

Review Article

Indian J Med Res 129, January 2009, pp 19-32

Informed consent & ethical issues in paediatric psychopharmacology

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Received September 26, 2007

Issues relating to informed consent and ethics in paediatric psychopharmacology limit research in this population. Children vary in their levels of cognitive development, and presence of psychiatric disorder may further impair their ability to give informed consent. In decisional impairment subjects, various methods used for consent are assent/dissent; inclusion of advance directives; and/or alternative decision-makers. India is emerging as a new market for clinical trials in recent years. Moreover, in India the socio-cultural realities are different from those in the western countries making it necessary for professionals to be cautious in conducting drug trials. In this review, issues regarding informed consent in children and adolescent with psychiatric diagnosis are discussed for information, discussion and debate by professionals, parents, society and legal experts to create awareness and to facilitate development of guidelines that are appropriate and applicable to the Indian system.

Key words Assent - children - informed consent - mature minor - psychopharmacology

Introduction

Drugs must be studied in children and adolescents to determine their safety and efficacy in them. Drug studies in adult humans may not adequately predict the pharmacokinetic, pharmacodynamic or toxic properties of drugs in children as growth, differentiation, and maturation can alter the kinetics, end organ responses, and toxicities of drugs in the newborn, infant, child, or adolescent as compared to the adult¹. There is a moral imperative to systematically study drugs in children so that they can enjoy equal access to existing as well as new therapeutic agents². Treatments that work for the adults may not be always beneficial or well tolerated by children (*e.g.*, tricyclic antidepressants are useful for the adult major depressive disorder but not so much for the depressed youth)³. Despite substantial and increasing use of the psychotropic medicines in children and adolescents, only a few of these drugs such as methylphenidate have been systematically

studied for its efficacy or safety⁴. Most of the psychotropic drugs do not have any specific labelling for the paediatric patients, other than a standard exclusionary statement that safety and efficacy have not been established in children; and it is primarily because of lack of efficacy data, concerns about the safety of these medications, ethical issues involved and absence of clear or good clinical practice guidelines to adhere to. When new treatments are introduced after clinical trials in adults, the clinicians are faced with the dilemma to either deprive children of the new treatment or subject them to the risk of an untested treatment that may or may not work the same way as in adults. This has forced the physicians and family members to make difficult choices, based on the extrapolation of information from the studies in the adults with similar conditions, resulting in the "off-label" use of these drugs⁵. Paediatric drug dosing has been empirically determined by the practitioners by trial and error method of adult dosage⁶. Possible long term effects

of the early exposure to these drugs have not been investigated and the impact of the psychotropics on the developing brain is largely unknown⁷. Most doctors and psychiatrists are not much familiar with the ethical issues as biomedical ethics as a subject in basic medical curriculum is often neglected and relegated to lower level of importance and often does not keep pace with the newer issues and challenges facing medical practice and research.

The central point in carrying out paediatric research is the lack of the necessary capacity in children required for informed consent². In this review issues relating to informed consent in children and adolescents with psychiatric diagnosis are discussed for information, discussion and debate to create awareness, and to facilitate development of guidelines for India as the systems here differ from the western counterparts on various socio-cultural, administrative and legal parameters.

The need for ethical guidelines

Historically, ethical guidelines to protect human subjects during scientific investigation were developed in recognition of past exploitation of human subjects and the acknowledged need to protect individual human rights. Federal regulations governing the protection of human subjects were published in 1974 in America⁸.

Some historical events

1947 - The Nuremberg Code: This is the first major international document to provide guidelines on research ethics, developed in response to the Nuremberg Trials of 23 Nazi doctors who performed unethical experimentation during World War II. It made voluntary consent a requirement in clinical research studies, emphasizing that consent can be voluntary only if participants are able to consent; they are free from coercion (*i.e.*, outside pressure); and they comprehend the risks and benefits involved. The Nuremberg Code was adopted by the United Nations General Assembly in 1948⁹.

1964 - Declaration of Helsinki: At the 18th World Medical Assembly in Helsinki, the World Medical Association adopted 12 principles to guide physicians on ethical considerations related to biomedical research. It emphasized the distinction between medical care that directly benefits the patient and research that may or may not provide direct benefit¹⁰.

1974 - The National Research Act: In 1974 the U.S. Congress signed the National Research Act into law, creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

1979 - The Belmont Report: After four years of work, this National Commission issued "The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research"¹¹. The Report set forth three principles underlying the ethical conduct of research.

(i) *Respect for persons:* It incorporates two ethical convictions. First, it recognizes the participants as autonomous agents. The participants are capable of deliberating and making individual decisions and choices. Second, there is a need to protect those with diminished autonomy – those who are impaired in decision-making skills, such as children, the aged, and the disabled.

(ii) *Beneficence:* There is an obligation to protect persons from harm by maximizing the potential benefits and minimizing risks. The good outcomes should be maximized not only to the participants but also for science and humanity.

(iii) *Justice:* Research should not be explorative, and there should be a fair distribution of the benefits and burdens of research.

