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REVIEW

Ethical issues in child psychopharmacology research and practice: emphasis on preschoolers

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Abstract
Introduction Psychoactive drug prescription for preschoolers has increased over the past decade and has been a controversial topic for those who prescribe, regulate, and research the use of psychotropics in this population. Children and adolescents are deemed vulnerable populations, at risk of being harmed by unethical or suboptimal practice and research and are in need of special protection. Historically, preschoolers have been therapeutic and research "orphans," excluded from pharmacological studies so that the evidence base for their treatment has to be extrapolated from other ages. Within the past few decades, several ethical principles guiding pediatric psychopharmacological research have been developed. The same principles could effectively guide the treatment of these patients. *Conclusion* Further studies are needed to elucidate the safety and effectiveness of psychotropics, and sound ethical guidelines for their involvement in psychiatric research are needed. This article reviews some challenges facing mental health care providers involved in prescribing or researching the use of psychoactive drugs in preschoolers. Some of these challenges are general to medical treatment and research with children, and others are particular to child psychopharmacological treatment and research.

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Introduction

The use of psychotropic medications in children and adolescents with psychiatric problems has been increasing steadily over the past few decades, leading to a need for an empirical research evidence base and specific ethical guidelines for both prescribing and investigating psychotropics in the pediatric population.

The ethics of medical practice and research have long been a subject of debate and dialogue among health care providers, philosophers/ethicists, lawmakers, and state agencies. Several documents including "The Nurnberg Code," The "Declaration of Helsinki," the "Belmont Report," and the "International Ethical Guidelines for Biomedical Research Involving Human Subjects" have identified five ethical dimensions for undergoing human research: human rights, validity, distributive justice, beneficence/nonmaleficence, and respect for autonomy/justice (Yan and Munir 2004). To a great extent, the same principles also apply, with appropriate modifications, to clinical practice.

In fact, research ethical principles obviously derive partly from practice ethics, and this is appropriate because research subserves effective practice and derives its justification from that supporting role. Beauchamp and Childress (1994) used four of these five research principles in developing a framework to define ethical practice (Table 1).

The ethics of treating and doing research with psychiatric patients in general and children and adolescents with psychiatric disorders in particular are even more complex

Table 1 Ethical principles that may apply to defining ethical medical practice

Ethical principles	
Respect for autonomy	Acting in such a way as to enable the patient in understanding and consenting to treatment; respecting the patient's wish for confidentiality; educating the patient about any limits to autonomy; adjust application of autonomy principle to a child's developmental stage
Justice	Acting in such a way as to ensure fair treatment and fair distribution of research benefits and risks
Beneficence	Acting based on the wish to "do good" or "prevent harm"
Nonmaleficence	Acting always in a way that first avoids harm ("primum non nocere"), always balancing benefits versus side effects

given these patients' status as "vulnerable populations," their developmental status of dependency, and the developmental aspects of judgment and decision-making (Table 2).

Vulnerability in psychiatric pediatric patients with special relevance to preschoolers; developmental aspects of judgement and decisions

Many ethicists are concerned about the impairment of mental capacity and judgment resulting from disorders causing severe cognitive impairment, including severe psychiatric disorders. Some (Lehrman and Sharav 1997) imply that such patients may be incapable of giving informed consent and require a close evaluation of the particular vulnerabilities resulting from the psychiatric comorbidities oftentimes presenting in combinations unique to the patient. Roberts and Roberts (1999) cite a research showing that although such patients have impairment of decision-making capacity while acutely ill, after treatment, they begin to resemble nonimpaired comparison groups. Roberts et al. (2000) found that patients with schizophrenia had "discerning views" and manifested more altruism than psychiatrists expected. In another study, the severity of psychopathology and global indices of dementia severity did not predict decisional capacity, which must be assessed case by case.

By definition patients with psychiatric illnesses have symptoms consisting of changes/impairment in the way they feel, think, and relate to their environment compared with people of similar background who do not have a psychiatric illness. Therefore, it may be reasonable to assume that even experiences or events of daily normal life may be perceived differently by patients with psychiatric illness, making it difficult to evaluate "minimal risk" and "minor increase over minimal risk" in this population (Kopelman 2004).

In 1994, the Food and Drug Administration (FDA) revised the pediatric labeling rule to address the issue of "orphaning clauses" in prescription drug labeling (e.g.,

Table 2 Examples of ethical issues in child psychiatric research resulting from subject age, psychiatric patienthood, and the combination

Belmont (1979) ethical principle	General research with children	Psychiatric research with any age	Child psychiatric research
Respect for person; autonomy principle	Children's developmentally limited ability to consent/assent	Questions about cognitive processing and suggestibility	Informed consent doubly limited: cognitive immaturity and impaired cognitive processing
	Developmental aspects of decision-making; suggestibility	Emotional influence on decision making	Both developmental and emotional impact on decision making
	Parents' rights and natural protective role	Paternalism of caregivers, guardians, state	Parents' protective role colored by emotional stress of disturbed child
	Coercive inducement; child's view of $ amount	Dependence on therapist/ physician	Coercion from both harassed parent and reimbursement
Beneficence	Conflict between need for placebo control and the right to best proven treatment	Placebo discontinuation trials in chronic disorders	Need for placebo to determine effective treatment when no or poor evidence base
Justice, equity	Need for research with children to help "research orphans"		Need for child psychopharmacologic research to guide ongoing psychopharmacotherapy for children
	Children's vulnerability	Vulnerability of mental impairment	Double vulnerability: children and mental impairment
	Fair reimbursement for research burden of parents		

"safety and efficacy not established for children"). "The 1998 Pediatric Rule" (National Archives and Records Administration 1998) was introduced and required premarketing testing in children for certain classes of drugs. The Food and Drug Administration (1997) Modernization Act provided an incentive to drug companies to conduct studies in children (a 6-month patent extension). The National Institutes of Health (1998) issued a policy requiring inclusion of children in research on treatments for conditions that may affect children. The response to such multisource federal initiatives has focused increased attention on the ethical problems of implementation (Twomey 2000).

The Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations (American Academy of Pediatrics—Committee of Drugs 1995) define "vulnerable populations" as those who may be at increased risk for abuse and exploitation such as handicapped or institutionalized children, those who are in life-saving emergency care or are dying, and those with chronic progressive or potentially fatal diseases but with no mention of psychiatric disorders. Because of the status as "vulnerable populations" historically, there was an increased reluctance to expose children and adolescents to unnecessary risk during research trials, leading to a scarcity of data on the effectiveness, safety, and pharmacokinetics of psychoactive agents at this age. Within the past few decades, although, pediatricians and others involved in caring for children argued that children have been "therapeutic orphans" because of the usage of most drugs in children having to be extrapolated from adult data. Trying not to keep potentially helpful treatments away from children and adolescents struggling with severe psychiatric symptoms, physicians were treating pediatric patients by prescribing psychotropics "off label."

Off-label prescribing of medications is a wide spread practice (Beck and Azari 1998). Some estimate that up to 60% of all drug prescriptions in the US written over a 1-year period are off label, and a big part of them target pediatric patients. Because the FDA has no authority to regulate the practice of medicine, it is up to the physician to make the decision as to whether to prescribe a medication off label. When doing so, physicians must balance the principle of beneficence (that implies the physician's duty to use their best professional judgment to treat patients with the goal to decrease the impairment caused by the illness and improve the patient's health and quality of life) with the principal of nonmaleficence and the regulatory objective of protecting patients from unsafe or ineffective treatments. In children, and in preschoolers in particular, this process is complicated by the lack of efficacy and safety studies in this age group.

Research with children to meet children's needs (e.g., Gordon et al. 2000; Chesney 2005) became an ethical imperative based on the principle of justice, which requires equitable sharing of the burdens and fruits of research. This is especially true for preschoolers who have been the most neglected age group for psychopharmacologic research. Under the principle of justice, the ethical imperative favors well-planned preschool research in balance with the beneficence/nonmaleficence principle (Greenhill et al. 2003).

Children and adolescents with psychiatric disorders pose a double challenge, because of considerations of both their psychiatric illness and their developmental level, when assessing their decisional capacity. Both children and "the mentally disabled" are defined as "vulnerable populations" because of their developmental status of dependency and limited judgmental and decisional capacity, and therefore, they are considered in need of special protection from abusive treatment and research practices (National Archives and Records Administration 1991; Solyom and Moreno 2005). Most of the more common disorders of younger children (ADHD, ODD, conduct disorder, anxiety) do not cause the degree of cognitive impairment (relative to a normal child's cognitions) that psychoses do. With a few exceptions (e.g., autism, mental retardation), the psychiatric disorder is usually not as impairing to the younger child's decisional capacity as is cognitive immaturity.

However, autonomy and decisional capacity vary by age and do not undergo a quantum leap at legal majority. At about age 7 and at puberty, children undergo qualitative and quantitative improvements in cognitive capacity, and by age 14, minors show the same risk–benefit reasoning as adults; 9-year-olds reach the same conclusions as adults and adolescents but by different strategies. Based on the principle of respect for autonomy, most experts recognize that older children and adolescents can participate in the consent process to varying degrees and should be allowed to do so to protect them from being subjected to treatment or research procedures against their will.

Preschoolers present an increased ethical challenge given that their brains have yet to undergo many critical stages of brain development (Vitiello 1998, 2003) and present the possibility of physiological and even anatomical vulnerability, with possible long-term detrimental effects of the interaction between psychoactive drugs and brain development. There is little knowledge on the long-term safety of psychotropic agents on the developing brain. There have been almost no pharmacokinetics studies and very few safety and efficacy studies in preschoolers to determine appropriate dosage and metabolism of different pharmacological agents. Because of the rapid pace of developmental

changes at this age, it is also difficult to predict side-effect profile and drug response based on known responses in older children.

Given the significant neurobiological changes that are part of the maturation process, the brains of preschoolers represent a different neurological milieu than school-age children. The recent availability of methods of brain imaging such as positron emission tomography, magnetic resonance spectroscopy, and single photon emission computed tomography, together with the development of more specific ligands for brain neurotransmitter receptors, should make it possible to further study the unique structural and functional characteristics of the brain at this stage of development. More research is needed to better understand the short- and long-term impact that psychopharmacological agents have on the structure and functioning of the brain in preschoolers.

There is only limited understanding of normal and abnormal behavior at this age, making it difficult to diagnose psychiatric illness in preschoolers. In the case of preschoolers, such developmental phenomena as normal separation anxiety, negativism, developmental hyperactivity, and imaginary playmates obfuscate the usual boundaries of psychopathology at this age. In-depth knowledge of normal development and careful and detailed history taking and direct observation by trained clinicians in various settings are of paramount importance to the complex process of diagnosing psychiatric illness at this age. The development of new, age-appropriate clinical rating scales could further facilitate the process of diagnosing psychiatric illness in preschoolers.

Because normal development at this age proceeds at a rapid pace, it may be more difficult to separate treatment effectiveness from the process of emotional and behavioral maturation. In this age group, studies so far have confirmed the validity of the diagnoses of attention deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorders (Lahey et al. 1998; Keenan and Wakschlag 1998). More studies are needed to confirm the validity of other diagnoses in preschoolers, as the lack of a reliable diagnosis will, of course, preclude any study regarding that condition in this population.

The preschool child's participation in the consent process is also more problematic because of a very immature level of autonomy and their normal stage of egocentric, magical, animistic, alogical, and pre-operational thinking. Normal preschool cognition does not allow decentering from details to assess such overall concepts as risk/benefit ratio, nor does it support the perception of another's view and the fact that someone may have a hidden agenda or priorities other than the child's. Therefore, a preschooler is not capable of assent. However, some ethicists consider preschoolers capable of dissent. In fact, some have proposed that subjects incapable of consent should nevertheless be able to decline research participation by indicating dissent in any way, verbal or nonverbal.

All minors should be evaluated as both individuals and as children of their parents, who have a crucial role in advocating for their children and arranging for them to receive treatment or participate in research. The parental role is even more critical in preschoolers compared with older children. The parents are assumed to advocate for the child's best interests. Unfortunately, some parents may not be able to carry out this advocacy role fully, either because of their own limitations or because the child's symptoms have stressed them so much. The treating physician or the investigator and associates must accept increased ethical responsibility for the child in the treatment of preschoolers and their involvement in research. This usually is not much of a problem for studies deemed to provide direct benefit to the child greater than the risks and discomforts, but for studies without direct benefit, especially those of more than minimal risk, additional safeguards must be implemented to carefully assess parental motivations and assure the child's protection.

