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Pharmacotherapy of ADHD in Young Children

ABSTRACT

Attention-deficit hyperactivity disorder (ADHD) is a disorder common throughout childhood, with recognizable symptoms as early as preschool in many cases. ADHD is often treated in young children by simply implementing strategies proven efficacious and safe in older children and adolescents, as limited data is available in children younger than age six. Research has been extended into this age group by the Preschool ADHD Treatment Study (PATS) and other recent trials, providing clinically relevant data on differences in tolerability and efficacy of ADHD pharmacotherapies, primarily methylphenidate. No published data is yet available on the use of atomoxetine in children under age six. Growth is an area of particular interest and concern in the pediatric population, with data demonstrating variability in the long-term rates of growth in height as well as weight. While pharmacotherapy holds the potential for significant benefit in young children with ADHD, concerns with variation in response and tolerability highlight the need for careful evaluation, close monitoring, and an ongoing risk/benefit analysis throughout the implementation and use of medication.

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INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a neurobiological disorder[1–4] affecting approximately 3 to 7 percent of school-aged children.[5] Symptoms of ADHD are often identifiable and impairing by age three, with epidemiological data estimating nearly two percent of 3- to 5-year-olds meet criteria for the diagnosis.[6] These preschool children are at significant risk for behavioral, social, family, and academic dysfunction when compared with same-aged children without ADHD.[7] DuPaul and colleagues studied 94 3- to 5-year-olds and found that children with ADHD demonstrated problematic behavior ratings that were 2 SD greater than those without the disorder.[7] Pre-academic deficits in math and reading, as well as fine motor skills, are also more frequently observed in children with ADHD at the time of school entry.[8–10] The combination of these deficits can persist throughout the child's school career and impair overall academic performance and social functioning. ADHD symptoms extend beyond the classroom and can tax parent and caregiver resources, creating a strained home environment for these young children. In a 2005 study by Escobar and colleagues, parents of children with ADHD reported more interference in daily life than the level reported by parents of normal controls as well as parents of children with asthma.[11]

Psychotropic medication research in the preschool population has unfortunately been limited. The lack of data, however, has not deterred clinicians from treating young children with available pharmacotherapies. As early as 1990, Wolraich, et al., reported that 34 percent of pediatricians and 15 percent of family practitioners were prescribing stimulant medications to preschoolers with ADHD.[12] From 1991 to 1995, a three-fold increase in the use of psychotropic medications children ages 2 to 5 years was observed.[13] The Medical Expenditure Panel Survey (MEPS) data analyzed by Zuvekas and colleagues in 2006 reported an estimated 0.3 percent of children under age six were being treated with psychostimulant agents from 1997 to 2002.[14] During that five-year period, the number of pediatric patients receiving stimulants increased from 2.7 to 2.9 percent; however, the rate of use in the preschool age group remained stable indicating that prescription of ADHD medications in the very young has not continued to increase. No data is currently available on the use of atomoxetine, the only non-stimulant agent approved for the treatment of ADHD, in children younger than six years of age. Thus, ADHD is a common disorder in young children with the potential for significant impairment and is often treated with medication. This paper will discuss clinical issues pertaining to the diagnosis of ADHD in preschool children, along with an overview of available data on pharmacotherapy of ADHD in this age group.

DIAGNOSTIC CONSIDERATIONS IN PRESCHOOL ADHD

Prior to the initiation of pharmacotherapy for ADHD, a careful diagnostic evaluation is essential. The DSM-IV-TR-defined diagnostic criteria for ADHD are not age-specific;[5] therefore, it is up to the clinician to evaluate the patient's symptoms in the appropriate developmental context. For example, an inappropriate diagnosis of ADHD may be made in a preschooler if there is failure on the part of the clinician to recognize developmentally appropriate inattention, motor activity, and oppositionality.[8] It is also important to be aware that problematic inattention and hyperactivity-impulsivity may be attributable to other factors. The astute clinician must consider an extensive differential diagnostic list in young children, such as lead

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toxicity, cognitive delays, learning disabilities, genetic disorders (e.g. Fragile X), sensory impairments in vision or hearing, or other neurodevelopmental delays. Alternate etiologies for ADHD-like symptoms may also include other psychiatric disorders, such as adjustment or anxiety disorders, depression, and pervasive developmental disorders, or general medical conditions, such as endocrine or seizure disorders.

