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Follow-up: Changes in Effectiveness and Growth After the End of Treatment**

MTA Cooperative Group
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National Institute of Mental Health Multimodal Treatment Study of ADHD Follow-up: Changes in Effectiveness and Growth After the End of Treatment

MTA Cooperative Group*

ABSTRACT. *Objective.* Intent-to-treat analyses of the Multimodal Treatment Study of ADHD (MTA) revealed group differences on attention-deficit/hyperactivity disorder symptoms ratings, with better outcome in groups of participants who were assigned the medication algorithm—medication alone (MedMgt) and combined (Comb)—than in those who were not—behavior modification (Beh) alone and community comparison (CC). However, the effect size was reduced by 50% from the end of treatment to the first follow-up. The convergence of outcomes suggests differential changes by treatment group between 14 and 24 months, which this report explores, both for benefits of treatment and for side effects on growth.

Methods. We documented reported medication use at 14- and 24-month assessments and formed 4 naturalistic subgroups (Med/Med, Med/NoMed, NoMed/Med, and NoMed/NoMed). Then we performed exploratory mediator analyses to evaluate effects of changes in medication use on 14- to 24-month change scores of effectiveness (symptom ratings) and growth (height and weight measures).

Results. The randomly assigned groups with the greatest improvement at the end of the treatment phase (Comb and MedMgt) deteriorated during the follow-up phase, but the other 2 groups (Beh and CC) did not. There were no significant differences in the 14- to 24-month growth rates among the randomly assigned groups, in contrast to significant growth suppression in the Comb and MedMgt at the end of the treatment phase. Changes in medication use mediated the 14- to 24-month change in attention-deficit/hyperactivity disorder symptom ratings: the subgroup that reported stopping medication (Med/NoMed) showed the largest deterioration, the subgroup that consistently reported (Med/Med) or never

reported (NoMed/NoMed) medication use showed modest deterioration, and the subgroup that reported starting medication (NoMed/Med) showed improvement. Changes in medication use also mediated growth effects: the subgroup that consistently reported medication use (Med/Med) showed reduced height gain compared with the subgroup that never reported medication use (NoMed/NoMed), which actually grew faster than predicted by population norms.

Conclusion. In the MTA follow-up, exploratory naturalistic analyses suggest that consistent use of stimulant medication was associated with maintenance of effectiveness but continued mild growth suppression. *Pediatrics* 2004;113:762–769; *ADHD, long-term effects, growth, clinical trial, follow-up.*

ABBREVIATIONS. ADHD, attention-deficit/hyperactivity disorder; MTA, Multimodal Treatment Study of ADHD; MedMgt, medication management; Beh, behavior modification; Comb, combined; CC, community comparison; ITT, intention-to-treat; ES, effect size; SNAP, Swanson, Nolan, and Pelham; ODD, oppositional defiant disorder; SS, social skills.

The literature on long-term effects of treatment of attention-deficit/hyperactivity disorder (ADHD)¹ is limited for measures of effectiveness^{1–7} and growth.^{8–12} The follow-up phase of the Multimodal Treatment Study of ADHD (MTA) allows us to address the long-term outcome of groups formed by random assignment to treatments—medication management alone (MedMgt), behavior modification (Beh), combined (Comb), and community comparison (CC)—by evaluating the status of these 4 groups over time.^{2,3,13} At the end of the treatment phase of the MTA,⁴ the 2 groups with the MTA medication algorithm as part of the assigned treatment (Comb and MedMgt) manifested less severe symptoms of ADHD than the 2 groups that did not (Beh and CC). In the companion paper, an intention-to-treat (ITT) analysis of outcome at the first follow-up revealed that the effect size (ES) of this contrast was reduced by ~50% from the end of treatment (ES: ~0.6) to the first follow-up (ES: ~0.3). Here we describe exploratory analyses to understand why this decrease in effectiveness occurred. Also, we present primary and secondary (exploratory) analyses of the effects of the MTA treatment on growth.

The ITT approach^{2–4,13} evaluates the effects of the treatments assigned rather than the effects of the treatments actually received. In this framework, the individuals who do not comply with the randomly assigned treatments or who change treatments over

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Reprint requests to James M. Swanson, PhD, University of California, Irvine, Child Development Center, 19722 MacArthur Blvd, Irvine, CA 92612. E-mail: jmswanso@uci.edu

*The MTA is a cooperative treatment study performed by 6 independent research teams in collaboration with the National Institute of Mental Health and the Office of Special Education Programs of the US Department of Education, Washington, DC.

In the cited methodology papers for this study, the treatment assignments were called medication (med), psychosocial treatment (PS), combined treatment (CT), and community-treatment assessment and referral (A&R). To reflect more accurately the actual treatments, the terminology is changed for all outcome papers to these more clear and more specific terms: medication management (MedMgt), behavioral treatment (Beh), combined treatment (Comb), and community comparison (CC).

