Developing Strategies for Psychopharmacological Studies in Preschool Children

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ABSTRACT

Objective: To identify the obstacles and special challenges—ethical, practical, scientific, and regulatory—faced by investigators who attempt to conduct psychopharmacological studies in preschoolers. **Method:** In a workshop held at the 47th Annual Meeting of the American Academy of Child and Adolescent Psychiatry, featuring interactive sessions designed to elicit discussion of the theory and feasibility of research in this young population, several key domains were identified: diagnosis and assessment, ethics, research design, special considerations for preschoolers, regulatory/industry issues, and education/training. **Results:** A Pediatric Psychopharmacology Initiative is needed to consolidate recommendations from this and other workshops and current federal, research, and regulatory committees. A scholarly review and a guide for institutional review boards and investigators should be prepared on issues related to preschoolers. Developmental specialists provide valuable expertise that can strengthen studies of pediatric psychopharmacology. "*N* of 1" case studies can provide valuable information to clinicians. Only preschoolers with severe symptoms that occur in several interpersonal contexts should be entered into trials. Indications for the study of symptom complexes (e.g., aggression) rather than specific diagnoses should be examined and considered for regulatory activities. Psychopharmacology practice parameters for preschoolers are needed. **Conclusions:** With preschoolers being increasingly treated with psychopharmacological agents, the need for investigations to address the safety and efficacy of these medications is becoming a central issue for researchers from many disciplines. *J. Am. Acad. Child Adolesc. Psychiatry*, 2003, 42(4):406–414. **Key Words:** preschool children, clinical trials, ethics, diagnosis.

Accepted November 19, 2002.

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The Research Forum on which this article is based was sponsored by the Research Workgroup of the American Academy of Child and Adolescent Psychiatry (AACAP). The Forum was held at the 47th meeting of AACAP, on October 25, 2000. Other professionals who participated in the Research Forum as breakout workgroup chairs and rapporteurs included C. Keith Conners, Ph.D., Helen Egger, M.D., Gregory Fritz, M.D., Samuel Judice, M.D., Bennett Leventhal, M.D., Henrietta Leonard, M.D., John March, M.D., David Mrazek, M.D., Judith Rapoport, M.D., Neal Ryan, M.D., John Walkup, M.D., and Deborah Zarin, M.D.

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0890-8567/03/4204–0406©2003 by the American Academy of Child and Adolescent Psychiatry.

DOI: 10.1097/01.CHI.0000046812.95464.FA

Pharmacoepidemiological studies have identified a threefold increase in the prescribing of psychotropic medications to U.S. children aged 2 to 5 years, using three geographically independent databases—two Medicaid and one private—during the years 1991 to 1995 (Zito et al., 2000). The greatest increase was noted in methylphenidate (MPH) prescriptions, with 1.2% of all children in those databases now taking this medication. This is consistent with the public perception of a marked increase in the use of psychopharmacological agents—primarily psychostimulants—in preschool children over the past decade. This increase has concerned some critics because psychostimulants are classified by the Drug Enforcement Administration as drugs of abuse. Studies have suggested that there are marked regional, gender, and racial variations in the children for whom these agents are prescribed (Angold et al., 2000; Jensen et al., 1999a,b; LeFever et al., 1999).

The increased prescribing of stimulants for preschoolers sparked concern in public, scientific, and policy com-

munities. This led to a White House Conference (Pear, 2000), a Surgeon General's Meeting and Call to Action (U.S. Public Health Service, 2000), and a National Institute of Mental Health (NIMH)/Food and Drug Administration (FDA) Conference on Research for Young Children. Why? The preschool years are a key developmental period for maturation of brain dopamine systems, the chemical target for the stimulants (Coyle, 2000). Little is known about the long-term effects of psychostimulants on brain development, particularly if treatment is initiated before age 6.

