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## ADHD, Multimodal Treatment, and Longitudinal Outcome: Evidence, Paradox, and Challenge

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### Abstract

Given major increases in the diagnosis of attention-deficit hyperactivity disorder (ADHD) and in rates of medication for this condition, we carefully examine evidence for effects of single versus multimodal (i.e., combined medication and psychosocial/behavioral) interventions for ADHD. Our primary data source is the Multimodal Treatment Study of Children with ADHD (MTA), a 14-month, randomized clinical trial in which intensive behavioral, medication, and multimodal treatment arms were contrasted with one another and with community intervention (treatment-as-usual), regarding outcome domains of ADHD symptoms, comorbidities, and core functional impairments. Although initial reports emphasized the superiority of well-monitored medication for symptomatic improvement, reanalyses and reappraisals have highlighted (a) the superiority of combination treatment for composite outcomes and for domains of functional impairment (e.g., academic achievement, social skills, parenting practices); (b) the importance of considering moderator and mediator processes underlying differential patterns of outcome, including comorbid subgroups and improvements in family discipline style during the intervention period; (c) the emergence of side effects (e.g., mild growth suppression) in youth treated with long-term medication; and (d) the diminution of medication's initial superiority once the randomly assigned treatment phase turned into naturalistic follow-up. The key paradox is that whereas ADHD clearly responds to medication and behavioral treatment in the short term, evidence for long-term effectiveness remains elusive. We close with discussion of future directions and a call for greater understanding of relevant developmental processes in the attempt to promote optimal, generalized, and lasting treatments for this important and impairing neurodevelopmental disorder.

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Attention-deficit hyperactivity disorder (ADHD) is a highly impairing neurodevelopmental disorder that originates in childhood. This condition is newsworthy on many fronts, particularly its fast-rising rates of diagnosis and of medication treatment across recent years.<sup>1</sup> Contrary to the myth that ADHD is merely a label for bothersome, fidgety behavior in boys, this disorder, whether defined categorically or dimensionally, is highly impairing, clearly present in girls (although at lower rates than in boys), and strongly heritable.<sup>2,3</sup> Still,

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ADHD is “revealed” most saliently in the context of achievement and vocational pressures, meaning that biological underpinnings and contextual factors are inseparable in terms of gaining full understanding of this clinical condition.<sup>1</sup> Given the extent to which problems of focus, inhibitory control, and self-regulation provide windows on both brain mechanisms and current cultural contexts, intensified basic and clinical research on ADHD remains a core priority. At the same time, this disorder mandates careful assessment and diagnosis, to differentiate it from normative behavior patterns, child maltreatment, or a number of other child/adolescent disorders.<sup>1</sup> Moreover, given the serious academic, social, familial, and accidental-injury consequences of ADHD, as well as its risk for incurring comorbid conditions and later substance abuse, the need for development and dissemination of efficacious and effective treatments is pressing.<sup>1,2</sup>

Two decades ago a landmark, randomized clinical trial for children with ADHD took place. This investigation, known as the Multimodal Treatment Study of Children with ADHD (MTA), directly contrasted, in a large and carefully diagnosed sample of children aged 7–9.9 years—all with the “combined” presentation of ADHD (i.e., high rates of both inattention and hyperactivity/impulsivity)—the following intervention strategies: (1) systematic medication procedures, involving an initial titration to establish the optimal medication and dosage, followed by monthly pharmacotherapy visits; (2) an intensive behavioral treatment package including home, school, and summer treatment components; (3) the combination of the first two interventions; and (4) treatment as usual in community settings. Treatments spanned 14 months; systematic, naturalistic, longitudinal follow-up then occurred for 15 years after the study treatments ceased.<sup>4</sup>

Although high levels of symptom-related improvement were yielded by the study’s medication algorithm—without statistically or clinically significant increment from the addition of intensive behavioral intervention<sup>5,6</sup>—additional analyses revealed that for composited outcomes of adult-rated symptoms, and particularly for functional impairments (i.e., academic achievement, peer-related social skills, and parenting practices), combination/multimodal treatment was optimal.<sup>7,8</sup> Furthermore, cost-benefit analyses suggested strongly that for complex cases with substantial comorbidities, the addition of behavioral treatment to medication was justified.<sup>9</sup> Moreover, moderator analyses highlighted that treatments were far less than optimal for children with pre-existing parental depression, severe child ADHD symptoms, and subaverage child cognitive skills.<sup>10</sup> At the same time, mediator analyses revealed that when accompanied by clinically significant improvements in parenting style, multimodal treatment yielded not just improvement but even normalization of school-reported behavior patterns.<sup>11</sup> Finally, and crucially, the initial superiority of medication with respect to symptom improvement gradually abated after the randomly assigned interventions ceased, becoming nonsignificant two years later.<sup>12,13,14</sup> At the same time, certain side effects (e.g., a slight diminution of ultimate adult height) persisted in some cases, leading to additional questions about the long-term advantages and disadvantages of pharmacologic intervention for ADHD.<sup>15</sup>

In all, inattentive and hyperactive-impulsive symptomatology and its functional consequences exact huge personal, familial, and economic costs. As a result, there is great need to analyze and discuss the promise and limitations of existing treatment strategies and

to prioritize high levels of investment in developing sustained, generalized, evidence-based interventions for the condition known as ADHD. Without such concerted efforts, high levels of suffering (for individuals, families, schools, and communities) and low rates of productivity are likely to persist.

