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Child Adolesc Psychiatric Clin N Am
17 (2008) 459–474

CHILD AND
ADOLESCENT
PSYCHIATRIC CLINICS
OF NORTH AMERICA

Understanding the Risk of Using Medications for Attention Deficit Hyperactivity Disorder with Respect to Physical Growth and Cardiovascular Function

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The treatment of attention deficit hyperactivity disorder (ADHD) with stimulant medications dates back to the late 1930s and has been common practice for decades. Hundreds of research reports have documented the therapeutic and adverse effects of methylphenidate and amphetamines have been well characterized, and stimulants in children. Frequent and less frequent adverse effects of methylphenidate and amphetamines are characterized and a dose-effect relationship demonstrated for some of them in school-aged children and preschoolers [1,2]. Decrease in appetite, stomachache, nausea, headache, insomnia, and nervousness are frequent on starting treatment but lead to treatment discontinuation in less than 5% of school-aged children, although higher rates were observed in preschoolers (approximately 9%) and in children who had pervasive developmental disorders (approximately 18%) [1–4]. The still lively debate about certain aspects of the safety of these medications attests to the difficulty of establishing safety issues conclusively and the need to evaluate risk in the context of the evolving clinical practice.

The use of medications for the treatment of ADHD has expanded considerably over the past decade, becoming common in adolescents and adults in addition to prepubertal children [5,6]. New formulations of

The opinions and assertions contained in this report are the private views of the author and are not to be construed as official or as reflecting the views of the Department of Health and Human Services, the National Institutes of Health, or the National Institute of Mental Health.

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1056-4993/08/$ - see front matter. Published by Elsevier Inc.
doi:10.1016/j.chc.2007.11.010

stimulants have been developed to allow extended pharmacologic activity with single dosing, and a novel, nonstimulant compound, atomoxetine, was introduced in 2003. These factors have contributed to bringing new attention to short- and long-term risks for pharmacologic treatment of ADHD [7,8].

Two distinct, persisting concerns about medications approved for the treatment of ADHD relate to their impact on physical growth, with possible implications for development and adult height, and to their cardiovascular effects, with possible implications for serious cardiotoxicity. The purpose of this review is to discuss these issues critically in light of current clinical practice and the need for further research.

Stimulants and physical growth

That long-term stimulant treatment of children can decrease growth velocity has been recognized for more than 30 years [9]. Several studies conducted in the 1970s and 1980s investigated the extent, persistence, and possible mechanisms of stimulant-induced growth suppression [10–16]. It was observed that the effect on weight typically emerges in the first few months of treatment, followed by attenuation, whereas the effect on height takes at least 1 year to become detectable. From these studies, the loss of expected growth in height was estimated at approximately 1 cm per year for children treated continuously (with daily doses above 20 mg of methylphenidate for 3 years or longer). Growth rebound was reported after drug discontinuation, and interruptions of stimulant treatment (drug holidays) attenuated this effect on growth [10,12]. Furthermore, no difference in final height was found between young adults treated with methylphenidate (average daily dose of 45 mg for 6 months to 5 years) and untreated peers [13]. Almost all these children, however, had discontinued stimulant treatment before age 13, leaving open the question of whether or not continuous treatment throughout puberty may have an impact on final growth.

Consequent to this considerable body of work, recommendations for periodic monitoring of weight and height were included in treatment guidelines and drug product labeling instructions, but the effect of stimulants on growth generally had been considered minor, transient, and of negligible practical importance [17,18]. More recently, with the continuous expansion on the use of stimulant medications and the increasingly longer duration of treatment of ADHD, which now is recognized as a persistent, lifelong condition rather than a spontaneously resolving developmental phenomenon, more attention is paid to possible long-term treatment effects, including effects on physical growth. It also is postulated that growth delay may be intrinsic in the ADHD condition rather than drug induced [19], but other studies have not found evidence that unmedicated ADHD are smaller than expected [20,21].

Several recently reported long-term treatment studies have provided an opportunity to evaluate the effects of stimulants on growth in greater detail.

