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REVIEW ARTICLE

Pediatric Off-Label and Unlicensed Drug Use and its Implications

Rajeshwari Gore, Preeta K. Chugh*, Chakra D. Tripathi, Yangshen Lhamo and Sandhya Gautam

Department of Pharmacology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India

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Abstract: ***Background*:** Worldwide, in the absence of standard pediatric prescribing information, clinicians often use medicines in children in a dosage form or for an indication that has not been approved for use. Inadequate clinical trials increase exposure to drugs that lack safety-efficacy data in pediatric population. Hence, off-label and unlicensed drug use must be regarded as a patient safety-issue that is known to be associated with increased risks of adverse drug reactions apart from under- or over-dosing due to lack of pharmacokinetic data. This review aims to give an overview of the worldwide reported rates of off-label and unlicensed drug use in different patient populations in pediatric settings, with a brief summary of the related adverse drug reactions (ADRs) and a discussion of the existing regulatory provisions and possible solutions for ensuring safe use of medicines in children.

***Method*:** Literature searches were conducted and we included studies that evaluated unlicensed or off-label drug use in various pediatric patient populations. The definition of off-label drug use and unlicensed drug varied between different studies.

***Results*:** Fourteen studies from different countries were included in the review and were grouped as: studies conducted in the patients admitted in neonatal intensive care units, in pediatric wards, in hospitalized children and in pediatric outpatient settings. The number of patients studied ranged from 34 in neonatal intensive care units to 355 409 hospitalized children. Many studies reported high rates of off-label (9% to 78.7%) and unlicensed (0.3% to 35%) drug use in different pediatric patient settings.

***Conclusion*:** Given the prevalence of unlicensed and off-label drug use, the cooperation of various stakeholders including health professionals, pediatric population and their parents/caregivers, regulatory authorities, and the pharmaceutical industry is integral to instituting individual measures to avoid exposing children to unnecessary risks and avoid depriving them of potentially effective pharmacotherapy. Initiatives to encourage clinical trials for licensing drug use in children by providing market exclusivity and patent extension could aid in bridging the gap between approval and contemporary drug prescribing practices. Enforcement of legislations in the drug development process and subsequent pharmacovigilance could improve the quality of information and accountability of pharmaceutical industry to support and facilitate drug research in children.

Keywords: Off label, pediatric, drug safety, prescription, children, adverse drug reactions, off label drug use, neonates.

INTRODUCTION

Worldwide, the medical fraternity and regulatory authorities aim to safeguard public health and ensure adherence to safety guidelines for the well-being of the patients. A drug is approved for a particular indication after documentation and review of evidence collected from randomized controlled clinical trials. These trials present clinical safety efficacy data and a positive risk-benefit ratio necessary for its approval [1]. At the end of this process, pharmaceutical companies are granted market authorization, and the drug gets a license for marketing in the country [2]. Therefore, under the Federal Food, Drug and Cosmetic (FD&C) Act, pharmaceutical manufacturers can promote, advertise and include information on the package insert/drug monograph for FDA (Food and Drug Administration) approved indications only. However, the regulatory authorities cannot control the manner in which a physician prescribes a drug [1]. This may include prescribing drugs that are approved or not approved for a particular indication. US-FDA states that a drug may be used in an off-label manner when it is used for a disease or medical condition that is not approved to treat or administered in a dosage form or a route [3]. European Medical Association (EMA) states that off-label drug use "relates to situations where the medicinal product is intentionally used for a medical purpose

*Address correspondence to this author at the Department of Pharmacology, Vardhaman Mahavir Medical College and Safdarjung Hospital, New Delhi, India; Tel/Fax: +919811581034; E-mail: docpreeta@yahoo.com

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not in accordance with the authorized product information. The focus is on the intention of the healthcare professional to use a product outside the authorized conditions of use." [4].

