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PEDIATRIC PHARMACOLOGY/DRUGS AND CHILDREN

Pharmacoepidemiology in pediatrics: Needs, challenges and future directions for research

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Summary Despite international initiatives to promote clinical research in pediatrics, there are still many gaps of knowledge in the use of drugs to treat this specific population. When important information cannot be derived only from clinical trials, use of available observational research tools is required. In this paper, we provide an overview of the particular interest of pharmacoepidemiological research into the evaluation of drug effects in children and adolescents. We also sought to underline the unique challenges and specific needs regarding this research. Implementation of innovative methodologies and expansion of database networks to perform necessary studies could further improve performances of observational research.

Abbreviations

AEFI	adverse events following immunization
CO	case-crossover
DDD	defined daily dose
FDA	Food and drug administration
EMA	European medicines agency
ICH	International conference on harmonization
ISPE	International society for pharmacoepidemiology
NSAIDs	non steroidal anti inflammatory drugs
OTC	over-the-counter
PIP	pediatric investigation plan (Europe)
PSP	pediatric study plan (US)
RCTs	randomized controlled trials
SCCS	self-controlled case series
SIG	special interest group

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Introduction

In the last two decades, international initiatives have been undertaken to promote pharmacological research in the pediatric population. From a regulatory perspective, both the US Federal drug administration (FDA) and the European medicines agency (EMA) requires that every drug under development with a potential indication in pediatrics, should be investigated in children, according to an agreed pediatric study plan (PSP — US) or pediatric investigation plan (PIP — Europe), respectively [1,2]. Between 2007 and 2011, the EMA made decisions about 682 PIPs and approved 60 PIPs including studies in neonates the most neglected age group in terms of research (15% of the 395 PIPs potentially relevant to neonates; waivers were sought in all other cases) [3]. Also, the EMA granted 152 drug authorizations (period 2007—2012) among which 31 (34%) initially included a pediatric indication and added 221 labeling changes pertaining to safety and efficacy in children [4]. Similar progress was observed in the US where from a total of 189 products studies under pediatric exclusivity between 1998 and 2012, 173 (92%) received new labeling information and 108 (57%) receiving a new or expanded pediatric indication [5]. These regulatory initiatives underline the necessity of extrapolating a maximum of information, when possible, from adult studies to avoid unnecessary clinical research in children and adolescents [6,7]. Although this may be possible for drug efficacy or dosing in some clinical contexts, it is widely agreed that drug safety should be specifically assessed in the youngest as potential adverse impact on growth and neurophysiological development cannot be evaluated in adult studies and children might be more vulnerable to adverse events due to differences in organ maturation [6,8—10].

To this regard, safety knowledge deriving from phase III randomized controlled trials (RCTs) may be incomplete. In fact, RCTs include few and clinically homogeneous patients who are followed for limited time periods. Hence, rare and long-term side-effects may be missed [11]. Observational studies are well suited to overcome these shortcomings. Drug utilization studies and the assessment of drug safety and effectiveness in real life medical practice are now part of the overall drug development process. These studies contribute to a better understanding of the treated population and respond to a need for risk minimization. Findings guide clinical practice as well as many public health decisions. In addition, the increasing use of electronic healthcare and claims databases for pharmacoepidemiological research contributed to an optimal use of research resources and reduced potential bias especially information bias (bias arising from measurement errors) [12].

Undoubtedly, implementation of pharmacoepidemiological studies to improve the knowledge on drug use and treatment effects is of particular interest in pediatrics. In fact, despite the above-mentioned regulatory initiatives that essentially concern newly developed drugs, there is still limited information and increasing concerns about the effects of many widely used drugs in children. Nevertheless, the implementation of these studies in pediatrics remains suboptimal. In a recent review of pediatric pharmacoepidemiological safety studies [13], authors noted that despite the increasing number of pharmacoepidemiological studies over time, this growth was mainly attributed to studies in adults and the observed pediatric/adult study ratio was 1:100. This review also noted that pediatric pharmacoepidemiological studies were almost exclusively conducted in developed countries and received very little private funding. In addition, the drugs under investigation concerned a small number of pharmaceuticals and the investigated outcomes mainly concerned symptoms, clinical signs or ill-defined conditions.

Current needs in pediatric pharmacoepidemiology

The unique challenges of drug research in pediatrics urged the creation of the pediatric special interest group (SIG) of the International society for pharmacoepidemiology (ISPE). This group has recently performed a survey among ISPE members to assess research, scientific and educational needs in the field of pediatric pharmacoepidemiology [14]. The survey highlighted the need to evaluate the effects of medicines in several medical fields mainly psychiatry/mental health and infectious diseases. The drug classes with the most pressing research needs were vaccines and antiretrovirals. Pediatric subpopulations deemed to be neglected in this research field were neonates, especially preterm ones, children presenting genetic variations or socioeconomic specificities such as foster children or those residing in low-income countries. The recent literature review [13] conducted by Osokogu et al., pointed out that drug safety research in adolescents was limited and that half of the currently evaluated drugs belonged to only three drugs classes: psychoanaleptics, psycholeptics and anti-infectives. The fact that these drugs are prescribed in the medical fields that are most in need for research, according to the ISPE survey, suggest that pediatric pharmacoepidemiological safety research is currently focused on medicines perceived as potentially harmful by clinicians. Missing knowledge on long-term effects on growth or development as well as changing type and/or susceptibility to adverse drug reactions during maturation has also been put forward and was the topic of the 3rd ADEPT conference organized by FDA in 2016 [15].

Regarding observational drug effectiveness studies, Dukanovic er al. (unpublished manuscript) showed that pediatric studies are limited in size, methods to control for confounding are inadequate, outcomes are not always clinically relevant, use of data sources may be improved and the type of drugs that are evaluated do not completely reflect routine utilization in paediatrics.

Confounding by indication is frequent in pharmacoepidemiological studies and is related to the fact that a drug is prescribed preferentially to patients with a higher (or lower) risk of presenting the event of interest. Most studies apply traditional methods to control for confounding by indication, including multivariate modelling analysis, matching and restriction. Propensity scores adjustment may be implemented but they are still seldomly used in pediatric pharmacoepidemiological studies [16,17]. Based on the literature review [13], an ISPE specific conference

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