MTA at 8 Years: Prospective Follow-up of Children Treated for Combined-Type ADHD in a Multisite Study

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ABSTRACT

Objectives: To determine any long-term effects, 6 and 8 years after childhood enrollment, of the randomly assigned 14-month treatments in the NIMH Collaborative Multisite Multimodal Treatment Study of Children With Attention-Deficit/Hyperactivity Disorder (MTA; *N* = 436); to test whether attention-deficit/hyperactivity disorder (ADHD) symptom trajectory through 3 years predicts outcome in subsequent years; and to examine functioning level of the MTA adolescents relative to their non-ADHD peers (local normative comparison group; *N* = 261). **Method:** Mixed-effects regression models with planned contrasts at 6 and 8 years tested a wide range of symptom and impairment variables assessed by parent, teacher, and youth report. **Results:** In nearly every analysis, the originally randomized treatment groups did not differ significantly on repeated measures or newly analyzed variables (e.g., grades earned in school, arrests, psychiatric hospitalizations, other clinically relevant outcomes). Medication use decreased by 62% after the 14-month controlled trial, but adjusting for this did not change the results. ADHD symptom trajectory in the first 3 years predicted 55% of the outcomes. The MTA participants fared worse than the local normative comparison group on 91% of the variables tested. **Conclusions:** Type or intensity of 14 months of treatment for ADHD in childhood (at age 7.0–9.9 years) does not predict functioning 6 to 8 years later. Rather, early ADHD symptom trajectory regardless of treatment type is prognostic. This finding implies that children with behavioral and sociodemographic advantage, with the best response to any treatment, will have the best long-term prognosis. As a group, however, despite initial symptom improvement during treatment that is largely maintained after treatment, children with combined-type ADHD exhibit significant impairment in adolescence. Innovative treatment approaches targeting specific areas of adolescent impairment are needed. *J. Am. Acad. Child Adolesc. Psychiatry,* 2009;48(5):484–500. **Key Words:** ADHD, adolescence, clinical trial, longitudinal. Clinical trial registration information—Multimodal Treatment Study of Children With Attention Deficit and Hyperactivity Disorder. URL: *http://www.clinicaltrials.gov*. Unique identifier: NCT00000388.

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The NIMH Collaborative Multisite Multimodal Treatment Study of Children With Attention-Deficit/Hyperactivity Disorder (ADHD), abbreviated as MTA, compared four distinct treatment strategies during childhood for 579 children diagnosed with *DSM-IV* ADHD, combined type. Children were randomly assigned to 14 months of systematic medication management (MedMgt), which was initial placebo-controlled titration, thrice-daily dosing, 7 days per week, and monthly 30-minute clinic visits; multicomponent behavior therapy (Beh), which included 27-session group parent training supplemented with eight individual parent sessions, an 8-week summer treatment program, 12 weeks of classroom administered behavior therapy with a half-time aide and 10 teacher consultation sessions; their combination (Comb); or usual community care (CC).[1,2] This randomized, six-site, controlled clinical trial, conducted in parallel at six performance sites, featured rigorous diagnostic criteria at study entry (when the children were in first through fourth grade) and compared the relative effectiveness of treatments of well-established efficacy.[3] Characterization of the MTA children's functioning and services use through adolescence, including their continued use of prescribed psychoactive medication, should provide key insights into the long-term course of ADHD and whether time-limited intensive treatment in childhood influences later outcome. This article reports psychiatric, academic, and social functioning outcomes attained by adolescence.

The initial MTA findings were based on comparisons of the three MTA-treated groups with one another and with the CC at the end of the 14-month treatment period.[1,2] At that time, all groups showed improvement over baseline, but Comb and MedMgt participants showed significantly greater improvements in ADHD and oppositional defiant disorder (ODD) symptoms than did Beh or CC participants. Although Comb and MedMgt did not differ significantly in any direct comparisons, Comb but not MedMgt had significantly better outcomes than Beh and CC for internalizing symptoms, teacher-rated social skills, parent–child relations, and reading achievement. Approximately half of the initial advantage of Comb and MedMgt had dissipated by the first follow-up evaluation, 10 months after the termination of treatment.[4,5]

By the next follow-up, 3 years after enrollment (22 months after the end of the randomly assigned treatment), there were no longer significant treatment group differences in ADHD/ODD symptoms or functioning.[6] That is, although the improvements over baseline for children in all four groups were maintained, the relative advantage associated with the intensive 14-month medication management in the MedMgt and Comb groups had dissipated.[6] Additional analyses failed to support the hypothesis that treatment-seeking biases accounted for these results.[7] Also, through growth mixture modeling, we identified three subgroups ("latent classes") of children with differing ADHD symptom trajectories between pretreatment and the 36-month follow-up (Fig. 1).[7] "Class 1" (34% of the sample) showed a gradual improvement over time, with an increasing significant benefit from medication use at 36 months. In contrast, "class 2" (52% of the sample) showed a larger initial improvement that was maintained over time, whereas "class 3" (14% of the sample) returned to pretreatment symptom levels after an initial positive response to treatment. The children in class 2 began the study with relative sociodemographic and behavioral advantage compared with the children in classes 1 and 3 (e.g., more married parents, higher IQ, lower behavior problem scores, better social functioning) and had originally been assigned disproportionately more to Comb or to MedMgt. A more detailed discussion of these and other findings from the MTA up to the 3-year follow-up may be found in Swanson and coworkers.[8,9]

The current study reports the next two follow-up assessments of the MTA sample, at 6 and 8 years after random assignment, when the sample ranged in age from 13 to 18 years. Our first aim was to determine the presence of any differential long-term effects of the randomized treatments on adolescent functioning. These analyses controlled for medication treatment during the follow-up period. Although continued merging of the treatment groups' average scores was highly likely, given

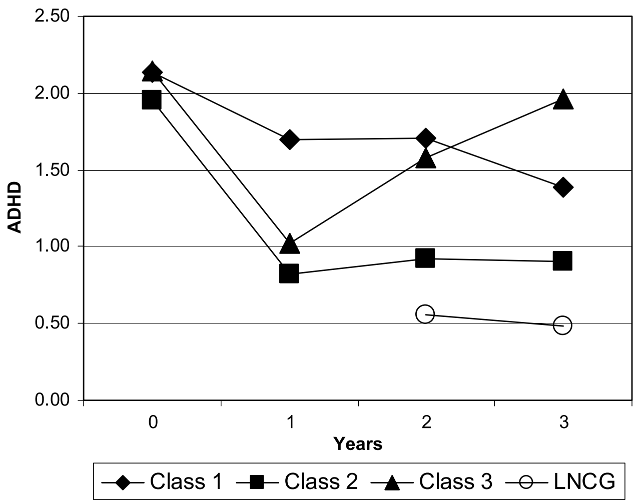

Fig. 1 Average ADHD symptom score over time by latent class. LNCG = local Normative Comparison Group. Reproduced with permission from Wolters Kluwer Health. Originally published in Swanson JM, Hinshaw SP, Arnold LE et al. Secondary evaluations of MTA 36-month outcomes: propensity score and growth mixture model analyses. *J Am Acad Child Adolesc Psychiatry*. 2007;46(8):1003–1014.

the trajectory of findings from the end of randomly assigned treatment through the 36-month findings,[6] delayed "sleeper effects" were possible (i.e., an emergence of treatment group differences not previously observed). Importantly, we sought to characterize the functioning of the children along an expanded and developmentally informed continuum of variables. Our second aim was to determine whether 36-month latent class membership, reflecting differential ADHD symptom trajectories across the first 3 years, predicted adolescent outcome at 6 and 8 years. The third aim was to compare the level of functioning of the adolescents with ADHD with that of non-ADHD peers. Overall, we sought to provide insight into the long-term course of ADHD combined type after 14 months of intensive high-quality treatment in childhood.