Off-label and unlicensed use of drugs is common in medical conditions which are comparatively rare or in patient populations where there is insufficient data regarding their clinical use [5-7]. In a recently conducted survey in USA, off-label use for 160 commonly prescribed medicines was found to be as high as 80% [8, 9]. Extensive evidence suggests off-label and unlicensed use of various drugs including antidepressant and antipsychotic medications in psychiatric practice, bevacizumab in retinal diseases and non-steroidal anti-inflammatory drugs (NSAIDS) like diclofenac, ketorolac to treat cystoid macular edema in patients undergoing ocular surgeries, and anti-infectives and anti-epileptics in hospitalized children [5-15]. In the pediatric population, out-patient off-label drug use has been reported to be as high as 90% compared to 40% in adult population [16, 17]. Furthermore, over a 10-year period during October 1995 to September 2005, the European Agency for the Evaluation of Medicinal Products (EMEA) licensed only 33% of all the active substances for use in children, 23% in infants and 9% in newborns [18]. As a consequence, unlicensed and off-label is common and widespread [2, 8, 15-17, 19-23]. This review aims to give an updated overview of the worldwide reported rates of off-label and unlicensed drug use in different patient populations in pediatric settings, with a brief summary of the related adverse drug reactions (ADRs) and a discussion of the existing regulatory provisions and possible solutions for ensuring safe use of medicines for children.

REVIEW OF LITERATURE

Literature searches were conducted using the PubMed and Google Scholar databases using the Medical subject headings/ 'key words' such as "off-label drug use," "off-label prescribing," and "off-label drug pediatric." Bibliographies of selected references were also evaluated for relevant articles. Regulatory drug information releases and labeling information were also utilized. We included studies published in English between the years 1990 and 2015 that evaluated and numerically reported unlicensed or off-label drug use in various pediatric patient populations. Studies where only abstract could be retrieved were excluded from the analysis. The definition of off-label drug use and unlicensed drug varied between different studies. Unlicensed drug use was defined as the use of a non-marketed drug, modified formulations including extemporaneous preparations, drugs or formulations with 'specials' manufacturing license, and imported drugs and chemicals used as drugs. Off-label drug use was defined as the use of a drug in a patient population, dosage form, dose, or route of administration that has yet not received regulatory approval in children [23-26].

Fourteen studies from different countries were included in the review that detailed the year of publication and data collection, type and duration of the study, number and type of patients, number of prescriptions, prevalence and definition of unlicensed and off-label drug uses, and the country where the study was performed [8, 12, 22, 27-37]. We divided studies into 4 groups: studies conducted in the patients admitted at neonatal intensive care units, in pediatric wards, in hospitalized children and in pediatric outpatient settings. The study included preterm neonates and children upto 18 years of age. The number of patients studied ranged from 34 in neonatal intensive care units to 355 409 hospitalized children (Table **1**).

In this analysis, unlicensed drug use rates in neonatal intensive care units were found to be between 11% and 13%, and off-label drug use rates were between 46.5% and 50.5% [30, 33]. Shah *et al*. reported that 78.7% of hospitalized children in the United States received at least one off-label drug and factors that were associated with off-label use included patients undergoing a surgical procedure, age older than 28 days, greater severity of illness, and all-cause in-hospital mortality [8]. The rates of use of off-label drugs in outpatient setting varied between 9% and 26% [35, 37]. These results highlight the large ranges of unlicensed and off-label drug use rates in different patient settings.

Unlicensed drug use may be attributed to physician's request to import an unlicensed drug into a given country due to lack of drug manufacturer's license (no local market interest or incomplete drug submission or administrative delays) or patients/parents request to obtain a potential drug therapy on the Internet or drug shortages (unavailability of pediatric formulations) [2]. The prevalence of off-label prescribing in pediatric practice remains high because, in case of many old drugs, no recent clinical research in children is conducted (*e.g*. morphine being indicated only for children 12 years and older) to update their drug monographs to include other age groups in their regulatory documentation. In addition, physicians usually prescribe drugs in children, using the currently available drug information in the literature, rather than reviewing information contained in the drug monograph [2].