A dozen studies addressing this issue have been published since 2000 (Table 1) [20–33]. These studies vary considerably in sample size, design, and methodology. Although most relied on prospective, longitudinal assessments of naturalistically treated children, others were retrospective chart reviews. Some used a normal control comparison, others an unmedicated ADHD sample. Most referred to population norms using *z* scores (ie, deviation from the population mean measured in SD units), but some relied on percentile changes (ie, movement from one population growth trajectory to another). A systematic review of studies addressing growth during stimulant treatment was published in 2005 and identified 29 studies, 11 of which reported an attenuation of growth with chronic treatment that was estimated at approximately 1 cm per year for the first 1 to 3 years of treatment [34]. The pattern that emerges from these studies is of early weight loss in the first 3 to 4 months of treatment, more marked among the heaviest children, followed by a resumption of weight growth; slowing in height growth becomes evident after approximately 1 year of continuous treatment and persists, although attenuated, over the years.

Among these studies, the Multimodal Treatment Study of ADHD (MTA) took advantage of a large sample size of children (N = 579), homogeneous for age (7–9 years), and randomly assigned to nonpharmacologic intervention, community treatment (average methylphenidate dose 23 mg per day), combined psychosocial and medication treatment (31 mg per day), or intensive medication treatment (38 mg per day) for 14 months [27,35,36]. Treatment consisted of immediate-release methylphenidate, given 3 times a day and continued 7 days a week with no drug holidays. In these treatment groups, mean growth was 6.19 cm, 5.58 cm, 4.85 cm, and 4.25 cm, respectively, for height, with a mean estimated loss of growth of 1.23 cm per year for the group medicated most intensively. For weight, growth was 4.53 kg, 3.13 kg, 2.52 kg, and 1.64 kg, respectively, with a mean estimated loss of growth of 2.48 kg per year for the group medicated most intensively [27]. These data strongly suggest that the effect of stimulants on growth is dose dependent, as also reported by other investigators [31].

One limitation of the MTA was that several children had received stimulant treatment before entering the study. Because the effect of medication on growth is strongest in the first few months of treatment and may be followed by rebound on discontinuation, prestudy treatment can bias the estimates of treatment effect during the study. Thus, stimulant effect on growth is assessed best in treatment-naïve subjects not exposed to stimulants [34]. The MTA sample has been followed naturalistically after the end of the 14-month controlled trial. Analyses of the data from the children who were medicated consistently, never medicated, or newly medicated confirmed a growth suppression effect, which was evident especially during the first 2 years of treatment and still detectable after 3 years, when the newly medicated group had grown on average 2.0 cm and 2.7 kg less than the unmedicated group [21].

Table 1
Recently reported studies of growth during stimulant treatment

Study	N	Age (years)	Drug	Dose[a]	Duration	Design	Findings
Kramer, et al, 2000 [22]	97	4–12	MPH	10–40 mg	36 months	Retrospective	Adult height and weight not affected
Sund and Zeiner, 2002 [23]	91	3–10	MPH AMP	24 mg 12 mg	12 months	Observational	Smaller weight growth on AMP
Lisska and Rivkees, 2003 [24]	84	—	MPH	22 mg	24 months	Observational	Decrease in height *z* scores
Poulton and Cowell, 2003 [25]	51	3–11	MPH AMP	27 mg 14 mg	6–42 months	Observational	1 cm/y and 1.2 kg less than expected
Biederman, et al, 2003 [26]	124	6–17	Multiple	Unspecified	Unspecified	Observational	No treatment effect on growth
MTA Cooperative, 2004 [27]	579	7–10	MPH[b]	0–39 mg[c]	14 months	Randomized	1.23 cm/y and 2.48 kg/y less growth
Faraone, et al, 2005 [28]	569	6–12	AMP-XR	10–30 mg	6–30 months	Observational	Decrease in height (−0.31) and weight (−0.63) *z* scores
Spencer, et al, 2006 [29]	178	6–13	OROS MPH	1.2 mg/kg 43.7 mg	21 months	Observational	0.23 cm less than expected 1.23 kg less than expected; no change in mean *z* scores
Pliszka, et al, 2006 [30]	113 66	8.5 (mean) 9.0 (mean)	MPH AMP	34.8 mg 22.7 mg	32 months 29 months	Retrospective	No change in mean *z* scores
Charach, et al, 2006 [31]	79	6–12	MPH or AMP	Unspecified	60 months	Observational	Dose-dependent decrease in height and weight *z* scores
Zachor, et al, 2006 [32]	81	8.5 (mean)	MPH or AMP	Unspecified	36 months	Retrospective	Decrease in *z* scores for weight but not for height

Swanson, et al, 2006 [20]	95	3–5	MPH	14.2 mg	12 months	Observational	1.4 cm/y less than expected; 1.3 kg/y less than expected; 0.30 decrease in height *z*; 0.53 decrease in weight *z*
Swanson, et al, 2007 [21][d]	320	7–10	MPH	Unspecified	36 months	Observational	Dose-related decrease in height and weight *z* scores; consistently medicated children were 2.3 cm shorter and 1.5 kg lighter than normal controls
Farietta-Murray, 2007 [33]	50	4–10	MPH AMP	Unspecified	24 months	Retrospective	Decrease in weight percentile only

Studies included were of at least 50 children and of at least 12-month duration.