METHOD

Participants

The MTA participants were 579 children with *DSM-IV* ADHD combined type. Each of the six participating sites randomized 96 to 98 children to one of four treatment groups (MedMgt, Beh, Comb, and CC). At baseline (pretreatment), participants were 7.0 to 9.9 years of age (mean 8.5 years, SD 0.8 years). The MTA recruitment strategy, procedures for diagnosing ADHD, treatment specifics, and sample demographics have been described elsewhere.[1,2,4,5,10–14]

Participants were reassessed at completion of the 14-month treatment phase, at 24 and 36 months, and again at 6 and 8 years after randomization. Participation rates were 97%, 93%, 84%, 78%, and 75%, respectively. There was no significant difference in any baseline characteristic between participants and nonparticipants for the 36-month assessment.[6] However, participants lost to the 8-year follow-up, compared with those retained, were more often male (87% versus 78%), had younger mothers (mean 25.9 years versus 28.0 years at child's birth), had less educated parents (mean 13.86 years versus 14.55 years of schooling for mothers; mean 13.51 years versus 14.35 years of schooling for fathers), had lower parent income (mean 37.73 K versus 43.24 K), and were more likely to have been on welfare (24% versus 17%) at baseline, all p values are less than .05. The remaining sociodemographic/adversity variables (e.g., age, grade, ethnicity/race, parent marital status, stable residency, parent job loss, child health, birth weight) were not significantly different and may be seen in earlier reports by treatment group[1] or by latent class.[7] Furthermore, 8-year participants were not significantly different from nonparticipants on baseline measures of intellect and achievement, parent and teacher report of ADHD and ODD symptoms, parent-reported aggression and conduct problems, or randomized treatment group assignment ($p > .05$). Mean ages at the 6- and 8-year assessments were 14.9 (SD 1.0) and 16.8 (SD 1.0) years, respectively.

A local normative comparison group (LNCG, $n = 289$) was recruited at 24 months to reflect the local populations from which the MTA sample was drawn. The LNCG children were randomly selected from the same schools and grades and in the same sex proportions as the MTA children. Children were not excluded because of ADHD (but see "Statistical Approach" regarding exclusion of LNCG children with ADHD from main analyses comparing functioning between the MTA and the LNCG children). The assessment battery included the Diagnostic Interview Schedule for Children Version-IV (DISC-IV)[15] and teacher-reported ratings of ADHD symptoms, which afforded examination of *DSM-IV* diagnoses and ADHD symptom severity. The LNCG had the same entry criteria as the MTA children except for ADHD diagnosis and age; they were matched to the MTA children's age at 24 months after randomization. Thus, data for the LNCG are only available starting at the 24-month assessment. At that time, average age of the LNCG (mean 10.4 years, SD 1.08 years) did not differ from that of the MTA sample ($t_{811} = 1.04$, $p = .36$). Percentage of the female subjects was similar in the LNCG (18.7%, $n = 54/289$) and the MTA samples (19.7%, $n = 114/579$, $\chi^2_1 = 0.13$, ns). The percentage of retained LNCG participants by 6 and 8 years was 87% (252/289) and 90% (261/289), respectively. The LNCG participants lost by the 8-year follow-up had less stable residency (29% versus 69% owned their own home or were in the military at baseline), younger mothers (mean ages 26.3 years versus 29.0 years at child's birth), and higher reading achievement scores (mean scores 110.3 versus 104.6) than those retained, but all other baseline variables were nondiscriminating ($p > .05$). Mean ages at the 6- and 8-year assessments were 14.5 (SD 1.2) and 16.6 years (SD 1.2), respectively.

Measures

Outcome Variables. Efforts were made to use the same child functioning variables analyzed in previous MTA reports and to expand outcomes into developmentally relevant domains. Measures included parent and teacher mean ratings of ADHD and ODD symptoms with the Swanson, Nolan, and Pelham Rating Scale (SNAP; adhd.net); parent and teacher mean ratings of aggression and conduct based on the *DSM-IV* symptoms of conduct disorder (CD)[16]; severity of delinquent behavior coded on a five-point ordinal scale using parent and youth report across several measures[17]; parent report of number of contacts with police and arrests by 8 years (Services for Children and Adolescents-Parent Interview [SCAPI])[18,19]; parent-reported mean rating of overall functional impairment with the Columbia Impairment Rating Scale (CIS)[20]; self-reported mean rating of depression (Children's Depression Inventory)[21] and anxiety symptoms (Multidimensional Anxiety Scale for Children)[22]; the Wechsler Individual Achievement Test (WIAT)[23] reading and math standardized scores; teacher-rated academic performance relative to other students using the mean of the first five items (α = .91 at 8 years) of the Academic Competence subscale of the Social Skills Rating System (SSRS)[24]; grade point average on a four-point scale taken from the final report card closest in time to the 8-year assessment (coded with more than 90% interrater agreement); parent-reported hours per week of special education (0 = none, 1 = up to 1 hour, 2 = up to 5 hours, 3 = more than 5 hours), counseling or therapy in school, or other school services such as help in the classroom to manage behavior or tutoring (SCAPI); posttreatment grade retention by 8 years (in lifetime for MTA versus LNCG comparisons); parent- and teacher-rated total social skills mean rating from the Social Skills Rating System[24]; parent-reported psychiatric hospitalizations by 8 years (SCAPI); and parent- or youth-reported accidents or citations stemming from vehicular moving violations. (Driving accidents/citations were analyzed for participants who drove or were eligible to drive based on age.) The LNCG participants who were eligible by age were more likely to have a license (116/203 = 57.14%) than the MTA participants (152/376 = 40.43%, χ^2_1 = 14.82, p < .001).

Two teachers (English and Math) provided ratings, which were averaged for analysis. Psychiatric diagnoses were based on the DISC-IV, with ADHD diagnosis based on the same algorithm used to establish study entry (for details and exceptions, see MTA Cooperative Group[1]). At the 8-year assessment, 55 MTA and 39 LNCG participants had turned 18 and were administered the DISC-IV,[25] the CIS worded for self-report,[20] the Beck Depression Inventory,[26] and the Beck Anxiety Inventory[27] instead of the parallel child measures. Results were not appreciably different when their data were excluded.

Medication Usage. From the parent-reported SCAPI, prescription medication use was defined as the proportion of days that children received any medication for ADHD in the past year.

Statistical Approach

The main analytic approach was mixed-effects regression modeling with point-in-time contrasts. The mixed-effects regression is an extension of the ordinary linear regression (see Hedeker and Gibbons[28] for a relevant overview, especially pp. 47–48). These analyses test whether groups (i.e., randomly assigned treatment group; membership in 36-month latent class 1, 2, or 3; MTA versus LNCG) differ as a function of time. In contrast to the traditional repeated-measures analysis of variance, mixed-effects regression models allowed us to include subjects with incomplete data across time and account for within-subject correlations between observations. We included individual point-in-time contrasts, treating group and time as fixed effects and the intercept as a random effect, to test the significance of group differences at 6 and 8 years. Power was sufficient (0.80 or higher) to detect small treatment group differences (effect size of 0.28 or larger at p < .05 or less). For five nominal (or categorical) variables analyzed at the 8-year endpoint only (i.e., police contact, arrested, grade retention, psychiatric hospitalizations, driving accidents/citations), we used a multinomial generalized linear model with a cumulative logit link function. Grade point average was analyzed as a continuous variable with a single 8-year endpoint comparison.

Three sets of analyses were conducted. First, for the MTA participants, mixed-effects models with the planned point-in-time contrasts were tested for each outcome measure to establish any remaining differences of initial treatment assignments by the 6- and 8-year assessments. Following our procedures for ensuring a limited number of clinically relevant treatment group comparisons from previous articles, the effects of treatment were tested using three orthogonal contrasts following statistically significant treatment-by-time interactions (or for end-point-only analyses, following statistically significant main effects of treatment): Comb + MedMgt versus Beh + CC, termed the *MTA Medication Algorithm effect*; Comb versus MedMgt, the *Multimodality effect*; and Beh versus CC, the *Behavioral Substitution effect*. We also tested an alternate set of planned contrasts distinguished by using behavioral treatment rather than medication algorithm as the primary divider (see Molina et al.[17]): Comb + Beh versus MedMgt + CC, the *Intensive Behavioral effect*; Comb versus Beh, the *Medication Addition effect*; and MedMgt versus CC, the *Intensity of Medication effect*. Site as a fixed effect and medication use (time-varying for repeated-measures analyses) were covaried, and p values greater than .025 are not reported as statistically significant to adjust for α inflation because of two sets of treatment group contrasts. Second, comparisons among the three previously identified 36-month latent classes[7] for the 6- and 8-year outcome measures were analyzed using mixed-effects regression models and point-in-time contrasts among the classes, controlling for site. Finally, the MTA subjects were compared with the LNCG subjects with mixed-effects regression models with point-in-time contrasts. The LNCG subjects who met diagnostic criteria for ADHD at recruitment (n = 31) were removed; results were not appreciably different with these subjects included. To assist with interpretation, in addition to observed means and percentages in the tables by group, effect sizes are presented for statistically significant group comparisons using Cohen d for means (SDs) and Cohen h for proportions, where 0.2 is considered a small effect size, 0.5 is considered a medium effect size, and 0.8 is considered a large effect size.[29] Because results were not affected by the inclusion of age as a covariate, we present findings without age covaried. IQ at study entry was controlled in the latent class and MTA versus LNCG comparisons for academic outcomes (WIAT scores, teacher-rated academic performance, grade point average, school services, grade retention). Data were from the 8-year data set closed on January 31, 2006.

