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Understanding the Risk of Using Medications for ADHD with Respect to Physical Growth and Cardiovascular Function

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Abstract

The effects of stimulant medications and atomoxetine on physical growth, including weight and height velocity, and on cardiovascular function, including blood pressure, heart rate, and electrocardiogram parameters, are critically reviewed in light of the most recent data and with attention to clinical implications and research needs. It is concluded that, while these medications have a favorable benefit/risk profile and do not induce clinically significant changes in growth or cardiovascular function in the large majority of cases, careful patient monitoring is needed to identify individuals at risk for negative outcomes. More research is needed to elucidate the mechanism of growth suppression better estimate the risk for rare but life-threatening events, and test the effectiveness of monitoring procedures.

Introduction

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 stimulants in children. Frequent and less frequent adverse effects of methylphenidate and amphetamines have been characterized, and a dose-effect relationship demonstrated for some of them in both school-age children and preschoolers (1,2). Decrease in appetite, stomach ache, nausea, headache, insomnia, and nervousness are relatively frequent upon starting treatment, but lead to treatment discontinuation in less than 5% of school-age children, although higher rates were observed in preschoolers (about 9%) and in children with pervasive developmental disorders (about 18%) (1-4). The fact that there is still a lively debate about certain aspects of the safety of these medications attests to both the difficulty of conclusively establishing safety issues and the need to evaluate risk in the context of the evolving clinical practice.

The use of medications for the treatment of ADHD has considerably expanded over the last decade, becoming common also among adolescents and adults in addition to prepubertal children (5,6). New formulations of stimulants have been developed to allow extended pharmacological activity after single dosing, and a novel, non-stimulant compound, atomoxetine, was introduced in 2003. These factors have contributed to bring new attention to both short- and long-term risks of pharmacological treatment of ADHD (7,8).

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.

Two quite 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 critically discuss these issues in light of current clinical practice and 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). A number of 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, while the effect on height takes at least one year to become detectable. From these studies, the loss of expected growth in height was estimated to be around 1 cm per year for children treated continuously with daily doses above 20 mg of methylphenidate for three years or longer. Growth rebound was reported after drug discontinuation, and interruptions of stimulant treatment ("drug holidays") were found to attenuate this effect on growth (10,12). Furthermore, no difference in final height was found between young adults who were treated with methylphenidate at an average daily dose of 45 mg for 6 to 5 years and untreated peers (13). It should be noted, however, that almost all these children had discontinued stimulant treatment before age 13, thus leaving open the question whether continuous treatment throughout puberty may impact final growth.

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

A number of recently reported long-term treatment studies have provided an opportunity to evaluate the effects of stimulants on growth with greater detail. More than a dozen studies addressing this issue have been published since 2000 (20-34) (Table 1). These studies vary considerably in sample size, design and methodology. While 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 (i.e., deviation from the population mean measured in standard deviation units), but some relied instead on percentile changes (i.e., movement from one population growth trajectory to another). A systematic review of studies addressing growth during stimulant treatment was published in 2005, and identified a total of 29 studies, of which 11 reported an attenuation of growth with chronic treatment that was estimated to be about 1 cm/year for the first 1-3 years of treatment (35). The pattern that emerges from these studies is of an early weight loss in the first 3-4 months of treatment, more marked among the heaviest children, followed by a resumption of weight growth; slowing in height growth becomes evident after about one year of continuous treatment and persists, though attenuated, over the years.

Among these studies, the Multimodal Treatment of ADHD study (MTA) took advantage of a large sample size of children (N=579), homogeneous for age (7-9 years), and randomly

assigned to non-pharmacological intervention, community treatment (average methylphenidate dose: 23 mg/day), combined psychosocial and medication treatment (31 mg/day), and intensive medication treatment (38 mg/day) for 14 months (27,36,37). Treatment consisted of immediate release methylphenidate given three times a day and continued seven 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, respectively, for height, with a mean estimated loss of growth of 1.23 cm/year for the most intensively medicated group. 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/year for the most intensively medicated group (27). These data strongly suggest that the effect of stimulants on growth is dose-dependent, as also reported by other investigators (32).

