Review



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*Review*

# Pediatric Epilepsy: Time for New Research Goals

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**Abstract:** Modern drugs have changed epilepsy, which affects people of all ages. But for young people with epilepsy, the framework of drug development has stalled. In the wake of the thalidomide catastrophe, the misconception emerged that for people <18y antiseizure medications (ASMs) need separate proof of efficacy and safety (E&S), overall called "pediatric drug development." This has been corrected to some extent. Authorities accept that ASMs are effective in <18y as well, but they still require "extrapolation of efficacy," as if minors were another species. In our view, the real problem is less that relevant parts of pediatric clinical epilepsy research over the past decades were useless, but that this has hampered research on meaningful challenges. We do not need to show that ASMs work also before the 18th birthday. But we need to learn how to best use ASMs to prevent brain damage in young patients and optimize ASMs use considering a broader range of aspects.

**Keywords:** epilepsy; pediatric drug development (PDD); therapeutic orphans; extrapolation of efficacy from adults to children; antiseizure medications (ASMs); pediatric investigation plan (PIP)

## Introduction

Antiseizure medications (ASMs) have changed epilepsy from the dramatic connotation of "falling sickness" to a chronic condition that can often, but not always be managed. ASMs prevent seizures in many patients, but not in all of them [1,2]. Epileptic seizures affect patients of all ages. Most seizures resolve on their own, but the younger a child is, the higher the danger that frequent seizures do not resolve on their own or even that status epilepticus (SE) can cause lasting brain damage; furthermore, disease progression is not only linked to seizure themselves [3–5].

## Material and Methods

We analyzed characteristics and impact of separate pediatric epilepsy clinical studies on antiseizure medications (ASMs) on the background of the history of US and European Union (EU) pediatric legislation, which resulted in "pediatric drug development" (PDD). Furthermore, we describe how the PDD requirements for ASMs evolved from the 1990s to today, and drew conclusions.

## Antiseizure medications (ASMs), pediatric drug development (PDD), and evidence-based medicine (EMB)

Drug approval is today based on regulatory clinical and other studies within an elaborate process. The United States (US) introduced the obligation to prove new drugs' efficacy and safety (E&S) in 1962 as a response to the thalidomide disaster. The resulting procedure has become standard worldwide in the following decades [6]. This framework requires, inter alia, a functional public administration, social trust, and a societal balance of influence of the classical healthcare professions, drug manufacturers, regulatory authorities, public opinion, patients, and for underage

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patients' caregivers/parents. Two additional factors have in the last decades come into play for young patients that we need to consider when reflecting about future epilepsy research. (1)

"Pediatric drug development" (PDD) assumes that in chronologically defined "children" separate drug approval is needed, resulting in separate "pediatric" labels [7–10]. "Children" and "pediatric" in quotation marks because the globally used age limit of <18y does not even come close to the end of puberty when the child's body becomes mature. The process of puberty has accelerated massively over the past 100y [11,12]. Clinical studies in adolescents are *physiologically* and *scientifically* not pediatric studies, but the regulatory authorities are maintaining this illusion. This is of specific relevance for epilepsy in young patients as epilepsy was the first broad clinical area where FDA and EMA halfway accepted that drugs work after and before the 18th birthday [13,14], triggered by academic neurologists' critical review of "pediatric" studies [15–18]. But even the term "extrapolation of efficacy" from adults to minors is misleading. Minors are not another species [19]. The PDD concept is best expressed by the mantra of children as "therapeutic orphans," [20] taken up by the American Academy of Pediatrics and the new discipline of developmental pharmacology [9,10]. (2) The other factor is the concept of evidence-based medicine (EBM). From 1962 onwards, in the wake of the US processing of the thalidomide disaster and the resulting modification of pharmaceutical law, randomized clinical trials to prove drugs' efficacy & safety (E&S) became widespread [6].