The Belmont Report explains how these principles apply to research practices; for example, it identifies informed consent as a process that is essential to the principle of respect. In response to the Report, both the U.S. Department of Health and Human Services and the U.S. Food and Drug Administration revised their regulations on research studies that involve people¹².

1980 - Policy Statement on Ethical considerations involved in research on human subjects: In India, the first major national document to provide guidelines on research ethics was brought out by the Indian Council of Medical Research (ICMR)¹³. It was subsequently modified once in 2000¹⁴ and then in 2006¹⁵.

In 1977 the American Academy of Pediatrics (AAP) published "Guidelines for the Ethical Study of Drugs in Infants and Children"¹⁶. Federal regulations specifically addressing research in children were published in 1978¹⁷ and in 1983¹⁸.

Ethical principles for the protection of all human subjects arise from three basic premises: (i) respect

for the rights of the individual; (ii) the obligation to protect the individual from undue risk; and (iii) fairness in distribution of the burdens and benefits of research.

The conduct of research in children carries with it the same ethical obligations as research in adults. However, children comprise an especially vulnerable population and must be provided added protection against violation of their individual rights and exposure to undue risk. This situation imposes special considerations when inviting participation in studies, assessing risks and benefits, and ensuring equitable participation and benefits in clinical research. Issue is further complicated when research is to be done on the mentally ill, who may not have adequate capacity to give informed consent.

The research in children is justified based on the need to provide adequate information on the efficacy and safety of promising interventions. The relation between anticipated benefits and foreseeable risks is the main gauge of the appropriateness of the study which must be as favourable as that of the available alternatives. The special attention is paid to the potential risk exposure in paediatric research, for which the investigator has to consider the known and the predictable effects of the drug established previously through studies involving the animals, adults, or other groups of children¹.

Informed consent

Informed consent represents one of the safeguards in research on mental illness. Consent is best conceived as a process (not an event) that allows for the expression of a free, authentic choice by an informed and capable person to or not to participate in research protocol¹⁹. Capacity for consent is not static phenomenon; it can change with the condition of the patient, for example, as children mature, emerge from altered state of consciousness, *etc.*

The theory of informed consent was founded on two distinct legal principles: There is right of every patient to determine what will or will not be done to his or her body (right of self determination) and fiduciary nature of the patient-doctor relationship enunciated with the primary purposes of promoting individual autonomy, and promoting rational decision making²⁰.

There are three essential elements to the doctrine of informed consent *viz.*, competency, information, and voluntariness.

Competency: Competency refers to some minimal mental capacity required to perform a specific, legally recognized act or to assume some legal role. Competency is a broad concept, encompassing many different legal issues and contexts. Its definition, requirements and applications can vary widely depending on the context in which it is invoked such as decisions about health care, executing a will, or standing a trial. Incompetent is a legal term applied to the individuals who are considered by law not to be mentally capable of performing a particular act or assuming a particular role²¹. A psychiatric patient who is adjudicated incompetent to execute a will is not automatically incompetent to do other things, such as consenting to treatment, testing as a witness, marrying, driving, or making a legally binding contract. Incapacity indicates a functional inability as determined by a clinician.

Competency in the civil and criminal context is commonly raised in two situations – when the person is minor or is mentally disabled. Competence is narrowly defined as cognitive capacity. There are firmly established criteria to determine the patients' competence. There are standards for determining incompetency in decision making which are communications of the choice, understanding of the relevant information provided, appreciation of the available options and consequences, and rational decision making²⁰. Psychiatrists usually prefer the rational decision-making as the standard of informed consent, but most courts accept the first two standards. Rational decision-making occurs when the patients' consent reflects the patients' freedom of choice, personal need and values applied to the risks and benefits of the appropriate treatment options²².

Information: Information is the most critical aspect of informed consent. There are three models for information.

(i) *Traditional model:* The information that a reasonable physician will disclose under circumstances or what the physician would follow as the customary disclosure practices in a particular community²².

(ii) *Patient oriented:* it refers to the “material” information that a reasonable person in the patient's position would want to know to make a reasonably informed consent²³. “Material risk” is one in which a physician knows or should know what should be considered significant by a reasonable person in the patient's position²².

(iii) *Hybrid method*: Combination of both the methods²⁴.

As there are no consistently accepted sets of information to be disclosed for any given medical or psychiatric condition, there are huge variations in how much information is to be given to a patient, bringing in the possibility of selectivity and bias in the information process. There is a need for standardization of this procedure. Basically information should have explanations in understandable language of the patient on the following elements: (i) the proposed course of treatment, (ii) alternative treatments available, (iii) existence of the potential benefits/potential risks of each treatment options, and (iv) no treatment at all.