One limitation of the MTA was that a number of children had received stimulant treatment prior to 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 upon discontinuation, pre-study treatment can bias the estimates of treatment effect during the study. Thus, stimulant effect on growth is best assessed in treatment naïve subjects who had not been exposed to stimulants (35). The MTA sample has been naturalistically followed after the end of the 14-month controlled trial. Analyses of the data from the children who were consistently medicated, never medicated, or newly medicated children confirmed a growth suppression effect, which was especially evident during the first two years of treatment and still detectable after three years, when the newly medicated group had grown on average 2.0 cm and 2.7 kg less than the unmedicated group (21).

While the preponderance of the evidence indicates that there is a statistically significant suppression of growth with stimulants, whether this effect is clinically significant is subject of debate. A difference in height of 2 cm over a three-year period may be considered by some of borderline practical significance, but this consideration would be based on group mean differences: some children can present with larger differences, which, in the context of the individual child situation, may be important. In fact, case reports have described particular clinical situations where the 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 (38). No generalizations are of course possible from such case descriptions, except that the growth of each individual patient should be carefully monitored during stimulant treatment, especially if other medications known for affecting growth are concomitantly prescribed.

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

A critical question is whether this loss of growth velocity is merely a transient delay, or final height can be affected. Prior studies had indicated that rebound occurs during drug holidays (with some reports suggesting that is occurs even when treatment is continued), and that, in any case, adult height is not affected (10,12,13,39). However, not all the studies have found evidence of growth rebound, or confirmed the benefit of drug holidays (24,25,30). Current evidence indicates that stimulant treatment does not, on average, influence final height, but further data from children continuously medicated 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 (38). An interesting investigation on the dental development of children who had received on average 30 mg of methylphenidate daily for more than four years did not find evidence of delay in dental maturation (40).

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 both 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%) (41). During the 14-month treatment in the MTA, about 10% of 198 treated with methylphenidate required a dose decrease due to anorexia, making this the most common reason for dose reduction in this study (37). Similar finding emerged from a retrospective review of naturalistically treated children (33). Children under age 6 appear to be even more sensitive to the anorexic effects of stimulants. In the Preschoolers with ADHD Treatment Study (PATS), about 40% of the children showed decrease in appetite, a rate that remained basically unchanged during the 10-month duration of treatment, in spite of the relatively low doses employed (2,42). It is therefore possible that the effect on height is caused by the reduced caloric intake during stimulant treatment (35). The effect on weight seems, however, to be limited to the first few months since starting treatment.

It has been hypothesized that the stimulant-induced increase in hypothalamic dopamine changes pituitary function thus slowing growth (43). Such an explanation is consistent with the fact that dopamine antagonists increase weight and appear to accelerate height growth (44). A number of 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 was found to increase growth hormone and decreas 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 month 8 and 14 assessment, was reported in a small number of children (45). Despite these hypotheses, the basic mechanism through which stimulants affect growth remains unknown and deserves further investigation.

Atomoxetine and Physical Growth

Atomoxetine is a non-stimulant, 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 (46). Acute treatment is on average accompanied by a slight decrease in weight of about 1 kg over a period of 2 –3 months. Several open-label studies of atomoxetine administered for 2 years or longer have been conducted, and two meta-analyses have been recently reported.

One meta-analysis included data from 13 studies of 6- to 7-year-old children who were treated with atomoxetine up to a mean dose of 1.47/kg/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 (47). The other meta-analysis pooled data from both children and adolescents age 6 to 16 (48). 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 both 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 has been considered negligible at the group mean level (47,48), but may be important at the individual patient level with extended treatment beyond two years. The mechanism of the effect is speculated to be through a decrease in caloric intake. Caloric supplementation has been 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 pharmacological activity (49). Hypertension and tachycardia are common in case of overdosing with these compounds (50). A number of placebo-controlled studies have documented a slight, but statistically significant, increase in blood pressure and heart rate in both children and adults during short-term administration of methylphenidate or amphetamine preparations (51-55). The magnitude of the increase over placebo is around 2-6 bpm for heart rate, 2-4 mmHg for systolic blood pressure, and 1-3 mmHg 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 mmHg on medication vs. 72.3 off medication) and heart rate (85.5 vs. 79.9 bpm) (56).

