

Moderators and Mediators of Treatment Response for Children With Attention-Deficit/Hyperactivity Disorder

The Multimodal Treatment Study of Children With Attention-Deficit/Hyperactivity Disorder

The MTA Cooperative Group

Background: Intent-to-treat analyses of the study revealed that medication management, alone or combined with intensive behavioral treatment, was superior to behavioral treatment and community care in reducing attention-deficit/hyperactivity disorder (ADHD) symptoms; but only combined treatment showed consistently greater benefit than community care across other outcome domains (disruptive and internalizing symptoms, achievement, parent-child relations, and social skills). We examine response patterns in subgroups defined by baseline variables (moderators) or variables related to treatment implementation (mediators).

Methods: We reconducted random-effects regression (RR) analyses, adding factors defined by moderators (sex, prior medication use, comorbid disruptive or anxiety disorder, and public assistance) and a mediator (treatment acceptance/attendance).

Results: Study outcomes (N = 579) were upheld in most moderator subgroups (boys and girls, children with and without prior medication, children with and without comorbid disruptive disorders). Comorbid anxiety disorder did moderate outcome; in participants without anxiety, results paralleled intent-to-treat findings. For those

with anxiety disorders, however, behavioral treatment yielded significantly better outcomes than community care (and was no longer statistically different from medication management and combined treatment) regarding ADHD-related and internalizing symptoms. In families receiving public assistance, medication management yielded decreased closeness in parent-child interactions, and combined treatment yielded relatively greater benefits for teacher-reported social skills. In families with high treatment acceptance/attendance, intent-to-treat results were upheld. Acceptance/attendance was particularly important for medication treatments. Finally, two thirds of children given community care received stimulants. Behavioral treatment did not significantly differ from, but medication management was superior to, this subgroup.

Conclusions: Exploratory analyses revealed that our study (the Multimodal Treatment Study of Children With Attention-Deficit/Hyperactivity Disorder [MTA]) results were confirmed across most baseline variables and treatment acceptance/attendance. In children with ADHD plus anxiety, behavioral treatment surpassed community care and approached medication-based treatments regarding parent-reported ADHD symptoms.

Arch Gen Psychiatry. 1999;56:1088-1096

OUR STUDY (the Multimodal Treatment Study of Children With Attention-Deficit/Hyperactivity Disorder [MTA])¹⁻⁴ was designed to address questions about separate and combined effects of pharmacologic and behavioral treatment for children with attention-deficit/hyperactivity disorder (ADHD) throughout a 14-month, multisite, randomized clinical trial. In the companion article,⁵ intent-to-treat analyses revealed that, for the outcome domain of ADHD symptoms, medication management resulted in better outcome than intensive behavioral treatment, combined treatment yielded better outcome than behavioral treatment but equivalent

outcome to medication management, and medication management and combined treatment (but not behavioral treatment)

*See also pages
1073 and 1097*

proved superior to community care. (In the method articles for this study, treatment assignments were referred to as *medication*, *psychosocial treatment*, *combined treatment*, and *community-treatment/assessment and referral*. To reflect more accurately the actual treatments, we have changed the terminology for all outcome articles to *medication management*, *behavioral treatment*, *combined treatment*, and

A list of the collaborators and investigators for this study appears on page 1095.

SUBJECTS, MATERIALS, AND METHODS

SUBJECTS AND STUDY DESIGN

As described in the companion report,⁵ the 6-site study randomly assigned 579 children diagnosed as having ADHD Combined Type, aged 7 to 9.9 years, to medication management, behavioral treatment, combination treatment, or community care for 14 months of treatment. The 3 active interventions (medication management, behavioral treatment, and combined treatment) were manualized, with careful monitoring of treatment fidelity performed throughout the intervention period. Multisource and multidomain assessments were performed at baseline, 3 months and 9 months into treatment, and at the end of treatment (14 months).

MEASURES

Moderator Variables

Girls constituted 20% of our sample. Nearly a third of the sample (31%) had been receiving psychoactive medication prior to our study.⁴ Oppositional-defiant disorder and CD diagnoses were based on parent interview with the Diagnostic Interview Schedule for Children 3.0⁴: DSM-IV ODD was present in 40% of the sample and CD in an additional 14%. Because DSM-IV versions of the Diagnostic Interview Schedule for Children for internalizing disorders were not available at the beginning of the study, we ascertained anxiety disorders via parent interview with the Diagnostic Interview Schedule for Children 2.3.¹⁷ Thirty-four percent displayed any DSM-III-R anxiety disorder or combination of anxiety disorders, disregarding simple phobia alone. Finally, from parent report, 19% of those in the sample were receiving welfare, public assistance, or Supplemental Security Income.

Mediator Variable

We defined an initial mediator variable for the active treatments on the basis of *as-intended* vs *below-intended* acceptance of treatment assignment and session attendance.^{15,16} Even though acceptance and attendance cannot guarantee implementation, they are necessary preconditions. We attempted to make our definitions parallel across treatments, but because of differences in treatment protocols, they were not identical.

For medication management, *as intended* was defined by all of the following: acceptance of the treatment after assignment, family attendance for least 80% of the monthly medication visits, and prescription written and delivered to family at those visits. *Below intended* incorporated refusal to participate, stopping treatment, moving, or dropping out prior to 80% of the visits, or continuing but with attendance below cutoff. For behavioral treatment, *as intended* was defined by all of the following: acceptance of treatment, parental attendance for at least 75% for the group parent training sessions (individual sessions were not counted), child attendance for at least 75% of the days of the summer treatment program, and child and paraprofessional both present in classroom for 75% of the intended days (therapist consultations with teacher were not counted). *Below intended* included refusal of any treatment components, low attendance, or discontinuation before achieving cutoffs. For combined treatment, *as in-*

tended indicated meeting acceptance/attendance criteria for both the medication and behavioral components.

