A new study of whether a popular but controversial drug is safe and effective for preschool children also raises ethical concerns about using young subjects in clinical trials

Planned Ritalin Trial for Tots Heads Into Uncharted Waters

Doctors like to say that medicine is an art as well as a science. But the science seems a bit thin when it comes to giving drugs to young children. Physicians write millions of prescriptions for children each year without solid evidence that the therapy they're offering is safe or effective. To fill in that knowledge gap, U.S. scientists are gearing up for a major clinical trial intended to measure the effects of a popular stimulant on a previously untested population—children aged 3 to 6. But in doing so, they are also running up against one of the hottest ethical issues in research.

The study, funded by the National Institute of Mental Health (NIMH) in Bethesda, Maryland, and set to begin in December, will recruit about 300 preschoolers diagnosed with attention deficit hyperactivity disorder (ADHD). Almost half will receive Ritalin, or methylphenidate (MPH), a drug used to help older children get along with playmates and fit into school routines. The scientists involved in the study admit that they are concerned about the drug's effect on the children's still-developing personalities and brains, as well as their inability to give informed consent. But they believe that such trials are the only way to answer concerns about rising use of the drug among this population. "We've put the study through an ethical wringer" to win approval, says NIMH director Steven Hyman.

Off label. Children under 6 aren't supposed to use Ritalin, but thousands do.

However, the demand for better scientific data runs counter to growing concern about human subjects research. "There is a big clash between the pressure to include children in clinical trials [and] discomfort about enrolling young children" in studies, says Norman Fost, a pediatric researcher and bioethicist at the University of Wisconsin, Madison. The ethical problems are reduced if the child volunteers have a chance of benefiting from experimental therapy, says Fost, who also notes that NIMH can be trusted to provide rigorous oversight.

Drugs without data

The idea for undertaking a trial like this arose 3 years ago, when psychiatrist Laurence Greenhill of the New York State Psychiatric Institute met with other academic researchers and NIMH to discuss the lack of safety and dose information for treating children under 6 with Ritalin. He proposed a large multicenter study that would enlist preschoolers in a test that would establish the best dose for very young children—a group rarely tested for any type of drug use. Peer reviewers at the National Institutes of Health (NIH) gave the proposal, called the Preschool ADHD Treatment Study (PATS), a favorable score in 1998. It then wended its way slowly through a series of ethics and policy review panels.

WARNINGS
Ritalin should not be used in children under six years, since safety and efficacy in this age group have not been established.
Sufficient data on safety and efficacy of long-term use of Ritalin in children are not yet available. Although a causal relationship has not been established, suppression of growth (i.e., weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored.

Its importance seemed to grow, as people became increasingly aware of the need for better scientific data for some popular prescription drugs. Companies have run very few drug trials that include young children, but this hasn't stopped doctors from writing prescriptions. By one estimate, 94% of drugs given to children are prescribed "off label" in this way.

In 1997, the Food and Drug Administration (FDA) drew up a "short list" of the 10 most widely prescribed products used for children without FDA approval. They ranged from the antiasthma drug Albuterol, approved only for children aged 12 and older, to the antidepressant Zoloft, approved for those 16 and older. Ritalin is on the list, prescribed 226,000 times in 1994 for off-label uses.

Early this year, epidemiologist Julie Zito of the University of Maryland, Baltimore, reported in the *Journal of the American Medical Association (JAMA)* that the off-label use of psychoactive drugs by youngsters has increased steadily. Using Medicaid and insurance data, she traced a tripling from 1991 to 1995 in the use of psychoactive medicines among children 2 to 4 years old. MPH topped the list, and Zito estimates that there may now be 150,000 to 200,000 U.S. children in this age group taking it.

Commenting on Zito's findings in the same issue of *JAMA*, Harvard University psychiatrist Joseph Coyle asked whether psychoactive drugs might affect the development of visual processing, language, motor skills, and memory of young children. The "disturbing prescription practices" documented by Zito, he said, deserve "more thorough investigation." Hillary Clinton and White House health policy staffers picked up the message in March, urging officials to warn the public of the risks of off-label use of psychoactive drugs. With such encouragement, NIMH moved ahead and on 30 September awarded $6 million to Greenhill and colleagues at five other psychiatric centers.

PATS is part of a broader effort to get better information on how prescription drugs affect children. Since the mid-1990s, advocates for children's health have been lobbying to get clinical researchers to include young volunteers in their studies, just as others campaigned to increase the representation of women and minorities in research. Now they've succeeded, and both FDA and NIH are taking steps to enroll thousands of children in clinical trials.

A 1997 law giving FDA new authority for such trials allows it to reward companies with exclusive marketing rights to a drug for 6 months if they agree to study the safety and efficacy of treating children. An April 1999 FDA rule requires companies seeking approval of a new drug to run tests that include

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Enforcers Halt NIH Study Called Less Risky Than Outdoor Play

How much risk should healthy children face in a research experiment? The answer can land even the best clinicians in hot water, especially if they read the rules differently from the government officials who must enforce them. Such a disagreement led to the sudden suspension last week of research on childhood obesity at the National Institute of Child Health and Human Development (NICHD), part of the National Institutes of Health (NIH) in Bethesda, Maryland. The crackdown was imposed by a new enforcement group called the Office for Human Research Protections (OHRP), which disagreed with researchers on how to interpret the words "minimal risk."