Consistent with the principle of respect for persons, from which the autonomy principle flows, respect for the person of a child or adolescent should include appreciation of developmental characteristics and needs (one of which is the right for the parent to take responsibility for the preschooler). Therefore, children and adolescents warrant a developmentally sensitive approach to obtaining assent/dissent and a careful evaluation of the parental capability to act in the preschooler's best interest. This may include the assistance of a consent monitor with clinical background in child development who could assess parental motivations and the strength of the positive attachment to the child, with the objectives to:

1. Honor dissent from children whose decision-making skills are judged meaningful and whose dissent is not just a manifestation of the disorder being treated (e.g., oppositional-defiant disorder)
2. Have the parent's consent override the child's dissent in research with direct subject benefit at least as great as the risks and discomforts (judged by Institutional Review Board [IRB])
3. For studies with less benefit than risk, have child dissent at the beginning exclude the subject, and dissent later in the study require approval of an IRB-appointed neutral clinician to continue

In practice, for studies with obviously greater benefit than risk, the consent monitor may be an unnecessary expense.

Ethical issues in the psychopharmacological treatment of children and adolescents

Increasing psychoactive drug administration to children and adolescents and especially preschoolers precipitated a national concern over such medications being used without an adequate evidence base to support the practice.

When treating psychiatric disorders in children and adolescents and especially preschoolers, one has to carefully consider the impact of development on the clinical presentations, response to treatment, and safety risks.

Drug-safety issues

The importance of carefully evaluating drug safety and the impact of these drugs on the immature, developing brain of the preschoolers cannot be underestimated. A significant body of evidence points to an increased risk of administering psychopharmacological agents to children and adolescents compared to adults. For example, there is evidence that drug toxicities may be age dependent (see the classic examples of toxicities induced by early exposure to oxygen, tetracyclines, aspirin, etc.). Early treatment with Phenobarbital may have long-lasting negative effects on cognition.

Safety issues in treatment with stimulants

Animal studies suggest that administration of stimulants induces a state of sensitization of the brain that may lead to later substance abuse (Vitiello 2001a,b). Such sensitization has not been demonstrated in humans, and there is no published clinical evidence that early treatment with stimulants predisposes to later substance abuse, but this is more an absence of evidence than evidence of absence. Another concern relates to the effects of treatment with stimulants in children who may be at risk for mania, depression, or psychotic disorders. Adolescents with these disorders frequently have a history of attention deficit hyperactivity disorder treated with stimulants in early childhood. More research is needed to clarify whether chronic treatment with stimulants can affect the presentation of other psychiatric disorders. Stimulant use has also been linked with slight growth inhibition and a risk of cardiovascular side effects in patients with underlying medical issues.

Safety issues in treatment with selective serotonin inhibitors

Recent studies have documented powerful effects of gestational exposure to selective serotonin inhibitors (SSRIs) on neonatal behavior and health including a higher rate of irritability, shivering, agitation, hypotonia, and an increased risk of persistent pulmonary hypertension of the newborn (Nulman et al. 1997; Sivojelezova et al. 2005; Cissoko et al. 2005; Chambers et al. 2006). There is also some evidence suggesting long-term behavioral changes in preschoolers exposed in utero to psychotropic medications (Nulman et al. 2002; Misri et al. 2006).

Animal studies have shown that transient administration of SSRIs in early life produced abnormal emotional behaviors in adult animals (Ansorge et al. 2004). Rodents administered with SSRIs prepubertally develop an increased density of serotonin transporters in the frontal cortex that persists into adulthood (Wegerer et al. 1999), and their prepubertal (as opposed to adult) response to serotonergic probes is dramatically different (Carrey et al. 2002). Although it is difficult to extrapolate such findings to developing humans, these studies emphasize the great need for further research.

The developmental psychopharmacology of the SSRIs is also of interest given the wide concern over possibly SSRI-induced suicidality in adolescents.

In 2004, the FDA introduced a black-box warning to all antidepressants including SSRIs to advise about the increased risk of suicide upon initiation of treatment with antidepressants in children and adolescents. This was based on pooled analyses of 24 placebo-controlled studies involving more than 4,000 pediatric patients (US FDA 2004a,b).

Suicide is the third leading cause of death in adolescents 15–19 years of age, and fourth leading cause of death among 10–14 year olds (Anderson 2004). And yet, epidemiological studies show that although the antidepressant use in pediatric patients has substantially increased, the overall youth suicide rates have been declining (Olfson et al. 2003). Between 1990 and 2000 in US, for each 1% increase in antidepressant use, there was 0.23 decrease in suicides per 100,000 adolescents per year (Kratochvil et al. 2006). Most postmortem studies in suicide victims, whether adolescents or adults, have found that a very high percentage of depressed patients at the time of suicide were not taking antidepressants. Literature from the preantidepressant era suggests that depressed patients were more likely to commit suicide as they were coming out of a depressive episode. Therefore, the evidence at present is inadequate to establish conclusively an association between the use of SSRIs and suicide in adolescents, and more research is needed.

The relationship between SSRI-induced behavioral activation, agitation, akathisia, and mania induction has not yet been clarified. Although self-harm is a rather uncommon phenomenon in preschoolers, the risk of other behavioral side effects such as activation and hypomania is increased and may be age-related, with children in the 5–9 age group having a higher incidence of such adverse events (Martin et

al. 2004). It is unclear whether activation or hypomania reflects unmasking of an underlying bipolar disorder or just an adverse effect on the developing brain. These behavioral effects are not unique to the treatment of youth with depression; they were also described in children taking SSRIs for the treatment of obsessive–compulsive disorder (March et al. 1998; Riddle et al. 2001).

Safety issues in treatment with antiepileptic drugs

Antiepileptic drugs (AEDs) are commonly prescribed in pediatric patients to treat juvenile bipolar disorder. Somnolence, agitation, sleep disturbances are among the most common side effects encountered with this medication group. Phenobarbital by far has the worst side-effect profile, and yet, it is the most widely prescribed antiepileptic drug in children up to the age of 11 years (Kwan and Brodie 2001), albeit not for bipolar disorder. Valproate, which is commonly used for bipolar disorder, has been associated with the development of polycystic ovary syndrome in adolescent girls. Weight gain associated with treatment with certain AEDs may increase the risk of developing endocrine and metabolic problems that could lead to life-long severe health problems.

