

Practical child and adolescent psychopharmacology



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Child and adolescent psychopharmacology at the turn of the millennium

Charles W. Popper

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Child and adolescent psychopharmacology is a leading edge of pediatric psychiatry and is rapidly growing. It has not always been this way.

Child and adolescent psychopharmacology essentially began in 1937, when Bradley reported that some children with behavior disorders showed a seemingly paradoxical improvement during treatment with racemic amphetamine (Benzedrine), which he had exploratorily used to treat 30 mostly preadolescent children in a residential treatment facility (Bradley, 1937). For over 60 years, psychostimulant treatment has basically remained unchanged. The characteristics of stimulant-responsive children have been studied and refined over the decades, and (what is currently called) attention-deficit/hyperactivity disorder (ADHD) has become the psychiatric model or prototype disorder for the medication treatment of children.

The prototype treatment: psychostimulants for ADHD

Throughout its existence, psychostimulant treatment has also been the prototype treatment used to express uneasiness about children receiving psychiatric medications. Although fully established scientifically, at least as much as antibiotic treatment, psychostimulant treatment is still controversial in some quarters. Concerns include trepidation about the inappropriate management of children in schools and homes, chemical control of children's minds and behaviors, poisoning of children's bodies, excessive dosing of medication, overmedicalization of child care, departure from the psychoanalytic or child guidance model, inadequate emphasis on the psychosocial themes, inappropriate attempts to find surrogates for adequate staffing and supervision, and social and psychological stigmatization.

Despite such misgivings, Bradley's approach has evolved into the widespread use of various psychostimulants to treat children with ADHD.

Psychostimulant treatment is no longer viewed as paradoxical, although there are many paradoxical aspects of this treatment. ADHD is one of the most thoroughly studied psychiatric disorders, but its pathophysiology is only roughly understood in terms of neuroanatomic chemistry. Psychostimulants appear to remain effective for years and even decades, but psychostimulants have only recently been demonstrated to sustain improvement over a period of 14–15 months (Arnold et al., 1997; Gillberg et al., 1997; The MTA Cooperative Group, 1999a,b), and longer-term treatment has still not been investigated in a controlled manner. Although ADHD is the most robust of syndromes in child and adolescent psychiatry, most children with ADHD are now recognized to have additional concurrent biopsychiatric disorders.

Even with successful drug treatment, stimulant monotherapy is often not sufficient for optimal outcome. For many individuals, psychostimulants need to be combined with additional psychopharmacologic agents in order to have clinically adequate effects.

The strategy of treating psychopathology with combinations of psychiatric drugs can be used to “tickle” multiple neuronal systems that underlie different clinical presentations. Yet, as treatment of ADHD becomes more complex, the psychostimulants remain the central element.

For many, and probably most, children with ADHD, concurrent educational interventions are needed to remediate the delayed acquisition of learned skills, including social skills, responsiveness to limits, behavioral self-discipline, persistence in effortful activities, self-correcting behavior, study skills, and enjoyment of calmness and quiet pleasures.

Although educational interventions combined with psychostimulants are often helpful, the multimodal combination of psychosocial intervention with psychostimulants may not be more advantageous than psychostimulant drugs alone for treating the core symptoms of ADHD (inattention and impulsivity/hyperactivity). Several studies have indicated that multimodal psychopharmacologic–psychosocial treatment, at least under some circumstances, is not (or only slightly) more effective than stimulant monotherapy for treating the core symptoms of ADHD, but may be more effective for treating features often associated with ADHD, such as academic underperformance, impaired social skills, oppositionality, and aggressivity (Gittelman Klein et al., 1976; Carlson et al., 1992; Ialongo et al., 1993; Pelham et al., 1993; MTA 1999a,b). It is possible that combination treatment might be more effective if inadequate stimulant doses or ineffective psychosocial treatments are used; however, it offers little more than stimulant monotherapy under conditions of optimal or appropriate treatment. Speculatively, though, further refinement

of the psychosocial treatments might produce a more potent combination.

Over 150 double-blind placebo-controlled studies have demonstrated the efficacy of psychostimulants for both the cognitive and behavioral symptoms of ADHD (Spencer et al., 1996). In addition to psychostimulants, at least 13 different investigative groups over the last 35 years have conducted double-blind placebo-controlled studies demonstrating the clinical efficacy of tricyclic antidepressants (TCAs) such as imipramine, desipramine, and amitriptyline for treating ADHD (Krakowski, 1965; Winsberg et al., 1972; Rapoport et al., 1974; Waizer et al., 1974; Kupietz and Balka, 1976; Yepes et al., 1977; Yellin et al., 1978; Werry et al., 1980; Garfinkel et al., 1983; Donnelly et al., 1986; Gualtieri and Evans, 1988; Biederman et al., 1989a,b; Gualtieri et al., 1991; Singer et al., 1995). Although TCAs are relatively useful in treating impulsivity and hyperactivity, they are less helpful for cognitive features of the disorder.

More than 60 years following their introduction, psychostimulants remain the treatment of choice for ADHD, partially because of their solid effectiveness in treating the behavioral symptoms and especially because of their unmatched effectiveness in ameliorating the cognitive symptoms. In some ways, child and adolescent psychopharmacology has never again reached the peak attainment of its original treatment. No subsequent medication has equaled the psychostimulants for relative diagnostic specificity, target symptom specificity, strength of response, sustained effectiveness over time, the large proportion of patients who respond therapeutically, or the huge number of patients who have benefited from its use.

