Challenges and Promises of Pediatric Psychopharmacology

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ABSTRACT

Most prescriptions for psychotropic medications are written by primary care physicians, yet pediatricians, many of whom are teaching residents and medical students about pediatric psychopharmacology, often feel inadequately trained to treat mental health concerns. Over the past several decades, the number, size, and quality of psychopharmacologic studies in youth has greatly increased. Here we review the current evidence for efficacy and safety of each of the major pharmacologic drug classes in youth (psychostimulants, antidepressants, mood stabilizers, and antipsychotics). Psychostimulants have a robust body of literature supporting their evidence as first-line treatment for attention-deficit/hyperactivity disorder. Selective serotonin reuptake inhibitors (SSRIs) have documented efficacy for pediatric depression and multiple different anxiety disorders with childhood onset. Combining cognitive-behavioral therapy with SSRI treatment enhances treatment benefit and minimizes adverse events of medication. Mood stabilizers, including lithium and anticonvulsant medications, have a less robust strength of evidence and come with more problematic side effects. However, they are increasingly prescribed to youth, often to treat irritability, mood lability, and aggression, along with treatment of bipolar disorder. Antipsychotics have long been a mainstay of treatment for childhood-onset schizophrenia, and in recent years, the evidence base for providing antipsychotics to youth with bipolar mania and autistic disorder has grown. Most concerning with antipsychotics are the metabolic side effects, which appear even more problematic in youth than adults. By better understanding the evidence-based psychopharmacologic interventions, academic pediatricians will be able to treat patients and prepare future pediatrician to address the growing mental health care needs of youth.

KEYWORDS: antidepressants; antipsychotics; pediatrics; psychiatry; psychopharmacology; stimulants

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OVER THE PAST several decades, the field of pediatric psychopharmacology has evolved from reliance on case reports, uncontrolled case series, and extrapolations from studies in adults to larger cohort studies and randomized placebo-controlled trials.[1,2] At the same time, the development of validated age-appropriate clinical measures more clearly defines pediatric psychopathology. These advancements have led to a much better understanding of the efficacy and tolerability of major psychotropic drug classes in pediatrics. With growing evidence, the acceptance of medication use in children with mental illness is expanding.[3]

The growing acceptance of pediatric psychopharmacology has at the same time created a series of challenges, which in recent years have led to controversies. There is a debate about the overdiagnosis of psychiatric disorders in childhood, the appropriateness of the diagnoses used to justify psychopharmacologic treatment, and the use of psychotropic medications for conditions with little evidence of benefit in the literature.[1,3,4] Concerns have been raised about treatment approaches that focus too narrowly on pharmacologic management and underutilize psychotherapeutic, behavioral, and family interventions.[1,5] Additionally, there is growing awareness of the long-term adverse effects of medications and the lack of knowledge about the effects of psychotropic medications on development.[1,6]

The majority of prescriptions for psychotropic medications are written by primary care physicians,[3,7] yet pediatricians often feel inadequately trained to treat mental health concerns.[8] In light of the ongoing challenges facing pediatric providers, many of whom are teaching residents and medical students about pediatric psychopharmacology, along with the increase in the number, size, and quality of psychopharmacologic studies in youth, we undertook to summarize the evidence-based psychopharmacologic interventions for pediatric mental disorders. With specific focus on the major pharmacologic drug classes in youth (psychostimulants, antidepressants, mood stabilizers, antipsychotics), we discuss the current evidence

for the efficacy and safety of these drug classes, identify the knowledge gaps, and review current practice guidelines. This review of the literature is not intended to provide specific treatment recommendations or focus on the array of nonpharmacologic interventions crucial to treat mental illness in youth.

