

Pediatric psychopharmacology: too much or too little?

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This paper provides a selective overview of the past, present and future of pediatric psychopharmacology. The acceptance of medication use in child psychiatry was based on the results of double-blind, placebo-controlled trials documenting the efficacy of drug treatments for attention-deficit/hyperactivity disorder, enuresis, depression, anxiety disorders, obsessive-compulsive disorder and psychoses. This period of success was followed by a series of challenges, including a growing awareness of the long-term adverse effects of medications and of the inadequacy of long-term drug surveillance. There is great concern today that children are being overtreated with medication, especially in the US. Further advances in pediatric psychopharmacology may come from examination of large medical data sets including both pharmacological and psychiatric information, which could lead to drug repurposing, as well as from preclinical translational studies such as those using human induced pluripotent stem cells.

Key words: Pediatric psychopharmacology, stimulant drugs, child psychiatry, attention deficit/hyperactivity disorder, obsessive-compulsive disorder, drug toxicity

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It has been an extraordinary personal and professional experience to see the development of the field of pediatric psychopharmacology across the last four decades, and to work throughout the successive challenges.

Initially, there was a strong climate against medication for children with mental disorders. In the US, the psychiatrists and psychologists interested in pharmacological research formed a small group clearly out of the “main stream”. Psychoanalytically oriented psychotherapy was the generally preferred treatment for children and adolescents.

Suspicion of medication was only overcome by the focus on double-blind trials and validated clinical measures. The assembly of large relatively homogeneous populations for those trials had a strong overall impact on the field by permitting a variety of clinical studies. The eventual acceptance of medication use in child psychiatry was based on the growing evidence of efficacy of drug treatments with large effect sizes for disorders that had been resistant to psychological treatments.

This period of success has been followed by a series of challenges. The acceptance of drug treatment has been often uncritical, including a drastic increase in polypharmacy. There has been a growing awareness of the long-

term adverse effects of medications and of the inadequacy of long-term drug surveillance. With the transition to managed care in the US, medication has shifted to more of a business model. Because non-medical therapists are less costly, psychiatrists in most insurance plans have been assigned exclusively to medication clinics. This may have increased the likelihood that they would prescribe drugs to children.

Also relevant to the backlash against the use of drugs in children is the growing alienation of the media from psychiatric illness. Not only are medications often described as unnecessary, but the diagnoses themselves, such as that of attention-deficit/hyperactivity disorder (ADHD), are sometimes perceived as unscientific and even harmful.

Finally, there is the awareness that most of our drugs still act on the monoaminergic and glutaminergic targets that have been known for decades. As our current medications are only partially successful, with 40–50% of patients having incomplete response and/or intolerance, the field still has a great deal to accomplish. Yet, the complexity of the search for new targets has made many pharmaceutical companies leave the field.

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THE EXCITEMENT OF DISCOVERY

As in adult psychopharmacology, several discoveries of psychotropic drugs for pediatric use have been serendipitous. This was the case for the use of stimulants for “minimal brain dysfunction” (1) and the use of antidepressants for enuresis (2). The funding of systematic case recruitment for clinical drug trials brought about a profound change in the field of child psychiatry, because of the increased scale of observations.

Stimulant medications were responsible for the actual “start” of pediatric psychopharmacology, as the patients of greatest interest were children with ADHD, one of the most common disorders in childhood, accounting for almost half of pre-adolescent contacts. The results of the studies concerning these drugs were electrifying. The clear and immediate benefits for the child and the family were particularly welcome as ADHD did not respond well to traditional psychotherapy.

A variety of double-blind, placebo-controlled studies demonstrated that stimulants improved on-task behavior in both healthy and hyperactive children (3,4). Stimulants did not merely make hyperactive children move less (3). For example, during athletic activities such as basketball or soccer,

hyperactive children on stimulants actually moved *more*, because their attention was focused on the immediate task, which was playing the active game (5). When the task was a quiet one, such as classroom learning, the stimulants decreased motor activity (5).