RESULTS

Medication Use Over Time

We first examined medication use because of its importance as a covariate in determining long-term treatment effects. As previously reported,[6] medication use varied at 14, 24, and 36 months according to initial random assignment: mean (SD)—0.71 (0.24), 0.67 (0.35), 0.66 (0.41) for MedMgt; mean (SD)—0.71 (0.22), 0.69 (0.35), 0.67 (0.39) for Comb; mean

(SD)—0.16 (0.28), 0.35 (0.44), 0.43 (0.46) for Beh; mean (SD)—0.54 (0.41), 0.58 (0.42), 0.59 (0.43) for CC, respectively. By the 6- and 8-year assessments, however, these group differences in medication use were no longer significant ($F_{3,457}$ = 1.11, ns, and $F_{3,408}$ = 0.60, ns, respectively. For the MTA sample as a whole, mean (SD) at 6 and 8 years is as follows: 0.42 (0.43) and 0.31 (0.42), respectively.

At 8 years, only 32.5% (132/406 with complete medication data) were medicated over 50% of days in the past year (versus 63.3% or 257/406 at 14 months). Treatment was still predominantly with stimulants (83%) or stimulants plus nonstimulant treatment (8%) with few reporting nonstimulant treatments alone (9%); average total daily dose of stimulant (in MPH equivalent units) was 44.93 mg (SD 26.08). Most of the youths medicated at 8 years had also been medicated at 14 months (75.0% [99/132]). Average total daily dose of those taking stimulants at both assessments was 43.36 mg (SD 24.33) at 8 years and 30.68 mg (SD 13.94) at 14 months. Thus, stimulant medication at 8 years more often reflected continued treatment, with increased dosage, rather than newly initiated medication.

Across time, 17.2% (70/406) of the children were medicated at every assessment beginning with 14-month reports, 20.4% (83/406) were not medicated at any of these assessments, and 62.3% (253/406) were medicated at least once but not every time. Of the total pool of children medicated at 14 months (n = 257), 61.5% (158) had stopped medication some time after 14 months and were not medicated at the 8-year follow-up.

Effects of Randomized Treatment on 6- and 8-Year Outcomes: Intent-to-Treat Analyses

Table 1 shows the results of the mixed-effects models at 8 years (if different, results of 6-year contrasts are discussed in text). There were no statistically significant effects of original randomized treatment group assignment on any of the 24 outcome variables tested. When treatment-by-time interactions were significant (eight variables), planned contrasts at 8 years were not. (As confirmed by additional contrasts, previously reported effects of randomized treatment group at 14 and 24 months accounted for the significant treatment-by-time interactions.) There were no statistically significant effects of randomized treatment group for the six variables analyzed only at the 8-year endpoint.

Two variables were statistically significant in the planned contrasts at 6 years only, and these effects were small. First, adolescents who received Comb had fewer school services at 6 years than adolescents who received Beh (p = .0204). Second, DISC diagnoses of anxiety or depression differed by group at 6 years. The children who received Beh had a lower rate of these diagnoses (4.3%) than the children in the Comb (17.7%), MedMgt (19.1%), or CC (16.4%) groups. The difference was reflected in four statistically significant contrasts: Comb + MedMgt > Beh + CC (p = .0050); Beh < CC (p = .0064); Comb > Beh (p = .0027); and Comb + Beh < MedMgt + CC (p = .0132).

Psychosis, mania, and hypomania occurred too infrequently for reliable statistical analysis, thereby failing to support the idea that previous stimulant medication may instigate appreciable increases in these disorders. Their prevalence (defined as presence of one or more of these three conditions) was 1.7% in Comb, 2.0% in MedMgt, 0.9% in Beh, and 2.9% in CC. Rates of tic disorder (new cases since enrollment, when tic disorder was among the exclusion criteria) were 5.2%, 5.0%, 3.6%, and 3.8%, and rates of elimination disorder were 0.9%, 1.0%, 0.9%, and 0%, for Comb, MedMgt, Beh, and CC, respectively.

Figure 2 illustrates the overall pattern of scores for six of the continuous variables. These graphs reveal convergence of the treatment groups from 36 months to 8 years and maintenance of improved overall functioning relative to baseline. An exception appears for WIAT math achievement, for which no randomized treatment group–related gains were detected at any assessment point (see also references 1 and 6).

Medication use in the past year, measured at each assessment and treated as a time-varying covariate, was associated with outcome over time in a pattern consistent with previous reports.[1,4,6] It was associated with symptom remission at 14 and 24 months, when medication use mostly reflected randomized treatment group assignment, but it was associated with worse hyperactivity-impulsivity and ODD symptoms and CIS impairment (or showed no association with other continuous variable repeated-measures outcomes) at 6 years. Most associations were not significant at 8 years. An exception occurred for WIAT math achievement. Past-year medication and math scores were positively

TABLE 1
8-Year Outcomes (Mean, SD, or Percentage) by Original Randomized Treatment Group

	Randomly Assigned Treatment				Mixed Effects or Multinomial Model Results, *F* or χ^2 (*df*), *p*		
	Comb	MedMgt	Beh	CC	Treatment	Time	Treatment by Time
ADHD symptoms	*n* = 119	*n* = 101	*n* = 112	*n* = 104			
SNAP inattention parent	1.38 (0.75)	1.45 (0.75)	1.40 (0.79)	1.39 (0.77)	1.26 (3), .7376	673.13 (5), .0001	65.68 (15), .0001
SNAP inattention teacher	1.28 (0.76)	1.44 (0.80)	1.29 (0.75)	1.20 (0.62)			
SNAP hyperactive/ impulsive parent	0.75 (0.69)	0.85 (0.64)	0.74 (0.68)	0.80 (0.72)	5.75 (3), .1243	1873.4 (5), .0001	94.52 (15), .0001
SNAP hyperactive/ impulsive teacher	0.64 (0.66)	0.72 (0.69)	0.64 (0.70)	0.55 (0.63)			
ODD symptoms							
SNAP ODD parent	0.98 (0.80)	1.11 (0.79)	1.01 (0.81)	1.03 (0.74)	4.07 (3), .2544	408.00 (5), .0001	51.26 (15), .0001
SNAP ODD teacher	0.48 (0.58)	0.61 (0.77)	0.52 (0.63)	0.46 (0.63)			
Antisocial behavior							
Aggression conduct parent	1.15 (0.24)	1.17 (0.22)	1.13 (0.17)	1.15 (0.23)	2.64 (3), .4511	72.34 (5), .0001	22.15 (15), .1040
Aggression conduct teacher	0.14 (0.17)	0.18 (0.25)	0.14 (0.19)	0.14 (0.23)			
Delinquency severity rating	1.52 (1.56)	1.55 (1.53)	1.82 (1.58)	1.60 (1.60)	0.09 (3), .9927	61.67 (5), .0001	13.38 (15), .5731
Police contacts, % once, % two or more times	42.1, 11.2	45.5, 13.1	31.5, 11.1	37.9, 9.7	6.44 (6), .3756		
Arrested, % once, % two or more times	18.9, 5.7	22.4, 10.3	17.4, 7.8	22.9, 6.7	3.57 (6), .7350		
Impairment: CIS	1.12 (0.71)	1.09 (0.69)	1.06 (0.72)	1.10 (0.71)	3.51 (3), .3199	422.29 (5), .0001	40.69 (15), .0004
Depression: CDI	8.00 (7.66)	5.78 (7.84)	7.84 (7.24)	7.19 (7.73)	6.19 (3), .1029	170.66 (5), .0001	19.30 (15), .2006
Anxiety: MASC	84.1 (18.3)	77.7 (14.9)	82.8 (16.7)	85.8 (19.7)	9.66 (3), .0217	842.20 (5), .0001	11.90 (15), .6866
Academic							
WIAT reading	94.7 (14.5)	96.1 (14.2)	96.2 (13.2)	95.6 (13.4)	0.78 (3), .8541	18.26 (5), .0026	23.83 (15), .0680
WIAT math	94.7 (17.4)	91.5 (14.8)	96.0 (17.0)	95.7 (15.9)	2.28 (6), .5156	151.51 (5), .0001	19.66 (15), .1852
SSRS academic performance teacher	2.95 (0.78)	2.91 (0.87)	3.14 (0.92)	3.30 (0.64)	2.37 (3), .4992	61.15 (5), .0001	17.56 (15), .2863
Grade point average	2.70 (0.56)	2.79 (0.57)	2.83 (0.56)	2.71 (0.59)	3.39 (3), .3354		
School services	0.46 (0.65)	0.40 (0.67)	0.46 (0.64)	0.47 (0.74)	37.92 (3), .0001	269.53 (5), .0001	197.02 (15), .0001
Grade retention, %	28.9	23.9	23.3	29.6	1.92 (3), .5890		
Social functioning							
SSRS social skills parent	1.24 (0.29)	1.26 (0.31)	1.21 (0.27)	1.27 (0.26)	1.87 (3), .6006	522.50 (5), .0001	35.59 (15), .0020
SSRS social skills teacher	1.16 (0.28)	1.18 (0.32)	1.21 (0.31)	1.19 (0.28)			
Other							
Psychiatric hospitalizations, %	10.4	10.4	12.3	8.3	1.77 (3), .6209		
Accident/citation/ticket, %	19.0	28.6	19.7	21.5	1.56 (3), .6691		
Diagnosis							
ADHD, %	29.3	32.7	33.0	25.7	4.54 (3), .2084	41.94 (4), .0001	29.15 (12), .0037
ADHD combined, %	9.5	9.9	8.9	6.7			
ADHD hyperactive, %	2.6	2.0	2.7	2.9			
ADHD inattentive, %	17.2	20.8	21.4	16.2			
ODD/CD, %	21.6	29.7	28.6	21.0	5.47 (3), .1406	83.35 (5), .0001	23.45 (15), .0751
Conduct, %	8.6	10.9	8.0	4.8			

