

3-Year Follow-up of the NIMH MTA Study

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ABSTRACT

Objective: In the intent-to-treat analysis of the Multimodal Treatment Study of Children With ADHD (MTA), the effects of medication management (MedMgt), behavior therapy (Beh), their combination (Comb), and usual community care (CC) differed at 14 and 24 months due to superiority of treatments that used the MTA medication algorithm (Comb+MedMgt) over those that did not (Beh+CC). This report examines 36-month outcomes, 2 years after treatment by the study ended.

Method: For primary outcome measures (attention-deficit/hyperactivity disorder [ADHD] and oppositional defiant disorder [ODD] symptoms, social skills, reading scores, impairment, and diagnostic status), mixed-effects regression models and orthogonal contrasts examined 36-month outcomes. **Results:** At 3 years, 485 of the original 579 subjects (83.8%) participated in the follow-up, now at ages 10 to 13 years, (mean 11.9 years). In contrast to the significant advantage of MedMgt+Comb over Beh+CC for ADHD symptoms at 14 and 24 months, treatment groups did not differ significantly on any measure at 36 months. The percentage of children taking medication >50% of the time changed between 14 and 36 months across the initial treatment groups: Beh significantly increased (14% to 45%), MedMed+Comb significantly decreased (91% to 71%), and CC remained constant (60%–62%). Regardless of their treatment use changes, all of the groups showed symptom improvement over baseline. Notably, initial symptom severity, sex (male), comorbidity, public assistance, and parental psychopathology (ADHD) did not moderate children's 36-month treatment responses, but these factors predicted worse outcomes over 36 months, regardless of original treatment assignment. **Conclusions:** By 36 months, the earlier advantage of having had 14 months of the medication algorithm was no longer apparent, possibly due to age-related decline in ADHD symptoms, changes in medication management intensity, starting or stopping medications altogether, or other factors not yet evaluated. *J. Am. Acad. Child Adolesc. Psychiatry*, 2007;46(8):989–1002. **Key Words:** attention-deficit/hyperactivity disorder, clinical trial, stimulant, behavior therapy, multimodal treatment.

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Despite decades of research examining the short-term effects of medication and behavioral treatments for attention-deficit/hyperactivity disorder (ADHD), few studies have compared the relative benefits of these treatments on children's longer term outcomes. The Multimodal Treatment Study of Children With ADHD (MTA) was designed to fill this gap. The initial report in 1999 described the results after more than 1 year (14 months) of prospective and carefully monitored treatment in a randomized clinical trial of 579 children ages 7.0 to 9.9 years, rigorously diagnosed with ADHD Combined type, who were assigned to one of four different intervention groups: intensive multi-component behavior therapy (Beh), intensive medication management (MedMgt), the combination (Comb), and routine community care (CC).

At the end of the 14-month treatment phase, children in Comb and MedMgt showed significantly greater improvement in ADHD and oppositional defiant disorder (ODD) symptoms than those in Beh and CC. Comb and MedMgt treatments did not differ significantly on any direct comparisons, but in several instances (internalizing symptoms, teacher-rated social skills, parent-child relations, and reading achievement) Comb proved superior to Beh and/or CC, whereas MedMgt did not. The study's systematic algorithm (comprising all MedMgt procedures) for initiating and maintaining medication (used in Comb and MedMgt) was superior to CC treatment, despite the fact that 68% of the CC-treated participants received medication sometime during the study. These first reports (The MTA Cooperative Group, 1999a,b) concluded that for ADHD symptoms, the study's MedMgt approach was superior to the study's Beh and CC approaches. In addition, although Comb did not yield significantly greater benefits than MedMgt for any single measure, it provided statistically significant although clinically modest advantages on composite outcome measures (Conners et al., 2001; Swanson et al., 2001) for those with comorbid anxiety plus disruptive behavior disorders (Jensen et al., 2001) and for parent and teacher satisfaction ratings (The MTA Cooperative Group, 1999a).

Our initial follow-up evaluation was 10 months following the completion of treatment. Analyses of ADHD and ODD symptoms at this 24-month assessment (The MTA Cooperative Group, 1999a,b) revealed that the groups receiving carefully monitored MTA MedMgt as part of the randomized treatment

(i.e., Comb and MedMgt) showed persisting significant superiority over the groups that did not (Beh and CC groups), although effect sizes were reduced by approximately half at this initial follow-up. An analysis of naturalistic subgroups based on actual (not assigned) treatment during the 14- to 24-month interval suggested that part of the decline in difference between the randomly assigned treatment conditions resulted from changing percentages of medication use during the follow-up. In other words, children from Beh were more likely to begin medication, and those from MedMgt and Comb groups were more likely to stop medication (The MTA Cooperative Group, 2004b) during the interval following cessation of the study's provisions for delivering and monitoring the randomly assigned intervention strategies. Thus, differences in the intensity or quality of treatment (or lack of treatment) during the 14- to 24-month poststudy interim may have resulted in the loss of some of the 14-month difference.

Indeed, once the delivery of randomly assigned treatments by MTA staff stopped at 14 months, the MTA became an observational study in which subjects and families were free to choose their own treatment but in the context of availability and barriers to care existing in their communities. The patterns of change in the use of medication differed for the four randomly assigned groups (The MTA Cooperative Group, 2004b) and across communities (Jensen et al., 2004); these were associated with medication history prior to the study and satisfaction (or lack of it) with the assigned treatment (Marcus and Gibbons, 2001). Because the initial treatment differences observed at the end of treatment (14 months) had partially declined at the first follow-up (by 24 months; The MTA Cooperative Group, 2004a,b), we considered it important to document the fate of the differential treatment effects over a longer period of time and explore these issues with respect to treatment adherence/continuation.

The available literature, including our 24-month analyses (The MTA Cooperative Group, 2004b), suggests that less optimal treatment effects are likely associated with insufficient treatment adherence and persistence. Thus, previous studies have reported nonadherence rates of 20% to 65% (Swanson, 2003). For example, one study of children ($N = 1,635$, ages 3–7 years) taking methylphenidate immediate-release revealed that 54.0% of subjects received only one

prescription and only 10.9% received five or more prescriptions during a 1-year period (Cox et al., 2004). Similarly, another study found that only 74% of children with ADHD initially assigned to stimulants took 50% or more of their pills over 12 months (Corkum et al., 1999); only 52% continued to use stimulant medication for 3 consecutive years (Thiruchelvam et al., 2001). Younger age, absence of ODD symptoms at school, and higher ADHD ratings by teachers predicted subsequent adherence. Follow-up evidence from this same study further confirms that higher teacher ratings of ADHD symptoms predict medication persistence after 5 years (Charach et al., 2004).

