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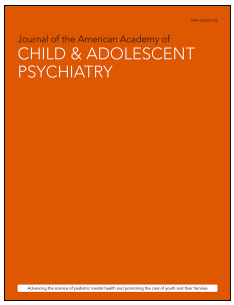

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A Randomized Controlled Trial of Interventions for Growth Suppression in Children With Attention-Deficit/Hyperactivity Disorder Treated With Central Nervous System Stimulants

RH = Promoting Growth in Children With ADHD

James G. Waxmonsky, MD, William Pelham III, MA, Adriana Campa, PhD, Daniel A. Waschbusch, PhD, Tan Li, PhD, Rebecca Marshall, MS, Lysett Babocsai, PhD, Hugh Humphery, MD, Elizabeth Gnagy, MA, James Swanson, PhD, Tomasz Hanć, PhD, Negar Fallahazad, BS, William E. Pelham IV, PhD

Editorial
Clinical Guidance
Supplemental Material

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Dr. Li and Mr. Pelham served as the statistical experts for this research.

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Abstract

Objective: To examine the impact of central nervous system (CNS) stimulants on the growth of children with attention-deficit/hyperactivity disorder (ADHD) and assess the efficacy and feasibility of weight recovery interventions on growth.

Method: 230 children ages 5-12 with ADHD with no history of chronic CNS stimulant usage were randomly assigned to receive daily CNS stimulants (78%, primarily OROS-Methylphenidate [OROS-MPH]) or behavioral treatment (22%) for 30 months. After 6 months, children evidencing a decline in body mass index (BMI) of >.5 z-units were randomized to one of three weight recovery treatments (WRTs): monthly monitoring of height/weight (MON) plus continued daily medication, drug holidays (DH) with medication limited to school days, or daily caloric supplementation (CS) with a 150-kcal supplement plus daily medication.

Results: Before WRT assignment, medication was associated with significant reductions in standardized weight and height (*p's*<.01). Adherence to CS and DH during WRT was high, with significant increases in daily caloric intake and decreases in weekly medication exposure (*p's*<.05). Across all WRT participants (n=71), weight velocity increased significantly after WRT randomization ($\bar{(\beta\_2)}$=0.271, SE=0.027, *p*<.001).When analyzed by what parents did (versus what they were assigned to), CS (*p*<.01) and DH (*p*<.05) increased weight velocity more than MON. No increase in height velocity was seen after randomization to any WRT. Over the entire study, WRT participants declined in standardized weight (-0.44z-units) and height (-0.20z-units).

Conclusion: Drug holidays, caloric supplementation and increased monitoring all led to increased weight velocity in children taking CNS stimulants, but none led to increased height velocity.

Clinical trial registration information: Novel Approach to Stimulant Induced Weight Suppression and Its Impact on Growth; https://clinicaltrials.gov/; NCT01109849

Key words: attention deficit/hyperactivity disorder, growth, CNS stimulants

Introduction

Central Nervous System (CNS) stimulants are a first line treatment for Attention-Deficit/Hyperactivity Disorder (ADHD)[1] and one of the most commonly prescribed medications in children and adolescents.[2] They have a well-established safety profile, with anorexia and weight loss being two common side effects.[1,3-5] Given these side effects, there has been long-standing concerns about growth suppression with these medications.[6]

Initial studies of immediate-release stimulants failed to find evidence of sustained growth suppression, but the average duration of use was only a few years.[7] While care guidelines differ about sequencing of nonpharmacological to pharmacological treatments, all recommend continuing pharmacological treatment when impairment worsens off medication.[1,5,8] Over the past three decades, there has been a substantial increase in the number of children using CNS stimulants, use of extended-release medications and the cumulative doses taken over the lifetime,[2,9-12] suggesting that the frequency and intensity of growth suppression may be greater than that observed in initial studies. In the NIH-funded Multimodal Treatment of ADHD (MTA) study, growth rates declined during the first two years of treatment, then stabilized but did not accelerate in those continuing medication.[13] In adulthood, consistently medicated participants were approximately one inch shorter than unmedicated participants and a half-inch shorter than age-matched controls.[9]

Drug holidays, or temporary breaks from medication, are commonly used to improve the tolerability of CNS stimulants.[5,7,14] In the MTA, children inconsistently taking CNS stimulants were almost one inch taller as adults than those consistently taking medication.[9] However, MTA inconsistent users included children permanently stopping medication and those taking temporary breaks, with wide variation in the timing and intensity of medication exposure across

participants. Therefore, the impact of prescribed drug holidays was not evaluated by the MTA. No prior work has randomly assigned children with documented growth suppression to continuous versus interrupted dosing to evaluate impacts on growth.