Furthermore, both efficacy data and information on safe dosing of psychostimulants for preschoolers are lacking (Greenhill, 1998). Although MPH is the only stimulant medication for which controlled efficacy data are available in preschoolers, its FDA-approved package insert warns against use in children younger than age 6. Basic metabolic differences between very young children and adults prevent the extrapolation of dosing and safety data from adult studies. This lack of data served as a rationale for a multisite trial now under way to determine the safety and efficacy of MPH in preschoolers with attention-deficit/hyperactivity disorder (ADHD) (Greenhill, 2001). While it is possible that the use of these medications is appropriate for severely disturbed preschool children, without safety and efficacy studies all such conclusions, pro and con, must remain speculative (Vitiello and Jensen, 1995).

The lack of evidence about preschoolers' response to psychotropics contrasts starkly with current clinician prescribing practices (Zito et al., 2000). There are significant barriers to safety and efficacy research in very young children, including concerns about the possible impact of long-term medication on developing brain systems, the lack of animal models for preschoolers with ADHD, the rapidity of developmental changes during the preschool period, and limitations in our knowledge of what is normal and abnormal behavior in the preschool period. Failure to address these barriers and find solutions compromises the quality of care that these children receive (Vitiello, 2001).

As a result of these concerns, at the 2000 Annual Meeting the American Academy of Child and Adolescent Psychiatry's (AACAP) Workgroup on Research sponsored a workshop "Optimal Strategies for Developing and Implementing Psychopharmacological Studies in Preschool Children," under the auspices of the NIMH and the FDA. The forum organizers invited senior investigators and scientists from the fields of child psychiatry, clinical child psychology, child development, neuroscience, neuropsychology, epidemiology, and pharmacology. Policymakers (FDA, NIMH, and Office of Human Research Protection) and pharmaceutical industry representatives also were invited. These stakeholders participated in a day-long meeting that included plenary presentations, workgroups focusing on key topics, and plenary reports with discussions of recommendations.

METHOD

The primary objective of this Research Forum was to identify the obstacles and special challenges (ethical, logistic, evidentiary) to conducting psychopharmacological studies in preschoolers and to assist the field by identifying "best practices" to be incorporated in preschool psychopharmacological study research methods. Specific objectives were as follows: (1) to identify any special research precautions necessary to ensure that appropriate preschool children are recruited, i.e., those who have stable disorders and not transient adjustment reactions; (2) to determine which other clinical interventions might first be tried before a preschool child would be eligible for treatment with an experimental psychotropic medication; (3) to determine what types of safety/side effects profile monitoring should be used as a standard part of psychopharmacological research in the preschool age range (e.g., language, cognitive, and motor assessments); and (4) to determine what special environments may be required to observe and test preschool children (e.g., equipping sites with preschool-sized chairs and tables, establishing bathroom procedures, and deciding whether children should be accompanied by parents during research procedures).

Invitations were sent to 135 professionals in related fields. All invitees and the 20 meeting registrants paid a $100 admission fee. Attendees who accepted and attended included 94 physicians (60%), 31 participants with Ph.D.s (21%), and 30 others (19%).

Plenary addresses included the following: (1) obstacles to implementing preschool research designs (B. Vitiello); (2) special doses and formulations required to conduct pharmacological research in preschoolers (J. Blumer); (3) assessment issues in research with preschoolers (B. Lahey); (4) ethical considerations (C. Fisher); (5) pharmaceutical industry perspectives (J. DeVeaugh-Geiss); (6) regulatory perspectives (T. Laughren); and (7) special challenges in studying preschoolers (C. Zeanah).

Workgroups were organized around the following themes: (1) diagnosis/assessment, (2) research design, (3) ethics/institutional review board (IRB), (4) preschool protocol modifications, (5) FDA/regulatory/industry, and (6) training/public issues. Using an interactive/consensus development format, the workgroups were charged to identify problems that obstruct research and make specific recommendations to address each of these obstacles.

Workgroups had a balance of investigators, clinicians, and community advocates. The workgroup chairpersons were chosen because of expertise and stature in the field.