The evidence base supporting the validity of a diagnosis of ADHD in preschool-aged children is growing.[8] An evaluation of 126 4- to 6-year-old children and 126 age-matched controls by Lahey's group found that the children with ADHD consistently demonstrated social and academic impairment on a range of variables, when compared to the children in the control group. The group's use of a structured diagnostic protocol demonstrated that the three subtypes of ADHD, primarily inattentive, primarily hyperactive/impulsive, and combined, can be reliably identified in 4- to 6-year olds.[8]

ADHD symptoms identified during the preschool years have a moderate degree of predictive value. Typical symptoms of ADHD identified in three-year-olds were predictive of impairing ADHD in 50 percent and 48 percent of cases at three- and six-year follow-up assessments, respectively.[5] The diagnosis of ADHD in a preschool child was found to be stable up to a period of three years.[16] Diagnostic subtype, however, demonstrated instability from preschool through elementary age in a 2005 report of a longitudinal study by Lahey, et al.[17] This study, which consisted of seven assessments in eight years, followed 118 4- to 6-year-olds with DSM-IV ADHD. The majority of children meeting criteria for ADHD at study entry, subsequently had persistent ADHD at the follow-up assessments, with combined subtype appearing the most durable (n=83). However, about one third of the children (n=31/83) with the hyperactive-impulsive subtype and half of those with the inattentive subtype (n=6/12) met criteria for a different subtype at least twice over the course of the follow-up assessments. Children with the hyperactive-impulsive subtype were most likely to shift into combined subtype in later years. Mean levels of hyperactivity-impulsivity were consistently different, while mean levels of inattentive symptoms saw less variability.[17] Clinicians must be mindful of the potential for the presentation of ADHD to change as the child ages, and especially of the fact that the full extent of impairment due to inattentive symptoms may not be apparent until the demands on a child's ability to attend exceed his or her capacity to do so.

PRACTICE GUIDELINES

Both the American Academy of Child and Adolescent Psychiatry (AACAP) and the American Academy of Pediatrics (AAP) have developed practice parameters in order to provide guidance for the evaluation and treatment of pediatric ADHD. The AACAP recommends that the initial assessment consists of a thorough developmental, medical, psychiatric and family history of the child, as well as a systematic assessment for DSM-IV symptoms.[18] Standardized rating scales, such as the Conners' Rating Scales for parents and teachers,[19,20] or the ADHD-IV Rating Scale[21] may be utilized to document baseline symptom severity. School reports of psychoeducational or other standardized testing, grades, behavior reports, and any individualized educational plans (IEPs) should be reviewed in the course of the diagnostic evaluation. Assessment of the child should include a mental status exam, approximation of IQ, speech and language ability, fine and gross motor skills, as well as visual and/or auditory deficits. Additionally, a physical examination and consideration of possible exposure to lead is recommended. Comorbid learning disorders, mental retardation, developmental disorders, or other psychiatric disorders should be identified or ruled out prior to initiation of treatment. The AACAP also advises the clinician to have a degree of suspicion of possible abuse in cases of young children presenting with ADHD-like symptoms. Performance across settings (classroom, peer group, family) should be assessed and monitored.[18]

In the case of young children with ADHD, the AACAP emphasizes the role of the family in treatment. Support and education for parents, including parent-training, can increase parent competence and overall adherence, as well as improve parent-child interactions.[18] Treatment goals should be individualized to the needs of the child and should be identified and monitored by the clinician in collaboration with caregivers and school personnel. Treatment selection is advised to be based on target symptom severity, comorbid conditions, treatment goals, family preferences, capacity for adherence with treatment, and access to services[22] and educational placement.[18] The treatment plan should be designed with long-term management in mind, emphasizing ongoing assessment of target symptoms, the severity and degree of impairment, and the effectiveness of and continued need for treatment. Educational planning and support for the child and caregivers should be ongoing components of treatment.[22]

Psychosocial interventions, such as parent-training and structured environments, should ideally be attempted before medications are introduced into the treatment plan. Behavioral therapy is an

evidence-based treatment consisting of a system of specific interventions aimed at altering the social or physical environment in order to modify the child's behavior.[23] In addition to increasing structure at home and school, parents and teachers are generally encouraged to implement one or more behavioral interventions, including positive reinforcement, time-out, response-cost, and token economy programs. The challenge of these interventions lies in the need for consistent implementation of the interventions and adaptation of the program to the changing needs of the child.[24] However, parent and teacher satisfaction has been shown to increase when behavior therapy is used alone or in conjunction with medication to treat ADHD.[22]