Evolution of child and adolescent psychopharmacology

The 1930s marked the beginning of modern child psychopharmacology, a time when few validated psychosocial or drug treatments were available even for adults. Not one of the present-day pharmacotherapies for psychiatric disorders was described in the first textbook of child psychiatry (Kanner, 1935), which advised against using “toxics and sedatives” to control children’s behavior. Two years later, the original papers on amphetamine treatment of behavior disorders of children (Bradley, 1937) were published. In the same year (in fact, in the same issue of the *American Journal of Psychiatry*), the finding that this drug treatment also improved cognitive functioning in the children and adolescents was reported independently by Molitch and colleagues (Molitch and Eccles, 1937; Molitch and Sullivan, 1937). Two years later, paradoxical phenobarbital-induced excitation was described in children with behavioral disorders (Cutts and Jasper, 1939).

In the 1940s, psychostimulants were examined more extensively in children by Bradley and independently by Lauretta Bender (Bradley and Bowen, 1940; Bradley and Green, 1940; Bradley, 1941; Bradley and Bowen, 1941; Bender and Cottingham, 1942). By the end of the decade, Bradley had treated 350 preadolescent children with psychostimulants (Bradley, 1950), essentially confirming the earlier findings and spelling out the major features of this treatment. The anticonvulsant phenytoin was reported to help some children with behavior disorders (Brown and Solomon, 1942; Lindsley and Henry, 1942; Walker and Kirkpatrick, 1947). Studies in the 1940s were largely focused on hyperactive children with brain damage, cerebral dysfunction, and developmental disorders.

In the 1950s, the biologic revolution in psychiatry began with the initial appearance of antipsychotic and antidepressant agents and a growth spurt of psychopharmacologic research in adults. Chlorpromazine was initially synthesized in 1950 and was reported to have antipsychotic properties in adults in 1952. The first anecdotal description of its use in children was published in 1953 (Heuyer et al., 1953) regarding six children and adolescents (ages 5–14) with psychosis and agitation treated with chlorpromazine in doses up to 2 mg/kg. There were seven additional reports on chlorpromazine for youths in 1955, including a placebo-controlled study of 195 hospitalized children with mixed diagnoses who were treated with doses of 30–100 mg (Freedman et al., 1955). A partial-blind placebo-crossover study was reported the following year (Hunt et al., 1956). Also during the 1950s, the treatment of childhood behavior disorders with diphenhydramine (Effron and Freedman, 1953; Freedman et al., 1955) and meprobamate (Litchfield, 1957; Kraft et al., 1959) was first described, and monoamine oxidase inhibitors (MAOIs) were reported to increase awareness and language production in children with autistic disorder (Freedman, 1958). Reserpine was found to be effective in reducing symptoms of irritable and hypertonic infants (Talbot, 1955). The first review article in the field was published by Freedman et al., 1955. The first National Institute of Mental Health (NIMH) grant in child psychopharmacology was awarded in 1958 to Leon Eisenberg, largely because of his careful methodology, to examine perphenazine treatment of hyperactive children (Eisenberg et al., 1961).

The 1960s were a time of large-scale expansion of treatment and research in pedipsychopharmacology. TCAs were first reported to be useful in treating enuresis (MacLean, 1960; Poussaint and Ditman, 1965), ADHD (Krakowski, 1965; Rapoport, 1965), and, seemingly, childhood depression (Lucas et al., 1965; Frommer, 1972). MAOIs were described for treating depressive (Frommer, 1967) and phobic disorders (Kelly et al., 1970) in children. Barbara Fish began to

report on various neuroleptics and diphenhydramine, including comparison studies, in hospitalized children with autistic disorder (Fish, 1960a,b). Neuroleptics were first described to treat children with Tourette's disorder (Chalas and Brauer, 1963; Chapel et al., 1964; Lucas, 1964). Chlordiazepoxide was used clinically (Skynner, 1961) and studied in 130 children (2–17 years old) with mixed diagnoses who were treated with doses of 30–130 mg daily (Kraft et al., 1965). Ansell first reported on lithium treatment in a series of children (Ansell, 1969a,b), although a single case report had been published previously (Van Krevelen and Van Voorst, 1959). These adventurous times also included some forays by Lauretta Bender into LSD (lysergic acid diethylamide) treatment of children with autistic disorder. Conducted with an intent to “break through the autistic defenses of severely [disturbed] children,” LSD was reported to heighten mood, increase alertness and awareness of reality, improve eye contact and interpersonal responsiveness, and reduce stereotypies, headbanging, and self-injurious behavior without causing psychotic reactions or significant adverse effects (Bender et al., 1962; Bender 1966). Keith Connors, Gabrielle Weiss, and John Werry were leaders in bringing pediatric psychopharmacology research on ADHD to a higher plane of methodologic rigor and moving it into the scientific age.

Despite the accelerating pace of child psychopharmacologic research, practitioners in the 1960s remained cautious and, in retrospect, overprotective. Medication treatments were viewed as palliative, and clinicians raised concerns over the potential for medication treatments to disrupt psychoanalytically oriented psychotherapies, interfere with a child's developing sense of self-control and responsibility, foster psychologic and physical dependence on medications, promote or induce drug abuse, expose small vulnerable beings to dangerous medications, and lead to over-reliance on medications to the exclusion of other coping strategies and interventions. These unfounded fears were part of more general doubts about biologic formulations by physicians and simplistic thinking by patients (Robinowitz and Wiener, 1990).