## ADHD: A BRIEF OVERVIEW

The subject of voluminous research, ADHD remains a fascinating and complex syndrome. Defined by developmentally extreme and impairing symptoms in the domains of inattention/disorganization and hyperactivity impulsivity,<sup>16</sup> ADHD—when diagnosed carefully—is associated with highly impairing outcomes in the core domains of academic performance, social relationships, parent-child interactions and family stress, and risk for serious accidental injury.<sup>2,17,18,19</sup> Thus, ADHD is not simply a societal or psychiatric label for fidgety, bothersome behavior or a sign of a society's intolerance of behavioral nonconformity. Instead, it represents a lack of full development of self-regulation, frequently accompanied by deficits in key executive functions (e.g., inhibitory control, working memory, planning, and the like) and highly likely to be accompanied by a variety of comorbid conditions (e.g., excessive aggression, depression and anxiety, learning disorders).<sup>1,2,16</sup> Understanding and treating this syndrome is a priority for both mental health and public health.

The unevenness of performance of individuals with ADHD is both puzzling to and frustrating for peers and other social partners. People showing high rates of relevant symptomatology can be quite engaging but seemingly oblivious to social cues, cognitively sharp but unable to complete tasks or manage their time, resourceful and full of ideas but without the inner resources to sustain intrinsic motivation or refrain from outbursts of pique or frustration. Academic underachievement is prevalent; over time, rates of substance abuse, delinquency, poor relationship functioning, and (particularly for girls) self-injurious behavior during adolescence and adulthood are alarming, occurring at far-beyond-normative levels and signaling the serious impairments accruing to this condition.<sup>2,20</sup> By adulthood, associate problems in close relationships and in vocational endeavors are rampant. Moreover, even though childhood ADHD is highly likely to be accompanied by comorbid psychiatric conditions, core ADHD symptomatology is typically responsible for much of the functional impairment accruing from this disorder.

The symptom domains linked to ADHD are highly heritable.<sup>21</sup> Yet, as with all other psychiatric syndromes, the effects of any specific risk alleles are quite small, and gene-environment interplay is likely to be of major significance for exacerbation of symptoms and impairments.<sup>17</sup> Additional risk factors include low birthweight, maternal ingestion of noxious substances (e.g., alcohol or nicotine), and other toxins (e.g., lead; pesticides).<sup>3</sup> Except in cases of severe physical and emotional deprivation, relevant symptomatology does not appear to stem from aberrant parenting practices per se, although overly harsh or lax parenting can be highly relevant for predicting developmental course.<sup>22</sup>

Current models of ADHD include disrupted attention, deficits in response inhibition, poor executive function/cognitive control more generally, and problems in arousal and reward

sensitivity. These models implicate neurotransmitter systems linked to dopamine and norepinephrine, with multiple pathways likely to be involved in the most severe cases.<sup>2,23,24</sup> At the same time, despite the clear neurophysiological roots of ADHD, it is in the context of family interactions, school demands, and (by adulthood) vocational settings and intimate relationships that the problems related to ADHD are elicited, maintained, and magnified. In other words, when work demands get harder, when emotion regulation is required, and when self-control is at a premium, ADHD tends to rear its head most explosively.

Typically revealing itself in early to middle childhood, ADHD extends into adolescence and adulthood in a majority of individuals.<sup>25</sup> Across these developmental periods, childhood ADHD portends problems in delinquency and antisocial behavior, substance abuse, risk for accidental injury (including risky driving), and (particularly in females) internalizing disorders and self-injurious behavior.<sup>26</sup> Indeed, when comorbid disorders, family dysfunction, and peer problems accompany ADHD-related symptomatology, the risk for poor outcome substantially intensifies, signaling the importance of (a) differential diagnosis and (b) ascertaining the comorbid conditions that may legitimately accompany ADHD. As noted above, thorough assessments are necessary in order to rule out competing conditions, including response to trauma; account for comorbid disorders; and differentiate symptoms from normal-range behavior patterns.<sup>1</sup>

## TYPES OF TREATMENTS

Many treatments for ADHD have been implemented over the years. However, no consistent evidence exists that one-on-one therapy with the child (still a common intervention strategy with many youth) provides meaningful benefit, even though for adults with ADHD, cognitive-behavioral therapy has shown real promise.<sup>27,28</sup> In addition, despite periodic surges in popularity, dietary interventions typically yield small effects; neurofeedback training (in which individuals learn to control their brain waves toward the end of enhancing self-regulation) has not received unequivocal support from controlled trials despite some promise; and specific cognitive training (e.g., exercises to enhance working memory) does not appear to provide generalized or lasting change.<sup>29,30,31</sup> Coaching for adolescents and adults has proliferated as well, but it remains relatively unspecified and unevaluated. Whereas some families and some individuals give testimonials to these kinds of treatment modalities—as well as far more esoteric alternatives that often crowd web pages with glowing case reports—to date the gold standard of randomized clinical trials has been met mainly by behavior therapy and pharmacotherapy. Specifically, the consistently evidence-based treatments for this condition involve (a) behavioral interventions (and for adults, cognitive-behavioral treatments, as noted),<sup>32,33</sup> and (b) medications, chiefly those that target dopaminergic and noradrenergic neurotransmitter systems.<sup>34,35</sup>