Because stimulant drug effects can be seen within 15–20 min, and since the effect on the behavior of hyperactive children is striking, a series of studies were able to compare *parent and teacher behavior* between periods when the child was on placebo or on stimulant (6,7). Parents were rated as highly critical and controlling during the placebo periods compared to when the child was on stimulant (8) and teachers received higher “teaching grades” when their hyperactive students were on medication compared to placebo (9).

More recently, the development of long-acting agents has provided a smoother treatment throughout the day, avoiding school involvement in drug administration. Long-term prospective follow-up studies of children with documented ADHD have showed that a substantial group of patients continue to have significant symptoms, with only about 40% truly remitting (10,11). This has led to studies of adult ADHD and a debate on stimulant drug treatment of the adult disorder and the problematic clinical cases of adult onset ADHD (12). These remain important controversies today.

Antidepressant treatments were initially studied in children with enuresis (13), but later extended to children with depression and anxiety disorders (14). There has been considerable controversy over how to define childhood depression, with many clinicians feeling that several symptoms (behavioral problems, anxiety, enuresis) could be an expression of underlying depression (15). For clinical medication trials, more operational definitions were required and an active experimental field compared various definitions in relation to family history, treatment response, long-term follow-up and so forth (16). The answer was complex, as some behavioral dyscontrol with

chronic irritability in fact *did* predict depression in later life (17,18), but a core group could be identified of about 1% of pre-pubertal children with similar symptoms to those seen in adult depressed patients, and such children did respond to treatment (19,20), although effect sizes varied widely across studies.

Later studies extended antidepressant treatment to pediatric anxiety disorders (21,22). These are now drug treatments of documented efficacy for pediatric generalized anxiety disorder, separation anxiety, social anxiety and panic disorder (23,24).

Studies of childhood onset obsessive-compulsive disorder (25) led to the development of specialty clinics for these children in several countries and to the recognition of the close association of this disorder with Tourette’s disorder (26). Again, double-blind, placebo-controlled drug treatment trials required assembly of large numbers of children, and the recognition that obsessive-compulsive disorder could best be diagnosed and assessed using the child as informant (27). Because a subgroup of patients appeared to have a very sudden onset of a severe variety of the disorder (as well as of motor tics and ADHD) in relation to streptococcal infection, highly innovative treatments using plasmapheresis or intravenous gamma globulin were introduced (28). The interest in infection-related acute psychiatric disorders remains high based on these studies and is an important area of future research.

Antipsychotics have been a mainstay of treatment for childhood, adolescent and adult onset psychosis (29). Low-dose antipsychotic medications are used even more frequently in child psychiatry for the treatment of Tourette’s disorder and for repetitive motor behaviors generally (30). The clinical indication for antipsychotics has been also extended to conduct disorders, although with only moderate efficacy rates (31,32).

Clinical trial publications in pediatric psychopharmacology paired with the satisfaction of extended treatment

options in ordinary clinical practice. Trainees were attracted to psychiatry by the treatment advances. The use of rating scales and double-blind design introduced the evidence-based approach that changed the field forever. More recently, initial research comparing behavior therapy and drug treatment has revealed that the *combination* of medication and non-drug treatment is the most effective in childhood depression, anxiety and obsessive-compulsive disorder (e.g., 33). This has led to an increased use and acceptance of these approaches.

PEDIATRIC PSYCHOPHARMACOLOGY: TOO MUCH?

There is great concern today that children are being overtreated with medication, especially in the US. The rapid shift to managed care has resulted in a split in mental health care-giving. Because of the higher cost, psychiatric care is primarily allotted to medication clinics. Non-drug therapies are provided primarily by psychologists, social workers and counselors. It is possible, and I speculate that it is probable, that the increase in medication use results in part from the desire of physicians to be helpful with what they have at hand given their lack of flexibility with respect to alternate treatment delivery.

