Every year, more than half of newly approved drugs and biologics considered likely to be prescribed for children lack labeling information on safe and effective use. Seeking to rectify this situation, the FDA recently issued final regulations requiring new drugs and biologics that are therapeutically important for children or will be commonly used in children to have labeling information on safe pediatric use.

This rule will also allow the FDA to require pediatric testing of already-marketed products in certain compelling circumstances, i.e., when a drug is commonly prescribed for use in children but the absence of adequate labeling could pose significant risks. The FDA (1999) has subsequently issued a written request for pediatric studies for buspirone (BuSpar), gabapentin (Neurontin) and lamotrigine chewable dispersible tablets (Lamictal), among other drugs.

The FDA’s actions reflect growing concern over the substantial and increasing use of psychotropic medications in children and adolescents, and the extensive need for pediatric psychopharmacology research.

Both problems confronting pediatric psychopharmacology and prospects for positive change were delineated recently by John T. Walkup, M.D., during a presentation he co-prepared with Mark A. Riddle, M.D., a fellow colleague from the Division of Child and Adolescent Psychiatry at Johns Hopkins University in Baltimore.

Speaking at the American Academy of Child and Adolescent Psychiatry’s 45th annual meeting in Anaheim, Calif., Walkup said that, "at least 10% of youngsters at any given time have a psychiatric disorder that would potentially respond to pharmacotherapy. The estimated prevalence of attention-deficit/hyperactivity disorder [ADHD] is 4%; of anxiety disorders, 2%; of major depressive disorder, 2%; of obsessive-compulsive disorder [OCD], 1%; and of other disorders, 1%. “The prevalence estimate for the other disorders category could even be higher, Walkup noted, if it included bipolar disorder, psychotic disorders, the pervasive developmental disorders, such as autism and episodic aggression.

A significant dilemma in treating these disorders, according to Walkup, is that many of the medications prescribed for children are prescribed off-label (Riddle et al., 1998a; Vitiello and Jensen, 1997). As an example, he pointed to a list of the 10 drugs most prescribed to children off-label in 1994. Out of the 10, three were psychotropic medications: fluoxetine (Prozac), with 349,000 prescriptions to treat children and adolescents under age 16 suffering from depression and OCD; sertraline (Zoloft), with 248,000 prescriptions to treat children suffering from depression; and methylphenidate (Ritalin), to treat children suffering from ADHD.

"Ritalin is approved for use in kids, but not approved for use in kids under age 6, yet there were 226,000 prescriptions for its use in children under age 6," Walkup said.

In explaining the lag in pediatric psychopharmacology research as compared to such research in adults, Walkup said that in the past it was viewed as a humanitarian and ethical principle not to do research studies on children, women of childbearing age or older adults. According to Walkup, it was not until 1979 that a pediatric-use section was developed for product information on drugs. Yet, medications that were originally tested on adult males and some females are increasingly being used on children and other populations.

"The risk of prescribing those medicines without information clearly outweighs the risk of studying them," he said. "Most medications used off-label to treat children and adolescents do not have adequate safety and efficacy data to support pediatric use."

Walkup discussed a comprehensive literature review of the efficacy of psychotropic medications in
children (Riddle et al., 1998b).

"What we tried to do...was to look at all the medications available for use in child psychiatry, attempt to create our own list of medicines [and indicate] where there is enough data to support use and where there are some questions," he said. The researchers conducted an extensive literature search, even checking the chapters in psychopharmacology texts to identify more obscure studies. They then set standards as to what they would consider adequate trials.

"What we determined is that we wanted a sample size of greater than 40 in two studies or greater than 80 in one study. And by current industry standards, this is pretty small," he said. "What we found was that there were no controlled studies for any of these significant psychiatric disorders in childhood: anxiety disorders except for obsessive-compulsive disorder, bipolar disorder, bulimia, sleep disorders and substance use disorders."

There are, however, "some medications where we really do have sufficient data that actually support the FDA [pediatric use] indications these medicines currently carry," he said. He pointed to plenty of studies supporting the efficacy of methylphenidate, d-amphetamine (Dexedrine) and pemoline (Cylert) for treatment of ADHD in children age 6 and older.