Abbreviations: AMP, amphetamine; MPH, methylphenidate.

[a] Highest mean daily dose.

[b] A few children received dextroamphetamine or other medications.

[c] The mean daily MPH doses were 0 mg in the behavioral therapy group, 23 mg in the community control, 31 mg in the combined medication management/behavior therapy group, and 38 mg in the medication management group.

[d] Based on the MTA study sample and reporting on the 36-month naturalistic follow-up.

Although the preponderance of the evidence indicates that there is a statistically significant suppression of growth with stimulants, whether or not this effect is clinically significant is a subject of debate. A difference in height of 2 cm over a 3-year period may be considered by some of borderline practical significance, but this consideration is based on group mean differences: some children can present with larger differences, which, in the context of individual children's situations, may be important. Case reports describe particular clinical situations where growth suppression was of concern. For example, a 10-year-old boy presented with an almost complete growth arrest after being treated with methylphenidate for 15 months concurrently with corticosteroids for asthma; bone age indicated a delay of 10 months with a 7-cm loss of projected adult height [37]. No generalizations are possible from such case descriptions, except that the growth of individual patients should be monitored carefully during stimulant treatment, especially if other medications known for affecting growth are prescribed concomitantly.

An indirect concern is whether or not the effect on height is paralleled by delayed growth in organs of the body besides the skeletal system. At this time, there are no data to support this concern. Although no effect on the onset of puberty is reported, this issue has not been addressed fully.

A critical question is whether this loss of growth velocity merely is a transient delay or if final height can be affected. Prior studies indicate that rebound occurs during drug holidays (with some reports suggesting that it occurs even when treatment is continued), and that, in any case, adult height is not affected [10,12,13,38]. Not all the studies, however, have found evidence of growth rebound or confirmed the benefit of drug holidays [24,25,29]. Current evidence indicates that stimulant treatment does not, on average, influence final height, but further data from children medicated continuously for more than 3 years and during puberty seem to be needed before settling this issue. Few studies have examined bone age in the context of stimulant treatment [37]. An investigation of the dental development of children who had received methylphenidate daily, at the average 30 mg for more than 4 years, did not find evidence of delay in dental maturation [39].

Relevant to understanding the effect of stimulants on growth is the elucidation of the underlying mechanism of action. Stimulants are known for decreasing appetite in children and adults. For instance, in a randomized controlled clinical trial involving 282 children, ages 6 to 12 years, the incidence of decreased food intake after 2 weeks of treatment was greater in the osmotic-controlled release formulation (OROS) of methylphenidate (22.5%) or in immediate-release methylphenidate (18.8%) group as compared with placebo (12.0%) [40]. During the 14-month treatment in the MTA, approximately 10% of 198 treated with methylphenidate required a dose decrease because of anorexia, making this the most common reason for dose reduction in this study [36]. Similar findings emerged from a retrospective review of children treated naturalistically [32]. Children under age 6

seem even more sensitive to the anorexic effects of stimulants. In the Preschoolers with ADHD Treatment Study, approximately 40% of the children showed decrease in appetite, a rate that remained basically unchanged during the 10-months' duration of treatment, in spite of the low doses used [2,41]. It is possible, therefore, that the effect on height is caused by the reduced caloric intake during stimulant treatment [34]. The effect on weight seems limited, however, to the first few months after starting treatment.

It is hypothesized that the persistant, stimulant-induced, increase in hypothalamic dopamine may affect pituitary function, thus slowing growth [42]. Such an explanation is consistent with dopamine antagonists increasing weight and seeming to accelerate height growth [43]. Studies in the late 1970s and early 1980s examined the possible effect of stimulants on diurnal and nocturnal plasma levels of growth hormone and prolactin. Acute administration of methylphenidate increased growth hormone and decreased prolactin, but no consistent changes in the plasma levels of these hormones were detected during chronic treatment [14–16]. More recently, a transient decrease in insulin-dependent growth factor after 4 months of treatment, which, however, was not evident at months 8 and 14 assessment, was reported in a few children [44]. Despite these hypotheses, the basic mechanism through which stimulants affect growth remains unknown and deserves further investigation.