### Behavioral Intervention

For youth with ADHD, direct contingency management programs in school or summer camp programs can motivate improved behavior, but more common are clinical behavior therapy interventions, which target parents and teachers as the recipients of intervention. These adults learn to break tasks down into component parts, provide regular reinforcement (including clear and non-emotional consequences for misbehavior), and strive, over time, to

promote the child's self-regulation. Peer groups, if highly structured, may provide important social benefits as well. A host of controlled studies reveal positive benefits of parent management and teacher consultation, which admittedly require substantial time and energy on the part of the adults who deliver prompts and reinforcement.<sup>36,37,38</sup>

## Medication

The main types of medications used to treat ADHD are called stimulants, which facilitate actions of dopamine, in particular. Noradrenergic agonists are also evidence-based interventions for this condition. Hundreds of controlled trials reveal the behavioral and cognitive benefits yielded by stimulants for individuals with ADHD—particularly when a proper dosage is administered and potential side effects (e.g., appetite suppression, sleep disruption) are avoided. Such effects may be sustained over at least two years.<sup>39,40,41</sup> Of course, however, medications alone cannot teach skills and competencies. Furthermore, although pharmacologic intervention is helpful for youth with ADHD even when comorbid conditions are present, the presence of conduct disorder, internalizing disorders, and learning disabilities mandates the use of concerted psychosocial treatment strategies to supplement treatments directed toward ADHD *per se*.<sup>42</sup> In short, it's not just a matter of reducing problem behavior but of facilitating problem solving, planning, error correction, academic performance, and social skills to yield real impact on the lives of individuals grappling with ADHD. It may well be that deficient dopamine neurotransmission underlies the need for regular, tailored rewards to assist managing this condition.

## Combination Treatments

In theory, the effects of behavioral and medication interventions should at least be additive: the brain's "fine tuning" via dopaminergic and/or noradrenergic enhancement may set the stage for better "take" of reward-based programs designed to teach skills and reduce problem behavior. Initial trials during the 1970s and 1980s showed trends along these lines, although in other cases the symptom reduction provided by medication alone produced a limit on any added benefit from behavioral intervention.<sup>43,44,45</sup> In addition, controlled trials of behavioral treatment, medication, and their combination were almost uniformly of relatively short duration (several months at longest), precluding definitive information on the potential for potentiation of pharmacologic with psychosocial treatment. Thus, a strong rationale came to exist, during the 1990s, for trials that would allow inference about the additive benefits of pharmacologic and psychosocial treatments over relatively long periods of time. Since then, in addition to the MTA study (the trial under discussion), other long-term trials have provided mixed information about whether behavior therapy and social skills interventions provide a significant increment over medication alone in terms of improving core outcomes.<sup>41</sup>

## SPECIFICS OF MTA DESIGN AND CORE FINDINGS

### Design Considerations

After a competitive request for applications and review of submitted proposals, the National Institute of Mental Health, which provided the bulk of funding for the initial years of the MTA, stipulated that the selected investigators would need to meet, face to face, once per

month for a year and a half to design a collaborative, parallel intervention across the six sites represented. The final MTA protocol was forged across an intensive set of such meetings. Following considerable discussion and debate, the design involved a between-subject randomized clinical trial for children aged 7.0–9.9 years of age who had been carefully diagnosed with ADHD-Combined type. (Indeed, the baseline assessment battery spanned nearly 10 hours, a far cry from the extremely quick assessments that all too often lead to designations of ADHD status at present.<sup>1</sup>) In other words, each participant had to show clinically impairing symptoms of both inattention and hyperactivity/impulsivity, yielding problems in both home and school settings.<sup>16</sup> Moreover, most of the common comorbidities accompanying ADHD (e.g., oppositional and aggressive behavior patterns, anxiety disorders, learning disabilities) were allowed. Funds were available to support a 14-month trial, to test whether the skill-building approach inherent in behavioral treatments could compete with (or significantly increment) the expected gains from medications.