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time remain in their assigned groups in the analyses of outcome. We expected that more individuals would choose to change treatments during the naturalistic follow-up phase when treatment was no longer delivered by MTA staff than during the 14-month treatment phase, so ITT analyses of assigned treatments of the MTA would progressively become less informative about actual treatments received. To address this issue, we documented for each case whether treatment with stimulant medication was reported (Med) or not (NoMed) at the 14- and 24-month assessments. (Because similar data were not collected regarding nonpharmacologic interventions, we did not perform an analogous set of analyses regarding the MTA behavioral treatment.) On the basis of the pattern of medication received over time, we formed naturalistic subgroups. Then, we used Kraemer's mediator/moderator method¹⁴ to explore whether patterns of medication use over time mediated changes in effectiveness and growth from the end of treatment to the first follow-up.

METHODS

Sample

At the 24-month assessment, 540 of the 579 subjects were evaluated (a 93% retention rate). None of the baseline demographic characteristics of the follow-up sample differed significantly from the complete randomized sample of 579 participants.¹³ The assessment battery administered in the follow-up phase has been described in detail elsewhere.^{2,3,13}

Assessments

Fourteen- to 24-month change scores were calculated for 5 conceptually distinct domains of functioning: 1) parent- and teacher-rated ADHD symptoms on the Swanson, Nolan, and Pelham (SNAP)¹⁵ rating scale; 2) parent- and teacher-rated oppositional defiant disorder (ODD) symptoms on the SNAP; 3) parent- and teacher-rated total social skills (SS) from the Social Skills Rating System¹⁶; 4) the Wechsler Individual Achievement Test reading score¹⁷; and 5) a negative/ineffective parental discipline score on this dimension derived from factor analysis.^{18,19} Change scores were also calculated for 2 domains of growth: 6) weight in kilograms and 7) height in centimeters.

Analyses

In contrast to the companion article, which analyzed absolute scores evaluation status at the 24-month assessment, we analyzed 14- to 24-month change scores to evaluate how assigned treatment affected the trajectory of outcome during the 10-month follow-up (ie, the direction and degree of change). For the 3 outcome domains for which both parent and teacher information was available (ADHD, ODD, and SS ratings), a source factor was specified (Rater), and a mixed-effects model^{20–25} was used, with the Rater factor nested within subject and a random intercept to accommodate the correlation among the 2 informants' ratings. For adjusting for the multiple tests across the 5 domains, a $P < .01$ significance level was adopted for each analysis to preserve a family-wise significance level of $P < .05$. To separate the overall effect of assigned treatment into nonoverlapping parts, we used the 3 orthogonal contrasts developed by Swanson et al⁴: the medication algorithm contrast (Comb+MedMgt vs Beh+CC), the multimodality superiority contrast (Comb vs MedMgt), and the psychosocial substitution contrast (Beh vs CC).

To supplement the ITT approach, we used medication status reported on the Services for Children and Adolescents Parent Interview (Hoagwood K, personal communication) at the end of treatment (14-month) assessment and at the first follow-up (24-month) assessment to form naturalistic subgroups. That is, regardless of initial random assignment, if medication use was reported at an assessment point, then the code for that case was "Med" for that point; if not, then the code was "NoMed." Hence, 4 natural-

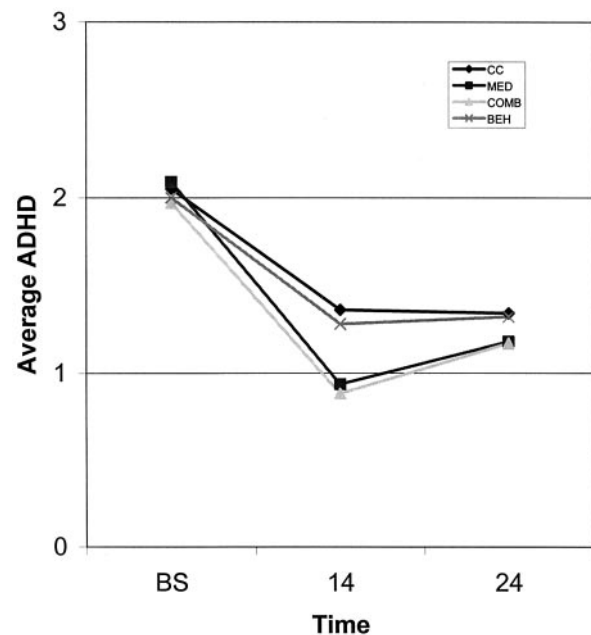
istic subgroups were formed to reflect the sequence of medication use over time (Med/Med, Med/NoMed, NoMed/Med, and NoMed/NoMed). This grouping variable (naturalistic subgroup) was analyzed to evaluate whether patterns of medication use affected 14- to 24-month change scores of effectiveness and growth.

