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Off-label Prescribing Practice in Pediatric Settings: Pros and Cons

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ABSTRACT

Off-label prescribing of medication for pediatric patients is a commonly followed practice attributed to the unavailability of data of efficacy, safety, and dosing of medicines regularly prescribed for children. This review article sheds light on the worldwide incidence of off-label prescribing practice, and the most commonly prescribed medicines through this approach. We performed a literature search on PubMed and Google Scholar. The search terms include "off-label prescribing", "Pediatrics", "Drug safety", and "Adverse reactions". Publications were eligible for inclusion when enrolled children < 18 years of age, defined off-label prescription in the article and included the frequency and types of medication prescribed off-label. The frequency of off-label prescriptions does not differ widely between the reviewed studies based on the locally reported data. However, the frequency and awareness related to this practice in developed countries seem higher than the others. In conclusion, off-label prescribing in pediatrics remains a common approach followed by medical practitioners in pediatric settings.

Keywords: Off-label prescriptions, pediatrics, off-label medications, drug safety, adverse reactions.

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INTRODUCTION

Off-label prescribing means the use of medicines in a way not listed in the product leaflet concerning its dose, age category, indications, or route of administration. The prescription of off-label and unlicensed medicines for children applies, especially in neonatal medicine and hospital practice [1-6]. One of the reasons for the off label prescribing in pediatrics is the non-availability of the standard therapeutic options for a specific disease or condition for children [7]. It can be due to the lack of specific guidelines of dosing and route of administration for a pediatric age group in any of the official formularies of the medicines prescribed for this age group. Many studies demonstrated a high rate of off-label prescribing in respiratory drugs [8], analgesics [9], antibiotics [10], and antiepileptics [11,12] among others.

Many reports showed that off-label prescribing medications are more frequent for children than adults, since the vast majority are only developed based on trial outcomes on adults [3]. The vast majority of medications are clinically evaluated only in adults and used as off-label for children with weak or no evidence related to correct dosing, safety, or efficacy of these drugs in pediatric patients [13]. Many factors have dispirited manufacturers from characterizing pediatric needs including the complexity of the clinical trials, lack of attention of the added value, and inconvenient return on financial resources for pediatric medicine development. Based on the clinical trials, conditions with a high pediatric disease burden showed only 59.9% of these trials were attributable to children [14]. As a result, the off-label use of drugs has become a worldwide phenomenon, especially in pediatric patients. There are some main reasons for the scarcity of substantial evidence regarding approving drug labeling in pediatrics [15]. So, before marketing a drug for clinical use, a balance between beneficial and harmful effects has to be established. However, it does not imply an inappropriate, illegal, contraindicated, or investigational use [16]. The wide use of off-label drugs in the pediatric population strongly supports the need for drugs convenient for children of all age groups. [17-19].

THE CONSEQUENCES OF OFF-LABEL DRUG USE IN PEDIATRICS

In addition to the lack of pediatric-specific details on some medicines, other formulation labels include statements such as “the safety and efficacy in pediatric patients have not been established,” and accurate evidence-based contraindications and warnings are involved in the label where indicated. In this regard, the pediatrician needs to recognize the distinction between the absence of FDA approval for a specific use, the dosing regimen in the former case against explicit warnings, and contraindications against the use in the latter. Considering best practices for therapeutic decision-making, it is important to predict that the FDA does not control the use of medications related to the practice of medicine [20].

In this regard, about 85 physicians of the Calabrian Society of Pediatrics admitted that 88% of the interviewed specialists do not have enough knowledge of the cautions/benefit ratio of off-label drug prescriptions, and 40% of them often routinely follow this practice [21]. Nevertheless, their awareness of consequences seems to be minimal, and with a low level of concern about the risk of side effects, efficacy, and issues related to informed consent [22]. Meanwhile, the withdrawal of approved medicines from the market due to limited use accompanied by the increased use of newer unapproved medications in pediatric patients without explaining the clear advantage over the older alternatives. This results in a loss of access to medicine with demonstrated effectiveness/safety and increasing the prescription of those that do not show such accurate evidence in the pediatric population [23]

