Ethical, clinical and practical considerations in designing clinical trials in pediatric psychopharmacology

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Since the beginning of this new century, drug development is changing; the concern of protecting children against clinical research is fading away and a new paradigm, which is not yet necessarily accepted by all of society, is now emerging; that of protecting children through clinical research. It is unethical to withold available treatments from children because of lack of research, consequently it is expected that the number of pediatric clinical trials will increase in the future. However, research is not deprived of risks, and it is necessary to maintain a perfectly well-balanced, scientific and ethical approach when designing pediatric clinical trials. Child psychopharmacology provides an opportunistic paradigm of the difficulties and challenges of pediatric drug development. The hurdles of developing and conducting research in the pediatric population are numerous and some of them are more exacerbated in the field of child and adolescent psychiatry than in other pediatric areas such as pediatric oncology. Designing clinical trials in children requires taking into account specific ethical, clinical and practical pediatric considerations, and discussions on the issues of risk, benefit and burden should always be carried out on a single clinical trial basis.

Keywords: child and adolescent psychiatry • child psychopharmacology • clinical trials • ethics • pediatric drug development • research in vulnerable population

Mental Health in children and adolescents remains a controversial, passionate and sensitive topic. In 2001, the WHO reported that suicide was the third leading worldwide cause of death among adolescents [101].

It is widely recognized that mental disorders in children and adolescents lead to a major burden for them and their families, and that mental health of children and adolescents constitutes a major area of concern for society.

Child and adolescent psychiatry is a rather young discipline, evidencing differences in cultural approaches, and is not recognized and established as a medical specialty worldwide. For many years, psychoanalysis was its only theoretical basis. In the USA, child psychiatry moved in the 1950s and 1960s to the university medical schools and combined with new fields of research such as epidemiology or biological and biochemical aspects of mental illnesses [1]. Childhood depression illustrates this well since the official recognition of depression in children and adolescents in Europe only took place in 1971, when the Union of European Pedopsychiatrists recognized and addressed the needs of depressed children and adolescents by declaring that depression is an important illness that constitutes a significant proportion of mental disorders in children and adolescents [2].

Philippe Auby⁺

*Author for correspondence: Corporate ICR France & Paediatrics, Lundbeck SAS, 37–45, Quai du Président Roosevelt, 92445 Issy-les-Moulineaux Cedex, France Tel.: +33 179 412 860 Fax: +33 179 412 857 E-mail: phia@lundbeck.com



Pediatric psychopharmacology is an even younger discipline, and despite the therapeutic effects of amphetamines in hyperactive children that were first described in 1937 [3], and thus preceded all the major discoveries of adult psychopharmacology, little innovation has occurred in pediatric psychopharmacology and the task of turning basic research findings into clinically useful applications still remains [4].

In Europe, only a few psychotropic medications are approved for use in the pediatric population, for instance, there is only one antidepressant, fluoxetine – a selective serotonin-uptake inhibitor (SSRI) – approved for the treatment of pediatric major depressive disorder (MDD).

Prescribing a psychotropic agent should never be considered trivial, yet it has become increasingly common to use these medications for a variety of mental health disorders in children and adolescents often without rigorous scientific data. A study of the prescribing trends in nine countries between the years 2000 and 2002 evidenced that the increase in psychotropic prescribing in children was not only confined to the USA and UK, but was also evident in the seven other examined countries (Argentina, Brazil, Canada, France, Germany, Mexico and Spain) [5].

The lack of pharmacology data is a general pediatric issue, but child and adolescent psychopharmacology can be used as a paradigm of the difficulties and challenges of pediatric drug development. If the hurdles of developing and conducting research in the pediatric population are numerous, some of them, potentially due to differences in public perception of 'somatic' versus 'psychiatric' drugs, are more exacerbated in the field of child and adolescent psychiatry than in other pediatric areas such as oncology. The WHO emphasizes the inherent risks of medicalization in any discussion of mental health problems of children and adolescents – or worse, the 'psychiatrization' of problems of normal living and normal psychosocial development.

The EMA emphasized that a large proportion of medicines used in children are actually prescribed off-label, and children have often been denied access to new or innovative medications. Because such situation is unethical, the need to obtain paediatric information for medicines used in children seems nowadays a matter of consensus on a global basis. Based on this, it first became clear in the USA, and more recently in the EU, that there was a need for a legal obligation for pharmaceutical companies to perform studies in pediatric populations.