Other interventions for promoting growth in children taking CNS stimulants include (a) increased monitoring of growth and (b) improving caloric intake. The latter intervention is based on the premise that negative caloric balance may cause growth suppression with CNS stimulants.[15,16] However, there has been even less assessment of these interventions.[17]

To address limitations of previous research, we recruited 230 treatment naïve youth with ADHD and randomly assigned them to CNS stimulant medication (MED) or behavior therapy (BT). After at least 6 months of treatment, those showing sustained BMI declines were re-randomized to one of three weight recovery treatments (WRT): drug holidays (DH), caloric supplementation (CS), or the control of monthly monitoring (MON) of height and weight. We hypothesized that: (a) children treated with CNS stimulants would exhibit reduced growth compared to those not receiving medication, (b) DH and CS would lead to increased weight gain (c) only DH would be associated with accelerated height growth.

Method

Participants

Participants were 230 children ages 5-12 meeting criteria for any DSM-IV ADHD subtype and using CNS stimulant medication under 30 days lifetime (unlikely to impact growth). The study was approved by the governing IRB. Parents gave written consent, with assent obtained from children. Exclusion criteria included IQ < 70, obesity or BMI below the 5th percentile, use of other psychotropics or any medication/supplement found to increase height/weight, Autism Spectrum Disorder or milk protein allergies. Participants were recruited

through mailings to schools, medical providers and community mental health providers. ADHD was diagnosed using the Disruptive Behavior Disorders Structured Interview, administered by masters-level or higher clinicians,[18] combined with parent and teacher ratings.[19] Psychiatric comorbidity was assessed by the NIMH Diagnostic Interview Schedule for Children IV, computerized version,[20] with comorbid diagnoses allowed if ADHD was the most impairing condition. Diagnoses were confirmed by two MD/PhD faculty.

ADHD Treatment Conditions

At baseline, families were randomly assigned to either medication (MED) or behavior therapy (BT) in a 4 to 1 ratio. This lead-in phase was used to ensure that only children manifesting measurable changes in weight and height entered WRT, with BT employed as an active control as ADHD itself is associated with altered growth.[13,15,21-23] Children in MED were initially treated with OROS-Methylphenidate (OROS-MPH), with dose titrated every two weeks until optimized. Treatment efficacy and tolerability were assessed by parent and teacher ratings.[24,25,26] Study physicians completed the Clinical Global Impressions Scale for Improvement and Severity (CGI-I, CGI-S) [27] at each visit. Optimal dose was defined as a tolerable dose where participants achieved a level of home/school functioning that left no meaningful room for improvement. If OROS-MPH was not efficacious or tolerated, alternative MPH or amphetamine products were prescribed.

In BT, participants received an 8-week parenting program,[28] social skills groups and ongoing school consultation, with additional treatment individualized as needed. Families in MED were offered the 8-week parenting program and one annual school consultation to incentivize enrollment.

Study treatment lasted up to 30 months. After 6 months, BT participants displaying moderate impairment or worse (CGI-S >3), were allowed to initiate medication to promote retention, as the study's primary goal was to measure growth, not treatment effects. All treatments were provided free of cost to participants.

Treatment Utilization

Participants were instructed to take study medication every day of the week. The number of pills dispensed and returned were recorded at each visit. Parents recorded days medication was given in monthly logs. Logs and pill counts were synchronized at each visit. As in the MTA, medication utilization was measured using total dosage in mg of methylphenidate equivalents.[9]

Height and Weight Measurements

Staff were trained and required to measure 10 adults and 10 children within 3 mm and 0.1 kg of the trainer. Children were measured wearing light clothing without footwear, using a standardized protocol on a calibrated, mounted stadiometer and digital scale. Weight was recorded to the nearest 0.1 kg and height to the nearest 0.1 cm. Measures were repeated three times, and the median value was used. Parent height was measured at baseline.