(Continued)

TABLE 1
(Continued)

	Randomly Assigned Treatment				Mixed Effects or Multinomial Model Results, F or χ^2 (df), p		
	Comb	MedMgt	Beh	CC	Treatment	Time	Treatment by Time
ODD, %	14.7	19.8	20.5	16.2			
Anxiety/depression, %	13.8	7.9	9.8	9.5	3.54 (3), .315	79.42 (5), .0001	28.54 (15), .0184

Note: Where applicable, means for parent and teacher reports are provided separately, but regression analyses yielded one overall test of treatment, time, and treatment-by-time effects. For four variables (police contacts, arrested, and diagnoses of ADHD and ODD/CD), additional descriptive statistics are provided for interpretation, but analyses were based on the first variable listed. SNAP measures rated 0 (not at all) to 3 (very much); aggression conduct parent measure rated 1 (never) to 4 (often); aggression conduct teacher measure rated 0 (not at all true) to 3 (very much true); CIS rated 0 (no problem) to 4 (a very bad problem); CDI rated 0 (best) to 2 (worst), 27 items summed; MASC rated 1 (never true) to 4 (often true), 45 items summed; SSRS academic performance teacher measure rated 1 (lowest 10% of class) to 5 (highest 10% of class); school services rated hours per week, 0 = none, 1 = up to 1 hour, 2 = up to 5 hours, etc.; SSRS social skills measures rated 0 (never) to 2 (very often). Results reported from analyses without age but with concurrent, time-varying, medication use as covariate. School services were those received during the whole school year, during which randomization and study treatment occurred (which accounts for apparent treatment group differences at time = 0 or baseline). ADHD = attention-deficit/hyperactivity disorder; Beh = behavior therapy; CC = community care; CDI = Children's Depression Inventory; CIS = Columbia Impairment Rating Scale; Comb = combined; MASC = Multidimensional Anxiety Scale for Children; MedMgt = medication management; SNAP = Swanson, Nolan, Pelham Rating Scale; ODD/CD = oppositional defiant disorder/ conduct disorder; SSRS = Social Skills Rating System; WIAT = Wechsler Individual Achievement Test.

associated at 36 months (p = .0011), 6 years (p = .0002), and 8 years (p < .0001) but not at 14 or 24 months (p > .05). Because past-year medication use at the later assessments generally reflected continued and not newly initiated medication, these findings suggest a uniquely beneficial effect of continued medication treatment on math achievement. These associations were present whether initial randomized treatment group assignment was included in the model.

Prediction of 6- and 8-Year Outcomes From 36-Month Latent Class

Table 2 shows the results for the 8-year outcomes when the independent variable is 36-month latent class membership (i.e., membership in one of the three ADHD symptom trajectories identified between baseline and 36 months; see Fig. 1). Statistically significant effects of 36-month latent class were found for 12 (54.5%) of the 22 variables tested, either as a significant effect of class with no class-by-time interaction (e.g., delinquency severity rating) or as a class-by-time interaction reflecting variation in the magnitude of class differences over time (e.g., SNAP inattention). The results of the associated statistically significant planned contrasts among the classes at 8 years revealed a consistent pattern across the variables. Children in class 2 (the class comprising 52% of the sample with the best initial treatment response and most favorable clinical presentation at baseline) fared better over time than children in classes 1 and 3. Effect sizes were small (mostly in the 0.2–0.3 range) when comparing classes 1 and 2 but larger (in the 0.4–0.6 range, representing medium effects) when comparing classes 2 and 3. Medium effect sizes were found for several statistically significant class 1 versus class 3 comparisons. Figure 3 illustrates for selected continuous variables the overall pattern of findings, namely that the differences in symptoms and functioning observed on the basis of latent classes established at the 36-month assessment generally maintain through high school age (although with some lessening in magnitude of difference by 8 years). All but one of the contrasts that were significantly different at 8 years was also significantly different at 6 years (ODD/CD diagnosis was not significantly different between classes 1 and 2 at 6 years). A small number of contrasts were significant at 6 years but not at 8 years (class 1 < class 3 aggression/conduct score; class 2 < class 1 CIS impairment score; class 2 < class 1 proportion with ADHD diagnosis).

Functioning Relative to the LNCG

Table 3 shows the results of comparisons between the MTA and the LNCG youths at 8 years. Statistically significant effects of MTA versus LNCG were found for 19 (90.5%) of the 21 variables tested, either as a significant effect of group with no group-by-time