The concern of protecting children against clinical research is fading away, and a new paradigm (which is not yet necessary yet accepted by all of society) is now emerging (i.e., protecting children through clinical research). Pediatric development is no longer an optional add-on strategy to adult development but is beginning to be truly integrated into clinical development plans, with pediatric evaluations being a regular part of every drug development process.

Over the past decade, under the instigation of the US pediatric legislation, the number of high-quality pediatric psychopharmacological studies has dramatically increased. The first critical pediatric legislative initiative was the 1997 US FDA Modernization Act that provided an incentive for pharmaceutical companies to study products for which there would be a health benefit in the pediatric population.

It can be considered that 2007 was a major milestone in reinforcing the global consensus of the need for more studies to obtain pediatric information for medicines used in the pediatric population. In the USA, the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act were amended and reauthorized, whilst in the EU, a legislation governing the development and authorization of medicines for pediatric use entered into force and the WHO launched a global campaign 'make medicines child size' aiming "to raise awareness and accelerate action to address the need for improved availability and access to safe childspecific medicines for all children under 12" [6,102].

Part of the US legislation is constituted by a voluntary process where the FDA would define the products that needed pediatric studies, outline the necessary studies, and issue sponsors a pediatric written request (PWR). On 31 January, 2010, 380 PWRs were issued in numerous pediatric conditions (numbers reflecting the number of drugs, i.e., active moiety, per sponsor), and such anteriority of the US legislation enables an interesting overview of the distribution of pediatric research areas (Table 1) [103].

Even if it would be hazardous to draw any firm conclusion, these figures, (i.e., psychiatric PWRs ranking 12th among the 15 divisions) tend to suggest that child and adolescent psychopharmacology remains in need of more clinical research. Psychopharmacology is far from being the only therapeutic response to mental disorders in children and adolescents; however, the current trend in psychopharmacology research does not seem to constitute an appropriate answer to the burden of mental disorders in pediatrics.

As a consequence of these worldwide pediatric regulatory obligations and initiatives, it seems reasonable to anticipate that this increased activity in pediatric psychopharmacology research will be sustained and more global studies will be enrolling pediatric patients in the forthcoming years.

However, pediatric clinical development is difficult and the hurdles of conducting clinical trials in the pediatric population are numerous, including ethical, clinical and practical issues. The critical questions about the

Table 1. Overview of the distribution of pediatric research areas per US FDA review divisions.		
Review division	Proposed pediatric study requests received	Written requests issued [†]
Division of Drug Oncology Products	45	47
Division of Neurology Products	69	45
Division of Metabolism and Endocrinology Products	104	42
Division of Cardiovascular Renal Drug Products	52	37
Division of Anti-Viral Products	33	37
Division of Analgesics, Anesthetics, and Rheumatology Products	60	35
Division of Anti-Infective and Ophthalmology Products	30	35
Division of Gastroenterology Products	48	21
Division of Pulmonary and Allergy Products	28	20
Division of Dermatology and Dental Drug Products	38	17
Division of Special Pathogen and Transplant Products	20	16
Division of Psychiatry Products	17	10
Division of Medical Imaging and Hematology Products	17	7
Division of Reproductive and Urologic Products	16	6
Division of Nonprescription Evaluation	8	5
Total	585	380
'This column will never equal the number of proposals submitted, because a written request may be issued without a proposal and a proposal		
may result in an action that is incomplete instead of a written request.		

Data taken from [103].

efficacy and safety of SSRIs in pediatric MDD provide an illustration of the challenges, difficulties and risks of pediatric psychopharmacological research.

Ethical considerations

Growing concern of pediatric off-label use of medicines

Over the last decade, the growing concern regarding the off-label use of medicines in children and their limited access to new or innovative medications has led researchers to recognize that such a situation is unethical. However the solution to increase psychopharmacological research is not widely understood and not necessarily perceived as the ethical answer, particularly in the field of child and adolescent psychiatry compared with other fields such as pediatric oncology.

