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OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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Pediatrics 2001;108;983-989

DOI: 10.1542/peds.108.4.983

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American Academy of Pediatrics

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Psychopharmacology for Young Children: Clinical Needs and Research Opportunities

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ABSTRACT. In response to concerns about the increasing use of psychotropic medications in preschoolers, the National Institute of Mental Health and the Food and Drug Administration convened a workshop in October 2000 to examine the current state of knowledge regarding psychopharmacology for young children and discuss a variety of topics relevant to research in this age group, including safety, efficacy, investigational methods, and ethical aspects. The meeting gathered researchers, practitioners, ethicists, industry staff, and family and patient representatives. Efficacy and safety of psychotropics have not been systematically evaluated in preschoolers. The major limitation to this research is the diagnostic uncertainty surrounding most manifestations of psychopathology in early childhood. Research in developmental psychopathology is needed to clarify diagnosis and provide sensitive and specific methods for clinical trials. Possible approaches to expanding the research basis of this area of clinical practice, including a recently started study of methylphenidate in preschoolers, are reported here. *Pediatrics* 2001;108:983-989; children, preschoolers, psychopharmacology, research, mental.

ABBREVIATIONS. FDA, Food and Drug Administration; ADHD, attention-deficit/hyperactivity disorder; OCD, obsessive-compulsive disorder; NIMH, National Institute of Mental Health; NIH, National Institutes of Health; HMO, health maintenance organization; PATS, Preschoolers with ADHD Treatment Study; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition; FDAMA, FDA Modernization Act.

Recent surveys have reported a sizable increase in the use of psychotropic medications such as stimulants, antidepressants, and clonidine in children,¹ including preschoolers aged 2 to 5 years.² These reports have raised multiple concerns. None of the medications identified in the surveys has received regulatory approval for children <6 years of age or been adequately tested for efficacy or safety in this age group. In particular, methylphenidate is approved by the US Food and Drug Administration

(FDA) for treating attention-deficit/hyperactivity disorder (ADHD) only for children ≥ 6 years. Some antidepressants, such as sertraline and fluvoxamine, have been approved for treating obsessive-compulsive disorder (OCD), but not depression, in school-aged children.^{3,4} The discrepancy between extent of usage and lack of supportive research data is most evident in the case of clonidine, an antihypertensive drug that is also used to manage withdrawal from substances of abuse in adults and to treat youths with Tourette disorder; the efficacy and safety of which have not been proven in children. In addition to concerns about the lack of efficacy data, there is concern about the safety of these medications. The impact of psychotropics on the developing brain is largely unknown, and possible long-term effects of early exposure to these drugs have not been investigated.⁵

In this context, the National Institute of Mental Health (NIMH) and FDA hosted a workshop in October 2000 to discuss the need to investigate the effects of psychotropic medications in young children, examine current obstacles to research in this area, and identify possible approaches to future activities. The meeting gathered researchers and clinicians involved in the diagnosis and treatment of young children with behavioral and emotional disturbances, researchers in animal and clinical pharmacology, ethicists, patient and family representatives, and representatives of the American Academy of Pediatrics, American Academy of Child and Adolescent Psychiatry, American Academy of Family Physicians, and pharmaceutical industry, in addition to staff from the National Institutes of Health (NIH) and the FDA. For the purposes of this meeting, the term *young children* refers to prepubertal participants, with special emphasis on preschool-aged children, and the term *psychotropic medications* to pharmacologic agents used to treat behavioral and emotional disturbances. The discussion revolved around 2 main sets of questions:

- What are the current clinical needs of young children with behavioral and emotional disturbances that can be addressed with appropriate pharmacologic research? Is research needed to study psychotropic medications that are already prescribed to young children in the community but without adequate efficacy and safety data? In parallel, should novel compounds be developed and tested for use in young children? In other words, does the severity of illness of these children justify the

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The views expressed in this report are those of the author and are not to be construed as official or as reflecting the views of the National Institute of Mental Health or the US Department of Health and Human Services.

Based on the proceedings of a National Institute of Mental Health research workshop; October 2-3, 2000; Rockville, MD.

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use of medications and consequent exposure to the risk of possible short- and long-term side effects? And if so, for which disorders or symptoms should medications be studied in young children? And which types of medications should be studied?

- For the clinical indications for which a rationale for drug developing and testing can be identified, how appropriate are current research methods? How can scientifically valid, developmentally sensitive, and ethically sound clinical trials be designed for studying psychotropic medications in young children?