Safety issues in treatment with antipsychotics

The use of antipsychotics in children and adolescents within the past decade has also increased. Antipsychotics have been prescribed to treat aggression, agitation, mood dysregulation, psychosis, self-injury, etc. in this age group, including preschoolers.

Long-term treatment with antipsychotics carries the risk of inducing Tardive Dyskinesia, a condition that remains difficult to treat. Other significant adverse reactions include extrapyramidal symptoms, akathisia, cognitive and emotional dulling, and irritability. Younger patients are more susceptible to developing hyperprolactinemia. The most worrisome side effect for the majority is the weight gain and possible metabolic syndrome, which may lead to life-long health problems. (Correll and Carlson 2006). The FDA issued a black-box warning about the development of diabetes in patients receiving antipsychotics.

Some studies also suggest that long-term treatment with antipsychotics may induce sensitization of the dopamine receptors that could be responsible for the antipsychotic withdrawal syndrome labeled as “hypersensitivity psychosis” that resolves quickly with the restarting of the antipsychotic dosage.

Research on drug safety still faces multiple challenges because of marked differences among trials in the methods used to elicit, measure, and report adverse reactions (Deveaugh-Geiss et al. 2006). More standardized methods of collecting safety data together with long term studies to evaluate possible effects that emerge over time or are caused by early exposure to medication during development could greatly facilitate drug-safety research. The development of a more centralized database of reported side effects may also help, together with pharmacoepidemiological studies of existent large naturalistic databases such as those maintained by the FDA and the health maintenance organizations. Increasing the emphasis in animal research on developing animals could also prove most helpful.

Given all the risks associated with prescribing pharmacological agents that can adversely affect the developing brain, the development of effective nonpharmacological therapies to treat psychiatric disorders in preschoolers should be a major public health priority. There is a question as to whether nonpharmacological treatments should ethically be tried in preschoolers before initiating psychopharmacological treatment or entering them in a psychopharmacological protocol.

Several studies have already proven the effectiveness of certain psychosocial approaches based on operant and social learning theory in the treatment and prevention of conduct problems (Kazdin and Wassell 2000; Wasserman and Miller 1998; Shaw et al. 2006). Parent training in behavior management (ambiguously referred to as parent management training) has also resulted in significant reductions in oppositional defiant behaviors and conduct problems (Bor et al. 2002; Reid et al. 2004; Streyhorn and Weidman 1989; Webster-Stratton et al. 2004).

Cognitive-behavioral therapy has successfully been employed in the treatment of OCD symptoms and depression in young patients; relaxation training has been helpful in managing anxiety symptoms and sleep difficulties.

Unfortunately, oftentimes, access to nonpharmacological treatments is limited; the cost could be prohibitive (although not necessarily a lot more expensive than psychopharmacology, nonpharmacologic treatments are often not as well covered by insurance) and/or the families may have difficulties following through with the recommendations.

There are still very few studies of psychotherapeutic interventions in preschoolers. Recently, the National Institute of Mental Health (NIMH) Multisite Preschool ADHD Treatment Study (Kollins and Greenhill 2006) included a trial of parent training in behavior management and then reevaluation before entering the pharmacology trial. Such a strategy insures that no child is exposed to the research drug risk without a chance to respond to a different intervention. This is appropriate for preschoolers because parent training is likely more effective at this age than with older children (the parent has greater control over the child and reinforcements, and the preschooler is still more

attached to parents than to peers) and because the preschooler is more developmentally plastic and not as stably entrenched in pathology at this age. More research on parental and behavioral interventions in this age group is much needed.

Based on the principle of autonomy, physicians have a duty to educate pediatric patients and their guardians about side effects and other risks of treatment options or nontreatment to assist parents in an informed treatment decision, obtain consent from the children's parents, and cultivate the child's assent to undergo a thorough evaluation that will result in treatment recommendations. An ethical question is whether physicians should inform about the off-label status of the prescribed medications, given that off-label status does mean that the use lacks some of the safety and efficacy data available with an approved use. In the case of preschoolers, there are very few FDA-approved psychopharmacological treatments and the off-label use is more of the norm, making research in this area a major priority.

Based on the principle of nonmaleficence, practitioners dealing with a child's refusal to cooperate have to weigh the child's ability to understand the process with the child's right to not have to be the subject of the evaluation against his/her will versus the potential benefits of the evaluation and future treatment and the parents' ethical and legal right to override a child's dissent.

Eliciting the youngster's cooperation and assent becomes very important when treating adolescents older than 14 who show the same risk–benefit reasoning as adults and who can find ways to be noncompliant if they do not agree with the treatment plan. When recommending treatment intervention, practitioners have to balance the potential benefits with potential adverse reactions/adverse outcomes (nonmaleficence) and discuss these aspects with both the parent and the child/adolescent to obtain informed consent and preferably assent from both (autonomy/justice). In doing so, they have to put first the needs of the child and ensure the best outcome by continuously balancing conflicting principles, professional knowledge, and legal framework. Sometimes parents' natural right to advocate for their children conflicts with the requirement to respect children's right to decline participation in research (principle of autonomy). Should a negativistic toddler's reflex "No" override the parents' judgment about what is best for the child?

Practitioners treating children also have to coordinate the care with other caregivers involved in the children's life, and in doing so, they have to always be aware of the different degrees of involvement and legal authority these caregivers have in making health-related decisions. They have to protect confidentiality (the principle of autonomy) and make sure that other decision makers protect the child's rights and put the child's interests first. When clinicians treating children have concerns that adults involved in decision making do not put the child's interest first (neglect or abuse), they are mandated to report their concerns to the appropriate agencies (beneficence/nonmaleficence; justice).

Above all, physicians have to respect the principle of justice in making sure they provide fair care to all patients, care based on their best judgment and care that meets professional standards. Based on the same principle of justice, physicians have to educate patients about treatment alternatives, and based on the principle of beneficence/nonmaleficence, they have to present the potential benefits and adverse outcomes of the decisions patients and their parents ultimately make when they accept or decline (autonomy) the physician's recommendations.