Although some of the available literature described the consequences of off-label prescribing, there has been unclarity in terms of specific guidance to help clinicians, guideline developers, and policymakers try to agree about the appropriateness of such use. Most clinicians regard off-label prescribing as suitable and that the benefits exceed the risks [24-26]. In 1917, due to the absence of evidence and approval of pediatric-specific medicines, the European Union adopted the pediatric regulations which guide manufacturers during the development of pediatric products to include more information on their use. Currently, a total of 273 new medicines and 43 additional pharmaceutical forms convent for use in the young patient were authorized in the EU and 950 PIPs were agreed by the EMA. Moreover, 486 waivers of the development of medical therapy in different medical conditions were agreed upon [27]. Besides, pediatric studies showed that the number of such trials in Europe approximately doubled from 96 to 164 [28]. In a 10-year study, the reported rate of pediatric off-label prescriptions ranges from 3.2 % to 95%. They included 1,323 prescriptions, 504 of them were off-label (38.1%) and 819 were approved. Accordingly, one can consider pediatric off-label prescribing as a common practice in clinical medicine. In 1917, some studies that evaluate new prescriptions revealed a relatively high rate of off-label prescriptions that may reach 38.1%. Despite the efforts to authorize clinical studies for pediatric drug labeling, there continues to be a high percentage of off-label use. However, the most alarming issue in these studies is that none of them highlighted the parental consent for off-label use; meanwhile, only two studies mentioned an adverse drug reaction secondary to such off-label use. Accordingly, physicians should be aware of the commonly prescribed off-label drugs in pediatric patients and be mindful of the known potential side effects and adverse reactions. They should also be aware of the probable new unlisted drug reactions or side effects [29]. Physicians should consider the involvement of the parents in the shared decision they make, examine all information about the drug, determine the family's priorities and risk tolerance, and make sure that the promising benefits outweigh the potential risks for that child [30].

WORLDWIDE STUDIES ON THE PEDIATRIC OFF-LABEL PRESCRIBING PRACTICE

Despite the numerous initiatives carried out since 2006 to allow rational medication to use in children, the prevalence of off-label use in outpatient pediatric practice remains high [31]. Meanwhile, the evaluation of many previous studies published during a decade did not reveal alarming ADR risks related to the off-label use [32,33]. Off-label prescribing in the pediatric population was very high. Most of the studies in this field are concerned about off-label drugs in European countries; they showed that the practice of pediatric off-label prescribing is a worldwide phenomenon and be an issue despite the increased awareness and passed legislation [34].

One of these studies showed that physicians prescribed one or more off-label systemic drugs at nearly one to a fifth of visits. Moreover, off-label drug prescribing in pediatric practice has been increasing in the US; physicians are prescribing medicines to treat children with unapproved conditions, like antidepressants, antihistamines, corticosteroids, and acid-suppressive drugs [30]. Another study recorded a high prevalence of both off-label and unlicensed prescribing in pediatric patients in the general medical ward in an Indonesian hospital setting. Antibiotic prescribing for unlicensed indications was a notable contributor and a potential public health issue relevant to these findings [35]. Other data supported the extending of the evidence base for psychopharmacologic treatment in pediatric patients; the major outcomes showed that 32.3% of all prescriptions were off-label, and 41.6% of patients received at least 1 off-label prescription. The most frequent off-label category was lower than the recommended age (72.2%). The off-label rates for each drug class include melatonin, 100%; antipsychotic agents, 95.6%; benzodiazepines, 72.5%; antidepressants, 51.1%; and ADHD medication, 2.7%. Prescription of 2 or more psychopharmacological agents per patient seems to be quite common (31.5%) [36]. Additionally, it has been reported that 8% of the allergy medications and 22% of the nasal corticosteroids were considered off-label based on the child's age [37]. The prevalence of pediatric off-label prescribing is notably increased in certain areas and associated with problems related to the difficulty of conducting clinical trials for specific clinical conditions. These issues are greater in neonatology and rare diseases or cases of children with a life-threatening disease or the terminal stage due to ethical reasons and sometimes for lack of resources [38,39]. Table 1 shows the pediatric off-label prescribing rate in different countries.

Table 1: The rate of pediatric off-label prescribing practice in different communities.