STIMULANTS AND OTHER ATTENTION-DEFICIT/HYPERACTIVITY DISORDER MEDICATIONS

Attention-deficit/hyperactivity disorder (ADHD) is the most prevalent mental disorder in children under age 18 and occurs in approximately 8% of youth.[9,10] The research database for the safety and efficacy of psychostimulants and other medications for ADHD has continually grown, including more recent research in preschoolers. There is strong support for the use of stimulants as first-line treatment for ADHD and growing evidence for the use of nonstimulant medication as second-line agents. All stimulant medications currently US Food and Drug Administration (FDA) approved for ADHD are either methylphenidate or amphetamine derivatives, both of which enhance the neurotransmission of dopamine. Nonstimulants approved by the FDA for ADHD in children age 6 and over include atomoxetine, a selective norepinephrine-reuptake inhibitor, and two selective alpha-adrenoceptor agonists (α-agonists), extended-release clonidine, and guanfacine.

EVIDENCE FOR EFFICACY

There are 2 high-quality, seminal studies comparing stimulant treatment with psychosocial interventions that have clearly influenced the guidelines used to treat ADHD.[11,12] The details are listed in Table 1. The Multimodal Treatment Study of Children With ADHD (MTA) demonstrated that combined treatment did not yield significantly greater benefits than medication management alone for core ADHD symptoms, although there was evidence of modest advantages for non-ADHD symptoms and other functional outcomes.[11,13] In the Preschool ADHD Treatment Study (PATS), methylphenidate appeared effective in treating preschoolers with ADHD, but at lower weight-adjusted doses, smaller effect sizes, and with different side effect profiles compared with school-age children.[12,14] There have been no major differences in efficacy or tolerability between methylphenidate and amphetamine-based medications and no consistent patient profile that preferentially identifies those who will respond to methylphenidate- versus amphetamine-based stimulants.[9]

Nonstimulant medications, including clonidine, guanfacine, and atomoxetine, while shown to be effective for the treatment of children and adolescents with ADHD, have much smaller effect sizes than stimulants.[15,16] Clinical consensus suggests that α-agonists may be more successful in treating the hyperactivity/impulsive symptoms than the inattention symptoms of ADHD and also may be helpful to address comorbid tics and/or insomnia.[9] Both extended-release clonidine and guanfacine also have evidence for their usefulness in combination with stimulants for the treatment of ADHD when stimulants are only partially effective, resulting in FDA indication for combination use.[16]

EVIDENCE FOR SAFETY

All stimulant formulations have roughly similar adverse event profiles, including a potential for delayed onset of sleep, appetite suppression, weight loss, headache, and abdominal pain. Less common adverse effects include tics and emotional lability or irritability. Emotional side effects may be more frequent in younger children and those with developmental delay.[1,14]

Stimulants have been associated with elevations in mean blood pressure (<5 mm Hg) and heart rate (<10 beats/min). A subset of individuals (5–10%) may have an even greater increase in heart rate or blood pressure at any given time.[17,18] Although one matched case–control study compared children who died of sudden death with those who died in motor vehicle accidents and found a significant association of stimulant use with sudden death, other studies have shown that the rate of sudden death in pediatric patients taking psychostimulants is comparable to children in the general population: both are extremely rare.[1,9,19] On the basis of these data, the FDA decided against a boxed warning on stimulants. Although there are no data to suggest that youth with underlying cardiac abnormalities or a strong family history of cardiac disease are at a greater risk for cardiac complications from stimulant medications, the potential risk is quite concerning. The American Heart Association and the

Table 1. Seminal Randomized Studies Comparing Stimulant Treatment With Psychosocial Interventions

Study	Sample Size	Age	Diagnosis	Randomly Assigned Treatment Groups	Study Duration	Conclusion
Multimodal Treatment Study of Children With ADHD (MTA)[11]	579	7–9.9 y	ADHD, combined type	Programmed behavioral intervention, immediate-release methylphenidate alone, combination of the 2, or community treatment	14 mo	All 4 treatment groups improved, with the greatest improvement in both groups with medications (no significant difference with combination vs medication alone).
Preschool ADHD Treatment Study (PATS)[12]	303	3–5.5 y	ADHD, combined type	Immediate-release methylphenidate, placebo	14 mo	Immediate-release methylphenidate was significantly superior to placebo.

ADHD indicates attention-deficit/hyperactivity disorder.