Assessment Schedule

Participants not using medication were assessed every three months. Participants using medication were seen monthly for 3 months after optimization and then at least every 3 months until study endpoint or until rerandomized to WRT. In WRT, assessments were completed monthly. At baseline and every visit after optimization, the child's food and beverage intake for the past 24 hours was collected using a standardized interview,[29] with caloric intake calculated using the Nutribase 2018 Pro edition.

Weight Recovery Treatment Conditions

Any time after 6 months, MED or BT (as BT assigned youth could cross to medication after month 6) participants whose BMI z-score declined by ≥0.5 z-units (or >1 z-unit plus raw weight loss from baseline if entry BMI >85th percentile) were randomized to one of three WRT arms: monitoring (MON), drug holiday (DH) or caloric supplementation (CS) (Figure 1). In all arms, dose increases were prohibited and weight and height were measured monthly. In CS and MON, parents were advised to medicate daily. In DH, parents were told to medicate only on school days and switched to either immediate-release MPH BID or MPH HCL extended-release capsules in effort to limit medication effects to school hours.[30] Participants with documented symptom worsening (CGI-S increasing by ≥1 point and score ≥4) could return to OROS-MPH on school days to ensure coverage for afterschool activities. In CS, participants received an 8oz 150kcal supplement drink to consume each evening (Nutripals®). MON participants did not receive any treatments beyond monthly weight and height checks. WRT ended when participants returned to their baseline z-BMI score for 2 consecutive visits and were cleared by the study nutritionist to end WRT. Participants crossing two major weight or height for age percentile lines [31] (or falling below the 5th percentile) were assigned to additional active WRT arms until stabilized. If not sufficient, stimulant dose was incrementally lowered until height/weight percentile stabilized.

Insert Figure 1 here

Data Analysis

As these analysis were designed to evaluate the impact of WRT, primary comparisons were between three groups: MON, DH, and CS (total *n*=71).

Verification of growth suppression. We first verified that growth suppression occurred by comparing children entering WRT to participants never using medication during the study. For WRT participants, we computed change in height and weight from study baseline to WRT initiation**.** For participants that did not enter WRT, we computed change in height and weight from baseline to the visit nearest 10.7 months from baseline (i.e., median time between baseline and WRT initiation for those in WRT). We then tested the statistical significance of the change for WRT versus never-medicated participants using permutation tests.

Timeframe of growth measurements. Time was scaled in months and centered at WRT initiation (i.e., time=0 at randomization). Measurements were filtered to include only those within 10 months of WRT initiation (before or after). The 10-month window was selected to restrict post-randomization follow-up to a time range in which there were few missing observations and to define a time interval where growth could reasonably be modeled as linear.

Covariates. Four time-invariant covariates were included in growth models: age at randomization to WRT, female (0/1), age-by-female interaction, and mother's height. One binary, time-varying covariate was created using structural auxological analysis (AUXAL) to project the age of minimal growth velocity to address the large variation in the timing of puberty between children that cannot be accounted through z-scores.[32] Growth measurements before this time point were considered prepubertal. This covariate equaled 1 whenever a measurement occurred after that child's AUXAL-projected age of minimal growth velocity. AUXAL projections were based only on measurements prior to WRT randomization.

WRT group membership. For intent-to-treat (ITT) analyses, dummy variables indicated randomization to DH and CS, with MON as the reference group. Ten cases were prohibited

from randomization to MON because they had a BMI <10th percentile at WRT entry (a feature of the safety protocol)—another dummy variable indicated whether randomization was restricted.

For per-protocol (PP) analyses, dummy variables indicated membership in DH and CS, with MON as the reference group. Per-protocol group membership was determined via review of calorie and medication logs. DH was defined as using medication >50% of weekends pre-WRT and < 50% during WRT, with at least a 25% decline in usage pre to post WRT. CS was defined as using supplement >50% of WRT days. MON was defined as not meeting criteria for DH or CS.

