

From a trickle to a flood

Pipelines fill with psychotropics for children

Joseph DeVeugh-Geiss, MD

Head, CNS Division, Duke Clinical Research Institute
Consulting professor of psychiatry and behavioral sciences
Duke University School of Medicine, Durham, NC

Pediatric prescribing stands to gain as pharmaceutical companies develop new indications and drugs for younger patients.

Most psychotherapeutic drugs have been studied only in adults and are not approved for use in children and adolescents. Nevertheless, most drugs used in adult psychiatric treatment are widely prescribed to pediatric patients, and prescribing to this young population has increased dramatically (*Box*).¹⁻³

Without the benefit of efficacy and safety data, one must rely on anecdotal reports and clinical judgment when choosing medications and determining dosages for children and adolescents. That may be changing soon, as more pediatric information is becoming available on psychotherapeutic drugs approved for adults and on agents under development.

Limited industry attention to pediatrics

The evidence gap between adult and pediatric practice⁴ can be attributed partly to child and adolescent psychiatry lagging behind adult psychiatry in embracing psychopharmacologic treatments. The primary reason, however, has been the pharmaceutical industry's history of limited interest in studying pediatric populations.

[An unprecedented step](#). In 1986 at Ciba-Geigy, I and col-





Box 1

DESPITE LIMITED DATA, PEDIATRIC USE OF PSYCHOTROPICS IS GROWING

Researchers have documented a dramatic increase in psychotropic prescriptions to children and adolescents in recent years.

Olfson et al¹ reviewed national trends across 10 years. They found the overall annual rate of prescription of psychotherapeutic drugs to children increased from 1.4 per 100 children in 1987 to 3.9 per 100 in 1996. Stimulant and antidepressant drug prescriptions mostly accounted for this nearly threefold increase.

Rushton and Whitmire² reviewed a North Carolina Medicaid population and found the number of children prescribed stimulants increased from 6,407 in 1992 to 27,951 in 1998; the corresponding numbers for selective serotonin reuptake inhibitor (SSRI) prescriptions were 510 and 6,984. These represent a fourfold and greater than tenfold increase, respectively, across 7 years.

Zito et al³ reported increases of 1.3- to 3.1-fold for stimulant and antidepressant prescriptions to preschool children (aged 2 to 4) between 1991 and 1995 in three healthcare settings.

leagues Richard Katz, PhD, Phyllis Landau, MD, and Georges Moroz, MD, began developing clomipramine, the first drug approved in the United States to treat obsessive-compulsive disorder (OCD). Knowing that OCD onset is common in childhood or adolescence, we proposed doing a pediatric study concurrent with the adult studies that would provide the basis for regulatory approval.

This approach was unprecedented and was initially met with considerable resistance. Ultimately, however, Ciba-Geigy included the pediatric study in the drug development program. As a result, clomipramine became the first psychotropic drug to be simultaneously studied—and eventually approved—for children and adolescents as well as for adults.^{5,6}

Clinical development programs at other pharmaceutical companies followed suit when designing studies of selective serotonin reuptake inhibitors (SSRI) for OCD (SSRIs were just reaching the market as antidepres-

sants). In some programs, pediatric studies were done after initial successful studies in adults with OCD. Even so, the industry continued to show little interest in including children and adolescents in routine clinical development of new drugs or in seeking regulatory approval for this population. This changed several years later, thanks to initiatives from the National Institute of Mental Health (NIMH) and the Food and Drug Administration (FDA).

RUPP and beyond

During the 1990s, NIMH convened meetings with the American Academy of Child and Adolescent Psychiatry (AACAP) and others that brought together representatives from academia, government, industry, and clinical practice, as well as patient advocates.⁷ Attendees discussed the need for new drug development to treat psychiatric disorders in children and adolescents and the obstacles to be overcome for progress to occur. As a result, NIMH in 1996 established Research Units in Pediatric Psychopharmacology (RUPP).

RUPP is a network of centers of excellence in child and adolescent psychopharmacology based in academic medical centers. Its purpose is to provide definitive studies of psychotropic drugs that are being used routinely in children and adolescents and to provide an infrastructure to support complicated multicenter trials. RUPP's focus is practical, evaluating treatments used in clinical practice.

To date, RUPP has completed and reported the results of two significant studies:

- a trial of fluvoxamine in anxiety disorders,⁸
- and a trial of risperidone in autistic disorder.⁹

Other studies are under way, and RUPP has advanced the field substantially.