RESULTS

Analyses of Effectiveness (Change Scores for Ratings of Symptoms)

At the first (24-month) follow-up, the absolute ratings of symptom severity (ie, status at each assessment point) presented in a companion article¹³ reveal that all 4 groups still had lower ratings of ADHD and ODD symptoms than at baseline, providing evidence of some persistence of the effects of the MTA treatments (as discussed in the companion article). However, the trajectories of the groups (Fig 1) during the follow-up phase are reversed compared with the trajectories during the treatment phase: the follow-up (14- to 24-month) change scores are positive, reflecting increased severity of symptoms—deterioration—from the end of treatment.

ITT analyses were performed, which revealed that the assigned treatment groups differed in the change from the 14- to 24-month assessments for 3 of the 5 outcome measures of change in effectiveness (ADHD, SS, and negative/ineffective parental discipline). The medication algorithm contrast was significant for 2 of these (ADHD, $P < .001$; SS, $P < .001$)



Assigned Treatment (n=521)	Change Scores	
	B-14 months	14-24 months
Comb (n=135)	-1.10	+0.27
MedMgt (n=120)	-1.10	+0.22
Beh (n=135)	-0.75	+0.04
CC (n=131)	-0.67	+0.02

Fig 1. Assigned (randomized) treatment groups: SNAP-ADHD ratings and change scores.

TABLE 1. Naturalistic Subgroups Based on Pattern of Medication Use

Report of Medication Status at 14- and 24-Month Assessments	Subgroup of Total (N = 521)
Reported consistent use of medication (Comb = 89, MedMgt = 80, Beh = 25, CC = 61)	Med/Med (n = 255)
Reported no use of medication (Comb = 15, MedMgt = 6, Beh = 78, CC = 40)	NoMed/NoMed (n = 139)
Reported stopping medication (Comb = 28, MedMgt = 31, Beh = 6, CC = 11)	Med/NoMed (n = 76)
Reported starting medication (Comb = 3, MedMgt = 3, Beh = 26, CC = 19)	NoMed/Med (n = 51)

and 1 other (ODD, $P < .004$), indicating that the deterioration was significantly greater in the 2 groups that were assigned to treatments that included stimulant medication by design than in the 2 groups that were assigned to treatments that did not. For example, the substantial deterioration reflected by increases in the average SNAP-ADHD ratings for the Comb (0.27 points) and MedMgt (0.22 points) groups was greater than the negligible deterioration reflected by slight increases in average SNAP-ADHD ratings for Beh (0.04 points) and CC (0.02 points) groups.

From the Services for Children and Adolescents Parent Interview, medication status was available at both the 14- and 24-month assessment times for 521 of the 540 participants in the follow-up. From end of treatment to the 24-month follow-up, the percentage who reported use of medication decreased for Comb (from 87% to 68%, a 21.8% drop) and MedMgt (from 93% to 69%, a 25.8% drop) but increased for Beh (from 23% to 38%, a 68.2% increase) and CC (from 55% to 61%, a 9.8% increase). This produced the 4 naturalistic subgroups shown in Table 1.

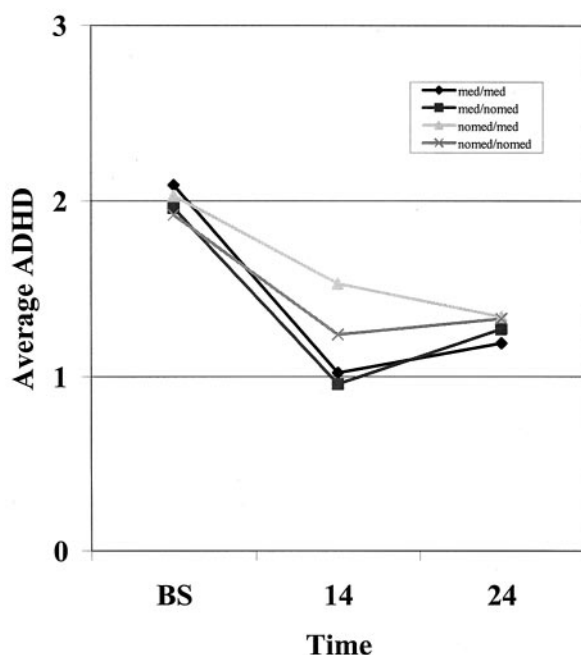
The variable defined by the naturalistic subgroups was used in the mediator analyses. As directed by Kraemer's method, we compared the primary analyses (Table 2, without the mediator variable) to the secondary analyses (Table 2, with the mediator included). In the secondary mediator analyses, the naturalistic subgroup variable was significant for 2 of