In short, the MTA Study was clearly designed as an effectiveness trial, involving treatments in real-world settings such as schools, with highly comorbid participants rather than mildly impaired cases treated in laboratory settings. Yet it also included core elements of efficacy trials, including random assignment of participants to treatment conditions, in order to bolster causal claims about the relative benefits of medication and behavioral treatments. Via a between-group design, conducted in parallel at the six sites, children and families were randomly assigned to one of the four following intervention conditions after parents had given thorough consent for participation, with rigorous cross-site training and monitoring performed throughout the trial to ensure that a unified set of claims could be made at the end of treatment.<sup>4,46,47</sup>

**Behavioral Treatment**—Here, intensive clinical behavior therapy was deployed. Thirty-five parent training sessions were offered, mostly in groups of six families but also including periodic individual sessions. In addition, twice-monthly teacher consultation was performed by the same psychologist who conducted the parent training, focused on integrating the home and school interventions. Next, children participated in an 8-week summer treatment program featuring direct contingency management. To promote generalization, a classroom aide (in the form of a counselor from the summer program) spent three hours per day in the classroom of the child's second school year of participation. In short, this treatment arm was designed to be intensive, exemplifying the kinds of behavior management and skill building that might stand up to a medication approach. Each treatment component was scrupulously manualized.<sup>48</sup>

**Medication Management**—Children and families assigned to this condition first underwent a 4-week medication titration trial, with daily switches of three stimulant (mainly methylphenidate) doses and placebo, intended to ascertain optimal dosage on the basis of regular parent and teacher ratings of symptoms, target behaviors, and side effects. Once the initial dose was selected, participants saw their pharmacotherapist for thirty minutes each month; information from the child's teacher helped to guide ongoing dosage monitoring and adjustment. Moreover, the child was seen alone at the end of each session, to promote adherence. This level of monitoring was intended to be far more intensive than usual care.



The recommendation of three doses per day (of the then-available short-acting formulations of stimulants), along with the recommendation for weekend doses, was made to ensure continuous waking coverage with medication. Formal behavior therapy was not permitted, to prevent overlap with our behavioral-treatment conditions; but common pediatric behavioral techniques were allowed, such as a star chart for dry nights if enuresis came up in the session. If we had excluded what physicians would commonly do in the course of medication management, it would not have given a fair chance for medication treatment to “work.” Again, a detailed manual guided the MTA pharmacotherapy protocol, including needed psychotherapeutic aspects of pharmacotherapy.<sup>49</sup>

**Combined Treatment**—Here, families received the multimodal combination of the first two conditions. Because of the more frequent contact with study professionals in this treatment arm, it was conceivable that medication dosage would be adjusted upward frequently. Thus, the design specifications were such that any adjustments in treatment had to initially involve the behavioral aspects of intervention rather than medication. As it turned out, the final medication dosages were significantly lower in Combined treatment than in Medication Management.<sup>6</sup>

**Community Comparison**—A major design issue related to the composition of our “community comparison” group: it would have been impractical and even unethical to insist on no intervention across 14 months for the remaining 25% of families in the MTA trial. Thus, this condition comprised treatment as usual in the community: families received a full report of the study’s assessment findings and a list of general sources of referral in the community but were not treated by MTA practitioners. As it turned out, 68% of the Community Comparison families procured stimulant medications for their children during the 14-month intervention period. Yet periodic service utilization interviews during the course of the trial revealed that such medication treatment was far less intensive than in our own Medication Management and Combination Treatment conditions, comprising, on average, brief visits with a pediatrician every six months, without afternoon dosing or school contact to guide medication adjustments.<sup>6</sup>

## Core Findings

Outcomes were measured at 3 months and 9 months into the treatment period and again at post-treatment (14 months). They spanned six core domains: ADHD, externalizing, and internalizing symptoms, and the important functional outcomes of academic achievement, parent-child interactions, and peer relations/social skills.<sup>50</sup> Given the six domains of outcome, with multiple measures per domain, stringent per-comparison alpha adjustments were made within domain to reduce Type I errors in interpretation of findings.

After the 14 months of active intervention, the core symptoms of ADHD showed significantly greater improvement in the Medication Management and Combination conditions than in Behavioral Treatment or Community Comparison conditions.<sup>5</sup> Indeed, symptom reduction was virtually identical in the first two conditions, a finding that received substantial media attention in the aftermath of the treatment phase of the investigation. For the other symptom areas and the domains of functional impairment, treatment differences

were smaller, with the most prevalent outcome that Combination Treatment was significantly superior to Community Comparison but with the other five contrasts not showing as consistent a pattern. Furthermore, one-fourth of the Behavioral Treatment participants required medication before the 14-month treatment period ended—either going back on medication if they had received pharmacologic intervention prior to the study or taking it for the first time if their symptoms and impairments worsened during the course of the study.<sup>6</sup>

In short, the core outcome paper<sup>5</sup> discussed the within-subject improvements, on average, for participants in all four randomly assigned treatments as well as the relative superiority of well-delivered medication treatment for ADHD, contrasted with intensive behavioral intervention or with far-less-rigorous medication intervention in the community. On the basis of these data, U.S. treatment guidelines for ADHD came to feature medication as a first-line treatment,<sup>51,52</sup> whereas parallel European guidelines did not.<sup>53</sup> Still, the MTA results were instrumental in increasing medication use and respectability, even in Europe.