WHAT DO WE KNOW ABOUT CURRENT PSYCHOTROPIC DRUG USE IN YOUNG CHILDREN?

No data from national probability samples are available. Surveys have been conducted using databases of insurance companies and Medicaid. The findings point to an increased use of several psychotropics in children.^{1,2} Based on 1 health maintenance organization (HMO) and 2 Medicaid databases, it is estimated that 0.51% to 1.23% of preschoolers received stimulant medications, 0.07% to 0.32% antidepressants, 0.19% to 0.23% clonidine, and 0.02% to 0.09% neuroleptics in 1995.² The most commonly prescribed medication was methylphenidate, followed at a distance by selective serotonin reuptake inhibitors, clonidine, and tricyclic antidepressants. The use of these medications has increased from 1991 to 1995, with stimulants showing a two- to threefold increase. Neuroleptics were less commonly prescribed, and their use does not seem to have increased over the survey period.² Ethnic differences have been reported, with a twofold greater likelihood of receiving medication for whites than for blacks.⁶ Most medication use in preschoolers seems to be for the treatment of ADHD because this is the most common clinician-made diagnosis listed in insurance records. However, the validity of these diagnoses is not known. Most of these medications are prescribed by pediatricians and other primary care physicians. Concern has been raised that primary care physicians may have neither the appropriate expertise in developmental psychopathology nor the time needed to conduct comprehensive psychiatric evaluations. There are also indications that pharmacotherapy is an uncommon treatment modality for preschoolers referred to HMO clinicians for mental disturbances. According to a survey of the 1997–1998 database of Kaiser Permanente in the northwestern United States, only 0.5% of the children under 5 years treated for behavioral or emotional disturbances were prescribed psychotropic medications. This low use rate is in contrast with the much more common use of psychosocial services by these children (DeBar, oral communication, 2000).

THE CLINICAL PERSPECTIVE: WHERE ARE THE NEEDS FOR RESEARCH?

In early childhood, both specific mental disorders and less discrete symptom presentations can occur for which a pharmacologic approach could be con-

sidered. Autism, other pervasive disorders, and ADHD have onset typically in preschool years. Autism is a severe disorder that affects as many as 1 in 500 children,⁷ and research to develop and test potentially effective pharmacologic treatments for children with autism would be of great clinical relevance. Treatment research is limited by an inadequate understanding of the pathogenesis of autism, but psychotropics are commonly used in an attempt to treat associated symptoms, such as stereotypies, compulsions, aggression, and self-injurious behavior. Amelioration of these symptoms can be clinically significant, although it does not correct the core features of the disorder. This symptomatic use of psychotropics in young children has not been tested systematically for efficacy and safety.

Behavioral disturbances consistent with ADHD, such as pervasive and functionally impairing hyperactivity and impulsiveness, are a common reason for clinical referral of preschoolers. These behavioral disturbances often persist and can portend more severe forms of psychopathology.^{8,9} Stimulants are used for preschoolers with ADHD, but no definitive study supports the efficacy and safety of these medications in this age group. Several controlled studies have investigated the short-term effects of methylphenidate given at dosages ranging from 2.5 to 20 mg.^{10–15} These trials show measurable efficacy but are clearly limited by small sample size, brief duration of treatment, and restricted range of efficacy and safety outcomes. To address these shortcomings, NIMH has recently funded a multisite clinical trial, the Preschoolers with ADHD Treatment Study (PATS), which will test the short- and intermediate-term effects of methylphenidate in preschoolers (3–5 years) as compared with school-aged children (6–8 years) with ADHD. PATS will enroll >200 children with impairing and persistent ADHD who have not derived adequate improvement from behavior therapy. Results from PATS are expected not sooner than 3 years from now (2004). The study will address the efficacy and safety of methylphenidate under rigorously controlled conditions, including a carefully selected sample of children with cooperative and motivated families, highly specialized clinicians, and an intensive schedule of repeated assessments for up to 1 year of treatment. However, it will not fully address the current use of stimulant medications in actual practice settings, where children with comorbid conditions and variable social backgrounds may be medicated with multiple compounds.¹⁶ It may be necessary to identify and follow larger, community-based samples to gather additional information relevant to practice use and long-term safety.

Only limited data exist on the efficacy and safety of antidepressants and mood stabilizers in school-age prepubertal children. Clinical trials of these agents in preschoolers do not seem possible given the current uncertainties about diagnostic validity of mood disorders in children <6 years old. Even if clinical reports of major depression and mania in 4- and 5-year-olds exist, very little research has been done to demonstrate replicability across raters and external validity of these diagnoses in preschoolers.