Outcome Measures

We analyzed 14 outcome measures from the 19 included in the companion article (these measures were those loading highest on factor analyses of our battery).⁵ Because random-effects regression (RR) analyses mandate at least 3 repeated data points, we excluded 4 measures with only 2 assessment points (peer sociometrics and reading, mathematics, and spelling achievement) as well as the extremely low base-rate oppositional-aggressive code from classroom observations. For the domain of ADHD symptoms, measures were parent and teacher ratings from the SNAP (an acronym denoting the names of the instrument's developers) inattention and hyperactivity-impulsivity scales¹⁸ plus behavior observations from the Classroom Observation Code¹⁹ (composite of interference, off task, and gross motor movement). For oppositional/aggressive symptoms, measures were parent and teacher ratings from the SNAP ODD scale. For internalizing symptoms, measures were parent and teacher ratings from the Social Skills Rating System (SSRS) internalizing scale²⁰ and child self-report ratings from the Multidimensional Anxiety Scale for Children (total score).^{21,22} For parent-child relations, measures were parent ratings on 2 scales from the Parent-Child Relationship Questionnaire²³: power assertion (negative interchanges) and personal closeness (eg, positive parenting, nurturance, companionship, prosocial behavior). For peer relations/social skills, measures were parent and teacher ratings from the SSRS total social skills scale (eg, cooperation, prosocial behavior, peer acceptance).

DATA ANALYSES

Because they are present prior to randomization, proposed moderator variables in clinical trials should be uncorrelated with treatment assignment, but proposed mediator variables, occurring after treatment, may be associated with treatment condition.⁶ We thus ascertained whether our acceptance/attendance mediator was associated with assignment to treatment. For each candidate moderator or mediator, we reapplied the RR model used in the intent-to-treat analysis,⁵ now including this variable both as a main effect and in interaction. In the presence of a significant overall interaction of the variable with treatment condition on the trajectory of response ($P < .05$), we attempted to localize the source of the effect using analytic and graphic methods. A significant overall interaction indicates that the effect of treatment in some cells is not what would be expected from an additive effect of treatment and the moderator/mediator alone; certain treatment effects must be enhanced in one subgroup and concomitantly decreased in the other. In the presence of a significant interaction, we performed pairwise comparisons of treatment groups, examined interactions of treatment condition with time at each level of the moderator/mediator, and evaluated treatment conditions within each moderator/mediator subgroup. We regard our analyses as generating hypotheses for clinical decision making and future research rather than as confirmatory. Thus, we do not use the Bonferroni corrections that were used in the intent-to-treat analyses.

community care.) However, according to at least 1 informant, combined treatment fared significantly better than community care for all of the additional outcome domains of oppositional/aggressive symptoms, internalizing symptoms, family relationships, academic achievement, and social skills, whereas medication management and behavioral treatment fared better than community care for only 1 ancillary domain each.

Intent-to-treat analyses evaluate the average effect of treatments in the population sampled. However, subgroups defined by baseline characteristics (moderators) or by different experiences during treatment (mediators) may show different patterns of response. Moderator analyses afford understanding of which types of participants respond optimally to each intervention and may thus facilitate clinical decision making. Mediators may identify causal paths from the different treatment modalities to particular outcomes.⁶ Because the sample size does not yield sufficient statistical power to examine fully moderator- or mediator-defined subgroups and because of repeated statistical testing, we regard these analyses as exploratory.

We included a wide range of background characteristics to facilitate detection of potential moderator effects and to enhance generalizability. Based on relevant literature and to minimize statistical testing, we selected candidate moderators a priori.⁵ First, understanding of sex differences in treatment research is needed, but a lack of such differences in extant investigations dictated no specific hypotheses. Second, we reasoned that prior treatment with psychoactive medication⁴ would be associated with less-favorable outcomes in behavioral treatment. Third, because comorbidity with oppositional-defiant disorder (ODD) and conduct disorder (CD) yields noteworthy impairment (eg, discordant parent-child relations, extreme peer rejection, poor prognosis),^{7,8} we believed that such comorbidity would require combined treatment for optimal benefit. Fourth, children with ADHD and significant anxiety have shown less-favorable patterns of response to stimulants than children with ADHD and no anxiety.^{9,10} We hypothesized that this comorbidity would predict a worse response to medication management. Fifth, because impoverished families (particularly those headed by a single parent) have difficulty participating fully in psychosocial treatments,^{11,12} we examined whether familial receipt of public assistance would predict worse response to behavioral treatment.

Regarding mediators, factors related to treatment acceptance and compliance have been salient in clinical trials with ADHD populations. Initial and long-term acceptance of medication¹³ and attendance at psychosocial treatment sessions¹⁴ have been low, potentially reducing effectiveness for those who do not maintain involvement. For the active treatments (medication management, behavioral treatment, and combined treatment), we defined a core mediator variable from initial treatment acceptance plus predefined levels of session attendance,^{15,16} reasoning that if a family accepted treatment and attended, the treatment would be more likely to “take.”

RESULTS

We tested for interactions of each of our variables (5 moderators plus the acceptance/attendance mediator) with

treatment condition on the trajectory of response for the 14 dependent variables, yielding 84 (6×14) RR analyses. In 11 of these, the omnibus interaction was significant; pertinent regression slopes for each treatment condition at the 2 levels of each moderator (eg, boys vs girls) or mediator (as intended vs below intended) are found in the **Table**.

MODERATOR ANALYSES

For each of the first 3 putative moderators (sex, prior medication, and comorbid ODD/CD), only 1 of the 14 core dependent measures yielded a significant overall interaction. For sex, the interaction was significant for the SNAP parent hyperactivity/impulsivity measure ($F_{3,904} = 2.88$; $P = .04$). In boys, combined treatment and medication management were superior to community care; but for girls, only combined treatment was superior to community care. For prior medication status, the interaction was significant for parent SSRS total social skills ($F_{3,887} = 3.22$; $P = .02$). In previously medicated children, medication management was superior to community care; for the previously unmedicated, the treatments did not differ statistically. For comorbid ODD/CD, the interaction was significant for teacher SSRS total social skills ($F_{3,629} = 3.09$; $P = .03$). In comorbid children, treatment groups did not differ statistically, but for the noncomorbid subgroup, the 3 active treatments were superior to community care. Because of the isolated and near-chance nature of these effects, we propose that overall intent-to-treat results are similar for boys and girls, children previously given medication and children who were not, and those with and without comorbid disruptive disorders.