Use of stimulant medication in the general pediatric population, if indicated, can increase on-task behavior, directability, attention, play quality, and mother-child interactions, while decreasing aggressive and oppositional behavior. Medication is advised to be initiated at low doses, and titrated slowly, with frequent monitoring.[18] Psychostimulants, currently available in short, intermediate, and long-acting sustained-release preparations, have been the mainstay of pharmacologic treatment of ADHD, offering one of the highest treatment responses in the psychopharmacology, with 75 percent of children responding to the first agent selected, and between 80 and 90 percent responding if two different stimulants are tried consecutively.[25] Multiple randomized, controlled trials compared stimulants to placebo show effect sizes in children and youth of 0.8 to 1.2.[26] A successful treatment strategy may ultimately involve a combination of medications with different durations of action (i.e., a sustained-release stimulant preparation given in the morning followed by a short-acting dose in the late-afternoon or early evening). If medication is indicated and a decision is made to initiate pharmacotherapy, the AACAP recommends dosing seven days per week.[18] While weight-based dosing guidelines for children are available, clinicians should be aware that young children may not abide by these.

Data are limited on the pharmacological treatment of preschool ADHD. To date only 10 placebo-controlled trials of psychostimulants have been published, all of these with methylphenidate.[27–36] A naturalistic study by Short, et al., in 2004 of stimulant treatment (either mixed amphetamine salts or methylphenidate) in 3- to 5-year olds showed that subjects had an 82 percent response rate a stimulant medication.[37]

Efficacy of stimulants in the preschool age group can be variable, however, and side effects, such as sadness, irritability, clinginess, insomnia, and anorexia, are more likely to occur with their use; thus, medication has historically been used in only the most severe cases or when parent-training and structured educational settings are not available or are unsuccessful.[18] Once treatment is initiated and optimized, clinic visits are recommended at least every 3 to 6 months in order to provide ongoing evaluation of the treatment plan, goals, and adherence throughout the treatment of a child with ADHD. Side effects should be monitored regularly, as well as vital signs and growth velocity.[22]

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PRESCHOOL ADHD TREATMENT STUDY (PATS)

The Preschool ADHD Treatment Study (PATS) is an NIMH-funded, six-site, randomized, controlled psychopharmacology trial assessing the safety and efficacy of methylphenidate in preschoolers. This eight-phase, 70-week study recruited 303 children, ages 3 to 5.5 years, and included a screening period, parent-training, baseline assessment, open-label safety lead-in, double-blind-crossover titration, double-blind parallel efficacy phase, followed by open-label maintenance and double-blind discontinuation. Parent and teacher ratings were used to assess medication response throughout the pharmacotherapy phases.[38]

Though complex, this study design will provide a wealth of knowledge on multiple aspects of the treatment of preschool children with ADHD.

In order to enter the pharmacotherapy portion of the study, families were first required to participate in a 10-week group parent-training program. The children with less than a 30-percent improvement in ADHD symptom severity following parent-training, proceeded to the methylphenidate treatment. The pharmacotherapy began with a five-week, double-blind, randomized, within-subject titration trial to identify the optimal dose of methylphenidate for each child. PATS utilized a conservative starting dose of 1.25mg/day immediate-release methylphenidate, given three times daily (TID). Following this phase, there was a four-week, double-blind, randomized, parallel design trial comparing children on optimal treatment with methylphenidate to those receiving placebo. This was then followed by 42 weeks of open-label methylphenidate treatment assessing longitudinal safety. A six-week randomized placebo discontinuation phase concluded the trial.[39]

PATS randomized 165 of the initial 303 preschoolers enrolled in the trial to the double-blind, placebo-controlled titration portion of the study. Immediate-release methylphenidate 2.5mg, 5mg, and 7.5mg given TID were all found to demonstrate significant decreases in ADHD symptoms compared to placebo ($p<0.01$, $p<0.001$, and $p<0.001$, respectively). The 1.25mg TID dose was not statistically superior to placebo. The mean optimal total daily dose of methylphenidate for the group was 14.2±8.1mg/day (0.7±0.4mg/kg/day). Although ADHD symptoms were significantly reduced on 2.5mg, 5mg, and 7.5mg given TID compared to placebo, effect sizes observed in the preschoolers (0.4–0.8) were smaller than those found in school-aged children on methylphenidate.[40] It should be noted, however, that doses greater than 7.5mg TID were not examined, which may in part account for the limited effect sizes.

