate and sodium bicarbonate	Calcium folinate

"–" not reported

the country of administration and extemporaneously prepared drugs. For example, there are changes in the drug formulation authorized but this takes time for prescribers to adopt, and also a time during which previously correct drug formulations deem off-label [39]. Another example is that the information regarding newly formulated drugs in the product information leaflets may seem outdated in drugs that are already in the market [54].

Consequences of off-label and unlicensed drugs

Among the included 47 studies, only 8 (17.02%) (Netherlands, Malaysia, Ireland, Korea Republic, Indonesia, Australia and two studies from Brazil) had reported consequences of off-label and unlicensed drug prescriptions, ranging from mild side effects (e.g., skin reaction) [44] to the fatal outcomes, such as renal failure [19]. Apart from the aforementioned consequences that were more direct to patients' health (i.e., patients' consequences), two studies [15, 46] reported other consequences which were indirect and impacted prescribers leading to medical legal-issues (i.e., prescribers' consequences).

Discussion

In the last decade, there has been a surge in concerns regarding off-label and unlicensed drug prescriptions in the pediatric population, mainly due to fewer clinical trials done in this population as compared to the adult population [3]. Though not an illegal act, off-label and unlicensed prescriptions require consideration of safety and consent, after a thorough assessment of the benefit-risk ratio. Recently, the use of off-label drugs and unlicensed prescriptions of drugs in children is at an increasing rate. Despite the implemented legislative regulations, the approved pediatric labeling is not efficient for pharmaceutical industry [60]. Currently, national governments are required by the World Health Organization to establish and maintain regulatory authorities for medicines [61].

We reviewed published literature from the last three decades to provide an up-to-date summary of the extent, reasons, and consequences of off-label and unlicensed drugs in hospitalized pediatric patients. The proportion of off-label prescriptions ranged from 7.4 to 99.5%. Comparing our review with the previously published literature, Moulis

Table 2 Summary of study characteristics of pediatric ward included in our review

Author, year	Proportion (%) for the off-label and unlicensed prescription (OL; UL)	Study design (sample size)	Study duration	Reasons and justifications of off-label or unlicensed prescription practice	Off-label or unlicensed ATC drug category mostly prescribed	Consequences of off-label and unlicensed drugs	Country
Tukayo et al., 2020 [15]	71.5; 7.9	Retrospective study (200)	3 mon	–	Anti-infective for systemic use; anti-infective for systemic use	Adverse reactions Medico-legal issues	Indonesia
't Jong et al., 2002 [16]	44; 28	Prospective cohort study (293)	19 wk	–	–	–	Netherland
Landwehr et al., 2019 [11]	54.0; 1.6	Retrospective study (190)	1 mon	Lack of appropriate pediatric formulations Lack of pediatric information in the package leaflets, i.e., phenylephrine	Nervous system; alimentary canal and metabolism	Increase in global antibiotics resistance	Australia
Lee et al., 2018 [20]	Combined proportion: 84.6	Retrospective study (2779)	12 mon	–	Nervous system; nervous system	Increased risk of all-cause mortality	Korea Republic
Zhu et al., 2018 [24] (antipsychotic only)	China: 15.8; 74.1 USA: 46.5; 22.0	Retrospective study (40,528)	4 y	Lack of pediatric information in the package leaflets Differences in license information between the two countries	Nervous system; nervous system	–	China
Di Paolo et al., 2006 [25]	25; 24	Prospective (60)	6 mon	–	–	–	Swiss
Aamir et al., 2017 [26]	81.1; 72.4	Cross sectional study (895)	12 mon	Lack of data regarding pediatrics prescription in the national essential drug list of Germany	Anti-infective for systemic use	–	Pakistan
't Jong et al., 2001 [27]	43; 28	Prospective cohort (293)	5 mon	–	–	–	Netherlands
Teigen et al., 2017 [29]	83.0; 59.0	Cross sectional study (400)	4 mon	Lack of pediatric license/information on the package leaflets	Anti-infective for systemic use; respiratory system	–	Norway
Santos et al., 2008 [30]	39.6; 55	Prospective cohort (272)	5 mon	–	–	–	Brazil
Ellul et al., 2015 [34]	Combined proportion: 44.5	Prospective study (924)	3 mon[a]	Unavailability of data regarding pediatric age group	Respiratory system; systemic hormonal preparations	–	Malta
Palmaro et al., 2015 [41]	37.6; 6.7	Cross sectional study (2313)	5 mon	–	Respiratory system; alimentary tract and metabolism	–	France
Mohamad et al., 2015 [42]	OL: 60.9	Prospective study (134)	6 mon	–	Dermatologicals	–	Malaysia
Langerová et al., 2014 [43]	9.01; 1.26	Cross sectional study (4282)	6 mon[a]	–	Respiratory system; various	–	Czech Republic