However, regarding comorbid anxiety disorder, the relevant interaction was significant for 3 outcome variables (parent SNAP hyperactivity/impulsivity: $F_{3,890} = 3.85$; $P = .009$; parent SSRS internalizing: $F_{3,864} = 5.04$; $P = .002$; and Multidimensional Anxiety Scale for Children: $F_{3,517} = 2.80$; $P = .04$). For the SNAP scale and the SSRS internalizing measure, in noncomorbid participants, combined treatment and medication management proved superior to community care; however, in participants with anxiety, the 3 active interventions (combined treatment, medication management, and behavioral treatment) did not differ statistically, all showing superiority to community care (**Figure 1** and **Figure 2**). The figures demonstrate that in participants without comorbidity, behavioral treatment showed a treatment trajectory similar to that of community care, less sharply downward in slope (indicating less improvement over time) than was evident for medication management or combined treatment; however, in children with anxious comorbidity, the behavioral treatment trajectory diverged downward from that of community care, no longer differing from those for combined treatment and medication management. Thus, relative to all other conditions, behavioral treatment showed unexpectedly strong benefit for children with ADHD and anxiety in contrast to those without the comorbidity. Also, for the SNAP hyperactivity-impulsivity measure, the specific contrast of combined treatment×medication management was sig-

Slopes for Each Subgroup of Significant Moderator and Mediator Variables*

Measure		Categorical Subgroup	Combined Treatment (n = 144)	Medication Management (n = 145)	Behavioral Treatment (n = 144)	Community Care (n = 146)
Moderator variable						
Sex	Parent SNAP (hyperactivity/impulsivity)	Male	-.175	-.179	-.102	-.087
		Female	-.172	-.108	-.104	-.105
Prior medication	Parent SSRS (total social skills)	No prior medication	.031	.018	.019	.020
		Prior medication	.023	.032	.023	.011
Comorbid ODD/CD	Teacher SSRS (total social skills)	No ODD/CD	.056	.052	.049	.013
		ODD/CD	.057	.055	.036	.040
Comorbid anxiety disorder	Parent SNAP (hyperactivity/impulsivity)	Nonanxious	-.170	-.171	-.087	-.099
		Anxious	-.188	-.156	-.126	-.057
	Parent SSRS (internalizing)	Nonanxious	-.045	-.039	.000	-.012
		Anxious	-.056	-.036	-.050	-.009
MASC (total score)	Nonanxious	-.051	-.029	-.022	-.036	
	Anxious	-.013	-.039	-.033	-.021	
Public assistance	Teacher SSRS (total social skills)	No public assistance	.052	.058	.041	.024
		Public assistance	.069	.035	.032	.047
	Parent-Child Relationship Questionnaire (personal closeness)	No public assistance	.012	.000	.006	.006
		Public assistance	.013	-.030	.036	.013
Mediator variable						
Attendance	Parent SNAP (inattention)	Below intended	-.151	-.074	-.092	...
		As intended	-.185	-.167	-.092	...
	Parent SNAP (hyperactivity/impulsivity)	Below intended	-.151	-.092	-.074	...
		As intended	-.177	-.179	-.010	...
Teacher SNAP (inattention)	Below intended	-.166	-.106	-.124	...	
	As intended	-.193	-.203	-.115	...	

*SSRS indicates Social Skills Rating System; ODD, oppositional-defiant disorder; CD, conduct disorder; SNAP, an acronym denoting the names of the instrument's developers; and MASC, Multidimensional Anxiety Scale for Children. Ellipses indicate variable not applicable.

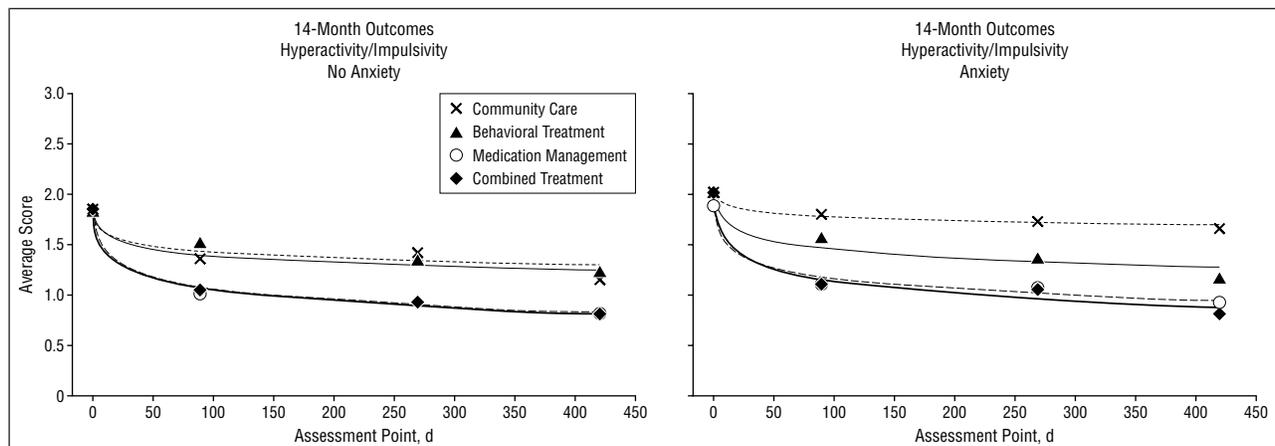


Figure 1. Random regression curves for treatment conditions with respect to no anxiety vs anxiety subgroups on the parent SNAP (an acronym denoting the names of the instrument's developers) hyperactivity/impulsivity measure (no anxiety: combined treatment, n = 92; medication management, n = 87; behavioral treatment, n = 90; community care, n = 100; anxiety: combined treatment, n = 50; medication management, n = 52; behavioral treatment, n = 50; and community care, n = 42).

nificant, suggesting that combined treatment showed relatively greater improvement over medication management for participants with anxiety than for those without anxiety. For the Multidimensional Anxiety Scale for Children, the interpretation of the significant interaction was less clear-cut.

