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REVIEW

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Ethical considerations in psychopharmacological research involving children and adolescents

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Abstract *Rationale:* Increased community utilization of psychotropic medications among children has brought attention to pediatric psychopharmacology research and associated ethical issues. *Objectives:* To discuss ethical aspects of child participation in psychopharmacology protocols. *Methods:* Selective review of relevant scientific and regulatory literature. *Results:* Efficacy and safety of psychotropics in children cannot be entirely inferred from adult data and direct participation of children in research is necessary. Child research must follow special regulations that are in addition to those common to all human research. For research with prospect of direct benefit, a critical factor is whether the risk/benefit ratio is favorable to the participating child. For research without such a prospect, the concepts of minimal risk and minor increase over minimal risk apply. However, the interpretation and application of these principles to specific protocols vary across settings and among ethics committees. Thus far, little empirical investigation has been conducted on children and parents' motivation for research participation, effectiveness of the informed consent and assent procedures, possibility of persistent consequences of exposure to experimental treatments and placebo, and validation of the concepts of minimal risk and minor increase over minimal risk. *Conclusions:* Research on human subject issues relevant to child participation is a promising approach to improving ethical methods and procedures of pediatric psychopharmacology.

Keywords Ethics · Psychopharmacology · Children · Research

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Introduction

Pediatric use of psychotropic medications has dramatically increased in practice settings during the last 10 years (Zito et al. 2002). More recently, an increase in psychopharmacological research in children has also occurred (Riddle et al. 2001). Concerns about the administration of these drugs to children (here defined as subjects of minor age, usually below 18 years) have been raised among scientists and the lay public (Coyle 2000), thus bringing attention to the ethics of testing psychotropic medications in children. The ethics of psychopharmacology research in children is framed in the context of the ethics of biomedical research in general and pediatric research in particular (DHHS 1991a, 1991b; American Academy of Pediatrics Committee on Drugs 1995; Emmanuel et al. 2000; FDA 2000, 2001). While a comprehensive discussion of the ethics of research in children is not possible within the limits of this paper, some critical aspects that are relevant to pediatric psychopharmacology research will be here addressed, with special attention to the regulatory principles currently used for determining the ethical acceptability of research protocols in this area of pharmacology. In approaching the ethics of pediatric psychopharmacology research, it may be helpful to address some general issues before moving to more specific considerations.

Is psychopharmacological treatment of children ethically acceptable? If so, under which circumstances?

Though not directly linked to research, these questions have important implications for research. A negative reply to the first question would make the need for research moot, and possible limitations to the clinical use

of psychotropics would need to be taken into account in research protocols. There is now evidence that mental illness often starts in the first two decades of life, and that many psychiatric disorders can be validly diagnosed in childhood and adolescence. Moreover, available data support the efficacy of certain psychotropics in improving children with a number of disorders, such as that of stimulants in attention deficit hyperactivity disorder (ADHD; Agency of Health Care Policy and Research 1999) and of selective serotonin re-uptake inhibitors (SSRIs) in obsessive–compulsive disorder (March et al. 1998), major depression (Emslie et al. 1997; Keller et al. 2001), and anxiety disorders (Research Units on Pediatric Psychopharmacology Anxiety Study Group 2001). A major limitation in our current knowledge in child psychopharmacology is that little is known about the possible long-term effects of psychotropic medications on the developing body, and on the brain in particular. This is especially important in the case of very young children, under 6 years of age (Coyle 2000). The possible risks of pharmacological treatment during development must be, however, weighed against the possible risks of untreated psychopathology. Even though research still needs to clarify the long-term impact of treatments, it is reasonable at least to hypothesize that early intervention may ultimately result in a better prognosis. Thus, there is strong empirical support for considering psychopharmacology as a valuable treatment modality for a variety of clinical situations involving children. In addition, there is an equally strong theoretical rationale for pursuing research on novel possible applications of psychopharmacology to the treatment of mental illness in children.

In some situations, where there is availability of effective psychosocial interventions, it may be prudent, especially in very young children, to reserve pharmacological treatment of still unproven efficacy and safety to those patients who have not adequately improved on psychotherapy or other non-pharmacological interventions. For instance, in a clinical trial of the efficacy and safety of methylphenidate in preschoolers with ADHD, which is in progress at six sites, children are started on medication only if a course of behavior therapy has not sufficiently controlled the symptoms (Vitiello 2001).

Is psychopharmacological research in children ethically acceptable?

