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A Clinical Review of Outcomes of the Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder (MTA)

Desiree W. Murray, Ph.D.,
Duke University Medical Center, 718 Rutherford St., Durham NC 27705, (919) 416-2082 phone, (919) 286-7081

L. Eugene Arnold, M.D.,
Ohio State University, Department of Psychiatry, 479 South Galena Rd., Sunbury OH 43074, (740) 965-1005 phone, (740) 965-4425

Jim Swanson, Ph.D.,
University of California at Irvine, Child Development Center, 19722 MacArthur Blvd, Irvine CA 92612, (949) 824-1824 phone, (949) 824-8737

Karen Wells, Ph.D.,
Duke University Medical Center, 718 Rutherford St., Durham NC 27705, (919) 416-2435 phone, (919) 286-5268

Karen Burns, B.A.,
Duke University Medical Center, 718 Rutherford St., Durham NC 27705, (919) 416-2448 phone, (919) 286-7081

Peter Jensen, M.D.,
The REACH Institute, 71 West 23rdSt, 8thFloor, New York NY 10010, (212) 845-4486 phone, (917) 438-0894

Lily Hechtman, M.D.,
Montreal Children's Hospital, Department of Psychiatry, 4018 Ste. Catherine St. W., Westmount Quebec Canada H3Z 1P2, (514) 412-4449 phone, (514) 412-4337

Natalya Paykina, M.A.,
Columbia University, NYSPI, 1051 Riverside Drive, Unit 74, New York NY 10032, (212) 543-6812 phone, (212) 543-6660

Lauren Legato, M.A., and
Columbia University, NYSPI, 1051 Riverside Drive, Unit 74, New York NY 10032, (212) 543-6836 phone, (212) 543-6660

Tara Strauss, B.A.
Columbia University, NYSPI, 1051 Riverside Drive, Unit 74, New York NY 10032, (212) 543-5187 phone, (212) 543-6660

Correspondence to: Desiree W. Murray.

Abstract

Over the past decade, the MTA has provided a bewildering wealth of data (70 peer-reviewed articles) addressing treatment-related questions for children with attention-deficit/hyperactivity disorder (ADHD); however, the take-home messages for clinicians may not always be clear. Therefore, this article reviews key findings, including relative benefits of medication and behavioral treatments, long-term effects at two and three years, treatment mediators and moderators, preliminary delinquency and substance use outcomes, and growth suppression related to stimulant use. Appropriate interpretations of the findings and their limitations are discussed and recommendations for clinical practice are derived.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common syndrome of pervasive inattention, overactivity, and impulsivity beginning in childhood. The Multimodal Treatment Study of Children with ADHD (MTA) has yielded more than 70 peer-reviewed articles, with complex findings regarding treatment outcomes for stimulant medication and behavioral treatments. Despite the breadth and depth of this literature, questions and misunderstandings about the meaning of the MTA have been ongoing in the popular media as well as in scientific communications [1, 2]. This has created challenges for clinicians to integrate some of the complex analyses and various interpretations and apply them to day-to-day treatment decisions. This paper therefore reviews key clinical findings from the MTA, with specific emphasis on 36-month outcomes and their implications, to assist clinicians in working with families with children with ADHD.

Medication vs. Behavioral Treatments

The MTA addressed the important clinical question of what treatments should be recommended for ADHD in elementary-aged children by comparing the relative benefits of medication and behavioral treatments for 579 children aged 7–9 years with ADHD, Combined Type. Participants were randomly assigned to one of four interventions: intensive multi-component behavior therapy including parent training, school consultation, and a summer treatment program (Beh) [3]; intensive medication management including initial titration and monthly reevaluations (MedMgt) [4]; the combination (Comb); and self-selected community care (Community Comparison, CC). At the end of the 14-month treatment period, children in Comb and MedMgt showed greater improvement than the other two groups in ADHD and Oppositional Defiant Disorder (ODD) symptoms as well as rates of diagnosis of these disorders, but did not differ significantly from each other in core symptoms.