the 5 outcome measures (change scores for ADHD and ODD symptom ratings). In the analysis of the SNAP-ADHD change score, after adjustment for the effects attributed to the naturalistic subgroup, the effect of assigned treatment (ie, differential deterioration across the 4 randomly assigned MTA groups) dropped in statistical significance from $P < .001$ to $P = .043$. The same pattern held for the medication algorithm contrast: after adjustment for the mediator, the significance values were reduced for the SNAP-ADHD change score (from $P < .001$ to $P = .013$) as well as for the SNAP-ODD change score (from $P < .01$ to $P = .037$). Thus, after controlling for the mediator, neither the main effect of assigned treatment nor the medication algorithm contrast was significant at the specified significance level of $P < .01$, indicating that the differences in 14- to 24-month deterioration were partially explained by the pattern of actual medication use in the follow-up phase of the MTA.

The 14- to 24-month change scores for these naturalistic subgroups reveal 3 patterns of change during the follow-up (Fig 2): 1) the 2 subgroups that did not change medication status showed slight deterioration, reflected by small increases in SNAP-ADHD ratings in the Med/Med subgroup of 255 cases (0.15 points) and in the NoMed/NoMed subgroup of 139 cases (0.10 points); 2) the Med/NoMed subgroup ($n = 76$) that stopped medication showed considerable deterioration (reflected by an increase in aver-

TABLE 2. Analyses of 14- to 24-Month Change in ADHD and ODD Ratings

Variable/Factor	Without Mediator			With Mediator	
	DF	χ^2	P Value	χ^2	P Value
Ratings of ADHD					
Site	5	2.72	.743	2.52	.774
Treatment (assigned)	3	17.30	.001	8.18	.043
Rater	1	28.13	<.001	27.50	<.001
Site \times treatment	15	20.66	.148	20.86	.141
Rater \times treatment	3	1.98	.577	2.40	.493
Naturalistic subgroups	3			13.15	.004
Comb+MedMgt vs Beh+CC	1	16.26	<.001	6.20	.013
Comb vs MedMgt	1	.62	.432	.61	.434
Beh vs CC	1	.06	.804	.42	.519
Ratings of ODD					
Site	5	6.44	.265	6.52	.259
Treatment (assigned)	3	8.74	.033	4.75	.191
Rater	1	6.15	.013	5.94	.015
Site \times treatment	15	25.55	.043	28.02	.022
Rater \times treatment	3	12.15	.007	12.48	.006
Naturalistic subgroup	3			11.7	.009
Comb+MedMgt vs Beh+CC	1	8.18	.004	4.37	.037
Comb vs MedMgt	1	.28	.598	.44	.508
Beh vs CC	1	.38	.536	.45	.504



Naturalistic Subgroups Based on Pattern of Medication Use (n=521)	Change Scores	
	0-14 months	14-24 months
Med/Med (n=255)	-1.10	+0.15
No Med/NoMed (n=139)	-0.68	+0.10
Med/No Med (n=76)	-1.00	+0.33
No Med/Med (n=51)	-0.50	-0.15

Fig 2. Naturalistic subgroups: SNAP-ADHD ratings and change scores.

age SNAP-ADHD ratings of 0.33 points); 3) the NoMed/Med subgroup ($n = 51$) that started medication showed the opposite pattern (improvement, reflected by a decrease in average SNAP-ADHD ratings of -0.15 points). Most of the 76 Med/NoMed cases that stopped medication were from the Comb ($n = 28$) and MedMgt ($n = 31$) groups, and most of the 51 NoMed/Med cases that started medication were from the Beh ($n = 26$) and CC ($n = 19$) groups.

We also evaluated the effects of possible moderator variables, defined by preexisting conditions present before randomization.^{3,14} The presence or absence of comorbid anxiety on entry to the MTA, which was a significant moderator of the treatment effect in the initial report of the MTA findings at the end of treatment,³ was not a significant moderator of 14- to 24-month deterioration for any of the outcome measures. The presence or absence of ODD at entry to the MTA, the most prevalent comorbid condition at baseline, was not a significant moderator in any of these analyses, either. Baseline severity was not a significant moderator of 14- to 24-month deterioration for any of the 5 outcome measures.

The exploratory mediator analyses clearly suggest some persistent benefits (symptom reduction) when medication is continued (eg, in the Med/Med subgroup) compared with when it is not used (eg, in the

NoMed/NoMed subgroup) or is stopped (eg, in the Med/NoMed subgroup). Of course, long-term benefits of treatment must be evaluated in light of potential long-term side effects that may become noticeable only after extended periods of treatment. The MTA follow-up provides an opportunity to evaluate 1 of the potential and controversial side effects of stimulant medication (growth suppression). Although measures of height and weight were missing for some of the 521 participants at 1 or more of the 3 assessment points (all of which are necessary to calculate the change scores), primarily because of unavailability of staff at all of the visits, complete growth data were available on 433 participants, which still provides a large sample size for the evaluation of this controversial topic.