Atomoxetine and physical growth

Atomoxetine is a nonstimulant, selective noradrenergic reuptake inhibitor approved for the treatment of ADHD since 2003. Gastrointestinal adverse effects, such as appetite decrease, vomiting, gastric upset, and abdominal pain, frequently emerge early in treatment but seldom lead to drug discontinuation [45]. Acute treatment is on average accompanied by a slight decrease in weight of approximately 1 kg over a period of 2 to 3 months. Several open-label studies of atomoxetine administered for 2 years or longer have been conducted and two meta-analyses reported recently.

One meta-analysis included data from 13 studies of 6- to 7-year-old children who were treated with atomoxetine (up to a mean dosage of 1.47/kg per day). At the end at the 24-month treatment, weight was on average 2.5 kg and height on average 2.7 cm less than expected based on baseline percentile [46]. The other meta-analysis pooled data from children and adolescents ages 6 to 16 [47]. After 24 months of treatment, there was a decrease of 2.7 percentile points for weight (corresponding to a mean 0.87 kg less than expected) and a decrease of 2.2 percentile points for height (0.44 cm less than expected). These differences between observed and estimated growth in these studies were statistically significant. The slowing in growth velocity was most evident after 18 months of treatment and tended to attenuate afterwards.

The clinical significance of this effect is considered negligible at the group mean level [46,47] but may be important at the individual patient level with

extended treatment beyond 2 years. The mechanism of the effect is speculated to be through a decrease in caloric intake. Caloric supplementation is suggested as a possible remedy, but its efficacy has not been tested. Because the therapeutic effect of atomoxetine requires continuous dosing, drug holidays are not an option during the academic year but may be considered for selected patients during summer vacations.

Stimulants and cardiovascular function

Stimulants are sympathomimetic agents that increase noradrenergic and dopaminergic transmission. An effect on heart rate and blood pressure can be considered an intrinsic feature of their pharmacologic activity [48]. Hypertension and tachycardia are common in case of overdosing with these compounds [49]. Several placebo-controlled studies have documented a slight, but statistically significant, increase in blood pressure and heart rate in children and adults during short-term administration of methylphenidate or amphetamine preparations [50–54]. The magnitude of the increase over placebo is approximately 2 to 6 bpm for heart rate, 2 to 4 mm Hg for systolic blood pressure, and 1 to 3 mm Hg for diastolic blood pressure. This conclusion is supported by 24-hour ambulatory recordings of blood pressure and heart rate of children medicated with stimulants, which found increases in diastolic blood pressure (75.5 mm Hg on medication versus 72.3 off medication) and heart rate (85.5 versus 79.9 bpm) [55].

Some studies, however, in spite of large sample sizes, did not find any differences in blood pressure or heart rate as compared with placebo [56,57]. In a large, open-label study involving almost 3000 children, ages 6 to 12 years, who were treated with extended release mixed amphetamine salts (up to 40 mg per day for up to 15 weeks), increase in systolic and diastolic blood pressure of less 1 mm Hg and increase in heart rate of approximately 1 bpm were detected, which were statistically significant mainly because of the large sample size but were considered without clinical relevance [58]. In this study, sustained blood pressure measurements above the 95th percentile were found in 2.5% and heart rate above 110 bpm in 3.6% of children. Although it is difficult to interpret causality in the absence of a control, as these changes might have happened regardless of treatment, these findings suggest that there are individual subjects who have clinically significant changes.

Open-label studies of children during long-term treatment indicate that these modest changes in heart rate and blood pressure tend to persist, a sign that full tolerance does not develop during chronic treatment [56,58]. Besides an increase in rhythm, no consistent ECG changes are attributed to stimulant medications. In particular, no clinically significant prolongation of the QT interval has been detected, although some studies found a statistically significant increase [53,57–59].

From a clinical point of view, two questions seem especially relevant. First, does even a slight elevation in blood pressure and heart rate increase

the risk for cardiovascular pathology in the long run? The risk for cardiovascular disease increases monotonically with increasing values of blood pressure without any specified cutoff point for no risk. Currently, there is no evidence that adults who were medicated as children are at increased risk for hypertension or cardiovascular events. This issue has not been investigated fully, however, especially as stimulant treatment can start early in childhood and last for years into adulthood.