Prior to the meeting, each workgroup was assigned a rapporteur to take minutes. Rapporteurs had been selected because of their personal styles, particularly because they were known to have strong opinions and skill in articulating them. This was done to foster ownership and advocacy of the workgroup's recommendations. The plenary session reports generated feedback from other attendees. The goal was to foster "buy in" of the consensus recommendations by the meeting attendees. An interactive format was used to maximize interchange

and flow of ideas, while building momentum toward identification of solutions and "best practices."

RESULTS

OPTIMIZING RESEARCH DESIGN FOR PRESCHOOLERS

Obstacles

There are no "gold standard" preschool protocols, treatment manuals, or human subject protection precedents, as discovered when the NIMH Preschool ADHD Treatment Study (PATS) was designed (Marshall, 2001). There is a danger that in an attempt to avoid missing something important, preschool clinical trials may include too many variables.

Psychosocial interventions, used extensively in preschool treatment programs, are not standard parts of clinical trials. Depending upon the research question being studied, it is not clear whether a psychosocial treatment arm should be included in each preschool clinical trial, with the requirement that all families participate in parent training prior to randomization, or whether adjunctive services and an attrition prevention program (ASAP) as used in the NIMH Collaborative Multisite Multimodal Treatment Study of Children With ADHD (MTA) (Abikoff et al., 2002) should be made available.

Recommended Solutions

- Investigators can use sequential cohort designs to examine for developmental issues during treatment studies. These studies block subject enrollment by age (ranging from 3 to 5 years) to identify common drug-related adverse events by developmental stage.
- Large health maintenance organization (HMO) databases can be used to study prescribing practices, the long-term safety of medications, or monitoring for drug sensitization.
- Preschool children should be included in large simple clinical trial networks, which are suitable for monitoring long-term safety of drugs. A conference and casebook on human subject review issues that arise in preschool clinical trials, similar to the NIMH-sponsored "Ethical Issues in Child and Adolescence" conference held in 1994, would be valuable.
- Effectiveness designs to compare treatments should be planned for preschoolers after fundamental questions of drug efficacy and safety have been addressed.
- "*N* of 1" intensive single-case design studies could be encouraged by professional associations such as AACAP, American Psychiatric Association (APA), and American Academy of Pediatrics (AAP). This would make best use of the preschool children whose severity of psychiatric illness and impairment make multiple interventions necessary and likely to occur when they are treated in the community. Workshops on "*N* of 1" designs could be conducted at annual meetings.
- Initial preschool psychopharmacology trials of a new drug molecule should target children with the most stable diagnoses. ADHD and autism remain stable and consistent over a wide age range; less evidence exists for oppositional defiant disorder, with the least evidence for mood disorders.
- Only preschool children with severe disorders should participate in psychopharmacology protocols.
- Preschool psychopharmacology protocols should include measures of impairment.
- Some difficult behaviors in young children appear to be context-specific, and studies that stratify for different contextual circumstances would be valuable. A more controversial option would be to exclude children with single-context problem behaviors.
- The AACAP should create a standing multidisciplinary committee—the Pediatric Psychopharmacology Initiative (PPI)—to monitor progress in psychopharmacological trial design for preschoolers. The group should include representatives of researchers, families, practitioners, professional associations, industry, and regulatory agencies. The PPI should meet regularly to monitor progress. In addition, the PPI can explore relevant clinical trial methodologies that have been developed by the Pediatric Oncology Group, asthma studies, and human immunodeficiency virus studies and apply them to the field of preschool psychopharmacology. It can promote the enhancement of existing FDA advisory committees with experts in pediatric psychopharmacology to assist them in evaluating protocols and other issues pertinent to psychiatric disorders in preschoolers. Working with other professional groups (AACAP, AAP, APA), the PPI was conceived as a venue for launching broad initiatives to "kick start" this new but important field of preschool clinical investigation.
- Networks of advisors could convene developmental specialists, nosology experts, and assessment researchers to help those designing and conducting protocols in preschoolers.