## ADDITIONAL ANALYSES AND LONGITUDINAL FOLLOW-UP

### Composited Outcomes

When secondary analyses were published several years after the initial publications, composite outcome measures were featured. First, parent and teacher ratings of ADHD were combined and then dichotomized, yielding an index of “excellent response” (ER), comprising post-treatment scores that were below ‘just a little’ on the rating-scale metric, trending toward rates found in normative samples. With this outcome measure, the rate of ER in the Combined condition was 68%, significantly better than the rate of 56% in Medication Management (Behavioral treatment yielded a rate of 34%, with Community Comparison trailing the pack at 25%).<sup>7</sup> A separate outcome analysis featured a factor score as the primary outcome, which amalgamated the three symptom domains of ADHD, externalizing (i.e., aggressive), and internalizing (i.e., anxious/depressed) plus three domains of functional impairment: objectively measured reading and math scores, parent-reported discipline practices at home, and teacher-rated social skills at school. Here again, the sharpest rate of improvement occurred with Combined treatment, followed respectively by Medication Management, Behavioral, and Community Comparison (all pairwise contrasts were significantly different).<sup>8</sup> In short, with composite outcome measures, including those tapping functional impairment, a significant increment over medication alone (of small effect) was found for multimodal intervention.

Recall that, in our Community Comparison condition, over two-thirds of the children received stimulant medications—the same intervention featured in the MM and Comb treatments. An important mediator analysis, however, revealed the following:<sup>6</sup> (a) medication in the Community Comparison group was dispensed with infrequent monitoring and at probably inadequate dosages; (b) outcomes of the medicated subgroup of Community Comparison participants were superior to those CC children who did not receive medication; and (c) the Behavioral Treatment results were statistically comparable, at post-intervention, to those of the medicated Community Comparison participants. Crucially, however, well-delivered medication—with accurate dosing, frequent monitoring, dosages spanning after-



school hours, contact with teachers, and clinical time with the child during each visit (to discuss issues of medication adherence, etc.)—in our Medication Management and Combined Treatment conditions proved far superior to medication practices in the community. Quality of delivery of pharmacologic intervention is crucial for optimal effects. The same is doubtless true for psychosocial interventions as well, although we did have the means for such a comparison in the MTA database.

The bottom line is that the planned comparisons related to the MTA's primary hypotheses showed clear benefits for medication, when rigorously dosed and monitored, for symptom reduction, even though alternative analyses including more reliable outcomes featuring functional impairment indicated significant superiority for multimodal intervention—i.e., significant incremental benefit of adding behavioral treatment to medication. Yet these latter findings appeared several years after publication of the core findings, with far less attention in the media.

## Moderators and Mediators

**Moderators of Treatment Response**—In a clinical trial, a moderator is a pretreatment (baseline) variable that distinguishes the treatment response of individuals in the trial's different conditions.<sup>54</sup> (Predictors are associated with better or worse outcome across the treatments, for the whole sample.) Importantly, several potential moderator variables did *not* yield significant findings in the MTA. For example, boys versus girls showed similar patterns of response, as did those youth who entered the study with versus without histories of receiving stimulant medication. In addition, and somewhat surprisingly, the 54% of the MTA sample who entered the study with comorbid diagnoses of aggressive behavior patterns (i.e., oppositional defiant disorder or conduct disorder) did not show an appreciably different response to any of the four randomly assigned treatments.<sup>6</sup>

Second, however, the presence of a comorbid anxiety disorder (all DSM categories except for specific phobias)—which comprised just over a third of the sample at pre-treatment—signaled important treatment-condition differences in response to intervention, particularly with regard to behavioral treatment. Specifically, the subgroup with ADHD plus any comorbid anxiety disorder showed a better response to Behavioral Treatment and Combined Treatment than did those lacking such comorbidity. Indeed, for youth with comorbid anxiety disorders, (a) response to Behavioral Treatment was comparable to response to Medication Management, and (b) response to Combined Treatment was even better.<sup>6</sup> Finer-grained examination of such response patterns revealed that children with ADHD plus anxiety disorder (but without disruptive behavior disorder comorbidity) were the ones who responded equally well all three MTA treatments. For those with both anxiety disorders *and* oppositional defiant or conduct disorders, multimodal (Combined) intervention was better than either unimodal treatment.<sup>55,56</sup> Although underlying mechanisms are not certain—for example, do youth with ADHD showing anxiety disorders respond better to contingencies? or are their parents better able to adhere to parent management training?—practitioners would be advised to evaluate for the presence of anxiety disorders in children with ADHD and consider behavioral treatment as a first-line approach for such youth and families. We

lacked sufficient sample size to assert, with confidence, precisely which anxiety disorders might be at play in this regard.