The second question relates to the debate about a possible link between stimulant treatment and sudden cardiovascular death [60,61]. In young people (first 3 decades of life), the incidence of sudden death from cardiac causes, defined as death that is instantaneous or occurs within 24 hours of an acute collapse [62], is estimated to range from 1.3 to 8.5 per 100,000 person-years, and a specific cardiac cause is identified in two thirds of the cases [63]. In older adults, sudden death typically occurs in the context of coronary atherosclerosis and is the result of ventricular fibrillation. Given the widespread use of stimulants for the treatment of ADHD in children and the increasing use in adults, it is not surprising that several cases of sudden death were reported to the Adverse Event Reporting System (AERS) of the Food and Drug Administration.

From January 1992 to February 2005, 20 cases of sudden death during treatment with amphetamine products were reported: 14 in children (under age 19) and 6 in adults; 6 of the 14 children had structural cardiovascular abnormalities or other predisposing factors for sudden death. During the same period, 18 cases of sudden death during treatment with methylphenidate were reported: 14 in children (6 had structural cardiovascular abnormalities) and 4 in adults [64]. The apparently similar incidence for amphetamine as for methylphenidate, despite the more common use of the latter, is intriguing, but may be due to reporting biases.

The estimated rates of sudden death based on these reports is below the background rates in the general population, but only a fraction of actual adverse events typically are reported to the AERS, so that accurate estimates of true incidence are not possible. Conclusions about presence or absence of a causal link cannot be drawn, therefore, from these data. Future analyses of systematically collected data from large numbers of patients in community settings treated naturalistically might be informative. Given the increasing use of stimulants for the treatment of ADHD in adults, it is important to investigate further possible adverse cardiovascular effects in this age group, with special attention to patients who have risks factors for heart disease, such as hypertension, atherosclerosis, smoking, or concomitant use of other drugs.

Even though a causal effect is not proved, it is plausible that stimulants, because of their sympathomimetic activity, may increase the risk for sudden cardiac death at usual therapeutic doses, especially in individuals who have predisposing factors. Therefore, the current product labeling for methylphenidate and amphetamine preparations informs that sudden deaths are

reported during treatment with these stimulant medications at usual doses in children and adolescents who have structural cardiac abnormalities or other serious heart problems and warns that these medications generally should not be used in individuals who have known serious structural cardiac abnormalities, cardiomyopathy, or serious heart rhythm abnormalities [65].

The current practice guidelines recommend a careful medical evaluation of children before starting stimulant treatment, including physical examination and collection of personal history of structural heart or rhythm abnormalities or of cardiovascular events, such as syncope, dizziness, palpitations, or chest pain at rest or during physical exercise, and of family history of sudden cardiac or unexplained death before age 30 [61,66]. Pulse, blood pressure, and adverse events during treatment should be monitored periodically during treatment. ECG or echocardiographic examinations currently are not required for individuals who do not have known personal or family risk factors but should be conducted in selected cases.

Not uncommonly, stimulants are prescribed concomitantly with other medications. In particular, α_2-adrenergic agents, such as clonidine or guanfacine, are prescribed off-label together with stimulants to children who have ADHD [67]. After the report of four cases of sudden death in children taking methylphenidate and clonidine in the mid-1990s, concerns were raised about the safety of this combination [68]. No causal link could be established, however, and no additional evidence of possible cardiotoxicity has emerged thus far.

Atomoxetine and cardiovascular function

Atomoxetine is a selective norepinephrine reuptake inhibitor and an effect on the cardiovascular system can be expected given its pharmacologic properties. A review of five placebo-controlled clinical trials involving 612 children, adolescents, or adults treated with therapeutic doses of atomoxetine up to 10 weeks confirmed an increase 5 to 9 bpm in mean heart rate with suggestions of a dose-effect relationship [69]. Moreover, 3.6% of the children and adolescents on atomoxetine versus 0.5% of those on placebo ($P = .02$) had an increase of at least 25 bpm to a value of 110 bpm or greater. Palpitations were more common in adults but not children or adolescents on atomoxetine. Systolic blood pressure was increased in adults but not in children and adolescents, whereas an increase in diastolic blood pressure was seen in children and adolescents but not in adults. In children and adolescents, the mean change in diastolic blood pressure was 2.1 mm Hg on atomoxetine versus −0.5 on placebo ($P = .002$). These changes occurred in the first few weeks of treatment and stabilized afterwards, with no further increases during long-term treatment of 1 year and longer [69]. No evidence that atomoxetine prolongs that QT interval were found [46,69].