Even so, RUPP has limitations. Its network cannot conduct studies on all psychotropic drugs that are in use today, and it is not positioned to evaluate investigational drugs (in development but not yet approved).

As a result, RUPP's network can only partially satisfy psychiatrists' need for information to guide the prescribing of psychotropics to children and adolescents.

FDA initiatives. Concurrent with the NIMH efforts, the FDA implemented the Pediatric Rule of 1994, which applied to all classes of drugs that might be used in younger patients. Under this rule, pharmaceutical manufacturers:

More than 200 drugs are being developed for children, including 21 agents for psychiatric use

- were required to review existing data for using their drugs in a pediatric population
- could extrapolate efficacy data from adults to children, if the course of disease and effects of drug treatment were sufficiently similar in adult and pediatric patients and if appropriate pharmacokinetic and safety data were provided for younger patients.

The rule did not require them to conduct new studies to obtain labeling of products for pediatric use.

FDAMA. The FDA's next step was included in the FDA Modernization Act (FDAMA) of 1997, which allowed the agency to ask pharmaceutical manufacturers to generate safety and effectiveness data for drugs likely to be used in pediatrics. In exchange, manufacturers received 6 months' marketing exclusivity (in addition to existing patent protection) for those drugs.

Many companies did sponsor additional safety and efficacy studies, although the incentive's structure clearly favored drugs with high sales volume. For example, consider two products with annual sales of \$200 million and \$800 million, respectively. Six months of exclusive marketing rights would generate \$400 million in additional revenue from the \$800 million product—double the annual revenue of the \$200 million product. The pharmaceutical company could obtain this benefit even if total pediatric use were quite small because the 6 months of exclusivity applied to all product sales, including pediatric and adult use.

The FDAMA had several other weaknesses:

- A manufacturer could obtain its benefit even if studies failed to demonstrate the product's efficacy in the pediatric population.
- The regulation provided no incentive to develop pediatric data for drugs that had lost patent protection.
- It did not induce pharmaceutical companies to include pediatric studies early in drug development.

Final Pediatric Rule. These concerns led to FDA's Final Pediatric Rule of 1998, which requires pediatric studies:

- for all new chemical entities (drugs in development and not yet approved)
- and for development programs seeking new indications, dosage forms, treatment regimens, or routes of administration for approved products.

For drugs in early development, this rule allows data to be collected from pediatric studies well before the manufacturer submits a New Drug Application (NDA) seeking marketing

Box 2

**DRUGS IN DEVELOPMENT FOR CHILDREN,
AS REPORTED BY MANUFACTURERS**

- 32 drugs for cancer
- 24 vaccines
- 16 for cardiovascular disease
- 16 for cystic fibrosis
- 16 for infectious diseases
- 11 for psychiatric disorders**
- 11 for respiratory disorders
- 10 for AIDS
- 10 for asthma
- 10 for genetic disorders

Source: Pharmaceutical Research and Manufacturers of America¹⁰

approval. Information on the new drug's efficacy, safety, and prescribing for pediatric use will then be available when it is marketed or very shortly thereafter. For drugs in late-stage development and nearing approval, the required pediatric data might not be available as quickly because pediatric studies will be conducted long after the development program in adults.

Drugs in development

As a result of these regulatory changes, the Pharmaceutical Research and Manufacturers of America (PhRMA) reports that nearly 200 drugs and vaccines are in development for children, (Box 2). In addition to the 11 drugs identified by PhRMA for treating psychiatric disorders in children and adolescents, at least another 10 were in the pipeline through the first 6 months of 2002 (Table).¹¹ By the time you read this, some of the drugs may have been terminated from development, new drugs may have been added, and others will have emerged from the development process to receive FDA approval for pediatric use.

Indications. Among the 21 compounds listed in development for 10 different psychiatric indications, 16 are already approved for adult use. One—donepezil—is marketed for management of Alzheimer's dementia symptoms, but for children and adolescents the agent is being developed for treatment of attention-deficit/hyperactivity disorder (ADHD).