Table 2 (continued)

Author, year	Proportion (%) for the off-label and unlicensed prescription (OL; UL)	Study design (sample size)	Study duration	Reasons and justifications of off-label or unlicensed prescription practice	Off-label or unlicensed ATC drug category mostly prescribed	Consequences of off-label and unlicensed drugs	Country
Bajcetic et al., 2005 [36]	48; 11	Prospective (544)	2 mon	–	Kawasaki disease, cardiac arrhythmias	–	Belgrade
Joret-Descout et al., 2015 [37]	36.5; 3.2	Cross sectional study (120)	1 d[a]	Diseases not covered by the regulatory body Drug indicated and approved only in adults An indication approved for children at a different age group Lack of an alternative treatment	Alimentary tract and metabolism	–	France
Czarniak et al., 2015 [39]	25.7; 2.6	Retrospective study (1037)	12 mon[a]	Lack of commercially available preparation	Cardiovascular system; systemic hormonal preparations	–	Australia
Lindell-Osuagwu et al., 2014 [45]	2011: 79; 53 2001: 58; 26	Prospective study (123)	2 mon	No direction for use in children (i.e., oxycodone)	Nervous system; not reported	–	Finland
Kimland et al., 2012 [48]	41; 4.6	Cross sectional study (2947)	2 d	Lack of pediatric information in the package leaflets	Nervous system; alimentary tract and metabolism	–	Sweden
Palčevski et al., 2012 [50]	19.7; 25.0	Prospective study (531)	12 mon[a]	Lack of pediatric information in the package leaflets	Alimentary tract and metabolism; anti-infective for systemic use	–	Croatia
Dos Santos et al., 2012 [52]	39.0; 12.0	Cross sectional study (342)	3 mon	Lack of information specifically for pediatrics on the drug information leaflets	Alimentary tract and metabolism; nervous system	–	Brazil
Lass et al., 2011 [53]	72.0; 15.0	Cross sectional study (151,476)	12 mon	Lack of information regarding pediatrics on the drug information leaflet New drug formulation	Anti-infective for systemic use; anti-infective for systemic use	–	Estonia
Khdour et al., 2011 [54]	35.3; 7.1	Prospective study (387)	5 wk[a]	Newly modified licensed drugs Lack of availability of suitably licensed drugs for newborns and infants	Anti-infective for systemic use; cardiovascular system	–	Palestine
van den Berg et al., 2011 [56]	43.0; 28.0	Prospective study (39)	2 wk[a]	Extemporaneous medication	Antineoplastic and immunomodulating agents	Bone marrow toxicity	Netherland
Dornelles et al., 2019 [9]	Winter season: 44.6; 27.0 Summer season: 45.1; 29.6	Prospective study (157)	6 mon	Lack of evidence on the effectiveness and safety of licensed drugs for pediatrics Lack of licensed alternative drugs for pediatrics	–	–	Brazil

OL off-label drugs, *UL* unlicensed drugs, *ATC* anatomical therapeutic chemical classification. [a]Date of starting and ending was not reported. "–" not reported