Voluntariness: Voluntarism encompasses the individual's ability to act in accord with one's authentic sense of what is good, right, and best in light of one's situation, values, and prior history¹⁹. For the consent to be considered legally voluntary, it must be given freely by the patient and without the presence of any form of coercion, fraud or duress that impinges on the patient's decision making capacity. In evaluating voluntariness the court typically examines all the relevant circumstances including the psychiatrist's manner, the environmental conditions and the mental state. Voluntarism provides safeguard against (i) Persuasion: Physician aims to "utilize the patients reasoning ability to arrive at a desired result", and (ii) Coercion: The doctor aims to manipulate the patient by introducing the extraneous elements which have the effect of undermining the patient's ability to reason²⁵.

Informed consent in children

The American Academy of Pediatrics (AAP) committee on bioethical statement of Informed consent notes that unlike other specialties "the doctrine of 'informed consent' has limited direct application in pediatrics". The statement explains that parents or other surrogates provide informed permission for diagnosis and treatment of children²⁴. As a part of the exercise, limitations were then taken to predict children as a group who are incapable to take informed decisions.

Competence in children (age gradual consent): The competence of children to take part in decision making for participating in research and treatment increases with age²⁶. Assessing the child's competence to understand may not be an easy matter and, in the past years, there has been a consistent tendency to underestimate the capacities of children in this

aspect²⁶. There is an increment in cognitive ability at about 7 yr and at about puberty, when adult like formal operations in thinking process are achieved²⁷. Lewis *et al*²⁸ found that children of 7-10 yr asked all the relevant information needed for the informed consent, and that reasoning of the 9 yr old about research risk is similar to that of the adults²⁹. Weithorn and Campbell³⁰ found out that 14 yr old children show the same concerns for risk-benefit as those of the 21 yr, and that the 9 yr old reach the same conclusion through a different reasoning strategy³. In a review of the evidence concerning the children's knowledge and understanding of the medical treatment, it is suggested that the children between 6 and 7 yr may view treatment as a punishment²⁶. Although children between 7-10 yr become aware that the purpose of the treatment is to make them better, they do not understand the reasons why doctors and nurses need to cause the pain. By 10 yr children have a more mature understanding of the treatment²⁶. Leikin after reviewing the literature, concluded that by the age of 9 children have enough cognitive capacity to make the decision to participate in the decision (not to make it by themselves)²⁹. Laor proposed that the children aged 12 and older should be able to consent to research on their own (like adults); those between 7-12 yr can consent but parents' assent is also needed (the reverse of the current rules); and before the age of 7 parental consent is needed, coupled with the child's assent³¹. It is suggested that a continuous process of empowerment for consent paralleling the maturational process should be followed^{29,31}.

It is important to mention that the age is only a rough guide to the level of the understanding about the treatment. Children of a particular age vary in their levels of the cognitive development. In the United States, the National Commission for the Protection of Human Subjects of Research recognizes the situations in which the requirement for parental consent for adolescents under 18 years to participate in minimal-risk research can be waived^{36,49}. In the United Kingdom, young people aged 16 and older are considered capable of giving informed consent, and those under 16 may consent to take part in minimal-risk research if participation is in their best interests and they are "mature minors" and refuse parental involvement⁵⁰. The Australian National Health and Medical Research Council's National Statement on Ethical Conduct in Research involving Humans requires consent from both young people and their parents to involve adolescents less than 18 yr of age

in any type of research³². It is recognized that because of wide individual variations, one cannot depend on the subjects' age to ensure sufficient understanding; even some adults have the difficulty understanding the information at times⁵.

Considering the competence issues in individuals who may not have decision making capacity or who are likely to experience fluctuating or progressively worsening decisional abilities, several safeguard mechanisms are available. These methods include (i) use of assent/dissent; (ii) inclusion of advance directives; and/or (iii) alternative decision-makers⁵.

(i) *Assent/dissent*: The ethical concept underlying assent and dissent is that a person may not be fully capable of consent but may be clear about his or her wishes to proceed or not to proceed with the course of action that may be burdensome, painful, or harmful, and that this expression of "choice" should be honored³³. Assent is the acceptance of an approach or positive action that is offered without a full and comprehensive exploration of the alternatives. Dissent is rejection of an approach or positive action that is offered without a full and comprehensive exploration of the alternatives¹⁹. These are commonly used in research with children or the developmentally disabled or decisionally compromised elderly (e.g., in dementia).

(ii) *Advance directives*: Psychiatric research advance directives are written documents in which the critical points during the research are pointed out to the prospective participant and the preferences are clarified in advance; this will help the researcher to uphold the wishes if the participant experiences the transient decisional compromise.

(iii) *Alternative or surrogate decision making*: There are two methods for alternative/surrogate decision making:

(a) "best interest model" in which the alternate decision maker offers judgment that is faithful to what he or she perceives as the decision that serves the well being and interests of the compromised persons (e.g., drugs for behavioural problems in mental retardation)³⁴.

(b) "patient preference model" in which the alternate decision maker makes the decision that closely represents the values and personal choice pattern of the compromised persons over his lifetime (e.g., choosing the drugs depending upon the side effects profile in psychosis with MR)³⁵.

In research "patient preference model" is often preferred as it represents most faithful and respectful depiction of the ill person's choice¹⁹.