Total daily doses of methylphenidate ranged from 3.75 to 22.5mg in the titration phase (mean 14.1mg, ±8.1mg), and subjects completing the maintenance phase had a mean total daily dose of 20.5mg (±9.7mg). Statistically but not clinically significant elevations of blood pressure and pulse were associated with methylphenidate treatment. Emotional outbursts, difficulty falling asleep, repetitive behaviors/thoughts, appetite decrease, and irritability were the adverse events most frequently reported across the study. Moderate to severe adverse events were experienced by 25 to 30 percent of children assigned to the two highest total daily doses (15 and 22.5mg/day) of methylphenidate, compared with 15 to 20 percent of those assigned to placebo. While there were no drug-related serious adverse events during PATS, there were 21 (11%) discontinuations due to adverse events.[41]

PSYCHOSTIMULANTS: PRACTICAL CONSIDERATIONS FOR YOUNG PATIENTS

One of the factors that can limit the use of certain psychotropic medications in pediatrics is that young children often cannot (or will not) swallow pills. An alternative for these children with ADHD is use of one of the extended release psychostimulants in capsules that can be opened and sprinkled on applesauce or pudding to facilitate swallowing (e.g., Adderall XR, Focalin XR, Ritalin LA, Metadate CD). Several of these stimulant preparations have been formally tested and have wording in their label specifically addressing this approach.

A transdermal delivery system for methylphenidate Daytrana has recently been approved by the FDA for children ages 6 to 12 years and is now commercially available.[42] The manufacturer, Noven Pharmaceuticals, recommends it be placed on the hip and worn for nine hours per day; however, it can be removed earlier if a shorter duration of action is desired or the child experiences side effects, such as appetite loss or insomnia, that need to be managed. Placement sites should be alternated to minimize possible irritation to the skin. The patch delivers 10, 15, 20, or 30mg of methylphenidate over nine hours via patches dosed as 27.5, 41.3, 55.0, and 82.5mg, respectively. Methylphenidate is delivered continuously while the

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patch is on and the therapeutic actions of the drug continue for up to two hours after it has been removed. Clinical trials have indicated that children using the methylphenidate patch experience improvement in academic, social, and behavioral functioning, and that the side effects they experience are consistent with those commonly associated with oral methylphenidate, including anorexia, decreased appetite, headache, insomnia, and abdominal pain. Some children experienced erythema at the patch site, but this generally resolved within eight hours of it being taken off. Very few children removed the patch prematurely in the clinical trials, and those who did often were identified as having comorbid conduct disorders.

ATOMOXETINE

There has also been interest in the use of non-stimulant treatment options for young children with ADHD. Atomoxetine (Strattera™) received FDA approval in November, 2002, for children ages six years through adulthood. It is a selective noradrenergic reuptake inhibitor,[43] which has been examined in multiple pediatric clinical trials, including children as young as six years old. No studies have been published looking at atomoxetine use in children under age six, but, not unlike the stimulants, clinicians are using it in the treatment of younger children none-the-less. Van Brunt, et al.,[44] reviewed the PharMetrics database and documented that prescriptions are being written for atomoxetine for children five years of age and younger, despite the lack of controlled data on its safety or efficacy in this younger population.

The lack of data on atomoxetine use in young children leaves clinicians to extrapolate information on safety and efficacy from the data available on older children and adolescents. Wilens, et al.,[45] presented data from a meta-analysis contrasting the efficacy and tolerability of atomoxetine between children (6–11 years) and adolescents (12–17 years) with ADHD. Data from 851 children (510 atomoxetine, 341 placebo) and 176 adolescents (107 atomoxetine, 69 placebo) participating in similar acute, double-blind, placebo-controlled studies were pooled and analyzed. No statistically significant differences between the age groups were found in the overall effects of atomoxetine on core ADHD symptoms, or the rate of and time to response. Reduction in the ADHD-IV-RS total score was statistically significant between the atomoxetine and placebo groups in both age categories ($p<0.01$), and both age groups on atomoxetine treatment had a time to response (25% reduction in ADHD-IV-Rating Scale (ADHD-IV-RS) total score) of approximately two weeks. Vital sign, height, weight, laboratory, and ECG changes were not statistically or clinically meaningful. Children, however, were more likely to report headaches ($p=0.45$) and somnolence ($p=0.47$) than adolescents taking atomoxetine. Decreased appetite was reported by 18.1 percent of children on atomoxetine and 11.3 percent of adolescents. This finding was not statistically significant.

