

Special Article

Findings from the NIMH Multimodal Treatment Study of ADHD (MTA): Implications and Applications for Primary Care Providers

PETER S. JENSEN, M.D.*
STEPHEN P. HINSHAW, Ph.D.†
JAMES M. SWANSON, Ph.D.§
LAURENCE L. GREENHILL, M.D.¶
C. KEITH CONNERS, Ph.D.‡
L. EUGENE ARNOLD, M.D.*
HOWARD B. ABIKOFF, Ph.D.||
GLEN ELLIOTT, Ph.D., M.D.†
LILY HECHTMAN, M.D.||
BETSY HOZA, Ph.D.**
JOHN S. MARCH, M.D.‡
JEFFREY H. NEWCORN, M.D.¶
JOANNE B. SEVERE, M.S.*
BENEDETTO VITIELLO, M.D.*
KAREN WELLS, Ph.D.‡
TIMOTHY WIGAL, Ph.D.§

ABSTRACT. In 1992, the National Institute of Mental Health and 6 teams of investigators began a multisite clinical trial, the Multimodal Treatment of Attention-Deficit Hyperactivity Disorder (MTA) study. Five hundred seventy-nine children were randomly assigned to either routine community care (CC) or one of three study-delivered treatments, all lasting 14 months. The three MTA treatments—monthly medication management (usually methylphenidate) following weekly titration (MedMgt), intensive behavioral treatment (Beh), and the combination (Comb)—were designed to reflect known best practices within each treatment approach. Children were assessed at four time points in multiple outcome. Results indicated that Comb and MedMgt interventions were substantially superior to Beh and CC interventions for attention-deficit hyperactivity disorder symptoms. For other functioning domains (social skills, academics, parent-child relations, oppositional behavior, anxiety/depression), results suggested slight advantages of Comb over single treatments (MedMgt, Beh) and community care. High quality medication treatment characterized by careful yet adequate dosing, three times daily methylphenidate administration, monthly follow-up visits, and communication with schools conveyed substantial benefits to those children that received it. In contrast to the overall study findings that showed the largest benefits for high quality medication management (regardless of whether given in the MedMgt or Comb group), secondary analyses revealed that Comb had a significant incremental effect over MedMgt (with a small effect size for this comparison) when categorical indicators of

Address for reprints: Peter S. Jensen, M.D., Center for the Advancement of Children's Mental Health, Department of Child Psychiatry, NYSPI/Columbia University, 1051 Riverside Drive, #78, New York, New York 10032; e-mail: pj131@columbia.edu; fax: 212-543-5260.

The MTA is a cooperative treatment study performed by six independent research teams in collaboration with the staff of the Division of Clinical and Treatment Research of the National Institute of Mental Health (NIMH),* Rockville, Maryland, and the Office of Special Education Programs (OSEP) of the U.S. Department of Education (DOE). The NIMH Principal Collaborators are Peter S. Jensen, M.D., L. Eugene Arnold, M.Ed., M.D., John E. Richters, Ph.D., Joanne B. Severe, M.S., Donald Vereen, M.D., and Benedetto Vitiello, M.D. Principal Investigators and Coinvestigators from the six sites are as follows: University of California at Berkeley/San Francisco† (UO1 MH50461): Stephen P. Hinshaw, Ph.D., Glen R. Elliott, M.D., Ph.D.; Duke University‡ (UO1 MH50447): C. Keith Conners, Ph.D., Karen C. Wells, Ph.D., John S. March, M.D., M.P.H.; University of California at Irvine/Los Angeles§ (UO1 MH50440): James M. Swanson, Ph.D.; Dennis P. Cantwell, M.D.; Timothy Wigal, Ph.D.; Long Island Jewish Medical Center/Montreal Children's Hospital|| (UO1 MH50453): Howard B. Abikoff, Ph.D., Lily Hechtman, M.D.; New York State Psychiatric Institute/Columbia University/Mount Sinai Medical Center¶ (UO1 MH50454): Laurence L. Greenhill, M.D., Jeffrey H. Newcorn, M.D.; University of Pittsburgh** (UO1 MH50467): William E. Pelham, Ph.D., Betsy Hoza, Ph.D. Helena C. Kraemer, Ph.D. (Stanford University) is statistical and design consultant. The OSEP/DOE Principal Collaborator is Ellen Schiller, Ph.D.

excellent response and when composite outcome measures were used. In addition, children with parent-defined comorbid anxiety disorders, particularly those with overlapping disruptive disorder comorbidities, showed preferential benefits to the Beh and Comb interventions. Parental attitudes and disciplinary practices appeared to mediate improved response to the Beh and Comb interventions. *J Dev Behav Pediatr* 22:60–73, 2001. Index terms: *ADHD, stimulants, behavior therapy, attention deficit, treatment, outcomes.*

Attention-deficit hyperactivity disorder (ADHD) is the most commonly diagnosed behavioral disorder afflicting children. Recent estimates suggest that the disorder prevalence rate across the United States ranges from 4% to 10%, with higher rates usually reported when diagnoses are made via rating scales,^{1,2} and lower rates when diagnoses are based on structured diagnostic interview.^{3,4} Given ADHD's prevalence and the personal and societal impact of the condition from childhood into adulthood,⁵ development of effective short- and long-term treatment strategies is essential.

Despite ample evidence concerning the short-term benefits of medication (principally stimulants) and behavioral therapy, uncertainty has continued among providers and researchers as to the relative merits of behavioral and medication treatments and their combination, particularly concerning treatment effects after the acute 2- to 3-month span of most studies. Few studies have subjected these two major forms of evidence-based treatment to head-to-head comparative trials, and before the recent publication^{6,7} of the National Institute of Mental Health (NIMH) Multimodal Treatment Study of Children with ADHD (the so-called *MTA Study*), no studies had compared these two treatments in any study longer than 4 months. As a consequence, critical questions such as *what treatment works best, and for whom, and for how long?* have persisted, not just because of the short-term nature of most previous studies, but also because of the lack of a longer-term behavioral-treatment-only group, the lack of statistical power in past studies (sample sizes generally under 100 total subjects), and the absence of a community control/comparison group.

In 1992, NIMH embarked on the development of a multisite clinical trial to address these unanswered questions. NIMH's Request for Applications (RFA)⁸ specified that participating sites must have demonstrated expertise in both medication and behavioral treatments and that all participating sites would be required to work together to fashion a single study that could be mounted across all participating sites. Six sites were selected from over 20 applications, and the principal investigators and coinvestigators from these sites joined to form a steering committee over the ensuing year to design the final protocol and oversee the study's implementation.^{9,10} Because aspects of the behavioral intervention were delivered in school settings, the Department of Education also cosponsored the study.

Initial findings from the study have been reported^{6,7} and continue to be documented.^{11–24} However, given the complexity of the study, the wealth of its findings, and a number of misinterpretations and/or misrepresentations of the study's findings that have required clarification,²⁵ a consolidated and concise report of the study's overall findings is necessary, with special emphasis on their

relevance for primary care providers who treat the bulk of these children. This paper briefly reviews the study's methods and describes major findings related to the following five questions.

1. Given the chronic nature of ADHD, what longer-term treatment (medication management, behavioral therapy, or the combination) yields the best outcomes and for which functioning domains?
2. Are there additional advantages that accrue when optimal treatments (without the usual limitations of managed care, access to trained providers, availability of insurance, school resources, etc.) are provided versus treatment as usual in the community?
3. Do some treatments work better for some patients than for others? In other words, are there any readily identifiable factors that *moderate* treatment outcomes such that the physician might a priori determine which treatment is most likely to work for a given patient without the usual approach of simply trying a treatment to see if it works?
4. Why and how did the treatments work? In other words, what aspects of the various treatments seem to account for the study's findings?
5. What is the overall behavioral health impact of the treatments, in terms of the proportion of children normalized?