Some studies, however, in spite of large sample sizes, did not find any differences in blood pressure or heart rate as compared with placebo (57,58). In a large, open-label study involving almost 3,000 children age 6-12 years, treated with up to 40 mg/day of extended release mixed amphetamine salts for up to 15 weeks, increase in systolic and diastolic blood pressure of less 1 mmHg and increase in heart rate of about 1 bpm were detected, which were statistically significant mainly due to the large sample size, but were considered without clinical relevance (59). In this study, sustained blood pressure measurements above the 95the percentile were found in 2.5%, and heart rate above 110 bpm in 3.6% of children. While 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 with 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 (57,59). Besides an increase in rhythm, no consistent electrocardiographic changes have been 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 (58-61).

From a clinical point of view, two questions appear especially relevant. First, does even slight elevation in blood pressure and heart rate increase the risk for cardiovascular pathology in the long run? In fact, the risk for cardiovascular disease increases monotonically with increasing values of blood pressure without any specified cut-off 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, however, fully investigated especially in light of the fact that 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 (62,63). In young people (first three 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 (64), has been estimated to range from 1.3 to 8.5 per 100,000 person-year, and a specific cardiac cause is identified in two thirds of the cases (65). In older adults, sudden death typically occurs in the context of coronary atherosclerosis and is due to ventricular fibrillation. Given the widespread use of stimulants for the treatment of ADHD in children and the increasing use also in adults, it is not surprising that a number of

cases of sudden death were reported to the Adverse Events Reporting System (AERS) of the Food and Drug Administration.

During the period January 1992-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 (66). The apparently similar incidence for amphetamine as for methylphenidate despite the more common use of the latter is intriguing, but it 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 are typically reported to AERS, so that accurate estimates of true incidence are not possible. Conclusions about presence or absence of a causal link cannot therefore be drawn from these data. Future analyses of systematically collected data from very large number of naturalistically treated patients in community settings might be informative. Given the increasing use of stimulants for the treatment of ADHD in adults, it will be important to further investigate possible adverse cardiovascular effects in this age group, with special attention to patients with risks factors for heart disease, such as hypertension, atherosclerosis, smoking, or concomitant use of other drugs.

Even though a causal effect has not been proven, 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 with predisposing factors,. Therefore, the current product labeling for methylphenidate and amphetamine preparations informs that sudden deaths have been reported during treatment with these stimulant medications at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems, and warns that these medications generally should not be used in individuals with known serious structural cardiac abnormalities, cardiomyopathy, or serious heart rhythms abnormalities (67).

The current practice guidelines recommend a careful medical evaluation of children prior to 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 prior to age 30 (63,68). Pulse, blood pressure, and adverse events during treatment should be periodically monitored during treatment. Electro- or echo-cardiographic examinations are currently not required for individuals without known personal or family risk factors, but should be conducted in selected cases.

Not uncommonly, stimulants are prescribed concomitantly with other medications. In particular, alpha-2 adrenergic agents such as clonidine or guanfacine have been prescribed off-label together with stimulants to children with ADHD (69). Following the report of four cases of sudden death in children taking both methylphenidate and clonidine in the mid-1990s, concerns were raised about the safety of this combination (70). No causal link could be, however, established, and no additional evidence of possible cardio toxicity has thus far emerged.

Atomoxetine and Cardiovascular Function

Atomoxetine is a selective norepinephrine reuptake inhibitor and an effect on the cardiovascular system can be expected given its pharmacological 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 5-9 bpm in mean heart

rate with suggestions of a dose-effect relationship (71). Moreover, 3.6% of the children/adolescents on atomoxetine vs. 0.5% of those on placebo (p=0.02) 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/adolescents, while an increase in diastolic blood pressure was seen in children/adolescents but not in adults. In the former, the mean change in diastolic blood pressure was 2.1 mmHg on atomoxetine vs. -0.5 on placebo (p=0.002). These changes occurred in the first few weeks of treatment and stabilized afterwards with no further increases during long-term treatment for one year and longer (71). No evidence that atomoxetine prolongs that QT interval were found (47,71).