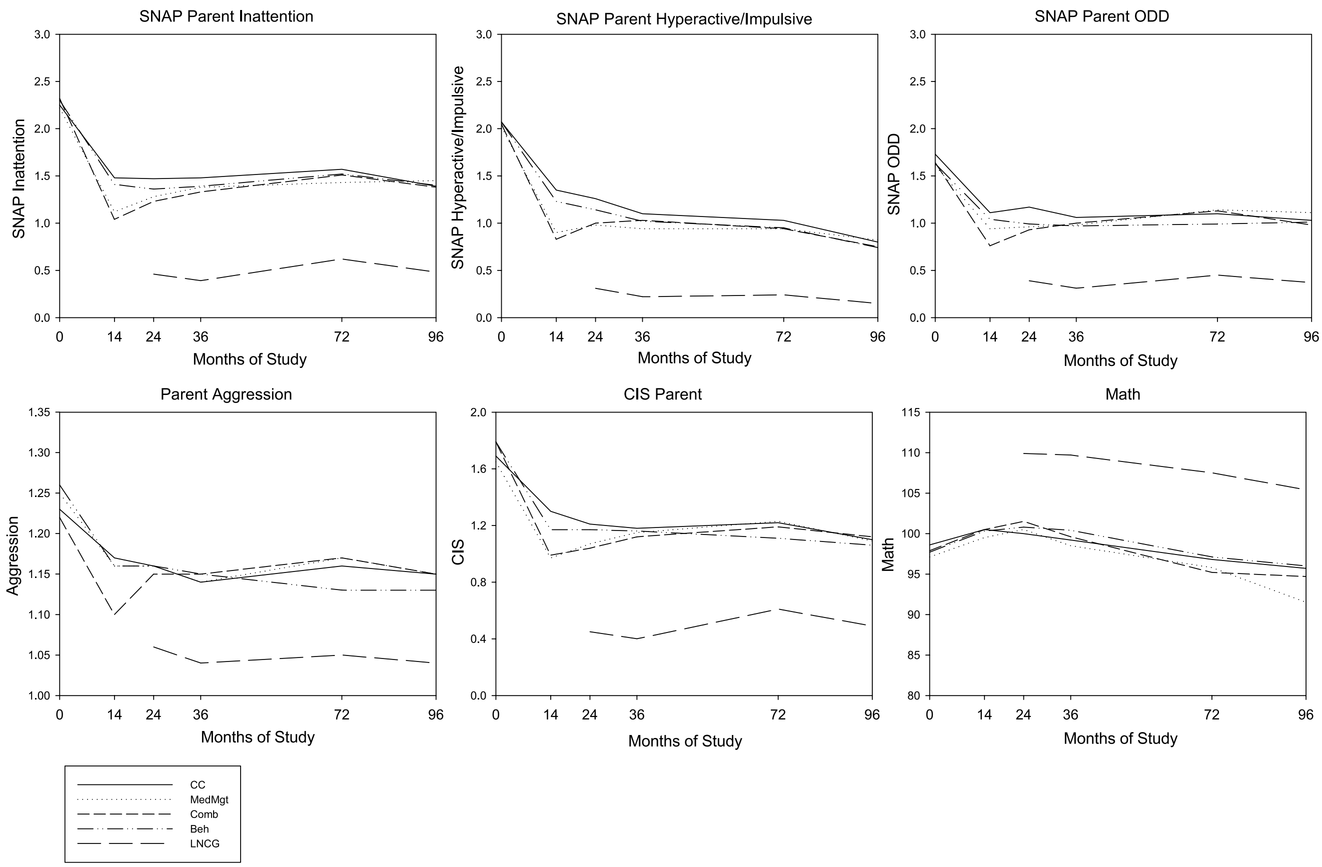

Fig. 2 Selected outcome variables for MTA children, graphed by originally randomized treatment group assignment and LNCG. Beh = behavior therapy; CC = community care; CIS = Columbia Impairment Rating Scale; Comb = combined; LNCG = local normative comparison group; MedMgt = medication management; ODD = oppositional defiant disorder; SNAP = Swanson, Nolan, Pelham Rating Scale.

interaction (e.g., delinquency severity rating) or as a group-by-time interaction reflecting variation in the magnitude of group differences over time (e.g., SNAP inattention). Two comparisons were not statistically significant (Multidimensional Anxiety Scale for Children anxiety and driving accidents/citations). Effect sizes in the far right column for statistically significant MTA versus LNCG group differences generally ranged from 0.4 to 1.0—medium to large effects, revealing worse outcome over time for the MTA children for each variable tested. All repeated-measures comparisons that were statistically significant at 8 years were also statistically significant at 6 years.

Figures 2 and 3 show the LNCG mean scores for selected continuous variables, contrasted with the mean scores for the MTA youths by treatment group (Fig. 2) or by 36-month latent class (Fig. 3). These figures illustrate the relatively poorer behavioral (ADHD and ODD symptom ratings), academic (WIAT math achievement), and overall functioning (CIS impairment) of the MTA youths relative to the LNCG youths. For example, for ADHD and ODD symptom ratings, where the MTA average score is a full SD higher than the LNCG (even higher for inattention ratings), Figure 2 shows that treatment-related decreases in symptoms do not "normalize" the children as a group. Figure 3 shows that both childhood ADHD diagnosis and latent class membership predict long-term outcome, but original random assignment does not. The Table 2 statistics and Figures 2 and 3 show that these findings are steady over time, from 24 months after baseline when the LNCG was recruited, through 8 years.

Rates of diagnosis of ADHD decreased from 43.0% at the 6-year assessment to 30.2% at the 8-year assessment for the MTA sample, versus 4.3% and 2.2%, respectively, for the LNCG sample. (Recall that these results exclude 31 LNCG with ADHD at recruitment. Rates of ADHD diagnosis at 6 and

TABLE 2
8-Year Outcomes (Mean, SD, or Percentage) by 36-Month Latent Class

	36-Month Latent Class			Mixed-Effects or Multinomial Model Results, F or c^2 (df), p			
	1	2	3				
	n = 154	n = 224	n = 63	Class	Time 36, 72, 96	Class by Time	Class Contrasts (Effect Sizes)
ADHD symptoms							
SNAP inattention parent	1.49 (0.73)	1.28 (0.75)	1.65 (0.81)	104.13 (2), .0001	60.76 (2) .0001	109.77 (4), .0001	2 < 1 (0.28), 2 < 3 (0.48)
SNAP inattention teacher	1.41 (0.72)	1.16 (0.71)	1.54 (0.76)				
SNAP hyperactive/ impulsive parent	0.82 (0.66)	0.65 (0.63)	1.12 (0.79)	131.40 (2), .0001	200.88 (2), .0001	105.85 (4), .0001	2 < 1 (0.26), 2 < 3 (0.70), 1 < 3 (0.43)
SNAP hyperactive/ impulsive teacher	0.77 (0.77)	0.50 (0.57)	0.81 (0.67)				
ODD symptoms							
SNAP ODD parent	1.06 (0.71)	0.89 (0.78)	1.40 (0.84)	83.61 (2), .0001	41.26 (2), .0001	40.06 (4), .0001	2 < 1 (0.23), 2 < 3 (0.64), 1 < 3 (0.45)
SNAP ODD teacher	0.63 (0.72)	0.37 (0.52)	0.74 (0.76)				
Antisocial behavior							
Aggression conduct parent	1.18 (0.27)	1.11 (0.16)	1.23 (0.24)	83.02 (2), .0001	19.14 (2), .0001	33.72 (4), .0001	2 < 1 (0.34), 2 < 3 (0.66)
Aggression conduct teacher	0.18 (0.24)	0.11 (0.17)	0.20 (0.22)				
Delinquency severity rating	1.76 (1.62)	1.41 (1.52)	2.05 (1.50)	29.92 (2), .0001	8.47 (2), .0145	1.55 (4), .8174	2 < 1 (0.22), 2 < 3 (0.42)
Police contacts, % once % two or more times	40.4, 12.2	34.4, 9.6	52.3, 12.3	9.38 (2), .0092			2 < 3 (0.25)
Arrested, % once % two or more times	20.6, 9.7	17.9, 4.9	24.7, 8.2	5.62 (2), .0603			
Impairment: CIS	1.03 (0.70)	0.95 (0.70)	1.26 (0.69)	31.60 (2), .0001	25.95 (2), .0001	26.80 (4), .0001	2 < 3 (0.44)
Depression: CDI	7.99 (7.57)	7.06 (7.01)	6.74 (7.51)	4.14 (2), .1261	9.78 (3), .0206	7.87 (6), .2475	
Anxiety: MASC	84.9 (19.5)	82.4 (16.3)	79.3 (17.9)	4.82 (2), .0900	405.37 (3), .0001	2.83 (6), .8298	
Academic							
WIAT reading	95.2 (13.8)	96.4 (13.7)	94.0 (14.3)	0.45 (2), .7985	54.00 (2), .0001	3.96 (4), .4116	
WIAT math[a]	92.8 (16.1)	97.1 (16.5)	89.6 (15.4)	4.53 (2), .1039	119.69 (2), .0001	3.62 (4), .4603	
SSRS academic performance teacher	2.92 (0.73)	3.17 (0.83)	3.09 (0.91)	5.26 (2), .0719	24.74 (2), .0001	21.10 (4), .0003	
Grade point average	2.76 (0.57)	2.79 (0.59)	2.63 (0.46)	1.43 (2), .4882			
School services	0.50 (0.71)	0.36 (0.61)	0.67 (0.76)	29.21 (2), .0001	77.37 (2), .0001	5.79 (4), .2150	2 < 1 (0.22), 2 < 3 (0.48)
Grade retention, %	41.1	33.8	28.8	6.31 (2), .0425			2 < 1 (0.15)
Social functioning							
SSRS social skills parent	1.21 (0.25)	1.30 (0.28)	1.11 (0.30)	66.95 (2), .0001	94.19 (2), .0001	32.58 (4), .0001	2 < 1 (0.33), 2 < 3 (0.67)
SSRS social skills teacher	1.11 (0.31)	1.25 (0.28)	1.14 (0.28)				
Other							
Psychiatric hospitalizations, %	13.4	7.6	12.7	1.73 (2), .4207			
Accident/citations/ticket, %	22.2	21.8	24.1	0.24 (2), .8862			
Diagnosis							
ADHD, %	28.1	26.5	48.4	33.31 (2), .0001	48.89 (2), .0001	20.11 (4), .0005	1 < 3 (0.42), 2 < 3 (0.46)
ADHD combined, %	7.2	6.4	21.0				

ADHD hyperactive, %	3.3	0.9	6.5				
ADHD inattentive, %	17.6	19.2	21.0				
ODD/CD, %	26.8	20.1	38.7	23.85 (2), .0001	7.96 (2), .0187	5.70 (4), .2224	2 < 1 (0.16), 2 < 3 (0.42)
Conduct	10.5	5.5	11.3				
ODD	17.0	15.5	27.4				
Anxiety/depression, %	8.5	9.6	17.7	3.88 (2), .1434	8.53 (2), .0141	6.27 (4), .1800	