Besides specific disorders, the treatment of young children often is aimed at controlling symptoms of mood and behavioral instability, such as aggression, impulsiveness, fears, and excessive worry, which do not necessarily meet clear-cut diagnostic criteria according to the current nosological system. These symptoms cannot be dismissed, not only for the functional impairment they produce but also because follow-up studies of clinically referred children into adulthood indicate continuity of psychopathology across the years,^{17,18} and early intervention may lead to better outcomes. However, almost no research has been done to test treatments for situations of diagnostic uncertainty.

In treating children, medication dosages and frequency of administration often are selected based on adult data. However, development can affect pharmacokinetics and drug disposition. Therefore, extrapolating adult dosages to children can have negative effects on both efficacy and safety.¹⁹ Pharmacokinetics and dosage-finding studies are necessary to identify dosage and frequency of administration appropriate to children. There are no universally accepted age categories to guide these studies, but differences in pharmacokinetics can be expected between very young children, school-age prepubertal children, and adolescents.

Besides medications, psychosocial interventions are also used to treat young children with behavioral or emotional disturbances. Little research has been conducted to study the effectiveness of psychosocial interventions in young children, and the long-term risk-benefit ratio of psychosocial and pharmacologic treatments is basically unknown. However, safety considerations seem to suggest that, when possible, nonpharmacologic interventions should be considered before young children are given medications of unproven efficacy and safety.

ARE CURRENT DIAGNOSTIC AND ASSESSMENT METHODS APPROPRIATE FOR TREATMENT RESEARCH IN YOUNG CHILDREN?

The ability to formulate valid and reproducible diagnosis of disorders and syndromes is a prerequisite for clinical trials. A valid diagnosis of autism can be reached as early as about 18 months of age by trained clinicians using validated instruments.^{20,21} There is also agreement that current methods allow a valid diagnosis of mood and anxiety disorders to be made in school-aged children, starting at about 6 years of age.²² A valid diagnosis of ADHD in preschoolers can be achieved through a careful and comprehensive evaluation.²³ However, concern remains that children with elevated but still developmentally normal levels of motor activity, impulsiveness, or inattention may be inappropriately diagnosed as having ADHD and consequently treated with medications. A related concern is that these symptoms may be the expression of a disorder other than ADHD, such as reactions to stressful environments, mood disturbances, or cognitive impairment. The specificity of the diagnosis of ADHD in young children is likely to be enhanced by requiring the presence of multiple, persistent, and substantial functional impairments. To this

end, the newly launched PATS has adopted stringent inclusion criteria, requiring that the symptoms of ADHD be documented for at least 9 months, as compared with the 6 months of the DSM-IV,²⁴ and medication treatment can be considered only for children who have not improved on behavioral therapy.

The current uncertainty about the diagnosis of mood, anxiety, and psychotic disorders in young children is a major impediment to designing clinical trials in this age group. Most of the currently available diagnostic instruments and symptom rating scales have been developed for older children, and few have been adapted and validated for use in preschoolers. An alternative approach to requiring categorical diagnoses for study entry would be to base inclusion criteria on symptoms rather than discrete disorders. Aggression, impulsiveness, mood instability, anxiety, and sleep disturbances are the most common reasons for clinical referral and treatment of children. However, the immediate clinical appeal of this approach is counteracted by the lack of evidence that these symptoms have the same meaning and are similarly responsive to interventions across different contexts (eg, ADHD, mood disorders, posttraumatic reactions, mental retardation, or pervasive developmental disorders). These symptoms can be produced by different conditions, emerge under different circumstances, and necessitate different forms of treatment. Before being able to test the efficacy of medications on specific symptoms as the sole target of treatment (independent of diagnosis), it is necessary to demonstrate consistency of treatment response across different clinical contexts. This could be accomplished by studying and comparing treatment effects on symptoms as they arise in different diagnostic conditions. When there are symptoms specific to a particular condition (eg, compulsive self-biting in Lesch-Nyhan disease), it is conceivable to develop selective pharmacologic treatments for these symptom indications.