Informed consent in adolescents

Adolescents are considered the "Consenting Minors". A minor who is near the age of majority, displays sufficient understanding of medical procedures, and can be medically emancipated in the treatment of certain conditions, including venereal disease, pregnancy, and drug abuse and is legally considered as a mature minor or emancipated minor². Emancipated minors are adolescents who may be eligible to give independent consent for themselves due to a variety of circumstances or runaways who refuse to identify themselves. These adolescents generally manage their own financial affairs and live independently away from their parental home. Emancipated minors may give permission for their children. These mature minors can give autonomous consent for their own medical treatment and participation on the research.

In research involving an "emancipated minor" or "mature minor", the investigator and the local ethical board must be very careful to protect the welfare of the minor subject. When obtaining informed consent from an emancipated or mature minor, the investigator and local ethical board must be knowledgeable about and in compliance with applicable state laws. In cases when minors are legally authorized to provide independent consent for particular treatments, permission from parents or legal guardians (when parents are not available, e.g., for institutionalized children) may be waived by the local ethical board, because it could violate the minor's privacy and prevent the adolescent from seeking necessary medical care².

The capacity of the emancipated or mature minor to partake in medical research depends upon the individual state laws, the type of research, and the risk/benefit ratio. The risk should be minimal, and answers to the scientific questions being asked must not be obtainable by using another group of adolescents whose parental involvement and consent are required. The research should be aimed at preventing or treating the medical condition for which the adolescent can legally and ethically give consent. For example, a researcher may investigate drug compliance in mature minors being treated for sexually transmitted diseases. The investigator must be confident that the minor is mature and competent enough to understand the

research, procedures, and risks and is independent enough to dissent comfortably if he or she does not want to participate. The investigator must be certain that the minor is not being coerced into agreeing to the research in order to please the investigator who may be involved in the minor's care. The investigator should determine if the parents can be informed by asking the minor's permission to involve the parents¹.

Application of the mature-minor principle in treatment

The historical notion of children as property items owned by their parents and lacking the right to consent to medical treatment, is changed in the western developed world³⁶. Children are now recognized as autonomous beings with discrete rights and interests³⁷. In the United Kingdom, the 1986 case *Re Gillick* established that children who satisfy the test of competency (*i.e.*, are deemed by their doctors to be "mature minors") can validly consent to their own medical treatment without parental consent³⁸. A requirement for confidentiality is a corollary of the mature-minor doctrine. Indeed, a major barrier deterring young people from accessing healthcare for sensitive issues, such as drug abuse or sexual health, is the fear that parents will be informed. It is usually in consulting about these sensitive issues that adolescents refuse to inform parents, leaving clinicians needing to assess mature-minor status before prescribing treatment that is in the adolescent's best interests³⁷.

Application of the mature-minor principle in research

There is evidence that adolescents' involvement in research has been hampered by absolute requirements for parental consent³⁶. For example, the requirement for active parental consent for school-based surveys has been shown to lower response rates by 40-67 per cent and cause under-representation of at-risk groups³⁹. Further, the right of adolescents, as a group, to benefit from research findings can only be upheld if they are given access to participation. On the other hand, there is a need to balance the right of young people to participate in research with their right to privacy and protection from risks and exploitation⁴⁰.

Consistent with earlier attitudes to children, human ethics committees and bodies producing research guidelines have taken a prominent role in protecting young people. However, research on child development and cognitive decision-making suggests that such caution is unwarranted. Cognitive maturation

also needs to be balanced with the insights that life experiences contribute to personal-risk assessment³⁷.

A particular danger of being overly protective is that young people may become "research orphans"⁵. Denying young people the right to participate in minimal-risk research because they refuse (or are unable) to obtain parental consent denies them their autonomy and the potential benefits of research, and compromises the validity of research (*e.g.*, homeless youth, intravenous drug users, or school truants)³⁷.

Keeping with the above principles, the following guidelines are formulated:

1. Informed permission/assent/consent

The right of a patient to give assent or consent or to withhold assent or consent for an investigational procedure or therapeutic intervention on an informed basis is well established in ethics and law. Participation in drug research should always be of free choice and ethical guidelines are not specific to all situations. It is unethical to obtain agreement for participation on the basis of coercion, inducement, or reward¹. The dictum is that no drug research may be performed in humans without the informed permission/assent/consent of the subject and of an individual legally qualified to act on behalf of the subject unless the need for permission/assent/consent is waived by the local ethical board.

2. Informing the consentor/permission giver/assenter

All important and reasonably expected consequences must be enumerated and explained to the subjects and/or parents in language easily understood by the consentor, permission giver, and assenter. If the document is not written in an easily understood language, an appropriate interpreter must be utilized. The consentor must be directed to and have full access to individuals qualified to answer all of their questions. The investigators and the local ethical board must specify the procedure and the minimum amount of information required to be provided to the child and parents in order to obtain a valid "informed" approval¹.