Table 3 Summary of study characteristics of NICU included in our review

Author, year	Proportion (%) for the off-label and unlicensed prescription (OL; UL)	Study design (sample size)	Study duration	Reasons and justifications of off-label or unlicensed prescription practice	Off-label or unlicensed ATC drug category mostly prescribed	Consequences of off-label and unlicensed drugs	Country
Sucasas Alonso et al., 2019 [18]	22.5; 8.0	Prospective study (84)	6 mon[a]	–		–	Spain
Kouti et al., 2019 [10]	38.1; 1.9	Retrospective study (193)	3 mon[a]	Lack of suitable oral forms of drugs for neonates	Anti-infective for systemic use	–	Iran
Costa et al., 2018 [19]	49.3; 24.6	Prospective study (220)	12 mon	Adaptations to newly introduced drug/drug formulations	Nervous system; anti-infective for systemic use	Renal and internal ear toxicity (i.e., gentamicin) Respiratory distress (i.e., fentanyl) Tachycardia (i.e., aminophylline)	Brazil
Arocas Casañ et al., 2017 [32]	41.4; 5.5	Retrospective study (41)	3 mon[a]	Not reported	Anti-infective for systemic use; nervous system	–	Spain
de Souza et al., 2016 [32]	99.5; 11.9	Retrospective study (192)	6 mon[a]	Lack of neonatal drug information on the package leaflets No warnings and precautions regarding the administration to neonates, on the package leaflets	Anti-infective for systemic use; alimentary tract and metabolism	Multivitamin toxicity following the prescription of multiple vitamin sources (i.e., E-Ferol syndrome) Hemodynamic instability (i.e., dobutamine) Metabolic bone disease Inborn errors of metabolism Fatal extrapyramidal effects	Brazil
Cuzzolin et al., 2016 [33]	Combined proportion: 87.7	Cross sectional study (220)	3 mon	Lack of license in the country (i.e., Italy) Unavailability of product information regarding the pediatric age group (i.e., fentanyl) Lack of Efficacy and safety information regarding the pediatric population (i.e., ranitidine, domperidone)	Cardiovascular system; blood and blood forming organs	–	Germany
Riou et al., 2015 [40]	59.5; 5.2	Prospective study (910)	2012	Lack of information in the drug information leaflets Lack of extensive safety and efficacy data on the drug information leaflet	Various; blood and blood forming organs	–	France

Table 3 (continued)

Author, year	Proportion (%) for the off-label and unlicensed prescription (OL; UL)	Study design (sample size)	Study duration	Reasons and justifications of off-label or unlicensed prescription practice	Off-label or unlicensed ATC drug category mostly prescribed	Consequences of off-label and unlicensed drugs	Country
Kieran et al., 2014 [44]	39; 19	Prospective study (110)	2 mon[a]	–	Anti-infective for systemic use; nervous system	Skin reaction to chlorhexidine Renal failure secondary to ibuprofen	Ireland
Laforgia et al., 2014 [47]	7.4; 11.4	Prospective study (126)	1 mon[a]	–	Cardiovascular; nervous system	–	Italy
Oguz et al., 2012 [51]	Combined proportion: 62.3	Prospective study (464)	24 h[a]	Lack of information specifically for pediatrics on the drug information leaflets	–	–	Turkey
Lee et al., 2013 [46]	34.1; 27.3	Prospective study (194)	3 mon	Extemporaneously prepared medicines Imported medicines not authorized in Malaysia The lack of suitable formulation for pediatrics	Anti-infective for systemic use; various	Jeopardizing the child's safety and drug efficacy Medicolegal issues	Malaysia
Nir-Neuman et al., 2018 [22]	NICU: 64.8; 5.9 PICU: 43.8; 3.4	Prospective study (NICU 134, PICU 56)	2 mon[a]	Licensed drug replacement (i.e., caffeine replaced by theophylline) Cessation of use of drugs (i.e., cisapride) Lack of pediatric information in the package leaflets	Anti-infective for systemic use; alimentary canal and metabolism	–	Israel
Aamir et al., 2018 [21]	52.1; 33.4	Prospective study (1300)	12 mon[a]	Limited licensed drugs available in pediatrics Lack of adequate clinical drug trials in pediatrics population	Anti-infective for systemic use	–	Pakistan