If research conducted in adults could adequately inform the pediatric use of psychotropics, there would be no need for direct experimentation in children, which would, therefore, not be ethically justifiable. Unfortunately, experience has painfully taught us that this is not the case. Developmental differences between children and adults have important implications for pharmacological effects (Coyle 2000). Even though adult data are relevant to pediatric psychopharmacology, research directly in children is necessary for a safe and effective use. For instance, without research in children we would not know of the phenobarbital-induced cognitive impairment in young children (Farwell et al. 1990) or of the lack of antidepressant efficacy of tricyclics in youths (Keller et al. 2001). The recognized public health importance of pediatric pharmacology research is reflected in a number of recent initiatives aimed at stimulating such research (U.S. Congress 1997, 2002; FDA 1998).

Is a specific research protocol in children ethically acceptable?

Only clinical research that can generate important new knowledge relevant to human health may be ethically acceptable. If both the rationale for the study and the proposed experimental design and methods are convincing, the ethics of the project is evaluated based on the regulations for human research (DHHS 1991a), as supplemented by those for children (DHHS 1991b). In addition to satisfying all the ethical requirements for human research in general, research in children must fall into one of the approvable categories described in subpart D (*Additional DHHS Protections for Children Involved as Subjects in Research*) of part 46 (Protection of Human Subjects) of the *Title 45* of the *Code of Federal Regulations* (DHHS 1991b). Recently, the Food and Drug Administration (FDA) has formally adopted the subpart D of the code of *Title 45* (FDA 2001). Legally, these regulations apply only to research funded or regulated by the U.S. federal government, such as studies supported by grants or contracts from the National Institutes of Health, or conducted under an investigational new drug application to the FDA. In fact, this policy sets the standard also for most non-federally sponsored research and is often referred to as the 'Common Rule" of clinical research.

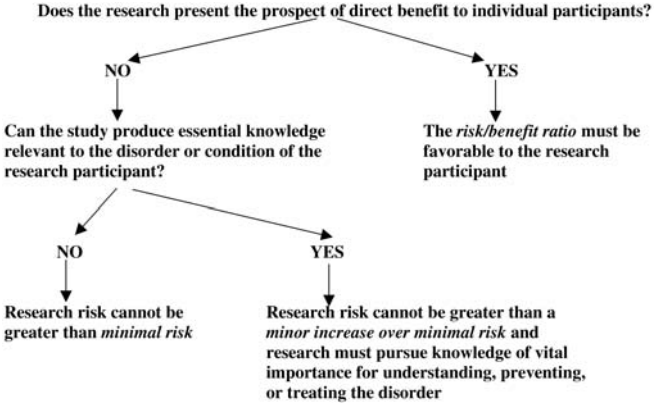

Fig. 1 Examining the ethics of a pediatric research study. Research not otherwise approvable, which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children, can be referred to the Secretary of Health (or the Commissioner of Food and Drugs if the study is FDA regulated) for review and possible approval (Department of Health and Human Services 1991a, 1991b). Also available on the Web site of the Office for Human Research Protections (OHRP) at: http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm

One approach to these regulations is to first determine whether the proposed research has prospect of direct benefit to the individual study participant (Fig. 1).

Research with prospect of direct benefit

Direct benefit is intended as a concrete probability, though not a certainty, that the health of a child entering the research protocol will improve as a direct consequence of participation. Possible financial advantages of research participation do not satisfy the 'benefit' condition. Controlled clinical trials, in which subjects are randomly assigned to different treatment options, typically offer a prospect of direct benefit. Even if placebo is one of these options, the randomized design offers a prospect of active treatment to each participant. Furthermore, for some psychiatric conditions, such as mood and anxiety disorders, the chances of improving on placebo are considerable so that placebo treatment cannot be considered 'absence of treatment' (Charney et al. 2002). Prospect of direct benefit alone does not make a study ethically acceptable. The risk/benefit ratio must be favorable to the child and at least as favorable to the child as that presented by alternative approaches. Elements that contribute to determining the risk/benefit ratio are: severity of the disorder, anticipated efficacy of study treatments (both experimental and comparison treatments), and foreseeable risks from study participation. Careful monitoring procedures of research subjects, with prompt identification and treatment of children who deteriorate during the study ('rescue procedures'), can substantially decrease the risk of participation and thus improve the risk/benefit ratio. In parallel, through the oversight of an independent data and safety monitoring board (DSMB) that periodically (usually every 6–12 months) reviews the interim cumulative data from the study, it is possible to identify possible trends in the efficacy and safety of the treatments under inquiry while the study is in progress. DSMB members can be unblinded to study assignments without compromising the investigators' blindness. Thus, if safety concerns emerge at DSMB review, research procedures can be changed or, depending on the circumstances, the entire study stopped. Should a DSMB interim review indicate that the study's research hypotheses have already been conclusively addressed, the study is terminated as continuation would be futile and unethical. For instance, a placebo-controlled discontinuation trial of risperidone in children with autism and severe behavioral disturbances was recently terminated at midstream by the DSMB because the interim data have already addressed the research hypothesis (Research Units on Pediatric Psychopharmacology Autism Network 2001). These monitoring procedures can substantially reduce the risk of exposure to ineffective or toxic treatments during clinical investigations. In addition, since clinical trials often take several years to be completed while progress in psychopharmacology is constant, it is essential to integrate new relevant findings in ongoing research protocols, periodically re-evaluate the risk/benefit ratio, and, if needed, revise the study procedures accordingly.