Note: Where applicable, means for parent and teacher reports are provided separately, but regression analyses yielded one overall test of treatment, time, and treatment-by-time effects. For four variables (police contacts, arrested, and diagnoses of ADHD and ODD/CD), additional descriptive statistics are provided for interpretation, but analyses were based on the first variable listed. SNAP measures rated 0 (not at all) to 3 (very much); aggression conduct parent measure rated 1 (never) to 4 (often); aggression conduct teacher measure rated 0 (not at all true) to 3 (very much true); CIS rated 0 (no problem) to 4 (a very bad problem); CDI rated 0 (best) to 2 (worst), 27 items summed; MASC rated 1 (never true) to 4 (often true), 45 items summed; SSRS academic performance teacher measure rated 1 (lowest 10% of class) to 5 (highest 10% of class); school services rated hours per week, 0 = none, 1 = up to 1 hour, 2 = up to 5 hours, etc.; SSRS social skills measures rated 0 (never) to 2 (very often). Results reported from analyses without age and without medication use as covariate. Only effect sizes for contrasts significant at $p < .05$ are reported. Effect sizes were calculated on observed data using Cohen d for means (SD) and Cohen h for proportions (0.2 [small], 0.5 [medium], and 0.8 [large]) after confirming correspondence with least squares estimated mean differences (which are less clinically interpretable). ADHD = attention-deficit/hyperactivity disorder; Beh = behavior therapy; CC = community care; CDI = Children's Depression Inventory; CIS = Columbia Impairment Rating Scale; Comb = combined; MASC = Multidimensional Anxiety Scale for Children; MedMgt = medication management; SNAP = Swanson, Nolan, Pelham Rating Scale; ODD/CD = oppositional defiant disorder/conduct disorder; SSRS = Social Skills Rating System; WIAT = Wechsler Individual Achievement Test.

[a] WIAT math achievement differed between the classes at $p < .05$ at 8 years, 1 < 2 (0.26) and 3 < 2 (0.46), but because of the marginally significant main effect ($p = .1039$), these differences are not interpreted.

8 years for the full LNCG sample were 8.0% and 5.0%, respectively, also significantly different from the MTA sample at $p < .0001$.) As shown in Table 3, Inattentive subtype was the most common diagnosis, followed by Combined and Hyperactive-Impulsive subtypes (analyses using alternative diagnosing algorithms are in progress). Approximately 25% to 30% of the MTA youths were in the spectrum of clinically significant antisocial behavior, with 25.1% meeting *DSM-IV* diagnostic criteria for ODD or CD, 26.8% arrested at least once by 8 years, and 30% earning a delinquency severity code of 3 or higher (moderately serious to serious behavior reported by the youth or parent). These percentages were each significantly higher for the MTA than for the LNCG youths. Group differences were not found for driving-related citations and accidents, perhaps because of the lag in time between the MTA and the LNCG groups' obtaining of driver's licenses.

Academic performance indicators showed that, on average, controlling for IQ, the MTA youths were performing approximately half an SD less well than the LNCG youths. The average teacher rating of academic performance was 3.08, corresponding to performance between the 30th and 70th percentiles compared with other students and grade-level expectations. This compares to an average rating of 3.54 for the LNCG students (a rating of 4 corresponds to performance between the 70th and 90th percentiles). Grade point average was lower for the MTA than for the LNCG youth, revealing deficiency in the MTA student's permanent school record—an ecologically valid and salient indicator of academic performance.

Psychiatric hospitalizations occurred more often for MTA than for LNCG, but diagnoses of psychosis, mania, or hypomania by 8 years were uncommon for both groups. Eight MTA children had developed one of these disorders, versus only one LNCG child (1.8% versus 0.4%). Tic (4.4% versus 1.7%) and elimination disorders (0.7% and 0.0%) were also infrequent for MTA and LNCG, respectively, by 8 years.

DISCUSSION

Three sets of findings resulted from this prospective longitudinal study of the MTA children into adolescence. Intent-to-treat analyses revealed no appreciable differences among the children based on their randomized

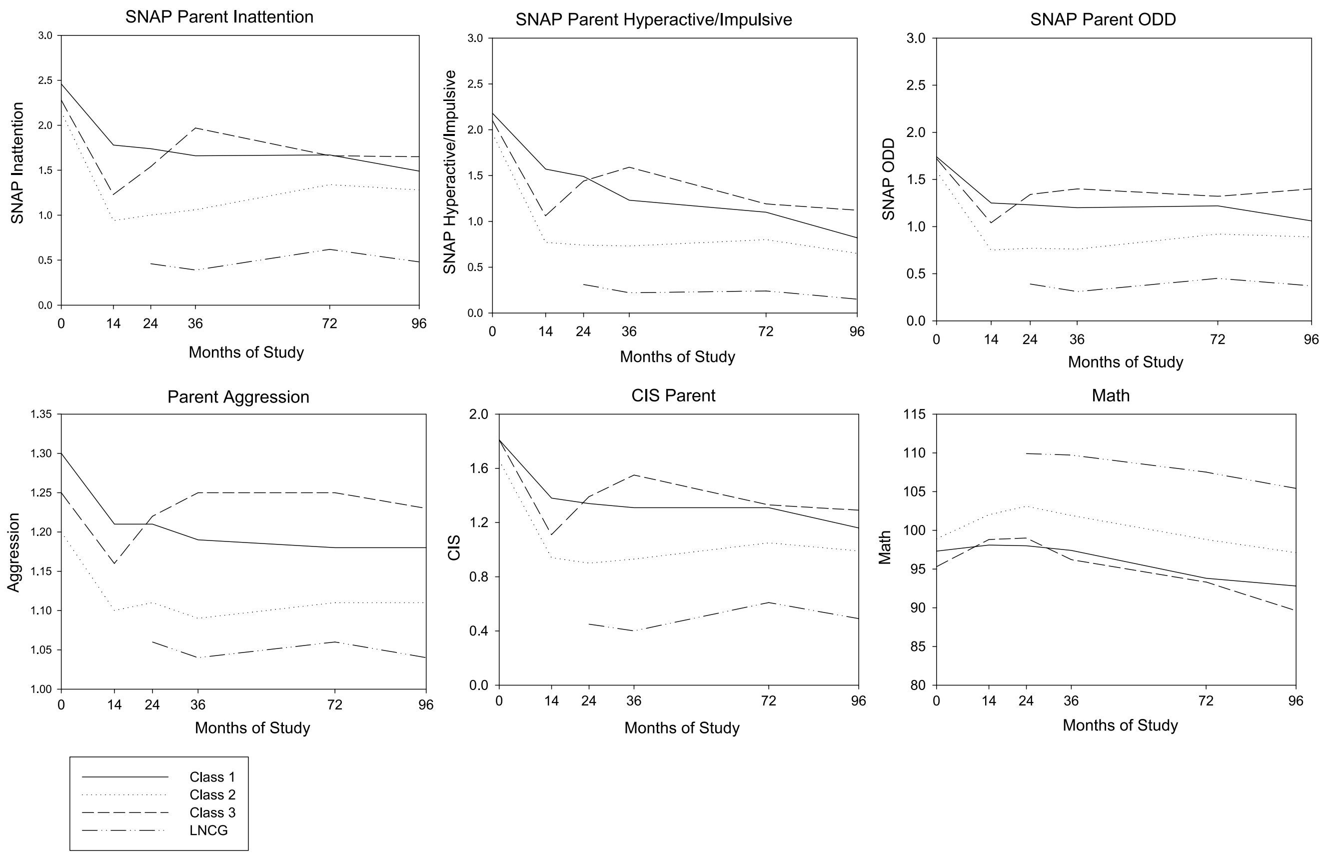

Fig. 3 Selected outcome variables for MTA children, graphed by 36-month ADHD symptom latent class and LNCG. CIS = Columbia Impairment Rating Scale; LNCG = local normative comparison group; ODD = oppositional defiant disorder; SNAP = Swanson, Nolan, Pelham Rating Scale.

treatment group assignment at 7 to 9 years of age. The ADHD symptom trajectory in childhood, however, was a strong predictor of outcome at both 6 and 8 years. Finally, despite overall maintenance of improvement in functioning relative to baseline (pretreatment), the MTA group as a whole was functioning significantly less well than the non-ADHD classmate sample (LNCG) recruited at 24 months. These findings provide evidence that the differential effects of the ADHD treatments, evident when the interventions were delivered, attenuated when the intensity of treatment was relaxed. To our knowledge, these findings are the first in the ADHD treatment literature to document, for a wide range of symptom and functioning outcomes, the sustained absence of long-term effects of an initial period of randomly assigned treatment (separate analyses of long-term effects on substance use, growth, and heart rate are in progress).