Analyses of Growth-Related Side Effects (Changes in Height and Weight)

First, we analyzed the growth of children during the 14-month treatment phase of the MTA. ITT analyses of these baseline to 14-month change scores reveal initial large and significant effects of assigned treatment on weight ($\chi^2 = 27.29$, $P < .001$) and height ($\chi^2 = 37.03$, $P < .001$). The MTA medication algorithm contrast was significant for height ($\chi^2 = 36.26$, $P < .001$) and weight ($\chi^2 = 17.86$, $P < .001$) as a result of smaller gains in the 2 groups that were assigned to receive our "carefully crafted" treatment with stimulant medication (for the Comb and MedMgt groups, 4.85 cm and 4.25 cm gains in height and 2.52 kg and 1.64 kg gains in weight, respectively) than in the other 2 groups (for Beh and CC, 6.19 and 5.68 cm gains in height and 4.53 kg and 3.13 kg gains in weight, respectively). In the analyses of weight but not height change scores, the behavioral substitution comparison of Beh versus CC was significant ($\chi^2 = 7.82$, $P < .005$), and the multimodality superiority comparison of Comb versus MedMgt just missed significance at our conservative level of $P < .01$ ($\chi^2 = 5.86$, $P = .016$).

The comparison of the unimodal treatment groups (MedMgt and Beh) may be most informative, because during the treatment phase of the MTA, most cases that were assigned to these group reported adherence to the assigned medication status. This produced the greatest between-group difference in reported medication use (MedMgt: 93%; Beh: 23%), which inversely related to group averages for gain in height (MedMgt: 4.75 cm; Beh: 6.19 cm) and in weight (MedMgt: 1.64 kg; Beh: 4.53 kg). Thus, the MedMgt versus Beh comparison provides conservative estimates of height suppression ($4.75 - 6.19$ cm = -1.44 cm over 14 months = -1.23 cm/year) and weight suppression ($1.64 - 4.53$ kg = -2.89 kg over 14 months = -2.48 kg/year) that occurred during the initial 14-month treatment phase of the MTA. These ITT estimates are protected from selection factors by the randomization process but are conservative as a result of the lack of complete compliance with the assigned treatments.

During the 10-month follow-up, the initial growth suppression effects seemed to dissipate: in ITT analyses of 14- to 24-month change scores, neither the

overall effect of assigned treatment nor any of the orthogonal comparisons was statistically significant. The 14- to 24-month gains in weight and height were approximately the same in the 4 assigned treatment groups for weight (Comb: 5.28 kg; MedMgt: 5.06 kg; Beh: 4.98 kg; CC: 4.58 kg) and for height (Comb: 5.69 cm; MedMgt: 5.69 cm; Beh: 6.16 cm; CC: 5.79 cm). Of course, this pattern could reflect a transitory effect of assigned treatment on growth, or it could be related to changes in the actual treatment received during follow-up.