It is in the context of evaluating the risk/benefit ratio that the ethics of using placebo as a comparison in a clinical trial is typically examined. If there is reason to believe that exposure to placebo would result in an inferior clinical outcome relative to an alternative available treatment and its use might be harmful, the risk/benefit ratio would not be favorable and the study not ethically acceptable. For disorders for which no treatment has been conclusively demonstrated to be efficacious, a placebo control is easily acceptable. Since treatment research in children has lagged behind that in adults, there are fewer psychopharmacological treatments of proven efficacy and safety in children, so that placebo is generally easier to justify in pediatric trials. It is more difficult to accept placebo when a treatment of known efficacy and safety already exists. For instance, the efficacy of stimulant medications in decreasing symptoms of ADHD is well proven (Agency of Health Care Policy and Research 1999). More recently, the efficacy of various SSRIs over placebo in treating youths with obsessive–compulsive disorder (March et al. 1998) and depression has also been reported (Emslie et al. 1997; Keller et al. 2001). While it would be desirable to test the superiority of novel treatments against standard ones, this is not always feasible or practical. Differences in safety profile and variability in patient treatment response can make new drugs of therapeutic value even if not superior to the existing ones. Equivalence studies, however, are not a scientifically valid way of establishing efficacy when placebo response is high and unpredictable, such as in mood disorders (Walsh et al. 2002). In these situations, the inclusion of a placebo comparison is needed in order to draw valid conclusions (Kupfer and Frank 2002). Generally, exposure to placebo that is not likely to cause harm is considered ethically acceptable. For instance, placebo is routinely used in studying novel treatments of ADHD, because withholding active treatment for a limited period of time (a few weeks) is not likely to harm participants, even if it may result in discomfort. Likewise, administration of placebo for a few weeks to children with major depression who do not suffer from psychosis or present high risk of suicidal behavior is usually considered ethically acceptable (Fost 2001; Charney et al. 2002). In adults, exposure to placebo for the 8–12 weeks of the typical clinical trial of antidepressants has not been found to result in persistent negative outcome at extended follow-up (Khan et al. 2000). Similar findings emerged from a recent follow-up of 87 youths 6 months and 12 months after completing an 8-week placebo-controlled trial of fluoxetine in major depression (Emslie et al. 2000). It must also be noted that the rate of spontaneous remission in adolescent depression can be as high as 48% during an 8-week period (Clarke et al. 1999) and that placebo response seems to average between 40% and 50% in adolescent clinical trials. Thus, administration of a placebo does not equal

'absence of treatment', and rather can be considered "non-specific, repeated clinical contact", which can lead to substantial improvement (FDA 2001).