Precise knowledge of the actual extent of adherence and persistence as well as an understanding of what factors predict treatment adherence has remained somewhat elusive. For example, one literature review from 1966 to 2000 found widely varying rates of adherence (35%–100%), with adherence rates decreasing over time (Hack and Chow, 2001). Recent national data show that problems related to continuity of ADHD medication may be increasing: thus, Olfson et al. (2003) found significant decreases in the intensity of treatment, with children receiving an average 3.0 fewer ADHD treatment visits per child in 1997 than in 1987. Although these trends would seem to work against medication adherence and persistence, the use of newer, once-daily forms of stimulant medication appear to predict greater medication persistence in analyses of large health care data sets (Marcus et al., 2005).

This report attempts to fill some of the present gaps in our understanding of long-term ADHD outcomes and their relationship to medication persistence. Here we explore the fate of the 14-month differences in initially assigned treatment groups over a longer follow-up time interval; we also examine whether persistence or loss of group differences is related to continued treatment utilization or other factors (e.g., initial severity, sex, comorbidity, parental psychopathology, socioeconomic status). Also, we explore possible moderators and mediators of ultimate outcomes in this well-described sample of children with ADHD, most of whom had been previously intensively (and successfully) treated by us, whereas others were not, as a function of initial random assignment. We examine several core outcomes as a function of the original random treatment assignment groups, baseline factors that in previous analyses of the MTA sample moderated 14-month outcomes (e.g., baseline comorbidity patterns, welfare status, parental psychopathology (Jensen et al., 2001; The MTA Cooperative Group, 1999b; Owens et al., 2003), and postrandomization factors (e.g., continuing medication use [The MTA Cooperative Group, 2004a,b]) that may have mediated significant differences in eventual outcomes.

METHOD

Sample

Table 1 shows the demographics, clinical characteristics, and original treatment assignment for 485 subjects (83.8% of the original 579) evaluated at 36 months. We found no significant differences in baseline characteristics between subjects participating

TABLE 1
Demographic Characteristics of MTA Subjects Participating in 36-Month Assessments ($N = 485$)

Variables	Totals Across All Treatment Groups	Combined Treatment ($n = 127$ of 145)	Medication Management ($n = 115$ of 144)	Behavioral Treatment ($n = 127$ of 144)	Community Control ($n = 116$ of 146)	Range of Means Across Sites
Subject variables						
Current age, y, mean (SD)	11.8 (0.95)	11.7 (0.92)	12.0 (0.92)	11.6 (0.90)	11.8 (0.99)	11.6–11.9
Male, no. (%)	383 (79.0)	97 (76.4)	94 (81.7)	100 (78.7)	92 (79.3)	71.4–87.1
Ethnicity, no. (%)						
White	299 (61.7)	76 (59.8)	77 (67.0)	71 (55.9)	75 (64.7)	22.9–80.6
African American	98 (20.2)	23 (18.1)	19 (16.5)	34 (26.8)	22 (19.0)	5.1–40.0
Hispanic	36 (7.4)	11 (8.7)	10 (8.7)	11 (8.7)	4 (3.5)	0.0–32.9
Other	52 (10.7)	17 (13.4)	9 (7.8)	11 (8.7)	15 (12.9)	2.2–17.7

Note: Variables presented are mean (SD) or number of subjects (percent).

in the 36-month assessment and those we were unable to follow (p value range, 0.15–1.0 except for sex, $p = .07$). Follow-up rates across sites ranged from 75.0% to 95.8%, but these differences were not significant. Similarly, follow-up rates varied nonsignificantly across the four treatment groups, from 80.8% to 92.4%. (For the sample's baseline values for these variables, please see Table 3 [The MTA Cooperative Group, 1999a].) No significant differences were found among the originally assigned treatment groups on any of the variables in this table at 36 months.

Assessments

Based partly on results from our analyses of 14- and 24-month data, we selected a priori five measures from distinct domains for being clinically relevant and either having shown previous sensitivity to treatment effect or representing a critical domain of function that should be checked: parent- and teacher-rated 18 ADHD symptoms from the Swanson, Nolan, and Pelham Rating Scale (SNAP; Swanson, 1992); parent- and teacher-rated ODD symptoms (also from the SNAP), Wechsler Individual Achievement Test (WIAT; Wechsler, 1992) reading score, parent- and teacher-rated total social skills from the Social Skills Rating System (Gresham and Elliot, 1989), and overall functional impairment, as measured by the Columbia Impairment Scale (Bird et al., 1993). The first four showed treatment effects at 14 months, the first two at 24 months, and the last was newly introduced as a global outcome. Also, as a categorical measure, we examined diagnoses of *DSM-IV* psychopathology defined by the Diagnostic Interview Schedule for Children IV (Shaffer et al., 2000). For teacher ratings of children in multiple classrooms, the average of the three major subject teachers was used.

Statistical Approach

We performed five major classes of analyses.

Intent-to-Treat Analyses. We used a mixed-effects (or random effects) regression model (The MTA Cooperative Group, 1999a,b) separately for each domain. This involves calculating a response curve for each child and averaging them by treatment group. We set the significance level at $p < .01$ for each of the five tests to maintain an overall α level of .05. We also evaluated change in diagnostic status regarding major *DSM* categories (ADHD, ODD, conduct disorder [CD], depression, anxiety disorders), analyzed categorically with a p value $< .05$.

Within each of the five clinical functioning domains, we performed orthogonal contrasts as previously described (The MTA Cooperative Group, 2004a,b; Swanson et al., 2001) to decompose the overall effects of treatment. (Orthogonal contrasts, tested as part of the main analysis, do not require correction for multiple tests as do post hoc comparisons.) These examined three statistically independent questions: The MTA Medication Algorithm Effect: do children exposed to the MTA intensive medication strategy (Comb or MedMgt) show persistence of superior outcomes over children not so exposed (Beh and CC)? The Multimodality Superiority Effect: do children assigned to Comb show superior outcomes over those assigned to MedMgt? The Behavioral Substitution Effect: do children exposed to intensive behavioral therapy (Beh) show superior outcomes over those in usual community care (CC)?

Diagnostic Outcomes. We examined change in ADHD diagnostic status and comorbidity over time using generalized estimating equation analyses to examine effects of treatment group and treatment \times

time interactions. In addition, treatment group differences in diagnoses at 36 months were examined by logistic regression analyses, entering site and treatment into the model.

Service Use Outcomes. We obtained measures from two domains of service use during the follow-up phase (use and dose of medication and use of special education services) from a structured interview developed for this purpose, the Services for Children and Adolescents-Parent Interview (SCAPI; Hoagwood et al., 2004; Jensen et al., 2004). We calculated the percentage of subjects in each treatment group who received the respective service between 24 and 36 months and computed χ^2 statistics to determine whether these percentages differed across treatment groups.