The recent warnings on the increased risk of suicide during antidepressant treatment in adolescents and increased risk of cardiac adverse reactions and even sudden death with psychostimulant use have complicated the ethical dilemmas around prescribing psychotropics in children and adolescents. In the case of adverse events that are rare or only suspected, not causally proven, the prescriber has to balance the risk of unduly alarming the family (nonmaleficence) against the need to provide full information. In research, of course, there is no choice but to disclose all known risks and warn that there may be unknown risks. This is best done in a calm, dispassionate manner, putting risks in context and perspective and ending with the assurance that the family should call the physician any time if anything unusual happens that they are not sure about.

Ethical issues in pediatric psychiatric research

Within the past two decades, various agencies have worked together to develop ethical and legal guidelines for psychopharmacological research in children (e.g., NIMH 2000a,b; March et al. 2004: AACAP 2002 Research Forum; etc.). Based on the principle of justice, children and adolescents have the right to treatment based on accurate, age-appropriate data that can only be obtained by undergoing sound psychopharmacological research trials. It is well agreed that there is a great need for more psychopharmacological research in preschoolers particularly (Minde 1998; Jensen 1998; Report of the Surgeon General's Conference on Children's Mental Health 2000; Vitiello 2001a,b).

The assessment of risk Based on the principle of nonmaleficence, this need has to be balanced with the children's right for protection from research risks. One way of accomplishing this goal is by first determining whether the proposed research has prospect of direct benefit to the participant. "Direct benefit" assumes that only children with psychiatric disorders will be included in treatment trials with the expectation that the health of the child will improve as a direct consequence of participation. Research protocols

should be tailored to specific pathologies and the unique vulnerabilities of the study populations. The involvement of healthy volunteers should be avoided. Trials for toxicity and pharmacokinetics should be carried out on patients who may directly benefit from participating in the study. The risk/benefit ratio must be in the child's favor.

The Federal Regulation 45CFR46 sections 404–7 describe four risk categories in children that potentially justifies research (Shah et al. 2004):

(1) Research that involves no greater than minimal risk to children
(2) Research that involves greater than minimal risk, but the risk is justified by the anticipated benefit to the participant, and the relation of the anticipated benefits to the risk is at least as favorable as that presented by alternative approaches
(3) Research that involves greater than minimal risk and no prospect of direct benefit to research participants, but the risk represents only a "minor increase over minimal risk;" or the research involves experience reasonably commensurate with those inherent in the child's medical, dental, psychological, social, or educational situation; or the research is likely to yield generalizable and vitally important knowledge about the child's disorder or condition
(4) Research that is not otherwise approvable, but that is determined by the IRB and a panel of experts as an important opportunity to understand, prevent, or alleviate a serious problem affecting children's health or welfare and will be conducted in accordance with sound ethical principles

The interpretation of "minimal risk" and "minor increase" in the minimal risk: patients with psychiatric disorders may experience daily life events differently because of the nature of the impairment caused by the symptoms of their disorders. One way of improving the risk/benefit ratio may be by carefully monitoring and identifying children whose condition deteriorates during their participation in the study and the provision for "rescue procedures" to promptly address their worsening symptoms (Vitiello 2003). Specially qualified (and possibly certified) investigators should evaluate high-risk protocols (such as hypothetical preventive treatments, challenges to provoke symptoms, invasive studies, etc.).

The use of placebo-controlled trials Placebo controls in treatment studies have come under fire at times on the basis that they deprive the subjects of effective treatment. The principle that research subjects should receive "the best proven diagnostic and therapeutic method" was articulated in the Declaration of Helsinki (World Medical Association 1964) and subsumed under the Belmont principle of beneficence (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979). This principle developed in response to such situations as leaving patients untreated or withdrawing effective treatment to study the natural progression of a disease (e.g., the notorious Tuskegee study, in which syphilitic patients were left untreated even after discovery of penicillin). It has received increased attention partly because of notorious relapses in a study of withdrawal of antipsychotic drug from stabilized, effectively treated schizophrenic patients (Lehrman and Sharav 1997). World Medical Association (WMA 2000) General Assembly revised the 1964 Declaration of Helsinki and in "paragraph 29" it states that "the benefits, risks, burdens, and effectiveness of a new method (of treatment) should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic, or therapeutic method exists." In October 2001, the WMA further clarified its position by affirming that "extreme care must be taken in making use of a placebo controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy exists, under certain circumstances: a) where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic, or therapeutic method, or b) where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm" (World Medical Association 2001). The US FDA did not endorse the Paragraph 29 of the 2000 revision (FDA 2001) although, overall, the FDA regulations pledge to abide by the Helsinki Declaration. Placebo-controlled studies are, in fact, required by the FDA in the process of drug approval.

The criticism of placebo is based on the assumption that there is an evidence-based effective treatment that is already established, and the argument is that a new treatment should be compared to the established standard treatment, not a placebo. However, in the case of children, few psychiatric disorders have well established, evidence-based treatments (notable exceptions are attention deficit/hyperactivity disorder and obsessive–compulsive disorder), and in preschoolers, the evidence base is even more limited.

Therefore, the ethical objection to placebo control should not apply to preschool research and only sparingly to older children, unless one argues that common usage establishes a treatment as accepted even in the absence of evidence for safety and efficacy. Such an argument would appear

ethically counterproductive, condemning children to unknown risks of "accepted" treatment of unknown efficacy. Placebo is needed to determine whether the commonly used psychoactive drugs are truly benefiting the children or merely subjecting them to useless risk for a placebo effect, and this is especially so for preschoolers. Some have made the argument that even for disorders with well-documented effective treatment the use of a placebo arm in a study of a new drug is more ethical by exposing fewer subjects to the unknown risks of the new drug (Young and Annable 1997). Without placebo, more subjects would have to be tried on the new drug in comparison to the old to demonstrate effect, and the principle of minimizing risk would seem to require the more efficient placebo-controlled study. Stringent application of the no-placebo argument would prevent much therapeutic research on such problems as allergy, headaches, and hypertension and would favor settling for the minimally effective treatment in most disorders. It seems more reasonable to judge each protocol on its individual merits, considering the severity of the disorder, the risks of delaying treatment, the adequacy and risks of the current accepted treatment, and the fact that placebo effect is often substantial.