In the 1970s, there was another quantum jump in the quantity and quality of psychopharmacotherapy research in youth. Howard Abikoff, Michael Aman, Eugene Arnold, Russell Barkley, Magda Campbell, Dennis Cantwell, Gabrielle Carlson, David Engelhardt, Kenneth Gadow, Laurence Greenhill, Rachel (Gittelman) Klein, William Pelham, Judith Rapoport, Daniel Safer, Robert Sprague, James Swanson, and Paul Wender began their careers and wide-ranging contributions to the field. Imipramine was reported to appear effective in treating children with school phobia and separation anxiety (Gittelman-Klein and Klein, 1971, 1973). Carbamazepine was first used to treat nonepileptic children with

behavior disorders (Puente, 1976; Remschmidt, 1976), and propranolol was introduced for treating children with brain damage or neurologic abnormalities (Schreier, 1979; Williams et al., 1982). Anecdotal reports on the use of antidepressants and lithium in children were occasionally published, but there was little systematic progress on treating mood disorders in youth, and many clinicians maintained doubt about whether mood disorders even existed in children. The NIMH in the United States held a consensus conference in 1977 which concluded that depression does in fact appear in children, but it could not agree on a definition, and a minority statement dissented with the conclusion that childhood depression exists (Schulterbrandt and Raskin, 1977). Moreover, the budding use of antidepressants was dampened by the report of a fatality (Saraf et al., 1974) in a 6-year-old child being treated with imipramine 15 mg/kg daily, a markedly excessive dose by today's standards and administered prior to the now routine use of electrocardiography (Saraf et al., 1978) to monitor cardiac conduction.

The year 1978 turned out to be a landmark in child and adolescent psychiatry and psychopharmacology. Kim Puig-Antich and colleagues issued an initial report suggesting that a substantial number of children with major depressive disorder, defined by *Diagnostic and Statistical Manual of Mental Disorders, Second Edition* (American Psychiatric Association, 1975) criteria formulated for adults, improved clinically when treated with imipramine (Puig-Antich et al., 1978). Puig-Antich also noted that these children often had concurrent separation anxiety disorder and that both syndromes appeared to improve with imipramine treatment, echoing the earlier findings of Rachel and Donald Klein, who used a more rigorous design in examining separation anxiety (Gittelman-Klein and Klein, 1971, 1973). Puig-Antich's study was historically pivotal in launching the ongoing surge in the use of psychopharmacologic agents in children, by bringing attention to the potential treatability of childhood depression. Ironically, this finding did not hold up to replication (Puig-Antich et al., 1987) and was not supported by many subsequent controlled trials with various TCAs (Jensen and Elliott, 1992). Toward the end of the decade, clonidine was first introduced for treating Tourette's disorder (Cohen et al., 1979, 1980).

At the start of the 1980s, the general use of these treatments was still quite limited, largely because psychostimulants remained the only child psychopharmacotherapy with well-demonstrated efficacy. Most residency training programs in child psychiatry taught about psychostimulants but not other medications. Many programs discouraged the use of any psychiatric medications in children, partly due to the dearth of scientific knowledge and partly due

to unscientific reasoning and historical tradition, but certainly not out of a lack of well-controlled demonstrations of psychostimulant efficacy. Antipsychotic agents were becoming less stigmatized and were generally used for psychotic disorders and some cases of severe impulsivity. TCAs were employed sparingly, but, over the course of the decade, clinicians gradually became comfortable in using TCA treatments, predominantly for major depression and separation anxiety disorder, as psychopharmacologic research on these disorders expanded. Lithium therapy remained uncommon. At mid-decade, a major third-party carrier in the United States was still refusing to pay for lithium treatment, even for hospitalized children, on the grounds that it was too experimental. By the end of the decade, though, a child with bipolar disorder was featured on the videotaped section of the national board examinations in child psychiatry in the United States. Clonidine, which quickly became a common treatment for Tourette's syndrome, began to be used to treat ADHD (Hunt et al., 1985), but the psychostimulants remained by far the most predominantly prescribed psychiatric medication for children.

In parallel with the expansion of psychopharmacologic research in children and adolescents, the clinical use of these treatments became increasingly prevalent during the mid-1980s. By the end of the decade, these treatments had spread far beyond the confines of university clinics, but their widespread use was not based on solid scientific documentation of their safety or efficacy. The extensive use of child psychopharmacologic treatments without adequate documentation in the medical literature became commonplace.

In the 1990s, child and adolescent psychopharmacologic treatment entered everyday psychiatric practice. Its speedy expansion led drug treatment, alongside and integrated with psychosocial interventions, to become the prevailing approach in child psychiatry by the mid-1990s. The use of psychostimulants in youth more than doubled between 1990 and 1995 (Safer et al., 1996; Zito et al., 1998). The shift from TCAs toward specific serotonin reuptake inhibitors (SSRIs) for treating children (Ambrosini et al., 1995) proceeded contemporaneously with their swift deployment in adults and, concurrently, the accumulation of studies on TCAs showed their ineffectiveness in treating childhood depression. The newly introduced SSRIs rapidly became the most commonly used child psychopharmacologic treatment, the first time that another medication had surpassed the psychostimulants in prevalence of use. Despite two initially negative studies of SSRI treatment in childhood depression (Simeon et al., 1990; Mandoki et al., 1997), a large-scale study of fluoxetine became the first demonstration of the value of SSRIs for treating children with major depressive episodes (Emslie et al., 1997, 1998). Toward the end of the decade,

the first and only randomized double-blind, placebo-controlled trial of lithium in treating bipolar disorder in youth yielded a positive outcome (Geller et al., 1998a). This study also showed that lithium reduced the associated substance-related disorders that appeared during bipolar episodes in those adolescents. In addition, the efficacy of lithium was first demonstrated for treating major depressive disorder in preadolescents who had a family history of bipolar disorder (Geller et al., 1998b). Other mood stabilizers (Ryan et al., 1999), atypical antipsychotics (Toren et al., 1998), and novel antidepressants became routine treatments during the 1990s, despite a relatively small amount of research in youth.