There is concern about the lack of research infrastructure for clinical trials in children in general and young children in particular. Recruitment into research protocols typically is challenging, especially when the drugs under study are easily available in the community. Recruitment difficulties may result in part from the rather strict inclusion criteria of current research protocols. Narrow inclusion criteria enhance the internal validity of the experiment but limit generalizability by selecting samples that do not necessarily represent the most prevalent clinical populations. Novel approaches to clinical trials should be considered, including designing large simple trials to be conducted in practice settings. These studies would use broad inclusion criteria and specific stratification for potential moderator variables, such as age, gender, main symptoms, diagnosis, and family issues. The application of this model should be viewed as complementary to phase III clinical trials and may be particularly useful for long-term safety and outcome assessments. The possible applicability of the clinical trial network model developed in pediatric oncology should be examined. Under this model, patients are routinely enrolled into re-

search protocols at clinical settings with the coordination of the National Cancer Institute. Most US children with cancer receive treatment as part of specific research protocols. However, there are major differences between pediatric oncology and psychopharmacology, including the fact that psychotropics usually are prescribed by primary care physicians, whereas antineoplastic drugs are administered in specialized settings; the presence of biological markers of disease in oncology (but not in psychiatry); and the life-threatening nature of cancer, which justifies exposure to potentially toxic medications.

ASSESSING THE SAFETY OF MEDICATIONS

Most concerns about the use of medications in young children relate to the possible negative effects of administering drugs at such an early age. Certain drugs that are safe in adults can cause severe adverse events in children.²⁵ The target of psychotropic medications is the brain, an organ that undergoes major developmental changes in the first few years of life.²⁶ The monoaminergic systems, on which psychotropics act, display great plasticity and rearrangement in the early life.²⁷ The short- and long-term consequences of exposing the developing brain to pharmacologic agents are largely unknown. However, the possible risks of treatment must be weighed against the adverse effects of an untreated disorder.

Animal models have been used to study the possible developmental neurotoxicity of drugs.²⁸ Drugs of abuse and anticonvulsants have been studied in these models.²⁹ Enduring effects of perinatal exposure to antidopaminergic drugs have been reported in rodents.³⁰ In parallel, it was found that early exposure to adverse environmental circumstances and stress can also have a long-lasting impact on the brain regulation of animals³¹ and humans.³² The relevance of animal models to the use of psychotropics in young children remains to be clarified. In humans, noninvasive imaging techniques could be considered for possible application to the study of the effects of medications on the developing brain, in addition to functional behavioral and cognitive assessments.

Various approaches to studying drug safety in humans can be considered: spontaneous reporting of adverse events by clinicians, active surveillance of patients naturalistically treated in clinical settings, and controlled clinical trials. Although spontaneous reporting can be effective in identifying acute and unusual adverse events, it lacks the sensitivity to detect more subtle or chronic toxicities. Active surveillance is a more sensitive approach. In some cases, only the presence of a randomized, controlled group allows detection of insidious neurotoxicities, as shown by the case of phenobarbital-induced cognitive decline in preschoolers that was demonstrated through a randomized clinical trial.³³

ETHICAL ASPECTS

In general, research in children is justified based on the need to provide adequate information on the efficacy and safety of promising interventions. This information is necessary to ensure proper treatment

of children. Extrapolation to young children of data collected in adults or older children is not always possible because of differences in development. Medications that are safe in adults or older children may still have specific toxicities when given to young children.³⁴ Research in young children is regulated by the rules for clinical experimentation in participants of minor age.³⁵ There are no specific rules for younger children as compared with older ones. The relationship between anticipated benefits and foreseeable risks is the main gauge of the appropriateness of a treatment study: The relationship must be at least as favorable as that of available alternatives.

For research in young children, special attention is paid to potential risk exposure and procedures for risk minimization. Risk can be minimized by carefully selecting medication dosage and thoroughly monitoring the possible emergence of adverse events. The benefit-risk ratio can be enhanced by recruiting patients with particularly severe symptoms and impairment. Child participation in research without the prospect of direct benefit (ie, non-treatment research) is allowed only if no greater than minimal risk is involved (or a minor increase over minimal risk, if the child has a disorder or condition relevant to the research project). There is no universally accepted interpretation of what constitutes minimal risk or a minor increase over minimal risk. A particular aspect of research in young children is that these participants usually are considered unable to give informed consent to research participation. Therefore, for young children, participation in experimental investigation is completely contingent on parental consent, and parents' judgment and responsibility are paramount. Research involving young children entails interpretation of bioethical rules and considerations that apply to children in general and their adaptation to the needs of these participants. Institutional review boards have little experience with the bioethics of psychopharmacology in young children. Careful weighing of benefits and risks from research participation, as compared with available alternatives (including no treatment), is necessary.