The AACAP 2002 Research Forum on placebo and alternatives to placebo concluded that the use of a placebo arm in a pediatric psychopharmacological study can be justified under certain conditions when there is negligible risk associated with placebo: (a) when there is no widely accepted standard-of-care treatment, and the study can identify a true treatment effect; (b) to differentiate a true tie from lack of effect when two or more active treatments fail to separate; (c) when, although a drug standard of care exists, the inclusion of a placebo arm will answer an important question; (d) when a proven treatment carries with it significant risks, and the study examines the safety and efficacy of a new treatment that offers a more favorable safety profile. The Research Forum also delineated situations in which a placebo is justifiable despite minimal or more than minimal risk: (a) when the risk of placebo is appreciably lower than that of standard treatment; (b) to elucidate the efficacy of effective treatment when there is a documented large placebo effect; (c) to help identify placebo responders during a placebo "run in" and further enroll only those who do not respond to placebo in the active treatment/further placebo phases; (d) when the study aim is to identify a more effective treatment with better side-effect profile than the existent standard of care; (e) when the study is aimed to identify improved treatments with higher probability of compliance and therefore efficacy; (f) to determine long-term efficacy of a treatment when only short-term efficacy is proven, and the delay of treatment does not result in adverse consequences; (g) when comparison with standard-of-care treatment is impractical; (h) when the aim of the study is to identify more cost-effective treatments when the cost of standard-of-care treatment is prohibitive; (i) when the risk is deemed minimal, and the study duration is short even when there is a standard-of-care treatment.

A placebo arm is deemed inappropriate when withholding a proven effective treatment increases the risk of more than minor harmful consequences or when withholding effective treatment causes irreversible damage.

The need for informed consent/assent is affected by children's level of understanding, both having to do with the principle of respect for persons and their autonomy. In this regard, one question is how much the parent should be allowed to influence the child's assent decision. The investigator administering informed consent should allow the parent to give advice, give permission, or reassure the child while closely monitoring for any parental attempts at exerting pressure or bribing, at which time the investigator has to intervene and make sure that both the child and parent agree voluntarily. Based on the principle of respect for autonomy, the investigator has to consider carefully the child's dissent even in the case of preschoolers. Based on the principle of beneficence, the investigator has to make sure that the study participants do not unwittingly deprive themselves of the opportunity for a new treatment through misunderstanding (Wadman 1998).

Reimbursement The ethical requirement (of Justice) to ease the research burden on families who cooperate with research conflicts to some extent with the Autonomy requirement for freedom from coercion. Justice requires family reimbursement for time, inconvenience, and expense but Autonomy requires that such reimbursement not be so attractive as to constitute "coercive inducement." There are few guidelines or federal regulations for IRBs to follow to evaluate reimbursement proposals (Grady 2005). One of the quandaries is that what would be fair and noncoercive reimbursement for a middle-class family, where a parent must take time off from work for research appointments (or go to the extra expense of a restaurant meal because there was not time to cook), might be overly attractive inducement to a welfare family. On the other hand, it does not seem fair to pay the welfare family less.

Justice also suggests that the child should have some direct recompense for nuisance and discomfort, but this is a rather controversial issue as some ethicists argue that the child should have no recompense at all to guard against undue influence. Most experts and IRBs agree that some small amount for the child, usually in the form of a small prize, is appropriate. Another challenge in pediatric research trials encompassing a wide age range is that younger children are more influenced by a small amount of

money than are older adolescents, but older adolescents may, like parents, deserve some reimbursement for lost time. It appears that child recompense should be graduated by age to some reasonable degree.

A further complication for very young children is that at the more suggestible younger extremes, where consent capacity is in most question, a child may be psychologically coerced by a parent who covets an attractive research reimbursement (Arnold et al. 1999), constituting indirect coercive inducement. The ultimate risk for this indirect inducement may occur with preschool children. On the other hand, it would seem we do not need to worry about direct coercive inducement of preschoolers themselves, who are incapable of assent, making direct inducement (by the payment offered) irrelevant.

One kind of subject/family compensation that would pose no risk of coercive inducement and seems consistent with all three Belmont principles would be insurance against any harm that results from the research. Such insurance appears so apt that it is difficult to understand why it has not become standard procedure, especially for children, where unknown long-term sequelae are most possible.

Other nonpharmacological screening-phase treatments In a review focused on ADHD treatment (Arnold 2002), several "alternative" or "complementary" treatments were noted to have convincing evidence of efficacy or controlled pilot data that looked promising for very young children, including: elimination or oligoantigenic diets had eight placebo-controlled trials showing behavioral benefit for a small subgroup; importantly, the most likely responders appeared to be preschoolers; massage has controlled studies showing favorable effect on hyperactivity, on-task behavior, and anxiety (Arnold 2002); vestibular rotary stimulation has controlled pilot data showing a moderate behavioral effect, most noted in the younger subjects.

These alternative treatments could serve as a placebo washout (possibly coupled with a single-blind placebo pill), refining the sample by preemptively purging it of placebo responders as well as responders to the alternative treatment and thereby improving both the science and ethics. At best, such screening trials could also efficiently generate publishable open pilot data for the alternative treatment while insuring that no preschooler is unnecessarily exposed to the study drug.

Conclusion

Further research is needed in child psychopharmacology, especially in the preschooler group, to develop effective and safe treatments. Some nonpharmacological treatments are also effective and have to be studied separately or in combination with psychopharmacological interventions. Issues specific to the preschooler complicate the development of ethical guidelines for the treatment of psychiatric disorders and psychopharmacological research in this age group. The ethical principles of respect for autonomy, justice, beneficence, and nonmaleficence that already guide human research can also be applied to the treatment of pediatric psychiatric disorders.