Even at present, and despite the widespread use of psychiatric medications in youth, few child psychopharmacologic treatments have been rigorously demonstrated to have efficacy in formal well-designed and well-controlled studies, efficiency in large populations treated in naturalistic clinical settings, or safety in short-term or long-term use.

Changing prescribing philosophies

Lifting the taboo

The long-standing taboo on psychopharmacologic “experimentation” in children, which had dominated the clinical practice of child and adolescent psychiatry, all but disappeared in the late 1980s. The taboo had long been used to justify reliance on psychodynamic treatments, which then viewed medications primarily in terms of hazards. Only in recent years did psychopharmacologic research come to be viewed as presenting important benefits to youth and not merely risks. It was increasingly recognized that studies in adults were not adequate for extrapolation to children and that the systematic avoidance of innovative treatments for youths was depriving them of important opportunities. Most crucially, clinicians became aware that the current generation of children and adolescents were still missing out on the benefits of the biologic revolution.

With the continuing expansion of empirical psychopharmacologic treatment of youth in the 1990s, a type of caution previously exercised by most child and adolescent psychiatrists began to break down and was gradually abandoned. Traditionally, newly developed medications were not generally used for treating children with psychiatric disorders until there was a clear “track record” of their safety and clinical effectiveness in adults, a process that typically required at least several years (Popper, 1987b). This protective strategy began to wear thin with the introduction of the SSRIs, because they offered a clear improve-

ment in effectiveness, tolerability, and adverse effects over the previously available antidepressants. With the SSRIs, for the first time, it took only about 1–2 years after the initial commercial introduction of a new drug class in the United States for it to begin to be used in significant numbers in American youths (and, once again, prior to documentation of pediatric efficacy). Concurrently, in the early 1990s, atypical neuroleptics were introduced in the United States and were almost immediately employed for treating children with Tourette's syndrome, autistic disorder, and psychotic disorders.

In addition, there was a shift in approach from "least restrictive" and "lowest effective dose" treatments to "most effective" treatment. The change in level of "caution" reflected the increasing comfort and decreasing rigidity of clinicians employing pedipsychopharmacologic methods.

Confronting clinical uncertainty

The scientific and clinical unknowns in child psychopharmacology remain quite broad. There is little available detail on the biochemical development of the brain (especially in humans), drug disposition in children, developmental changes in the responses of target sites of drug action, or developmental differences in drug neurotoxicity (Popper, 1987a). Ethical and legal implications of child psychopharmacologic treatments, the integration of drug and psychosocial child therapies, and the psychotherapeutic implications of these treatments remain poorly understood. However, for better and for worse, current clinical attitudes no longer regard this lack of knowledge as a major obstacle to the use of these medication treatments in children. Instead, it has been customary to view this paucity of information as a challenge requiring child and adolescent psychiatrists to update the field while practicing it.

In this situation, clinicians are attuned to watch carefully for potential adverse effects and complications. Exercising such caution in the face of uncertainty, they may be less likely to consider the possibility that some unknown drug effects may be therapeutic. We know from preclinical investigations that psychopharmacologic agents can cause beneficial as well as untoward influences on the central nervous system during development. For example, a medication treatment for acute symptoms might speculatively also delay or reverse brain degeneration associated with a psychiatric disorder. We must realize that potentially serious adverse effects will surely continue to be uncovered in children, but we should also expect currently unknown beneficial drug effects to emerge. The promise of new findings on drug effects, both good and bad, remains an essential part of this field. Despite the scientific unknowns and ethical dilemmas (and impasses), parents and practitioners appear willing

to take chances – because they judge that the risks of child psychiatric disorders themselves appear, in general, to exceed the risks of the child psychopharmacologic treatments (Popper, 1987b).

The rise of therapeutic empiricism

The case for delaying the use of these treatments until their safety and efficacy are formally demonstrated is logically strong, but compellingly impractical. Such studies would take years or decades to produce results, and the seemingly logical “conservative” approach would prevent the current generation of youths from receiving the new and generally improved modern methods of psychiatric treatment.

Empirical treatments have, then, proceeded in concert with studies of efficacy and tolerability, and eventually a selection of “older” treatments can be based on scientific grounds. In psychiatry now, and in pediatrics, research empiricism supplements and augments therapeutic empiricism in clinical practice in developing old drugs for new uses. In contrast, new drugs for initial applications cannot be introduced until they have scientifically demonstrable safety and (in at least some indications) demonstrable value.

The preoccupation of child psychiatry with psychoanalysis has given way to a more eclectic and empirical clinical methodology. The former tension between the biologic and psychodynamic conceptualizations, for many years viewed as a substantive division in theoretical understanding and choice in treatment selection, has essentially dissolved. This resolution has allowed these approaches to become coupled and integrated in clinicians’ work.

Unified biologic and psychosocial treatment has now become the “standard of care” for most if not all psychiatric disorders of youth. Specific questions about how to balance these treatments are being worked out empirically in clinical practice and research. Therapeutic empiricism (Popper, 1990) has become the watchword by which clinicians decide when to treat and when to delay the use of medication and psychosocial treatments.

At the turn of the millennium, clinical knowledge and know-how in psychopharmacology is surprisingly widespread among everyday practitioners. There is increasingly broad, deep, large-scale, and well-funded research in child psychopharmacology, which is now a focus of substantive government effort and financial support. The general discussion and sophisticated questions at national and local conferences demonstrate how extensively child and adolescent psychopharmacology is practiced and understood by large numbers of psychiatrists.