DESIGN MODIFICATIONS FOR STUDYING PRESCHOOLERS

Obstacles

Pediatric psychopharmacology rating scales for school-age children are not necessarily age-appropriate, validated, or quantifiable when used with preschool children. Developmentally appropriate questions must be asked about poor appetite, irritability, and aggressive interactions with peers.

Practically no pharmacokinetic studies have been done in preschoolers to determine appropriate doses to be used in psychopharmacology trials. One cannot use weight-adjusted doses because clearance for both hepatically and renally eliminated drugs in the 2- to 6-year-old age range is more rapid than it is in older individuals. In pharmacokinetic studies, children should be stratified by age at 2-year intervals.

Preschool children have more difficulty swallowing pills than older children, so standard pills or capsules may not be suitable.

Because of the dynamic nature of this patient group, key tolerability and dose range data cannot be gathered in the randomized clinical trial, but must be determined by a separate dose-ranging study.

Recommended Solutions

- The study drug should be formulated as a suspension, powder, rapidly dissolving tablet, or transcutaneous delivery system to increase palatability. If the medication is in liquid formulation, it must be concentrated, because preschoolers will not swallow a large amount of liquid medicine.
- A dosing strategy should be developed that involves dose escalation with age-appropriate stopping rules. Dosing frequency should be minimized to increase adherence.
- Age-appropriate specific safety and outcome measures should be used.

ASSESSMENT ISSUES

Obstacles

The lack of validity data on preschool psychiatric diagnoses makes it difficult to set meaningful inclusion and exclusion criteria. Only three diagnoses—ADHD, oppositional defiant disorder, and autism—have been shown to have predictive validity in preschoolers when they meet symptom and impairment criteria (Keenan and Wakschlag, 2000; Lahey et al., 1998; Lord et al., 1994).

It is difficult to establish stable and reliable diagnoses in preschool children. This is complicated by preschoolers who show severe pathology in only one setting or interpersonal context. Identifying medication-related adverse events is complicated by limited language function.

No standardized instrument is available to measure executive functioning in preschoolers.

It is difficult to rely on the available behavior rating scales developed for school-age children because preschoolers' symptoms are less discriminatory or pathognomonic, i.e., less indicative of a specific diagnosis.

The psychometric trials for assessment instruments include no tests of or instruction for combining input from different respondents, especially those who might have their own pathology. This problem is not unique to the preschool age range.

Assumptions of threshold differences between different ethnic groups may lead to significant undertreatment of some groups to the detriment of child and family.

Recommended Solutions

- Behavior rating tools for preschoolers are needed that use briefer time frames (e.g., use 1-week rather than 1-month time frames).
- Behavior rating tools must be sensitive to treatment effects when used in repeated-measures studies so they can detect symptom continuities over several developmental stages.
- Assessment strategies for preschoolers have used methods suitable for adults and school-age children, but do not address the special developmental issues of preschoolers. Assessment tools that are appropriate for preschoolers include (1) empirically validated parent and teacher checklists down to the toddler years (e.g., Achenbach's Child Behavior Checklist); (2) adapted structured interviews for the preschooler (e.g., creating the Preschool Acute Psychiatric Assessment from the Child Acute Psychiatric Assessment); (3) the use of constellations of impairing *DSM-IV* symptoms that can be identified reliably in preschoolers.
- Input from multiple informants in preschool clinical trials, including parents and teachers, when available, is essential. This should be done during baseline and follow-up conditions. These should be supplemented with standardized laboratory-school protocols.

- Measures need to be developed to track short-term side effects of medication on vigilance, rigidity of responses on cognitive measures, memory (Fletcher et al., 1989), enuresis (particularly with neuroleptics), ritualistic and repetitive behaviors, and weight gain. Adverse effect measures and protocol designs should be designed to assess both short-term and long-term effects ("phenobarbital effect") of medications.

ETHICAL/IRB CHALLENGES

Obstacles

IRBs are concerned that because individual preschool children entering research may not have stable, chronic disorders, it is difficult to estimate the risk of giving an experimental treatment. The lack of basic data about the diagnostic validity, symptom expression, responsiveness to treatment, and toxicity of drugs in preschool children makes it much more difficult to estimate risk in preschool than in older children.