Regarding familial receipt of public assistance, 2 outcome measures showed significant interactions: teacher SSRS total social skills ($F_{3,667} = 2.56; P = .05$) and for Parent-Child Relationship Questionnaire personal closeness ($F_{3,906} = 3.48; P = .02$). For the SSRS measure for fami-

lies receiving public assistance, combined treatment seemed superior to all other conditions, whereas for those not receiving such assistance there was no difference (**Figure 3**). Regarding the Parent-Child Relationship Questionnaire, all 4 treatments were equivalent in families without public assistance. For those receiving assistance, medication management was the only condition for which parent-reported positive interchanges decreased across the 14-month treatment; for all other conditions positive interchanges increased or stayed level (**Figure 4**). This finding was even more pronounced in

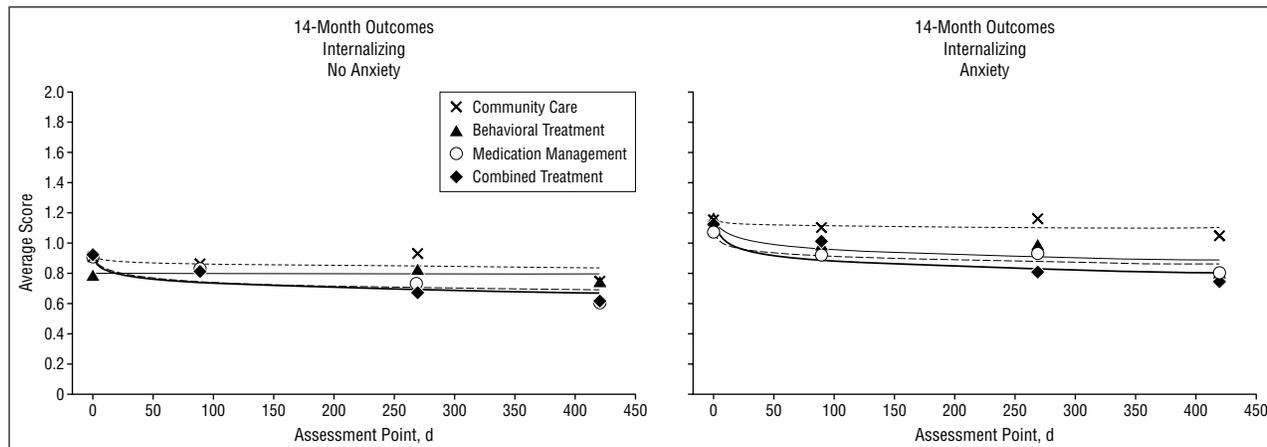


Figure 2. Random regression curves for treatment conditions with respect to no anxiety vs anxiety subgroups on the parent Social Skills Rating System internalizing measure (no anxiety: combined treatment, $n = 92$; medication management, $n = 88$; behavioral treatment, $n = 90$; and community care, $n = 100$; anxiety: combined treatment, $n = 50$; medication management, $n = 52$; behavioral treatment, $n = 50$; and community care, $n = 42$).

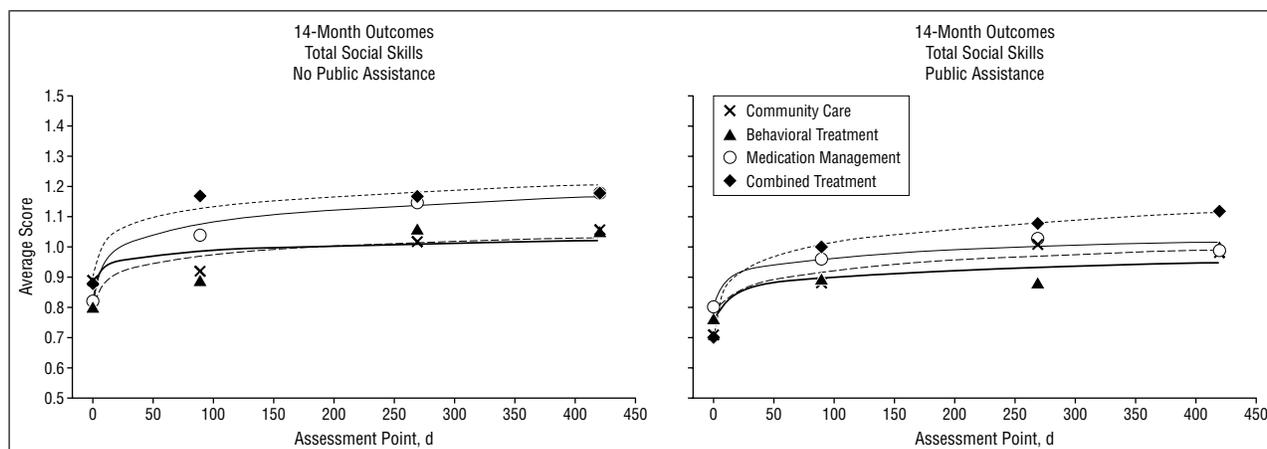


Figure 3. Random regression curves for treatment conditions with respect to no public assistance vs public assistance subgroups on the teacher Social Skills Rating System total social skills measure (no public assistance: combined treatment, $n = 115$; medication management, $n = 116$; behavioral treatment, $n = 122$; community care, $n = 116$; public assistance: combined treatment, $n = 28$; medication management, $n = 28$; behavioral treatment, $n = 21$; and community care, $n = 29$).

an exploratory analysis in which we combined public assistance with single-parent status as the moderator.

MEDIATOR ANALYSES

Only 13 (9%) of 144 of participants given medication management and 5 (3%) of 145 participants given combined treatment refused medication throughout the study. Additionally, none of the 144 participants given behavioral treatment and only 1 (<1%) of 145 participants given combined treatment refused behavioral treatment. Overall, acceptance/attendance differed across treatment groups ($\chi^2_2 = 16.6$; $P < .001$), confirming that this potential mediator was associated with treatment condition. Specifically, acceptance/attendance was higher in medication management (78% as intended) than in behavioral treatment (63%) or combined treatment (61%), which did not differ. In combined treatment, 81% showed as-intended acceptance/attendance for the pharmacologic component (similar to the level for medication management alone) but only 64% for the behavioral component (similar to the level for behavioral treatment alone), suggest-

ing that neither component of combined treatment helped or hindered acceptance/attendance with the other.

We added the attendance mediator to the RR analyses for the 14 core outcome variables, in which only the 3 active treatments were considered (we lack data on acceptance/attendance for the community care group). The overall interaction was significant for 3 measures: parent SNAP inattention measure ($F_{2,678} = 3.70$; $P = .03$); parent SNAP hyperactive/impulsive measure ($F_{2,677} = 7.03$; $P = .001$); and teacher SNAP inattention measure ($F_{2,514} = 4.55$; $P = .01$). The results in the Table suggest that for these variables, as-intended acceptance/attendance enhanced the treatment response for medication management, whereas below-intended acceptance/attendance decreased the response. Thus, results for the as-intended subgroup confirm the intent-to-treat results, but in the below-intended subgroup, medication management was less effective—comparable to behavioral treatment—with combined treatment clearly superior to both (**Figure 5** and **Figure 6**).