CONCERNS REGARDING USE OF OFF LABEL AND UNLICENSED DRUGS

This is a growing concern regarding off-label and unlicensed use of drugs because it exposes children to certain drugs that lack license for pediatric use with a higher incidence of either over- or underdosing of drugs in different age groups and ADRs [38]. Children differ pharmacokinetically from adults and their responses change with growth and maturation. Hence, simply lowering doses of adult medications is not recommended as it may jeopardize the safety of children. Studies have shown that such extrapolation of data from adult studies was appropriate only in 6% of drugs; as dosing requirements, side effects vary according to the age, type and severity of disease and age-related variations in receptor function, effector system and homeostatic mechanisms of the body [23, 38-40]. It may also result in treatment failure and serious consequences in terms of disease complications or ineffective therapy [41-44]. Underdosing may expose drug users to risks of developing resistance in case of antimicrobials without adequate therapeutic effect [45-47]. In case of infectious conditions, it may lead to development of carrier states and chronic progression of disease states. It also increases the

Table 1. Worldwide unlicensed and off-label drug use rates in different pediatric settings.

Reference (Year/ Country)	Patients, no. (Prescriptions, no.)	Patient's Age	Study Design, Study Duration	Definition of Unlicensed Drug Use	Rate of Unlice-nsed Drug Use, %	Definition of Off-Label Drug Use	Rate of Off-Label Drug Use, %
Neonatal Intensive Care Units							
O' Donnell *et al.* (2002/Australia)	97 (1442)	GA 22.7 to 41.4 weeks	Prospective, 10 weeks	Modification of the marketed formulation; imported drugs.	11	Unapproved age range, indication, dose, frequency (greater dose and increased frequency); route of administration; contraindicated use	47
Lopez-martinez *et al.* (2003/Spain)	48 (236)	Not Specified	Prospective, 3 months	Unapproved formulation, imported drug, unauthorized drug compassionate use of drugs	13	Unapproved age range, indication, dose , frequency, route of administration	50
Dell'aera *et al.* (2004/Italy)	34 (176)	19 preterm, GA 26 to 36 weeks, 15 full term: GA 37 to 39 weeks	Cross -sectional, 2 months	Unauthorized drugs, compounding	12	No pediatric information in the label; unapproved indication, dose, route of administration, or duration of treatment	50.5
Laforgia *et al.* (2011/Italy)	126 (483)	77 preterm: GA 23 to 36 weeks 49 full term	Prospective, 1 month	No data	11.4	Unapproved indication, dose, route of administration, treatment duration; contraindication or warning specified in marketing authorization	46.5
Pediatric Wards							
Turner *et al.* (1996/ UK)	1046 (4455)	1 day-18 years	Prospective, 13 weeks	Modification of the marketed formulation and imported drugs.	35 (off-label or unlice-nsed drugs use)	Unapproved age range, indication, dose, and frequency (greater dose and increased frequency); route of administration; contraindicated use	35 (off-label or unlicensed drug use rate)
Conroy *et al.* 11 (1998 / UK, Sweden, Germany, Italy, Netherlands)	624 children (2,262)	4 days to 16 years	Prospective, 1 months	Modification of marketed formulation, unapproved formulation, chemicals used because no marketed drug is available, drugs used before their approval, imported drugs.	0.3 to 14 varies with centre	Unapproved age range, indication, dose, and frequency; route of administration; use of a formulation not suitable for pediatrics	23 to 66 (varies with centre)
Jain *et al.* (2008/India)	600 (2064)	1 month - 12 years	Prospective, 2 months	No data	No data	Administration of a greater/lesser dose, higher/lower frequency, administration for indications not described, drug not licensed in that age group, alternative routes of administration	50.62

(Table 1) contd….