Clinical trials have not yet determined the efficacy of psychotherapeutic interventions for each specific diagnosis in the preschool age range.

It is not clear whether the diagnosis for research inclusion should be more stringent than diagnosis made in practice. If too stringent, the most seriously ill preschool children will be the only ones to be involved in psychopharmacology research. It is unfair for one subgroup to bear all the risks or reap all the benefits of research. It will also confound the sampling and reduce the scientific validity and generalizability of the study.

New treatments in preschoolers may have unknown risks, including (1) the introduction of concurrent and long-range developmental effects, (2) new side effects of the drug, (3) risks of repeated data collection (e.g., blood tests), and (4) not using adequate medical monitoring appropriate for preschoolers. However, if the drug being studied is highly popular—e.g., MPH being given to preschoolers with presumed ADHD—and it is going to be given whether or not the child is in a research study, then there is increased benefit for research participation.

Criteria do not exist to help investigators and IRBs to make design decisions that maximize benefits or minimize risks. This includes whether a preschool clinical trial should use a placebo, enter all control groups into a parent training component, use a comparator treatment that reflects the local standard of care or a best practice, or set criteria for breaking blinds and terminating the study. The PATS protocol recruits only children who fail a psychosocial treatment. However, responders to the initial psychosocial treatment may respond even better to the medication, but have been "protected" from getting that treatment.

Traditional consent forms do not cover the special needs of preschoolers and their families. Questions include when a preschool child's verbal or nonverbal response represents dissent, when a child's dissent can be overridden by guardian permission, how to determine whether the parents truly understand the consent procedure, and the possible impact of study participation on future and current health insurance coverage.

Standard consent can be coercive when applied to preschoolers and their families, particularly if the child's preschool teacher refers the patient, if large cash inducements exist for parental participation, or if the lack of treatment alternatives in the community where the study takes place forces the family to join the research.

IRBs traditionally have not included developmental experts, so they may not have a sense of how specific risks may shift as the child gets older. This makes it difficult to assure families that investigators and IRBs have the ability to provide adequate protections for preschoolers.

Recommended Solutions

- Preschool and developmental specialists should be included in investigative teams to participate in the planning and implementation of research.
- Parent advisory groups can be established for studies of preschool children to provide guidance on issues of developmental appropriateness of the studies' assent and consent procedures and evaluation of risk.
- A substantive clinical and basic neurobiological review of preschool research procedures using established methodologies, such as the McMaster Group Taxonomy, is needed to synthesize the evidence on diagnosis, symptoms, and psychopharmacological treatments in the preschool age group.
- NIMH should be encouraged to convene a conference of IRB chairs to work on developing casebooks and guidelines.
- A guide (booklet and/or Web sites) of resources (bibliographies, special advocacy groups, names and e-mail addresses of experienced IRBs) should be assembled. This task will be difficult, considering that there is little experience with research in preschoolers and that it is difficult to make general statements about risk that

are valid across situations, type of condition being treated, medication being tested, etc.
- Investigators should be encouraged to provide reconsent for families in clinical trials at each stage of the protocol and annually.

REGULATORY CHALLENGES

Obstacles

Labeling of only four psychotropic medications includes the preschool age group: MPH, amphetamines, and haloperidol or chlorpromazine. Yet many other psychotropics, including selective serotonin reuptake inhibitors and tricyclic antidepressants, are often prescribed for behavior problems in this age group (Zito et al., 2000).

The FDA has not, thus far, been approached with development programs targeting the nonspecific signs and symptoms—such as aggressive outbursts—that are most often the focus of practitioners using psychotropic medications in children. The agency does not, at this point, have a sufficient information base for deciding which, if any, nonspecific signs would be appropriate targets for treatment, what ages within the preschool range would be appropriate to target, what primary outcomes should be used, what assessment measures are appropriate, how many studies would be needed to determine the efficacy of the drug, and what special developmentally appropriate safety assessments should be required for preschooler studies.