Mediating Effects of Interim Medication and School Services Use. Given evidence of substantial changes over time in medication use across the four groups and given that medication use accounted for substantial differences in outcomes at previous assessment points (Marcus and Gibbons, 2001; The MTA Cooperative Group, 2004a,b), we performed mixed-effects regression analyses on each of the five dimensional outcome variables on all available time points (baseline and 14, 24, and 36 months), entering "medication use" as a time-dependent covariate at each of the follow-up periods, to determine the extent to which subsequent medication use (after initial random assignment) accounted for the effect/noneffect of original treatment assignments. For these analyses, medication use was defined as the percentage of days that subjects received ADHD medication (stimulants, bupropion, tricyclics) during the interval since the previous assessment, estimated from parental report on the SCAPI. This definition is different from two that had been used in the 24-month report (The MTA Cooperative Group, 2004b), which were based on whether medication was used at all during the interim since the previous assessment (a 10-month interim at the 24-month follow-up) and whether it was used in the 30 days before the 24-month assessment. In contrast, for the analyses presented here, we chose to use percentage of days medicated, as because it offered a more stable estimate of time-varying medication effects for analytical purposes than did our previous definitions. In addition to this continuous measure, we also used a categorical measure: medication use was defined as high if medication was used for a majority of the days since the previous assessment ($\geq 50\%$); otherwise ($< 50\%$), medication use was coded low/negative.

We also examined the potential mediating impact of receipt of special education services on 36-month outcomes. For these analyses, we used a dichotomous split of time at > 1 hour/week.

Moderator Analyses. For tests of suspected moderators, to avoid the possibility of chance findings, we examined only those variables for which we had found significant moderator or mediator effects in 14- or 24-month analyses. For moderator tests, we repeated the mixed-effects regression on change scores from baseline to 36 months with the following baseline variables (each in separate analyses) and their interaction with randomly assigned treatment group: presence/absence of comorbidity (defined by parent-reported Diagnostic Interview Schedule for Children diagnoses of anxiety, major depression, ODD, CD), ADHD symptom severity on the SNAP, sex, use of public assistance (a binary variable from a baseline demographic questionnaire completed by the parent), parental Beck Depression Inventory scores, and child's baseline use of special educational services based on the SCAPI described above. We examined not only medication use variables described earlier in the mediator tests but also the child's use of special educational services received during the 24- to 36-month posttreatment interval, again as defined by the SCAPI.

RESULTS

Intent-to-Treat Analyses of Original Treatment Groups

Table 2 shows the 36-month outcomes by originally assigned treatment groups for the five outcome domains. By 36 months, none of the randomly assigned treatment groups differed significantly on any of the five clinical and functional outcomes (parent and teacher ADHD and ODD symptoms, reading achievement scores, social skills, and functional impairment).

Figure 1 shows the changes over time in between-group differences for ADHD and ODD symptoms and functional impairment, i.e., the substantial initial baseline to 14-month differences that were largely related to the MTA medication algorithm effect, a halving of this effect by 24 months, and its disappearance by 36 months.

Effect sizes (Cohen's *d*) of the medication algorithm effect at 14 and 36 months, respectively, were as follows: ADHD symptoms: 0.86 and 0.10; ODD symptoms: 0.49 and 0.06; impairment: 0.37 and 0.02; social skills: 0.42 and 0.04; and reading achievement score 0.12 and 0.05. However, despite no significant group differences at the 36-month assessment, substantial improvement was manifested by all of the groups: thus, the ranges of effect sizes for improvement from baseline to 36 months across all of the treatment groups were 1.6–1.7 for ADHD, 0.7 generally for ODD, 0.9–1.0 for impairment, 0.8–0.9 for social skills, and 0.1–0.2 for reading.

Diagnostic Outcomes

Changes in diagnostic status over time were examined for ADHD and comorbid disorders including ODD, CD, anxiety, and depressive disorders, using generalized estimating equation analyses. Significant effects as a function of treatment and treatment \times time interactions were found for ADHD and depression but not for ODD, CD, or anxiety disorders. As seen in Figure 2A, this appeared principally to be a function of the dramatic reductions in subjects' meeting ADHD diagnostic criteria from baseline at 14 and 24 months in Comb and MedMgt, followed by more similar rates of ADHD diagnosis across all four treatment groups at 36 months.

Differences in ultimate diagnostic status at 36 months were examined by logistic regression analyses, entering site and treatment into the model. These

analyses indicated no significant treatment group differences in diagnostic status for ADHD or for comorbid conditions. Of note, however, time effects (indicating significant reductions in rates of comorbidity over time, but no effect of treatment) were seen for ODD/CD, anxiety, and depressive disorders, indicating a general drop in comorbid diagnosis rates, regardless of initial treatment assignment. A table describing the actual changes in frequency of comorbid conditions and the accompanying logistic regression analyses are available on the *Journal's* Web site at www.jaacap.com via the Article Plus feature. Figure 2 shows the proportion of subjects at each time point meeting diagnostic criteria for ADHD (combined type) and ODD or CD.

Service Use Outcomes

To understand the apparent loss of benefits for randomly assigned medication (Comb or MedMgt) by 36 months, we sought to understand the extent to which subjects were actually taking medication (based on parent reports of compliance). Figure 3 shows that at 14 months, >90% of children assigned to MedMgt and Comb were in the high use medication category (i.e., reportedly taking it at least 50% of the time from baseline to the 14-month assessment), compared to 60% and 14% of children assigned to CC and Beh, respectively. Medication use changed substantially over time, however. Thus, during the 24- to 36-month assessment interim, the percentage of children with high use decreased to approximately 71% for Comb and MedMgt, remained relatively steady at 62% for CC, and increased to 45% for Beh. Despite this convergence in use rates across groups by 36 months, medication use rates and total daily doses continued to differ significantly at 36 months (Table 2).

We also examined the differences in educational services use from 24 to 36 months, using a dichotomous split of time at >1 hour/week. In contrast to the medication use differences as a function of original treatment assignment, no significant differences were found across treatment groups in educational services use.