Because of the clear benefits of medication in medication management and combined treatment, we

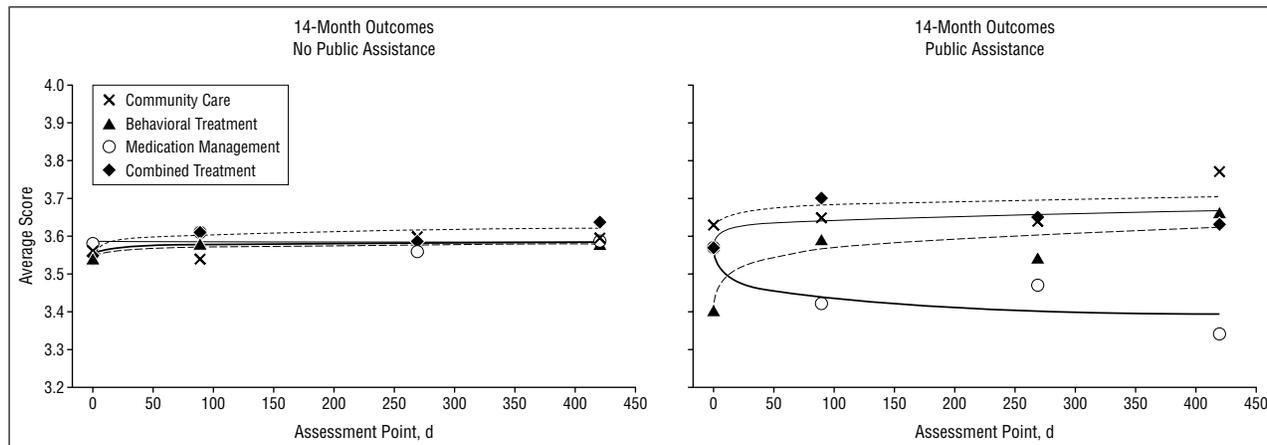


Figure 4. Random regression curves for treatment conditions with respect to no public assistance vs public assistance subgroups on the Parent-Child Relationship Questionnaire personal closeness measure (no public assistance: combined treatment, $n = 116$; medication management, $n = 114$; behavioral treatment, $n = 122$; and community care, $n = 116$; public assistance: combined treatment, $n = 28$; medication management, $n = 28$; behavioral treatment, $n = 22$; and community care, $n = 30$).

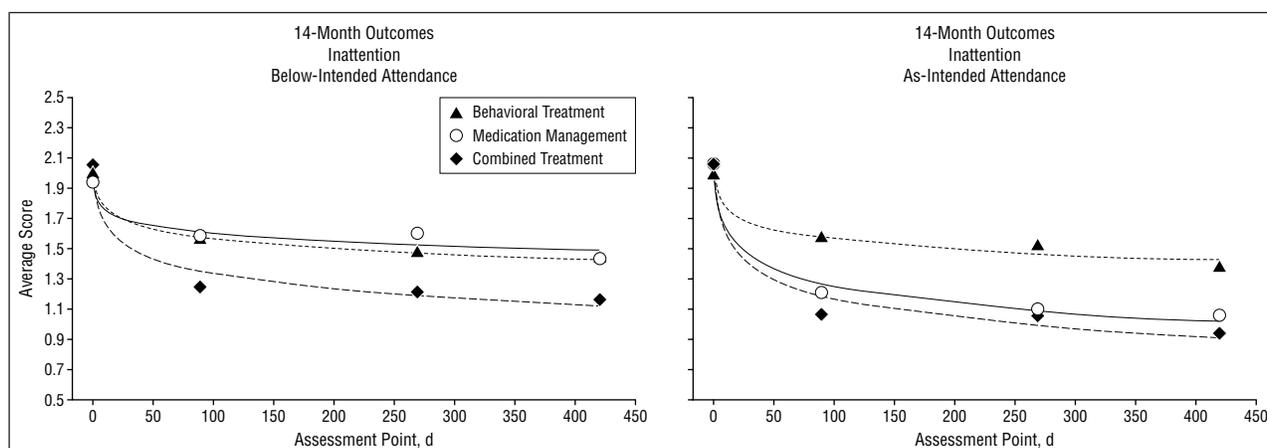


Figure 5. Random regression curves for manualized treatment conditions with respect to below-intended vs as-intended acceptance/attendance subgroups on the parent SNAP (an acronym denoting the names of the instrument's developers) inattention measure (below intended: combined treatment, $n = 56$; medication management, $n = 25$; and behavioral treatment, $n = 54$; as intended: combined treatment, $n = 89$; medication management, $n = 117$; and behavioral treatment, $n = 90$).

explored whether stimulant medication had any influence on treatment response in community care. From quarterly telephone interviews regarding service utilization,⁴ we ascertained that two thirds of the community care sample had received stimulant medication from community practitioners for at least one 3-month interval (in many cases, the medication had been received throughout the entire period). This situation is comparable to the criteria for medication management and combined treatment, in which all subjects randomly assigned to medication were counted as medicated regardless of how long they received medication over the 14 months of treatment. For purposes of illustration, we compare the medicated and non-medicated subgroups of the community care condition with the 3 active conditions for the outcome of teacher SNAP hyperactivity/impulsivity measure (**Figure 7**). The community care unmedicated subgroup showed a less favorable response than the community care medicated subgroup, which did not differ from that of behavioral treatment. Thus, the intensive interventions constituting behavioral treatment seem to be as robust as typical pharmacologic treatment in the com-

munity. In addition, medication management showed a greater reduction of symptoms than did the community care medicated subgroup, suggesting that the nature of the pharmacologic protocol in the sample (eg, initial titration, monthly monitoring, "thrice-daily" dosing, necessity of contact with teacher prior to each visit) may increment the benefits of medication over and above community care.