Comb was superior to Beh and/or CC on parent-rated oppositional/aggressive symptoms, internalizing symptoms, teacher-rated social skills, parent-child relations, and reading achievement [5]. In secondary analyses with composite measures [6] and on categorically defined success rates [7] Comb was also superior to MedMgt. There was a modest clinical advantage for Comb for children with co-morbid anxiety/depression and oppositional/conduct disordered behavior [8] and for parent and teacher satisfaction [5]. Relative to CC,

Comb also had less comorbidity at 14 months [9]. Groups including the behavioral treatments demonstrated greater changes in self-reported parenting behaviors [10] and Comb was superior to MedMgt on measures of parent-child interaction obtained from blind observers [11]. Children in the Comb group achieved slightly better outcomes with 20% lower doses of methylphenidate than those who received medication alone [12]. Thus, behavioral treatment was an important addition to medication for improving key functional outcomes, enhancing children's overall outcomes, and minimizing exposure to stimulant medication.

Of interest, intensive behavioral treatments provided in the study were equivalent in efficacy to community care which consisted of stimulant medication for 67% [5]. In addition, almost three-fourths of the Beh group was successfully managed without medication for 14 months. Overall, 68% of children were considered to have been successfully treated in the Comb group, 56% in the Medmgt group, 34% in the Beh group and 25% in the CC group [7].

Another important clinical finding at 14 months was that children prescribed medication through the study did significantly better than those treated with medication in the community [5], which was prescribed at significantly lower dosages (19 vs. 33 mg./day) and was taken only about half as long (5.5 vs. 10 months). Notably, the MTA medication algorithm included monthly visits with a pharmacotherapist who monitored effectiveness and side effects based upon parent and teacher input and made dosage adjustments about 3 times per year. Thus, the quality of medication management appears to have significant implications for treatment responsiveness.

Long-term Treatment Effects

To date, published MTA data have examined two and three year follow-up effects of the four treatment groups. At the 24 month assessment, ten months after MTA study treatments ended, Comb and MedMgt retained superiority over Beh and CC, although the size of this effect was half of that found immediately post-treatment [13]. Part of this decline was thought to be related to children in Beh starting medication who had not previously taken it, and children in Comb and MedMgt stopping medication who had been taking it. That is, failure to maintain an effective intervention may explain the attenuation of long-term benefits rather than a reduction in medication effects. In fact, part of the continuing superiority of the two MTA medication groups was due to their higher rates of medication use between 14 and 24 months. However, even when medication use was stopped, there was some persistence of benefit for those assigned to the intensive medication algorithm. Although the actual clinical benefit at follow up was rather modest (with an average of 36% of study participants approaching normalization of core symptoms), these findings support residual long-term relative superiority of the MTA Medication Algorithm for two years [13].

At 36 months (after 22 months of naturalistic follow up), differences were no longer found between any of the groups formed by the original random assignment. However, all the groups improved substantially across all outcome areas. More specifically, regardless of assigned treatment, levels of symptoms and rates of diagnoses about two years after the study treatments were provided did not differ in any meaningful way across groups and

reflected substantial improvement across domains compared to baseline. About half the children continued to meet full criteria for ADHD and less than one-third met criteria for Oppositional Defiant Disorder (ODD) or Conduct Disorder (CD), although symptom levels remained above those of a Local Normative Comparison Group (LNCG) recruited from the same classrooms as MTA children and matched for gender and ethnicity [14].

As expected, greater medication use produced better outcomes at end of study treatment and 24 months. However, children medicated between 24 and 36 months were more symptomatic than those not taking medication [14]. This suggested that parents of more severe children sought more treatment for them, a hypothesis consistent with the finding that 36 month outcomes were also worse for children who had received special education services during the follow up period. When examined using more rigorous statistical methods, however, the self-selection hypothesis for medication was not supported [15]. Of note, the statistical method used to evaluate this hypothesis assumes that selection biases can be modeled as a simple linear combination of multiple, complex variables – an assumption which may or may not be correct. Future research, perhaps with new samples, will be needed to determine whether the sensible, but unsupported self-selection hypothesis is correct, and if so, for whom.

In order to understand outcomes further, subgroups of participants with different patterns of improvement in ADHD symptoms were identified using methodology identifying latent subclasses based upon trajectories over time [16]. As described by Swanson et al. [15], Class 1 (34% of the sample) showed initial small improvements followed by gradual improvement over time; Class 2 (52%) had initial large improvement that was maintained over three years; and Class 3 (14%) showed initial large improvement followed by deterioration. The class with the most favorable outcomes (Class 2) was not as severely impaired at baseline and had lower rates of psychosocial adversity. In addition, it included more participants who had received the MTA medication algorithm whether or not they were taking medication at 36 months, suggesting that some children benefited from this early medication treatment, with or without long-term medication use. For Class 1, those taking medication were doing significantly better at all time points than those who were not, and this difference increased over time, reflecting long term benefit of actual medication. Class 3, with the worst long-term outcomes, had high severity scores at baseline, lower IQs, more comorbidity, lower social skills, and other risk factors. These children likely needed longer or additional treatments than were provided in the MTA. For further details regarding a number of methodological, design, and implementation issues important for the interpretation of these findings, readers are referred to Swanson et al. [1, 2].