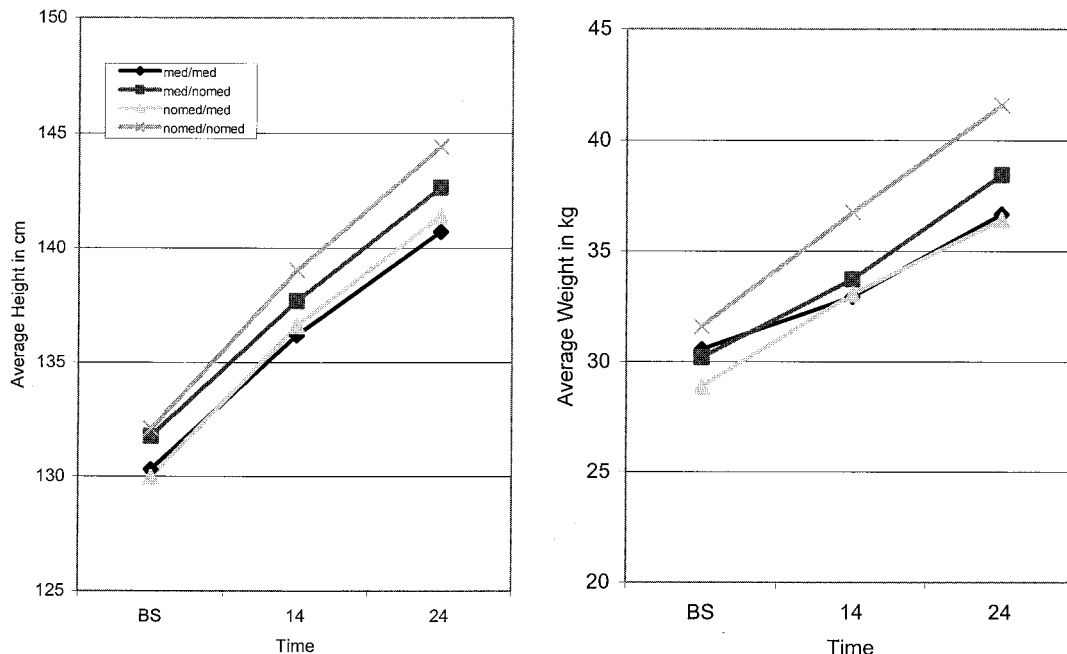
To evaluate the hypothesis that this loss of significance might be explained by medication use during the follow-up, we performed mediator analyses adjusting for membership in the naturalistic subgroups. (Height and weight data at both assessment points were missing for some of the children on whom ADHD and ODD ratings were collected [33 in MedMgt, 17 in Comb, 36 in Beh, and 38 in CC], so the naturalistic subgroups and the mediator analyses were based on 433 rather than 521 cases.) The baseline and 14- and 24-month averages for height and weight for the 4 naturalistic subgroups are shown in Fig 3. In the analyses of 14- to 24-month change scores (Table 3), the mediator (Medication Status) was significant for both height ($\chi^2 = 16.16$, $P < .001$) and weight ($\chi^2 = 13.32$, $P < .004$).

To understand the overall mediator effect of naturalistic subgroup, we compared the "untreated

clinical control" group (NoMed/NoMed) with the consistently treated subgroup (Med/Med). The differences in the 14- to 24-month change scores suggest significant growth suppression effects for both height ($4.53 - 5.40 = -0.87$ cm) and weight ($3.81 - 4.83 = -1.02$ kg), with moderate effect sizes (.34 for weight and .46 for height). This pattern did not change when initial baseline or 14-month height and weight were used as moderators of the 14- to 24-month changes.

In contrast to the assigned treatment groups, the naturalistic subgroups are not protected by randomization. Instead, membership in these subgroups was determined by each family's decisions after randomization whether to accept or maintain the assigned treatments over the course of the initial treatment phase and during the first follow-up phase of the MTA. Possibly related to self-selection was an initial difference in size: the Med/Med subgroup was 1.69 cm shorter and 0.96 kg lighter than the NoMed/NoMed subgroup at the baseline assessment. Over time, these initial differences became progressively larger (Fig 3): the smaller Med/Med subgroup lagged progressively farther behind the larger NoMed/NoMed subgroup, so from baseline to the first follow-up, the initial height difference increased from 1.69 cm to 3.70 cm and the initial weight difference increased from 0.96 kg to 4.79 kg.

Moderator analyses were used to control for ef-



Naturalistic Subgroups Based on Pattern of Medication Use (n=433)	0-14 Change Scores		14-24 Change Scores	
	Mean (sd) Change in Height	Mean (sd) Change in Weight	Mean (sd) Change in Height	Mean (sd) Change in Weight
Med/Med (n=222)	5.88 (1.80) cm	2.36 (3.00) kg	4.53 (1.61) cm	3.81 (2.84) kg
No Med/NoMed (n=106)	6.93 (2.21) cm	5.14 (3.53) kg	5.40 (2.18) cm	4.83 (3.10) kg
Med/No Med (n=63)	5.94 (1.84) cm	3.54 (3.84) kg	4.94 (2.06) cm	4.73 (3.42) kg
No Med/Med (n=42)	6.64 (1.49) cm	4.21 (3.43) kg	4.79 (1.62) cm	3.37 (2.87) kg

Fig 3. Naturalistic subgroups: height and weight at assessment points and change scores.

TABLE 3. Analyses of Change in Weight and Height From 14 to 24 Months

Variable	Weight Change			Height Change	
	DF	χ^2	$P > \chi^2$	χ^2	$P > \chi^2$
Site	5	10.63	.059	16.82	.005
Treatment	3	2.80	.423	.79	.851
Site \times treatment	15	17.53	.288	12.02	.678
Medication status	3	13.32	.004	16.16	.001
Med/Med vs NoMed/NoMed	1	9.80	.002	15.14	<.001
Med/NoMed vs NoMed/NoMed	1	1.18	.277	4.31	.038
NoMed/Med vs NoMed/NoMed	1	5.88	.015	4.66	.031

fects of age and gender, but these factors were not significant, indicating that the patterns of growth suppression held for the 3 age cohorts that entered the MTA (at 7, 8, and 9 years of age) and for girls as well as boys. Another method to control for age and gender is to analyze *z* score transforms based on age and gender norms from the National Center for Health Statistics.¹³ The *z* score averages were positive at baseline, confirming the observations based on raw scores that the ADHD participants in the MTA were larger than the population norms. Despite these initial differences, the change scores did not reflect regression to the mean (which would have resulted in convergence at the follow-up assessment). Instead, the direction of change in *z* scores was opposite for the 2 naturalistic subgroups: the average *z* scores for height and weight increased over time for the larger NoMed/NoMed subgroup and decreased for the smaller Med/Med subgroup.