OL off-label drugs, *UL* unlicensed drugs, *ATC* anatomical therapeutic chemical classification, *NICU* neonatal intensive care unit, *PICU* pediatric intensive care unit. [a]Date of starting and ending was not reported. "–" not reported

Table 4 Summary of study characteristics of PICU included in our review

Author, year	Proportion (%) for the off-label and unlicensed prescription (OL; UL)	Study design (sample size)	Study duration	Reasons and justifications of off-label or unlicensed prescription practice	Off-label or unlicensed ATC drug category mostly prescribed	Consequences of off-label and unlicensed drugs	Country
Bavdekar et al., 2009 [17]	70.58; –	Prospective exploratory (300)	7 mon	–	Hypertension, hepatic encephalopathy, heart rate	–	India
García-López et al., 2017 [34]	53.9; 8.6	Prospective study (42)	Not reported	–	Alimentary tract and metabolism; cardiovascular system	–	Spain
Jobanputra et al., 2015 [35]	41.25; 21.01	Prospective study (482)	12 mon[a]	Lack of drug information regarding pediatrics age group on the drug information leaflet	Nervous system; anti-infective for systemic use	–	Netherlands
de Abreu Ferreira et al., 2012 [49]	23.4; 12.6	Cross sectional study (73)	1 y	–	–	–	Brazil
Conroy et al., 2000 [55]	54.6; –	Prospective (51)	4 wk	–	–	–	UK

OL off-label drugs, *UL* unlicensed drugs, *ATC* anatomical therapeutic chemical classification, *PICU* pediatric intensive care unit. [a]Date of starting and ending was not reported. "–" not reported

Table 5 Summary of study characteristics of neonatology ward included in our review

Author, year	Proportion (%) for the off-label and unlicensed prescription (OL; UL)	Study design (sample size)	Study duration	Reasons and justifications of off-label or unlicensed prescription practice	Off-label or unlicensed ATC drug category mostly prescribed	Consequences of off-label and unlicensed drugs	Country
Schweigertova et al., 2016 [38]	43.0; 4.8	Cross sectional study (202)	6 mon	Lack of product information Change of drug formulation	Alimentary tract and metabolism; nervous System	–	Slovak Republic
Nguyen et al., 2011 [58]	19.6; 16.6	Cross sectional study (65)	4 mon	Lack of evidence-based information data on pediatrics	Blood and blood forming organs; various	–	France
Lass et al., 2011 [57]	31.0; 0.1	Prospective study (490)	8 mon	Lack of/outdated pediatrics information in the drug information leaflets	Respiratory system drugs	–	Estonia
Mazhar et al., 2018 [23]	29.7; 12.9	Prospective study (138)	3 mon	–	Anti-infective for systemic use; various	–	Saudi Arabia

OL off-label drugs, *UL* unlicensed drugs, *ATC* anatomical therapeutic chemical classification. "–" not reported