3. Parental/guardian permission

It is assumed that the parents are the people who know their child best, have their child's best interest at their heart, and are the people most likely to act for the benefit of their particular child²⁶. In most instances the adult legally acting on behalf of the minor must give

his or her permission before the minor is approached for his or her assent. For nontherapeutic research with greater than minimal risk both parents must give their permission if feasible¹.

Assent of the child: Assent should be obtained from children who are competent to understand. The purpose, risks, and benefits of a study should be explained to the subjects at a level appropriate to their intellectual age or the mental age (which may not be same as the chronological age as in mentally retarded children). Assent should usually be obtained from any child with an intellectual age of 7 yr or more. This provides the opportunity for a child 7 yr or older to refuse participation in studies or procedures done for research purposes. Assent may be waived in therapeutic research studies in which, in the opinions of the parents, investigators, and the local ethical board, the child's participation in an investigational treatment may be of such benefit that the child's welfare would be significantly jeopardized by failing to provide assent¹.

4. Withdrawal of consent or active dissent

The principles that govern permission/assent/consent govern its withdrawal also¹. The parent, child, emancipated minor, or mature minor has the right to revoke permission/consent/assent at any time during the study. If the investigator identifies reluctance in the parents or child about continued participation in a research protocol, the child's continuation in the study should be re-evaluated.

5. Protection for vulnerable populations

Specific populations that may be at increased risk for abuse and exploitation require special considerations.

(a) *The handicapped child:* Children who are mentally, physically, or emotionally handicapped must be stringently protected from disproportionate participation in research studies while protecting their right to participate and share in the benefits of research studies. Some studies may be limited to child subjects who are handicapped because certain diseases, clinical problems, and behaviour patterns are found principally or exclusively in such children¹. These children may need to be studied because their handicapping conditions or other medical therapy that they are receiving may affect the pharmacodynamics or pharmacokinetics of some drugs².

(b) *Institutionalized children:* Children institutionalized because of their special care requirements or under the supervision of a court or social welfare agency acting in lieu of a court should rarely be considered for inclusion in research studies. Institutionalization invariably deprives them of some of the safeguards necessary for the conduct of ethical investigations (e.g., studies on any type of treatment in mental retardation or autism). In general, these children should only be involved in studies of specific conditions unique to them or to the type of institution in which they reside. They should have access to experimental drug therapy when the research therapy is the only treatment available for the illness from which they may be suffering. Access to the experimental therapy may be through nonvalidated compassionate use¹.

(c) *Patients with chronically progressive or potentially fatal disease:* Unique feature of performing research in this group of patients is convergence of multiple ethical considerations which needs special attention, in addition to the scientific aspects of the study. Obtaining truly informed consent/participation may be difficult because of the child's debilitated condition or the mental and emotional state of the parents. The decision-making capacity of the parents may be impaired because the disease process may be genetically or congenitally acquired and they may feel guilty, depressed, and helpless, or may suffer from the same condition affecting the child. Investigational therapies may represent the standard of care or the only available treatment for some chronically progressive or potentially fatal diseases. In some situations, placebo-controlled, randomized clinical trials may not be ethically defensible or acceptable to the subject. In other situations, placebo-controlled trials are necessary to obtain reliable data when there are a few or no studies of the efficacy or the risks of investigational treatment, and a placebo trial may represent the most ethical approach. In this case, the investigator must help the subject and parents understand the importance of the controlled trial, the comparative benefits and risks of receiving active treatment in comparison to a placebo, and that the active treatment may in fact prove to be harmful¹.

(d) *Patients in emergency life saving care:* Conducting research in patients requiring emergent life-saving care presents a special problem, because the patient usually is incapable of giving consent and the parents may not be available to provide permission⁵¹. In this group of patients, research is imperative to provide therapeutic advances in their care.

Research in patients requiring emergency care may be conducted and informed consent/permission/assent altered or waived when all of the following conditions are met: (i) the clinical condition is potentially life-threatening or permanently disabling and the only known therapy is investigational or nonvalidated; (ii) informed consent/permission/assent cannot be obtained at the time the investigational treatment needs to be started; and (iii) there is no accepted therapy that is clearly superior to the experimental therapy.

Also the local ethical committee must see to it that the following criteria must be met: (i) there is minimal differential risk between the therapies that are being compared or either therapy might be selected even if the patient does not participate in the research protocol; (ii) there is minimal added risk from participation in the research protocol; (iii) subjects and/or parents will be provided with all pertinent information regarding the study as soon as possible; and (iv) the alteration or waiver will not adversely affect the rights and welfare of the subjects.

If the parent or child subsequently does not agree to further participation in the study, experimental procedures should be discontinued if doing so does not jeopardize the care and welfare of the patient. In the event participation is denied, no further data regarding the subject should be collected and the refusal of participation reported to the local ethical board and reported in all publications as the cause of the subject's withdrawal from the study.

The local ethical committee takes on heightened responsibilities when approving this type of research, because it must be convinced of the medical necessity of treating the condition urgently and should be confident that nearly all parents/children would give assent/permission/consent if they could be informed before the start of the study¹.