Forty cases of overdose on atomoxetine up to 480 mg in children/adolescents were reviewed: tachycardia (mean 131 ± SD 14 bpm) and hypertension up to 136/95 mmHg occurred, but no other arrhythmias were detected (72). Between November 2002 and February 2005, seven cases of sudden death during atomoxetine treatment were reported to the AERS, including 3 children (age 2.5-12 years) and 4 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 (66).

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.

Alpha-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 to children with ADHD either alone or in combination with stimulants, especially in the presence of tic disorders or when other treatments have proven insufficient (73). Clonidine and guanfacine have prominent cardiovascular effects. They decrease blood pressure and can cause orthostatic hypotension, with dizziness, palpitations, and rapid heart beat, upon standing. Bradycardia is also a possible side effect. For these reasons, blood pressure and heart rate must be measured before and during treatment. ECG monitoring is not usually 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 abruptly discontinued, rebound hypertension can occur. Gradual tapering off, by decreasing the daily dose by 0.05 mg every 3-4 days is therefore recommended.

Tricyclics and Cardiovascular Function

Although their use in children has much decreased, tricyclic antidepressants may still be prescribed off-label for the treatment of ADHD in particular cases when stimulants or atomoxetine do not prove effective (73). Tricyclics delay cardiac conduction and their use requires special attention to possible cardiotoxicity. Before starting treatment, the child should receive a complete physical examination with ECG recording. Treatment should be considered only if the following limits are not exceeded on the ECG: 200 msec for the PR, 120 msec for the QRS, and 450 msec for the QTc, 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. Reports of sudden death in children receiving therapeutic doses of tricyclics have made, even though a causal association has not been demonstrated (74).

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

Conclusions

The last few years have seen a flurry of studies investigating growth in children treated with stimulants because of ADHD. Overall, the findings overall confirm that stimulants cause a slowing in growth velocity for both weight and height, which can persist, though attenuated, for at least 3-4 years during continuous treatment. A slight decrease in weight and height velocity has also been 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 semi-annually in children receiving pharmacological treatment, and the appropriateness of the treatment, or its intensity, reconsidered if there is substantial deviation from the individual child growth trajectory.

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

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

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Table 1

Recently Reported Studies of Growth During Stimulant Treatment [a]

Study	N	Age (years)	Drug	Dose[b]	Duration	Design	Findings
Kramer et al., 200022	97	4-12	MPH[c]	10-40 mg	36 months	Retrospective	Adult height and weight not affected
Sund & Zeiner, 200223	91	3-10	MPH AMP[d]	24 mg 12 mg	12 month	Observational	Smaller weight growth on AMP
Lisska & Rivkees, 200324	84	-	MPH	22 mg	24 months	Observational	Decrease in height z scores
Poulton & Cowell, 200325	51	3-11	MPH AMP	27 mg 14 mg	42	Observational	1 cm/year an 1.2 kg less than expected
Biederman et al., 200326	124	6-17	Multiple	Unspecified	Unspecified	Observational	No treatment effect on growth
MTA Cooperative, 200427	579	7-10	MPH[e]	0-39 mg[f]	14 months	Randomized	1.23 cm/year and 2.48 kg/year less growth
Faraone et al., 200529	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., 200630	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., 200631	113 66	8.5 (mean) 9.0 (mean)	MPH AMP	34.8 22.7	32 months 29 months	Retrospective	No change in mean z scores
Charach et al., 200632	79	6-12	MPH or AMP	unspecified	60 months	Observational	Dose dependent decrease in height and weight z scores.
Zachor et al., 200633	81	8.5 (mean)	MPH or AMP	unspecified	36 months	Retrospective	Decrease in z scores for weight but not for height
Swanson et al. 200620	95	3-5	MPH	14.2 mg	12 months	Observational	1.4 cm/year less than expected 1.3 kg/yr less than expected 0.30 decrease in height z 0.53 decrease in weight z
Swanson et al. 200721, [h]	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	50	4-10	MPH AMP	unspecified	24 months	Retrospective	Decrease in weight percentile only

[a] Included were studies of at least 50 children and of at least 12 month duration

[b] Highest mean daily dose

[c] MPH: methylphenidate

[d] AMP: amphetamine

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

[f] The mean daily MPH dose was 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.

[g] 229 completed treatment

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