Our results suggest that the initial clinical presentation in childhood, including severity of ADHD symptoms, conduct problems, intellect, and social advantage, and strength of ADHD symptom response to any treatment, are better predictors of later adolescent functioning than the type of treatment received in childhood for 14 months. This conclusion follows from our analyses comparing the children's 6- and 8-year functioning on the basis of their previous ADHD symptom "latent class" membership, when children in "class 2" were characterized by the strongest and most enduring decrease in ADHD symptoms between baseline and 36 months. Compared with children in classes 1 and 3, class 2 children also had better scores at baseline on a range of variables that included symptom severity, conduct problems, learning problems and IQ, social skills, and family characteristics conferring socioeconomic advantage (fewer marital breakups and better financial picture). These findings reflect, in a clinical sample, the moderate degree of stability in relative rank ordering of children's behavior or personality also seen in nonclinical samples.[30] Yet for most of the MTA children (those in classes 1 and 2), functioning was still substantially improved over baseline levels, suggesting

TABLE 3
8-Year Outcomes (Mean, SD, or Percentage) for MTA and LNCG

	Group		Mixed Effects or Multinomial Model Results, F or χ^2 (df), p			Effect Size
	MTA	LNCG	Group (MTA vs. LNCG)	Time	Group by Time	
ADHD symptoms	*n* = 436	*n* = 232				
SNAP inattention parent	1.40 (0.76)	0.48 (0.48)	512.13 (1), .0001	14.48 (2), .0007	14.83 (2), .0006	(1.36)
SNAP inattention teacher	1.30 (0.74)	0.73 (0.64)				
SNAP hyperactive/impulsive parent	0.77 (0.68)	0.15 (0.24)	384.46 (1), .0001	189.92 (2), .0001	39.06 (2), .0001	(1.09)
SNAP hyperactive/impulsive teacher	0.64 (0.67)	0.24 (0.40)				
ODD symptoms						
SNAP ODD parent	1.03 (0.79)	0.37 (0.46)	253.12 (1), .0001	26.64 (2), .0001	12.17 (2), .0023	(0.95)
SNAP ODD teacher	0.51 (0.65)	0.22 (0.42)				
Antisocial behavior						
Aggression conduct parent	1.15 (0.22)	1.04 (0.07)	135.89 (1), .0001	32.30 (2), .0001	10.46 (2), .0054	(0.60)
Aggression conduct teacher	0.15 (0.21)	0.05 (0.11)				
Delinquency severity rating, % 3 or higher	1.62 (1.57), 36.4	1.10 (1.50), 21.8	107.90 (1), .0001	32.17 (3), .0001	7.66 (3), .0536	(0.34)
Police contacts, % once, % two or more times	39.0, 10.9	14.0, 3.2	58.75 (1), .0001			(0.47)
Arrested, % once, % two or more times	19.8, 7.0	11.6, 2.6	18.82 (1), .0001			(0.38)
Impairment: CIS	1.09 (0.70)	0.49 (0.46)	238.30 (1), .0001	32.83 (2), .0001	6.60 (2), .0369	(0.96)
Depression: CDI	7.31 (7.27)	5.77 (7.21)	17.37 (1), .0001	39.95 (3), .0001	3.79 (3), .2846	(0.21)
Anxiety: MASC	82.8 (17.7)	82.9 (15.7)	0.15 (1), .6975	874.42 (3), .0001	1.31 (3), .7257	
Academic						
WIAT reading	95.7 (13.8)	102.0 (11.6)	21.30 (1), .0001	83.15 (2), .0001	3.19 (2), .2025	(0.48)
WIAT math	94.6 (16.4)	105.4 (16.6)	44.27 (1), .0001	142.01 (2), .0001	12.68 (2), .0018	(0.66)
SSRS academic performance teacher	3.08 (0.82)	3.54 (0.83)	53.49 (1), .0001	0.12 (2), .9436	10.82 (2), .0045	(0.56)
Grade point average	2.75 (0.57)	3.02 (0.61)	19.17 (1), .0001			(0.45)
Grade retention %	37.3	17.9	31.38 (1), .0001			(0.43)
Social functioning						
SSRS social skills parent	1.24 (0.28)	1.46 (0.22)	268.22 (1), .0001	29.06 (2), .0001	14.68 (2), .0006	(0.84)
SSRS social skills teacher	1.19 (0.30)	1.37 (0.30)				
Other						
Psychiatric hospitalizations, %	10.4	1.3	12.62 (1), .0004			(0.44)
Accident/citation/ticket, %	22.2	27.6	1.37 (1), .2417			
Diagnosis						
ADHD, %	30.2	2.2	223.36 (1), .0001	6.74 (2), .0343	3.47 (2), .1768	(0.88)
ADHD combined, %	8.8	0				
ADHD hyperactive, %	2.5	0				
ADHD inattentive, %	18.9	2.2				
ODD/CD, %	25.1	4.7	144.72 (1), .0001	11.87 (3), .0079	2.38 (3), .4973	(0.60)
Conduct, %	8.1	2.2				

(Continued)

TABLE 3
(Continued)

	Group		Mixed Effects or Multinomial Model Results, F or χ^2 (df), p			Effect Size
	MTA	LNCG	Group (MTA vs. LNCG)	Time	Group by Time	
ODD, %	17.7	2.6				
Anxiety/depression, %	10.4	5.2	16.06 (1), .0001	10.27 (3), .0164	1.39 (3), .7088	(0.19)

Note: Where applicable, means for parent and teacher reports are provided separately, but regression analyses yielded one overall test of treatment, time, and treatment-by-time effects. For four variables (police contacts, arrested, and diagnoses of ADHD and ODD/CD), additional descriptive statistics are provided for interpretation, but analyses were based on the first variable listed. SNAP measures rated 0 (not at all) to 3 (very much); aggression conduct parent measure rated 1 (never) to 4 (often); aggression conduct teacher measure rated 0 (not at all true) to 3 (very much true); CIS rated 0 (no problem) to 4 (a very bad problem); CDI rated 0 (best) to 2 (worst), 27 items summed; MASC rated 1 (never true) to 4 (often true), 45 items summed; SSRS academic performance teacher measure rated 1 (lowest 10% of class) to 5 (highest 10% of class); SSRS social skills measures rated 0 (never) to 2 (very often). School services data not available for LNCG. Results reported from analyses without age as covariate but with IQ controlled for outcomes in academic domain. Only effect sizes for contrasts significant at $p < .05$ are reported. Effect sizes were calculated on observed data using Cohen d for means (SD) and Cohen h for proportions (0.2 [small], 0.5 [medium], and 0.8 [large]) after confirming correspondence with least squares estimated mean differences (which are less clinically interpretable). $n = 31$ LNCG cases with ADHD at recruitment removed from analyses; results were not appreciably different when they were included. ADHD = attention-deficit/hyperactivity disorder; Beh = behavior therapy; CC = community care; CDI = Children's Depression Inventory; CIS = Columbia Impairment Rating Scale; Comb = combined; LNCG = local normative comparison group; MASC = Multidimensional Anxiety Scale for Children; MedMgt = medication management; MTA = NIMH Collaborative Multisite Multimodal Treatment Study of Children With Attention-Deficit/Hyperactivity Disorder; SNAP = Swanson, Nolan, Pelham Rating Scale; ODD/CD = oppositional defiant disorder/conduct disorder; SSRS = Social Skills Rating System; WIAT = Wechsler Individual Achievement Test.

that sustained improvement (not normalization) relative to the child's initial presentation for treatment is achievable. Gains may be greatest for children with the least severe initial presentation,[31] although severity of initial presentation such as co-occurrence of conduct problems may not drive which treatment works best.[2]

It is tempting to conclude that intensive medication management beyond 14 months could have resulted in continued differences between the randomly assigned treatment groups. This assumption is partially based on our previous report that the MTA medication algorithm resulted in a greater reduction of symptoms than the community-provided medication treatment, suggesting that aspects of the MTA pharmacological protocol (e.g., initial titration, monthly monitoring including input from teacher, higher dosing, t.i.d. dosing) may improve results over those of community care.[2] In addition, in a previous multimodal treatment study where medication was carefully titrated and monitored for 2 years, treatment gains were maintained for the entire period.[32] However, after 14 months, the MTA became an uncontrolled naturalistic follow-up study, and inferences about potential advantages that might have occurred with continued long-term study-provided treatment are speculation. Moreover, with one exception (math achievement), children still taking medication by 6 and 8 years fared no better than their nonmedicated counterparts, despite a 41% increase in the average total daily dose, failing to support continued medication treatment as salutary (at least, continued medication treatment as monitored by community practitioners). Additionally, failure to find better outcomes associated with continued medication treatment occurred despite the arrival of improved long-acting stimulant medications that more effectively produce the 12-hour/day coverage of the MTA medication algorithm. Dramatic increases in prescriptions for these medications, beginning with osmotic-release methylphenidate (Concerta) in 2000 followed by Adderall XR, showed widespread and immediate acceptance of their use during the MTA follow-up period.[33] Finally, a previous analysis of the MTA data through 3 years did not provide evidence that subject selection biases toward medication use in the follow-up period accounted for the observed lack of differential treatment effects.[7] Thus, although the MTA data provided strong support for the acute reduction of symptoms with intensive medication management, these long-term follow-up data fail to provide support for long-term advantage of medication treatment beyond 2 years for the majority of children—at least as medication is monitored in community settings. Decisions about starting, continuing, and stopping medication may have to be made on an individualized basis, avoiding untested assumptions about continuing benefit and using periodic trial discontinuations to check for need and benefit.