Forty cases of overdose on atomoxetine (up to 480 mg) in children and adolescents were reviewed: tachycardia (mean 131 ± SD 14 bpm) and

hypertension up to 136/95 mm Hg occurred, but no other arrhythmias were detected [70]. Between November 2002 and February 2005, seven cases of sudden death during atomoxetine treatment were reported to the AERS, including three in children (ages 2.5–12 years) and four in adults. No evidence of causality can be derived from these cases, as there are multiple confounders and alternative explanations for these deaths other than atomoxetine [64].

Based on this information, physical examination (with heart rate and blood pressure measurements) and history taking should be part of the routine assessments before starting atomoxetine, followed by periodic checking of heart rate and blood pressure during treatment.

α_2-Agonists and cardiovascular function

Clonidine and guanfacine are marketed as antihypertensive drugs and do not have an official indication for the treatment of ADHD. They are, however, prescribed off-label alone or in combination with stimulants to children who have ADHD, especially in the presence of tic disorders or when other treatments prove insufficient [71]. Clonidine and guanfacine have prominent cardiovascular effects. They decrease blood pressure and can cause orthostatic hypotension, with dizziness, palpitations, and rapid heartbeat, when standing. Bradycardia also is a possible side effect. For these reasons, blood pressure and heart rate must be measured before and during treatment. ECG monitoring usually is not required, unless there is personal or family history of arrhythmias, cardiac malformations, or sudden unexpected death. With chronic treatment, tolerance to the hypotensive effects develops so that if the drug is discontinued abruptly, rebound hypertension can occur. Gradual tapering (decreasing the daily dose by 0.05 mg every 3 to 4 days) therefore is recommended.

Tricyclics and cardiovascular function

Although their use in children has decreased, tricyclic antidepressants still may be prescribed off-label for the treatment of ADHD in particular cases when stimulants or atomoxetine do not prove effective [71]. Tricyclics delay cardiac conduction and their use requires special attention to possible cardiotoxicity. Before starting treatment, children should receive a complete physical examination with ECG recording. Treatment should be considered only if the following limits are not exceeded on an ECG: 200 milliseconds for the PR interval, 120 milliseconds for the QRS interval, and 450 milliseconds for the corrected QT interval; and the heart rate should be regular and not higher than 100 bmp. If there is personal history of arrhythmias, dizziness, fainting, palpitation, or heart abnormalities, a more thorough evaluation by a cardiologist is appropriate. Family history of sudden, unexpected death or life-threatening arrhythmias may be reason for avoiding use of tricyclics. There

are reports of sudden death in children receiving therapeutic doses of tricyclics, even though a causal association is not demonstrated [72].

During treatment, ECG evaluation should be repeated after reaching a plasma steady state (usually after 4 days on a stable dose) and again if the dose is increased above 3 mg/kg per day. Plasma levels should be checked to make sure the subject is not a slow metabolizer. Plasma levels of imipramine and desipramine combined usually are approximately 80 to 225 ng/mL and should not exceed 300 ng/mL.

Summary

In past few years, there has been a flurry of studies investigating growth in children treated with stimulants because of ADHD. Overall, the findings confirm that stimulants cause a slowing in growth velocity for weight and height, which can persist, although attenuated, for at least to 4 years, during continuous treatment. A slight decrease in weight and height velocity also is observed during treatment with atomoxetine. The clinical and practical significance of this effect on growth is debatable, and further investigations are needed to clarify the exact mechanism of the effect and the impact on final height. From a clinical perspective, weight and height should be assessed at least semiannually in children receiving pharmacologic treatment, and the appropriateness of the treatment, or its intensity, reconsidered if there is substantial deviation from the individual child growth trajectory.

Stimulants and atomoxetine have cardiovascular effects with increase in heart rate and blood pressure. These changes usually are not clinically significant in the short term, but their possible significance for the long-term deserves further investigation. Although a causal link between therapeutic stimulant use and sudden cardiac death is not established, there are concerns that treatment may increase the risk for sudden death in patients who have structural cardiac abnormalities, so that careful pretreatment assessment and clinical screening currently is recommended.

Most important, safety considerations must be evaluated in the context of the therapeutic benefit from these medications, which is proved. Overall, when pharmacologic treatment of ADHD is prescribed correctly and monitored carefully, the balance between anticipated benefits and risks for harm is favorable.

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