Reference (Year/ Country)	Patients, no. (Prescriptions, no.)	Patient's Age	Study Design, Study Duration	Definition of Unlicensed Drug Use	Rate of Unlice-nsed Drug Use, %	Definition of Off-Label Drug Use	Rate of Off-Label Drug Use, %
Hospitalized Children							
Bajcetic *et al.* (2003/ Serbia)	544 (2037)	4hr-18 years	Prospective, 2 years	Unapproved formulation	11	Unapproved age range:dose or route of administration	47
Shah *et al.* (2007/ USA)	355409	18 years or younger	Retrospective Cohort, 1 year	No data	No data	Use of specific drug in a patient younger than FDA approved age range for indication of that drug	78.7
Kimland *et al.* (2012/ Sweden)	2947 (11294)	0-18 years	Drug Utilisation Survey, 2 separate 2 day periods	Not authorized in Sweden	4.6	Used outside the terms of Summary of Product Characteristics	34
Pediatric Outpatient Departments							
't Jong *et al.* (1998/ Netherlands)	6141 (17453)	>=16 years	Retrospective, 1 year	Drug unapproved in children	15.3	Unapproved age range, indication, dose, and frequency; route of administration; use of an unapproved formulation	13.6
Gavrilov *et al.* (1998/Isreal)	132 (222)	1 months to 18 year	Retrospective, 2 months	Modification of a marketed formulation	8	Unapproved age range, indication, dose, frequency; route of administration	26
Olsson *et al.* (2007/Sweden)	268465 (2.19 Million)	>18 Years	Retrospective, 1 year	Modification of the marketed formulation; unauthorized drugs	6.7	No pediatric information; unapproved age range; mention in the monograph that no clinical trials were performed in children; drug not recommended or contraindicated in children	13.5
Langerova *et al.* (2012/Czech Republic)	4282 (8559)	>15 Years	Prospective, 6 months	Drug unapproved in children	1.26	Unapproved age range	9

risk of documented/undocumented adverse drug effects in children [17, 31, 38, 48-50].

Extemporaneously prepared drugs that are compounded at pharmacies, are widely used in the pediatric population, probably because of limited or no availability of a specific drug, dosage, or formulation suitable for children. Though these pharmaceutical dosage forms aim to be efficacious and meet quality standards, their inherent risks due to compounding errors, non-validated stability of the product and reactions to ingredients and excipients are an important concern [23, 51].

Underreporting of adverse reactions is known in relation to unlicensed or 'off-label' use due to legal and liability concerns. This assumes greater importance in pediatric population as children may be unable to or have difficulty in expressing problems that may therefore, go undetected [38]. A prospective pharmacovigilance survey of drug prescribing in office-based pediatricians, reported that 60% of the ADRs involved an off-label prescription with a significant association between off-label prescribing and ADR (relative risk 3.44; 95% CI, 1.26–9.38 [17]. A study involving 10,699 medicine courses that were administered to 1,388 pediatric patients tested the hypothesis that off-label and unlicensed status is a risk factor for ADRs. Their results indicated that off-label and unlicensed medicines were significantly more likely to be implicated in an ADR than an authorized medicine (OR 2.25, 95% CI 1.95 to 2.59) [52]. Similar findings were reported in a prospective intensive surveillance among pediatric inpatients that off-label drug use is associated with a significantly greater number of ADRs (67%) compared to labeled use (33%) with greatest odds with those medicines that completely lacked pediatric labeling (OR 2.84, 95% CI 1.37-7.09) [48]. Research involving a cohort of 46,021 patients who received 151,305 incident prescribed drugs concluded that the rate of Adverse Drug Events (ADEs) for

off-label use (19.7 per 10,000 person-months) was higher than that for on-label use (12.5 per 10,000 person-months) (adjusted hazard ratio, 1.44; 95% CI, 1.30-1.60). Off-label use that lacked strong scientific evidence had a higher ADE rate (21.7 per 10,000 person-months) compared with on-label use (AHR, 1.54; 95% CI, 1.37-1.72) [53]. A 4-year post-marketing active pharmacovigilance program that analyzed reports from 3539 ADRs, concluded that eight percent of ADRs were associated with off-label use [54]. In addition, early warning signs of ADR may go unrecognized and patient may present with late sequelae. This assumes even greater importance in premature infants and neonates with altered pharmacokinetic-pharmacodynamic responses and multiple morbidities; considering high prevalence of off-label drug use in infants [19, 55, 56]. Similar findings were observed by Lindell-Osuagwu *et al*., 2014 that these rates were higher in children less than 2 years admitted in intensive care units and pediatric wards in Finland [57]. This may result in serious consequences as medication errors are reported to be up to 8 times greater in neonatal intensive care units than in other departments [58]. Thus, an international consensus is evolving to conduct clinical trials in neonates and infants with emphasis on regular updating of existing Summary of Product Characteristics with regard to medications already on the market [27, 30-32, 58, 59].