The MTA study's importance for primary care providers stems from four principal factors. First, it is the largest clinical ADHD trial to date. In fact, when one sums the sample sizes from all previous randomized clinical trials that have tested the relative efficacy of behavioral, pharmacologic, and combined treatments (e.g., both medication and behavioral treatments), only just over 600 subjects had been studied before this point,²⁶ with the largest previous study totaling only 103 subjects. The MTA's sample size of 579 nearly doubles the total number of children that have been treated in rigorous clinical trials comparing behavioral and medication treatments, alone and in combination.

Second, of all available comparative clinical trials studies reviewed by the McMaster University Evidence-Based Practice Center,²⁷ only the MTA met the full criteria for study quality. Given the balanced team of experts in both behavioral treatment and pharmacotherapy within and across six sites, coupled with the replication of the same findings across all sites, substantial confidence is warranted in the study's execution and results. Based on a variety of independent sources, the study used the best methods available, and the findings appear credible and robust.^{27–28}

Third, the inclusion of a community comparison group is noteworthy, because it allows the comparison of the relative

benefits of treatments as usually delivered by community providers versus the intensive, carefully monitored treatments delivered by the MTA study investigators.

Fourth, the design of the study explicitly attempted to make the study as useful as possible to "real-world" clinicians and families. For example, comorbidity (except for psychosis or Tourette's syndrome) did not constitute an exclusion factor, given the authors' assumption that many children treated in community settings would have complex clinical presentations, not just uncomplicated ADHD. Similarly, for treatments that were chosen, the authors attempted to make them the highest quality possible, while still keeping in mind that such treatments, if effective, should ultimately be used and useful in the real world. Thus, the medication management approach developed for the study was explicitly one that the investigators believed *could* be used by primary care providers (monthly hour medication visits, general counseling and guidance, provision of reading materials), even though it was more intense than is normally done and required a careful initial dose titration (a method unlikely to be used in standard office practice). Thus, in the current parlance, the MTA blended the primary component of "efficacy" studies (i.e., random assignment to treatment conditions) with many aspects of "effectiveness" trials (e.g., participants with real-world comorbidities and provision of treatment in children's homes and schools). Study methods are described in detail below.

METHODS

The Multimodal Treatment of ADHD (MTA) recruitment, screening, and selection procedures were developed to collect a carefully diagnosed, impaired sample of children with attention-deficit hyperactivity disorder (ADHD) and with a wide range of comorbidities and demographic characteristics representative of patients seen clinically.⁹⁻¹¹ For eligibility, children (of either sex) were between ages 7.0 to 9.9 years, in first through fourth grades. All met DSM-IV criteria for ADHD, Combined Type (the most common subtype at this age), using the Diagnostic Interview Schedule for Children (DISC), parent-report, version 3.0.⁶ The presence of comorbidities such as oppositional defiant disorder (ODD), conduct disorder (CD), internalizing disorders, or specific learning disabilities *were not* exclusionary conditions, because the investigators wanted to determine the potential interaction of these factors with treatment outcomes. A four-phase entry procedure screened potential participants, ascertained caseness, and assessed each child before randomization.⁹⁻¹¹ Teacher input was necessary, and children were required to score above the 90th percentile on standardized teacher rating scales to be eligible for study participation. In addition, all sites had to recruit children from four referral sources—primary care practices, schools, mental health settings, and advertisements—to assure that the final sample would be broadly generalizable to the types of children with ADHD found in usual settings. Subjects entering the fourth phase did not differ from initial phone screen subjects on parental education, ethnicity, or gender. Then, in a four-

group parallel design, 579 children were assigned randomly to (1) medication management (MedMgt), (2) behavioral treatment (Beh), (3) the combination (Comb), or (4) community comparison (CC) for 14 months.

Multimodal Treatment of ADHD

Medication Management. During the first month of treatment, the MedMgt arm consisted of an initial titration period, testing placebo versus three different doses of methylphenidate (5 mg, 10 mg, and 15/20 mg, depending upon the child's weight) (Table 1). For those children for whom methylphenidate was not effective, further testing on other stimulants or imipramine was done in the second month of the 14-month treatment period. Once an effective medication was found, MedMgt children usually received stimulant medication three times a day, ongoing follow-up, medication monitoring, and continued support in monthly half-hour visits. Parents were provided supplementary reading material when they requested such, and the pharmacotherapists offered counseling and general advice as needed, but *not* any behavioral treatment. By protocol, pharmacotherapists initiated contact with the child's teacher before each monthly visit and spent time alone with the child during each visit. See Greenhill and colleagues¹³ for additional details concerning this treatment component.

Behavioral Treatment. Parents of children assigned to the Beh treatment received 35 sessions (8 individual, 27 group meetings) to teach them behavioral management techniques and how to coordinate the child's care with the school. Children assigned to Beh treatment attended the day-long sessions of the *Summer Treatment Program*²⁹ for 8 weeks. The program taught the children sports and social skills and gave them an opportunity to practice and refine their academic skills. The same therapist who provided parent training and supervised the summer program counselors consulted with the child's teacher in the spring and fall and supervised a behavioral aide who worked directly with the child in the classroom for 12 weeks in the fall. Consistent with clinical practice, the overall behavioral therapy components were slowly tapered over the last 4 to 6 months of treatment, during which time the parents and teachers were taught to carry on themselves, with telephone availability of the therapist as needed. See Wells and colleagues¹² for additional details and documentation of the MTA psychosocial treatment component.

Combined Treatment. Children assigned to the Comb arm received both Beh and MedMgt components, but care was taken to integrate these two intensive therapies as much as possible to reduce any burden on families. For example, to minimize travel inconvenience, a Comb family's visit for the MedMgt component might be scheduled for the same day as their parent group meeting delivered via their Beh component. The pharmacotherapist and the behavior therapist met regularly to share information and ensure that the treatment plan was integrated for optimal effect for each family. When problems in the child's response to treatment were found, treatment algorithms provided for initial adjustments in the behavioral management, and when that failed to produce a satisfactory response, adjustments in the medication program were made.¹³

Table 1. MTA Study Treatment Conditions^a

	Medication Management Strategy (MedMgt)	Behavioral Treatment Strategy (Beh)	Combined Strategy (Comb)	Community Comparison Group (CC)
Active Treatment	1-month blind titration with methylphenidate for best dose; if unsatisfactory, open titration with d-amphetamine, pemoline, TCA. When effective drug regimen is found, maintain with monthly visits; adjust dose as indicated by monthly monitors and by algorithm.	Intense, multi-component, including 27 group and 8 individual sessions (interspersed with the groups) of parent training, structured 16–20-session teacher/consultation, 8-wk full-time Summer Treatment Program, and 12 wk of half-time paraprofessional aide (PPA), all integrated in complementary fashion, with phone calls between visits.	Integration of all treatment components in first 2 conditions (except bibliotherapy), with (a) more extensive data base available from behavioral therapist to assist medication adjustment decisions and (b) information from pharmacotherapist to assist in decisions about escalation of behavioral interventions.	<i>None by MTA Staff.</i> Assessed-only at same time points as active treatment groups. Families obtain treatment of own choosing in the community. If already has a treatment provider, referred back for treatment; if not, given list of referral agencies, including community MH Center, which can help find community treatment.
Supplementary Treatment	Supplementary general advice and bibliotherapy without systematic behavioral intervention.	Supplementary general advice; no medication.	Supplementary general advice; no bibliotherapy.	None.
Case Manager	Pharmacotherapist is case manager.	Therapist/consultant (TC).	Therapist/consultant, with weekly advice from combined-treatment clinical team.	None.
Emergency Services	ASAP ^b emergency services as needed.	ASAP ^b emergency services as needed.	ASAP ^b emergency services as needed.	None.