DISCUSSION

The analyses reported here suggest that pattern of actual medication use during the follow-up phase of the MTA mediates outcome on measures reflecting both clinical effectiveness (manifestation of symptoms) and side effects (growth rates). We found that the deterioration of effectiveness during the follow-up phase of the MTA (the partial loss of the initial benefit of ADHD and ODD symptom reduction) was greater for the 2 groups that initially showed the greatest benefits of treatment (Comb and MedMgt) than for the 2 groups that initially showed the smallest benefits (Beh and CC). Exploratory mediator analyses suggest that the large beneficial effects of original assignment to Comb and MedMgt may have waned because these groups had a larger number of cases that stopped and a smaller number of cases that started medication during the follow-up than the Beh and CC groups.

Thus, in the ITT analyses of the assigned treatments, the apparent reduction of the effects of stimulant medication may reflect more the lack of maintenance of an effective intervention than the reduction of the effects of medication when it was taken. This interpretation is consistent with the longstanding view that stimulant medication provides symptomatic relief for as long as it is administered but has limited carryover effects when stopped. The effect of Beh was smaller than the effect of medication but was maintained, suggesting that generalization occurred, perhaps because parents continued to implement the practices that they had learned.

Our mediator analyses used naturalistic subgroups formed by choices regarding acceptance and adherence to assigned treatment during the 14-month treatment phase and decisions to continue or to change the medication component of treatment during the 10-month follow-up phase when the MTA was no longer providing the interventions. In the Med/Med subgroup that accepted and decided to continue medication, the ADHD and ODD ratings increased nominally during follow-up (0.15 and 0.08, respectively), which could be interpreted as a reduction in the effects of stimulant medication over time. However, similar small increases in ADHD and ODD ratings (0.10 and 0.08, respectively) were observed in the NoMed/NoMed subgroup, which had not received medication at either assessment. Thus, the slight deterioration in both of these subgroups seems to characterize the natural history of the disorder independent of treatment with medication. This suggests that either consistent pharmacologic and behavioral treatments maintained most of their effects over time or that some other variable was operating consistently across these groups during the first 2 years of the MTA.

A surprising number of cases in the MedMgt and Comb groups stopped treatment with stimulant medication that was effective for reducing ADHD and ODD symptoms, and a surprising number of cases in the Beh group never initiated this component of treatment that has a strong empirical basis of effectiveness. The reasons for these counterintuitive decisions are unclear, but data on parental satisfaction with the MTA treatments offer a clue (Pelham WE, personal communication): despite greater symptom reduction in the MedMgt group than in the Beh group, the satisfaction ratings by parents and teachers were higher for the Beh group, and parent evaluations of the relative effectiveness of the treatments in reducing referring problems (vs symptoms) were equivalent across the randomly assigned groups. Thus, the full extent of effectiveness of the treatments for ADHD,²⁸ as well as their limitations, may not be captured by the ratings of symptoms. Important aspects of quality of life, adaptive functioning, and tolerability may be missed by the operational definitions of effectiveness and side effects based on parent and teacher symptom ratings alone. Such factors may have contributed to subjective ratings of satisfaction with the Beh treatment and willingness to continue psychosocial treatment or to stop pharmacological treatment during the initial phases of the MTA follow-up.

In the literature, the clinical significance of growth side effects has been discounted on the basis of a variety of hypotheses. Some of these can be partially addressed by the MTA follow-up. For example, Satterfield et al¹¹ hypothesized that an initial growth suppression effect would dissipate and growth rebound would occur even if medication was continued and summer holidays were not provided. However, so far, our exploratory analyses of naturalistic subgroups do not support this hypothesis, because we observed that a significant growth suppression effect occurred during the second year of treatment in the subgroup that was treated continuously with medication (Med/Med). Also, Spencer et al¹² hypothesized that the presence of ADHD rather than its treatment with medication was associated with slower-than-normal growth rate. In contrast, we observed a greater-than-normal growth rate in the unmedicated subgroup (NoMed/NoMed), which does not support that hypothesis. However, we did observe a smaller growth suppression effect in the subgroups without continuous treatment (NoMed/Med and Med/NoMed) than with consistent treatment (Med/Med), which offers some support for the hypothesis proposed by Safer et al and Gittelman and Manuzza¹⁰ that interrupting treatment with stimulant medication may limit its growth suppression.