7. The newly dead patient

This type of research involves the administration of a drug to an individual who is brain dead but still has vital body functions. Research on the newly dead patient may provide critical information that would be impossible to obtain otherwise^{41,42}. When this type of extremely rare research is considered; the local ethical board must take every measure to protect the rights and dignity of the subject and his or her family/legal guardians. The respect afforded to living subjects and their families should be extended to newly dead

patients and their families. The studies must create no additional costs to the family or third-party payers. The following condition must be met before the study is approved by the local ethical board¹:

(i) Investigational procedures occur after the patient has been declared brain dead by a physician who is not involved in the research and the death certificate is signed.

(ii) The medical question addressed by the research must be a very important question that is not amenable to other experimental approaches.

(iii) Permission must be obtained from the parents or legal guardian.

(iv) The research procedures are brief.

(v) If organ donation has been approved, the research procedures should not alter the chances of successful organ donation.

(vi) An autopsy will not be performed or the study should not interfere with the results of the autopsy.

(vii) The drugs to be used meet the purity requirements for drugs for human use.

8. Placebo/observational control groups

Placebo or untreated observational control groups can be used in paediatric studies if their use does not place children at increased risk. The argument against using normal controls is that they do not stand to benefit themselves from the results. According to the guidelines of Committee on Drugs¹, the conditions under which placebos may be ethically employed in drug research in children include the following: (i) when there is no commonly accepted therapy for the condition and the agent under study is the first one that may modify the course of the disease process; (ii) when the commonly used therapy for the condition is of questionable efficacy; (iii) when the commonly used therapy for the condition carries with it a high frequency of undesirable side effects and the risks may be significantly greater than the benefits; (iv) when the placebo is used to identify incidence and severity of undesirable side effects produced by adding a new treatment to an established regimen; or (v) when the disease process is characterized by frequent, spontaneous exacerbations and remissions and the efficacy of the therapy has not been demonstrated. This is particularly important when dealing with research on drugs for autism and mental retardation.

Determination of benefits and risks

Research studies may be considered ethically permissible when they have a potential benefit to the individual child or provide generalizable knowledge, and when potential benefits outweigh potential risks. The evaluation of benefits should take into account the importance of learning about a disease process or biologic function, providing innovative treatment for the subject's own benefit, and the understanding by the child that he or she has contributed to the study of a childhood disease. In addition, the seriousness of the condition being treated and the risks of the proposed study must be considered. Studies that promise no demonstrable benefits to the child participating in the study or to children in general should not be conducted, irrespective of the minimal nature of the attendant risks. Inherent risks of the proposed study must be evaluated in the broadest context. These risks include the known and predictable effects of the drug as determined from prior animal and clinical studies or experiences, and the risks of the research procedures themselves. It must be realized that the drugs or procedures may cause adverse effects that have not been identified in previous studies. Studies to be carried out in children must be scrutinized for all potential risks, including those that are not usually of concern when considering studies in adults. These risks include discomfort, inconvenience, pain, fright and separation from parents or familiar surroundings, effects on growth or development of organs, and size or volume of biologic samples. Risks and fears may be minimized by limiting the number and type of invasive tests in the study, by improving or developing noninvasive and safe methods of monitoring biological effect, and by fully preparing and informing the subjects about the study procedures. Attempts should be made to use the least invasive procedures that provide scientifically valid information¹.

What are the risks of research?

The risks of involving young people in research vary, ranging from potentially major side effects from novel therapeutic interventions to minimal risk for participation in descriptive studies or health surveys. Minimal risk research may be described as research in which the risk of harm is "not greater than ordinarily encountered in daily life during performance of routine physical or psychological examinations or tests". While some people may be concerned that surveys of health risk behaviours that include questions about

sexual intercourse or self-harm might encourage these behaviours, there is no evidence to support this view⁵². Important ethical issues that arise in relation to minimal risk research with young people (*e.g.*, financial compensation, privacy, the implications of uncovering people at risk of harm or illegal activity) are similar for adults, but with the added complexity of the potential need to involve parents or guardians. Ethics committees need to ensure that these issues are identified in the research plan and deal with it appropriately. On the other hand, there are potential benefits to young people from participating in research. Health surveys may provide them with a greater understanding of their own behaviours, which may assist them in seeking help. The process of obtaining informed consent may lead to increased self-respect and decision-making capacity in young people, who also value the opportunity to be altruistic³⁷.

Ethical aspects and treatment in child psychiatry

Psychopharmacology with children and adolescents has to face an inherent paradox: on one hand, it is unethical to use treatment procedures without scientifically proved efficacy; and on the other hand, there are ethical problems to examine the efficacy of treatment methods scientifically. This contradiction has been called the "inherent paradox of clinical trials in psychiatry"³².

