Off-Label Prescribing in Pediatric Population

Subjects: Pediatrics | Pharmacology & Pharmacy

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Off-label prescribing is widespread among pediatricians, and it is unlikely that this trend will soon be bound by a uniform legal framework. This is necessitated by the fact that there are four variables: the patient's health condition, the physician's experience and knowledge, the legislative measures (laws, directives, guidelines, and recommendations), and finally, the pharmaceutical industry. There is considerable concern worldwide about the use of off-label medicines in children.

off-label use | children | neonates | pediatrics | safety | prescription | legislation

1. Introduction

Off-label use is very common and generally legal unless it violates ethical guidelines or safety regulations. Often the reason is to respond to patients' medical needs or enable access to innovative medicines, especially when there is no alternative option [1][2]. Compared to the drugs that are authorized for adults, those licensed for pediatric use are comparatively a much smaller fraction. In addition, off-label use of medicines is in general not supported by the same level of evidence as medicines licensed for adults [3]. This may result in increased uncertainty on efficacy as well as the risk for adverse drug reactions (ADRs).

Once a medicinal product is licensed, it is the prescribers who assess the benefit–risk ratio and decide whether that medicinal product should be prescribed. All prescriptions that do not comply with the licensed Summary of Product Characteristics (SmPC), whether indication, age, dose or dosage regime, route of administration, mode of use, etc., fall under 'off-label use' [4]. The SmPC is a legal document, approved by national regulatory agencies, EMA, FDA, TGA, etc., as part of the marketing authorization of each medicine. However, for better or worse, 'off-label' is a real fact, a working phenomenon, despite not completely legitimate, that slowly paved its way into therapeutic regimens, and we already accepted it as a regular practice [5][6].

Medicines regulation controls how medicinal products are marketed, not how they are prescribed [4]. Regulatory approval is a costly and time-consuming process. It is obvious that not every drug will be tested for every eventual indication in its entirety. Thus, the regulation of therapeutic freedom adopts "an anything not explicitly prohibited is permitted" approach and assumes that medicines can be used in ways not specified in the label as long as they are prescribed by a competent professional based on scientific knowledge [4][7]. Healthcare providers are not required to limit prescriptions or recommendations to the indications approved by their country's drug regulatory body. Despite the risk, healthcare professionals often prescribe various medications that do not contain regulatory labels for use in pediatrics. The standard of care for many conditions involves off-label uses. When this process is

unavoidable, it should always be guided by a rigorous benefit/risk assessment since healthcare professionals are solely responsible for off-label use [8]. In other words, properly understanding why off-label use is common and "usually appropriate, rather than rare and usually inappropriate", requires understanding [9].

The reason that many medications in children are administered in an off-label manner, is: (1) there are not enough legalized medicines for the pediatric population, and (2) there are not enough pharmaceutical dosage forms suitable for use in children [10]. The existence of many legal restrictions on the conduct of clinical trials in children further leads to a lag in the regulation of medicines for pediatric use, and hence the development of pediatric dosage forms suitable for both parenteral and oral use [11][12].

2. The Need for Pediatric Drugs

2.1. Features of the Children

Childhood is characterized by periods of rapid growth, maturation, and development. It is widely acknowledged that children constitute a diverse and heterogeneous population, encompassing preterm neonates to post-pubertal adolescents, and are not simply miniature versions of adults [13]. The characteristics of children, in terms of physiology and development, differ from those of adults, and these also differ in the age range from newborn to adolescence [14][15]. The pharmacokinetics (PKs) and pharmacodynamics (PDs) of drugs may be altered by age and development and can be significantly affected by different factors to an extent that is not well studied to date [16][17]. In addition, the age groups of children themselves differ from each other [18].