Indeed, there are still vivid debates surrounding the societal and cultural meaning of childhood behavioral and emotional disturbances. Debates around child and adolescent psychiatry and psychopharmacology are more exacerbated than in some other pediatric areas and involve cultural realities and political considerations. In order to develop a response to these controversies, the Hastings Center, supported by a grant from the US National Institute of Mental Health, developed an interesting initiative launching a 3-year project built around five pediatric workshops [7]. Reporting the outcome of the first workshop, Parens and Johnston wrote what could be perceived as an optimistic view that debates about the treatment of childhood emotional and behavioral disturbances will not only grow more common, complex and public, but should also become more productive in the future than those in the past. They emphasize in their conclusion "that all should agree, however, that what we might call 'therapeutic humility' – being clear about the limits of understanding – is called for, as is more research on both the causes of behavioral and emotional disturbances and the most effective and respectful ways of responding to them" [7].

Humility is key in pediatric research in general and in child psychopharmacology in particular, both young and changing domains. This permanent ongoing lessons-learned process encompasses numerous aspects among them ethical issues that have to be continuously, reassessed from the pediatric perspective [8].

The discussion of ethical aspects can take numerous paths, among them the following three key considerations:

- Is the research scientifically justified and ethical?
- Have the issues of consent and competence been addressed?
- Has the potential conflict of interest been assessed?

Need for scientifically justified & ethical research

It is of paramount importance to always ensure that the highest scientific and ethical standards are met in human clinical trials. The Nuremberg code, which paved the way for the development of contemporary ethics of medical research, was developed in response to the unthinkable atrocities performed by the Nazis in the name of medical science, in direct link with the subsequent Nuremberg trials at the end of World War II [104]. This ten-point document calls for principles for human experimentation such as informed consent and absence of coercion, properly formulated scientific experimentations and permanent need to balance risks/benefits to the subjects [104].

Examples from the past show that, historically the enrollment of children in research could move to inacceptable paths, raising serious ethical concerns [9]. The Willowbrook hepatitis studies performed at the Willowbrook State Hospital, Staten Island, NY, USA in the 1950s and 1960s illustrate these ethical challenges. If parents provided consent for these studies, Hoop et al. report that the voluntarism of their consent has been questioned because admission to the overcrowded hospital depended on agreement to participate in the study [9]. With the current and foreseen increase in the number of pediatric psychopharmacological studies and the need to perform global studies, geographic disparities in children's mental health care will lead to major debates if participation in clinical trials is the only way for sick children to gain access to affordable care [10]. Developing drugs for pediatric patients cannot afford to be perceived as medical colonialism. Of course, public awareness, but also health professional education with regard to the needs and challenges of pediatric research will play an important role in avoiding such hurdles in the development of medicines for children. In this respect, the composition of the European Pediatric Committee (PDCO) demonstrate a remarkable approach; among the 27 experts with competence in the development and assessment of pediatric medicinal products, six of them, appointed by the European Commission, represent healthcare professionals (three representatives) and patients' organizations (three representatives).

Statistical power, multicenter studies & cultural differences

Studies should not only be scientifically justified, they should also be scientifically sound. The number of children or adolescents in clinical trials is generally smaller than those for adults. Therefore the statistical component of the study protocol has to be carefully developed as the risk of potential inadequate power to answer research questions has to be thoroughly assessed. If unpowered, the clinical studies may lead to the conclusion that there is no difference between groups, when actually there is (a type II error), exposing children and adolescents to an unacceptable risk. Therefore, child and adolescent psychopharmacology will only be possible by involving numerous sites, clearly following a multicenter study model, bearing in mind the risk that more sites may yield more negative trials; this can only be achieved by worldwide global studies which will also trigger specific ethical challenges. The choice of countries in which to conduct pediatric programs has to be carefully made and will not be unique or easy, but will depend on the pathologies or conditions explored and the countries' organization of their mental health system. Schizophrenia research in adolescents may, in this respect, be easier in a globalization model than pediatric bipolar mania research as questions regarding the appropriateness of the dramatic increase in the number of young patients with a diagnosis of bipolar disorder in the USA contrasts with the worldwide rarity of the diagnosis of schizophrenia in adolescents, including the US. Concerns over transferability of the results between developing and industrialized countries are often raised. The Adolescent Depression Antidepressant and Psychotherapy (ADAPT) trial showed that a significant proportion of adolescents presenting with MDD [11] improved with regular standard therapeutic intervention, in this case not demonstrating superiority of combination treatment (cognitive behavioral therapy + fluoxetine) to medication alone provided in routine clinical care. Therefore, in countries where no elaborated mental healthcare system is available, there are concerns that effect of medication may be greater than in countries where a variety of interventions are easily available [10]. Such concerns may vary depending on the studied pathologies and the countries involved in the clinical trials, and this aspect should be taken into account and addressed in the study design; an example of this challenge is evidenced by the diagnosis issue and the requested means to ensure a valid and consistent cross-cultural diagnosis.