Delinquency and Substance Use

Early delinquent behavior and substance use is an important area of functioning examined in the MTA [17]. Children with ADHD have been shown to be at increased risk for serious conduct problems and antisocial behavior, although it is not clear whether this is due to ADHD itself or to the co-morbidity of ADHD with other externalizing problems [18, 19]. Other work has suggested a counter-intuitive protective effect of stimulant use on future alcohol and drug use for children with ADHD [20], although this was not present at follow-

up [21]. In order to understand the early development of these outcomes, 11–13 year old children in the MTA (n = 487) were compared to the LNCG group (n = 272).

At 36 months, 27.1% of MTA children had engaged in moderately serious delinquency (e.g., shoplifting, stealing from someone's desk or locker, hitting someone and causing injury, and carrying or using a weapon) compared to only 7.4% of LNCG children. Only about one-third of those children actually met criteria for CD, but having a diagnosis of CD significantly increased the chances of being delinquent. Similarly, MTA children reported significantly higher rates of illicit substance use (primarily alcohol and cigarettes) than did LNCG children (17.4% vs. 7.8%), and use of substances was predicted by moderate to serious delinquent behavior. Thus although the majority did not exhibit delinquent behavior or use illicit substances, a subgroup of MTA preadolescents with ADHD were using substances precociously at an early age, warranting clinical concern.

As might be expected, children who received intensive behavioral treatments in the study showed lower rates of substance use at the 24 month follow up than those who did not. However, randomized study treatments did not have any impact on delinquency and substance use at 36 months. Children with more serious delinquency were more likely to be medicated after study treatment ended, presumably reflecting this group's overall poorer level of functioning rather than an adverse effect of medication. However, it is not possible to determine whether these children would be doing worse without medication, or whether long term medication delivered in response to chronic, serious problem behaviors may not be efficacious. There was no relationship between use of prescription medication for ADHD and substance use; future analyses will evaluate whether a protective or predisposing effect may exist at older ages. For clinicians, these findings suggest that additional interventions beyond those provided in the MTA may be needed to address these areas of concern for some children with ADHD.

Growth Suppression

Concerns of growth suppression related to stimulant medication have existed for decades, although at the time the MTA began there was strong consensus that these were not clinically significant with regard to long term effects [22]. This was based upon hypotheses that growth rebound would occur when medication was discontinued or that children with ADHD simply grow slower for a longer time, although data at that time were fairly inconsistent and not based upon any prospective long-term studies. To address these concerns empirically, the height and weight of 370 MTA children who had different pattern of medication use (primarily methylphenidate) were examined over time [23].

Results indicate that average relative size was negatively related to the average cumulative exposure to stimulant medication, with children consistently medicated since before the study having the smallest height and weight gains over three years. Over 36 months, children newly medicated in the study grew an average of 2 cm and 2.7 kg less than stimulant-untreated children with ADHD. By analysis of originally assigned treatments, growth slowing of about 1 cm/yr was found for the medicated groups relative to Beh for the first 14 months, but this attenuated to non-significance at the 24-month and 36 month

assessments. However, an alternative analysis by actual medication use showed an effect the second year.

Growth suppression was maximal in the first year, decreased in the second year, and absent in the third year. However, there was no evidence of growth rebound when treated children were compared to untreated children of the same age. Similarly, these data do not support the hypothesis that children with ADHD have inherently small size or delayed maturation, as those who had not taken medication prior to the study were significantly larger than average, and grew at a faster rate than LNCG children. This may suggest a disorder-related growth acceleration which could be related to dopamine levels [24]. Results must be considered in the context of limitations including lack of random assignment and lack of follow up through puberty, which has occurred but has not yet been reported. Data are consistent with a recently published prospective study of preschoolers [25] and with two clinical chart reviews [26, 27], but not with two others [28, 29].