ROLE OF THE STAKEHOLDERS

The practice of use of off-label and unlicensed drugs is subject to conflicting expectations of stakeholders like patients, medical practioners, pharmaceutical industry and regulatory authorities. Health care decision makers and clinicians usually favor drugs with approved indications and information for children versus other drugs in their current pediatric practice [19]. However, lack of adequately tested (due to non-inclusion of children in clinical trials) and/or formulated medications authorized for use in appropriate pediatric age groups results in off-label and unlicensed prescribing [8, 23, 38]. The physicians need to balance avoid exposing children to unnecessary risks and to avoid depriving them of potentially effective pharmacotherapy in disease management [2]. Rational and appropriate prescribing of off-label drugs that is backed by adequate scientific evidence does not amount to negligence if the physician has acted in good faith keeping the patients best interest in mind [24]. Disclosure of the off-label status of the drugs; if prescribed and possible risks and benefits, should be communicated to the families in pediatric division. When use of a drug is truly investigational, a well-designed clinical trial with consent of patients and/or their legal guardians despite the risks of investigational therapy rather than individual patient care should be carefully documented [60]. Likely off-label use of a drug should be promptly identified by the medical community; experiences obtained from patients and clinical responses should be shared with peers through publications, presentations and scientific meetings [5]. Physicians need to understand that they play a key role in communicated risk-reduction strategies, by sharing knowledge and publishing their experiences that could form the basis for a formal safety-efficacy study. Prescribing physicians should keep themselves updated about newer treatment options through these meetings and scientific literature. In addition, documentation of use of off-label drugs and their effects should be undertaken for assessment and evaluation through computerized patient record systems [23, 24]. Communication, general training and feedback of the physicians and pharmacists is also an important step in recognition and assessment of any ADRs to off-label and unlicensed use of drugs. A closer relationship between the regional pharmacovigilance centres, national patient safety agencies, community and hospital pharmacists, poison centres, and patients/parents/caregivers is to be encouraged to report adverse reactions to health professionals [38]. Pharmacovigilance for products on the market need a more proactive, approach to detect new safety signals, monitor for any consequential safety concerns and to take appropriate measures to address them. Pediatric pharmacovigilance with targeted active and passive data collection and recording with primary and secondary care data linkage in relation to all medicines, groups of medicines or individual medicinal products specially, novel therapies, should complement active post-marketing surveillance, ad-hoc epidemiological studies, databases linking treatment and medical outcome, registries and laboratory investigations. Competent authorities could provide explicit reassurance that the personal data regarding the reporter will be protected if they report a suspected ADR of a medicine is being used on an off-label or unlicensed basis [38]. Continuous ADR educational programmes, training, scientific meetings and integration of ADRs' reporting into the activities of the pediatricians (hospital-, university- or community-based), pediatric pharmacists or medicines information centres and staff involved in pediatric clinical trial networks would be valuable in pharmacovigilance monitoring [38]. Academic training in pharmacovigilance-related activities during undergraduate and postgraduate programmes, coordinated at the national and transnational levels could also improve conduct of pharmacovigilance for medicines used by the pediatric population [61].

Despite a number of initiatives at the national regulatory level to stimulate pediatric medicines development [60], clinical trials in pediatrics is limited due to various issues involving the consent depending on the age, the necessity to provide an appropriate drug formulation, the pharmacokinetic/ pharmacodynamic variations, and the inclusion of distinct age groups of relevance within the target pediatric population [2, 38]. US-FDA states that children should be included in only those clinical trials which provide atleast a minimal health benefit or cure from diseases or its complications. For instance, many children suffer from otitis media and could be included in trials of drugs being evaluated for treating middle ear infections [62]. These trials should be conducted in a fair and standardized manner and scientifically valid information provided to the prescribing physician. Specific pediatric proposals thus, when undertaken need to strike a fine balance between the advantages and the associated risks. In addition, during the drug development process, with an increase in the number of indications, the cost and time required for completion of a drug trial increases. Drug manufacturers' have traditionally shied away from increasing the number of indications for a single drug as any delays in regulatory approvals grossly impacts the revenues due to shortened patent life [63].