While investigators may be hesitant to subject preschoolers to the repeated blood tests involved in pharmacokinetic studies, the FDA needs basic pharmacokinetic data as part of the information base for approval of safe and effective dose ranges.

Under the Food and Drug Administration Modernization Act (FDAMA), the FDA encourages pharmaceutical companies to conduct added research in pediatric populations by awarding 6 additional months of patent exclusivity. So far, however, the agency has made awards only to study adult psychiatric disorders not well characterized in the preschool age range: depression, obsessive-compulsive disorder, and generalized anxiety disorder. ADHD, a better-defined preschool disorder, has not been the subject of FDA requests for FDAMA studies. The agency, upon advice of experts in this disorder, has decided to wait to see the results of the NIMH PATS study of MPH treatment before requesting psychostimulant studies in this age group.

While the FDA has become involved in relatively frequent discussions on preschool psychopharmacology, there is no existing partnership between FDA, industry, and NIMH to tackle the obstacles involved in preschool psychopharmacology trials, as now exists in the pediatric oncology group or in the acquired immunodeficiency syndrome research group. Even if the partnership existed, many of the existing research components that facilitate the national Pediatric Oncology Program—easily validated diagnoses; clear endpoint; surrogate markers; a powerful, effective infrastructure; and effective recruitment methods—do not exist for preschoolers with psychiatric disorders.

Legal barriers deter the pharmaceutical industry from initiating studies of psychotropics in preschool children; these barriers include the following: (1) There is a liability for a new indication. If a pharmaceutical company has an indication for use in an age range, the company assumes liabilities. If that same drug can be used only off-label in an age range, the company has no liability; the prescriber assumes the liability if the drug is used off-label. (2) There is a legal liability because of diagnosis. If the public perceives the diagnosis to be overused or used inappropriately, the company can be sued, as was the case of Novartis with MPH in the treatment of ADHD. (3) When developmental concerns are involved, as they are for preschoolers, liability can extend for decades after drug use, including problems such as failure to achieve developmental milestones.

It is difficult to predict the drug response of a preschooler from the known responses of school-age children. The drug response may be related to developmental stage, so a medication that works in a 10-year-old may be nontherapeutic for a 2-year-old. Even so, an unfavorable efficacy or safety profile that appears in one age group could carry over to the perception of safety for another age group (negative halo effect).

If the protocol stipulates only severely ill preschoolers be enrolled, recruitment may be slow and the financial return may be small. Also, the company may not know the correct methods of targeting difficulties in enrollment.

Recruitment methods needed to enroll preschoolers in clinical research differ from the tried and true methods pharmaceutical industries have used for adult protocols.

Pharmaceutical companies have very little experience or confidence in marketing psychotropics to families of preschoolers.

The pharmaceutical industry has a lack of experience in conducting clinical trials in preschoolers and has been

deterred by increased costs required for developing products for this age range, e.g., the need for special formulations, the need to do extensive pharmacokinetic work, and the inability to obtain safety data from normal adult volunteers that could apply to preschoolers.

There has been a lag time of three decades to conduct studies on approved psychotropic medications in preschool children. This means that previously approved psychotropics for school-age children have lost their patent protection, thereby removing the industry's sole incentive to support research in this area.

Recommended Solutions

- The FDA should enhance current internal advisory subcommittees with expertise in child psychiatry and psychopharmacology.
- If there are data to support the existence of valid symptom complexes (such as aggression) that can be reliably measured, the FDA should be encouraged to consider them as possible indications for drug use in New Drug Applications and in package inserts.

SPECIAL CHALLENGES IN DOING RESEARCH WITH PRESCHOOLERS

Obstacles

Preschool children can exhibit severe symptoms in one setting but miss an Axis I *DSM-IV* diagnosis by not showing the psychopathology in any other setting. The lack of agreement among different reporters about the child's behavior makes diagnosis difficult.