A meta-analysis of the youngest children studied to date with atomoxetine, 323 six- and seven-year olds with ADHD (126 in double-blind and 197 in open-label studies), was reported by Kratochvil, et al.[46] In the placebo-controlled trials, children receiving atomoxetine had statistically significant improvements on the ADHD-IV-RS total score ($p<0.001$), inattentive ($p=0.002$) and hyperactive/impulsive ($p<0.001$) subscale scores. Significant improvements were noted in open-label study participants as well ($p<0.001$) on these measures. Three subjects (2 on atomoxetine, 1 on placebo) in the double-blind studies, and eight in open-label subjects discontinued due to adverse events. A treatment effect size of 0.7, comparable to that reported in older children and

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adolescents was observed in the pooled group of 6- and 7-year olds,

Kratochvil, et al.,[47] completed a meta-analysis of long term treatment (≥2 years), with 13 studies of atomoxetine which included 272 six- and seven-year-olds. Of these, 97 children had reached the 24-month point in the ongoing treatment studies. Subjects had a mean decrease of 19.27 (SD 12.72, $p<0.001$) from a baseline score of 42.14 (SD=8.32) on the ADHD-IV-RS, with t-scores indicating that symptom severity decreased from 3.2 SD above the norm to 1.3 SD above. Marked improvement was noted one month into treatment, with continued improvement accrued during the first year, and improvement maintained throughout the remainder of the 24 months analyzed. Only 11 subjects discontinued at any point during the two-year period due to adverse events, and eight of these did so within the first six months of treatment. Twenty-two percent of subjects reported abdominal pain at some point in the clinical trial, and decreased appetite was reported by 21.3 percent. Vital sign, laboratory and ECG changes for the group were not clinically significant.

GROWTH OUTCOMES

Children with ADHD do not appear to follow the same growth patterns of the age-matched general population[48]. An analysis of 4,434 6- to 17-year-olds was conducted in order to characterize the height and weight of children with ADHD. Baseline height and weight values were transformed to percentiles and z-scores. At baseline, mean percentiles across all subjects were 51.6 (z=0.06) for height and 61.7 (z=0.43) for weight. Subjects who had been previously treated with a stimulant were found to be shorter than those who were stimulant-naive (48.8 percentile versus 56.3 percencile; z-score -0.04 vs 0.22; $p<0.001$). The youngest subjects were larger relative to the age-matched population than the older subjects on measures of relative height and weight ($p<0.001$). No differences were noted with respect to gender. These researchers concluded that ADHD children were taller than expected at earlier ages, and, in some cases, were also heavier. Because age-matched subjects with prior stimulant use were shorter and lighter than those that were not treated previously, Swanson, et al., concluded that stimulant treatment may have resulted in growth suppression.

Concerns about growth and prolonged stimulant use in children have been present for decades, with early as well as more recent studies associating stimulant use with diminished weight gain.[49–51] Some studies have also suggested that stimulants may negatively affect height[49,52,53] while others[54,55] concluded that although small deficits in height were evident during early adolescence in children with ADHD, they were not present in late adolescence and were unrelated to the use of psychotropic medication. Spencer, et al., also concluded that there was no evidence of weight deficits or a relationship between malnutrition and short stature in those treated with stimulants.[54,55] In a recent study of seventy nine 6- to 12-year-old children being treated with psychostimulants for ADHD over a 5 year period, Charach, et al., again raised concerns regarding growth.[56] The investigators determined that daily use of a stimulant medication was associated with negative z-scores for height (z-score= -0.11, $p<0.01$) and weight (z-score= -0.29, $p<0.01$). Those children receiving ≥1.5mg/kg/day of methylphenidate showed diminished weight gain after one year of treatment, and those receiving ≥2.5mg/kg/day of methylphenidate showed diminished gains in height after four years.[56]