COMMENT

Our primary aims were to illuminate and challenge intent-to-treat findings from our study⁵ by examining prerandomization (moderator) and treatment-related (mediator) variables. Our results were consistent across boys and girls, participants with and without prior medication treatment, and subgroups with and without comorbid ODD or CD; study results were generalizable across these important variables. The lack of moderator effects for comorbid disruptive behavior disorders is striking; given the multiple impairments and poor prognosis of children with the combination of ADHD and aggression, the lack of clearly demonstrated superiority

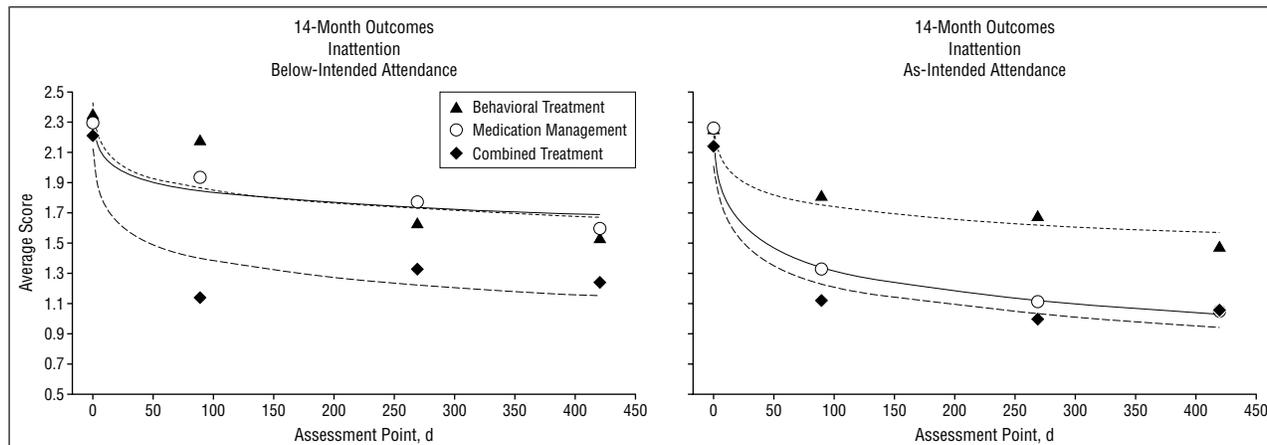


Figure 6. Random regression curves for manualized treatment conditions with respect to below-intended vs as-intended subgroups on the teacher SNAP (an acronym denoting the names of the instrument's developers) inattention measure (below intended: combined treatment, $n = 55$; medication management, $n = 27$; and behavioral treatment, $n = 53$; as intended: combined treatment, $n = 89$; medication management, $n = 117$; and behavioral treatment, $n = 90$).

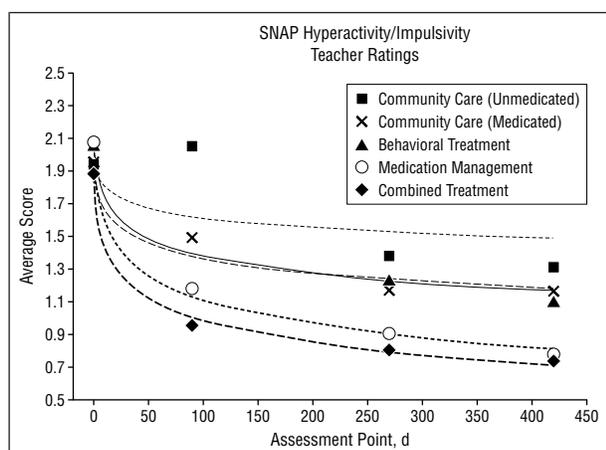


Figure 7. Random regression curves for treatment conditions, with community care subgrouped by medicated vs unmedicated status on the teacher SNAP (an acronym denoting the names of the instrument's developers) hyperactivity/impulsivity measure (combined treatment, $n = 144$; medication management, $n = 145$; behavioral treatment, $n = 144$; community care unmedicated, $n = 48$; and community care medicated, $n = 98$).

for combined treatment regarding this subgroup is noteworthy.

There were, however, differences in treatment results for our participants with and without comorbid anxiety. For the 34% of the sample with Diagnostic Interview Schedule for Children-defined anxiety disorders, behavioral treatment showed an enhanced response for parent-reported ADHD and internalizing symptoms. Specifically, behavioral treatment was (like medication management and combined treatment) superior to community care in the highly anxious subgroup. Also, combined treatment fared better than medication management in selected instances. For participants without anxiety, however, results were parallel to the intent-to-treat analyses with regard to ADHD symptoms, in that medication management and combined treatment (which did not differ statistically) outperformed behavioral treatment and community care (which also did not differ statistically).

Contrary to our hypothesis, comorbid anxiety disorder status was not associated with a pattern of worse

response to medication management. This prediction stemmed from results of short-term, fixed-dose investigations reporting that children with ADHD and anxiety show a less robust response to stimulants than do children with ADHD without anxiety disorders.^{9,10} However, MTA pharmacotherapy included individualized titration, 14 months of treatment, and a monthly management strategy. The results of a recent investigation²⁴ that also included long-term (12-month) individualized stimulant treatment are similar to those reported here; children with ADHD with and without anxiety improved similarly in the domains of ADHD symptoms and ancillary (internalizing) problems. These parallel findings suggest that medication-induced improvements hold across anxious and nonanxious subgroups and result in reductions in children's levels of anxiety-related symptoms.

Our moderator effect on internalizing symptoms is provocative, in that behavioral treatment targeted difficulties characteristic of ADHD as well as such associated areas as aggression, academic productivity, and social skills; however, it did not direct specific treatments to anxiety or other internalizing features. Our finding of significant improvement with either behavioral or pharmacological interventions, neither of which directly targeted anxiety, suggests that effective treatment of core ADHD symptoms can ameliorate anxiety and that at least some of the anxiety attributable to a number of children with ADHD may flow from the stress of ADHD-related problems and impairment. It is conceivable that provision of behavioral interventions that are geared specifically toward anxiety symptoms and disorders^{25,26} would result in greater benefits.

The relatively greater improvements in behavioral treatment for children with ADHD and anxiety were limited to parent report, which may be biased, in that parents were actively involved in the behavioral treatment protocol. Analogous teacher ratings and objective measures of ADHD-related symptoms from the Classroom Observation Code did not yield a similar moderator effect.

Most outcomes for families receiving public assistance showed patterns of treatment response similar to those for families of higher socioeconomic strata, but we

Principal Collaborators

National Institute of Mental Health, Rockville, Md: Peter S. Jensen, MD (Office of the Director); L. Eugene Arnold, MD (Department of Psychiatry, Ohio State University); John E. Richters, PhD (Developmental Psychopathology and Prevention Research Branch); Joanne B. Severe, MS (Research Projects and Publications Branch); Donald Vereen, MD (Office of Drug Control Policy); and Benedetto Vitiello, MD (Child and Adolescent Treatment and Preventive Interventions Research Branch).

Office of Special Education Programs, US Department of Education, Washington, DC: Ellen Schiller, PhD.