To increase the availability of suitable, licensed drugs for children, enforcement of various legislative measures has increased prospective pediatric drug testing *via* industry-sponsored studies, investigator-initiated studies, and consortia, such as the National Institute of Child Health and Human Development–funded Pediatric Trials Network [60]. The FDA Modernization Act that was introduced in 1997 intends to encourage pharmaceutical companies for including children in clinical trials by providing market exclusivity and patent extension [24, 64]. In addition, if a drug has been used in an off-label manner for a long period of time, the decision to give pediatric license depends on the number of children already being treated and evidence of safety and efficacy obtained from them [65]. The Belmont Report recommends the involvement of children in clinical trials to promote healthy development and better ways to treat childhood illnesses [66]. There is a strong emphasis on keeping the risk as low as possible even during drafting of the study protocol. According to the US-FDA, low risk is defined as "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" [67, 68]. Also, there should be enough evidence that any research-related pain, discomfort or stress will not be severe and that any potential harms will be transient and reversible [67, 69].

Two important steps taken in US to curb the use of unapproved drugs in children are the introduction of the Pediatric Research Equity Act (PREA) and Best Pharmaceuticals for Children Act (BPCA) [60]. In PREA, the drug companies are required to conduct studies of their products in children under certain circumstances. To initiate a pediatric clinical trial, there should be sufficient data available on the investigational drug and it should demonstrate an acceptable low risk or a prospect of direct benefit (PDB). The Pediatric Research Equity Act of 2007 states that "if the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies" [67, 70]. Hence, if the pediatric studies are required, they should be conducted with the same drug and for the same use for which they were approved in adults. Best Pharmaceuticals for Children Act (BPCA) aims to obtain pediatric data that are adequate to support pediatric labeling by allowing the drug companies an additional six months of marketing exclusivity if they conduct a FDA-requested pediatric study [71]. The EMA also proactively supports studies on off-patent drugs for off-label uses, especially for children. EU (European Union) funds those studies that involve off-patent Pediatric drugs in the priority list and may contribute to development of pediatric use marketing authorization [44, 72, 73]. While, Japan has a liberal approach and allows use of drugs for off-label indications after filing for a New Drug Application without preliminary clinical studies to evaluate its efficacy [44, 74]. These measures help not only to improve the understanding of pharmacokinetics and pharmacodynamics of drugs in children but also help in balancing the needs of the stakeholders. For the patients, this ensures availability of safe and effective drugs that are approved on the basis of scientific evidence and ethically sound studies. For the manufacturer', this ensures protection of their patents and monetary incentives for drugs approved for new indications. These measures aim to expand both pediatric labeling information and the knowledge base from which health-care decision makers can make informed therapeutic decisions [60].

The revision of the FDA Modernization Act (2009) also allows the pharmaceutical manufactures' to circulate information on unapproved uses their drugs through journal articles or book chapters. But the FDA mandates that this information should be accurate and not modified or edited in a prejudiced way. The manufacturers' should also be transparent on their role as study sponsors' for clinical trial or conflict of interest, if any should be stated. FDA also prohibits "misbranding" of medications, *i.e.* promoting misleading information in terms of off-label uses of a drug for unapproved uses. Further, to aide reporting of off-label prescribing, the Truthful Prescription Drug Advertising and Promotion (Bad Ad) Program was introduced for the health care professionals and patients in 2010 [24, 75]. Despite these regulations, many pharmaceutical manufacturers' have indulged in promoting off-label uses, which has led to large settlements for illegal marketing. In 2012, off-label marketing of paroxetine in children (approved only for adults) cost Glaxo-SmithKline a record amount of $3 billion [24].

CONCLUSION

Off-label and unlicensed drug use is highly prevalent as many medicines prescribed to the pediatric population have not been adequately tested and/or formulated and authorized for use in appropriate pediatric age groups. Off-label and unlicensed prescribing has been identified as a potentially important contributor to preventable adverse drug events and medication errors associated with insufficient labeling. Stakeholders including health professionals, pediatric population and their parents/caregivers, regulatory authorities, and the pharmaceutical industry recognize the enormity of the problem and could play an active role in a number of initiatives that aim to increase the availability of appropriately formulated, properly tested medicines authorized for pediatric use. Therapeutic decision making that relies on the strong scientific evidence and the importance of the benefit for the individual patient and legislative initiatives at the national level could help achieve the goal that any and all drugs used to treat children will have age-appropriate evidence sufficient for safe prescribing.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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