New trends

Excessive use

Public fears of rampant overmedication of children are quite understandable and hardly unjustified. In 1970, the Washington Post erroneously reported that 5–10% of public school students in Omaha were being treated with stimulants (Maynard, 1970), a revelation that was generally viewed as scandalous. More recently, a careful study examining about 30 000 students in two cities found an 8–10% prevalence of drug treatment for ADHD, with the highest rate, among white boys in fifth grade, at 18–20% (LeFever et al., 1999). Such high rates do not imply generalized overtreatment. It is well known that the use of child psychopharmacologic treatments varies drastically among nations, regional divisions, cities, medical schools, clinics, and individual physicians (Gadow, 1997).

In fact, the under-use as well as over-use of psychiatric medications remains a prominent current problem – if over-use means treatment of children who do not have the relevant disorder or need medication, and if under-use means failure to treat youths whose disorders are best treated with medications. Numerous studies have indicated that concerns about massive overmedication are unfounded; even at present, undertreatment appears to be more of a problem than overtreatment (Jensen et al., 1999). Debates about overtreatment and undertreatment, both in individuals and in populations, highlight the perennial uncertainty and endless process of revision throughout medicine, so practitioners in child and adolescent psychopharmacology can anticipate this to be an ongoing source of tension for decades to come.

Money-oriented medicine

Some nations have learned to administer health care in a relatively altruistic and cost-effective manner, but the system of health care in the United States has become dominated by financial rather than medical management. Financially managed medicine is a direct result of the historical inability of physicians to control prices or provide for the needs of the whole population. Caps on costs, often at the expense of quality, have influenced all aspects of medicine, including psychopharmacotherapy, psychosocial treatment, and psycho-management, with equally injurious effects.

Evidence-based medicine, a force emerging from the combined efforts of third-party commercialism and scientific academicism, emphasizes science as the basis for sound or improved practice (Evidence-Based Medicine Working Group, 1992). However, overly rigid use of evidence-based medicine could present a threat to the valuable benefits yielded by therapeutic empiricism for

psychiatric and general medical treatment. Given the major gaps in the evidence base, especially in child psychiatry, many common clinical decisions must be made on the basis of less rigorous evidence, including qualitative data (Graham, 2000) and clinical practice surveys (Hickie et al., 1999).

The risks of evidence-based psychiatry are particularly striking when combined with overly zealous financial management (Berk and Janet, 1999). It is commonly believed that financially based medicine, unless repaired, will lead to “bargains” that weaken and eventually bankrupt the system of care.

Third-party managers, questioning the value of the initial psychiatric comprehensive evaluation, have managed to fund clinical evaluations that are shorter than is medically necessary. A thorough child psychiatric/psychopharmacologic evaluation may take 4–7 hours, yet managed care in the United States pays for and expects physicians to make treatment decisions after one hour or less of psychiatric assessment. Shorter evaluations may be hypothetically more cost-effective, but longer evaluations are almost certainly more likely to identify multiple diagnoses, anticipate problems, and avoid setbacks.

Evidence-based medicine applies mainly to the needs of the “‘average’ randomized patient” (Feinstein and Horwitz, 1997), leaving others out. In any case, there is little evidence supporting the value of strict evidence-based medicine vs. therapeutic empiricism. Even when there are differences in treatment outcome, they may not be clinically significant. The relative usefulness of these two approaches will be decided empirically, with luck by an equitable balance of medical and administrative research.

Changing training programs

Psychopharmacology in residency training programs went from being a luxury frill in 1985 to a staple component in 10 years. Most residents in child psychiatry in the United States are now finishing their training with substantial experience in psychopharmacologic techniques, supplementing other clinical skills. Even for the most biologically oriented trainees, it quickly becomes clear in actual practice that prescribers must talk to children, engage their cooperation in treatment, promote their self-observation and awareness of treatment effects, educate them and their families about psychiatric disorders and interventions, and be prepared to respond effectively to a wide range of potential psychosocial barriers to treatment.

Despite the increasing reliance on diagnosis, the gradual de-emphasis of developmental principles in treatment, the decreasing reliance on one-to-one psychodynamic therapies, and the floating of responsibility for individual child psychiatric patients among multiple types of therapists, most residents in child

and adolescent psychiatry continue to be trained in psychopharmacology in a manner that promotes a multifaceted approach to treatment.

Academic child and adolescent psychopharmacology

Academic medicine continues to provide critical leadership in training and research, and has maintained a superlative record of creating and adapting to new developments in concepts and treatments, but some features of the traditional disdain toward the clinical observations made by nonuniversity practitioners and individual clinicians' observations have lingered. Nonetheless, in child and adolescent psychopharmacology, as in other fields of medicine, clinical knowledge grows largely by nonacademic mechanisms. In the United States, pedipsychopharmacology is a model medical field whose information explosion has been largely fueled by the empirical observations made by clinicians and whose new findings are rapidly expressed in the daily practice of clinicians throughout the country.

Academic research in child and adolescent psychopharmacology consists mainly of controlled clinical trials of medications already in general use, early phase testing of drugs recently marketed or soon to be marketed, neurochemical investigations of children with defined biopsychiatric disorders, and studies in developmental neurobiology. For the most part, ideas for new applications of "old" medications are generated by clinicians in the field.

The pace of child psychopharmacologic innovation and academic research is continuing to intensify. The rapid growth of investigation is reflected in the numbers of double-blind placebo-controlled studies, long-term and follow-up research designs, multisite studies, well-organized research departments, specialized research units in pediatric psychopharmacology (RUPPs), young and established contributors, larger case series, original research articles, and medical journals publishing articles on child psychopharmacology.