The study in question, by NICHD pediatrician Jack Yanovski, is examining genetic factors that affect body weight. Since its approval in 1996, the trial has enrolled more than 190 children aged 6 to 10. Some are obese and others are normal children of obese parents, considered at risk for obesity. The plan was to follow them for 15 years and collect data and blood samples, and perform x-rays and abdominal magnetic resonance imaging scans.

The controversy arises from an invasive procedure that is part of the study. It requires children to stay overnight in the hospital; two intravenous catheters are inserted and clinicians infuse insulin and sugar while taking blood samples. This "clamp" study was designed to manipulate blood sugar levels over a specific range (80 mg to 200 mg per deciliter) and measure each child's response. Children were paid up to $270 per visit.

The government overseers who approved the study in 1996 assumed that the children were exposed to "minimal risk," according to a 3 November letter from OHRP enforcement officer Michael Carome to NIH intramural research chief Michael Gottesman. Federal guidelines don't allow young children to be in a trial that has no therapeutic benefit—like this one—unless the risk is minimal. The standards were intended to ensure that a nontherapeutic experiment doesn't pose a greater risk than the child would encounter in a normal visit to the doctor, says Norman Fost, an ethicist at the University of Wisconsin, Madison, who helped draft the federal standards 2 decades ago.

According to minutes from NICHD's ethics review, members felt that the children probably were exposed to bigger risks by "playing actively on sidewalks and streets" than they faced in the intravenous blood sugar study. But 4 years later, OHRP rejected this logic, concluding that the clamp study is not like a routine visit to the doctor.

Yanovski has been instructed to consider how to make amends for being out of compliance with federal rules. This may mean informing everyone in the trial that the research involves more than minimal risk. OHRP wants a decision and a report by 8 December.

NICHD will provide both, says Gottesman. But he insists that the research is benign and that it "will be extremely important for understanding the physiology of obesity and learning how to intervene to prevent it." Yanovski, he adds, is "an enormously thoughtful, caring pediatrician" who makes Marcus Welby, the avuncular TV doctor, look mean. **–E.M.**

children, if children are suitable candidates for therapy. In the psychiatric area, an FDA official said recently, the agency has already requested pediatric studies of drugs for posttraumatic stress, mania, social anxiety, and "premenstrual dysphoric disorder." Soon, it may ask companies to study pediatric drugs for "conduct disorder" (a type of aggressiveness), panic disorder, and schizophrenia.

In parallel, the National Institute of Child Health and Human Development has created a 13-site network to provide technical support for more than 50 industry-sponsored trials of nonpsychiatric drugs. A recent announcement boasts of access to a pediatric population with 160,000 inpatient admissions and 2.3 million outpatient visits annually. NIMH has set up a seven-site clinical network to support similar work called the Research Units on Pediatric Psychopharmacology. All of these changes, a recent NIH announcement notes, have produced "an unprecedented surge in the number of pediatric drug trials."

But PATS is the first major trial for preschoolers. "We are breaking new ground with this study; there was no prototype," said Benedetto Vitiello, chief of NIMH's branch of child and adolescent treatment and preventive intervention, who spoke last month at a public forum on the PATS trial in New York City.*

Trials and tribulations

Designers of the PATS trial have faced some novel challenges. One of the first was to develop a definition of ADHD for 3-year-olds. A child may be included only if an experienced clinician using an agreed-on set of behavioral criteria makes the ADHD diagnosis, a parent and a teacher both rate the child as troubled, and the child has exhibited symptoms for 9 months. Another hurdle is overcoming skepticism about the diagnosis, which has been controversial for decades. Today, ADHD is said to be a common disorder, affecting as much as 5% of the school-age population.

But critics question whether it makes sense to rely so heavily on chemicals, because ADHD isn't defined by a biochemical or even physical abnormality. These doubters range from the die-hard variety, like the Bethesda, Maryland, psychiatrist Peter Breggin, to moderate skeptics like pediatrician William Carey of the Philadelphia Children's Hospital. Carey has written that the "assumption that ADHD symptoms arise from cerebral malfunction has not been supported, even after extensive investigations." The "very fuzzy" diagnosis of ADHD for school-age children includes a broad range of normal behaviors, he says.

Breggin, meanwhile, has signed up as an expert witness for parents of ADHD children who this year filed lawsuits against the manufacturer of Ritalin and psychiatric organizations in several states, alleging that they conspired to promote the drug. Breggin and

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Developing debate. Enrolling preschool children in any type of clinical trial raises a host of ethical questions.