REGULATORY ASPECTS OF PEDIATRIC PSYCHOPHARMACOLOGY

A traditionally neglected area, pediatric psychopharmacology has recently seen an unprecedented expansion. For instance, NIMH-funded research for clinical trials in youths has more than doubled in the last few years. In addition, a number of industry-sponsored studies have been started, following the FDA Modernization Act (FDAMA).³⁶ This law has allowed FDA to extend by 6 months the product exclusivity of selected drugs of pediatric interest in return for industry-sponsored studies in children. FDAMA is scheduled to sunset in 2002 unless renewed by Congress. In addition to FDAMA, new regulations (the "Pediatric Rule") have given FDA the authority to require that pediatric studies be conducted on drugs currently under development for use in adults whenever a potential use in children can be anticipated.³⁷ These new regulations and

FDAMA have provided both the regulatory authority and financial incentives necessary for initiating industry-supported studies in children.

As of September 2000, the FDA has issued written requests to industry for pediatric studies on 157 different drugs under FDAMA. Of these drugs, 18 are medications for treating psychiatric or neurologic disorders. Medications that are already off patent protection are not included in this initiative. Under the Pediatric Rule, the FDA has required the industry to conduct pediatric studies in several areas, such as posttraumatic stress disorder, social anxiety disorder, mania, and premenstrual syndrome. Other indications, such as schizophrenia, panic disorder, conduct disorder, and ADHD under 6 years of age, are being actively considered. So far, none of the requested pediatric studies of psychotropics has included children <6 years of age. For instance, studies of medications to treat depression or anxiety disorders usually include children aged ≥ 7 years. Uncertainty about the diagnosis of mental disorder in preschoolers has precluded FDA from requesting studies of psychotropics in younger children.

RECOMMENDATIONS

A number of recommendations were made at the workshop and are summarized here:

1. More detailed pharmacoepidemiologic studies are needed to document evolving patterns of psychotropic drug use in young children and clarify the paths leading to drug prescribing, including the relative contribution of factors such as presence and intensity of specific symptoms, functional impairment, comorbidity, family history of mental illness, previous or concurrent psychosocial treatment, social context, parental attitudes, and characteristics of the prescribing physician.
2. There is an urgent need to develop effective treatments for children with autism and other severe developmental disorders. Whenever possible, advances in understanding the pathogenesis of autism should be applied to develop targeted treatment interventions. In the meantime, medications that are used to control behavioral problems that commonly emerge in the context of pervasive developmental disorders, such as aggression, impulsiveness, compulsion, and self-injurious behavior, should be tested for efficacy and safety.
3. Research should be conducted to inform clinicians on how to treat common symptoms, such as aggression, extreme impulsiveness, severe mood instability, and anxiety disturbances, which are frequent causes of functional impairment and reason for clinical referral of young children.
4. Efficacy and safety of antidepressants and mood stabilizers in treating school-age prepubertal children (6 years and older) with mood disorders (depression, bipolar disorder) must be studied. Similar research in preschoolers is limited by uncertainty about the validity of these diagnoses in this age group.
5. Research on developmental psychopathology is needed to study the clinical validity and prognostic meaning of mood and anxiety symptoms in young children. The systematic and prospective follow-up of well-characterized cohorts of children with behavioral and emotional dysfunction could elucidate the predictive value of these symptoms by documenting continuities and discontinuities between early symptoms and later psychopathology.
6. Clinical trials in preschoolers must use thorough and sensitive assessments capable of detecting possible adverse effects of medications on physiologic functions and physical and mental development. Assessment instruments that have been developed for use in adults or older children must be revised and adapted to younger children. In some cases, new instruments must be developed. Efficacy and safety measurements must be broad and comprehensive, with attention to functional impairment in addition to symptoms.
7. Whether early treatment has a favorable impact on the prognosis and natural course of mental illness remains a major question that must be addressed by the development of appropriate study design and methods of inquiry.
8. Because of developmental differences, safety of medications must be specifically studied in young children because they cannot be inferred from data collected in older children or adults. Both basic and clinical neuroscience research should be conducted to provide better understanding of the pharmacogenetics and ontogeny of drug effects on the developing brain to elucidate the short- and long-term consequences of treatment. A recent program announcement specifically requests grant applications for such studies.³⁸
9. For medications currently prescribed to preschoolers in medical practice without adequate safety data, consideration should be given to creating registries of patients who are treated naturally in the community and can be systematically monitored for appropriate safety parameters.
10. The FDA should continue to use the authority derived from recent legislative and regulatory changes to request child studies of industry when appropriate. In general, research on the effects of psychotropics that are used to treat depression, OCD, and other anxiety disorders is warranted in children ≥ 6 years. Research on the effects of antipsychotics and mood stabilizers in adolescents should be required, and consideration should be given to requiring these studies in prepubertal children of school age. The feasibility of similar studies in prepubertal children is less clear. Given the current diagnostic uncertainty in preschoolers, it seems premature for FDA to systematically request studies in this age group at this time. If research funded by NIMH

or other sources provides the rationale and methods for clinical trials in this age group, studies in preschoolers should be considered as part of the regulatory requirements for these drugs.