Growth modeling. We fit multilevel spline models[33] in Mplus 7.4[34] to model participants' growth 10 months before and 10 months after WRT randomization. Repeated measurements of weight or height were nested within children. Time-invariant covariates included: child age, child sex, the interaction of age and sex, and maternal *z*-height. A time-varying covariate indicated whether the child was prepubertal at each measurement. Three random effects comprised the child's growth curve: β_{0i}, β_{1i}, and β_{2i}. Parameter β_{0i} estimated the child's weight or height at WRT randomization (i.e., kg or cm). Parameter β_{1i} estimated the child's growth rate in the 10 months prior to WRT randomization (i.e., kg/month or cm/month). Finally, parameter β_{2i} estimated the child's *change* in growth rate at WRT randomization (i.e., change in kg/month or cm/month). Contrast coding was used to compare β_2 in MON versus DH versus CS. These contrasts evaluate the key question: whether the change in growth velocity at randomization to WRT differed among the WRT groups. Additional details on model specification and contrast procedure are provided in Supplement 1: Parameterization of Multilevel Growth Models, available online. A separate model was fit for each combination of outcomes (height versus weight) and treatment group definition (intent-to-treat versus per-

protocol). Missing data in covariates was minimal and was addressed using multiple imputation (see Supplement 2: Handling of Missing Data, available online).

Results

The sample's mean age was 7.6 years and most were male participants, consistent with the MTA.[13] Most participants were of Hispanic ethnicity, with 11% having parents whose primary language was not English (see Table S1, available online). Only 5 (2.1%) participants previously used any CNS stimulants. All 230 participants were randomized, with 180 to MED and 50 to BT as planned (see Figure S1, available online). There were 143 MED and 24 BT participants who used any study medication, with 72 (43%) of medication users entering WRT. One WRT case originally assigned to BT never used medication (low entry BMI) so was excluded from subsequent WRT analyses, leaving 71 medication using participants for growth modeling (65 from MED, 6 from BT).

Rates of Weight and Height Growth Prior to WRT

To verify WRT participants experienced a reduction in growth before entering WRT, we compared them to non-WRT participants never using medication with at least 12 months of data (n=40). At study entry, WRT participants were more impaired (means of 4.56 versus 5.01, p<.05), lighter (baseline difference of 0.38 z-units), shorter (difference of 0.25 z-units) and had a lower BMI (difference of 0.38 z-units) versus never-medicated participants, with no other significant differences. After adjusting for differences in standardized height and weight at study entry, WRT participants exhibited a significant change in standardized height (p<.01) and weight (p<.01) versus never-medicated participants (Figure 2) from study entry to WRT entry (see Supplement 3: How Growth of Children in WRT and Never Medicated Children Was Compared,

available online). Between group differences would amount to 0.66 cm and 3.7 kgs over a year (see Supplement 4: How Values Were Translated Between Raw Height and Weight and Z-Scores, available online).

Insert Figure 2 here

WRT Assignment

Of the 71 medicated participants entering WRT, 24 were randomized to CS, 24 to MON, and 23 to DH. Table 1 compares groups at WRT randomization. The mean time from study entry to WRT initiation was 12.9 months (*SD*=6.5), with 18.6 months (*SD*=6.6) from WRT initiation to WRT exit. WRT participants had an average of 22.7 (4.99) growth assessments, with 13.1 (5.6) occurring during WRT. There were 5 (7%) participants who discontinued the study while in WRT. Thirteen participants (18%) met criteria to exit WRT, having a mean WRT duration of 14.1 (range 4.8-22.2) months. WRT completers' mean change in measurements during WRT were: z-height (−0.18 units), z-weight (+0.40 units), z-bmi (+0.73 units).

Insert Table 1 here

In DH, 105 WRT days occurred during summer-break, amounting to 1.5 summers off medication based on school schedules. Within DH, 7 (30%) were maintained on the school-hours only regiment with 16 (70%) reverting back to school-day use of OROS-MPH due to worsening

ADHD symptoms after school. Seven participants (9.7%) needed additional WRT assignments to stabilize BMI, with one needing to be removed from medication to gain weight.

Medication Usage

ITT. As intended, DH participants were medicated for fewer WRT days than CS or MON ($p < .05$). Both MON and DH had significant reductions in percentage of medicated days from pre-WRT to during WRT (MON: 82% to 69%, DH: 75% to 53%, *p*'s<.05), with most unmedicated days occurring on weekends. Adherence to weekend holidays in DH was high as parents gave medication on only 5% of weekend days. (Figure 3A and see Table S2, available online). WRT participants' mean MPH dose when medicated was 24.3 mg (SD=6.6), for a weight-adjusted dose of 0.97 mg/kg/day at WRT entry and a mean cumulative exposure of 14,188 mg over the entire study (see Table S3, available online).