MTA, Multimodal Treatment of Attention-Deficit Hyperactivity Disorder.

^aSubjects in all 4 arms received comprehensive assessments at baseline, 3 months, 9 months, and 14 months.

^bASAP, Adjunct Services and Attrition Prevention. Each treated subject has a bank of eight "ASAP sessions" that can be used in emergencies, monitored by a cross-site clinical panel.

Community Comparison. Families of CC-assigned children were provided a list of referral sources and/or were referred back to their original care provider. Like children and families in the other three groups, they were assessed at regular intervals throughout the study (baseline, 3 months, mid-point, and 14 months). CC children received whatever treatments were agreed upon by parents and were available within their communities; two-thirds of these children received stimulant medication via local providers (usually primary care physicians). Community treatments were much less intensive than MTA-delivered interventions. For example, CC children treated with methylphenidate (the most frequently used medication) usually received twice-daily dosing (averaging 2.1 doses/day, 18.7 mg total daily dose), with a mean of 2.3 visits/year. More extensive information concerning study treatments and outcomes is reported elsewhere.^{6,7,9,10}

Sample

Participants were referred for study entry from several sources: almost half were referred by schools, 18% responded to newspaper ads, 9% came from mental health settings, 8% learned of the study by word of mouth, 6% were referred by pediatricians, and the rest came from other sources. Each site was required to recruit from all sources

and not just one "convenient" source. No attempt was made to stratify on referral source.

Demographic characteristics of the final selected MTA participants were as follows: 80% male and 20% female; 61% white, 20% black, and 19% Hispanic, racially mixed, or other ethnic origins. Mean age at study entry was 8.5 years. Sixty-nine percent of the children lived in two-parent families, 30% in one-parent families, and 1% lived with other relatives (e.g., grandparents, aunts, or long-term foster families). Nineteen percent of the families were receiving some type of public assistance, and 30% of children had been previously treated with stimulant medications. All children had to meet the criteria for the ADHD-Combined type.³⁰ In addition, parents were interviewed with the Diagnostic Interview Schedule for Children (DISC) to determine the presence of other psychiatric disorders at baseline. The DISC determined the following co-occurring conditions: 33.5% of children with a comorbid anxiety disorder (38.7% including simple phobia), 14.3% with conduct disorder, 39.9% with oppositional defiant disorder, 3.8% with affective disorder, and 10.9% with tic disorder (Fig. 1). Only 31.8% of children had pure ADHD, that is, ADHD only with no comorbidities. Formal diagnoses of learning disability were not available because the DISC does not make that determination.

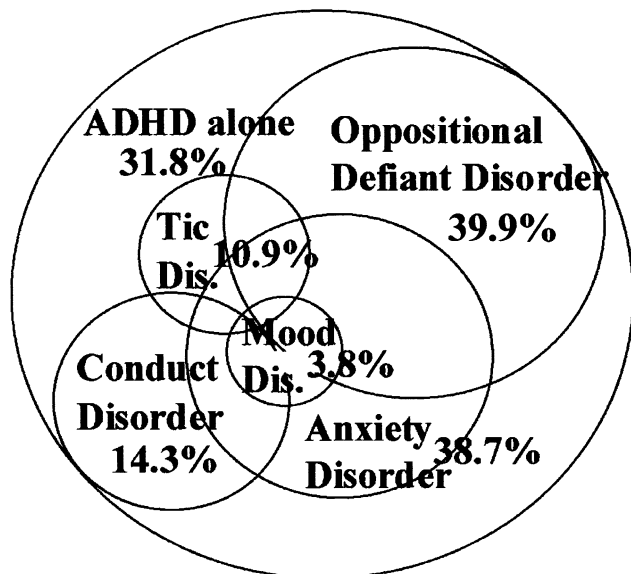


Figure 1. Overlap of co-occurring disorders in Multimodal Treatment of ADHD (MTA) Sample ($n = 579$) at baseline, prior to randomization to the four treatment groups. All subjects met criteria for attention-deficit hyperactivity disorder (ADHD), Combined-Type.

Assessments

For all subjects, repeated assessments were made from baseline (early in the spring of Year 1) to 14 months (late spring, Year 2) across six different symptom and functioning domains using a variety of valid and objective measures. A total of 19 outcome measures spanned six domains: (1) ADHD symptoms: inattention and hyperactivity-impulsivity subscales of parent- and teacher-completed SNAP ratings (an acronym denoting the names of the instruments developers);³¹ (2) oppositional/aggressive symptoms: parent and teacher SNAP oppositional defiant disorder (SNAP ODD) subscale; (3) social skills: parent- and teacher-completed subscale from the Social Skills Rating System (SSRS);³² (4) internalizing symptoms (anxiety and depression): internalizing subscale from parent- and teacher-completed SSRS³² and children's self-ratings on the Multidimensional Anxiety Scale for Children (MASC);³³ (5) parent-child relations: two composited scales from the Parent-Child Relationship Questionnaire; and (6) academic achievement: three subscales from the Wechsler Individual Achievement Test (WIAT)³⁴ (reading, math, spelling). These measures show acceptable psychometric properties and are reviewed extensively (see Hinshaw and colleagues¹¹ for extensive description of all assessments). Objective measures of videotaped parent-child interactions are currently being analyzed.

RESULTS

The overall 14-month findings are reviewed below, with comparisons of the outcomes across the four treatment groups, based on the original five questions outlined at the beginning of this article: (1) which treatment(s) work best for each type of outcome; (2) how do optimal (Multimodal Treatment of ADHD [MTA]-delivered) treatments compare with community treatments; (3) which treatments work best

for which children (treatment moderators with the goal of eventually matching patients to treatments); (4) why do treatments work (treatment mediators), and (5) what proportion of children were normalized by each of the treatment modalities.

Question 1: Which Treatments Work Best for Each Type of Outcome?

ADHD Symptom Outcomes. Findings from the intent-to-treat analyses are outlined in detail in two publications.^{6,7} These outcomes are presented in graphical form in Figure 2. In general, these analyses indicated that the combination (Comb) and medication management (MedMgt) interventions did not differ from each other in any clinically or statistically significant fashion in the degree of improvement in core attention-deficit hyperactivity disorder (ADHD) symptoms, whether inattention, hyperactivity-impulsivity, or overall ADHD symptom ratings. In addition, analogous proportions of children in these two medication-groups (Comb, MedMgt) no longer met full criteria for ADHD at study endpoint (90% and 88%, respectively). In sharp contrast to the generally equivalent results in comparisons *between* Comb and MedMgt treatments, Comb and MedMgt were both clinically and statistically superior to behavioral treatment (Beh) and community care (CC) *for ADHD outcomes*, with effect sizes generally 0.5 to 0.6¹⁵ in terms of their degree of clinical superiority (generally considered a moderate effect). Beh and CC subjects did not differ from each other on any ADHD outcome measures.