Over forty books whose titles indicate a major focus on child and adolescent psychopharmacology have appeared in English over the last five decades, including textbooks, monographs, trade books, periodicals (except medical journals), and "book-like" special issues of medical journals. Unsurprisingly, the number of such publications has been accelerating: one book in the 1950s, one in the 1960s, 13 in the 1970s, 15 in the 1980s, 23 in the 1990s, and two so far in the 00s (Fisher, 1959; Freed, 1962; Blanco, 1972; National Institute of Mental Health, 1973; Connors, 1974; Gittelman-Klein, 1975; Spiel, 1976; Bosco and Robin, 1977; White, 1977; Wiener, 1977; Mendlewicz and van Praag, 1978; Werry, 1978; Cohen, 1979; Food and Drug Administration, 1979; Gadow, 1979; Klein et al., 1980; Gadow and Gadow, 1981; Raskin et al., 1981; Scruggs et al.,

1982; Nissen et al., 1984; Campbell et al., 1985; Rapoport et al., 1985; Wiener, 1985; Gadow, 1986a,b; Krasnegor et al., 1986; Popper, 1987; Voss, 1987; Aman and Singh, 1988; Gadow and Poling, 1988; Rothenberger, 1990; Weizman and Weizman, 1990; Green, 1991; Greenhill and Osman, 1991; Shaffer, 1992; Van Hasselt and Hersen, 1993; Werry and Aman, 1993; Rosenberg et al., 1994; Green, 1995; Richardson and Haugland, 1995; Riddle, 1995; Theesen, 1995; Wiener, 1995; Kutcher, 1997; Reiss and Aman, 1997; Rosenberg et al., 1997; Findling and Blumer, 1998; Roemmelt, 1998; Walsh, 1998; Wilens, 1998; Dulcan and Benton, 1999; Greenhill and Osman, 1999; Werry and Aman, 1999; Nutt, 2000; Kutcher, 2001).

About 100–150 papers are now published annually on child and adolescent psychopharmacologic treatment, in addition to about another 50–75 studies on other biodevelopmental aspects of pediatric psychiatry. About 80% of these articles are published in two peer-reviewed journals. The *Journal of Child and Adolescent Psychopharmacology*, which turned 10 years old in 2000, is the first medical journal to focus specifically on pharmacologic and biologic aspects of child and adolescent psychiatry. The *Journal of the American Academy of Child and Adolescent Psychiatry*, the long-established central journal in the field, is now publishing about 20% of its articles on clinical psychopharmacology. The *Child and Adolescent Psychopharmacology Newsletter*, founded and edited by Stanley Kutcher since 1997, has become a widely read update and review (Kutcher, 1997). The *Brown University Child and Adolescent Psychopharmacology Update*, edited by Henrietta Leonard, has been published since 1999 (Leonard, 1999). In addition, a child and adolescent psychopharmacology discussion group (listserv) on the Internet has over 225 subscribers on its mailing list; it can be accessed through CHILD-PHARM@MAELSTROM.ST JOHNS.EDU or its moderator (raybehr@sprynet.com).

Beyond quantitative expansion, the quality of funded research has been keeping pace with the expansion of the field. Controlled studies increasingly examine carefully specified populations with systematically assessed diagnoses, explicit clinical inclusion and exclusion criteria, specified comorbidity, multiple observers and observation techniques, a range of clinical outcome measures, and advanced methods of statistical analyses.

Efficacy and effectiveness

Clinicians as well as researchers are becoming more familiar with the limitations of double-blind placebo-controlled studies. The relevance of these studies has been called into question by the findings that some drugs that appear efficacious in controlled studies do not render a useful clinical effect in actual

“naturalistic” treatments and, similarly, that some drugs observed to have value in the hands of clinicians working with real-world patients appear ineffective in controlled studies. The difference between drug “efficacy”, as defined in rigorously controlled studies, and drug “effectiveness,” as defined in large-scale naturalistic studies, is emerging as an important distinction in understanding the clinical properties of medications. To a degree, this distinction breaks down in newer and more sophisticated studies that examine formulaic algorithm-based treatments in large populations of children.

In general, both drug efficacy and naturalistic effectiveness studies are needed to evaluate fully the clinical promise and valid scope of a drug treatment. Drug–placebo comparisons are essential for the work of the United States Food and Drug Administration (FDA), whose role is to determine whether commercially marketed drugs are safe and efficacious. In contrast, clinical decision-making is often promoted more directly by drug comparison studies (comparing drug against drug), which identify how different drugs or treatments compare in clinical efficacy.

Both clinical practitioners and clinical researchers in child and adolescent psychopharmacology contribute essential information that strengthens available treatment. This is not a field where the academics have a hegemony over the production of clinically important findings. Both clinicians and researchers are ahead of each other in certain respects, and both spur the successes of the other.

Combined medication treatments

Simplicity and clarity remain important features of optimal care, but the effectiveness of psychopharmacologic monotherapies is quite limited in many cases. The use of multiple concurrent psychiatric medications, though formerly denigrated as “polypharmacy,” has appropriately become a common practice and even a routine part of the “standard of care.”