In neonates, it is particularly difficult to detect small but significant effects as outcome measures are more difficult to assess [15]. Developmental stages can also alter the action and response to a drug. This is true for the desired action and ADRs [19]. Unfortunately, history taught us that different drug effects seen in children can be toxic, as seen with chloramphenicol, valproate, and tetracycline, or enhanced, as seen with some treatments for leukemia [20]. In addition, the natural course of disease in children may differ from that seen in adults, and they may suffer from diseases not common in adults [21]. Understanding the differences in physiology at different stages of development assists with designing drug formulations and dose regimens [22]. Age-related periods in a child's development are defined as neonate/newborn (ages 0–29 days); infant (>28 days–12 months); toddler (>12–23 months); preschool child (2–5 years); school-aged child (6–11 years); and adolescent/teen (12–18 years).

2.2. Drug Formulations for Children

The development of age-appropriate dosage forms and strengths is a major challenge for the pharmaceutical industry [23]. Our knowledge of child-appropriate formulations has many gaps, and the industry faces many challenges in the process of creating appropriate formulations for all age groups [24][25]. The availability of suitable dosage forms is also limited even when the drug is approved for use by children. The complexity comes from the fact that accurate dosing is needed for different age groups [26]. It is unlikely that a single formulation will be appropriate across the pediatric population, necessitating multiple product variants [27]. Pediatric dosage forms

must also be adapted to the chemical–pharmaceutical properties of the active substance and excipients, taste masking, the quantity taken, acceptability, and convenience to the patient as well as to caregivers [28]. The excipients used in pediatric formulations need to be appropriate for the age group [29][30] to avoid the consequences of excipient toxicity [31]. All these factors further complicate the manufacturing process.

The oral route of administration remains the most preferred due to its convenience and stability [32]. Recent advances in pharmaceutical technology led to the development of various types of tablets, such as melts [33], chewable and orodispersible tablets, oral lyophilizates and oral films, powders, granules [34], and pellets or sprinkles for reconstitution; however, generally, liquid products are preferred, especially in children under 6 years old [35]. The major barrier in the development of oral liquid formulations is the taste-masking of drugs, a hurdle that can be very costly and may not be totally achievable [36].

Drug acceptability is of great importance for receiving adequate therapy [37]. Pediatric formulations must be appropriate for the child to ensure compliance with the medication [28]. Different pharmaceutical forms may differ in their pharmacokinetic profile, highlighting the risks associated with the use of drugs that are not intended for use in children or were manipulated. The manipulation or extemporaneous preparation of medicines by pharmacists has its risks due to the lack of sufficient data on the quality of the final product [38][39]. Frequently, additional adjustments to medications are made by parents and caregivers to enhance adherence, especially in the pediatric demographic, where 19% of administered medications undergo manipulation [40][41].

Due to the diverse factors that influence the development of pediatric dosage forms, not forgetting the high manufacturing cost, it is lagging in pace compared to the development of adult dosage forms [42].

2.3. Dosing in Children

Drug dosage determination is challenging in children since traditional pharmacokinetic studies are difficult to conduct and are subject to a greater number of ethical considerations [22]. Modifications related to typical growth and development necessitate the use of evidence-based approaches to determine safe and efficient medication doses for children at various developmental stages. Additionally, it is crucial to design suitable delivery systems for these medications. Due to the lack of sufficient studies related to PKs in children, it is still a common practice to calculate pediatric doses from data obtained from the adult population [27]. However, dosage adjustments are often more complex than simply reducing the dose set for adults based on the child's age or weight [43].

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) emphasized the absence of pediatric clinical trials and dosing details as critical clinical gaps. There is now a demand for increased pediatric data in the assessment of new drugs [44]. Recently, Shaniv et al. [45] identified eight different neonatal formularies worldwide (Europe, the USA, Australia-New Zealand, Middle East), and six of them were compared. Each formulary varies in style and monograph template, drug information, dosing information, and update routine. Healthcare professionals may retrieve required drug dose details; however, institutions usually give access to only one formulary (if any), thus limiting the amount of essential information. For example, Suwa et al. [46] compared 72

products with pediatric indications in the USA and found that only 83% (60/72) and 43% (32/72) of the products had pediatric indications in the UK and Japan, respectively.