Other Functioning Outcomes. For outcomes other than ADHD symptoms (oppositional/aggressive symptoms, internalizing symptoms, social skills, parent-child relations, and academic functioning), a different pattern of findings emerged (Fig. 3). For these analyses, the three active MTA-delivered treatments rarely differed from each other. In addition, only the Comb intervention fairly consistently showed evidence of statistical superiority to the CC condition. In several instances, Comb proved superior to Beh (14-month academic functioning: Wechsler Individual Achievement Test [WIAT] reading scores, parent-reported internalizing [anxiety-depression] ratings, parent-reported oppositional/aggressive symptoms), whereas MedMgt subjects usually scored in between both groups, showing no significant differences from either of the other two MTA treatments. For these functioning outcomes, it is important to note that the relative advantages of the Comb intervention over the other interventions—though adjudged to be real—was small, with overall effect sizes of 0.26 to 0.28.^{14,15} Thus, statistical testing between Comb and the two other MTA-treated groups often failed to show significant differences, despite the fact that it usually placed first, showing numerical superiority over other modalities for 12 of 19 outcome measures. By way of comparison, MedMgt, Beh, and CC each placed first—4, 2, and 1 times each, respectively. But because the original design and sample sizes selected for the study were based on 80% power to detect effect sizes of 0.4 or greater, smaller effects (e.g., .26 to .28, the apparent difference between Comb and

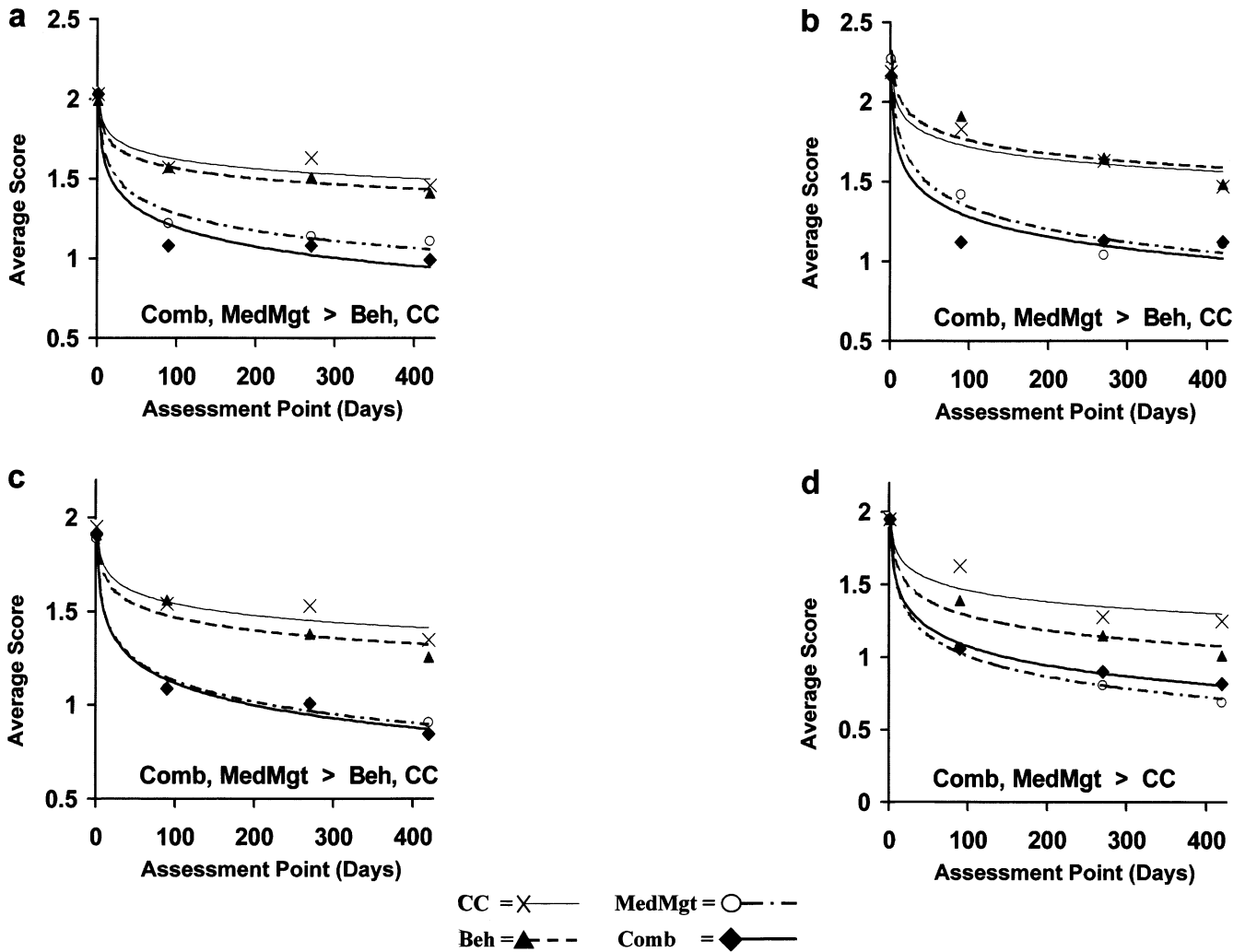


Figure 2. MTA treatment effects over 14 months on ADHD symptom outcomes. Parent- and teacher-rated SNAP inattention (A and B, respectively) and parent- and teacher-rated SNAP hyperactive-impulsive symptoms (C and D, respectively). Symbols represent mean scores for the four groups at the study’s assessment points (baseline, 3 months, study mid-point, and end-point): combined treatments (Comb), ◆; medication management (MedMgt), ○; behavioral treatment (Beh), ▲; and community care (CC), ×. Symbols overlap at several time points (particularly at baseline). Thus four symbols may not be apparent at every time point. Lines for each of the four groups represent the best-fitting rate of change curves based on random regression analyses. For each graph, results of six Bonferroni-protected pairwise comparisons are shown just below the plotted lines, as seen in A, “Comb, MedMgt > Beh, CC.” This short-hand designation indicates that Comb and MedMgt were both statistically superior to Beh and CC (denoted by the > symbol). Likewise, the comma (,) between Comb and MedMgt indicates that these two groups did not differ statistically from each other, just as Beh and CC did not differ from each other.

MedMgt) would not be discernible by traditional methods, particularly after Bonferroni corrections for multiple comparisons. Thus, caution is warranted to avoid premature and inappropriate conclusions that the Comb intervention did not offer anything over and above MedMgt, or that Comb and MedMgt did not offer anything over and above Beh, for these non-ADHD functioning outcomes.

As one means of addressing the issue of *overall outcomes* (combining *both* ADHD symptoms *and* other functioning domains), the authors conducted secondary analyses to explore the utility of a single, statistically derived composite measure of treatment outcome for the MTA trial.¹⁴ Total scores from 25 baseline assessment measures were analyzed by principal components analysis, and a composite was created from the sum of 17 of the standardized scores

retained by the Varimax rotated factor analysis. The factor analysis produced two source factors from parents and teachers. A composite of these measures was internally consistent (alpha = 0.85) and reliable (baseline to 3-months test-retest = 0.86). Using this approach, Comb was significantly better than all other treatments, with effect sizes ranging from small (0.28 for comparison to MedMgt) to moderately large (0.70 for comparison with CC).

Question 2: What Are the Benefits of State-of-the-Art (MTA-Delivered) Treatments versus Treatments as Delivered in the Community?