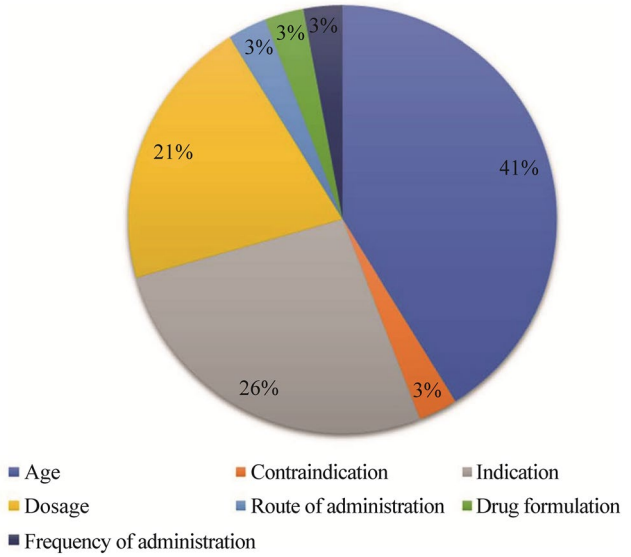

Fig. 2 The proportion of studies reporting most frequent off-label prescription categories

et al. [14] and Gore et al. [12] reported that the ranges were 36.3–97.0% and 9–78.7%, respectively. These are quite narrower than the range reported in our review. Magalhães et al. [62] also showed a similar more restricted range as compared to our study (i.e., 12.2–70.6%). On the other hand, Balan et al. [63] reported a more extensive range of off-label prescriptions compared to our study (i.e., 1.2–99.7%). All the reported ranges are considerably wide. We believe that the reasons for the wide ranges are due to high heterogeneity between the reviewed studies that could be attributed to different opinions among prescribers depending on their experience and drug availability in their local settings. The evidence, as shown in our study, is that different countries have different extents of off-label prescription [22, 33]. Moreover, drugs information evolves over time with newer drug formulation emerging as technology evolves. This means that studies published in different times could have different definitions of off-label prescription, even for the same drug. The finding that different extents of off-label prescriptions were prescribed in winter and summer times could be attributed to different disease patterns in the two seasons. For example, winter season is likely to have an increased number of upper and lower respiratory illnesses compared to summer season, meaning more respiratory system drug prescriptions in the winter than summer.

In our review, the most frequent category of off-label prescription was prescription outside the age range. Authors believe the reasons to be attributed to the fact that fewer clinical trials have been done in the pediatric population due to ethical issues regarding this smaller and fragile population as compared to the adult population [6]. This finding, however, contradicts those reported by Tukayo et al. [15], Kouti et al. [10], Dornelles et al. [9] and Costa et al. [19] who reported, respectively, that the most frequent categories were indications, dosage, formulation and administration frequency. The reasons could be attributed to heterogeneity among reviewed studies. Even though our review included hospitalized pediatric patients, other studies involved intensive care unit patients while others involved general ward patients. Intensive care unit patients are regarded to be sicker with probably more prescriptions as compared to general wards' patients. Moreover, different hospitalized patients have different diagnoses that could mean different drug prescriptions, frequencies, formulations, dosages, and routes of administrations.

The proportion of unlicensed prescriptions ranged from 0.05 to 74.14%. This range is wider that those reported in