Mediating Effects of Interim Medication and School Services Use

To explore the possible effects of service use changes on outcomes, we assessed the impact of parent-reported medication compliance in the interims since previous

TABLE 2
36-Month Outcomes: Symptoms, Functioning, and Services Use

Tx Group	Social Skills												Med Use ^b	Special Education (% Receiving Spec Ed Svcs, 24-36 Mo)	Last Dose (in MPH- Equivalents mg ^c)		
	ADHD Sx		ODD Sx		SSRS Total P and T)		Impairment (CIS)		Reading (WIAT) Standard Score, Mean (SD)		Med Use ^b						
	Item Mean (SD) ^a (N = 485) (Lower = Better)	36 mo	Item Mean (SD) ^a (N = 485) (Lower = Better)	36 mo	Item, Mean (SD) ^a (n = 478) (Higher = Better)	BL	Item Mean (SD) (n = 407) (Lower = Better)	36 mo	BL	36 mo	BL-14	14-24				24-36	
Time	BL	36 mo	BL	36 mo	BL	36 mo	BL	36 mo	BL	36 mo	BL-14	14-24	24-36	24-36 mo	24-36 mo		
Comb	2.02 (0.45)	1.20 (0.53)	1.39 (0.67)	0.91 (0.66)	0.95 (0.20)	1.12 (0.24)	1.71 (0.67)	1.09 (0.67)	96.3 (14.8)	97.7 (13.7)	90.8%	71.0%	70.4%	37.7%	(7.4)	20.2 (18.4)	
MedMgt	2.06 (0.38)	1.21 (0.58)	1.42 (0.71)	0.93 (0.63)	0.92 (0.21)	1.13 (0.25)	1.69 (0.61)	1.13 (0.69)	95.9 (13.8)	97.8 (13.5)	92.1%	71.6%	71.8%	25.0%	(6.2)	23.3 (22.1)	
Behav	2.06 (0.43)	1.27 (0.57)	1.40 (0.61)	0.93 (0.67)	0.91 (0.18)	1.12 (0.23)	1.80 (0.61)	1.15 (0.65)	95.3 (13.8)	98.3 (14.1)	13.7%	34.9%	45.2%	32.0%	(7.0)	14.1 (20.1)	
CC	2.03 (0.43)	1.26 (0.61)	1.43 (0.60)	0.97 (0.71)	0.95 (0.20)	1.13 (0.24)	1.70 (0.58)	1.16 (0.62)	94.4 (13.6)	96.0 (14.6)	59.5%	62.3%	62.4%	34.5%	(7.6)	17.6 (19.9)	
Mixed-Effects Models or ANCOVAs ^d												χ^2 on the % 24-36 mo ^e		ANOVA			
Site <i>f</i> (<i>p</i>)	χ^2 (5 <i>df</i>) = 6.08 (<i>p</i> = .30)	χ^2 (5 <i>df</i>) = 8.45 (<i>p</i> = .13)	χ^2 (5 <i>df</i>) = 6.88 (<i>p</i> = .23)	χ^2 (5 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (5 <i>df</i>) = 6.88 (<i>p</i> = .23)	χ^2 (5 <i>df</i>) = 6.04 (<i>p</i> = .98)	χ^2 (5 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (5 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (5 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (5 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (5 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (5 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (5 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (5 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (5 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (5 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (5 <i>df</i>) = 6.03 (<i>p</i> = .01)
Site × Tx	χ^2 (15 <i>df</i>) = 10.7 (<i>p</i> = .77)	χ^2 (15 <i>df</i>) = 15.4 (<i>p</i> = .43)	χ^2 (15 <i>df</i>) = 6.04 (<i>p</i> = .98)	χ^2 (15 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (15 <i>df</i>) = 6.04 (<i>p</i> = .98)	χ^2 (15 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (15 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (15 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (15 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (15 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (15 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (15 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (15 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (15 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (15 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (15 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (15 <i>df</i>) = 6.03 (<i>p</i> = .01)
Rater	χ^2 (1 <i>df</i>) = 0.11 (<i>p</i> = .74)	χ^2 (1 <i>df</i>) = 0.11 (<i>p</i> = .74)	χ^2 (1 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (1 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (1 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (1 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (1 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (1 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (1 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (1 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (1 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (1 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (1 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (1 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (1 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (1 <i>df</i>) = 6.03 (<i>p</i> = .01)	χ^2 (1 <i>df</i>) = 6.03 (<i>p</i> = .01)
Rater × Tx	χ^2 (3 <i>df</i>) = 6.08 (<i>p</i> = .11)	χ^2 (3 <i>df</i>) = 6.08 (<i>p</i> = .11)	χ^2 (3 <i>df</i>) = 2.13 (<i>p</i> = .55)	χ^2 (3 <i>df</i>) = 2.13 (<i>p</i> = .55)	χ^2 (3 <i>df</i>) = 2.13 (<i>p</i> = .55)	χ^2 (3 <i>df</i>) = 2.13 (<i>p</i> = .55)	χ^2 (3 <i>df</i>) = 2.13 (<i>p</i> = .55)	χ^2 (3 <i>df</i>) = 2.13 (<i>p</i> = .55)	χ^2 (3 <i>df</i>) = 2.13 (<i>p</i> = .55)	χ^2 (3 <i>df</i>) = 2.13 (<i>p</i> = .55)	χ^2 (3 <i>df</i>) = 2.13 (<i>p</i> = .55)	χ^2 (3 <i>df</i>) = 2.13 (<i>p</i> = .55)	χ^2 (3 <i>df</i>) = 2.13 (<i>p</i> = .55)	χ^2 (3 <i>df</i>) = 2.13 (<i>p</i> = .55)	χ^2 (3 <i>df</i>) = 2.13 (<i>p</i> = .55)	χ^2 (3 <i>df</i>) = 2.13 (<i>p</i> = .55)	χ^2 (3 <i>df</i>) = 2.13 (<i>p</i> = .55)
Tx	χ^2 (3 <i>df</i>) = 0.94 (<i>p</i> = .82)	χ^2 (3 <i>df</i>) = 0.85 (<i>p</i> = .84)	χ^2 (3 <i>df</i>) = 0.34 (<i>p</i> = .95)	χ^2 (3 <i>df</i>) = 0.85 (<i>p</i> = .84)	χ^2 (3 <i>df</i>) = 0.34 (<i>p</i> = .95)	χ^2 (3 <i>df</i>) = 0.34 (<i>p</i> = .95)	χ^2 (3 <i>df</i>) = 0.34 (<i>p</i> = .95)	χ^2 (3 <i>df</i>) = 0.34 (<i>p</i> = .95)	χ^2 (3 <i>df</i>) = 0.34 (<i>p</i> = .95)	χ^2 (3 <i>df</i>) = 0.34 (<i>p</i> = .95)	χ^2 (3 <i>df</i>) = 0.34 (<i>p</i> = .95)	χ^2 (3 <i>df</i>) = 0.34 (<i>p</i> = .95)	χ^2 (3 <i>df</i>) = 0.34 (<i>p</i> = .95)	χ^2 (3 <i>df</i>) = 0.34 (<i>p</i> = .95)	χ^2 (3 <i>df</i>) = 0.34 (<i>p</i> = .95)	χ^2 (3 <i>df</i>) = 0.34 (<i>p</i> = .95)	χ^2 (3 <i>df</i>) = 0.34 (<i>p</i> = .95)