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References

American Academy of Pediatrics—Committee of Drugs (1995) Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations (RE9503) 95:286–294

Anderson GM (2004) Peripheral and central neurochemical effects of the selective serotonin reuptake inhibitors in humans and nonhuman primates: assessing bioeffect and mechanism of action. Int J Dev Neurosci 22:397–404

Ansorge MS, Zhou M, Lira A, Hen R, Gingrich JA (2004) Early-life blockade of the 5-HT transporter alters emotional behavior in adult mice. Science 306(5697):879–881 (Oct 29)

Arnold LE (2002) Treatment Alternatives for attention-deficit/hyperactivity disorder. In: Jensen PS, Cooper J (eds) Attention deficit hyperactivity disorder: state of the science; best practices. Civic Research Institute, Kingston, NJ

Arnold L, Stoff D, Cooke E, Cohen DJ, Wright CB, Kruesi M, Hattab J, Arnold LE (1999) Treatment alternatives for attention-deficit/hyperactivity disorder (ADHD). J Atten Disord 3:30–48

Beauchamp TL, Childress JF (1994) Principles of biomedical ethics. Oxford Univ. Press, Oxford

Beck J, Azari E (1998) FDA, Off-label drug use, and informed consent: debunking myths and misconceptions. Food Drug Cosmet Law J 53:71–104

Bor W, Sanders M, Markie-Dadds C (2002) The effects of the Triple P Positive parenting program on preschool children with co-occurring disruptive behavior and attentional/hyperactive difficulties. J Abnorm Child Psychol 30:571–587

Carrey NJ, Dursun S, Clements R, Renton K, Waschbusch D, MacMaster FP (2002) Noradrenergic and serotonergic neuroendocrine responses in prepubertal, peripubertal, and postpubertal rats pretreated with desipramine and sertraline. J Am Acad Child Adolesc Psych 41:999–1006

Chambers CD, Hernandez-Diaz S, Van Marter LJ, Werler MM, Louik C, Jones KL, Mitchell AA (2006) Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. New Engl J Med 354(6):579–587

Chesney RW (2005) Children as clinical research subjects. J Pediatr 146:579–580 (May)

Cissoko H, Swortfiguer BG, Jonville-Bera AP, Autret-Leca E (2005) Neonatal outcome after exposure to selective reuptake inhibitors late in pregnancy. Arch Pediatr 12:1081–1084

Correll C, Carlson HE (2006) Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents. J Am Acad Child Adolesc Psych 45(7):771–791

Department of Health and Human Services–2000–Report of the Surgeon General's Conference on Children's Mental Health: a National Action Agenda

Deveaugh-Geiss J, March J, Shapiro M, Andreason P, Emslie G, Ford L, Greenhill L, Murphy D, Prentice E, Roberts R, Silva S, Swanson JM, Van Zwieten-Boot B, Vitiello B, Wagner KD, Mangum B (2006) Child and adolescent psychopharmacology in the New Millenium: a workshop for academia, industry, and government. J Am Acad Child Adolesc Psych 45(3):261–270

FDA (2001) FDA ignores Helsinki Declaration's new thinking on placebo trials. FDA week, Feb 9

Food and Drug Administration (1997) Modernization act of 1997. 21 USC 321

Gordon B, Prentice E, Anderson J (2000) Conflict between research design and minimization of risks in pediatric research. IRB 22(3):1–6

Grady C (2005) Payment of clinical research subjects. J Clin Invest 115(7):1681–1687 (July 2005)

Greenhill L, Jensen P, Abikoff H, Blumer JL, DeVeaugh-Geiss J, Fisher C, Hoagwood K, Kratochvil CJ, Lahey B, Laughren T, Leckman J, Petti TA, Pope K, Shaffer D, Vitiello B, Zeanah, C (2003) Developing strategies for psychopharmacological studies in preschool children. J Am Acad Child Adolesc Psych 42:406–414 (April)

Jensen PS (1998) Ethical and pragmatic issues in the use of psychotropic agents in young children. Can J Psychiatry 43:585–588

Kazdin AE, Wassell G (2000) Therapeutic changes in children, parents, and families resulting from treatment of children with conduct problems. J Am Acad Child Adolesc Psych 39:414–420

Keenan K, Wakschlag LS (1998) More than the terrible twos: the nature and severity of behavior problems in clinic-referred preschool children. J Abnorm Child Psychol 28(1):33–46

Kollins SH, Greenhill L (2006) Evidence base for the use of stimulant medication in preschool children with ADHD. Infants Young Child 19(2):132–141

Kopelman LM (2004) Minimal risk as an international ethical standard in research. J Med Philos 29(3):351–378

Kratochvil CJ, Vitiello B, Walkup J, Emslie G, Waslick BD, Weller EB, Burke WJ, March JS (2006) Selective serotonin reuptake inhibitors in pediatric depression: Is the balance between benefits and risks favorable? J Child Adolesc Psychopharmacol 16(1/2):11–24

Kwan P, Brodie MJ (2001) Neuropsychological effects of epilepsy and antiepileptic drugs. Lancet 357:216–222

Lahey BB, Pelham WE, Stein MA, Loney J, Trapani C, Nugent K, Kipp H, Schmidt E et al (1998) Validity of DSM-IV attention-deficit/hyperactivity disorder for younger children. J Am Acad Child Adolesc Psych 37(7):695–702

Lehrman NS, Sharav VH (1997) Ethical problems in psychiatric research. J Mental Health Adm 24:227–250

March J, Beiderman J, Wolkow R, Safferman A, Mardekian J, Cook E, Cutler N, Dominquez R, Feruson J, Muller B, Riesenberg R, Rosenthal R, Sallee F, Wagner K, Steiner H (1998) Sertraline in children and adolescents with obsessive–compulsive disorder: a multicenter randomized controlled trial. J Am Med Assoc 280 (20):1752–1756

March J, Kratochvil C, Clarke G, Beardslee W, Derivan A, Emslie G, Green E, Heiligenstein J, Hinshaw S, Hoagwood K, Jensen P et al (2004) AACAP 2002 research forum: placebo and alternatives to placebo in randomized controlled trials in pediatric psychopharmacology. J Am Acad Child Adolesc Psych 43(8):1046–1056 (August)

Martin A, Young C, Leckman JF, Mukonoweshuro C, Rosenheck R, Leslie D (2004) Age effects on antidepressant-induced manic conversion. Arch Pediatr Adolesc Med 158(8):773–780

Minde K (1998) The use of psychotropic medications in preschoolers: some recent developments. Can J Psychiatry 43:571–575

Misri S, Reebye P, Kendrick K, Carter D, Ryan D, Grunau RE, Oberlander TF (2006) Internalizing behaviors in 4-year-old children exposed in utero to psychotropic medications. Am J Psychiatr 163(6):1026–1032 (June)

National Archives and Records Administration (1991) 45 Code of Federal Regulations (CFR). Subtitle A, part 46, Subpart D