Perhaps the most important clinical finding from these data is that use of stimulant medication may slow growth in height and weight up to two years in pre-pubertal children with ADHD, Combined Type. However, it is important to note that for children beginning medication in the primary grades, the total amount of growth suppression averaged slightly less than an inch in the first two years of consistent medication with no further suppression the third year even if the medication was continued. The total amount of growth loss and whether future rebound may occur will be examined in analyses of data from future follow-up assessments.

Factors Influencing Treatment Outcomes

Clinicians may wonder whether MTA findings apply to any particular case given the child and family's unique characteristics. Questions related to which treatments are best for which child have been addressed by the MTA, which is large enough to allow examination of a number of potential moderating variables, including the child's gender, ethnicity, and co-morbidity as well as the family's socio-economic situation and parental psychopathology. However, there are many possible moderators that could be evaluated, so these multiple tests should be considered exploratory.

As can be seen in Table 1, comorbidity profiles may influence initial response of ADHD symptoms to behavioral and medication treatments. At the end of the 14-month treatment phase, children with ADHD and an anxiety disorder (one-third of the MTA sample) responded better to behavioral treatment than those without comorbid anxiety, children with ADHD and ODD or CD responded best to treatments including medication, and those with "double comorbidity" with both anxiety/depression and CD/ODD (25% of the MTA sample) responded best to the combination of behavioral and medication treatments [8, 30]. None of these moderator effects were found at 36 months [14], perhaps because of the overall improvement seen for all children. Contrary to expectation, neither comorbid anxiety nor manic symptoms were associated with worse response to medication during active MTA treatment [30, 31].

Combination treatment appeared to improve social skills and prevent deterioration in parent-child relationships to a greater degree in the 19% of families who began the study receiving some form of public assistance [30]. Socio-economic status was also a predictor of worse 36 month outcomes [14]. In addition, differential treatment responsiveness was seen by ethnicity in exploratory analyses such that African-American children showed relatively better response to behavioral treatment alone than did Caucasian children, and Latino children responded more favorably to combination treatment than medication management alone. Importantly, however, when receipt of public assistance and single parent status were considered, ethnicity effects were no longer significant [32]. Thus, ethnicity may only indirectly impact treatment via other factors such as having the ability or resources to attend appointments and engage in treatment. Perhaps more surprising was that while all minorities together did significantly better with Comb than MedMgt, on average Caucasian participants did not seem to benefit incrementally from Comb. This suggests that addition of behavioral treatment to medication may be most important for minorities [32].

Additional moderator effects were identified by Owens et al. [33] for treatments including MTA medication (Comb and MedMgt). As expected, treatment response rates defined by a summary of ADHD and ODD symptoms were lower for children with greater risk factors including IQ < 100, greater initial ADHD severity, and higher parental depression. More specifically, parents reporting a Beck Depression Inventory score ≥ 9 and children with extreme ADHD symptom severity (mean ≥2.33 on 0–3 rating) at baseline showed lower rates of child behavioral normalization. When these two factors were combined with lower IQ, response rates dropped to 0% for MedMgt and 25% for Comb. Thus, MTA treatments appeared least effective for those with the greatest number of risk factors.

Regarding gender, few differences were seen in 14-month response between boys and girls [30]. However, at 36 months girls were over-represented in Class 2, which had the best outcomes [15], and being female was a predictor of greater long-term improvement [14]. Better outcomes for girls may be related to less severe symptoms, particularly impulsivity [34]. Finally, exploratory analyses suggest that prenatal exposure to maternal smoking may be related to increased growth suppression from early and persistent stimulant treatment [35].

Understanding the Treatment Process

It is also helpful for clinicians to understand the processes and mechanisms that yield clinically significant change for children with ADHD. One of the key mediators of medication efficacy in the MTA was attendance at treatment sessions “as intended”, with lower 14-month parent and teacher ratings of ADHD symptoms found for children whose parents met this threshold as compared to those who did not. However, “treatment as intended” did not mediate outcomes for behavioral treatments. “As intended” for medication treatment was defined as attendance at 80% of the 13 monthly monitoring visits with a prescription written and delivered. For behavioral treatment, “as intended” was defined by parent attendance at 75% of the 27 group parent training sessions, child attendance at 75% of the 40 days of the summer treatment program, and child and paraprofessional both present in the classroom for 75% of 12 school weeks. Overall attendance as intended was

higher for MedMgt (78–81%) than for behavioral treatments (61–63%), which is not surprising given the significantly higher participation demands placed on participants in the behavioral groups. Relative to other parent training studies, however, MTA attendance rates were actually higher [36–38].