Orthogonal contrasts	MTA meds vs. Comb vs. MedMgt: Beh vs. CC:	MTA meds vs. Comb vs. MedMgt: Beh vs. CC:	MTA meds vs. Comb vs. MedMgt: Beh vs. CC:	MTA meds vs. Comb vs. MedMgt: Beh vs. CC:	MTA meds vs. Comb vs. MedMgt: Beh vs. CC:
	not: $p = .45$; $p = 0.57$;	not: $p = .77$; $p = 0.48$;	not: $p = .90$; $p = 0.61$;	not: $p = .61$; $p = .30$;	not: $p = .77$; $p = 0.76$;
	$p = .914$	$p = .60$	$p = .82$	$p = .77$	$p = .13$

Note: As expected, site differences emerged on 2 measures due to differences in local populations. The lack of significant site \times treatment (Tx) interaction shows that these did not affect validity of the Tx comparisons. Similarly, there were no rater \times Tx interactions, indicating that rater differences between parents and teachers did not affect Tx comparisons. Because age at baseline was significantly different between MedMgt and Beh (see Table 1), this analysis was repeated with age covaried as a check. It made no practical difference. The site \times treatment interaction and rater \times treatment interaction remained clearly nonsignificant with age covaried. Tx = treatment; ADHD = attention-deficit/hyperactivity disorder; Sx = symptoms; ODD = oppositional defiant disorder; SSRS = Social Skills Rating System; CIS = Columbia Impairment Scale; WIAT = Wechsler Individual Achievement Test; BL = baseline; Spec Ed Svcs = Special Education Services; MPH = methylphenidate; Comb = combination of medication management and behavior therapy; MedMgt = medication management; Beh = behavior therapy; CC = usual community care; ANCOVA = analysis of covariance; ANOVA = analysis of variance; $f(p)$ = F statistic; p value; MTA = Multimodal Treatment Study of Children With ADHD.

^a The baseline and 36-month item means (SDs) for the first 3 measures (ADHD Sx, ODD Sx, and social skills) are for average of teacher and parent ratings in the nested analysis.

^b Proportion of subjects on medication $\geq 50\%$ of the time. BL-14 = during study treatment period; 14-24 = 14-24 months; 24-36 = 24- to 36-month study interval.

^c Medication doses last reported during the 24- to 36-month follow-up period for those who took stimulants during that time, with other stimulants converted to methylphenidate (MPH) equivalents (e.g., 10 mg D-amphetamine = 20 mg MPH). Mean doses were not significantly different by site.

^d Significance level for the mixed-effects regression models and ANCOVAs was set at $p = .01$ to adjust for 5 analyses. Only the first 3 analyses have dual raters nested within subjects. In the absence of dual raters, a standard ANCOVA was performed.

^e Wald χ^2 was used to test the orthogonal contrasts in a logistic regression model for the percentages of subjects taking medication in the 24- to 36-month period.

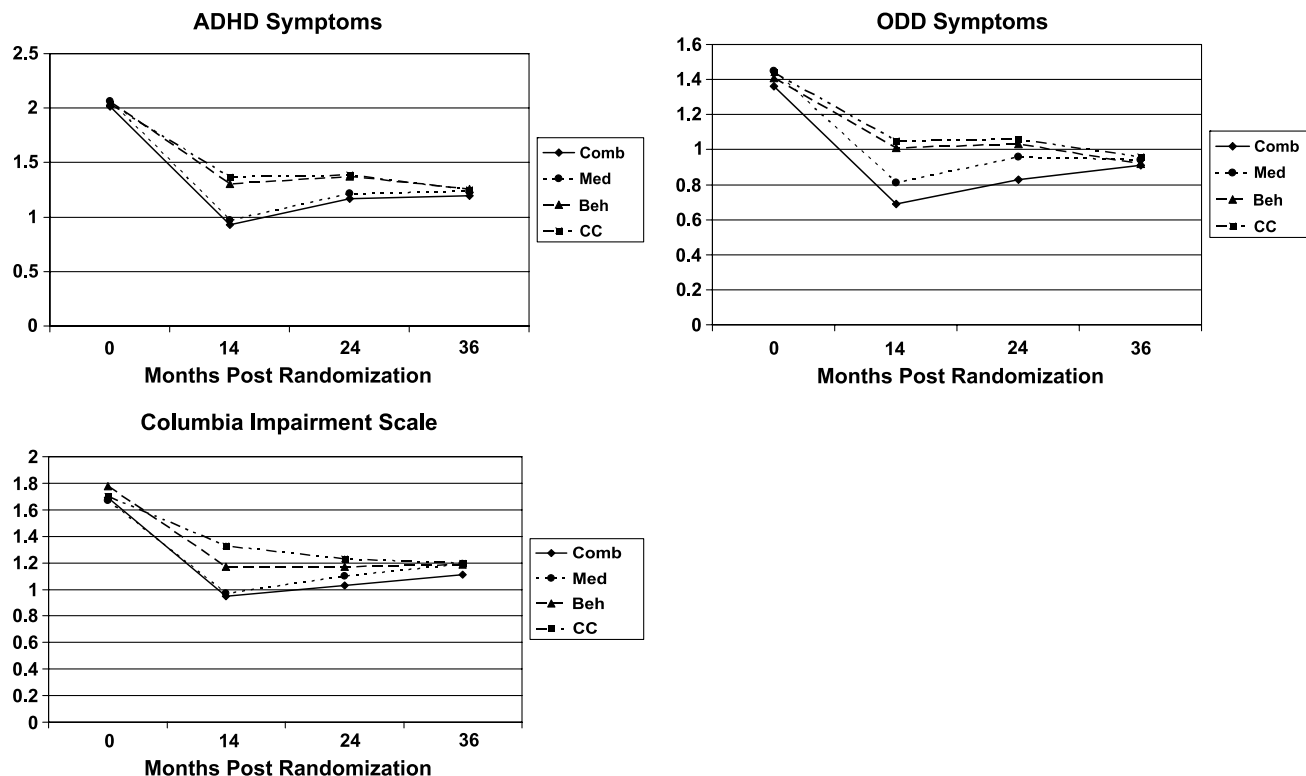


Fig. 1 Average ADHD and ODD Symptoms and Columbia Impairment Scale scores through 36 months. Comb = combination of medication management and behavior therapy; Med = medication management; Beh = behavior therapy; CC = usual community care.

assessments. Using a continuous medication use variable (percentage of days medicated in the interim) as a mediator, and ADHD SNAP symptoms as the outcome, we found both a significant main effect (effect size = -0.30) and a medication use × time interaction (effect size = 0.12) for the overall 0- to 36-month period. For the period from baseline to 14 months, daily medication compliance relative to taking no medication (adjusted for randomly assigned treatment group) decreased the average mean SNAP item score by approximately 0.3 units on the 0–3 scale. By 36 months, however, the difference in change scores between sustained medication use and no medication use was only 0.06 units on the 0–3 item mean.