* Research Forum on Optimal Strategies for Developing and Implementing Psychopharmacologic Studies in Preschool Children, Annual Meeting of the American Academy of Child and Adolescent Psychiatry, 25 October, New York City.

California neurologist Fred Baughman Jr. blasted the use of Ritalin in congressional testimony on 29 September. Baughman called the ADHD diagnosis "a total fraud." Enrolling young children in a trial of MPH, he adds, is "outrageous" and "immoral." Robert Findling, a psychiatrist at Case Western Reserve University in Cleveland, Ohio, who conducts research in this field, dismisses such views as "nihilist" and says that they don't carry much weight among the experts.

Greenhill acknowledges that ADHD is "not a well-defined psychiatric disorder in this age group." Findling agrees but says that ambiguity should not be an excuse for inaction. "Just because we don't know what causes it doesn't mean it's not a problem," he argues. "This is not just benign fidgetiness. ... Parents will tell you how awful it is that these kids can't be taken out in public because they're so impaired. We know they suffer for years and years. "

Hyman agrees that researchers have not identified any distinguishing biological hallmarks of ADHD. But he says that the disorder is well defined in behavioral terms, that ADHD children who fail to receive treatment often suffer life-changing harm, that older ADHD kids appear to benefit from drug therapy, and that no "really gross side effects" have been documented. All this adds up to a strong argument for the trial, he believes. "Without good clinical data, every child who receives this medication represents an uncontrolled experiment," says Hyman. "That is entirely unacceptable."

Assessment of efficacy is another major issue. How will researchers know whether a 3-year-old is functioning "on-task" during therapy—one of the goals of giving MPH? Greenhill explains: "We're going to set up a laboratory classroom, and we'll observe common tasks done in nursery school," such as stacking blocks and stringing beads on a thread. Children will be asked to sit in a circle and take part in group events. The test will be whether the child is "compliant" and participates or "attends for a few seconds before drifting away and doing everything else in the room."

The PATS researchers have taken other steps to allay qualms about the effects of MPH therapy itself and the difficult issue of getting informed consent. Each family will begin the trial with a 10-session "training" period in which researchers will attempt to treat ADHD with nonchemical therapy. Only if this fails will a child be assigned randomly to drug therapy or a placebo group. To address concerns about the effect of MPH on young children, only very low doses of MPH will be used in the initial stage—so low that a planning memo calls the level "homeopathic."

In fact, Greenhill anticipates that this initial dose may have no effect. Once safety has been demonstrated, children will receive gradually higher doses until they reach a "best dose," which they will receive for 40 weeks. No child will be enrolled who lacks the language skills to "indicate that he or she is in distress," and parents will be given information and asked to give fresh consent on behalf of their child at each of the five stages of the trial.

After what Vitiello calls "zillions" of safety and ethics reviews and funding approval, the trial received a final green light from the data safety monitoring board. Greenhill says the clinics will begin recruiting the first subjects in a few weeks.

–ELIOT MARSHALL

MEETING NINTH INTERNATIONAL CORAL REEF SYMPOSIUM

Reef Migrations, Bleaching Effects Stir the Air in Bali

NUSA DUA, INDONESIA—More than 1500 marine biologists, ecologists, conservationists, and community activists met at this Bali resort from 23 to 27 October for the Ninth International Coral Reef Symposium. Topics included the dynamics of reef fish communities and the lingering impacts of coral bleaching.

Staying Close to Home

Marine biologists have long known that adult fish that inhabit coral reefs don't stray far from home. But their larvae were presumed to be scattered by currents to distant shores, where they join existing communities, settle, and mate. This "open system" was thought to result in a thorough mixing of the gene pool, characterized by widespread homogenous populations. In the last few years, however, some scientists have begun to question that assumption. "The evidence is accumulating that reef fish communities are closed systems," in which the vast majority of larvae return to the reef where they were born, says Robert Warner, a marine biologist at the University of California, Santa Barbara (UCSB). If that new vision holds up to scrutiny—and there are skeptics—it would not only change ideas about fish population dynamics but would also have implications for protecting marine biodiversity and managing fisheries.

Domingo Ochavillo and colleagues at the University of Southern California in Los Angeles have employed genetic tools to look at interbreeding among three different populations of the rabbitfish *Siganus fuscescens* that live within 350 kilometers of contiguous reefs along Luzon Island in the Philippines. When the researchers examined the mitochondrial DNA, says Ochavillo, they found that each population had a distinct pattern, suggesting little genetic mixing among them. The group also found that late-stage larvae settling on a particular patch of reef shared the same genetic pattern as the local adults. Ochavillo and his colleagues obtained further evidence after releasing 500 larvae at a point 2 kilometers from shore. "They started swimming toward where they had been born," says Ochavillo, leading him to conclude that "larval dispersal may not be as widespread as usually assumed."

Other studies support this so-called self-recruitment, in which larvae return to the community of their origins. Robert Cowen, a marine biologist at the University of Miami, fed data on actual Caribbean currents and information on survival

Community watch. The fondness of reef fish for their origins puts a premium on local preservation.

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