The pharmacological treatment of childhood psychiatric disorders should be considered when children have a disorder that is significantly affecting their psychosocial functioning and there is enough evidence that medication(s) will be beneficial and tolerated³. The implementation of any plan requires carefully obtained informed consent from parents before the plan is initiated. Although the parents provide the informed consent for the children, clinicians should strive hard to obtain the assent from the child. Consent should include a general discussion of the selected therapeutic modality, its intended purpose, the availability of any alternative treatments (including the choice of no treatment) and the nature of the any adverse effect that could result⁴³. Each therapist follows the ideal to have the good relations with his or her patients and to treat them on the basis of the mutual understanding and acceptance. However, there are cases in which compulsory treatment cannot be avoided. These include (*i*) patients with life-threatening disorders who refuse all kinds of treatment and who would die if an adequate treatment was not

administered (severe anorexia nervosa, highly suicidal, *etc.*). In these cases the children/adolescent consent can be substituted by their parents/guardian, and (ii) another possibility is the parents' refusal to give consent to an absolutely necessary treatment of their child (maltreatment, misuse or neglect of the child). The children or adolescent's assent/consent can be taken and the rights of the parents can be transferred to the local youth agency³².

The criteria for admission in the institution given by the American Academy of Child and Adolescent Psychiatry are⁴⁴

(a) The patient must be assessed by a psychiatrist who must be a child and adolescent psychiatrist for patients 13 yr of age or younger. For patients 14 yr of age and older, a psychiatrist with a documented adolescent training and demonstrated competence in the work with the adolescent is required.

(b) There must be a DSM-IV-TR diagnosis because of this patient must be an imminent risk to self or to others or be gravely disabled or experiencing medical complications arising from a psychiatric illness.

(c) A failure of the appropriately intensive treatment in a less restrictive setting must be clearly documented.

The child or adolescent and the family must be informed of the reasons for the inpatient admission and why such is the least restrictive intervention. Effort should be made to have the patient and the family voluntarily agree to hospitalization. When such hospitalization is involuntary, the family and the patient should be so informed.

When recommending treatment interventions for the preschoolers, the practitioners have to balance the potential benefits with potential adverse reactions/adverse outcomes and discuss these aspects with both the parents and child to obtain informed consent and preferential assent from both. In case of adverse events that are rare or only suspected, not casually proven, such as increased risk of suicide during antidepressant treatment or increased risk of cardiac adverse reactions with psycho-stimulants, the prescriber has to balance the risk of unduly alarming the family against the need to provide full information. In research, of course there is no choice but to disclose all known risk and warn them that there may be unknown risk, putting risks in context and perspective. The session should end with assurance that family should call physician if anything untoward happens⁴⁵. Children

should not be subjected to prophylactic interventions, *e.g.*, prophylactic antipsychotics in high risk children or institutionalization of children from dysfunctional families, in their best interests or for public health reasons when there exists effective and conservative alternative interventions, such as behavioural modification, that could be employed to avoid adverse health consequences⁴⁶.

There are no criteria for the electro convulsive therapy (ECT) in children but American Academy of Child and Adolescent Psychiatry has given guidelines for ECT in adolescent⁴⁷. The indications for giving ECT in adolescent are:

(i) **Diagnosis:** Severe, persistent major depression or mania with or without psychotic features, schizoaffective disorder, or, less often, schizophrenia. ECT may also be used to treat catatonia and neuroleptic malignant syndrome.

(ii) **Severity of symptoms:** The patient's symptoms must be severe, persistent, and significantly disabling. They may include life-threatening symptoms such as the refusal to eat or drink, severe suicidality, uncontrollable mania, and florid psychosis.

(iii) **Lack of treatment response:** Failure to respond to at least two adequate trials of appropriate psychopharmacological agents accompanied by other appropriate treatment modalities.

Consent of the adolescent's legal guardian is mandatory, and the patient's consent or assent should be obtained. State legal guidelines and institutional guidelines must be followed⁴⁷.

Indian scene

India is the second most populated country of the world and is a relatively young nation where children (aged 0-14 yr) constitute 37.77 per cent of the population. In India, there is a high availability of the patient population and unavailability of trained child psychiatrists or those who have sufficient experience with child patients. Being more traditional and class oriented society, there is greater acceptance of social distance between individuals and between the patient and the doctor in India. The doctor is identified with superior class and the patient assumes a submissive position vis-a-vis him, where authority is vested with the physician, and patients often want the doctor to make decisions for them. Most patients are unaware of their rights or are culturally conditioned not to exercise

their own choices. In such situations it is extremely important to ensure that the doctors follow ethical safeguards.

Further, India is a collectivist society; patients and children welcome participation of family members in decision making in contrast to the western society where they put high emphasis on individual autonomy. In Indian culture the authority of the parents is near absolute and children are not given to exercise any consent/opinion in normal course. Children often find it hard to give their opinion and look up to the parents for their decision. The lack of the education is also a factor which causes children as well as parents not to fully understand the implications of giving consent to the study. It has been seen that sometimes parents see participation in research as an advantage such as free medical treatment or financial benefit.

