

Challenges to Pediatric Psychopharmacology

Psychopharmacology has revolutionized psychiatry during the 2nd half of this century. In the past 2 decades there has been a marked increase in the number of journal articles, chapters, and books on pediatric psychopharmacology (Campbell and others 1985; Simeon and Ferguson 1990; Simeon and Wiggins 1990; Werry and Aman 1993; Rosenberg and others 1994; Simeon and others 1995); a journal (*Journal of Child and Adolescent Psychopharmacology*) and a newsletter (*Child and Adolescent Psychopharmacology News*) are now devoted to this subject. Pediatric psychopharmacology research has resulted in an ever-increasing number of psychotropic drugs used in the therapy of child psychiatry patients, in increased numbers of children treated, and in a significant broadening of clinical indications. It has also contributed to significant progress in hypothesis testing, study design, development of interview techniques and rating scales, diagnostic classification, and pharmacokinetics. Psychotropic drugs have thus become not only therapeutic agents but also important tools in the study of the biological, behavioral, cognitive, and social manifestations of child growth and of various psychiatric disorders among children. The increasing acceptance of psychotropic drug therapy of children and adolescents by psychiatrists, pediatricians, and general practitioners has, however, been accompanied by growing concerns among therapists, parents, educators, regulatory agencies, and the public over the potential hazards of medications and of their prolonged use.

Progress in pediatric pharmacotherapy has been much slower than in adult pharmacotherapy, however. There are relatively few conclusive findings in the therapy of child and adolescent psychiatry disorders and few established indications for drug therapy. The paucity of placebo-controlled clinical studies has been due to a combination of factors, such as ethical and legal concerns about the well-being of children, resistance to the use of medication in children, and inadequate research funding of pediatric psychopharmacology. There are established indications for pharmacotherapy for attention deficit hyperactivity (ADHD) and conduct disorders, symptoms of childhood autism and other childhood

psychoses, Tourette's disorder, obsessive-compulsive disorder, and enuresis. There are as yet too many "probable" or "possible" indications based on open studies and case or anecdotal reports. For example, there are no established drug indications for the treatment of major depressive and dysthymic disorders; bipolar disorders; overanxious, panic, and separation anxiety disorders; eating disorders (anorexia and bulimia nervosa); and learning and language disorders. This lack stands in sharp contrast to the conclusive psychopharmacology findings for most of these disorders in adult patients.

The clinical practice of pediatric psychopharmacology is thus based on the rather limited research findings and on extrapolations from adult psychopharmacology. For example, antidepressant drugs are used for a variety of child and adolescent psychiatric disorders such as enuresis; insomnia and parasomnia; attention deficit, conduct, depressive, obsessive-compulsive, and panic disorders; school phobia; and bulimia. The majority of reported studies with children have used tricyclic compounds, particularly imipramine, to treat these patients. While antidepressants appear to have a role in the management of attention and/or conduct disorders, their more precise therapeutic profiles and indications require further research. Specifically, the role of antidepressants in separation anxiety as well as in panic disorder in adolescents needs to be investigated further.

A variety of childhood psychiatric disorders are treated with antipsychotic medications. In general, these drugs should be given only to very disturbed children or to those who have not responded to other types of medication. Most of the children receiving antipsychotic drugs in clinical practice are not psychotic. Antipsychotics are used for the relief of symptoms in children with various types of psychoses and to facilitate other forms of therapy, but their role in altering the basic course of a psychotic disorder is limited. These drugs are also used in the management of aggression, temper tantrums, psychomotor excitement, stereotypies, and hyperactivity unresponsive to other therapy. The efficacy of antipsychotics in autism is symptomatic and limited. Haloperidol

and pimozide, dopamine-blocking neuroleptics, are the most effective drugs in Tourette's disorder.

While benzodiazepines and other anxiolytics are used frequently in child psychiatry practice, data about their efficacy are very limited. This shortage of data is due to a lack of recognition of anxiety in children, the heterogeneity of clinical samples, the lack of reliable assessment methods, and the theoretical biases about the nature of childhood anxiety and its management. The probable indications for anxiolytics are insomnia, night waking, night terrors, and somnambulism, whereas anxiety is a possible indication.

Different psychotropic drugs are widely used to treat pathological aggression in children, but indications are vague and mechanisms of action unclear. Available findings demonstrate the efficacy of lithium in chronic aggressive conduct disorders, bipolar disorders, and periodic mood or behavior disorders in children who have a family history of bipolar disorder. Stimulants may reduce aggressive behavior in most hyperactive children. The therapeutic effects of anticonvulsants and propranolol in the management of aggressive behavior in children and adolescents are based on anecdotal evidence and on adult studies. The preliminary findings are promising, but they need to be investigated further.