Country	Frequency of off-label prescribing practice
Australia	Pediatric off-label prescription rate =54% [8].
France	Pediatric off-label prescriptions equal 42% [40]
United States	16-62% pediatric off-label/unlicensed prescription. In the neonatal wards setting 55-80%. In the community setting 11-37% [41]
India	27.9-35.7% pediatric off-label/unlicensed prescription [42,43]
Indonesia	50.8-65.9% pediatric off-label prescription [44].
Brazil	56.0% pediatric off-label prescriptions [45].
Canada	38.2% pediatric off-label prescriptions [46].
Sweden	64% pediatric off-label prescriptions [47].
Italy	60% pediatric off-label prescription [48].
Spain	41.4-53.9% pediatric off-label prescriptions [49].
Jordan	28% pediatric off-label prescriptions [50].
Palestine	35.3% pediatric off-label prescriptions [51].
UK	65% pediatric off-label prescriptions [13].
Malaysia	Out of 442 evaluated prescriptions, 34.1 % were off label [52].

Iran	38.1% off-label prescriptions and 1.9% unlicensed use of medications [53].
Ethiopia	Out of 800 prescriptions, 607 (75.8%) include off-label use of drugs [54].
China	47.9% of the pediatricians acknowledged that they had prescribed off-label drugs [55].

The global estimate of pediatric off-label prescribing practice includes most medicinal formulations and exclude those containing electrolytes, nutrients, blood products, vaccines, and essential elements. That's why the true proportion of off-label use of products may have been ignored in those studies. Although intravenous carbohydrates and electrolytes are given orally probably show a low risk, the administration of drugs by non-approved route may be associated with a high risk of errors [56-64].

OFF-LABEL DRUGS-RELATED PROBLEMS IN CHILDREN

Children are not small adults. Their characteristics like age, weight, and surface area can change rapidly and need to be properly considered for accurate dosing of medicines. During growth, many physiological changes occurred in terms of body constituents (body water, plasma proteins, body fat, hormones, and clearance that can be affected by pH fluctuations, enzyme deficiency, and GI motility). All these changes will significantly affect the pharmacokinetic behavior of drugs and consequently dosing requirements. Some factors such as gender, race, inherited and acquired pathologies, and diet may also influence drug pharmacokinetics in children [65-67]. Besides, drugs may especially affect a child's physical and cognitive development, bone tissue, immune and sexual maturation [68]. In the preterm neonate, drug elimination is lower than usual due to the insufficient drug-metabolizing enzymes of the liver and immaturity of renal function. Consequently, the prescribed doses for the infants should be lower than the calculated weight-adjusted doses [69]. Meanwhile, toddlers and preschool children have a higher metabolic capacity and may need doses higher than the weight-adjusted doses [70]. Moreover, many obstacles were characterized during drug administration in this age group, and their inability to address or report ADRs is critical in this regard. Accordingly, further evidence of both the efficacy and safety of many therapeutic agents is required during prescribing pediatric off-label prescribing of medications [71,13,3,72,46].

The guide to adopting an ideal pediatric drug use should rely on a better understanding that the pharmacokinetic and pharmacodynamic characteristics are changing over a child's growth from infancy to adulthood [73]. Based on the currently available research outcomes, the specific physiological and pharmacological characteristics during childhood should not be ignored [74]. Hence, such practice led to demonstrate that problems related to drug prescribing in children have raised awareness among policymakers. The prescribers should be more aware of the potential impacts of off-label prescribing and take special measures toward reducing the prevalence of off-label prescribing and associated adverse effects [75]. In this regard, many reports indicated that ADRs in pediatric patients are more severe compared with adults since they are mostly associated with hospital admission, prolonged hospitalization, permanent disability, or even death [76,77].

MEDICATIONS COMMONLY PRESCRIBE OFF-LABEL IN PEDIATRICS

In the past few decades, many administrative and regulatory initiatives were considered globally to improve the clinical use of drugs in children. However, pediatric off-label prescribing practice is still found to be relatively high and the number of prescribed items in this way is also increasing following the increase of the approved items. Table 2 shows some of the reported data about the classes of medications that are prescribed off-label in pediatric practice.

Table 2: Drugs commonly used as off-label in pediatric practice.