National Archives and Records Administration (1998) 21 CFR parts 201, 312, 314, and 601—FDA. Pediatric patients regulations requiring manufacturers to assess the safety and effectiveness of new drugs and biological products; proposed rule (DOCKET no. 97N-0165) RIN 0910-AB20

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1979) The Belmont report: ethical principles and guidelines for the protection of human subjects of research. Fed Regist 44(76):23192–23197

National Institutes of Health (1998) Policy and guidelines on the inclusion of children as participants in research involving human subjects, March

NIMH (2000a) NIMH research forum. Recommended strategies for developing and implementing psychopharmacologic studies in preschool children. American academy of child and adolescent psychiatry 47th annual meeting, Oct. 25, 2000. Jointly sponsored by National Institute of Mental Health

NIMH (2000b) NIMH Workshop on Long-Term Drug Safety (Research Units in Pediatric Psychopharmacology, RUPP)—Sept. 25. NIMH Neurosciences Center, Rockville, MD

Nulman I, Rovet J, Stewart DE, Wolpin J, Gardner HA, Theis JGW, Kulin N, Koren G (1997) Neurodevelopment of children exposed in utero to antidepressant drugs. N Engl J Med 336:258–262

Nulman I, Rovet J, Stewart DE, Wolpin J, Pace-Asciak P, Shuhaiber S, Koren G (2002) Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study. Am J Psychiatry 159:1889–1895

Olfson M, Shaffer D, Marcus SC, Greenberg T (2003) Relationship between antidepressant medication treatment and suicide in adolescents. Arch Gen Psychiatry 60:978–982

Reid MJ, Webster-Stratton C, Baydar N (2004) Halting the development of conduct problems in head start children: the effects of parent training. J Clin Child Adolesc Psychol 33(2):279–291 (June)

Riddle M, Reeve E, Yaryura-Tobias J, Yang H et al (2001) Fluvoxamine for children and adolescents with obsessive compulsive disorder: a randomized controlled multicenter trial. J Am Acad Child Adolesc Psych 40(2):222–229

Roberts LW, Roberts B (1999) Psychiatric research ethics: an overview of evolving guidelines and current ethical dilemmas in the study of mental illness. Biol Psychiatry 46:1025–1038

Roberts LW, Warner TD, Brody JL (2000) Perspectives of patients with schizophrenia and psychiatrists regarding ethically important aspects of research participation. Am J Psychiatry 157:67–74

Shah S, Whittle A, Wilfond B, Gensler G, Wendler D (2004) Research in children: assessing risks and benefits. Pediatr Res 56(2):165–166

Shaw DS, Dishion TJ, Supplee L, Gardner F, Arnds K (2006) Randomized trial of a family-centered approach to the prevention of early conduct problems: 2-year effects of the family check-up in early childhood. J Consult Clin Psychol 74(1):1–9 (Feb)

Sivojelezova A, Shuhaiber S, Sarkissian L, Einarson A, Koren G (2005) Citalopram use in pregnancy: prospective comparative evaluation of pregnancy and fetal outcome. Am J Obstet Gynecol 193:2004–2009

Solyom AE, Moreno JD (2005) Protection of children and adolescents in psychiatric research: an unfinished business. HEC Forum 17 (3):210–226

Streyhorn JM, Weidman CS (1989) Reduction of attention deficit and internalizing symptoms in preschoolers through parent–child interaction training. J Am Acad Child Adolesc Psych 28:888–896

Twomey JG (2000) Ethical implications of pediatric drug research policy initiatives. IRB pp 2–7 (March–April)

US FDA (2004a) Public health advisory. Worsening depression and suicidality in patients being treated with antidepressant medications. March 22, 2004. Available at http://www.fda.gov/cder/drug/antidepressants/AntidepressanstPHA.htm

US FDA (2004b) Public health advisory. Suicidality in children and adolescents being treated with antidepressant medications. October 15, 2004. Available at http://www.fda.gov/cder/drug/antidepressants/SSRIPHA200410.htm

Vitiello B (1998) Pediatric psychopharmacology and the interaction between drugs and the developing brain. Can J Psychiatry 43:582–584

Vitiello B (2001a) Long term effects of stimulant medications on the brain: possible relevance to the treatment of attention deficit hyperactivity disorder. J Child Adolesc Psychopharmacol 11:25–34

Vitiello B (2001b) Psychopharmacology for young children: clinical needs and research opportunities. Pediatrics 108:983–989

Vitiello B (2003) Ethical considerations in psychopharmacological research involving children and adolescents. Psychopharmacology 171:86–91

Wadman M (1998) Ethical protection for subjects could stifle psychiatric research. Nature 394:713 (Aug. 20)

Wasserman GA, Miller LS (1998) The prevention of serious and violent juvenile offending. In: Loeber R, Farrington DP (eds) Serious and violent juvenile offenders: Risk factors and successful interventions. Sage, Thousand Oaks, CA, pp 197–247

Webster-Stratton C, Reid MJ, Hammond M (2004) Treating children with early-onset conduct problems: intervention outcomes for parent, child, and teacher training. J Clin Child Adolesc Psychol 33(1):105–124 (March)

Wegerer V, Moll GH, Bagli M, Rothenberger A, Ruther E, Huether G (1999) Persistently increased density of serotonin transporters in the frontal cortex of rats treated with fluoxetine during early juvenile life. J Child Adolesc Psychopharmacol 9:13–24

World Medical Association (1964) Declaration of Helsinki IV, 18th world medical assembly. Amended Hong Kong, Sept 1989. Council for international organizations of medical sciences (CIOMS). Geneva 1993

World Medical Association (2000) Declaration of Helsinki, ethical principles for medical research involving human subjects, adopted by the 52nd World Medical Association General Assembly, Edinburgh, Scotland, October

World Medical Association (2001) Declaration of Helsinki, note of clarification on placebo-controlled trials. World Medical Association, Newsletter, October

Yan EG, Munir KM (2004) Regulatory and ethical principles in research involving children and individuals with developmental disabilities. Ethics Behav 14(1)

Young SN, Annable L (1997) The use of placebos in psychiatry: a response to the draft document prepared by the tri-council working group. A position paper of the Canadian College of Neuropsychopharmacology. J Psychiatry Neurosci 21:354–359