Insert Figure 3 here

Per protocol. Using per protocol classification, there were 17 in DH, 23 in CS with 31 in MON. The primary switch from ITT to PP was reclassification from DH to MON due to weekend use not declining sufficiently because of low pre-WRT levels of weekend use. Per protocol, DH included 122 summer days, equating to 1.76 summers off medication. Unlike ITT, only DH (90% versus 53 %, *p*<.05) significantly decreased the percentage of days medicated from before to during WRT (see Figure S2A and Table S2, available online).

Supplement Usage and Calorie Intake

ITT. Mean caloric intake on medicated weekdays changed from pre-WRT to during WRT by +6% for DH (*ns*), +14% for MON (*ns*), and +20% for CS ($p<.05$) (Figure 3A). In CS, supplement was taken 78% of days (82% of medicated and 64% of unmedicated days).

Per protocol. Mean caloric intake on medicated weekdays changed from pre-WRT to during WRT by −1% for DH (*ns*), +17% for MON ($p<.05$), and +21% for CS ($p<.05$) (see Figure S2A, available online). In CS, supplement was taken 81% of days (85% of medicated and 66% of unmedicated days).

Impact of WRT on Weight

Estimated growth curves are displayed in Figure 3B. Growth parameters are reported in Table 2. Across all WRT participants (n=71), weight velocity increased significantly after WRT randomization (B_2=0.271, SE=0.027, p<.001). Neither z-height nor z-weight at study or WRT entry significantly correlated with z-weight change during WRT.

Insert Table 2 here

ITT. All WRT groups gained significantly more weight ($p < .001$) than they would have had they continued their pre-randomization trajectory (Table 2): MON (an additional 2.3kg), DH (an additional 2.9kg), CS (an additional 3.0kg) (see Supplement 5: How WRT Effect Sizes Were Calculated, available online). All groups displayed a marked increase in weight velocity after WRT initiation (i.e., the growth curves inflect at WRT randomization) (Figure 3B). There were no significant between-group differences in weight velocity after WRT initiation.

Per protocol. All WRT groups gained significantly more weight over 10 months ($p < .001$) than they would have had they continued their pre-randomization trajectory: MON (an additional 1.8kg), DH (an additional 3.4kg), CS (an additional 3.0kg) (see Table 2). In contrast to

intent-to-treat results, DH ($p < .05$) and CS ($p < .05$) increased weight velocity significantly more than MON (see Figure S2B, available online). Over the 10-month WRT randomization assessment period, a child classified as DH would be expected to gain 1.6kg more than had that child been classified as MON, and a child classified as CS would be expected to gain 1.2kg more than one in MON.

Impact of WRT on Height

Across all WRT participants (n=71), there was no significant change in height velocity before versus after WRT randomization (β_2=0.017, SE=0.019, *ns*). Neither z-height nor z-weight at study or WRT entry significantly correlated with z-height change during WRT.

ITT. No WRT group significantly increased their height velocity, nor were there any statistically significant between-group differences. One effect size was non-negligible: over the 10 months post-randomization WRT assessment period, children in CS gained 0.35cm more than they would have had they continued their pre-randomization trajectory. However, CS was growing more slowly than DH or MON before WRT *($p < .01$ for weight; $p < .10$ for height)* (Table 2, Figure 3B). The increase only brought CS to a velocity comparable to the other WRT arms.

Per Protocol. When analyzed per protocol, results were largely unchanged (see Figure S2B, available online). Again, CS exceeded anticipated height gain by 0.43cm, but this difference was not statistically significant.

Growth Trajectories Over the Entire Study

Estimating the magnitude of weight and height suppression associated with CNS stimulants was not the focus of this paper but will be explored in future papers. A preliminary estimate can be derived from the mean change in standardized weight (−0.44 z-units) and height

(−0.20 z-units) of the WRT group over the 30 months of assessment. This equates to 2.4kg and 1.3cm less versus expected values. Among children with at least 12 months of growth data, never-medicated youth had mean changes in standardized height and weight of +0.3cm and +0.9kg respectively, while youth who used study medication for at least one day but did not meet WRT criteria exhibited mean changes of -0.6cm and -0.6kg (see Table S3, available online).

