ADHD Psychopharmacology Across the Lifespan

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is defined by developmentally abnormal and persistent levels of hyperactivity, impulsivity, and/or inattention that emerge by age 7 years, cannot be ascribed to other mental or medical conditions, and cause impairment in at least two contexts, typically school and home for children and adolescents and work and social domains for adults. ADHD affects about 5% of the general population younger than 19 years old, and some surveys have reported even higher rates [1,2]. The manifestations of ADHD change as the child grows. Over time, hyperactivity tends to abate, whereas inattention and impulsivity persist and become more prominent [3]. ADHD often continues into adolescence and adult years, although the estimated rates of persistence vary widely according to the definition being used. Persistence of full criteria for ADHD was found to be only 15% by age 25 years; however, if cases that are in partial remission but still present prominent ADHD symptoms are included, the rate increases to about 65% [4]. These data are consistent with an estimated point prevalence of ADHD of about 4% in the adult general population [5,6]. Thus, ADHD, which was first identified as a concern in school-age children, is now recognized as a condition affecting individuals across the entire lifespan, from preschool to adulthood. In parallel, the use of medications for treating ADHD, which was primarily restricted to elementary school children, has become common also among adolescents and adults.

The purpose of this review is to briefly examine the current status of pharmacotherapy of ADHD across the lifespan in light of the most recent research findings. Although the focus is on pharmacologic treatment, psychosocial interventions are available to treat ADHD in children, adolescents, and adults, and treatment choice should be based on the individual needs of each patient, previous treatment history, and patient and/or parent preference. In some cases, ADHD can be managed successfully without resorting to medication, and an initial attempt to address symptom-related dysfunction with nonpharmacologic interventions should usually be considered, especially in young children. In any case, medication should be prescribed as part of a comprehensive approach addressing the behavioral, educational, and interpersonal needs of the patient [7,8].

Preschoolers

ADHD often starts in preschool years, but children tend to be diagnosed only after entering school, when the difficulties of meeting the academic demands bring attention to the behavioral and cognitive deficits. Although most preschoolers with ADHD are managed without pharmacologic intervention, some severe levels of hyperactivity and impulsiveness interfere with children’s ability to attend preschool and/or participate in age-appropriate social activities. For these children, behavioral interventions are not always effective—hence the need to consider pharmacologic treatment for especially severe cases [9].

At this time, no medication has both adequate evidence of efficacy and safety from controlled clinical trials and approval by the US Food and Drug Administration (FDA) for use in this age group. In fact, although amphetamines are FDA approved for use in children age 3 years and older, this indication is not based on empirical evidence from investigations in preschoolers but rather reflects the lower standards for labeling that existed more than 30 years ago when these products were first approved.
for clinical use. On the other hand, methylphenidate has demonstrated short-term efficacy and tolerability in controlled studies of preschoolers, but it is not currently FDA approved for use in children younger than 6 years old. As for atomoxetine, no sufficient data are currently available in this age group.

The best available information on the therapeutic activity of methylphenidate comes from the Preschool ADHD Treatment Study (PATS), a publicly funded study that evaluated the efficacy and tolerability of immediate-release methylphenidate in 3- to 5-year-old children with ADHD. The study design included multiple, sequential phases, starting with a nonpharmacologic, behavioral interventions in an attempt to control symptoms without medication [9]. Only children with prominent and severe hyperactivity and impulsivity unresponsive to psychosocial intervention (n = 165) entered the medication phase, during which doses ranging from 1.25 mg to 7.5 mg given three times a day were blindly assessed versus placebo [10]. Doses as low as 2.5 mg three times a day were significantly better than placebo at decreasing ADHD symptoms. The mean optimal dose was 14 mg per day.