The rates of increase of pediatric psychotropic drug prescription in the US are alarming (30,34). Multiple psychotropic treatments have also become more common. There is extensive use of atypical antipsychotics for non-psychotic children. An increased prescription of antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), particularly for ADHD, has been reported. The duration of stimulant drug treatment has also greatly increased (34–36). Particularly worrisome is the trend to prescribing medications (particularly stimulants) for pre-school children (37). An additional concern is that children in institutional

or foster care seem to receive higher doses and multiple medications to a particularly high extent (35).

It is clear that the rate of stimulant treatment exceeds that of strictly diagnosed ADHD (38,39). Since stimulants improve cognitive function irrespective of diagnosis (4), it is probable that individual troubling symptoms are being treated in children who do not meet full diagnostic criteria for ADHD. This remains a highly controversial issue.

While childhood treatment of ADHD with stimulants does not increase substance abuse at a later age (40), it is also true that longer-term treatment of the disorder is more usual today. This has raised complex clinical and ethical issues (12). While short-term administration of stimulants with drug holidays did not have a long-term influence on height, the more sustained and longer use of these drugs has raised this issue once more (41). The identification and treatment of ADHD in adults, particularly those without clear childhood history, has generated further controversy; this remains a clinical dilemma of great regulatory concern in the US (42). One bright spot is the probability that long-acting stimulant preparations in wide use today may be less prone to abuse (43).

First-generation antipsychotics carry a high risk for tardive dyskinesia following long-term use (44). This was a particular issue in institutionalized patients, and several US states legislated a yearly drug holiday with observation for movement disorders.

Today, the increased use of atypical antipsychotics in children and adolescents is also a major issue. Originally thought safer because of decreased risk of tardive dyskinesia, these drugs are now known to be at increased risk for cardiometabolic syndrome, particularly in adolescents (45). These medications remain of major importance, including clozapine, the most effective (and toxic) of all for childhood psychosis (46,47). However, the physician now has to weigh the lower risk of akathisia and tardive dyskinesia against the greater risk of obesity

and cardiometabolic syndrome. In the childhood schizophrenia studies, weight gain with clozapine appeared at a high rate, possibly higher than that of adult onset patients (48).

The use of low-dose antipsychotic medications is widespread in child psychiatry for conduct disorders, as augmentation of SSRIs for pediatric obsessive-compulsive disorder, and for Tourette's disorder and motor tic disorders (29). Collectively, these cases are far more common than those of childhood psychoses, and the problems of obesity and the cardiometabolic syndrome are even more alarming. One of the most disturbing aspects of drug-related obesity in children is that weight loss occurs slowly and incompletely when the drug is stopped.

Antidepressant drug treatment in children has also come under criticism (49). Initial trials with tricyclic antidepressants have not been replicated (50). Results of double-blind trials of SSRIs have been more compelling in adolescents (51), but the effect sizes vary widely, with possibly better responses with fluoxetine (52).

Suicidality in children on antidepressants became a major concern in 2004, when the Food and Drug Administration (FDA) issued a warning (53). This controversial move raised concerns that these effective agents might not be prescribed for severely depressed children (54). The FDA action both reflected and fueled public suspicion and backlash against pediatric psychopharmacology. Part of the issue was the failure to distinguish between suicidality and actual self-harm, but everyone involved in this issue agreed that current post-marketing surveillance of drugs is inadequate (55).

PEDIATRIC PSYCHOPHARMACOLOGY: WHAT IS THE FUTURE?

In the early history of our field, serendipitous discoveries led to treatment trials of medications with large effect sizes. Building on these accidental approaches, further advances

in psychopharmacology may come from examination of large medical data sets through single payer medical systems including both pharmacological and psychiatric information. This could lead to drug repurposing, that is, drugs given for other medical purposes may be found to influence the course of some psychiatric conditions. This form of "psychopharmacological epidemiology" has not been systematically pursued for treatment effects in child or adult mental disorders, although epidemiology has been of major importance for studies of adverse drug events.

Clinically, there has been interest in repurposing riluzole for psychiatric use (56). This is a glutamate antagonist approved for treatment of amyotrophic lateral sclerosis (57), which had theoretical support as an alternative treatment for obsessive-compulsive disorder in children and adolescents. In spite of promising pilot results (58,59), however, a double-blind trial did not show significant efficacy (60).