The pharmacotherapy of childhood and adolescent psychiatric disorders is determined by a variety of medical as well as nonmedical factors. Significant factors that determine the type of research and use of psychotropic drugs in children and adolescents include the therapist's theoretical orientation, the availability of drugs and professional resources, regulatory guidelines, economics, prevailing public opinion, media attitudes, and parental cooperation and education. The fate of psychostimulant use in children is a good illustration of these problems. Since the discovery of the effects of benzedrine in hyperactive children 60 y ago, psychostimulants have been the best-investigated and the most useful pharmacotherapy of ADHD and yet, possibly because of their popularity, controversies about their use appear to have grown. In many countries outside North America, psychostimulants are either not marketed, not available, or seldom prescribed for ADHD.

Many psychiatric disorders, such as attention deficit, oppositional, and conduct disorders, autism, separation anxiety, specific developmental (learning) disorders, enuresis, parasomnias, and anorexia nervosa, occur 1st or predominantly in children and adolescents. Since there are either no comparable or adequate models of these disorders in adult psychiatry, clinical trials in children and adolescents with already marketed and new investigational drugs are essential. Unfortunately, most psychiatric disorders in children and adolescents persist into adulthood and have a high prevalence (for

example, attention deficit and conduct disorders, affective disorders, eating disorders, anxiety disorders, obsessive-compulsive disorders), often leading to suicide or substance abuse and resulting in high costs to and suffering of the individual, his or her family, and society.

Psychotropic drug effects and indications in children and adolescents often differ significantly from those seen in adults. There are also significant age differences in drug-induced adverse effects. For example, in contrast to adults, children more commonly experience neuroleptic-induced dystonias, withdrawal dyskinesias, and cardiovascular changes, while akathisia due to neuroleptics is rare among children, and dysphoria—not euphoria—is associated with dextroamphetamine use. The evaluation of the therapeutic and adverse effects of psychotropic drugs in children, therefore, is extremely complicated and is based more on a symptomatic than a disease model. Maladaptive behaviors due to variations of temperament or interactions with the environment, comorbidity, and the evolving clinical manifestations of child psychiatry disorders necessitate careful and frequent reevaluations of pharmacotherapy. Significant placebo and halo effects on the child, parents, teachers, and therapists can also make the interpretation of the usefulness of drug therapy difficult. For example, placebo-controlled studies of antidepressants in the therapy of major depressive disorders in children and adolescents have generally indicated that drugs are not more effective than placebo. Yet the use of antidepressants in this population is a widespread, often standard, practice. Thus extrapolations of findings from adult to child psychopharmacology can be difficult, misleading, or irrelevant. Even for established drug indications in children, clinicians are often confronted with unresolved questions, such as how early in life to start drug therapy and when it is safe to stop.

The rapid advances in the fields of genetics and neurosciences may soon determine the biological and clinical predictors of mental illness. A greater knowledge, however, will also impose major new ethical dilemmas on consumers, therapists, and society; should a child at a high risk for developing schizophrenia or bipolar illness or for completing suicide receive prophylactic pharmacotherapy as soon as the risks are identified in the hope of preventing or arresting the disorder, or should treatment be delayed? Would it be malpractice if the patient meanwhile developed the disorder?

An important limitation for the use of psychotropic drugs in children is that the vast majority of product monographs lack specific safety, efficacy, or dosage information for children, in spite of the frequent use of these drugs in clinical settings. Most marketed psychotropic drugs are not evaluated for safety and efficacy for use in child and adolescent psychiatric disorders. The paucity of research data in pediatric

psychopharmacology thus contributes to the treatment of many children with untested or unsafe medications, while many others are deprived from potentially useful drug therapies. Current drug treatment practices in child psychiatry in Canada, the United States of America (USA), and many other countries have raised serious concerns and controversies among therapists, consumers, and government regulatory agencies. As a response to these concerns, important initiatives have recently been undertaken. For example, the National Institute of Mental Health and the Food and Drug Administration in the USA have recommended that during the process of new drug development, medications likely to be prescribed to children and adolescents should be tested in pediatric age groups before the drug is marketed for use in adults. The Health Protection Branch in Canada has recommended that manufacturers of those drugs for which proper documentation is lacking or insufficient be asked to consider conducting clinical trials to establish appropriate efficacy and safety information for the pediatric population.

A concerted national and international collaborative effort in public education, professional training, and multidisciplinary research is a priority. This goal can be achieved only if mechanisms are developed to fund educational, training, and pediatric psychopharmacology programs. Pediatric psychopharmacology should bring into focus the joint efforts of basic scientists, clinicians, the industry, granting, and government agencies to develop and implement safe and effective drug therapies. Recent advances in noninvasive techniques may greatly contribute to our understanding of the complex maturational changes of the various neurotransmitter systems and of the developmental aspects of pharmacokinetics and pharmacodynamics. The application of pharmacoepidemiology and pharmacoeconomics to the study of mental health in children and adolescents can also further advance the quality of their lives. The pharmaceutical

industry should play an essential role in supporting all such programs, beyond the funding of individual drug trials. It is essential, however, that child psychiatrists reach a greater consensus on diagnoses and treatments based on empirical criteria, resolve conflicting differences of theoretical orientation and traditional beliefs, and learn how best to integrate drug therapy with other treatment modalities to achieve the most benefit for their patients.

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