Another moderator finding was that for the one family in five who participated in the MTA trial who received public assistance—that is, those families in the lowest socioeconomic strata who required welfare support of one kind or another—only Combined Treatment yielded meaningful benefit with respect to the outcome of teacher-reported social skills.<sup>6</sup> Thus, for the study's most disenfranchised families, it took both well-delivered and systematically monitored medication plus intensive home and school behavior therapy to yield important gains in the social/peer domain. Furthermore, in an examination of the interactive influence of a several moderator variables considered simultaneously, Owens and colleagues found that, for children receiving either Medication Management or Combined Treatment, (a) caregiver symptoms of depression and (b) more severe initial ADHD symptomatology in the child predicted *worse* outcome than for those with less-depressed parents or only moderate levels of ADHD severity. For children with subaverage IQ scores as well, this pattern was intensified. In short, once a child has been diagnosed with ADHD, difficulties at home (parental depression), more severe symptoms, and worse-than-average intelligence predict a less robust response to intervention (in this case, pharmacologic treatment).<sup>10</sup> It may be that early preventive nonmedical intervention—before symptoms have yielded sufficient impairment to consolidate into a diagnosis—may be particularly crucial for children with ADHD, especially those from lower-SES families, as highlighted in recent professional treatment guidelines.<sup>52</sup>

**Mediators of Treatment Response**—Unlike moderators, *mediators* are those variables defining processes that occur during the period of active intervention, with potential explanatory power for how treatments exert their effects.<sup>54</sup> One basic mediator process is participation in treatment: It may well be the case that families who attend more sessions encourage more gains in their children's behavior over time. Intriguingly, however, we found that attendance patterns at parent training sessions in the Behavioral Treatment and Combined Treatment conditions were *not* associated with differential patterns of outcome. On the other hand, attendance at pharmacotherapy sessions *was* clearly linked to child outcome.<sup>6</sup> Indeed, without regular participation in such sessions, families could not receive medication prescriptions.

One possible speculative explanation here may relate to the intensity of the MTA behavioral treatment package: perhaps the full dose was not necessary for optimal effect. That is, parents who felt their child had already achieved sufficient improvement declined what they perceived as “overdosage.” Also, benefits of behavioral intervention may continue through missed visits, whereas medication only works while taken.

We tested another key mediator process, related to whether changes in family interactions and family discipline style during the course of intervention would explain or mediate important school-related outcomes. Before examining relevant results, we first raise the point of whether parental discipline could actually be an important explanatory variable for differential outcome in relation to ADHD, which has been established as a highly heritable condition. Wouldn't it be the case for such a biologically mediated, neurodevelopmental

disorder that environmental and contextual factors are relatively unimportant? Yet it's mistaken to think that mental disorders with high genetic liability are impervious to environmental input. In fact, recent work utilizing genetically informative designs reveals that family processes (particularly parental hostility) are important for the developmental course of this condition, independent of potential genetic mediation of such traits.<sup>57</sup> Moreover, investigators have been interested in parental discipline styles not so much as a causal factor related to the onset of the relevant symptoms but instead as an important contextual set of variables that may shape (or maintain) symptom expression and, in particular, comorbidity<sup>19,58</sup> For example, there may be a vicious cycle in which the child's symptoms exasperate and perturb the parent, who reacts hostilely, exacerbating symptoms in a child who needs extra support (in biological families, such processes would exemplify gene-environment correlation).

In sum, we hypothesized that for those parents who showed clear improvements in parenting during the MTA treatment period, in the form of reductions in ineffective and negative discipline practices, their children would demonstrate the greatest responses to intervention, particularly for participants receiving behavioral treatment. The key outcome was teacher-reported social skills and impulsive/disruptive/aggressive behavior patterns (note that we chose teacher-reported outcomes in order not to confound the source of information on parenting with the source of information on child outcomes).

The key finding was that for families in the Combined Treatment condition who demonstrated the largest improvements in negative/ineffective discipline, their children's (a) social skills improved dramatically and (b) disruptive and aggressive behavior was reduced *into the normal range* by the end of treatment—a pattern not found in Combined Treatment when parenting did not show such improvements, nor in Behavioral Treatment alone.<sup>11</sup> This finding suggests that the improvement in parental discipline facilitated the child's response to medication in school. In other words, the crucial mechanism whereby children receiving the multimodal combination of pharmacologic and psychosocial treatment promoted normalization of school-related outcomes was through major improvements in parental discipline style. Thus, a strongly heritable condition like ADHD is malleable with respect to clinically significant improvements in parenting, further signaling the transactional pathways underlying the developmental course of children with impairing attention and impulse-control problems.

We note, as well, that later publications utilizing objectively observed parenting behavior as the outcome measure revealed the clear superiority of Behavioral and Combined Treatment over Medication Management and Community Comparison conditions.<sup>59</sup> Medication alone, which reduced children's problem behavior, was not sufficient for change in parenting skills and practices per se. Clearly, to teach and motivate more adaptive parenting, active psychosocial strategies are needed. The parent has to be taught to "shift gears" to reinforce the child's medication-linked behavioral improvement. It is undoubtedly the case that bidirectional processes are at work in families of children with ADHD: early problem behavior, linked to difficult temperament, elicits combinations of lax and harsh parenting, which in turn promote worse child behavior. Intervening at the level of parenting, in

addition to pharmacologic treatment for the child, is essential in promoting meaningful change.

