1 Child and adolescent psychopharmacology at the turn of the millennium

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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 Cottington, 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). Annell first reported on lithium treatment in a series of children (Annell, 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 Conners, Gabrielle Weiss, and John Werry were leaders in bringing pedipsychopharmacology 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 pedi-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.