The multipronged approach to influencing different brain neurotransmitter systems goes well beyond the former “one disease/one treatment” model, which is often simplistic in medicine, weakly applicable to most psychiatric disorders, and almost irrelevant to child psychiatric disorders. However, multiple concurrent drug treatments have rarely been studied with regard to safety or therapeutic effect, with methylphenidate/desipramine being the only such combination to have received systematic investigation in children (Rapport et al., 1993; Pataki et al., 1993; Carlson et al., 1995). In addition to the increased likelihood of adverse effects with two or more pharmacotherapies, medical regimens consisting of three or more drugs can give rise to multiple

concurrent drug interactions, generating at times genuinely unpredictable effects (Fisman et al., 1996). When rigorously conducted, however, multiple concurrent drug treatments can add significantly to the sophistication and effectiveness of child psychopharmacologic treatment.

Setbacks

The march of progress has not been without setbacks. It was fully predictable that these innovative treatments would be the source of significant problems themselves, including some serious ones.

Limited benefits

The widely held, empirically based belief in the 1980s that TCAs can effectively treat major depression in youth has been tempered by the findings of controlled research. Double-blind placebo-controlled studies have repeatedly shown no generalized clinical efficacy of TCAs in childhood depression (Jensen and Elliott, 1992; Birmaher et al., 1996; Findling et al., 1999; Ambrosini, 2000), even in the recent studies with current methodology (Kye et al., 1996; Birmaher et al., 1998; Klein et al., 1998). Estimates of the pooled effect size of 0.35 standard deviations (95% confidence interval of 0.16–0.86) and the pooled odds ratio of 1.08 (95% confidence interval of 0.53–2.17) indicate no significant clinical value is likely to be uncovered by further controlled trials (Hazell et al., 1995).

However, TCAs appear to be decisive in certain youths with depressive disorders, as demonstrated in the responses of individual patients to dose changes as well as to drug discontinuations and restarts. Even some researchers who demonstrated a lack of clinical efficacy of TCAs in controlled trials continue to use the drugs in their own clinical practices. Despite the spate of negative studies which formally demonstrate that they do not work significantly better than placebo, TCAs remain possible secondary and supplementary agents for treating depression in youth.

The SSRIs do not have the potential to replace the role of the TCAs in treating enuresis (bedwetting), ADHD, or SSRI-induced frontal release, which includes frontal disinhibition (King et al., 1991; Riddle et al., 1991a) and frontal apathy (Hoehn-Saric et al., 1990; Walkup, 1994; Popper, 1995a). It remains unclear whether TCAs are less effective in treating depression in youths than in adults for developmental pharmacodynamic reasons or perhaps other reasons, including the possibility that the usefulness of TCAs in major depression was historically overvalued in adults.

In a similar, but less conspicuous reversal, naltrexone treatment of autistic

disorder was another example of overly optimistic estimates of therapeutic drug effects that were later determined to be unfounded or at least overrated.

Adverse effects in youth

Certain adverse drug effects in children and adolescents were not anticipated by studies of adults, including the classic example of psychostimulant-induced growth slowing. In a similar manner, valproate-induced polycystic ovary disease appears to be a problem mainly of young women (Isojärvi et al., 1993), resulting from the hormonal consequences of weight gain (Isojärvi et al., 1996, 1998). Lamotrigine is known to be more of a dermatologic risk to children than to adults (Li et al., 1996; Messenheimer, 1998), both with respect to Stevens Johnson syndrome (1/1000 in adults, 1/200 in children) and rash of any type associated with hospitalization (3/1000 in adults, 1/100 in children).

The induction of frontal apathy and disinhibition by SSRIs may be more common in youths than adults (Popper, 1995a). TCAs appear more likely to induce increased blood pressure (Kuekes, 1992) and perhaps sinus tachycardia (Leonard et al., 1995) in youths than adults. In addition, there are suggestive data that akathisia may be more prevalent in youths than adults treated with conventional neuroleptics (Keepers et al., 1983). Extrapyramidal symptoms (Mandoki, 1995) and perhaps obsessive-compulsive symptoms may be more common in youths than adults treated with atypical neuroleptics. Nefazodone-induced hepatic failure might, speculatively, be more common in youths (Aranda et al., 1999). The list of age-related adverse drug effects will enlarge, and the search for other untoward developmental-pharmacodynamic changes will become a staple of this field.

Sudden death

Beyond the traditional concerns about the risks of TCA overdose (Frommer et al., 1987), the appearance of sudden medically unexplained deaths in children and adolescents treated with desipramine have raised major concerns with considerable justification. Although the initial three cases (Abramowicz, 1990) identified by the FDA were generally viewed as inconclusive (Elliott et al., 1990; Popper and Elliott, 1990; Biederman, 1991; Elliott and Popper, 1991; Riddle et al., 1991b), three subsequent cases (plus another that could be equally attributed to concurrent neuroleptic treatment) convinced most clinicians that desipramine should be used sparingly in children (Riddle et al., 1993; Zimnitzky and Popper, 1994; Varley and McClellan, 1997), especially for nonlethal disorders such as ADHD and enuresis (Popper and Zimnitzky, 1995). Sudden deaths attributable to desipramine exceed the risks of other TCAs (Biederman

et al., 1995), but the risks might be comparable in magnitude in both children and adults (Popper, 1994). Although baseline screening and ongoing medical monitoring, including electrocardiography, might be able to prevent some of the deaths due to long Q-T syndrome, even invasive angiography would not necessarily prevent other sudden deaths associated with other cardiac abnormalities (Popper and Zimnitzky, 1995). These rare catastrophes were particularly worrisome because of the previously extensive use of desipramine, whose value in treating childhood depression is now known to be small.