Indeed, long-term monitoring of children with ADHD may be wise, given the pervasive differences in symptoms, functioning, and apparent need for services found between the MTA and LNCG samples in adolescence. In an effort to fully appreciate the MTA children's functioning as adolescents, we expanded the range of variables studied. These results showed that, although symptoms and impairment remained appreciably improved over baseline levels, normalization was generally not achieved. We found poorer performance for the MTA children as a group versus LNCG children for 91% of the variables. For example, although we replicated an expected decrease in parent- and teacher-rated symptoms of hyperactivity and impulsivity,[34–36] the MTA children's scores on all of the ADHD symptom measures were still substantially higher than those of their former classmates. Standardized achievement test scores, teacher ratings of academic performance, and even grades earned in high school were lower for the ADHD than for the LNCG group. The MTA children also had a twofold higher rate of grade retention. Rates of delinquency and arrest were higher in the ADHD sample, and psychiatric hospitalizations were more common, occurring for 10% of the ADHD sample versus only 1% of the LNCG (although this difference did not seem to be a function of increased rates of psychosis, mania, or hypomania, dispelling concerns that CNS stimulant treatment triggers such disorders at high rates[37]).

In contrast to this pattern of lower functioning, on average, in the MTA versus the LNCG samples, only 30% of the MTA children fulfilled *DSM-IV* criteria for ADHD by the 8-year follow-up. This figure is low compared with some previous estimates of ADHD persistence in adolescence[36,38,39] and may be an underestimate that fails to consider age-appropriate symptom cutoffs. Indeed, arguments have been put forth that the symptom count thresholds developed for the diagnosis of ADHD in children may be overly stringent for adolescents and adults.[40] Moreover, there is some evidence that remission of symptoms does not equate with recovery of function.[35,36] For example, only modest associations were found between ADHD symptom reports and various measures of impairment in daily functioning across four separate ADHD samples spanning the elementary to early adulthood years.[41] A comparison of diagnostic algorithms in relation to indicators of impairment was beyond the scope of this article but would be a fruitful analysis to aid future nosology decisions, particularly with regard to developmental changes in these associations. Our results also lend some support to the idea that indicators of functioning (beyond symptoms) may be crucial, if not more important than measurement of symptoms, in the design and study of treatments for ADHD.[41,42] Direct measurements of academic performance in school (specifically, grades earned as a reflection of homework completion and quiz and test performance), behavioral transgressions including office referrals, disciplinary actions and conflict with parents, and social dysfunction ultimately drive treatment-seeking behavior and probably mediate long-term outcome. Given the wide-ranging differences between the MTA and the LNCG samples in variables that transcend the symptoms of ADHD and their potential importance as treatment targets, future clinical trials may be forced to broaden narrow definitions of primary outcome variables.

Taken together, these 8-year findings point to a crucial need for development of treatments that are efficacious, accessible, and lasting for high school–aged youths with ADHD and their parents. The available literature on this topic is small and in need of innovation.[43] Unfortunately, teenagers with ADHD are not easy to treat. There is the temptation, despite our failure to find long-term advantage of medication treatment, to somehow improve adherence to medication treatment. However, an underrecognized problem in the treatment of adolescent ADHD is the dramatic decline in medication adherence with the onset of adolescence.[44,45] In the current study, 62% of the MTA children taking medication at 14 months (posttreatment) had stopped by the 8-year follow-up, despite the advances in long-acting stimulant medications. This decline is important in the larger context of studies finding poor adherence, more generally, with stimulant treatment regimens.[46] Thus, treatments may need to target motivational variables to encourage adolescent participation in nonpharmacological interventions (as well as pharmacological interventions that may be acutely effective for a given individual)[47] and that also address continued family and school involvement.[48] There are also data to suggest that periodic psychosocial treatments for 10 years are effective, including for diagnosis of ADHD (for the children in the fast-track study with high externalizing behaviors at baseline).[49] Whether these strategies assist parents and adolescents with motivation to maintain treatment, and whether these results would apply to children diagnosed with ADHD combined type, is a subject of future study.

Overall, the findings of this 6- and 8-year follow-up of the children in the MTA indicate that treatment-related improvements for the children in the MTA are generally maintained, but differential treatment efficacy continues to be lost at and beyond 36 months; initial patient characteristics and demographics and improved ADHD symptom response to any of the MTA treatments or to community care predicts high school–aged functioning for a range of outcomes; on average, children with combined-type ADHD, despite having received 14 months of intensive state-of-the-art behavior therapy or medication management, are functioning less well than their non-ADHD age-mates across most indices of functioning. Some children were lost to follow-up, and their families were demographically disadvantaged. Thus, the MTA versus the LNCG group differences that we observed may be underestimates. Our findings suggest that community treatments can improve ADHD symptoms and associated impairment, but even when preceded by intensive medication management and/or behavioral therapy for 14 months, continuing community interventions are unable, on average, to "normalize" children with ADHD. These findings apply to a range of symptom and functioning indices including delinquency, arrests, grade retentions and letter grades earned in school, and psychiatric hospitalizations that occur for an important minority of the sample. Hence, there is a practical need to pursue further research to develop and deliver more effective sustainable interventions and to shift the emphasis in the field from reliance on ADHD symptoms as the key outcome of treatment to include measurement of impairments that bring families in for treatment and that are likely to mediate adulthood functioning.

The NIMH Collaborative Multisite Multimodal Treatment Study of Children With Attention-Deficit/Hyperactivity Disorder (MTA) was a National Institute of Mental Health (NIMH) cooperative agreement randomized clinical trial involving six clinical sites. Collaborators from the National Institute of Mental Health: Peter Jensen, M.D. (currently at Columbia University), L. Eugene Arnold, M.D., M.Ed. (currently at Ohio State University), Benedetto Vitiello, M.D. (Child and Adolescent Treatment and Preventive Interventions Research Branch), Kimberly Hoagwood, Ph.D. (currently at Columbia); previous contributors from NIMH to the early phase: John Richters, Ph.D. (currently at National Institute of Nursing Research); Donald Vereen, M.D. (currently at National Institute on Drug Abuse). Principal investigators and coinvestigators from the clinical sites are as follows: University of California, Berkeley/San Francisco: Stephen Hinshaw, Ph.D. (Berkeley), Glen Elliott, Ph.D., M.D. (San Francisco); Duke University: C. Keith Conners, Ph.D., Karen Wells, Ph.D., John March, M.D., M.P.H., Jeffery Epstein, Ph.D.; University of California, Irvine/Los Angeles: James Swanson, Ph.D. (Irvine), Dennis Cantwell, M.D., (deceased, Los Angeles), Timothy Wigal, Ph.D. (Irvine); Long Island Jewish Medical Center/Montreal Children's Hospital: Howard Abikoff, Ph.D. (currently at New York University School of Medicine), Lily Hechtman, M.D. (McGill University); New York State Psychiatric Institute/Columbia University/Mount Sinai Medical Center: Laurence Greenhill, M.D. (Columbia), Jeffrey Newcorn, M.D. (Mount Sinai School of Medicine); University of Pittsburgh: William Pelham, Ph.D. (currently at State University of New York at Buffalo), Betsy Hoza, Ph.D. (currently at University of Vermont), Brooke Molina, Ph.D., Patricia Houck, MS. Original statistical and trial design consultant: Helena Kraemer, Ph.D. (Stanford University). Follow-up phase statistical collaborators: Robert Gibbons, Ph.D. (University of Illinois at Chicago), Sue Marcus, Ph.D. (Mt. Sinai College of Medicine), Kwan Hur, Ph.D. (University of Illinois at Chicago). Collaborator from the Office of Special Education Programs/U.S. Department of Education: Thomas Hanley, Ed.D. Collaborator from Office of Juvenile Justice and Delinquency Prevention/Department of Justice: Karen Stern, Ph.D.

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