Sensitivity Analyses

First, we extended the follow-up to 24 months after WRT randomization (see Table S4, available online), yielding results similar to those above. Second, we compared WRT groups using changes in standardized height and weight (versus growth models in the raw metric). From WRT entry to 10 months out, there were no differences between groups in changes in z-weight or z-height (see Table S5, available online). From WRT entry to WRT end, DH increased z-weight more than MON in intent-to-treat ($p<.10$) and per protocol ($p<.05$) analyses; there were no other significant between-group differences.

Discussion

In 230 youth with ADHD, consistent versus no use of CNS stimulants was associated with significantly reduced weight and height velocity. Medicated participants exhibiting a sustained deficit in standardized BMI were then randomly assigned to one of three commonly employed weight recovery treatments: increased growth monitoring (MON), drug holidays (DH) and caloric supplementation (CS). All groups significantly increased their rate of weight gain but there were no significant between-group differences. When analyzed per protocol, DH and CS increased weight velocity significantly more than MON. Although DH significantly reduced MPH exposure and CS significantly increased caloric intake, no group increased in height velocity.

This was the first randomized ADHD trial designed to examine the impact of CNS stimulants, drug holidays and caloric supplementation on weight and height. Previous ADHD studies were primarily chart reviews and post-hoc analyses, with growth measured at irregular intervals using inconsistent methods. There were wide variations in participants' age, gender and pubertal status that were often unaccounted for. [7,15,35-37] The MTA corrected many of these deficits and employed an unmedicated ADHD comparison group, since ADHD itself may impact growth.[13,15,22,23] However, limitations remained. Approximately one-third of participants used medication prior to MTA entry, potentially confounding results;[38,39] medication use was assessed retrospectively covering periods of up to 3 years, while growth was measured only 10 times spanning 16 years.[9] In contrast, over 95% of our participants were stimulant naïve; medication use and caloric intake were tracked monthly during WRT with growth measured an average of 22 times in 3 years, and we accounted for variation in pubertal onset.

WRT increased weight gain with impact similar to that seen in a trial of cyproheptadine.[17] Standardized weight did not return to pre-medication levels, potentially concerning for children underweight before starting medication. Prior work found that baseline weight/height predicts the degree of change in growth observed with medication.[15,40] We found no significant correlation between these parameters and changes during WRT. MON participants experienced the smallest increase; however, the change was clinically and statistically significant despite restrictions on what study providers could recommend versus the other arms or versus routine care. It appears monthly weight checks may promote parents to adjust medication frequency and increase calories.

It has been theorized that increasing weight or interrupting dosing would promote growth.[15,16] Despite significant changes in both, height velocity did not significantly increase for

any group. Over the entire study, WRT participants grew 1.3cm less than expected based on pre-WRT levels. Results are similar to what was observed for stimulant naïve youth who consistently used medication during the first two years of the MTA. The MTA defined consistent usage as taking medication at least 50% of days,[9] so most WRT participants, even those in DH, would have been classified as consistent users. Other studies also observed that medication holidays impacted weight but not height.[35,36] Therefore, it appears that larger reductions in medication usage beyond limiting it to only school days may be needed to meaningfully impact height velocity. Moreover, increasing weight velocity should be not be interpreted as sign of pending height rebound.

Medicated youth not meeting WRT criteria experienced smaller declines in standardized weight and height, suggesting that many medicated youth will not experience meaningful slowing in growth. The MTA and others found associations between adult height and total lifetime exposure to CNS stimulants.[9,41] Future work should assess for additional predisposing factors for growth suppression with CNS stimulants.

We did observe a nonsignificant increase in height velocity for CS during WRT. Pre-WRT, CS experienced the largest decline in weight velocity and were growing significantly slower than DH or MON. Past work has found that caloric supplementation leads to accelerated height in severely underweight children.[42,43] Therefore, it is possible that only children experiencing marked weight loss with CNS stimulants, which is relatively uncommon,[13] may exhibit increased height velocity with caloric supplementation.