Four other approved drugs appear to be in development for new indications, including mania (topiramate), autism (secretin), Tourette's syndrome (mecamylamine), and ADHD (modafinil). Among the five new chemical entities (NCEs—



Table

PSYCHOTROPICS IN DEVELOPMENT FOR CHILDREN AND ADOLESCENTS, LISTED BY INDICATION

Indication	Drugs in development	Company
Attention-deficit/hyperactivity disorder	ABT-089	Abbott Laboratories
	Atomoxetine	Eli Lilly and Co.
	Donepezil	Eisai
	Mecamylamine	Layton BioScience, Inc.
	Methylphenidate	
	Attenade	Celgene
	MethylPatch	Noven Pharmaceuticals
	Ritalin QD	Novartis Pharmaceuticals
	Modafinil	Cephalon
SPD 420	Cortex Pharmaceuticals	
SPD 503	Shire Pharmaceuticals Group	
Depression	Fluoxetine	Eli Lilly and Co.
	Mirtazepine	Organon
	Nefazodone	Bristol-Myers Squibb Co.
	Sertraline	Pfizer
	Venlafaxine	Wyeth
Obsessive-compulsive disorder	Fluoxetine	Eli Lilly and Co.
	Fluvoxamine	Solvay Pharmaceuticals
	Sertraline	Pfizer
Anxiety	Busipirone	Bristol-Myers Squibb Co.
Tourette's syndrome	Mecamylamine	Layton BioScience Inc.
Schizophrenia	Risperidone	Johnson & Johnson Pharmaceutical Research and Development
Mania	Topiramate	Johnson & Johnson Pharmaceutical Research and Development
Autism	Secretin	Repligen
Posttraumatic stress disorder	Sertraline	Pfizer

investigational drugs not yet marketed with any indication), four appear to be in development for ADHD and one for a disorder of childhood listed only as behavioral disorders.

Development programs. Twenty-four development programs are geared toward creating medications for children and adolescents, including 10 for ADHD, 5 for depression, 3 for OCD, and 1 each for anxiety, Tourette's syndrome, schizophrenia, mania, autism, and posttraumatic stress disorder (PTSD). Nearly one-half these agents are already approved for similar indications in adults.

The pharmaceutical companies' decisions to conduct clinical trials in children and adolescents for this group of drugs may be attributable, to some extent, to incentives and the potential for financial gain. Whatever the reasons, the regulatory changes that stimulated this work will have accomplished their goal if they produce evidence of efficacy, safety, and tolerability of these marketed drugs in children and adolescents.

Noncommercial research. In addition to industry-sponsored drug development, much pediatric psychopharmacology research is also being conducted in academic and government settings. NIMH and the AACAP are sponsoring trials for a range of pediatric disorders, including ADHD, autism and other pervasive development disorders, bipolar disorder, body dysmorphic disorder, depression, OCD, PTSD, schizophrenia, social phobia, and Sydenham chorea.^{12,13}

Unmet needs

The breadth of indications being investigated in pediatric psychopharmacology

gy clinical trials shows that progress is being made. Missing are NCEs being developed for indications other than ADHD, but the FDA's Final Pediatric Rule does create the expectation that pediatric studies will be included in all future new drug development programs.

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 **Related resources**

- ▶ Food and Drug Administration pediatric Web site. <http://www.fda.gov/cder/pediatric>
- ▶ American Academy of Child and Adolescent Psychiatry. Pediatric Psychopharmacology Initiative. <http://www.aacap.org/research/ppi.htm>

DRUG BRAND NAMES

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|--|------------------------------|
| Busipirone • BuSpar | Mirtazapine • Remeron |
| Clomipramine • Anafranil | Modafinil • Provigil |
| Donepezil • Aricept | Nefazodone • Serzone |
| Fluoxetine • Prozac | R-methylphenidate • Attenade |
| Fluvoxamine • Luvox | Risperidone • Risperdal |
| Imipramine • Tofranil | Secretin • SecreFlo |
| Mecamylamine • Inversine | Sertraline • Zoloft |
| Methylphenidate • MethylPatch,
Ritalin QD | Topiramate • Topamax |
| | Venlafaxine • Effexor XR |

DISCLOSURE

The author reports that he receives grant/research support from Synaptic Pharmaceutical Corp., is a consultant to GlaxoSmithKline, Elan Corp., and Cytospect, and owns stock in GlaxoSmithKline. No GlaxoSmithKline products are mentioned in this article.

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The pace of drug development for psychiatric disorders in children has increased from a trickle to a steady flow of agents and indications in the pipeline. Psychiatrists can expect more data on drug efficacy, safety, and dosing for pediatric prescribing in the near future.

BottomLine

Have a case from which other psychiatrists can learn?

Check your patient files for a case that offers "lessons learned" and send it to pete.kelly@dowdenhealth.com. Keep it to 2,000 words, outlining history and treatment options, with interspersed commentary to reinforce the key points.

If you have questions before writing, check with Senior Editor Pete Kelly. Our Editorial Board and Case History Editor will review your article—and you'll hear from us soon.