Based on the awareness of the limitations of traditional determinants of clinical decisions, EBM became in the view of clinicians a new paradigm. EBM was certainly a step forward in replacing traditional personal authority by the dictate of independently produced data [21–23]. EBM with young people defines a group of people according to chronological, not physiological, criteria. These chronological criteria are administrative in nature, not scientifically based. Clinicians tend to overlook that most large clinical trials were and are registration studies for new drugs, not simply independent data. An exception was pediatric oncology, where chemotherapeutic agents had already existed for decades but were systematically tested for malignancies in minors since the 1960s [9,10,24]. These studies and the resulting treatment protocols resulted in saving the life of hundreds of thousands of minors, but not in drug labels, which representatives of the European Medicines Agency (EMA) criticized seriously [25].

The 18th birthday is an administrative age limit and does not correspond to a physiological change. Drugs treat the body, not the legal status. Amplifying the original US PDD approach, the EU and its EMA demand a "pediatric investigation plan" (PIP) for all new drugs, except those that target a disease the EMA recognizes as non-existing in "children". Companies have to commit to "pediatric" studies, resulting in a repetition of clinical development in minors <18y, subdivided into preterm neonates; neonates; infants & toddlers; children; and adolescents [26]. EU-PIP-demanded studies recruit worldwide.

There was no crisis in the treatment of minors with epilepsy, but in 1994 the US National Institute of Health (NIH) organized a conference on drug treatment of children with epilepsy as part of the emerging PDD movement [9,10,19,27]. Clinicians then used ASMs in minors irrespective of separate "pediatric" approval. But now the regulators wanted separate proof of E&S also in "children". The non-government participants opined that drug efficacy for focal seizures in adults justified their approval in young patients provided safety & PK were proven. We call this approach "common sense" in contrast to the strict regulatory approach that has dominated the next 30 years and which we dare to call "dogmatic." Sheridan et al. did not address the difference between the physiological and legal/administrative meanings of the term "child." [27].

**Crumbling dogmatic regulatory PDD approach**

Since 2019 the FDA accepts extrapolation of efficacy for focal-onset seizure (POS) epilepsy in young patients down to two years [13], justified by advances in understanding disease pathophysiology and progression in epilepsy research [14]. The EMA accepts this at present down to 4y. A review of all studies from 1970-2010 on adjunctive therapy in POS in adults and children concluded that ASMs are effective for POS in children as well, once efficacy is proven in adults

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[15–18]. Under 2y there were not enough patients and trials. In our view, the term "extrapolation" of the efficacy of ASMs from adults to "children" is misleading. "Extrapolation" implies a fundamental difference between adults and "children". There are real differences between babies and adults, but it is the same species – one head, two arms, one liver, etc. Furthermore, children grow and do not remain newborn and vulnerable until they reach the official age of maturity.

Extrapolating observed toxicities in preterm newborns to all "children" (and silently switching the use of the term "child" from its physiological to its legal/ administrative meaning), the PDD advocates managed to convince lawmakers that separate "pediatric" labels would resolve a major healthcare crisis and would allow a fundamental step forward in pediatric healthcare [28]. What clinicians had advised in 1994 was decades later accepted by the FDA and eventually also the EMA: regarding ASMs, it is legitimate to call "pediatric" patients small adults: the underlying pathophysiological process is the same in patients ≥2 years. Young patients will respond similarly to ASMs, provided an equivalent serum concentration-time profile. Neurology was one of the first clinical disciplines to openly challenge the children-are-therapeutic-orphans concept. However, it is not sufficient to "just" accept that ASMs are effective before and after the 18th birthday. It is necessary to candidly address the misconception that separate labels in patients <18y have any substantial clinical benefit. The formulas and dosing tables used by pediatricians and family doctors in the 1960s were largely sufficient, except for preterms. To put it provocatively, the entire PDD movement was a regulatory exercise with much official success but no real clinical progress.

Several more clinical areas face the same dilemma. Separate "pediatric" and adult rheumatoid arthritis do not exist [29]. The conditions summarized under "juvenile idiopathic arthritis" (JIA) are different disorders of whom several start early and persist into adulthood [30–32]. Patients with systemic juvenile idiopathic arthritis (sJIA) diagnosed early do not switch to classical rheumatoid arthritis later. Only the patients' *administrative* status changes. Conventional malignant melanoma in adolescents and adults is the same disease and needs the same treatment [33,34]. There are rare forms of pediatric melanoma, but no pediatric conventional melanoma. Also, fractures are not pediatric before the 18th birthday.