Eleven percent of the PATS preschoolers discontinued treatment because of adverse effects such as decreased appetite, weight loss, sleep difficulties, irritability, and repetitive behaviors or thoughts [11]. This rate is substantially higher than that observed in school-age children, especially when considering the relatively low doses used in PATS. As a comparison, in the Multimodal Treatment of ADHD study (MTA), which evaluated daily doses greater than 30 mg in 7- to 9-year-old children, the rate of discontinuation due to adverse effects during the acute treatment phase was less than 5% [12,13]. There may be differences in the pharmacokinetics of methylphenidate between preschoolers and older children. In one study, preschoolers had higher plasma peak levels of methylphenidate and slower clearance, which means greater pharmacologic exposure [14].

In PATS, 140 children who had improved acutely on methylphenidate entered a 10-month maintenance treatment during which they continued to show good control of ADHD symptoms [15]. However, the dose had to be increased gradually to a mean of 20 mg per day. With long-term treatment, preschoolers were sensitive to the growth-suppressing effect of methylphenidate, with an annual growth of about 1.4 cm less than expected for height and about 1.3 kg less than expected for weight [16].

Taken together, the results of PATS show that lower doses of methylphenidate and a slower titration should be considered in preschoolers compared with older children. Acute improvement can be maintained and enhanced with continuous treatment, but methylphenidate can impair physical growth, and so careful, prospective assessment of weight and height is recommended. PATS also showed the validity of assessing and monitoring ADHD symptoms in preschoolers with rating scales such as the Swanson, Nolan, and Pelham scale (SNAP), originally developed for school-age children [17].

One limitation of PATS, which was designed about 10 years ago, is that it studied immediate-release methylphenidate rather than the currently more commonly used extended-release formulations. Despite this discrepancy with current practice, the findings remain informative about the efficacy and tolerability of methylphenidate in very young children. In this age group, however, pharmacotherapy remains a second-line treatment for severe ADHD unresponsive to psychosocial interventions [7,18].

School-Age Children
The effectiveness of stimulants in the treatment of ADHD in school-age children is supported by numerous controlled studies [7]. A variety of formulations of methylphenidate and amphetamines are FDA approved for use in children 6 years old and older. In addition to immediate-release preparations, these also include a number of extended-release formulations, a skin patch for transdermal delivery of methylphenidate, and an amphetamine prodrug [19,20]. Atomoxetine, a nonstimulant selective reuptake inhibitor of norepinephrine, is also approved in this age group [21]. Several other compounds, such as the α-2 agonists clonidine and guanfacine, the dopamine- and norepinephrine-enhancer bupropion, tricyclic antidepressants, and the antinaeuroleptic agent modafinil—although not approved by the FDA for the treatment of ADHD—have been investigated and found to be, with varying degrees of evidence, efficacious [22]. Tricyclics have prominent safety risks in overdose due to their effects on cardiac conduction and are now seldom if ever used for ADHD treatment, because safer alternatives are available.

Over the years, detailed guidelines for the treatment of children with ADHD have been developed and provide direction regarding appropriate treatments and sequences [7,18,23]. Stimulants are considered the first-line pharmacologic treatment, followed by atomoxetine (Table 1). On average, methylphenidate and amphetamines have similar efficacy [24]. Approximately 75% of children treated with either methylphenidate or an amphetamine preparation substantially improve, and when nonresponders are administered the other stimulant, the cumulative response is about 85% [24]. Atomoxetine is also effective, although less so than stimulants [25••]. When compared with placebo, stimulants usually show a large treatment effect size (ie, approximately 0.7 or higher) and a number needed to treat (NNT) as low as 2, which is extremely favorable. Atomoxetine, though clearly superior to placebo, shows a medium treatment effect size, with a NNT around 6 [23••]. However, there are suggestions of substantial intersubject variability in treatment response to medications. Understanding the underpinnings of this heterogeneity may lead to more targeted and individualized treatment approaches [26]. For patients at high risk for substance abuse or with comorbid anxiety or tics, atomoxetine may be the preferred initial treatment [7].

The MTA, a 14-month, multisite, controlled clinical trial comparing medication management, behavioral