11. The FDAMA has been extremely effective in starting new industry-supported studies in children. This initiative should be continued beyond the current scheduled sunset date.
12. The FDA advisory groups that deal with psychotropic medications should consider enhancing their expertise in pediatric psychopharmacology, and consideration should be given to forming a subgroup specifically dedicated to pediatric psychopharmacology.
13. A standing workgroup should be formed to identify research opportunities, discuss potential approaches, and monitor progress in the area of psychopharmacology for young children. This group should include representatives of all interested parties, such as researchers, practitioners, family and patient advocacy groups, industry, and federal regulatory and research agencies.

CONCLUSION

Reports of a large increase in the use of psychotropic medications in young children have brought attention to the need to test the efficacy and safety of pharmacologic treatments of potential therapeutic value in this age group. None of the currently used psychotropics has been adequately studied in children under 6 years. However, research in this age group must contend with major challenges, most notably the diagnostic uncertainty that surrounds most manifestations of psychopathology at such an early age and the lack of adequate instrumentation to detect treatment effects. This meeting, the first to be specifically focused on psychopharmacology research for young children, served as an opportunity to identify clinical needs and possible research approaches to be considered in planning future investigations.

ACKNOWLEDGMENTS

This report is based on the activities at a workshop hosted by the National Institute of Mental Health and the Food and Drug Administration on October 2–3, 2000.

I gratefully acknowledge the input of the workshop participants and the speakers, who included the following: Adrian Angold (Duke University Medical Center), L. Eugene Arnold (Ohio State University), Joseph Biederman (Harvard Medical School), Gabrielle Carlson (New York State University at Stony Brook), Lynn Debar (Kaiser Permanente), Joseph DeGeorge (Food and Drug Administration), Graham Emslie (Texas University, Dallas), Laurence Greenhill (Columbia University), Deborah Hirtz (National Institute on Neurologic Disorders and Stroke), Kimberly Hoagwood (National Institute of Mental Health), Thomas Laughren (Food and Drug Administration), Tish Michael (Children and Adults with ADHD), Dianne Murphy (Food and Drug Administration), Robert Nelson (University of Pennsylvania), John O'Brien (American Academy of Family Physicians), William Pelham (New York State University at Buffalo), Mark Riddle (Johns Hopkins University), Stephen Spielberg (Pharmaceutical Research and Manufacturers of America), Charles Vorhees (University of Cincinnati), Karen Wagner (American Academy of Child and Adolescent Psychiatry), Richard Walls (American Academy of Pediatrics), Benjamin Wilfond (National Institutes of Health), and Julie Zito (University of Maryland).

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DESPITE WARNINGS, 3 VOW TO GO AHEAD ON HUMAN CLONING

“Despite warnings from leading experts that the experiments in human cloning would inevitably lead to babies that are deformed, or die soon after birth, a fertility doctor, a chemist, and a scientist-entrepreneur nevertheless vowed today to press ahead with separate efforts to create the first cloned human being . . . Because all 3 operate in secret, it is difficult to assess how serious they are or whatever their assertions are realistic . . . The consensus among the panel and most of those who testified before it was that cloning people was not safe, given that when clones were born a high proportion died soon after birth and many survivors were plagued with genetic problems. “We are seeing a great range of abnormalities,” said Dr Ian Wilmut, who as director of the Roslin Institute in Scotland led the effort to clone Dolly (the sheep). “We should expect a similar outcome if people attempt to produce a cloned human.” Dolly’s birth was announced in 1997. In the years since, scientists have succeeded in cloning 5 species of mammals: sheep, goats, pigs, mice, and cows. Dr Wilmut said 18% of cloned mice died; among goats, the figure is 38%.”

Stolberg SG. *New York Times.* August 8, 2001

Noted by JFL, MD

Psychopharmacology for Young Children: Clinical Needs and Research Opportunities

Benedetto Vitiello

Pediatrics 2001;108:983-989

DOI: 10.1542/peds.108.4.983

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