Principal Investigators and Coinvestigators

University of California, Berkeley/University of California, San Francisco: Stephen P. Hinshaw, PhD (Department of Psychology, University of California, Berkeley); Glen R. Elliott, MD, PhD (Department of Psychiatry, University of California, San Francisco).

Duke University, Durham, NC: C. Keith Conners, PhD, Karen C. Wells, PhD, and John March, MD (Department of Psychiatry and Behavioral Sciences).

University of California, Irvine/University of California at Los Angeles: James Swanson, PhD, and Timothy Wigal, PhD (Department of Pediatrics and Cognitive Science, University of California, Irvine); Dennis P. Cantwell, MD (deceased) (Department of Psychiatry, Neuropsychiatric Institute, University of California at Los Angeles).

Long Island Jewish Medical Center, New York, NY/Montreal Children's Hospital, Montreal, Quebec: Howard B. Abikoff, PhD (Department of Psychiatry, New York University School of Medicine); Lily Hechtman, MD (Department of Psychiatry, McGill University, Montreal).

New York State Psychiatric Institute/Columbia University/Mount Sinai Medical Center, New York, NY: Laurence L. Greenhill, MD (Department of Psychiatry, Columbia University); Jeffrey H. Newcorn, MD (Department of Psychiatry, Mount Sinai School of Medicine).

University of Pittsburgh, Pittsburgh, Pa: William E. Pelham, PhD (Department of Psychology, State University of New York at Buffalo); Betsy Hoza, PhD (Department of Psychological Sciences, Purdue University, West Lafayette, Ind).

Statistical and Design Consultation

Helena C. Kraemer, PhD (Department of Psychiatry and Behavioral Science, Stanford University, Palo Alto, Calif).

observed a tendency for families receiving public assistance (single-parent or dual-parent) assigned to medication management to show an unexpected decrease in parent-reported closeness and positive interactions with their child. The mechanisms underlying such an effect are speculative, but it is conceivable that for stressed families with fewer economic and social resources, behavioral improvements induced by stimulant medications—in the absence of systematic psychosocial treatment—allowed parents to relax positive interactions and rewarding consequences for their children. Furthermore, for families receiving public assistance, combined treatment seemed to enhance teacher-reported social skills relative to all other conditions. Both results are in need of replication.

Although these moderators served to qualify several intent-to-treat findings, the acceptance/attendance mediator strengthened the overall pattern of results; the as-intended acceptance/attendance subgroup showed an accentuation of the predominant intent-to-treat pattern for core ADHD symptoms, with combined treatment and medication management superior to behavioral treatment (and community care). Because we found no effect of as-intended acceptance/attendance on the treatment response of participants given behavioral treatment, we cannot contend that the relatively weaker performance of behavioral treatment in the intent-to-treat analyses was “pulled down” by a subgroup of poor attendees. Instead, we found that acceptance/attendance in medication management (including the regular receipt of prescriptions) was crucial for its success. Finer-grained, condition-specific mediators related to

compliance and quality of management (eg, actual parent or teacher implementation of behavioral programs), rather than acceptance/attendance per se, may reveal subgroups for which effects of behavioral treatment were stronger.

For treatment supplementation—a family's decision to use treatment in the modality different from the initially assigned condition—a differential pattern was evident: 3 (2%) of 144 medication management families added behavioral treatments in the community, whereas 38 (26%) of 144 behavioral treatment families initiated stimulant treatment in the community (reasons were clinical deterioration, the treatment team's determination of need for additional treatment, or families seeking extra care on their own). Nonetheless, whether we examined just the as-intended subgroups (as above) or performed censored analyses in which we carried forward the last data point prior to treatment supplementation, the pattern of our results was substantially the same.⁵ In addition, prior medication status seemed to moderate the effect of behavioral treatment with respect to treatment supplementation; among behavioral treatment families with prior medication, half added medication before 14 months, whereas only one sixth without prior medication added pharmacologic intervention.

In our examination of participants given community care subgrouped by medication status, we found that, for teacher-reported ADHD symptoms, community care participants given medication fared better than the unmedicated subgroup despite a potential selection bias for the more severe cases to receive medication. Medication effects were therefore demonstrable, even in our participants given com-

munity care. However, participants in the behavioral treatment condition seemed comparable with children given community care who received medication, revealing benefits of our behavioral treatment. Further analyses of the community care condition subdivided by medication status will need to control for selection biases.

Overall, as befits clinical trial methods, we have featured RR procedures that preserve initial random assignment. Finer-grained analyses of subgroup and treatment supplementation effects as well as heightened focus on the clinical significance of our findings are important future directions. For example, when we amalgamate outcome measures into composites or examine categorical indicators of excellent clinical response vs less-dramatic response, combined treatment shows a significant advantage over medication management that is of small to moderate effect size, even for core ADHD and disruptive symptoms.²⁷ Our overall conclusions suggest the relative strength of medication-based interventions across 14 months of treatment for ADHD-related symptoms and the modest superiority of combined treatment for both oppositional/aggressive symptoms and specific functional domains.

Accepted for publication July 28, 1999.

This study was supported by grants UO1 MH50461 (Drs Hinshaw and Elliot), UO1 MH50447 (Drs Conners, Wells, and March), UO1 MH50440 (Drs Swanson, Cantwell, and Wigal), UO1 MH50453 (Drs Abikoff and Hechtman), UO1 MH50454 (Drs Greenhill and Newcorn), and UO1 MH50467 (Drs Pelham and Hoza) from the National Institute of Mental Health, Bethesda, Md.

The opinions and assertions contained in this study are the private views of the authors and are not to be construed as official or reflecting the views of the Department of Health and Human Services, Washington, DC, or the National Institute of Mental Health, Rockville, Md.

The Multimodal Treatment Study of Children With Attention-Deficit/Hyperactivity Disorder (the MTA study) is a cooperative treatment study performed by 6 independent research teams in collaboration with the Division of Clinical and Treatment Research, National Institute of Mental Health, and the Office of Special Education Programs, US Department of Education, Washington, DC.

Corresponding author: Stephen P. Hinshaw, PhD, Department of Psychology, Tolman Hall #1650, University of California, Berkeley, CA 94720-1650 (e-mail: hinshaw@socrates.berkeley.edu).