It is difficult to include the entire preschool age range within one study because known developmental differences in behavior affect the stability of the psychopathology over time. Clinical trials require stable symptom pictures across time to obtain an accurate estimate of drug efficacy. Aggression, for example, is much more stable for the period age 3 to 5 than it is for the period age 2 to 5. Activity level in the preschool years is the highest in the human life cycle, so it is difficult to differentiate abnormal levels of hyperactivity from normal developmental variation and perturbation. High activity in preschoolers may not always be the result of ADHD.

The planning of most pediatric psychopharmacology protocols, including those for preschoolers, lacks input from developmental experts. Often there is no standardized method for assessing the interpersonal contexts in these trials.

Many developmental periods exist within the preschool age range, so it is difficult to identify stable and reliable inclusion and exclusion criteria.

Standard medical procedures, such as venipuncture or magnetic resonance imaging, do not make adjustments for preschoolers' natural anxieties about these procedures, nor do they take into account the developmental concerns of preschoolers and their families.

Very young children might tire or become uncooperative during a long study visit without appropriate break or rest periods.

Special furniture and other special physical requirements need to be addressed.

Recommended Solutions

- Developmental expertise—in both normal and psychopathological development—in the form of a coinvestigator or consultant should be included on every protocol's design team.
- The study should be designed to have sufficient power to test for age differences across the age range. Children in the age range of 24 to 36 months should be kept separate from those in the 37- to 60-month age range.
- The protocols for preschool children should be modified to address the needs of these children and their parents by (1) walking the parent and child through the protocol first, (2) working to establish the partnership with the parent, and (3) formulating more palatable forms of medications (liquids, wafers that dissolve).
- Psychosocial components, such as parent training, can increase the benefit of a clinical psychopharmacology trial to families. Psychosocial components make drug studies more palatable, synergize with drug effects, and make them less aversive to the public at large. The NIMH PATS study requires that all its research participant preschooler families take 10 sessions of parent training before deciding to enter the medication trials. This increases the benefit and decreases the risk for the research participants. Whether this two-part design would work for other clinical research questions involving preschoolers would have to be examined in the context of those studies.
- Programmatic development of a treatment intervention should follow a rational, stepwise approach to research in this age group, starting with dose-finding and tolerability studies, before embarking on large clinical trials.

- The baseline assessment should include a developmental battery, as well as observations of the preschoolers with a parent, an observation in school with teacher and with peers, and observations with siblings (if any). A rationale must be provided for the researcher's selection of contexts, settings, and domains within the protocol.
- For inclusion into a study, the preschooler's symptoms should be assessed cross-contextually. The child should be assessed across multiple interpersonal contexts (e.g., for family, assess the child with parents and with siblings; for teacher, assess the child's interaction with the teacher and with classmates; for the examiner, assess the child's interactions with the examiner), across multiple physical settings, and across multiple domains (e.g., cognitive, behavioral).
- Children should be selected who have pervasive pathology that is stable across situations.

TRAINING/PUBLIC ISSUES

Obstacles

The media have not always presented a positive picture about research, and this can have a major impact on recruitment and retention in a clinical research trial involving preschoolers. Also, the media play a central role in the dissemination of information and the generation of public opinion.