**The dogmatic regulatory approach to "children" is far from over.**

For every head of a medical department, raising funds for clinical research is a key responsibility. Industry-paid funds triggered by regulatory demands were and are a temptation. The number of ongoing "pediatric" studies has diminished, but clinicians have not yet processed sufficiently the fundaments of the temptations of "pediatric" clinical studies.

The flawed belief that the 18th birthday corresponds to a physiological change has resulted in superfluous clinical studies in adolescents and exaggerated studies in younger minors, where dose-finding would have been clinically required. The main conclusions by Pellock, Arzimanoglu, et al. were eventually accepted by FDA/EMA, but large international clinical studies in "children" that often were physiologically no longer children continued worldwide. Also the formal – and flawed - distinction between adult and "pediatric" patients continues to be maintained [18]. Of course, there are adult and pediatric patients. But their distinction by the administrative age limit of 18 is not scientific.

The division of the medical world into "pediatric" and "adult" disciplines is *administrative*. Whether a 15-year-old casualty is placed in a pediatric or adult surgical ward is medically irrelevant. It is an administrative question. But the same disease before or after the 16th, 17th or 18th birthday should neither have different names nor should be treated differently. This is the case when there is a pediatric and an adult rheumatology department in the same hospital, and where adult and "pediatric" rheumatology use different names for the identical disease, e.g. sJIA [35]. The separation of administrative and scientific aspects of medicine is a task that will keep us spellbound for decades to come.

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**A necessary paradigm shift**

"Pediatric" ASM drug studies were performed worldwide in up to 118 medical centres [9,10,19,36–38]. Parents have become reluctant to allow the participation of their loved ones in "pediatric" epilepsy studies [39]. The studies demanded by regulatory authorities would need more "pediatric" patients than exist worldwide [9,10,40]. The EMA knows the lack of feasibility of the "pediatric" studies it demands**.** Nonetheless, the PIPs continue, and FDA and EMA continue to publish common statements that explain "pediatric" requirements even for vaccines and drugs against COVID-19 [41].

Well-intended but flawed regulatory requirements in the name of EBM, PDD and "better medicines for children" [42], led to many pointless publications. The EMA has issued PIPs for most modern ASMs, demanding studies in "children" <18 years. Some have translated into studies, others are in various stages of preparation, many are ongoing, and some PIPs have silently been converted into waivers, i.e. no "pediatric" studies are required any more [9,10,19]. Our focus goes beyond criticizing flawed "pediatric" research. In our view, the current focus of pediatric epilepsy research is too much focused on drug approval. They require complex and expensive logistics but do not improve treatment. Instead, we propose a shift away from clinically pointless, but formally regulatorily justified "pediatric" studies to clinically meaningful studies. Such studies will *not* prove again that ASMs work before and after the 18th birthday. Instead, we propose to simply accept their efficiency and instead explore how they can be better used.

Young children cannot take ASMs on their own. In young children, self-management means the administration of emergency ASMs by parents/caregivers. Patel et al. initiated a regional project to involve parents. This reduced the number of SE emergency admissions by 28% [43]. A paper on acute seizure action plans (ASAPs) compares the self-management guides for patients and caregivers in asthma and diabetes to SE [44]. Stredny et al. emphasize infrequent or restricted use of home rescue medications by caregivers [45]. Buchhalter aims at recommendations from a broad stakeholder group including caregivers [46]. The pediatric status epilepticus research group (pSERG) investigated the timing and escalation of ASM administration in pediatric SE both in the prehospital and in-hospital settings [47,48]. Training of caregivers is addressed by several authors [4,49,50].