Class of Medication	The mostly used off-label drugs
Antiviral agents	Cidofovir, Valacyclovir, Famciclovir [29]
Antibacterial agents	Cefadroxil, Cefazolin, Cefepime, Ceftazidime, Ceftriaxone, Amikacin, Amoxicillin, Vancomycin, Cephazolin, Ciprofloxacin, Flucloxacillin, Gentamicin, Ampicillin, Ticarcillin-Clavulanic acid [45,58,78-81,29,8]
NSAIDs	Naproxen, Acetylsalicylic acid, Diclofenac, Ketorolac, Metamizole, Acetaminophen, Parecoxib [82-88]
Opioid analgesics	Acetaminophen-Codeine, Codeine, Morphine, Alfentanil, Hydromorphone, Tramadol, Fentanyl, Oxycodone [89-96,29,85]
Antipsychotic agents	Olanzapine, Oxcarbazepine, Clozapine, Haloperidol, Lurasidone [97,98,29,36]
Anticonvulsants	Phenyltriazine, Lamotrigine, Fosphenytoin, Gabapentin, Lorazepam, Clonazepam, Diazepam, Midazolam [99-103,80,18,29,86]
Antidepressants	Mirtazapine [104]
Sedatives	Trazodone, Dexmedetomidine, Etomidate [105,106,29,85]
Anesthetics	Lidocaine, Ketamine [85,107-109]
Diuretics	Furosemide, Spironolactone, Acetazolamide, Hydrochlorothiazide [110,87,100,18]
Hormones	Adrenaline, Dobutamine, Dopamine, Melatonin, Desmopressin [86,84,87,111,112]
H2-blockers	Ranitidine [87]
Proton pump inhibitors	Lansoprazole [43,113]
Phosphodiesterase inhibitors	Sildenafil [114,115,87]
Cardiovascular agents	Clonidine, β-blockers, Perindopril, ACEIs [96,116,117]
Essential elements	Iron [118]
Anticoagulants	Heparin, Low Molecular Weight Heparin [119,84]

Bronchodilators	Fenoterol, Salbutamol nebulizer, Ipratropium, Inhaled corticosteroids [29,120,86,80]
Antihistamines	Chlorpheniramine, Dimenhydrinate, Loratadine, Dexclorfeniramine [80,93,18,120,121]
Antifoaming agents	Dimethicone [87]
Muscarinic blockers	Atropine, Hyoscine N-Butyl bromide [29,85]
Decongestants	Phenylephrine [80]
5-HT_3 antagonists	Ondansetron [85]
Antitussive agents	Dextromethorphan [122,123,88]

BENEFITS OF OFF-LABEL DRUG USE IN PEDIATRICS

Although off-label drug use is considered necessary in certain circumstances, one should never forget that more than 70% of Physicians' Desk Reference (PDR) entries lack specific pediatric labeling [124], and around three-fourths of prescription drugs now a day marketed in the US lack pediatric use information with disclaimers for pediatric use in labels [125]. Meanwhile, about 28% of drugs listed in various guidelines do not have accurate pediatric prescribing information. Nonetheless, a high percent of off-label drug use indicates that the licensing system is inadequately protecting the children's right to access safe medicines [30]. Considering the high rate of using drugs beyond their prescribing license in general practice, pediatricians declared that off-label prescribing was necessary for pediatric practice and make use of the available evidence, professional opinion, and personal experience more than what is mentioned in the product license [32].

The most frequent approaches of off-label prescribing are related to the use of a drug in the unapproved age group or when a drug is not indicated for a specific case, even that most drugs of the same group have been approved for such a disease, and mainly when a drug is not prescribed according to the approved indications for the aim of lifesaving. Physicians are frequently failed to consider the pathological characteristics of similar diseases and prescribe the same drug to treat many cases if the patient has any of the disease symptoms even when the drug indicated only for one of these conditions [126,17]. For many decades, the lack of drug evaluation in children has been considered as a factor favoring off-label prescribing. Currently, there have been many incentives to promote the clinical evaluation of drugs in children, as the promotion of good prescribing practice for antibiotics [127]. As a phenomenon, prescribing off-label drugs is widely followed in pediatrics; it is not illegal, and in some cases considered as a best practice. However, it places a sounding responsibility on the prescribers to assess the risks and benefits of such use in their patients. While this may be acceptable as an alternative option, it is unacceptable when it becomes a routine and common way of prescribing medicines [128]. Such use may be appropriate, especially during exceptional use in a properly informed patient with a serious disease, when there are no alternative or indicated drugs, and when the potential benefits outweigh the expected risks [129].

RISKS OF OFF-LABEL PRESCRIBED DRUGS IN PEDIATRICS

Many studies acknowledged the high incidence of ADRs among children treated with off-label drugs compared to those receiving on-label approved drugs [130,131,17]. Many of the prescribed medications have not been evaluated for safety and efficacy in children, and supported by week evidence; accordingly, such clinical practice may result in a high incidence of ADRs [132]. It can be explained by the lack of clinical research in the younger population due to ethical, scientific, and technical causes, besides commercial priorities. It is mostly followed based on the level of healthcare and patient characteristics [73].