Minimal risk

The potential lack of direct benefit for children and adolescents involved in clinical trials evidences a complex paradox of pediatric research. If the need to obtain pediatric information for medicines used in children seems nowadays a matter of consensus [105], the evaluation of the true benefit to a child or an adolescent of taking part in a clinical research will rather divide opinions. There is no consensus of what is a minimal risk for pediatric patients. As a result of the emphasis on the protection of children and young people, institutional research boards (IRBs) often insist that many protective mechanisms are built into interventional medicinal trials, and research that involves more than a small amount of risk tends to be rejected [12]. Inconsistency of definitions and understanding of 'minimal risk' may either prohibit major research or expose participants to unjustified risks of harm [12]. Therefore, discussion about the issues of risk, benefit and burden has always to be done on a single clinical trial basis.

Use of placebo

The use of placebo in pediatric research is emblematic of these concerns. Scientific equipoise, meaning the scientific community being uncertain as to which treatment is best, often requires the use of placebo. Pediatric placebo-controlled trials will still be necessary in some cases, such as for the evaluation of the efficacy and safety of antidepressants. Prompted by reports of suicidality associated with SSRI antidepressants, the efficacy and safety of SSRIs in pediatric MDD was reviewed by agencies in Europe and the USA and led both agencies (the EMA and FDA) to make strong recommendations and warnings, limiting the use of these agents in children and adolescents. If we consider the outcome of randomized clinical trials with SSRIs in pediatric MDD on their primary outcome, it still remains to be proven whether SSRIs are also efficacious in this population [13]. Most of the clinical studies did not demonstrate superiority of active treatment when compared with placebo and to date only fluoxetine is approved in the EU and USA, for children and adolescents with MDD, and escitalopram in the USA for adolescents with MDD.

Two meta-analyses published in 2007 [14,15] concluded that SSRIs may be effective in child and adolescent depression, with a more modest effect compared with anxiety disorders. Both reported a rather high, but quite variable, placebo response in this population. The reasons why many of these studies have failed remain unclear. Although some of these antidepressants may not be beneficial (probably tricyclics), these failures are most probably linked to methodological flaws. Numerous methodological questions have been raised with regard to patient recruitment, study design [16], lack of dose-finding studies [17] or correlation between placebo response band number of study sites [18].

This questioned efficacy of SSRIs in pediatric MDD illustrates the need to maintain placebo-controlled research in this field, at least until significantly more medications are available. The discrepancies between clinical observations and clinical trials are obvious in pediatric MDD. It is recognized that randomized clinical trials (RCTs) are better able to demonstrate causal relationships between treatments, but RCTs are also associated with their methodological limitations; not all subjects agree to randomization and strict exclusion and inclusion criteria may pose additional problems [19]. Such methodological and ethical requirements must be taken into consideration when designing any pediatric protocol.

Another important point to consider is to ensure that confidentiality of the subject is maintained during collection, storage and analysis of the study. Different approaches exist depending on countries and an example of specific requirements can be found in the US with the 'Privacy Rule' under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 [106].

Consent & competence

The voluntary participation of the human subject and clear and accurate information about the research are absolutely essential. In the landmark Belmont report of 1979 [107], three basic ethical principles for the protection of subjects were outlined: respect for persons, beneficence and justice. Research in such a vulnerable population of mentally ill minors introduces more complexity. Not only parental permission or parental consent and child assent have to be sought but all the psychopathological representations and emotional conflicts inherent of mental disorders must be considered when designing and implementing a clinical trial.