MTA-delivered Treatments versus Community Care. These analyses revealed that Comb and MedMgt were

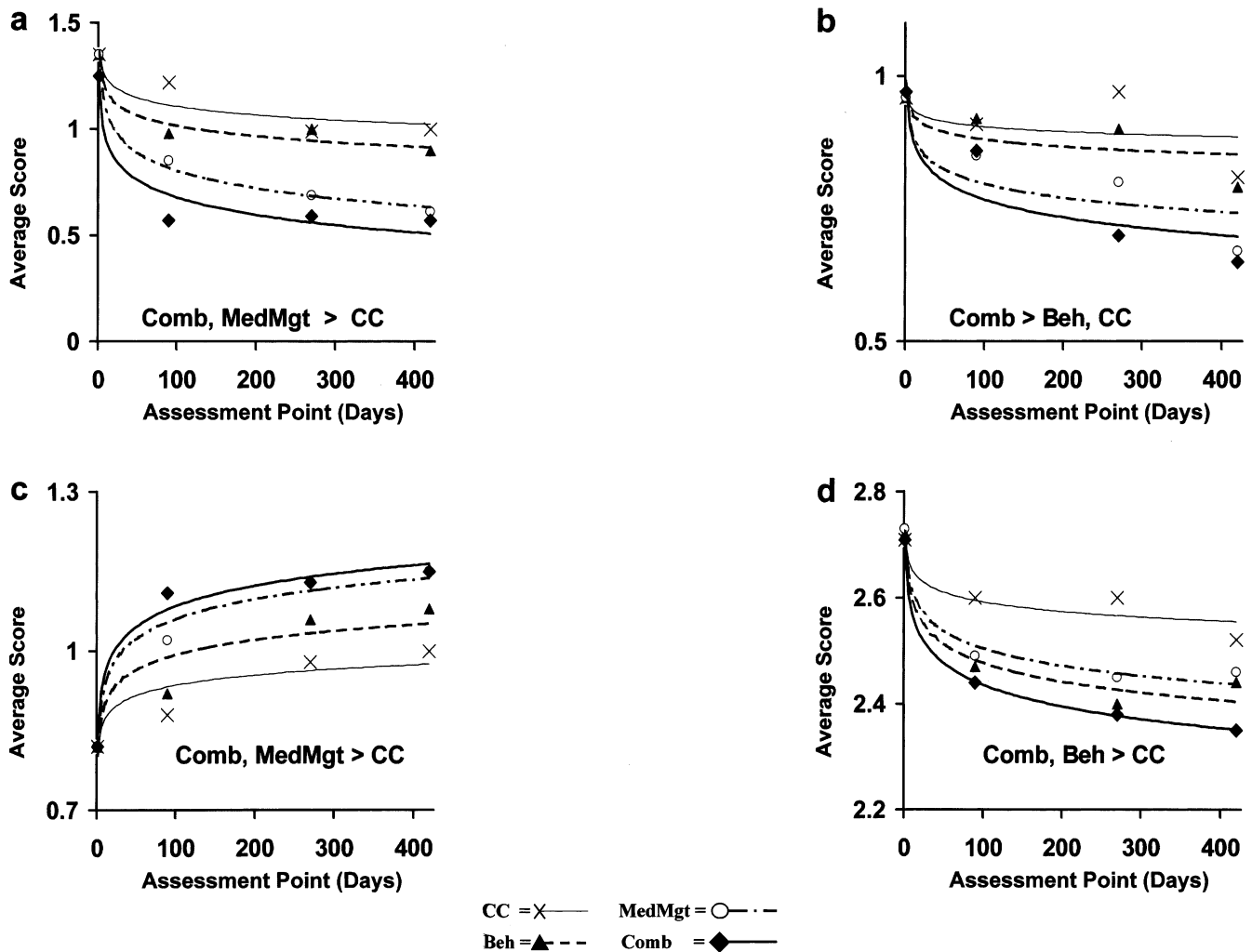


Figure 3. MTA treatment effects over 14 months on functioning outcomes. (A) Teacher-rated SNAP oppositional defiant disorder and aggression symptoms; (B) parent-rated anxiety symptoms; (C) teacher-rated social skills; and (D) parent-rated parent-child arguing. Symbols represent mean scores for the four groups at the study's assessment points (baseline, 3 months, study mid-point, and end-point): Comb, ◆; MedMgt, ○; Beh, ▲; and CC, ×. Symbols overlap at several time points (particularly at baseline). Thus four symbols may not be apparent at every time point. Lines for each of the four groups represent the best-fitting rate of change curves based on random regression analyses. For each graph, results of six Bonferroni-protected pairwise comparisons are shown just below the plotted lines, as seen in A, "Comb, MedMgt > CC." This short-hand designation indicates that Comb and MedMgt were both statistically superior to CC (denoted by the > symbol). Likewise, the comma (,) between Comb and MedMgt indicates that these two groups did not differ statistically from each other. In addition, Beh is not listed because it did not differ from any of the other three groups.

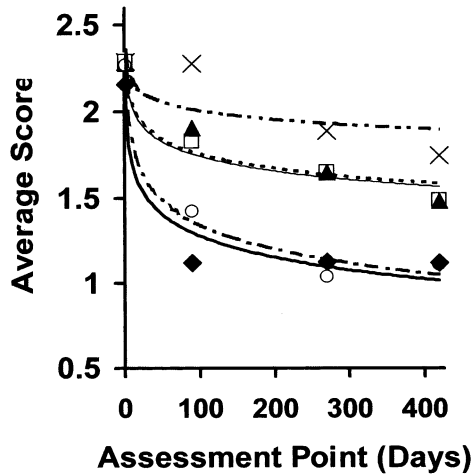
generally superior to CC for parent- and teacher-reported ADHD symptoms, whereas Beh was not. In non-ADHD domains, MedMgt and Beh were superior to CC on one domain each (teacher-reported social skills and one measure of parent-child relations, respectively). In contrast, Comb was significantly superior to CC on all five non-ADHD domains of functioning (parent-reported oppositional/aggressive behaviors, internalizing symptoms, teacher-reported social skills, parent-child relations, and WIAT reading achievement scores).

Comb and MedMgt were generally quite superior to CC even though 68% of CC subjects were also treated with medication. However, it is noteworthy that whereas MTA-treated subjects received medication on a three-times-daily regimen (actual average: 2.9 methylphenidate doses/day),

CC-medication-treated subjects received only twice-daily dosing (average: 2.1 doses/day). Methylphenidate doses were generally higher for MTA-treated versus CC-treated subjects (32.8 mg vs 18.7 mg/day, respectively). Likewise, MTA-treated subjects' medication visits were of longer duration than CC subjects' medication visits (30 min vs 18 min) and much more frequent (8.8 vs 2.3 visits/year).³⁵ Other differences included monthly phone contacts made by the pharmacotherapists to the teachers to get information and feedback to guide medication adjustments. These components may have enhanced the effectiveness of MTA medication management over medication treatments provided in the CC group. Figure 4 shows the random regression analysis for one outcome, teacher reported inattention symptoms, and CC subjects are broken out,

**Key Differences,
MedMgt vs. CC:**

- Initial Titration**
- Dose**
- Dose Frequency**
- #Visits/year**
- Length of Visits**
- Contact w/schools**



x — = CC (Not Medicated)
 □ — = CC (Medicated)
 ▲ - - = Beh
 ○ - - = MedMgt
 ◆ — = Comb

Figure 4. MTA treatment effects over 14 months on teacher-rated inattention. The community care (CC) group is separated into two groups based on whether the families sought out and obtained any medication treatment for the child during the study period. Mean attention scores at each time point for CC children who were or were not treated with ADHD medications during the study are denoted by the □ and × symbols, respectively. The following symbols represent mean scores at study assessment points for the other three groups treated by MTA staff: Comb, ◆; MedMgt, ○; Beh, ▲. Key differences explaining why MTA-delivered medication may have been more effective than CC-delivered medication are listed on the left side of the figure.

allowing visual inspection of those who did or did not receive medication during the 14-month period.

**Question 3: For Whom Do Treatments Work?
Matching Patients to Treatments**

Based on theoretical considerations and prior research, a wide range of variables was explored vis-a-vis their potential impact as *moderators* of treatment outcomes. These variables included age, gender, ethnicity, socio-economic status and parental education, and the presence/absence of specific comorbidities. Moderator variables are those factors that *modify* the overall intent-to-treat random regression analyses described above. In other words, despite these overall findings from these analyses, were there some subjects for whom the overall findings did not apply? For example, though Comb and MedMgt were generally superior to Beh and CC for ADHD symptoms, did these average findings apply equally to boys and girls? These findings are reported in detail elsewhere⁷ and indicated that only two factors showed evidence of a meaningful impact: (1) the presence of a comorbid anxiety disorder (parent-reported) at baseline and (2) family status of being on public assistance or welfare.