There are various kinds of medicine-related problems in pediatric practice. They can be summarized as heterogeneous nature of the pediatric population, inability to swallow solid dosage forms, lack of standard dosage, off-label drug use, less acceptance of bitter oral formulations, stability and safety of excipients, needle phobias, calculation errors by healthcare providers, poor adherence, lack of available dosage forms and concentrations which necessitate additional calculations and manipulations of commercially available dosage forms or preparation of extemporaneous formulations, lack of familiarity between adult and pediatric guidelines, confusion between adult and pediatric preparations, limited published information, administration errors and use of inappropriate measuring devices [133]. A survey of 150 million off-label prescriptions in the US indicated that 73% had little or no scientific support [134]. This is especially for safety, with gross under-reporting of ADRs, which may be even more pronounced for unapproved vs. approved uses of medicines. However, there is now many pieces of evidence of resulting harm, with increased incidence and seriousness of risks associated with off-label use in children [13,135]. The European Medicine Agency (EMA) database from 2002-2004 reported 820 suspected ADRs in children taking an unapproved medicine, 130 of which were fatal, and 361 of them resulted in prolonged hospitalization [136]. Another study of spontaneous ADR reports in Swedish children over one year identified 158 cases of ADRs, 42.4% of which associated with off-label drug use. They were frequently serious rather than non-serious ADRs and were mostly due to prescribing non-approved dose for a non-approved age [137]. However, other studies have shown that there might be an association between off-label drug use and ADR risks [138,139]. Moreover, off-label drug use allows unregulated experimental uses of medicines, and there is a lack of research standards for clinical study design, documentation, data collection methods, and statistical analysis. Similarly, some studies have shown a significant association between off-label drug use and ADRs in pediatric patients [140,141,137].

CLINICAL TRIALS IN CHILDREN

The severity, frequency, and types of drugs most usually involved in ADRs are of specific interest in pediatrics since clinical trials are done mostly in adults; it makes prescribing off-label medicines for pediatric patients more likely to be under suspension [142]. Despite many regulatory modifications in pediatric drug development, the percent of clinical trials in pediatrics is still very scarce compared with adults, which has resulted in prescribing the medicines in an off-label pattern [143]. Conducting clinical trials in children is limited due to many reasons such as ethical consideration and practical difficulties,

specifically when dealing with young children. Objections of parents to provide permission to include their children in the clinical trials added other barriers to this issue. On contrary, this may harm their interests since it precludes the possibility of developing medicines tailored to their specific needs [144]. Besides, pediatric patients merely account for the minority of the population in the pharmaceutical market. Based on economic considerations, it is not productive for the pharmaceutical industry to undertake extensive clinical trials in pediatric patients [145,146].

As a result, many drugs prescribed for children have not been evaluated especially in the pediatric population and a lack of pediatric information occurs. Also, it is not uncommon that the dosages for children are hypothesized from data of clinical trials conducted in the adult population [147]. Despite the efforts aimed at increasing the involvement of children in clinical trials in the USA and the European Union, their number is still limited. One of the most important causes behind that is the decision of a child taking part in a clinical trial is made by their parents. A surveyed study mentioned that 59.8% of the parents would allow their children to participate in clinical trials only if the case is life-threatening; 51.3% of them would conform to a clinical trial only if a child has a chronic disease. The percent of parents who would allow their healthy children to participate in a clinical trial is very low [18]. Based on a survey outcome, the parents of pediatric patients are aware of the possible ADRs associated with the off-label use of drugs and think that increasing the number of pediatric clinical trials is important [148]. As an example, analgesics such as opioids and nonsteroidal anti-inflammatory drugs (e.g., diclofenac) have been highlighted by several authors as drug types for which clinical trials are most needed to obtain appropriate efficacy, safety, and dosage data for all pediatric age groups [46,72].

CONCLUSIONS

Prescribing off-label medications is a common practice in the pediatric population, especially in neonates and younger age groups. Research on more age-specific groups is highly recommended to confirm medicine safety and effectiveness for the pediatric population. However, clinical decision making should be governed by the availability of the best evidence and waiting for more data in this regard.

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CONFLICT OF INTEREST

There are no conflicts of interest.

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