Using a dichotomous definition, high versus low/no, medication use contrasts were computed at each time point (adjusting for treatment group, site, and rater), with findings again confirming significant medication effects from 0 to 14 and 0 to 24 months (0- to 14-month effect size = 0.27 SNAP units, SE 0.042, $p < .0001$; 0- to 24-month effect size = 0.17 SNAP units,

SE 0.042, $p < .0001$), but no significant mediating effects of medication use for the overall 0- to 36-month period (effect size = 0.01, SE 0.043, $p = .855$).

To better understand this loss of significance of the randomly assigned treatment effect, post hoc analyses were done to compute 24- to 36-month difference scores in ADHD ratings, examining the extent to which medication use between 24 and 36 months mediated clinical change. Interestingly, 24- to 36-month medication use was a significant marker (0.13 SNAP units), not of beneficial outcome, but of deterioration. That is, participants using medication in the 24- to 36-month period actually showed increased symptomatology during that interval relative to those not taking medication. A possible explanation may be selection effects, in which children doing well on medication may have stopped taking it, whereas those doing poorly while not on medication may have started taking it.

To further explore this possibility, we conducted post hoc analyses of overall change in SNAP scores in Comb/MedMgt children with high use ($\geq 50\%$) at 14

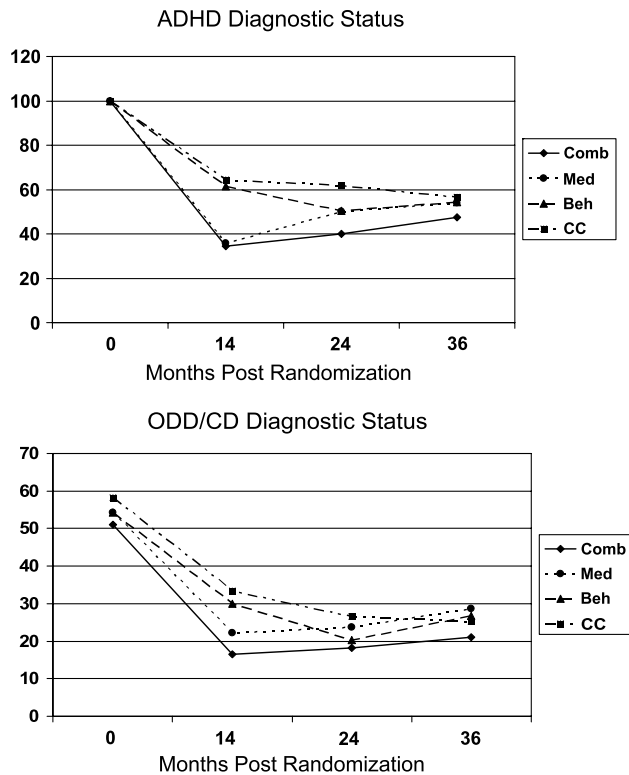


Fig. 2 Percentage of subjects meeting ADHD and ODD/CD criteria from baseline through 36 months. Comb = combination of medication management and behavior therapy; Med Mgt = medication management; Beh = behavior therapy; CC = usual community care.

and 24 months but low/no use (<50%) by 36 months, comparing them to Beh/CC children with low/no medication use at 14 and 24 months but high use at 24 to 36 months (Fig. 4). As one might expect if selection effects were operative, Comb and MedMgt subjects who discontinued medication during the 24- to 36-month period had been doing well at 24 months (improvement from baseline of >0.9 on the 0–3 item mean of ADHD symptoms) and continued to improve through 36 months, whereas Beh/CC subjects who began high medication use during the 24- to 36-month period had not been doing as well at 24 months (improvement of only 0.6 from baseline), but then improved slightly after starting or increasing medication use. These findings highlight the likelihood of self-selection factors among subjects in their 24- to 36-month medication use, in which increases or decreases in medication use may be the result rather than the cause of 36-month symptom levels. (See Article Plus for Medication Switcher Analysis, www.jaacap.com.)

We also examined the mediating impact of educational services use from 24 to 36 months. Disregarding treatment group, educational services at 24 to 36 months significantly ($p = .007$) predicted 36-month ADHD symptom change in the direction of those receiving such services for 24 to 36 months having a worse 36-month outcome, similar to the same finding for medication use. The interaction with randomized treatment assignment was not significant ($p = .11$), but CC participants who received educational services improved by 0.6 units on the 0–3 ADHD ratings, whereas those without educational services improved by 0.9 ADHD units ($p = .0006$). Mediating effects of 24 to 36 months of educational services for the other four outcome measures were nonsignificant (p values .29–.78).

Moderator Analyses

Additional analyses of all five primary outcome variables explored comorbidity as a moderator (The MTA Cooperative Group, 1999b) of initial treatment assignment. Using a mixed-effects random regression model for change from baseline to 36 months, we tested for treatment group \times baseline comorbid diagnosis interactions. Baseline diagnostic comorbidity was defined as ODD/CD without anxiety, anxiety without ODD/CD, ODD/CD and anxiety, and neither ODD/CD nor anxiety (Jensen et al., 2001). No significant moderator effects of comorbidity were found (treatment \times comorbidity group interactions: ADHD symptoms, $p = .26$; ODD symptoms, $p = .56$; social skills, $p = .18$; WIAT reading score, $p = .76$; Columbia Impairment Scale, $p = .21$).

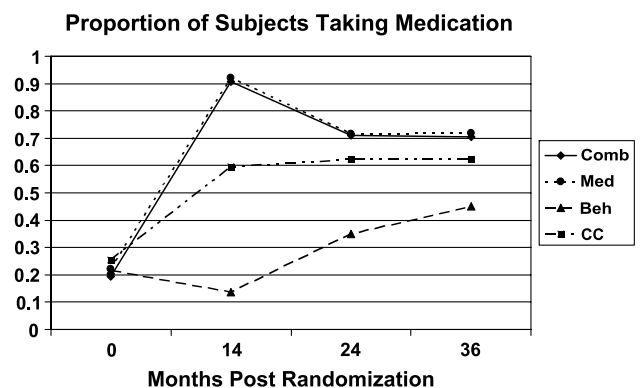


Fig. 3 Percentage of subjects using medication >50% of days, by treatment group through 36 months. Comb = combination of medication management and behavior therapy; Med Mgt = medication management; Beh = behavior therapy; CC = usual community care.