For OCD, Walkup said there is good data on clomipramine (Anafranil) for use in children age 6 and older, fluvoxamine (Luvox), for children age 8 and older and sertraline, for children age 6 and older. For tic suppression, there is some data supporting pimozide's (Orap) use in young people age 12 and older. (Fluvoxamine was the first selective serotonin reuptake inhibitor [SSRI] approved by the FDA for OCD in children-Ed.)

"On the other hand, there are some medicines that we are currently using that have an FDA indication, but there really isn't any data that supports their use in children," he said.

A number of these medications were grandfathered in, according to Walkup. They were approved for use in the United States, and as a result, the indications were expanded to include children without sufficient supportive data. There are, for example, no current studies supporting the use of amphetamine salts (Adderall) in children 3 years of age or older, although there are some studies underway. Other FDA indications for use of drugs in children that lack sufficient supportive data, Walkup said, include d-amphetamine in young children ages 3 to 5 years; amitriptyline (Elavil) for depression in young people age 12 years or older; and chlorpromazine (Thorazine), thioridazine (Mellaril) and haloperidol (Haldol) for young children experiencing hyperactivity, behavior problems or pervasive developmental disorders.

"Again lithium compounds [Eskalith and Lithobid] have been grandfathered in for use in mania and bipolar disorder in kids over 12 years of age and...diazepam [Valium] for anxiety disorders in kids over 6 months of age," he said.

There are some medicines, not many, Walkup added, where there is no FDA pediatric use indication but where there is sufficient data to support such use. He cited some studies using bupropion (Wellbutrin) and imipramine (Tofranil) for ADHD in 6- to 12-year-olds, studies of desipramine (Norpramin) in children and adolescents and fluoxetine in children 8 years of age and older who are depressed (Emslie et al., 1997).

In addition, Walkup said, there are some interesting studies about the use of lithium for aggression in children over age 5 (Campbell et al., 1995) and naltrexone (ReVia) for hyperactivity in autism (Kolmen et al., 1997; Willemsen-Swinkels et al., 1996).

Long-term safety and efficacy data on the use of psychotropic medications in children is lacking, Walkup added.

"Mostly what we do are short-term studies. And in short-term studies, you really don't get a sense of how long the medicines work, whether they are continuously effective and whether any long-term side effects develop as a result," he said.

There are three long-term studies using methylphenidate for ADHD and a couple of studies looking at long-term use of SSRIs for treatment of OCD in children and adolescents that have yet to be published, Walkup said. Henrietta Leonard, M.D., at Rhode Island Hospital in Providence (Leonard et al., 1991) did a double-blind discontinuation trial. Joseph Deveaugh-Geiss and colleagues (1992) conducted a multisite clomipramine trial and described in their article the results of their one-year open extension. Walkup added that he and colleagues are involved in collecting data for a one-year open extension of the fluvoxamine trial. Beyond challenges of insufficient research data, Walkup also pointed out problems with an inadequate research infrastructure, difficulty in recruiting children and adolescents for studies, vocal opponents to pediatric pharmacology, and media sensationalism.