Most pediatric drug dosing is usually based on weight (mg/kg) or body surface area (BSA; mg/cm^2) [47]. Utilizing total body weight (TBW) is a widespread and suitable method for calculating drug doses in children. Nevertheless, it is important to note that pediatric drug dosages cannot be directly standardized from an adult dose based solely on TBW (i.e., 60 kg adult is not equal to 60 kg child) when pediatric dosing data are unavailable [48]. Additionally of note is a very pressing issue in the last 15–20 years about drug dosing in obese children [49]. In obese children, dosing based on body weight and BSA might result in doses exceeding the maximum recommended for adults. To address this, alternative weight measures, such as ideal body weight (IBW) and adjusted body weight (ABW), were devised to better accommodate these variations. This is because the volume of distribution (Vd) and clearance (Cl) are mostly affected by physiological changes (body mass, extracellular water, tissue perfusion, and proportions of lean and fat tissue) that occur during childhood development [50][51]. Generally, hydrophilic active substances should be dosed on IBW, partly lipophilic on ABW, and lipophilic on TBW [52]. Collectively, the physiological and pharmacokinetic changes in children with obesity may require adjustments to the loading and maintenance dose, dose interval, and time to reach a steady state in certain medications—a severely hampered process when it comes to off-label use [53].

2.4. Conducting Clinical Research with Children

Well-designed controlled clinical trials provide reliable evidence of treatment efficacy through rigorously controlled testing of human interventions. Conducting pediatric trials is challenging due to the heterogeneity of the population and specific ethical issues [54][55]. Ethical concerns about the inclusion of children in clinical trials are disproportionately high, resulting in strict laws and ethical guidelines [56][57]. The safeguarding of children traces back to the Nüremberg code, which permits clinical investigations only in individuals capable of giving informed consent [58], followed by the “Belmont Report” [59], ICH Guideline For GCP [60] and ICH Topic E11 [61], Directive 2001/20/EC, Ref. [62], and others. In the USA, the National Institute of Health (NIH) considers, under a legal framework, the inclusion of children in clinical trials unless there are “scientific or ethical reasons to exclude them”. Furthermore, in 1998, the FDA approved a requirement that new drugs intended for use in children entering the market must undergo prior evaluation on “clinical tests in the pediatric population to determine their security, effectiveness and correct dose” [63][64].

In Canada, the revised version of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans—TCPS 2 (2022) stipulates that the inclusion of pediatric patients in clinical trials is permissible only when the study’s objectives cannot be achieved through alternative means, informed consent is secured from parents or legal representatives, and the research poses no more than minimal risk to the children [65]. Moreover, numerous countries formulated ethical guidelines and regulatory frameworks for conducting clinical research involving children [1].

The number of clinical trials conducted in children is relatively small worldwide [66]. There exist neither mandatory requirements nor enough financial drivers for the development of pediatric medicines. The high development costs and low expected returns of new medicines for children do not usually attract the pharmaceutical industry to invest in this area. Globally, the population of children aged 0 to 14 is declining. For 2022, they comprise 25%, in comparison to 30% and 35% in 2000 and 1980, respectively. In 2022, in the EU, children under 14 years only account for 15% of the total population [67].

A high level of evidence is a prerequisite that seriously limits available drug treatment for children, as the underlying evidence is low across ages and drug classes. In a recent analysis by van der Zanden [68], findings revealed that only 14% of all off-label records (n = 2718) were substantiated by high-quality evidence, with 4% stemming from meta-analyses or systematic reviews and 10% from high-quality randomized controlled trials (RCTs). Furthermore, ethical, harmful, and consent concerns often pose challenges in obtaining institutional review board approval for clinical trials involving children [69]. Some researchers advocate for concurrently conducting phase I/II clinical trials for both adults and children, emphasizing the importance of interim reports from adult trials to inform and enhance clinical studies involving children [70][71][72][73]. This approach aims to minimize the time required to gather valuable and valid data on pediatric treatment while safeguarding children from exposure to ineffective and harmful treatments [74]. Consequently, the scientific community bears the responsibility of encouraging clinical trials in children to uncover novel and effective treatments. Viewing pediatric clinical research from a broader perspective, it underscores both the right of children to access efficient, evidence-based treatments and the obligation of health authorities and regulatory agencies to provide high-quality, evidence-based medical care.