For both of these subgroups of families, two major differences emerged. First, Beh appeared more effective than in the primary analyses, such that it diverged from CC subjects and appeared similar in magnitude and direction of effects to MedMgt. Second, Comb diverged from MedMgt, such that substantially greater gains accrued to Comb versus MedMgt subjects in the moderator subgroups. Outcomes apparently affected by these moderators included parent-reported hyperactivity and inattention, parent-child relations, and teacher social skills.

Said another way, for subjects with a baseline comorbid anxiety disorder or on public assistance, Comb appeared to offer meaningful advantages over MedMgt for parent-reported ADHD symptoms, teacher-reported social skills, and parent-child relations. And in contrast to the primary analyses, Beh appeared quite comparable to MedMgt for these same outcomes for these particular subgroups of subjects.⁷

Given the multiple comorbid subgroups in the MTA sample, most notably anxiety and disruptive behavior disorders (oppositional defiant disorder or conduct disorder together totaled over 54% of the sample), additional analyses were done to compare four subgroups of children, based on the presence/absence of an anxiety disorder and the presence/absence of a disruptive behavior disorder. For these four subgroups (ADHD-only, ADHD+Anxiety-only, ADHD+Disruptive-only, and ADHD+Anxiety+Disruptive), findings indicated that these comorbid groupings yielded meaningful information that might be used to guide treatment considerations. As seen in the graphical presentation of effect sizes in Figure 5, ADHD-only and ADHD+Disruptive-only subjects achieved meaningful benefits over CC subjects only if they received MedMgt or Comb interventions. For these children, effect sizes for Beh over and above CC were essentially nil. However, ADHD+Anxiety-only subjects responded well and similarly to all MTA-delivered interventions. Moreover, doubly-comorbid (ADHD+Anxiety+Disruptive) subjects clearly showed the greatest benefits for the Comb intervention.

Because the subgroup of ADHD+Anxiety+Disruptive subjects constituted only 24.7% of the 579 MTA subjects and because they showed greater clinical benefits via Comb (vs MedMgt) interventions, it is possible that a more cost-

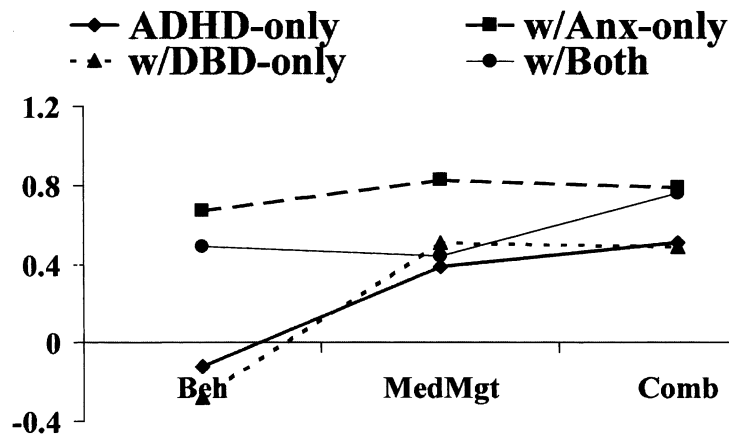


Figure 5. Effect sizes of MTA treatments on parent-rated ADHD symptoms as a function of four comorbidity patterns: ADHD-only, ADHD+Anxiety-only, ADHD+DBD-only (disruptive behavior disorder-only), and ADHD+Anxiety+DBD (ADHD w/Both). Effect sizes for the CC group are not shown because, by definition, they are set at zero. All other treatment groups must show greater improvement than CC subjects to show a positive effect (above the x axis). (Jensen et al, 2001)²⁴

effective strategy would be to use Comb interventions for this particular needy and severely impaired subgroup. Similarly, in terms of matching patients to treatments, clinicians might consider that ADHD+Anxiety-only subjects (14.0% of the overall sample) respond equally well to MedMgt and Beh interventions. This finding may provide them information to guide them in offering an evidence-based, similarly efficacious option to parents and families who prefer not to use medication.

Question 4: Why and How Did the MTA Treatments Work?

Analyses of factors that *mediate* treatment outcomes are necessarily post hoc and are not protected by randomization. Thus, factors such as compliance/attendance, medication dose, relationship with the therapist (therapeutic alliance), parental attitudes/beliefs about the treatment, and change in parenting practices over the course of study are all possible explanations of why a given treatment may have worked, either within or across treatment arms. But because such factors all occur *after* randomization, it cannot be known with certainty that the particular factor has caused the particular effect. To demonstrate causality, additional studies that attempt to systematically vary those factors via random assignment are required.

Nonetheless, mediator (after randomization) analyses of the MTA study data can either tend to support (or not) overall study findings. *If* analyses suggest the presence of possibly important treatment mediators, additional studies would then be warranted to explore, define, and refine the active ingredients of an effective treatment. If, for example, compliance/attendance is related to specific outcomes, that finding would suggest that either failing to get an adequate dose (by not complying) or some other psychological factor externally observed as a noncompliant attitude would be a possible explanatory factor. Finding such effects, future studies might then randomly assign and compare subjects on the basis of different doses or the presence or absence of specific psychological factors, or they might even experi-

mentally induce a particular psychological state in an attempt to better control for these nonrandom factors in the original study design.

With these cautions in mind, MTA investigators examined a number of possible treatment mediators: overall treatment compliance/session attendance,⁷ characteristics of the medication treatment,³⁵ cognitive factors in the parent,¹⁹ use of behavioral methods at home (William Pelham et al, unpublished data, 2000), and changes in parenting practices over the course of the study.^{18,20} Other factors, such as therapeutic alliance, are planned for future analyses as well, but have not begun.

Initial analyses exploring treatment mediators examined the impact of attendance and apparent compliance with the treatment protocol. These analyses indicated that attendance at regular medication visits, where pills were counted and new prescriptions were provided on a monthly basis, was strongly related to treatment outcomes. Those subjects not taking medication or refusing medication treatment altogether show significantly inferior outcomes on many, though not all, domains.⁷ Similarly, several MTA investigators^{7,35} have explored the impact of medication compliance and the optimal use of medication, within both the MedMgt and the CC groups. These analyses confirmed original results, namely that high quality medication practices were likely important factors explaining a substantial portion of the successful outcomes in MTA medication-treated subjects. Of interest, by the study end, 73.4% of MedMgt and Comb subjects were maintained on methylphenidate, with an additional 10.4% on dextroamphetamine, 1.4% on pemoline, 1% on imipramine, 0.3% on bupropion, 0.3% on haloperidol, and only 13.1% on no medication whatsoever. In contrast, only 67.4% of CC subjects received some form of ADHD medications (usually methylphenidate in over 80% of these cases).

To explore potential psychological processes underlying treatment outcomes, Hinshaw and colleagues¹⁸ conducted mediator analyses to determine whether changes in self-reported parenting practices were corre-

lated with the effects of behavioral, medication, or combination treatments on teacher-reported outcomes (disruptive behavior, social skills, internalizing symptoms). Findings indicated that Comb families showing the greatest reductions in negative/ineffective parenting practices also showed in parallel the greatest teacher-reported benefits of treatment vis-a-vis regular community care. Thus, the success of combination treatment for school-related outcomes appeared closely related to reductions in negative and ineffective parenting practices at home. In fact, children in the Comb condition whose parents showed substantial improvement in negative/ineffective discipline were rated by their teachers as normalized in terms of rates of disruptive (ADHD and aggressive) symptomatology at school. Of note, similar reductions in negative parenting practices among Beh-treated children did *not* yield appreciably different success rates, suggesting that positive changes in parenting practices could result in meaningful school changes if those same children also had the benefit of medication during the school day. Stated differently, for medication to exert its optimal effect in school, parents had to change their home disciplinary practices.