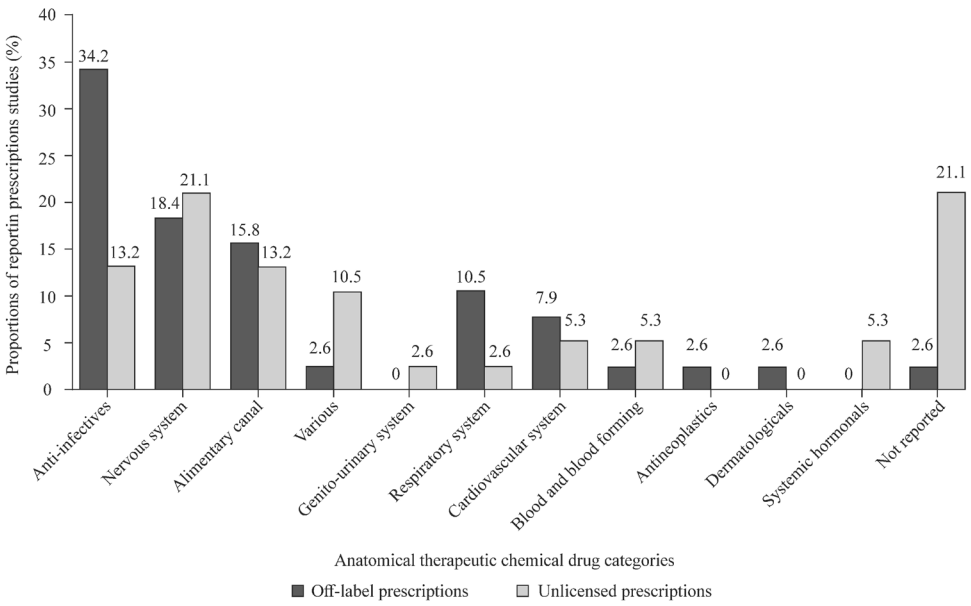

Fig. 3 Proportions of studies that reported mostly prescribed categories of drugs according to anatomical therapeutic chemical classification

three previously published studies [12, 14, 62], which were 0.3–35%, 18.6–40.2%, and 0.2–47.9%, respectively. Generally, all of these ranges are considerably wide. Besides high heterogeneity among the reviewed studies, variation in the definition of unlicensed drugs among different countries could be another potential reason for the differences. For example, the same drug can be licensed in one country, but not licensed in another.

Although not reported in the majority of included studies, the most commonly reported reason for off-label prescriptions was a lack of information specifically for pediatrics on the drug information leaflets. This was not entirely the case as Costa et al. [19], who reported the reason to be a delayed adaptation to newly introduced drug/drug formulations, in Brazil. Prescribers, pharmaceutical companies, and drug authorities should collaborate to tackle the barriers mentioned above and others, such as lack of suitable formulation for pediatrics, imported unlicensed drugs, and extemporaneously prepared drugs.

Only a few studies reported the consequences of off-label and unlicensed prescriptions. These could be bearable or very serious, including deaths. However, at present, it is evident that the pediatric population is a "therapeutic orphan" [64, 65]. Until adequate trials and authorized drugs for the pediatric population become available, unlicensed and off-label medication should not be abruptly banned in this population. The practice should, instead, be closely monitored while pharmaceutical companies, prescribers, and drug authorities collaborate to foster trials and to authorize adequate drugs for this population.

Study limitations and strengths

Our study had several limitations that originated from the study level and review level. At the included study level, different studies were broadly different from one another in terms of participants' demographic characteristics, different study methodologies, and studies from diverse countries across the globe. Hawthorne effect could also have impacted prescribers' responses [34]. At the review level, our study design is a narrative review with no quantitative data. However, we believe that this review could contribute to providing a broad picture on this topic by qualitatively summarizing evidence on the extent, reasons, and consequences of off-label and unlicensed drugs prescription as quantitative strategies like meta-analyses might not be the optimal option to reach to objectives of this review. Despite several previously published literature on this review's topic, our review currently considers pediatric population as a "therapeutic orphan" therefore does not discourage off-label or unlicensed prescriptions, but offers recommendations for closely monitoring the practice to prevent and/or mitigate adverse consequences, until when there are adequate authorized drugs for the population in the market.

In conclusion, impacting patients' safety and prescribers' practice, off-label and unlicensed prescription is extensive and requires progressively meditative interventions. However, the pediatric population is currently a "therapeutic orphan". Unless adequate pediatric clinical trials and licensed drugs become available, off-label and unlicensed drug prescription should not be discouraged but should be promoted in an organized manner. We therefore encourage prescribers to follow our recommendations to (1) regularly review and timely update the locally authorized drug database; (2) consult the locally authorized drug database or drug information leaflet before prescription; (3) consider prescribing an off-label or an unlicensed drug only if absolutely necessary after discussion with patients' parent/legal guardian on risks and benefits; (4) signing consent form; (5) monitoring the patient closely and preparing to mitigate adverse reactions after an off-label or unlicensed drug prescription, together with proper documentation and submission of the report to the country's drug authority.

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Compliance with ethical standards

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