3. Legislative and Ethical Measures for Off-Label Restriction

Over the past two decades, changes in drug regulation generated by the FDA and EMA resulted in substantial changes in how new drugs with potential use in children are studied and labeled [75][76]. To achieve child's health protection and to ensure that medications are used ethically, in 2007, the European Union (EU) issued legislation for the development and authorization of pediatric drugs [77][78]. In addition, pharmaceutical companies are required to submit a pediatric investigation plan (PIP) to the EMA's Pediatric Committee (PDCO) for every new medicine unless an exemption (waiver) is granted [79]. Ten years after Pediatric Regulation came into force, a total of 273 new medicines and 43 additional pharmaceutical forms appropriate for use in children were authorized in the EU [80].

Several governmental regulations were established to address off-label use in children. For example, the Pediatric Research Equity Act (PREA) of 2003 mandates pharmaceutical companies to investigate the impacts of new drugs on children when these drugs have the potential for pediatric prescriptions [81]. Studies conducted under PREA are obligatory, while those under the Best Pharmaceuticals for Children Act (BPCA) are voluntary. BPCA incentivizes pharmaceutical companies with an additional six months of patent exclusivity for drugs already on the market if they conduct clinical trials involving children [82]. These regulations not only underscore the importance of obtaining

pediatric safety, efficacy, and dosing information but also contribute to the transparency of the drug approval process.

In the United States, once a drug receives approval for a specific purpose, physicians have the liberty to prescribe it for any other purpose they deem safe and effective in their professional judgment, irrespective of official FDA-approved indications [4]. The FDA lacks legal authority to regulate medical practice, allowing physicians to prescribe drugs off-label. Contrary to common belief, the use of drugs off-label is legal in the USA and many other countries. In 2014, the American Academy of Pediatrics issued a statement addressing the off-label use of pharmaceuticals in children [83]. The statement advises pediatricians that “Off-label use is neither incorrect nor investigational if based on sound scientific evidence, expert medical judgment, or published literature”. Moreover, the statement advocates for increased support and incentives for clinical testing of drugs in children and the publication of all results, regardless of positive outcomes [83]. Therefore, for doctors to be able to treat their patients safely and avoid experimental treatments, their choices should be based on scientific evidence [84]. This leads to the conclusion that for such evidence to be available, doctors and manufacturers should be incentivized to collect and publish data on off-label use. This would contribute to driving the off-label use process.

In the United Kingdom, physicians are permitted to prescribe medications off-label. In line with guidance from the General Medical Council, the physician must ensure there is ample evidence or experience supporting the medicine’s safety and efficacy. Off-label prescribing may be deemed necessary when no appropriately licensed medicine is accessible to address the patient’s requirements or when the prescription is part of approved research [85].

In China, a guideline was introduced in 2022 with the aim of aiding the management of pediatricians, pharmacists, medical managers, policymakers, and primary care physicians in handling the off-label use of drugs in pediatric cases. Additionally, the guideline offers recommendations for shaping future healthcare policies [86].

An important ethical issue in this context is determining the responsible party for informing parents or caregivers when a child is prescribed an off-label drug. Occasionally, physicians do not provide this information, while on the other hand, the pharmacist is obligated to give it [87]. Hence, two possibilities follow: (1) the parents are stressed and refuse to give their child a drug with no established efficacy and safety and (2) the parents return to the doctor in search of another alternative drug [88]. To avoid complications, it is a physician’s obligation (evidenced by giving informed consent), later confirmed by the pharmacist.

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