Parental informed consent follows a process close to adult informed consent. It should provide precise and understandable study information to the parents and caregivers, set up clear and fair expectations and take into account specific family needs. Parents should understand the difference between research and therapy, understand the trial procedures, and the investigator and the study team should thoroughly explain the alternative therapeutic strategy.

The child assent process means further challenges. It is defined as a child's affirmative agreement to participate in research, and further clarification is given that "mere failure to object should not, absent of affirmative agreement, be construed as assent" [20]. The American Academy of Pediatrics recommends that active agreement by a minor (not qualified to give consent) to participate in a research study generally applies to children who have reached an intellectual age of at least 7 years. More recently, it was suggested that assent is generally applicable to developmentally normal children between 8 and 14 years of age [20]. The assent should provide understandable study information and expectations. At the age of 14 years it is usually considered that adolescents have reached adult information level.

For this process, pragmatic experience tends to recommend that site study team should be deeply involved.

Potential conflict of interest

There is a growing movement against commercially funded research. On 2nd August 2010, the Los Angeles Times stated that when weighing the results of a medical study it is important to consider who supplied money to conduct the research [108]. According to an analysis of a sample of 546 registered drug trials (among them 346 [63%] were primarily funded by industry, 74 [14%] by government sources, and 126 [23%] by nonprofit or nonfederal organizations), those funded by industry were less likely to be published within 2 years of study completion and were more likely to report positive outcomes than were trials funded by other sources [21]. Industry-funded trials reported positive outcomes 85% of the time compared with 50% of the time for government-funded trials and 72% of the time for trials funded by nonprofit or nonfederal organizations. Among the nonprofit or nonfederal studies, those that received industry contributions were more likely to be positive (85%) compared with those that did not have any industry support (61%) [108]. To ensure unbiased presentation of results, transparency, control institutions and open access publication are key [10].

Clinical considerations

Clinical evaluation of pediatric patients needs a developmental approach, not only on the physical side but also for domains such as mental or social functioning. Heterogeneity is the rule in pediatric population, as large differences exist between newborn children and teenagers. In child and adolescent psychiatry, further to heterogeneity, comorbidity is also the rule.

Ethical and clinical aspects are intimately linked and therefore, only two clinical aspects will be developed (i.e., the issues of reliable diagnosis and appropriate scales).

Reliability of diagnosis

Making a proper and reliable diagnosis is difficult and should always be performed by an experienced and adequately trained physician (for example, a child and adolescent psychiatrist). It is also recommended to confirm and ensure the reliability of the diagnosis by utilizing structured interviews for instance the NIMH Diagnostic Interview Schedule for Children – Version IV (NIMH DISC-IV) [22] or semi structured interviews such as the Kiddie-SADS-Present and Lifetime Version (K-SADS-PL) [108].

Appropriate scales

Special attention should be given to assessment tools, and scales appropriate for children (depending on age group) have to be used. Basically two approaches have been followed. Specific scales have been developed for Children and Adolescents such as the Children Depression Rating Scale-Revised (CDRS-R) to assess depressive symptoms. This 17-item scale based on a semi structured interview with the child (or an adult informant) and is designed and validated for children aged 6–12 years; it can also be used for adolescents. The CDRS-R is considered as the 'gold standard' for the measure of treatment outcome in pediatric MDD and requires specific training [23]. Other scales have been validated in the pediatric population (children and adolescents aged 5–17 years), including the Young Mania Rating Scale (Y-MRS). This 11-item scale is based on child/adolescent self-reporting and clinician observation. The Y-MRS is considered the 'gold standard' for the measure of treatment outcome in pediatric mania and also requires specific training [24].

Practical considerations

Discussions on the issues of risk, benefit and burden should always be done on a single clinical trial basis.

Lessons learned form research evidenced that pediatric trials are harder to perform than adult ones.

Specialized settings

Pediatric trials need to involve specialists who are sensitive to a child's needs and fears and who have received study-specific training. Pain, fear and distress must be prevented and minimized when unavoidable. In this respect, it is recommended to favor noninvasive techniques when possible and prevent, minimize and potentially treat pain if pain is unavoidable. Specific attention should be given to child-friendly environments.