Recommended Solutions

- Media should be encouraged to facilitate research by helping to destigmatize mental illness, defining mental disorders in preschoolers as medical illnesses, and removing the impression that treating mental illness is simply treating bad behavior. The media can help by incorporating families and children, not just professionals, in news stories about preschoolers with mental disorders.
- Investigators should be encouraged to work with members of the media to approach the psychopharmacology of preschoolers as one of many issues related to the care that children receive for mental illnesses in this country. It is equivalent to their difficulty obtaining access to care and lack of parity in insurance coverage.
- Providing proper training of investigators was a high priority. Funding agencies were encouraged to set aside two early investigator grant awards for junior investigators to develop expertise in the area of preschool psychopharmacology.
- Parent advocates should be invited to participate in media debates whenever special interest groups against psychiatric care for children are invited on televised debates. Parent advocacy plays a helpful role in mediating the relationship between investigators and the media.
- Parents of preschoolers should be involved during the initial design of the trials. They are best equipped to speak to the media in response to community concerns where the trials take place.
- There is a need to seek reimbursement from HMOs and third-party payers for parent training when a preschooler is found to have an impairing symptom or a mental disorder.
- Research assessment methods should be sensitive to the presence of child abuse as a cause of the behavior, particularly when assessing children for symptoms of aggression and sleep disorders. Psychopharmacologists need to be trained in the assessment of preschool children for prior or ongoing abuse and neglect, so they can avoid simply giving these children medication and returning them to an abusive environment.
- Professional organizations, such as the AACAP and the AAP, were encouraged to develop practice parameters for the psychotropic drug treatment of preschoolers with psychiatric disorders. These practice guidelines can help researchers know community standards of care that affect randomization, use of placebos, standard treatment time-frames, well-validated endpoints, stopping rules, and guidelines for changing treatment before the trial starts. The organizations can also encourage training programs to include coursework on the treatment of preschool children.
- Web sites of professional organizations can be used to collect "*N* of 1" reports, while ensuring the quality of information and confidentiality. These organizations could give discounts to meeting registrants for every successful "*N* of 1" case that is entered onto the group's Web site. The principles of good clinical practice and trial design also can be applied to the "*N* of 1" treatment trials of individual children in the private practitioner's office.

DISCUSSION

Although the six different workgroups at the AACAP's Research Forum on preschool clinical trials were given different domains and problem areas, a set of common recommendations emerged by the end of the meeting:

- Preschool children recruited into trials should have stable psychiatric disorders or symptom complexes and not transient adjustment reactions. The evidence base of stable diagnoses—ADHD, oppositional defiant disorder, and autism—makes them suitable candidates for preschooler research protocols.
- Only those preschoolers with severe symptoms should participate in psychopharmacological studies. One wants be sure to distinguish variants of normal behavior from behavior that might be considered pathological and meriting treatment.
- Stratification procedures can be used to include preschoolers in studies who have their serious impairment in only one setting or with one caretaker. When possible, preschool psychopharmacology protocols should use multiple informants, multiple domains, multiple settings, and diverse interpersonal contexts. However, preschoolers may not always be exposed to the multiple informants or multiple situations that commonly form the environment for school-age children.
- New behavioral measures, with norms, should be developed that target the specific symptoms found in preschoolers. Investigators should use standardized testing situations to increase reliability of measures and provide a safe environment to carefully track the effects of psychopharmacological agents. The standardized University of Irvine laboratory school classroom (Wigal et al., 1998) has recently been modified for preschoolers to provide surrogate measures more appropriate for that age range (e.g., bead-stringing tasks instead of math tests).
- Measures should be developed that target executive function impairments (e.g., vigilance, working memory, cognitive rigidity) specific to preschoolers' cognitive development. Language, cognitive, and motor assessments should be included as a necessary part of preschool pediatric psychopharmacology protocols.
- Long postexperimental observation phases should be included in the trial design to evaluate the impact of the research intervention on later development.
- Clinical psychopharmacological trials should include a behavioral component, such as parent training.
- Research sites can be equipped with preschool-sized chairs and tables, established bathroom procedures, and the option that children may be accompanied by parents during research procedures.
- Developmental experts should be invited to collaborate at every step of the research process, so that elements of design (e.g., selection of outcome measures) as well as patient care issues (how to walk families through the protocol before they enter) could benefit from these specialists' input.
- The AACAP should be encouraged to form a PPI to monitor progress in the field of preschool clinical trials. By including developmental specialists, assessment researchers, and representatives from FDA, NIMH, professional associations (AACAP, APA, AAP, and American Academy of Family Physicians), parent advocacy groups, and the pharmaceutical industry, the PPI will be well equipped to pursue the recommendations of the Research Forum 2000.

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