Serious questions have also been raised about the combined use of clonidine and methylphenidate (Fenichel, 1995). Although the three initially reported cases were readily attributable to other medical factors (Popper, 1995b), new cases might generate greater concern. The only subsequently reported death on this drug combination involved a 10-year-old boy with a history of several incidents of syncope prior to starting the medication combination (Cantwell et al., 1997). The child went swimming, felt faint, rested for 45 minutes, swam again for another 45 minutes until he felt faint again, and then had a seizure. At autopsy, he was found to have a congenital cardiac abnormality of the left coronary artery. The history of syncope prior to starting the blood pressure-lowering medication and the continuing exertion despite hypotensive symptoms that day may have, in retrospect, been a significant risk to a child with potential cardiac vulnerability. In all four cases of methylphenidate-clonidine death, other medical factors presented risks that probably exceeded an unproven risk hypothesized to be associated with the drug combination.

The risks associated with psychopharmacologic treatment cannot be stated with certainty, because unknown risks and dangers are likely to be described in the future. Serious overestimation of effectiveness and underestimation of the dangers of these treatments can be expected for years to come, so it is critical to temper enthusiasm or satisfaction in prescribing these treatments with a respectful doubt about the ultimately determined effects of each treatment.

Rising expectations

While the standards of care are changing, the expectations of care are changing as well. Heightened public understanding of psychiatric disorders and treatments, increasing acceptance of child psychopharmacology, the swelling of newly introduced drugs and drug classes, the unmasking of blindly anti-psychiatry and antim medication forces in society, and the new focus in medicine on "quality of life" (in addition to symptom amelioration) have led to a much higher visibility of psychopharmacologic treatments and a sense of promise in

child psychiatry. Child psychopharmacology and child psychiatry are now mainstream medicine, and they carry all the attendant hopes, unrealistic expectations, and disappointments.

Rush to use

New psychiatric drugs are employed more quickly for clinical treatment of children than in the past. Although it has previously taken years of postmarketing experience before new psychiatric medications were put to use for children, the erosion of this protective delay is certain to bring a comeuppance.

Indeed, at this point, a new corner is being turned: new psychiatric drugs are coming into clinical use more rapidly than they can be effectively investigated. New drugs are replacing old drugs while the postmarketing studies on old drugs are not yet completed, and this is especially so for the new psychiatric drugs used in children and adolescents. SSRIs became predominant in child and adolescent psychiatry when TCAs were still being evaluated for the treatment of mood and anxiety disorders. Atypical neuroleptics replaced conventional antipsychotic medications for treating a variety of child psychiatric disorders approximately as quickly as for adult disorders. Anticonvulsant mood stabilizers are now routinely used to treat children with bipolar disorder, starting even before the first adequately controlled prospective study had been conducted of lithium treatment of bipolar disorder in children or adolescents.

The potential for rapid drug obsolescence, resulting from the fast expansion of pharmacologic alternatives, might conceivably herald an age when new drugs are quickly replaced before they can be adequately examined and understood.

This shift has already begun, and it certainly challenges the traditional manner in which clinical decision-making about medications is made. Whether this shift will pose mainly advantages or disadvantages remains to be seen and will itself require ongoing study.

In addition to exposing patients to potentially serious risks, a decreasing reliance on completed formal drug studies might come to make clinical decisions increasingly subject to the subtle effects of pharmaceutical advertising.

The role of industry and technology

Major pharmaceutical houses are now quite interested in child and adolescent psychopharmacology, perhaps the clearest and most convincing sign of the “coming of age” of this field, and pharmaceutical manufacturers have for years been reaping benefits from off-label treatments in child psychopharmacology.

Even though the FDA asserts that approved labeling is specifically intended to regulate pharmaceutical advertising (Food and Drug Administration, 1982), many physicians have regarded them as guides and used them inappropriately as restraints on their prescribing practices. With the FDA now placing more emphasis on the pediatric use of medications in clinical practice and drug trials in children prior to marketing (Food and Drug Administration, 1992), new conduits are being established for new drugs to receive drug package insert labeling for child psychiatric treatment (Laughren, 1996). In the 1997 FDA Modernization Act (Food and Drug Administration, 1997), the US Congress gave clearance for the FDA to grant time extensions on exclusivity patents of already marketed drugs to pharmaceutical houses that conduct clinical research in children. These governmental actions have further spurred the industry to devote resources to research on children (Walkup et al., 1998), which in turn is leading to more advertising of psychiatric drugs for use in children.

Medication advertisement

The approaches by pharmaceutical companies to the marketing of medications are generally expected to influence physicians' prescribing, alter market share, and enhance company revenues. Although largely educational in nature, these approaches still raise concern. Direct-to-consumer advertising on television and magazine pages carries potential advantages (Pines, 1998) and disadvantages (Tsao, 1997; Schommer et al., 1998) for the public, evokes disapproval from most physicians (Lipsky and Taylor, 1997), and poses nettlesome issues for the FDA (Baylor Henry and Drezin, 1998). The detailing techniques of company representatives who promote drugs to physicians include marketing methods whose mechanisms and effects are not well understood by physicians (Roughhead et al., 1998).

Pharmaceutical advertising in medical journals might appear to be more reliable because of the careful surveillance by the FDA in the United States and similar regulatory agents in other nations (Lexchin, 1997). Nonetheless, certain drug advertisements in medical journals are misleading at best. In some instances, the phrasing and figures in drug advertisements are meaningless or perplexing. More insidious factors in commercial medical advertising include the widespread use of subtle communications pitched to the so-called "cognitive unconscious" and the impact of obvious emotional appeals. (Franz Ingelfinger used to talk about the *New England Journal of Medicine* receiving an advertisement for an endocrinologic drug that contained the silhouette of a physician looking down, with a banner saying, "How would you feel, Doctor, if your genitals began to shrink?") Drug advertisements in medical journals are