### **Cost Benefit Analyses**

The MTA investigators teamed with health economists to ascertain whether, for “simpler” cases of ADHD without comorbidities versus more complex cases with impairing comorbid disorders, single-modality versus multi-modal treatments would be viewed as cost-effective.<sup>9,60</sup> In an intriguing analysis, based on levels of overall impairment following intervention, Foster and colleagues found that, for non-comorbid youth with ADHD, Medication Management was effective clinically as well as cost effective. However, for youth with comorbid anxiety disorders or comorbid disruptive behavior disorders, payers willing to spend more to justify eventual savings would be likely to prefer behavioral strategies, usually in combination with medication.<sup>9</sup> In short, it may well be that transcending symptoms of ADHD to include comorbid conditions and levels of life impairment reveals the importance of multimodal treatment over pharmacologic intervention alone, particularly in terms of long-range cost offset (e.g., preventing juvenile justice-related outcomes).

### **Side Effects**

Any treatment, whether pharmacologic or psychosocial, incurs the risk of “treatment emergent symptoms” (commonly termed side effects). In the MTA the typical short-term side effects linked to stimulant medication (appetite reduction, sleep disruption) were typically managed adequately by alterations of dosage or timing of pill delivery. However, there has been a longer-term question of whether, over time, stimulants may suppress the ultimate stature (height) of a child. Initial analyses revealed that previously medication-naïve children who were medicated throughout the MTA treatment trial—as well as during the initial two-year follow-up—showed a reduction of height of approximately one inch.<sup>61</sup> This same level of growth suppression was noted, more recently, across a 10-year follow-up interval.<sup>15</sup> That is, intensive, consistent stimulant treatment causes, on average, a nearly 1-inch growth lag the first year that is not caught up over the next 10 years if medication is continued. The underlying message is that positive versus negative effects of treatments must be weighed by clients as well as those funding those interventions.

### **Naturalistic Follow-up**

As noted in passing within the previous section on side effects, the MTA investigators prioritized longitudinal follow-up beyond the 14-month period of active intervention, to explore the persistence of any initial benefits or the potential emergence of “sleeper” effects across time. In effect, all participating families became members of the Community Comparison condition after the formal period of intervention ended, in that MTA staff no longer provided treatment—and families needed to fend for themselves in terms of procuring services for their children. (Of course, a given family’s experiences during the trial may have influenced their subsequent treatment decisions, revealing the complexities involved in making inferences about lasting gains, plus the need for equally complex statistical strategies for analyzing follow-up data.) In sum, after the clinical trial per se, the MTA entered a 15-year phase of naturalistic follow-up.

Ten months after the end of formal treatment, the relative advantage of the Medication Management and Combined Treatment conditions over Behavioral Treatment and Community Comparison with respect to ADHD symptomatology had been reduced by half. Specifically, participants in Behavioral Treatment (a third or more of whom were now receiving medication) continued to show some improvement but the initially medicated participants (some of whom had stopped medication) had begun to backslide. In another year's time participants across all four randomly assigned treatments were in an essential dead heat with respect to nearly all core outcomes: The initial advantages for optimally medicated participants had dissipated.<sup>12,62,63,64</sup> This pattern—of initial superiority of medication-based treatments that tapered and then evaporated once intensive, manualized treatments had ended—has continued across all years subsequent follow-up.<sup>65</sup> Still, this convergence of results is at a level significantly improved from baseline, at least for ADHD symptoms.

In the absence of a multi-year randomized trial, of course, it is impossible to assert with certainty whether the tapering of the effectiveness of medication is related to the lack of a continued, intensive medication treatment, to the tendency for participants with the highest severity of symptoms to remain medicated, or to some other selection-related factors. However, careful propensity analyses showed that such selection biases were not likely explanations,<sup>66</sup> leaving open the possibility that medications targeting dopamine and norepinephrine neurotransmission may, at least in some cases, have an “expiration date” with respect to their effectiveness over the course of continuous administration. Medication may not be an extended, hoped-for panacea in all individuals,<sup>67</sup> despite the multiple short-term randomized clinical investigations showing significant benefit compared to placebo in children, adolescents, and adults.

In short, just like behavioral treatments, which are known to lack continued benefit once the contingencies are lifted, medication for ADHD may not always be a viable lifelong option (for detailed discussion of the intricacies of the MTA as it transformed from a randomized clinical trial to naturalistic follow-up investigation, see Swanson and colleagues<sup>68,69</sup>). The core question, therefore, is *which* intervention strategies, delivered at *which* time intervals and at *what* levels of intensity, are optimal in promoting maintained change for different subgroups of youth with ADHD.

## DISCUSSION

### Key Findings

The initial reported findings of the MTA related to medication's superiority were highly influential in the press, in subsequent published treatment recommendations, and undoubtedly in much clinical practice. Even though alternative analyses of outcomes, reports of moderator and mediator processes, cost-benefit analyses, and follow-up findings (see above sections) provided a far more complex picture of effectiveness than the early publications had revealed, medication as a treatment has continued to soar in popularity.<sup>70</sup> Indeed, even if behavioral and multimodal treatments are sought, too few practitioners are skilled in their use, and reimbursements are usually far from adequate.<sup>1</sup> Graduate and professional training in evidence-based interventions is a major priority.