A further dimension is the patient's quality of life (QoL). Today, seizure control is considered the primary goal. But when a patient is treated with many drugs, his life plays out in a haze. A further challenge can be weight increase. Parents, doctors and older patients should decide together on balancing priorities. This might include the acceptance of occasional seizures in return for a better overall QoL. In the balance of influence between regulatory authorities, the pharmaceutical industry and clinicians, the clinical world has for too long accepted regulatory positions. One major element will be to better integrate parents into the prospective care of children at risk for epileptic seizures or those who have already had seizures [51]. Hopefully, parents' advocative groups for Dravet syndrome, Lennox Gastaut Syndrome, Sturge Weber Syndrome, and more will contribute to funds, coordination, and intellectual processing of such a new strategy.

In 1994, reimbursement of drugs not approved for "children" was not a problem [27]. Today, administrative aspects have acquired a stronger role in medical care. But the lack of "pediatric" approval is no valid clinical justification for separate studies.

**Future pediatric epilespy research**

The avenue of the future will not be to ask for ever more large, multicenter, pediatric-specific randomized clinical trials, nor more standardized diagnostic and treatment algorithms along with prospective multicenter studies [52–54].

Regulatory authorities love the narrative that only on-label drugs are safe for children and adults [55]. However, the entire discipline of paediatrics with the sub-disciplines of pediatric neurology, oncology, and neonatology emerged decades before the term "off-label" emerged in 1988 [56]. There is the temptation of too much respect for the regulatory authorities. They have an

important role in drug approval, but they are not scientific authorities. They have no right to tell clinicians what to do. They have exaggerated by demanding pointless "pediatric" studies, and they continue to do so.

A recent paper reviews the current international literature on management protocols for SE in the pediatric emergency room [57]. In our view, it would be desirable that fewer children with SE reach the pediatric emergency room at all because the caregivers were able to interrupt it early. Follow-up in the hospital or with the treating pediatric neurologist will be necessary for some or even most children. The younger children are, the more caregivers are always around. But the potential role of caregivers is often not sufficiently addressed [4,58–60]. Self-management of epilepsy has in the last years been more discussed. But in contrast to asthma or diabetes mellitus, it is still in its infancy [61–63].

The current advances in the genetic of epilepsies and therefore the diagnosis has attracted the interest of phramaceutical companies on rare epileptic syndromes leading to a more selected clinical development in the area of epilepsy. Substantially, some new recently approved drugs and others under study have been developed specifically for the treatment of seizures in well-idnetified syndromes and not more in general for some seizures types. This new approach has sligtly changed the way ASMs have been labelled while the main outcome in this studies is not really changed. In other words, while these drugs are approved well below the age of 18, they are still studied for their efficacy against seizures with the same old parameters (e.g., 50% seizure reduction). While this is encouraging indicating new paradigms to come, it is urgent to have new rules for approval (e.g. 75% seizure reduction, higher seizure freedom rates) but also in outcomes. For example, the impact on patients‘ and families‘ quality of life, disease progression etc.

## Open questions

Pellock et al. accepted the age limit of two years for pragmatic reasons. Novotny et al. confirmed that adjunctive topiramate does not reduce the daily rates of POS in infants aged 1-24 months [36]. What is the true age limit? Parents might be too enthusiastic to administer emergency medication. There will never be a perfect scheme regarding decisions on the balance of QoL vs. intake of multiple drugs. For such discussions and decisions, EBM does not provide any valid guidance.

## Conclusions

Authors representing regulatory authorities from around the world recently described PDD as an ecosystem [64], which we regard as a Freudian slip. Ecosystems have inflows and outflows. The inflow of the PDD ecosystem is the payments enforced by the pharmaceutical industry. The outflow of PDD studies are "pediatric" labels.

Self-management is not a radically new concept. However, we have put our thoughts into the context of flawed demands for ASMs‘ E&S studies in "children". Involving and training parents will have many new challenges. Partially, our conclusions are self-evident. Partially, they are certainly controversial. We do not want to antagonize those that were involved in these trials. But the time has come to candidly address "pediatric" research in neurology and beyond; suspend ongoing questionable trials; reject newly submitted ones to Institutional Review Boards (IRBs)/ ethics committees (ECs), and focus on ways to better engage caregivers and parents.

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