Question 5: What is the Overall Impact of the Various Treatments in Terms of Proportions of Children Normalized?

To supplement the primary analyses, MTA investigators developed and analyzed a qualitative outcome measure of success to explore the study’s clinical relevance and practical significance.¹⁵ Thus, the end-of-treatment status of each subject was evaluated based on a combined overall rating completed by both parents and teachers of DSM-IV symptoms of ADHD and oppositional defiant disorder (ODD), using the SNAP scale developed by Swanson et al.^{15,31} This rating scale allowed parents and teachers to score each symptom as 0 (none), 1 (Just a

Little), 2 (Moderate), or 3 (A Lot). All items were tallied and then divided by the mean number of items to yield an average item response, and then parents and teachers scores were averaged. A low overall symptom-severity rating (less than 1) was met by 88% of a sample of comparison children drawn from the children’s classrooms. This threshold was specified as a criterion for successful treatment, i.e., normal. Logistic regression analyses were used to compare success rates for the treatments. Results showed that the success rates for MTA treatments mirrored the primary results, with the following proportions of children being normalized in each of the groups: Comb, 68%; MedMgt, 56%; Beh, 34%; and CC, 25%. These findings should be viewed in the context of the symptom scores of children drawn from the same classrooms, 88% of whom were in the normal range, and in view of the fact that none of the MTA children scored in the normal range before randomization (Fig. 6).

These secondary analyses suggest what clinicians should expect if MTA treatment algorithms are adopted to replace the usual treatment of children with ADHD: (1) adopting the MTA MedMgt approaches may as much as double the success rate in most settings, and (2) adopting Comb treatment interventions may modestly increase the success rate further, matching the small effect size of the Comb versus MedMgt contrast reported earlier, although the extent of this increase is likely to vary across settings. In contrast, substituting the Beh-only approaches for the usual treatment may increase success rates in some settings but decrease it in other settings.¹⁵

DISCUSSION

As discussed in the introduction, findings from the Multimodal Treatment of ADHD (MTA) study may have considerable implications for primary care providers. Our findings are discussed in the order of the original five questions.

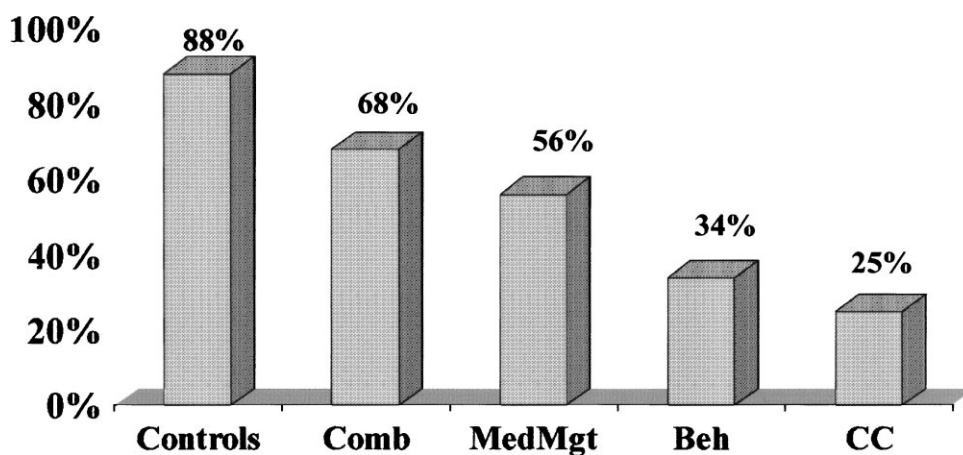


Figure 6. Percent “normalized” at 14-month endpoint across the four MTA groups. The classroom controls were drawn from the same classroom cohorts as MTA children were originally, and were age- and gender-matched to assure comparability with MTA subjects. The “normalization” indicator was based on a composite of parent and teacher ratings, with the overall symptom cutoff required to be indicative of “little or no” symptoms (Swanson et al, 2001).¹⁵

Question 1: Which Treatments Work Best for Each Type of Outcome?

All four groups showed marked reductions in symptoms over time, with significant differences among them in terms of the magnitude of change. Combination (Comb) and medication management (MedMgt) treatments were clinically and statistically superior to behavioral treatment (Beh) and community care (CC) in reducing children's attention-deficit hyperactivity disorder (ADHD) symptoms. The combination of behavioral intervention and stimulant medication—multimodal treatment, the current "gold standard" for ADHD interventions—yielded no statistically greater benefits than MedMgt for core ADHD symptoms. However, this "null" effect may have been due to imprecise measurement and the lack of power to find small effects, as evidenced by secondary analyses based either on a composite score or cross-setting summary measures.^{14,15} When precision of measurement was thereby increased, a statistically significant (though small) increment of Comb over MedMgt was detected.

For other areas of function (oppositional/aggressive behaviors, internalizing symptoms, social skills, parent-child relations, and academic achievement) few differences among MTA treatments were noted, and when found they were generally of small magnitude. In fact, Comb, MedMgt, and Beh never differed significantly among themselves, with three exceptions (Comb > Beh for parent-reported internalizing problems and oppositional/aggressive symptoms and for WIAT reading achievement). Nevertheless, Comb produced significantly greater effects than CC for several secondary and functional domains, whereas MedMgt and Beh did not produce effects greater than CC for these same domains.

Thus, the MTA extends the findings of previous studies demonstrating short-term, robust efficacy of medication management out to a period of 14 months, showing that these effects continue during longer-term treatment. In contrast to frequently expressed concerns, Comb and MedMgt children tolerated medication well, including third doses given in the afternoon. The relative improvements attributed to medication management also parallel findings from other longer-duration stimulant trials.^{36–38}

Whether there is greater value for multimodal treatments for ADHD depends upon which intervention is considered as the comparison. If one assumes that a behavioral intervention should always be used as the first line ADHD treatment (often the preference for many parents and the practice in many European countries²⁸) and that the possibly greater benefits of combined treatment should be determined, then Comb appears to offer a great deal of benefit over Beh alone. But if one provides carefully monitored medication treatment similar to that used in the MTA as the first line of intervention, results presented here suggest that many (but not all) treated children may not require intensive behavioral interventions, at least in terms of core symptoms of ADHD. Starting with Beh may have advantages in patient and family acceptance; the consumer satisfaction ratings by parents and teachers at the end of

MTA treatment showed significantly better acceptance of Beh and Comb than of MedMgt alone.

Question 2: What Are the Benefits of State-of-Art (MTA-delivered) Treatments versus Treatments as Delivered in the Community?

With respect to comparisons of MTA treatments to CC, Comb and MedMgt fared substantially better than CC on most ADHD outcome measures, whereas Beh did not. Comb also fared significantly better than CC for all 5 non-ADHD domains (parent-reported oppositional/aggressive symptoms, parent-reported internalizing problems, teacher-reported social skills, parent-child relations, and reading achievement) according to at least one informant. In contrast, MedMgt and Beh each fared better than CC in one non-ADHD domain only (teacher-rated social skills and parent-child relations, respectively).