Rapamycin, a commercially available immunosuppressant, has been found highly effective in the treatment of tuberous sclerosis, a rare genetic disorder associated with widespread brain and somatic abnormalities and with autism spectrum disorder (61). This rare disease model is leading to proposals of new treatment targets (62,63) related to the role of mTOR (mammalian target of rapamycin) in pathways affecting protein synthesis, cell division and cell growth.

Mutations in the FMR1 (fragile X mental retardation) gene can cause cognitive deficits, ADHD, autism and other social-emotional problems. Studies of metabotropic glutamate receptor (mGluR5) pathway antagonists in multiple animal models of fragile X syndrome have demonstrated benefits in various behaviors (64). Several trials of mGlu5 antagonists have been designed (65). There is considerable optimism about the ultimate usefulness of the study of this and other rare single gene disorders that cause autism, as the pathways and targets that are revealed may inform treatment

development for wider patient populations (66).

Genetic-based animal models of autism, ADHD, obsessive-compulsive disorder and schizophrenia have generated putative candidates, but this has not led to successful clinical trials. This failure may be due to the complexity of human disorders, for which animal models may prove unsuccessful. It may be that the dramatic changes underlying human brain evolution make us vulnerable to mental disorders that are uniquely human. Post-mortem human brain studies may ultimately generate new targets, as gene expression studies of post-mortem brains in autism have implicated pathways for both brain development and immune responses (67).

An obstacle to drug discovery is our limited understanding of human brain development. The tools that we have for measuring brain functioning and connectivity are growing, but only recently sizeable multimodal normative brain developmental data have become available, with large prospective studies ongoing in Rotterdam (68), San Diego (69) and Philadelphia (70). The Rotterdam studies will extend from the prenatal period through adolescence (68), but the perspective for new drug treatments is remote.

Clinically, there is a growing dissatisfaction with existing diagnostic entities, which are perceived as being too heterogeneous and thus not helpful to drug development (71). The DSM-5 is going to place emphasis on psychopathological dimensions, and this may be a useful step forward (72). Other approaches in treatment development have been based on intermediate phenotypes or specific biomarkers, including genetic variables, as in the glutamate trial mentioned above. The Research Domain Criteria project (73,74) involves measurement of common physiological, neuropsychological, or brain imaging markers to identify a patient subgroup or alternately be themselves a target for treatment. Examples of this approach could include sensory gating such as pre-pulse inhibition, or specific cognitive tests such as the Continuous Performance Test or the California Test of

Verbal Learning (75). In children with anxiety disorders, newer treatments are being proposed in relation to patterns of brain activation in response to emotionally loaded stimuli as well as to cognitive bias associated with these disorders (22).

Human induced pluripotent stem cells would seem ideal for the study of neurodevelopmental disorders. Using Rett syndrome as a model, neurons derived from human induced pluripotent stem cells from people with the syndrome have been found to have fewer synapses and some electrophysiological defects (76). Identification of cellular mechanisms for schizophrenia and for autism with the attendant possibility of *in vitro* treatment trials to normalize developmental trajectories is under study at several centers (77).

The development of real translational clinical neuroscience will hopefully be the ultimate answer, but this does not address the critical shortage of new drugs in development.

CONCLUSIONS

Pediatric psychopharmacology has historically been a vibrant field. The excitement of new treatments, such as stimulants and more recently the SSRIs, not only brought help to otherwise treatment-refractory patients but inspired two generations of academicians. These academics leveraged the treatment trials into complex pharmacological and clinical studies.

Looking back, it is apparent that there was over-acceptance of drug treatment, leading to reductionist biology. Market forces in health care delivery also drove the process of over-prescribing (78).

There are now imaginative new approaches to psychiatric diagnosis (such as the Research Domain Criteria project) and astonishing preclinical translational studies (such as the study of human induced pluripotent stem cells), but new treatments remain unfortunately remote.

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