REFERENCES

- Richters JE, Arnold LE, Jensen PS, Abikoff H, Conners CK, Greenhill LL, Hechtman LT, Hinshaw SP, Pelham WE, Swanson JM. The National Institute of Mental Health Collaborative Multisite, Multimodal Treatment Study of Children With Attention-deficit Hyperactivity Disorder (MTA), I: background and rationale. *J Am Acad Child Adolesc Psychiatry*. 1995;34:987-1000.
- Arnold LE, Abikoff HB, Cantwell DP, Conners CK, Elliott G, Greenhill LL, Hechtman L, Hinshaw SP, Hoza B, Jensen PS, Kraemer HC, March JS, Newcorn JH, Pelham WE, Richters JE, Schiller E, Severe JB, Swanson JM, Vereen D, Wells KC. National Institute of Mental Health Collaborative Multimodal Treatment Study of Children With ADHD (MTA): design challenges and choices. *Arch Gen Psychiatry*. 1997;54:865-870.
- Arnold LE, Abikoff H, Cantwell DP, Conners CK, Elliott G, Greenhill LL, Hechtman LT, Hinshaw SP, Pelham WE, Swanson JM, Vereen D, Wells K, Newcorn JH, March JS, Kraemer HC, Richters JE, Schiller E, Severe JB, Swanson JM, Vereen D, Wells K. Comprehensive assessment of childhood attention-deficit hyperactivity disorder in the context of a multisite, multimodal clinical trial. *J Attention Disord*. 1997;1:217-234.
- The MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry*. 1999;56:1073-1086.
- Kazdin AE, Weisz JR. Identifying and developing empirically supported child and adolescent treatments. *J Consult Clin Psychol*. 1998;66:19-36.
- Hinshaw SP. Psychosocial intervention for childhood ADHD: etiologic and developmental themes, comorbidity, and integration with pharmacotherapy. In: Cicchetti D, Toth SL, eds. *Rochester Symposium on Developmental Psychopathology: Developmental Approaches to Prevention and Intervention*. Vol 9. Rochester, NJ: University of Rochester Press; 1999:221-250.
- Jensen PS, Martin D, Cantwell DP. Comorbidity in ADHD: implications for research, practice, and DSM-V. *J Am Acad Child Adolesc Psychiatry*. 1997;36:1065-1079.
- DuPaul GJ, Barkley RA, McMurray MB. Response of children with ADHD to methylphenidate: interaction with internalizing symptoms. *J Am Acad Child Adolesc Psychiatry*. 1994;33:894-903.
- Pliszka SR. Effect of anxiety on cognition, behavior, and stimulant response in ADHD. *J Am Acad Child Adolesc Psychiatry*. 1989;28:882-887.
- Dumas JE, Wahler RG. Predictors of treatment outcome in parent training: mother insularity and socioeconomic disadvantage. *Behav Assess*. 1983;5:301-313.
- Webster-Stratton C. Predictors of treatment outcome in parent training for conduct disordered children. *Behav Ther*. 1985;16:223-243.
- Greenhill LL, Osman BO, eds. *Ritalin: Theory and Patient Management*. New York, NY: Mary Ann Liebert; 1991.
- Schachar RJ, Tannock R, Cunningham C, Corkum PV. Behavioral, situational, and temporal effects of treatment of ADHD with methylphenidate. *J Am Acad Child Adolesc Psychiatry*. 1997;36:754-763.
- Greenhill LL, Abikoff HB, Arnold LE, Cantwell DP, Conners CK, Elliott G, Hechtman LT, Hinshaw SP, Hoza B, Jensen PS, March J, Newcorn J, Pelham WE, Severe JB, Swanson JM, Vitiello B, Wells K. Medication treatment strategies in the MTA study: relevance to clinicians and researchers. *J Am Acad Child Adolesc Psychiatry*. 1996;35:1304-1313.
- Wells KC, Pelham WE, Kotkin RA, Hoza B, Abikoff H, Abramowitz A, Arnold LE, Cantwell DP, Conners CK, Del Carmen R, Elliott G, Greenhill LL, Hechtman LT, Hinshaw SP, Jensen PS, March JS, Schiller E, Severe J, Swanson JM. Psychosocial treatment strategies in the MTA study: rationale, methods, and critical issues in design and implementation. *J Abnorm Child Psychol*. In press.
- Shaffer D, Fisher P, Dulcan M, Davies M, Piacentini J, Schwab-Stone M, Lahey B, Bourdon K, Jensen P, Bird H, Canino G, Regier D. The second version of the Diagnostic Interview Schedule for Children (DISC-2). *J Am Acad Child Adolesc Psychiatry*. 1996;35:865-877.
- Swanson JM. *School-based Assessments and Interventions for ADD Students*. Irvine, Calif: KC Publishing; 1992.
- Abikoff H, Gittelman-Klein R, Klein D. A classroom observation code for hyperactive children: a replication of validity. *J Consult Clin Psychol*. 1980;48:555-565.
- Gresham FM, Elliott SN. *Social Skills Rating System: Automated System for Scoring and Interpreting Standardized Tests* [computer program]. Version 1. Circle Pines, Minn: American Guidance Systems; 1989.
- March J. *Manual for the Multidimensional Anxiety Scale for Children (MASC)*. Toronto, Ontario: Multi-Health Systems; 1998.
- March JS, Parker JDA, Sullivan K, Stallings P. The Multidimensional Anxiety Scale for Children (MASC): factor structure, reliability, and validity. *J Am Acad Child Adolesc Psychiatry*. 1997;36:554-565.
- Furman W, Giberson RS. Identifying the links between parents and their children's sibling relationships. In: Shurman S, ed. *Close Relationships in Socio-emotional Development*. Norwood, NJ: Ablex; 1995:95-108.
- Diamond IR, Tannock R, Schachar RJ. Response to methylphenidate in children with ADHD and anxiety. *J Am Acad Child Adolesc Psychiatry*. 1999;38:402-409.
- Kendall PC. Treating anxiety disorders in children: results of a randomized clinical trial. *J Consult Clin Psychol*. 1994;62:100-110.
- Kendall PC, Flannery-Schroeder E, Panicelli-Mindel SM, Southam-Gerow M, Henin A, Warman M. Therapy for youths with anxiety disorders: a second randomized clinical trial. *J Consult Clin Psychol*. 1997;65:366-380.
- Swanson JM, Kraemer HC, Hinshaw SP. Conceptual and methodologic issues in the evaluation of treatment effectiveness for attention-deficit hyperactivity disorder. *J Child Psychol Psychiatry*. In press.