The divergence of the Med/Med and NoMed/NoMed subgroups increased over time, as a result of an additional growth suppression effect during the 10-month follow-up phase (-0.87 cm in height and -1.02 kg in weight) over and above the growth suppression effect during the 14-month treatment phase (for these restricted subgroups, 1.05 cm in height and 2.98 kg in weight) for the consistently medicated subgroup. When adjusted for the difference in months of these 2 phases, the estimated height suppression as a result of continuous medication treatment seems to be approximately the same during the initial treatment phase ($-1.05 \times 12/14 = -0.9$ cm/year) and the first follow-up phase ($-0.87 \times 12/10 = -1.04$ cm/year) of the MTA, whereas the estimated weight suppression seems to be somewhat larger during the initial treatment phase ($-2.98 \times 12/14 = -2.55$ kg/year) than during the follow-up phase ($-1.02 \times 12/10 = -1.22$ kg/year).

The growth suppression effects noted above during this follow-up (1 cm/year in height and 1.25 kg/year in weight) could be related to a medication effect, with the continuously treated subgroup having slower growth than the untreated subgroup. Alternatively, the Med/Med subgroup, defined by unknown self-selection factors (and at baseline somewhat smaller than the NoMed/NoMed subgroup) could have had a slower growth rate before the start of the study, which continued during the treatment and follow-up phases of the MTA. The latter interpretation suggests that the growth suppression effect was attributable to preexisting factors rather than or in addition to treatment with medication. Our data cannot make a determination of the validity of these alternative interpretations.

In addition, we should emphasize that ultimate height and weight of the MTA participants cannot be

determined by the 24-month follow-up analyses presented here. At this first follow-up, our observations were of the children in the MTA when they were between the ages of 9 and 11 years, which is before the expected phase of accelerated growth in adolescence and before the expected age when growth slows and final height is approximated (~ 16 years of age in girls and 18 years of age in boys).²⁹ The rate of growth as well as the length of the growth phase together determines ultimate (adult) height, and it is possible that the consistent treatment with medication may reduce the rate but lengthen the duration of growth, so final height would be delayed but not reduced. In fact, some studies suggest that the stimulant treatment regimes used in the 1970s did not affect final height.³⁰ In future follow-up assessments of the MTA, we will address important question about the temporary or permanent nature of the medication-related growth suppression of height and try to estimate the magnitude and clinical significance of any long-term effect in the follow-up of naturalistic subgroups.

Limitations

First, an important limitation of this report is that the naturalistic subgroups were established by self-selection, not by randomization. Thus, the results of our 14- to 24-month mediator analyses are considered exploratory, as outlined by Kraemer et al.¹⁴

Second, we should acknowledge some limitations of our procedures for the measurements of height and weight, which matched good clinical practice but left some factors uncontrolled. For example, there was no control for time of day or for clothing worn (other than shoes, which were removed) when the growth measurements were taken. This may have increased the variability, especially in weight, and thus reduced the power of statistical tests for true differences that might exist. However, we have no reason to suspect that any uncontrolled factors related to height and weight measurement were confounded with either randomly assigned treatment groups or naturalistic subgroups.

Third, we are aware that other measures of exposure to medication could be used to define medication status, such as the number of months on medication. Our operational definition of status during the 30 days before the assessment points was chosen to capture the effects of medication on ratings of effectiveness, not on the long-term effects on growth. Including some cases that had been on medication for only the last few months of the 10-month follow-up may have weakened the observed medication-related growth suppression effects on height.

CONCLUSION

The analyses presented here offer hypotheses that can be tested in the subsequent follow-up assessments that are planned in the MTA follow-up: 1) if the apparent differential deterioration of the effectiveness of the assigned treatment continues, then the outcomes of the 4 randomly assigned MTA groups (Comb, MedMgt, Beh, and CC) will converge over time; 2) this convergence may be partially ac-

counted for by changes in treatments received that eventually result in approximately the same percentage of subjects on medication; 3) for the naturalistic subgroup continuously treated with medication, a persistent long-term reduction of ADHD symptoms will be manifested; 4) this beneficial effect will be accompanied by height suppression with a magnitude dependent on the length of treatment with medication, so that the ultimate height of children who have ADHD and are treated with stimulants will be reduced or delayed compared with children who have ADHD and are not treated with stimulants; and 5) when growth-related side effects are better defined, the medication regimen recommended so far by the MTA may need revision to include provisions for drug holidays and lower doses. These questions will be addressed in the follow-up phase of the MTA that is now in progress, which will track this sample through adolescence and into adulthood.

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