Research without the prospect of direct benefit

While the risk/benefit ratio is the specific critical element in deciding the ethics of research with prospect of direct benefit, research without the prospect of direct benefit is regulated according to the concepts of minimal risk and minor increase over minimal risk. Studies aimed at studying mechanisms of action of drugs, pharmacokinetics, or metabolism do not typically offer a direct health benefit to research participants. This type of research is approvable if it does not involve more than minimal risk, defined as "risk for harm not greater than ordinarily encountered in daily life, or during routine physical or psychological examinations or tests" (section 46.102(i) in DHHS 1991a). The prevailing interpretation is that the daily life, exams and tests of a normal child are to be used as reference. There is, however, no agreement on the boundaries of minimal risk. The interpretation and application of the general definition to specific research projects vary across settings and institutional research boards (IRBs). A minor increase over minimal risk can be considered acceptable only if: (a) it presents "experiences to the subjects that are commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations" and (b) the study has the potential to generate new knowledge considered of "vital importance" for understanding or treating the child's disorder or condition. Under this regulation, a number of psychopharmacological studies that do not offer the prospect of direct benefit can be approved. For instance, pharmacokinetics studies in normal children are not usually approvable, because drug administration per se would usually exceed minimal risk, but may be acceptable in children suffering from conditions that the drug is intended to treat, provided the research does not entail more than a minor increase over minimal risk. Studies that use medications as research tools, not to treat or diagnose, but to better understand pathogenesis or mechanisms of drug action, form a separate category of non-therapeutic investigation, which is approvable if conducted in children with a relevant disorder or condition and if not involving more than a minor increase over minimal risk. At the National Institute of Mental Health (NIMH), these studies are subject to additional scrutiny by an ad-hoc human subject committee of the National Advisory Mental Health Council before they can be approved for funding.

Parental permission and child assent

Specific to child research is the requirement of parental informed permission in order to participate. Permission from only one parent is sufficient, except for research without prospect of direct benefit and involving greater than minimal risk, which requires permission from both parents (unless one of them is deceased, unknown, incompetent, not reasonably available or when only one parent has legal responsibility for the child). In addition, assent must be obtained from the child as allowed by her/his cognitive capacity. Assent is meant to be an explicit, affirmative agreement to participate, not merely absence of objection. Children of 7 years of age or older are usually considered capable of understanding the essential elements of research participation and of providing assent (American Academy of Pediatrics Committee on Drugs 1995). For this purpose, written assent forms, with language appropriate to the child's developmental stage, are used in parallel to parental consent forms. In the case of younger or cognitively impaired children, although a formal assent is not obtained, efforts should be made to inform them of the study procedures in terms appropriate to their cognitive development. During research, an unequivocally expressed desire by the child to quit the protocol has to be respected, although transient episodes of frustration and uncooperativeness should not be necessarily interpreted as requests to leave the study. Close collaboration between researchers and parents is crucial in these situations.

Research on ethical aspects of research

The general ethical principles and regulations are currently applied to specific research protocols based on expert interpretation and IRB consensus. Recently, researchers have started studying the validity of the procedures intended to protect human subjects in some areas of adult psychopharmacology (Roberts et al. 2002). Little similar research has been thus far conducted in child psychopharmacology. Still, empirical data could help guide investigators, IRBs, and research participants on a variety of ethical issues relevant to child participation in research. The NIMH, as part of the National Institutes of Health (NIH), solicits grant applications for studying ethical aspects of human research (NIH 2002). The following are just a few questions relevant to the debate that could be addressed through research:

- What are the motivations of children and parents for enrolling in psychopharmacological research protocols? What are the implications, if any, for the fairness of subject selection as one of the essential ethical requirements of clinical research?
- How effective are assent and consent forms in informing research participants and their families?
- How effective is the process of obtaining parental permission and child's assent? How can it be improved?
- How do children who have participated in a research protocol perceive the experience?
- Does feedback from research participants and their families provide empirical validation of the application

of the concepts of minimal risk and no greater than a minor increase over minimal risk to specific procedures?
- Do subject individual characteristics predict negative reaction to research participation? For instance, a recent study has examined the association between pre-research psychological features and post-research outcome in a small sample of children participating in non-therapeutic invasive research, and found that children with increased baseline anxiety were more likely to report negative research experiences (McCarthy et al. 2001).
- Does placebo administration actually result in negative health outcomes (e.g., substantial worsening of illness, suicidal behavior, or hospitalization)?
- Does placebo administration carry negative health consequences that extend in time beyond several weeks, thus impacting the prognosis of the illness? One study has looked at this issue in children with depression and found no negative outcome (Emslie et al. 2000).
- How effective are the confidentiality procedures in protecting the privacy of children and families? Though not specific of psychiatric research, protection of privacy is especially important in mental health for the potential stigma associated with psychiatric disorders.

Conclusions

Research in pediatric psychopharmacology is needed in order to develop effective and safe treatments. Since adult research is not always applicable to children, direct participation of children in research is often necessary. Determining the ethics of a child research protocol requires attention to specific elements, in addition to the general rules for human research. Currently, few empirical data are available to guide investigators, families and ethical committees in the interpretation and application of the ethical principles to the reality of specific research protocols. Research on ethical aspects of pediatric psychopharmacology is needed.

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