Against the backdrop of soaring rates of ADHD diagnoses and medication treatment, and given additional information about the limitations of medication as a sole treatment modality, reconsideration of the MTA findings has been brewing, including many of the study's primary investigators.<sup>71</sup> ADHD is far from a set of symptoms that, when lowered, is "cured." Despite the clear benefits of medication in most cases of ADHD, initial gains may not sustain, and side effects such as growth suppression must be taken into account. For comorbid cases, in particular, it is apparent that several channels of intervention are mandated; the presence of anxiety disorders with ADHD should steer practitioners to behavioral/psychosocial interventions. The complex, transactional nature of biological vulnerability, discordant family interactions, peer rejection, and classroom struggles faced by far too many youth with this condition requires a fundamental reconceptualization of needed intervention, which might include direct support for parental depression and ADHD-related symptomatology,<sup>72</sup> academic remediation, peer and friendship coaching,<sup>73</sup> organizational skills training,<sup>74</sup> well-coordinated parent-teacher interchange, and attention to nutritional support.<sup>75</sup> In addition, despite recent evidence that specific cognitive training for ADHD (e.g., working memory training) does not lead to generalized gains, it may well be the case that combining skills- and reinforcement-based behavioral interventions with neurocognitive intervention holds promise.<sup>76</sup> Moreover, the stunning mediator finding that parents in multimodal treatment the largest improvements in reducing negative/ineffective discipline were precisely those whose children were normalized in terms of school behavior

### Paradox

Despite the clear evidentiary base for medication and behavioral treatments related to ADHD and despite suggestions that medication treatment may actually be neuroprotective for individuals with ADHD (despite prevalent fears and stereotypes that they will disrupt brain functioning),<sup>77</sup> the effects of each dissipate rapidly when (a) the medication is terminated or (b) the contingencies are lifted. Thus, both behavioral and medication treatments are best viewed as palliative rather than curative. The paradox is that, despite their proven short-term benefits, no clinically significant and enduring intervention (or intervention combination) exists for this condition, as of yet. Perhaps this fact should come as no great surprise, given the complex etiological pathways linked to its emergence and maintenance of this condition.<sup>17,23,78</sup> It will take advances in basic science—related to the formation of synaptic pathways underlying attention, response inhibition, intrinsic motivation, and self-regulation—and (a) extending efficacious treatments and (b) developing new treatments altogether to meet the considerable challenge ahead (indeed, see Abikoff for cogent discussion of the challenges of promoting generalization in the treatment of ADHD<sup>79</sup>). Intervention for ADHD must be viewed as a lifelong enterprise, with a major need to implement developmental extensions of evidence-based treatments into adolescence and adulthood, as well as development of new treatments appropriate for each age. The clinical picture of ADHD's trajectory is devastating in far too many cases, with outcomes of academic and vocational failure, low levels of organizational skills and executive functions, substance abuse, self-injury, and interpersonal tumult, demanding a concerted effort to rethink our fundamental attitudes and approaches toward this condition.



## Conclusion

For a number of important reasons, clinical trials should be preregistered, with hypotheses and primary outcome measures publicized in advance of presentation of outcomes and with data analyses emphasizing such procedures as “intent to treat,” meaning that once a participant is randomized to a particular condition, he or she should always be analyzed with respect to that condition.<sup>80</sup> In other words, clinical trials should not typically be subject to an “infinite regress” of alternative analyses, which may encumber the risk of promotion of chance-level, after-the-fact conclusions. Still, there is good reason to consider that the primary outcomes of the MTA, presented separately by domain and informant, yielded experimentwise alpha correction procedures that overlooked the clinical significance of multimodal treatment, particularly for measures linked to functional impairment. Composited outcome measures, potentially more difficult to interpret clinically but presumably more reliable and robust, provided evidence for preferential benefit from combined treatment. In addition, understanding of moderator and mediator analyses emphasizing the stronger response of comorbidity-defined or SES-linked subgroups (or of parenting/discipline as a key mediator) with respect to multimodal intervention is essential for full appreciation of the overall, average effects of the randomly assigned treatments. In addition, and crucially, comprehending the differences between immediate response to treatments, even as intensive as those in the MTA trial, and longer-term outcomes into adolescence and beyond presents a challenge to the assumption that ADHD is amenable to significant long-range alteration from childhood-focused treatments alone. Finally, as effective as medications are for promoting symptom change, it may well take skill building and positive-habit-forming approaches related to behavioral and other forms of psychosocial intervention to produce needed long-term improvements in the too-often dismal trajectories related to ADHD.

The challenge ahead is therefore great. Even when stigma is overcome<sup>81</sup> and an appropriate diagnosis is made—and evidence-based treatment initiated—far more remains to be done. Most saliently, the field needs to rethink the ways, beyond altering individual neurochemistry per se, in which families, schools, and peer groups must be included in the effort to foster self-regulation and age-appropriate competencies across the lifespan. Given the increasing evidence for long-range impairments in the clear majority of individuals with ADHD, such reconceptualization and renewed effort is of paramount importance.

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