Other reasons for failure to detect increased height velocity could include an insufficient intensity or duration of intervention, especially for DH. Reduced rates of weekend use before assignment to DH may have impacted the ITT analysis, but per protocol analysis corrected for

this and still found no evidence of growth acceleration. DH attempted to limit medication to school-hours versus just school days by switching to shorter duration medications. Only 30% of DH participants continued on shorter acting medications due to impairing symptoms after school. Therefore, if more intensive holidays are needed to increase growth, it seems most families would not tolerate them. Prior work observed increased growth only during the second of two consecutive summers off medication versus children continuously treated.[37] However, that study did not account for group differences in age or timing of the pubertal growth spurt. No acceleration in height velocity was observed when we included all WRT assessment points (Table S3), totaling nearly two full summers, making it unlikely that insufficient duration was a factor. Results were similar when we examined standardized versus raw height (Table S4).

Adherence to weekend drug holidays was high. Parents were much more likely to deviate protocol by not giving weekend medication when asked to, even before weight loss was identified as a concern (i.e., prior to WRT). Intermittent adherence is common for psychotropic medication, especially CNS stimulants on weekends.[44,45] Therefore, clinicians should assess current rates of weekend use before recommending drug holidays to improve tolerability. Results also demonstrate that some children may experience meaningful reductions in height and weight velocity even when not using medication daily.

Supplement adherence was also strong, with rates comparable to studies in nutritionally at-risk children and higher than that reported for cyproheptadine to increase weight in children with ADHD.[17,42] The randomly assigned CS group maintained their level of medication use post-randomization, while MON decreased usage on their own accord. It may be that parents are more comfortable continuing ADHD medication when provided with an active intervention to address side effect concerns.

While 30 months is long for a treatment trial, the primary limitation is study duration and lack adult outcomes. We completed a sensitivity analyses using all WRT timepoints through 24 months, with little change in results. However, it is still possible that treatment effects may have emerged after this time or that larger samples may be necessary to detect treatment effects for growth. Associations between ADHD and BMI in medicated youth shift with age.[46] In the MTA, standardized BMI increased over adolescence regardless of medication usage,[9] and ADHD is associated with obesity in adults.[47-49] Therefore, more intensive efforts to increase weight in childhood may not be advisable for many youth with ADHD.

Another major limitation was participants deviating protocol for medication administration. While few parents gave medication when not assigned to, parents frequently reduced weekend medication use on their own. Future work should examine the role of parental preference about dosing schedules for improving adherence. Reduced weekend use prior to WRT in those subsequently assigned to DH and during WRT in MON (see Table S1, available online) may explain why the randomized arms did not show significant differences for weight velocity. When examined per protocol, DH and CS were superior to MON, albeit outside the inferential protection of randomization. Therefore, our capacity to say that these treatments increase weight gain more than frequent monitoring must be qualified by this limitation. For height, there were no substantial differences between ITT and per-protocol results.

Finally, design features may have altered the degree of growth suppression. Our threshold for initiating WRT was likely milder than that employed in clinical practice, since our goal was to prevent growth suppression. The average MPH dose was below that in the MTA medication only arm, likely due to limits on increasing dose during WRT and the availability of psychosocial treatments for all participants, which predicts less frequent dose changes.[50]

However, our trial mimicked modern dosing practices with daily use of extended-release stimulants [1,5,8] whereas the MTA and other studies employed immediate-release MPH.[37,38] We still observed significant weight and height suppression in the pre-WRT period. Lack of WRT effects on height were not due to failure to induce meaningful height suppression in the pre-WRT period.

In treatment naïve youth, CNS stimulants were associated with significantly reduced weight and height velocity. Increased monitoring of growth, drug holidays, and caloric supplements all significantly increased weight gain, with per protocol analysis showing larger effects for drug holidays and caloric supplementation. All treatments were tolerable except for switching to shorter-acting preparations during schooldays. Despite increasing weight velocity, no treatment increased height velocity. Therefore, in children taking CNS stimulants, it appears that limiting medication exposure to school days or increasing calories is not sufficient to meaningfully counteract the growth suppression observed with initiating CNS stimulants.