Pediatric psychopharmacology relies on an inadequate research infrastructure, according to Walkup. "I wasn't seriously trained in psychopharmacology, it was something I learned from other colleagues..."
and on my own," he said, adding that the vast majority of divisions of child psychiatry in the country do not have a large psychopharmacology component. "Once you have a research infrastructure, sometimes it is very difficult to recruit kids into pediatric psychopharmacology trials, especially if you are asking kids to undergo the traditional parallel-group, double-blind, placebo-controlled trials," he said. When asked up front to take the risk of having the child or adolescent go on active medicine or on placebo for an extended period of time, most families prefer to opt out of that choice and go to their local practitioner, according to Walkup. Adding to these problems are a "number of opponents who are increasingly vocal regarding the use of pediatric psychopharmacologic agents," Walkup said. "[Some] very prominent opponents [include] the Church of Scientology, which has waged a very active campaign...about Ritalin and more recently about fluoxetine, and some folks who are very outspoken. Peter Breggin, M.D., of the Center for Study of Psychiatry and Psychology in Maryland, has written a very controversial book, Talking Back to Ritalin: What Doctors Aren't Telling You About ADHD and Stimulant Drugs for Children." Media coverage of pediatric psychopharmacology, Walkup said, "is often sensationalized and quite misinformed." He drew attention to such statements in popular press as "we have replaced reading, writing, [and] arithmetic in our classrooms with reading, writing and Ritalin," and "overprescribing antidepressants to kids is a form of child abuse." Despite these problems, Walkup said the prospects for the future of pediatric psychopharmacology are very promising. He pointed to the development of research units on pediatric psychopharmacology, the creation of training institutes at the American Academy of Child and Adolescent Psychiatry meetings, drug companies spending more money to support the "kinds of important studies that need to be done," and support from the American Academy of Pediatrics, the National Alliance for the Mentally Ill and the National Institute for Mental Health (NIMH). "The National Institute of Mental Health has been very active [not only] in developing information through grants but also through setting up mechanisms for information dissemination like [the] ADHD consensus conference [held last November in Washington, D.C.], so that all practitioners and all families in [the] U.S. have the information we need to make decisions about treatment with psychotropic medicines," Walkup said. The impetus for creating research units on pediatric psychopharmacology (RUPPs), according to Walkup, came from a 1995 conference cosponsored by the NIMH and the FDA (Vitiello and Jensen, 1997). The conference brought together more than 100 research experts, family and patient advocates and representatives of mental health professional associations. "Out of that [conference] came a mandate to begin to study drugs that were currently available for which there was no information about their use in kids," according to Walkup. To help bootstrap the field by providing the infrastructure for centers to complete the necessary safety, dose-ranging and efficacy studies in children and adolescents, the NIMH set up and funded the RUPPs. Currently, research units on pediatric psychopharmacology are at Columbia University College of Physicians/New York University; Johns Hopkins University School of Medicine in Baltimore; the University of Pittsburgh; Yale University; University of California, Los Angeles; Indiana University; and Ohio State University/Kennedy Krieger Institute. The last four RUPPs are funded under NIMH grants for pediatric psychopharmacology in treating autism and other pervasive disorders. "Part of what we are supposed to be doing are systematic clinical trials, even including some open-label trials in an effort to collect information on whether medicines work and then moving on to efficacy trials, which are the traditional double-blind trials, and finally to effectiveness studies which are the use of medicines in a research design that is more exportable to clinicians' offices," Walkup said. "These studies all have different goals. The open trials, as I mentioned, are for finding new treatments, efficacy trials are to bring new medicines to the market...the effectiveness trials are really the comparison of treatments and creating designs that give you information about how to use the drug in your practice."

Although well-designed and well-conducted unmasked and uncontrolled clinical trials of psychotropic medications in children are needed, Walker believes that some publications standards should be imposed (Walkup et al., 1998). He also raised questions about other study designs. For example, would a period of open treatment, followed by a double-blind discontinuation, be acceptable to the FDA and other review bodies? In multisite trials, he said, "there is this tension between having a number of sites in order to complete the trial quickly, and having all the sites develop real expertise with the study, so it is conducted accurately." One of the problems with long-term studies, Walkup added, is that they are uncontrolled: "They tend to be used as an incentive for patients to enter double-blind trials, so that if you put in the time and effort to participate in a double-blind trial, at the end of the double-blind trial, you have an opportunity to get active medication for free for an
extended period of time."
Effectiveness studies, Walkup said, often have complicated designs and are very costly. The Collaborative Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder (the MTA) involved 576 children ages 7 to 9 years (Arnold et al., 1997). It was "a huge trial requiring multiple sites and a fair amount of financial support," Walkup said. He added that a similar multimodal treatment study will be conducted for children with depression and another for children with anxiety is in the planning stage.
Pediatric psychopharmacology research, Walkup believes, will soon move into "networks of university sites and private practitioners who work collaboratively and systematically to collect information about medication usage, usefulness and side effects."
Overall, "there are great prospects for pediatric psychopharmacology," Walkup said. "We continue to push forward, but every once in a while we do experience unfair criticism and blindsiding from the media. We really believe we are doing something that is worthwhile and needs to be supported. Over time, I believe, we will win out, but clearly there are some times when it is a tough fight."

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