Ethical guidelines for the biomedical research on human subjects issued by the Indian Council of Medical Research¹⁵ state that before undertaking research in children the investigator must ensure that children will not be included in research that could be carried out equally well in adults, assent should be obtained to the extent of the child's capability, a parent or a legal guardian of each child has given the proxy consent, research should be conducted in the settings in which child and parent can obtain adequate medical and psychological support, interventions to provide direct diagnostic, therapeutic or preventive benefit of the individual child subject must be justified in relation to anticipated risks involved in the study and anticipated benefit to the society, adequate justification is needed in subjects who have reduced autonomy (prisoner, students *etc.*) and child's refusal to participate in the research must always be respected unless there is no medically acceptable alternative to the therapy provided/tested, provided the consent has been obtained from parents/guardians.

Prior to the subject's participation in the study, the written informed consent must be obtained from the subject or if the subject is incapable of giving an informed consent, for example, children, unconscious or suffering from the severe mental illness or disability, by the subject's legal representative or guardian or if the subject and his/her legal representative is unable to read/write, by an impartial witness who should be present during the entire informed consent process.

Before undertaking any research, the investigator must provide the individual with the following

information in the language he or she is able to understand which should not only be scientifically accurate but should also be sensitive to their social and cultural context. The relevant informations to be provided are aim and method of research, the expected duration, the benefit that might be expected as an outcome to the subject or the others, any alternative procedures or course of treatment that might be advantageous to the subject as the procedure or treatment to which he/she is being subjected, confidentiality of the records of the child and the anticipated consequences of the breach of confidentiality, identity of the research teams including their contact details, foreseeable extent of the information on possible current and future uses of the biological material and of the data to be generated from the research and if the material is likely to be used for the secondary purposes or would be shared with others, clear mention of the same, risk for discovery of the biologically sensitive information, free treatment for research related injuries, right to withdrawal from the study at any time during the course of the study without the penalty or loss of benefits which the subjects would otherwise entitled to¹⁴.

Participants in the research may be paid for the inconvenience and time spent, and should be reimbursed for expenses incurred, in connection with their participation. During the period of research if the participant requires treatment for complaints other than the one being studied or develops complications (temporary/permanent) during the research, necessary free ancillary care or appropriate referrals may be provided. In case of the permanent disability necessary compensation has to be given. All payments, reimbursement and medical services to be provided to research participants should be approved by the institutional ethics committee (IEC). Care should be taken: (i) when a guardian is asked to give consent on behalf of an incompetent person, no remuneration should be offered except a refund of out of pocket expenses; (ii) when a participant is withdrawn from research for medical reasons related to the study the participant should get the benefit for full participation; (iii) when a participant withdraws for any other reasons s/he should be paid an amount proportionate to the amount of participation; (iv) in case of emergency the participants/parents/legal guardians should know about the person to be contacted which usually is a member of the research team or the contact person specifically designated for this person¹⁵.

Growing interest now of global pharmaceutical companies to recruit cases from India in their studies appears to be driven by factors such as low cost and easy availability of the patient population and ease of obtaining consent and less stringent ethical criteria providing for easy recruitment. Most doctors and psychiatrists may or may not be much familiar with the ethical issues as biomedical ethics as a subject in basic medical curriculum is often relegated to lower end of importance and often does not keep pace with the newer issues and challenges facing medical practice and research. Because of these issues, the doctors must exhibit greater caution and concern in India for inclusion of children in research to avoid exploitation/coercion.

Apart from registered institutions, now a day in India, research is done at private clinics and hospitals that may not have their local ethical boards. These research sites must come under the purview of a regulatory body like the ICMR for adhering to ethical guidelines. Establishment of ethical boards in each hospital/institution should be mandatory. In addition, the process of obtaining informed consent is often inadequate in studies done in India and the investigators and the research staff needs more training.

Conclusions

It is time in India to set up Ethical Review Boards (ERBs) in every institute/medical college and for research ethics to become essential requirement to be adhered to. Mostly clinicians caring for children and adolescents are frequently the investigators and this may have potentially coercive influence on subjects and parents as they may feel obliged to participate in the research due to dependent relationship established between the clinical investigators and subject's family. Attempts should be made to mitigate this, possibly by having an investigator who is not involved in the patient's care, obtain approval for participation, and be assured that those who consent or give permission are capable and understand the risks and benefits of the study and act in the child's best interests.

Based on studies of children and adolescent decision-making capacity, there are grounds for ethics committees to consider allowing young people aged over 14 yr to participate in minimal risk research without parental consent/legal guardian in accordance with the mature-minor principal. Ethics committees would need to be fully informed about adolescents'

developmental capacities with respect to the mature-minor concept, as well as have a sound understanding of the changing nature of health risks faced by young people. Ethics committees have a central role in deciding the level of protection required and the necessary level of involvement of adolescents and their parents/legal guardians in providing consent to participate.

It is essential that consumers and community members, including young people and parents, are engaged in this debate in order to align research practice with good clinical practice guidelines, socio-cultural values and the law. Research involving children carries with it additional responsibilities for the investigators, for the local ethical boards and for the sponsors.

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