Appropriate formulations

As evidenced by the WHO campaign, 'Make Medicines Child Size', pediatric formulations are also required. Age-appropriate formulations have yet to be developed for numerous compounds and this can constitute a technical issue that has to be solved prior to starting any clinical trials, taking into account specific age-appropriate pediatric formulations or route of administration if necessary. Solid oral dosage forms that are acceptable for adults are often inappropriate for children, particularly below 6 years of age; consequently, alternative formulations are often required.

Long-term issues

Clinical studies cannot be performed without thinking of mid- to long-term management care, and when studies in child and adolescent psychiatry are conducted, this must be connected with the guarantee of the availability of appropriate healthcare for participants after they finish participating in the study [10].

The long-term use of numerous drugs raises specific concerns for safety and tolerability, and therefore long-term safety studies will be needed for both ethical reasons (continuing to provide drugs if they are not available to the population involved in the clinical trials) and safety/tolerability issues. It should be considered to collect data on growth, sexual maturation, cognitive, emotional and behavioral development.

Clinical trial conduct

One of the practical aspects is to ensure that clear information has been given to children, adolescents, parents and caregivers in order to ensure optimal patient and family involvement. Specific attention should be given to school attendance during trials and to parent's attendance (dependent on work and hours constraints). Avoiding hospitalization is a must and out-patient studies should be favored. Rescue therapy should be considered, but can bias randomized clinical trials and can turn to be unethical [25].

Considering that global clinical trials are now the rule rather than the exception, cultural aspects should also be taken into consideration when designing pediatric trials.

Slow recruitment

Recruitment is almost always slower compared with adult studies [26] except in pediatric oncology, not only due to demographic or epidemiological reasons but also owing to multifactorial factors relating to doctor, parent, child and trial; one of the key factors being that the threshold for gaining consent is often higher and more complex [27]. This needs to be taken into account when planning the study. As speed is always an issue, realistic expectations have to be understood before starting any trial and feasibility should be discussed not only with investigating sites, but also with patients' organizations or representatives.

Finally, establishing an independent Data Monitoring Committee (DMC) or Data Safety Monitoring Board (DSMB) should always be considered, even in noncritical indications, especially as children are not capable of expressing themselves in the same way as adults do, and in order to detect any potential harm to the patients as early as possible.

Future perspective

Given the lack of pediatric data and pediatric formulations for a large proportion of drugs that are already available and the new regulatory requirements to provide pediatric data for drugs in development, it is anticipated that many more pediatric studies will be conducted in the forthcoming years. Child psychopharmacology represents an opportunistic paradigm of the difficulties and challenges of pediatric drug development.

Conclusion

At the beginning of this new century, drug development is changing; the concern of protecting children against clinical research is fading away, and a new paradigm is now emerging (i.e., protecting children through clinical research). Children and adolescents have often been denied access to new or innovative medications because of lack of adequate research and Paediatricians have learned to live with medicines used being used off-label. Because such situation is unethical, the need to obtain paediatric information for medicines is more and more recognized. There are at present clear ethical, scientific and regulatory reasons to conduct clinical studies in pediatric populations; furthermore, there are potential economic incentives for pharmaceutical companies. The hurdles of developing and conducting research in the pediatric population are numerous. Designing clinical trials in children requires taking into account specific ethical, clinical and practical pediatric considerations. Ultimately, it is through well-conducted research that children will gain access to new medications and receive safe and optimal drug therapy.

Disclaimer

Philippe Auby is a Lundbeck employee. The views presented in this article are those of the author and should not be understood or quoted as being made on behalf of Lundbeck A/S or its affiliates.

Executive summary

- Despite mental disorders in children and adolescents constituting a major area of concern for society, compared with adult psychopharmacology, little innovation has occurred in pediatric psychopharmacology and a large proportion of medications are prescribed off-label.
- The need to obtain pediatric information for medicines used in children is more and more recognized and following the US pediatric legislation initiatives, a new EU pediatric regulation came into force in 2007 integrating pediatric development in the EU registration process for new drugs.
- More pediatric clinical studies are anticipated in numerous conditions including mental disorders.
- Pediatric clinical research is never easy and pediatric pharmacology constitutes a valuable illustration of its challenges, difficulties and risks.
- All research should be scientifically and ethically justified and discussions on the issues of risk, benefit and burden should always be carried out on a single clinical trial basis.

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