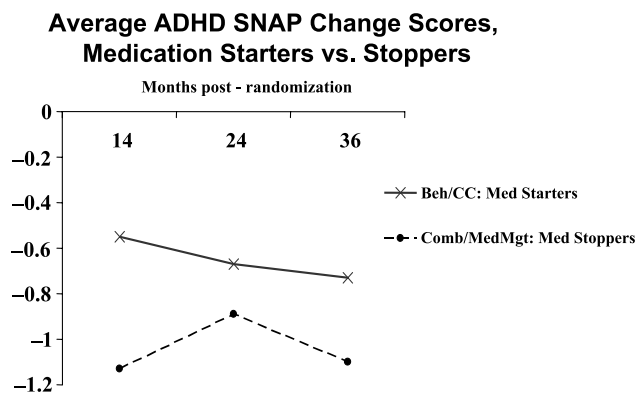


Fig. 4 Average ADHD change scores on the SNAP Rating Scale, comparing Beh subjects who started medication versus Comb subjects who stopped medication between 24 and 36 months. SNAP = Swanson, Nolan, and Pelham Rating Scale; Comb = combination of medication management and behavior therapy; Med Mgt = medication management; Beh = behavior therapy; CC = usual community care.

We also found no significant moderating effects for sex (p values .24–.87 for the five outcomes), the family's receipt of public assistance (p values .08–.56 [.08 for ODD symptoms, others >.12]), parent Beck Depression Inventory score (p values .46–.85), parent inattention self-rating on the CAARS (p values .08–.98 [.08 for WIAT reading score, others >.14]), or baseline use of educational services (p values .051–.78 [.051 for ADHD symptoms, others >.29]).

Although they did not moderate differential treatment effects, sex, public assistance, and parental inattention predicted overall improvement: Thus, boys and subjects on assistance improved less for ADHD, respectively ($p = .0004$ and $p = .0004$), ODD ($p = .005$ and $.003$), impairment ($p = .004$ and $.03$), and social skills ($p = .0001$ and $.01$), with nonsignificant differences in reading scores (WIAT, $p = .48$ and $p = .582$) scores. Those with high parent inattention improved less on ADHD ($p = .04$), impairment ($p = .007$), and reading ($p = .04$).

DISCUSSION

Our primary (intent-to-treat) analyses revealed that the modest significant advantages we found at the 24-month assessment for the MTA Medication Algorithm (i.e., Comb or MedMgt vs. Beh or CC [The MTA Cooperative Group, 2004a,b]) were completely lost by 36 months. Likewise, we found no differences in rates of ADHD diagnosis and other comorbid conditions across the originally assigned treatment groups at 36 months.

Even though medication use patterns changed significantly from 14 to 36 months, with more cases assigned to the Comb and MedMgt conditions stopping medication and more cases from the Beh starting medication, the initial differences in medication use (especially Beh) and the two MTA medicated groups (Comb and MedMgt) were not completely eliminated. That is, at 36 months, 71% of Comb and MedMgt participants were using medication at high levels compared to 62% and 45% of CC and Beh participants, respectively. Groups also continued to differ in average medication doses as well. Yet these medication use variables during the year from 24 to 36 months did not reveal any advantage on 36-month outcomes and instead showed a tendency toward disadvantage. We hypothesized that this unexpected pattern may be due to a tendency of those who are doing well either to stay off medication or to discontinue it and those doing poorly either to start taking it or to continue it. This may hold for any modality of treatment because we found a similar pattern of disadvantage ($p = .007$) for educational services: those receiving a higher level of such services were doing worse at 36 months than those receiving a lower level (or none), especially for CC, in which improvement was only about half as great ($p = .0006$) for those receiving >1 hour/week of special educational services. Selection effects may be operative here, that is, that those children with worse problems receive more treatment, either with medication or with educational services. This hypothesis is further tested and discussed in the companion paper in this issue by Swanson et al. (2007).

Although our original randomly assigned treatment groups no longer differed at 36 months, we were struck by the remarkable degree of improvement in all four groups seen from baseline in all of the later assessment points in symptoms and overall functioning (ADHD: 1.6–1.7 SD units of change; ODD: 0.7 SD; global impairment: 0.9–1.0 SD; social skills: 0.8–0.9 SD; see baseline to 36-month means, Table 2). This degree of improvement found in all of the subjects over time, regardless of which treatment these children received, may not have received sufficient attention in the previous treatment research literature. Thus, to the extent that previous studies focus on moderate differences found among various treatment groups over short-term treatment periods, they may miss the

important larger context that all of the differences found among various treatment groups occur on top of the substantial improvement that occurred in MTA-studied children with ADHD overall. Such changes may represent benefits specific to study participation and attention, or they may reflect a natural waning of symptoms (sometimes called a “clock-setting cure” [Lambert and Bickman, 2004]) that occurs in at least a subset of children with ADHD, or statistical regression to the mean given that the sample was selected for having high scores on one of the outcome measures (ADHD symptoms). Of course, without an untreated control group, no firm conclusions about the possibility of more positive ADHD outcomes can be drawn with confidence.

Generally, adolescent prospective follow-up studies of children with ADHD (Barkley et al., 1990, Biederman et al., 1996, Gittelman et al., 1985, Lambert et al., 1987, Satterfield et al., 1982, Weiss et al., 1971) have reported that adolescents previously diagnosed with ADHD still had significant ADHD symptoms. Biederman et al. (2000) showed that hyperactive and impulsive symptoms tended to decrease whereas inattentive symptoms tended to persist. The less severe picture in the MTA compared to other follow-ups could be explained by several factors: referral from a variety of sources, not just mental health clinics; treatment history, with 45% to 71% of MTA subjects still taking medication at follow-up, whereas in most other adolescent follow-ups, subjects were no longer taking medication (Hechtman, 1985); or age at follow-up, with MTA subjects at 36 months still somewhat younger (range 10–13, mean 11.8 years) than in other follow-up studies (range 13–18 years, mean ~15 years). Perhaps MTA subjects are still too young to encounter key adolescent challenges, allowing a somewhat more positive outcome at this point. Further follow-up will help clarify this important issue. Whether the differences between other reports and this one are due to sampling differences or to changes in treatment strategy over time is also a question deserving of further study.

Limitations

The results reported here must be viewed in light of three important limitations of the design: First, the MTA was designed to fill a gap in the literature by evaluating the longer term (14-month) efficacy/effectiveness of treatments that had documented short-

term benefits. However, the design did not provide tests of absolute efficacy/effectiveness (which would have required an untreated control group), nor did the 14-month treatment design provide a meaningful test of the benefits of intensive treatment periods longer than 14 months. Study developers concluded that it would not be feasible to include either of these two study features (Arnold et al., 1997).