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Table 1: Growth Measurements at Randomization to Weight Recovery Treatment (WRT)

Analysis	Measurement	WRT Group		
		Monitoring	Drug Holiday	Caloric Supplementation
Intent-to-treat	Participant *z*-height	-0.07 (0.66)	-0.59 (1.00)	-0.28 (0.85)
	Maternal *z*-height	-0.03 (0.46)	-0.42 (0.47)	-0.01 (0.61)
	Participant *z*-weight	-0.37 (0.55)	-1.01 (0.97)	-0.67 (0.83)
	Participant *z*-BMI	-0.47 (0.58)	-0.99 (0.84)	-0.75 (0.74)
Per protocol	Participant *z*-height	-0.22 (0.78)	-0.57 (0.96)	-0.24 (0.88)
	Maternal *z*-height	-0.16 (0.48)	-0.35 (0.52)	-0.00 (0.62)
	Participant *z*-weight	-0.51 (0.66)	-1.04 (0.97)	-0.64 (0.86)
	Participant *z*-BMI	-0.57 (0.61)	-1.05 (0.91)	-0.74 (0.75)

Note: Maternal *z*-height collected at baseline visit. Participant measurements from visit at which child was randomized to one of three WRT groups. When groups are defined per protocol, differences between monitoring and drug holiday groups is statistically significant for participant *z*-weight and participant *z*-BMI ($p < .05$).

Table 2: Estimated Growth Parameters

Analysis	Metric	Group	Growth Parameter: β_0 Intercept	Growth Parameter: β_1 Growth per month prior to randomization to WRT	Growth Parameter: β_2 Change in growth per month after randomization to WRT	Which between-group differences in β_1 are significant?	Which between-group differences in β_2 are significant?
Intent-to-treat	Weight (kg)	Monitoring	26.8 (0.8) ***	+0.048 (0.035)	+0.231 (0.036) ***	None	None
		Drug holiday	24.4 (0.8) ***	+0.051 (0.033)	+0.275 (0.056) ***		
		Caloric supplement	25.5 (0.6) ***	-0.028 (0.034)	+0.292 (0.050) ***		
	Height (cm)	Monitoring	130.8 (1.0) ***	+0.407 (0.020) ***	-0.001 (0.032)	None	None
		Drug holiday	128.2 (1.3) ***	+0.388 (0.019) ***	+0.002 (0.028)		
		Caloric supplement	128.9 (1.0) ***	+0.355 (0.020) ***	+0.037 (0.031)		
Per protocol	Weight (kg)	Monitoring	25.9 (0.5) ***	+0.096 (0.026) ***	+0.181 (0.037) ***	MON > CS MON > DH	MON < CS MON < DH
		Drug holiday	25.1 (1.2) ***	-0.012 (0.027)	+0.338 (0.049) ***		
		Caloric supplement	25.6 (0.7) ***	-0.043 (0.038)	+0.303 (0.049) ***		
	Height (cm)	Monitoring	129.8 (0.9) ***	+0.408 (0.018) ***	-0.006 (0.030)	None	None
		Drug holiday	128.9 (1.5) ***	+0.386 (0.022) ***	+0.011 (0.036)		
		Caloric supplement	129.1 (1.0) ***	+0.353 (0.020) ***	+0.043 (0.028)		

Note: Intercept reflects estimated height or weight at randomization to Weight Recovery Treatment. Estimates are those for a male child age 8.90 years with mother z-height of -0.13 (mean values of covariates). CS = caloric supplement, DH = drug holiday, MON = monitoring.
*** $p < .001$.

Figure 1: Study Flowchart

Note: ADHD = attention-deficit/hyperactivity disorder; BMI = body mass index; OROS-MPH = OROS methylphenidate.

Figure 2: Pre-Weight Recovery Treatments (WRT) Growth Velocity in Never Medicated Children versus Eventual WRT Participants

Note: For children that eventually entered WRT, median time between study entry and WRT initiation was 10.7 months. For children that were never medicated, the visit closest to 10.7 months after study entry was used for comparison.

Figure 3: Daily Exposures and Estimated Growth by Intent-To-Treat Weight Recovery Treatments (WRT) Group

Note: In panel B, curves are estimated growth for a male child age 8.90 years with mother z-height of -0.13 (mean values of covariates). In panel B, dashed lines show estimated growth had child continued on pre-WRT trajectory. CS = caloric supplementation; DH = Drug Holiday; MON = increased monitoring of weight.

A Randomized, Controlled Trial of Interventions for Growth Suppression in Children With ADHD Treated With CNS Stimulants

RH=Promoting Growth in Children With ADHD

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