The authors' finding that MTA treatments (most notably Comb) offered benefits over CC for oppositional/aggressive behaviors, internalizing symptoms, peer interactions, parent-child relations, and reading achievement has not been previously reported in long-term studies. The differential benefits in these non-ADHD domains are consistent with the theoretical aims of multimodal approaches, however. For example, though medication is known to reduce negative peer interactions, increases in positive social behavior have been difficult to demonstrate.³⁹ Such changes might require intensive and long-term application of the behavioral components of combined treatments, such as those provided in the MTA's Summer Treatment Program and school-based interventions.²⁹

Although Comb and MedMgt were generally superior to CC, CC treatments also usually included medication. Thus, it is somewhat remarkable how much more effective the MTA medication approaches were compared with CC-delivered medication. Yet, analyses conducted by Greenhill and colleagues³⁵ suggest that this finding is likely to be due in large part to the MTA medication approach, which used three-times-daily dosing, as well as higher, yet carefully monitored, daily doses to maximize positive effects and minimize side effects. In addition, the substantially greater adherence to the medication regimen shown by MedMgt and Comb subjects, as well as the regular contact between providers and teachers that was maintained for these families, may have conveyed substantial benefits to the MTA's medication treatment regimen over CC-delivered medications.

These findings may have considerable import for primary care providers, suggesting that physicians in the community (CC subjects) tend to use lower than optimal doses and twice daily, rather than three-times daily, dosing. In the authors' experience, providers and parents alike may be sometimes afraid of the medication and too often settle for a less than a complete response (full normalization). The monthly medication monitoring and follow-up visits employed by the MTA pharmacotherapists stand in further contrast to the twice-yearly physician visits for medication monitoring provided to families in the CC group. Given this lack of communication and general disconnect between

physicians and families, as well as the lack of systematic and regular feedback between physicians and teachers, problems which were documented in the ADHD Consensus Development Conference,⁵ it should not be surprising that medication approaches under typical conditions do not yield optimal outcomes, perhaps because of very concrete and practical problems such as compliance and under- or overdosing. To the extent that routine ADHD treatment practices could more effectively address such problems, better outcomes seem likely.

Question 3: For Whom Do Treatments Work? Matching Patients to Treatments

Findings from the intent-to-treat moderator analyses⁷ and further subgroup analyses^{22,25} suggest that some children do in fact show a preferential benefit from specific treatments in a pattern different from the overall pattern of findings. Parent-reported anxiety disorder as a comorbidity with ADHD may have considerable impact on children's treatment responses, depending upon whether the anxiety occurs with or without a disruptive disorder such as ODD or conduct disorder (CD). A simple rule of thumb that summarizes these findings suggests that if a child presents with an ADHD/Anxiety-only profile, *all* interventions (other than routine community care) are likely to be effective. If a child presents with ADHD-only or ADHD/CD-ODD, treatments with medication appear especially indicated, and Beh-alone strategies may be contraindicated. And finally, if a child presents with ADHD/Anxiety/CD-ODD, Comb interventions may offer substantial advantages over other treatments, particularly in overall impairment and functioning outcomes. By way of caution, however, additional research is needed to further examine the validity of parent-reported anxiety disorders in children, because these conditions were usually not similarly reported by the children. Thus, further analyses by March and colleagues²² suggest that parent-reported anxiety disorders may in some instances reflect components of oppositional behavior with negative affectivity in the parent-child relationship, in addition to or in place of anxiety symptoms.

Regardless, findings suggest that more precise matching of patients to treatment using patients' comorbidity profiles may mitigate initial clinical uncertainty, reduce the number of therapeutic trials until a workable treatment is found, and yield larger treatment gains for specific patients. Such considerations highlight the need for careful clinical assessments of children presenting with ADHD, because the ADHD diagnosis alone may not be sufficient to determine optimal treatments for specific children. These findings argue against a one-size-fits-all approach to treatment. Of course, these results cannot necessarily be generalized beyond the ADHD-Combined type; other ADHD subtypes (e.g., inattentive subtype) may warrant somewhat different treatments. Moreover, replication of these findings in new samples is very much needed.

Unanswered to date in the MTA study are important questions concerning behavioral and combined treatments for ADHD. What are the relative costs of the various treatments, and how do cost-benefit ratios differ for various

subgroups based on their comorbidity and severity profiles? Are there some children for whom medication management is no longer necessary, and if so, why does this occur? Might the behavioral component of combined treatment allow some children to be successfully weaned off medication? Will findings differ as children age, such that those who have learned increased skills via behavioral interventions eventually function better than those receiving only medication? Follow-up study of MTA subjects past 14 months (currently underway) will address some of these critical questions. In addition, the MTA study cannot address whether initial treatment with behavioral interventions may afford reductions in dosage levels once medication treatment is initiated, even though preliminary findings do suggest that Comb-treated (vs MedMgt-treated) children were maintained on lower total daily stimulant doses by 14-month study endpoints.¹⁷

Question 4: Why and How Did the MTA Treatments Work?

As noted above, the actual quality of and compliance with the medication treatments are likely important factors in the effectiveness of the MTA treatment strategies. Yet medication alone is not likely to tell the full story. Behavioral treatments may help families actively cope with their child's disorder and make the necessary life accommodations to optimize family functioning, even when such treatments are not as effective as medication in reducing children's ADHD symptoms. Indeed, 14-month endpoint analyses indicated that parent satisfaction ratings differed significantly by treatment group, with pairwise contrasts showing that treatment satisfaction scores for Comb and Beh parents were significantly superior to MedMgt parents' ratings (though not differing between themselves), suggesting that the Beh components benefited this area of family-relevant outcomes. Relatedly, further analyses suggested that actual changes in parents' attitudes and disciplinary practices accompanied evidence of increased benefits of the combined treatments,¹⁸⁻²⁰ such that the only MTA subgroup identified to date that yielded full normalization of school-based disruptive behavior patterns included families receiving Comb treatment that significantly improved their negative and ineffective discipline practices during the trial. Such factors must remain active areas of ongoing investigations in refining and improving behavioral and combined treatments.

Question 5: What is the Overall Impact of the Various Treatments on the Proportions of Children Normalized?

Findings suggest that high quality treatments may have considerable impact on restoring ADHD children to normal or near-normal functioning at home and in the classroom. Because essentially none of the ADHD children met the normal criteria that were met by 88% of comparison children drawn from the same classrooms at study outset, the notion that ADHD is just normal behavior labeled by uninformed parents or overwhelmed teachers appears not

only implausible, but preposterous. But even more importantly, substantial proportions of these children could be helped and returned to essentially normal functioning, particularly through the Comb and MedMgt interventions. To deny such children an appropriate diagnosis *and* high quality treatments cannot be defended on ethical, scientific, or pragmatic grounds. Unfortunately, given the current situation in which constraints are often placed on the amount of time available within busy pediatric practices and school classrooms to diagnose, treat, follow-up, and coordinate interventions for these children, substantial changes in schools and health systems appear necessary. Further studies of the costs and cost-effectiveness of the various interventions, both in terms of short- and long-term outcomes, as well as for specific subgroups of especially impaired ADHD children (such as those doubly comorbid with ADHD, anxiety disorders, and CD/ODD), are planned. Coupled with the current long-term follow-up of the MTA sample, such data may be useful to demonstrate the need and pragmatic benefits of intensive,

high quality interventions and careful follow-up with these children.

Summary

The absence of any *site x treatment x time* interactions suggests that both the pharmacological and behavioral treatments could be delivered with fidelity across six very different clinical settings. However, the utility of these treatments will ultimately be determined by the degree to which they are feasible, transportable, and affordable in "real world" settings—topics for future research. In the interim, however, the MTA study, by virtue of its size, scope, and length, its parallel-groups design, its explicit use of manualized, evidence-based treatments, its high degree of compliance across arms and over the course of the study, and its comprehensive range of outcome assessments, sets an important benchmark for future trials testing new treatments for childhood ADHD.

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