The PATS study examined growth of preschoolers before and after treatment with methylphenidate given TID (mean total daily dose 14.2mg), seven days per week for approximately one year. At baseline, the average age of the children was 4.4 years. Interestingly, at baseline the heights and weights were greater than expected for age (by 2.4cm, and 1.78kg respectively). During treatment a reduction in growth rate was statistically significant (z-height -0.0304/yr, z-weight -0.530/yr; $p<0.0001$). For the 95 children who completed the year

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of treatment, the annual rate of growth was 20.3 percent less than anticipated for height (-1.38cm/yr), and 55.2 percent less than expected for weight (-1.32kg/yr). The PATS investigators concluded that the risks of reduced growth rates must be considered in relation to the benefits anticipated with stimulant medication treatment for preschool children with ADHD.[57]

While no other data are available on the long-term treatment of preschool children with ADHD and growth, several other studies in older children are discussed here to provide a more comprehensive overview of ADHD pharmacotherapy and growth. Spencer, et al.,[58] followed 178 children ages 6 to 13 years taking OROS methylphenidate over 21 months. At baseline, the children had heights approximately those expected for their ages, although slightly heavier than anticipated. Height increased during the course of the study; however, at month 21 subjects were an average of 0.23cm shorter than expected. Body mass index (BMI) decreased during the first four months of treatment, and weight did not increase during that time. Afterwards, *z*-scores for weight and BMI remained relatively constant, with the children weighing an average of 1.23kg less than anticipated at Month 21. Drug holidays did not impact growth in this study, and other than slight decreases in weight during the initial four months of treatment, the effects of OROS methylphenidate on growth were not clinically significant.

Weight and height data on children and adolescents treated with atomoxetine for at least two years was recently reported by Spencer et al.[59] A meta-analysis of data from 412 subjects ages 6 to 16 years taking atomoxetine at a maximum dose of 1.8mg/kg/day was conducted and showed that after two years, height and weight values were close to those predicted based on the patients' height and weight at baseline. Weight increased an average of 10.8kg (0.87kg less than expected, 2.7 percentiles less than expected) and height increased an average of 13.3cm (0.44cm and 2.2 percentiles less than expected). The smallest quartile of subjects at baseline had increases in their end-point percentiles, while the quartile who were largest at baseline had decreases at the final measurement. The authors concluded that atomoxetine had only a minimal effect on growth outcomes in this analysis, and that for the patients at the highest risk, the smallest quartile, there seemed to be no effect.

In the 2006 study by Kratochvil, et al.,[48] of 272 six- and seven-year-olds undergoing long-term treatment with atomoxetine, weight and height measurements at the 24-month point were 2.5kg and 2.7cm less than expected based on the subjects' baseline weight and height percentiles. Deviations from the expected weights and heights were again greatest in the children who were in the upper percentiles at baseline, and least in those children who were the smallest.

CONCLUSIONS

Careful consideration should be given before making the diagnosis of ADHD in a young child, and determination of the need for medication must be thought through with caution. Guidelines from the AACAP and AAP offer some consensus on the best way to evaluate a young child and determine if and when pharmacotherapy is appropriate. If medication is warranted, many factors should be considered including identification of target symptoms and desired outcomes, the ability of parents/caregivers to ensure compliance with medication as well as appointments, close monitoring of acute and chronic side effects, the financial resources of the family, and the ability of the child to take the medication.

Methylphenidate continues to have the most data supporting its use in young children below the age of six and, therefore, should be considered first. It should be initiated at a low dose and gradually titrated to the optimal dose, determined both by tolerability and resolution of target symptoms. With stimulants, the treatment regimen can be tailored to the child's individual needs, utilizing short-acting medication, long-acting preparations, and for some a combination of the two. In the event that swallowing is an

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issue, the transdermal patch may be an option for some children. Preschool data is still forthcoming on non-stimulant agents such as atomoxetine.

If a decision is made to initiate pharmacotherapy, monitoring growth is, among other things, essential in a young child. Careful height and weight monitoring will be necessary throughout the course of pharmacotherapy, with appropriate interventions or changes in treatment initiated if a failure to gain weight or to increase in stature becomes apparent. Ensuring caloric intake through supplements or other behavioral and dietary strategies may likely be a component of the treatment plan.

With all pharmacotherapies, a careful assessment of the risks and the benefits of available treatments is crucial, as is consideration of the risks of not treating. The decision to treat or not, and the selection of a treatment, should be done as part of an open dialogue between the clinician, the child, and family.

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