Second, the original random treatment assignments began to dissipate upon termination of study treatment at 14 months. Indeed, there had been attenuation of the use of originally assigned treatment strategies even at 14 months, with 26% of the Beh group having started supplemental medication and only 86% to 88% of the two groups assigned to systematic medication still taking it at the 14-month assessment (The MTA Cooperative Group, 1999a). Because the effects of initial randomization were gradually lost after 14 months, subsequent outcomes may have been increasingly influenced by dissipation of treatment intensity and adherence (e.g., many fewer medication follow-up visits, flat vs. previously increasing medication doses [Jensen et al., 2004]). Thus, our data do indicate that rigorous medication compliance wanes over time, as suggested by Figure 3. Had the recently available once-daily stimulant preparations been available and used throughout the study, in view of recent evidence of greater compliance (Marcus et al., 2005) and effectiveness (Steele et al., 2006) with such agents, our 36-month findings may have been different to the extent that long-term medication benefits depend on high degrees of sustained compliance/adherence.

Our finding of no clinically or statistically significant treatment differences by 36 months could also be due to other explanations, including the reliability and validity of our medication use measures (relying solely on retrospective reports by caregivers) or the overall loss of medication treatment intensity after 14 months in the Comb and MedMgt groups.

We cannot rule out any of these possibilities, but we note that Abikoff and colleagues (2004) found no loss of medication effect from 12 to 24 months when medication continued to be followed and carefully adjusted through 24 months, offering some support for the possibility that the partial loss of the MTA’s medication algorithm effect from 14 to 24 months in fact may have been due to loss of treatment intensity and follow-up. Whether the complete loss by 36

months of our 14-month medication algorithm benefits was similarly due to loss of treatment intensity cannot be ruled out.

Other explanations are possible as well, and several alternatives, including self-selection factors and the possibility that only certain subgroups show persistent benefits at 36 months, are explored in the companion paper in this issue by Swanson et al. (2007).

Third, the inclusion/exclusion criteria and the necessity for informed consent limit the generalizability of our findings to children with ADHD Combined type whose treatment started before age 10 and whose parents were willing to have them randomized to the study treatment possibilities and could commit to frequent treatment visits.

Clinical Implications

It would be incorrect to conclude from these results that treatment makes no difference or is not worth pursuing. Indeed, the 14-month intensive medication algorithm yielded significant advantage for the first 24 months, although not to 36 months. Intensive medication management may only make a persistent long-term difference if it is continued with the same intensity as during the MTA's initial 14-month period. In contrast, starting or adding medication at a less than optimal intensity and too late in child's ADHD clinical course (particularly if a child's behavior is deteriorating) may not only be ineffective but also (if not carefully examined in data analysis) even make medication appear to be associated with worse outcomes.

Because there was no untreated control group and because all of the treatment groups were improved in terms of relevant symptomatology at 36 months compared to baseline, it is possible that all of the treatments worked, but at different rates or during different time periods. Thus, an important clinical message to be taken from our findings is that all of the treatment groups showed significant improvement over time. These data suggest that clinicians should offer hope to children and families, thereby addressing the discouragement that many families may feel if negative outcomes from previous studies are presented and discussed in isolation. Analyses of problems such as substance use and delinquency (see companion paper by Molina et al., 2007, this issue) may, however, point to less optimistic conclusions for a subgroup of children.

It is interesting that both medication and educational services for 24 to 36 months were markers for poorer outcome at 36 months, suggesting that those who are doing poorly get more treatment yet still do not do as well as those for whom treatment is not considered essential. The converse, of course, is that many patients are eventually able to stop treatment and continue doing well.

Prognostication may benefit from the findings that girls and those not living on public assistance improve more over the 36 months than boys or those on public assistance. Thus, demographic factors accounted for greater effects on outcome at the 36-month assessment than original random treatment assignment, even though all of the groups improved.

Important questions remain: Which children can discontinue medication and continue to do well? Are there some children who do well whether they ever take medication? Are there other groups of children who benefit only from intensive medication and show decreasing benefit over time, perhaps to the extent that the medication regimen is not as carefully monitored and adjusted (usually by an increase in dose) as was done during the initial 0- to 14-month treatment period? Do some children show gradual deterioration, either without effective treatment or in spite of intensive treatments? These pressing questions are the subject of a companion paper (Molina et al., 2007) in this issue and future reports.

The Multimodal Treatment Study of Children With ADHD (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 S. Jensen, M.D. (currently at Columbia University, New York), L. Eugene Arnold, M.D., M.Ed. (currently at Ohio State University), Joanne B. Severe, M.S. (Clinical Trials Operations and Biostatistics Unit, Division of Services and Intervention Research), Benedetto Vitiello, M.D. (Child and Adolescent Treatment and Preventive Interventions Research Branch), Kimberly Hoagwood, Ph.D. (currently at Columbia University, New York); 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 co-investigators from the clinical sites are University of California, Berkeley/San Francisco: Stephen P. Hinshaw, Ph.D. (Berkeley), Glen R. Elliott, M.D., Ph.D. (San Francisco); Duke University: C. Keith Conners, Ph.D., Karen C. 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 P. Cantwell, M.D. (deceased, Los Angeles), Timothy Wigal, Ph.D. (Irvine); Long Island Jewish Medical Center/

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Incidence, Prognosis, and Risk Factors for Fatigue and Chronic Fatigue Syndrome in Adolescents: A Prospective Community Study Katharine A. Rimes, DPhil, Robert Goodman, PhD, Matthew Hotopf, PhD, Simon Wessely, MD, Howard Meltzer, PhD, Trudie Chalder, PhD

Objective: The objective of this study was to describe the incidence, prevalence, risk factors, and prognosis of fatigue, chronic fatigue, and chronic fatigue syndrome in 11- to 15-year-olds. **Methods:** A random general population sample ($n = 842$) of British adolescents and their parents were assessed at baseline and 4 to 6 months later. The main outcomes were fatigue, chronic fatigue, and chronic fatigue syndrome, operationally defined. **Results:** The incidence over 4 to 6 months was 30.3% for fatigue, 1.1% for chronic fatigue, and 0.5% for chronic fatigue syndrome. The point prevalence was 34.1% and 38.1% for fatigue, 0.4% and 1.1% for chronic fatigue, and 0.1% and 0.5% for chronic fatigue syndrome at time 1 and time 2, respectively. Of participants who were fatigued at time 1, 53% remained fatigued at time 2. The 3 cases of chronic fatigue and 1 case of chronic fatigue syndrome at time 1 had recovered by time 2. Higher risk for development of chronic fatigue at time 2 was associated with time 1 anxiety or depression, conduct disorder, and maternal distress; in multivariate analysis, baseline anxiety or depression remained a significant predictor of chronic fatigue. Increased risk for development of fatigue at time 2 was associated with time 1 anxiety or depression, conduct disorder, and older age; in multivariate analyses, these factors and female gender all were significant predictors of fatigue. **Conclusions:** The incidence rates for chronic fatigue and chronic fatigue syndrome in this adolescent sample were relatively high, but the prognosis for these conditions was good. This prospective study provides evidence for an association between emotional/behavioral problems and subsequent onset of fatigue/chronic fatigue. *Pediatrics* 2007;119:e603–e609.