The lack of mediator effects for behavioral treatments may be explained by the fact that medication works while it is taken and thus visit attendance to get the next prescription is critical, whereas behavioral treatment could be continued by parents and teachers even with missed visits. In fact, other analyses found that actual changes in parent discipline practices influenced children's behavior and social skills. Specifically, changes in negative and ineffective practices for parents in Comb treatment explained improvements in teacher-reported social skills. Indeed, children whose parents showed the greatest reduction in negative/ineffective discipline were rated as having normalized school behavior [39].

Application to Community Practice

Application of MTA results to community practice is certainly limited by sample characteristics. Although large and relatively diverse geographically, ethnically, and socio-economically, all children were diagnosed with ADHD, Combined Type, and thus, findings may not be relevant for children with ADHD, Inattentive Type. Indeed, psychosocial treatments may need to be adapted for inattentive-only children [40]. Moreover, children with certain comorbidities such as Pervasive Developmental Disorder, Intellectual Disabilities, psychosis, Tourette's Disorder, and severe Obsessive-Compulsive Disorder were excluded from the MTA in addition to children who had been hospitalized in the last 6 months or were being treated with an antipsychotic medication. Thus, caution is warranted in applying MTA results to these groups.

Additional cautions in interpreting results arise from the MTA's design and hypotheses. Cunningham [41] suggested that the effects of behavioral treatment may have been underestimated due to the lack of an untreated control group and the possibility that families assigned to medication alone benefited from informal behavioral interventions in the community. Indeed, studies using alternate designs such as within-subject and multiple baseline yield considerably higher effect sizes than those seen in the MTA [42]. On the other hand, the benefits of medication alone could have also been underestimated due to the MedMgt group stopping medication and the Beh group starting medication [43]. Similarly, had children in the Comb group received higher doses of medication more like those in MedMgt, even greater medication superiority might have been demonstrated.

For most MTA children, the combination of medication and behavioral treatments optimized outcomes at 14 months. As suggested by 36-month findings [15], some families benefit by relatively brief (14-month) treatments, while others relapse if intensive treatments are not continued. Although MTA-like behavioral interventions as a package are unlikely to be available in clinical practice given realities of managed care [44], it is possible that alternative or less intensive treatments might be effective if they are matched to the individual child and parent's needs and/or comorbidity profiles [8, 45]. The most expensive and intensive treatments could be reserved for those children with the greatest risk factors

[46] and for whom effective treatment may prevent substantial costs to educational and juvenile justice systems [47]. It should be noted, however, that matching treatments to children also poses numerous challenges and has few empirical guidelines [48].

The high rates of success in the MTA associated with three-times-a-day dosing with immediate-release methylphenidate established this as “state of the art” treatment at the time it was conducted in 1994–1997. Since then, extended release formulations of methylphenidate (e.g. Concerta) and amphetamine (e.g., Adderall) matching this duration of action have become widely used [49]. The monthly medication monitoring visits and physician-teacher communication used in the MTA remain applicable to current practice. Unfortunately, there is little indication that such practices are used any more frequently now than they were a decade ago [50].

Given MTA findings, clinicians should discuss the possibility of relatively small long-term decrements in both height and weight associated with consistent use of stimulant medication in the context of the individual child’s benefits to assist families in weighing the risk-benefit ratio. To minimize the risk of growth suppression, Swanson et al. [1, 2] recommend that follow up should occur frequently (e.g., every two months) and should be informed by school input so that dosage may be adjusted as needed. Growth should be monitored on growth charts and data reviewed every six months or year to assess change over time. In addition, as intermittent medication use was associated with less growth slowing compared to continuous use, planned drug holidays could be considered. Medication efficacy should also be assessed annually through brief periods of medication discontinuation to weigh risks vs. benefits.

Conclusions

For most elementary school-aged children with ADHD Combined Type, the combination of medication and behavioral interventions appears to produce the greatest improvement in symptoms and functional outcomes for at least one to two years and may be particularly important for children with certain comorbid conditions and from lower socio-economic backgrounds. Concurrent behavioral interventions may lower medication doses needed and enhance parent satisfaction which may facilitate adherence to long-term treatments and minimize side effects such as growth suppression. Behavioral interventions are also needed for the development of positive aspects of parenting. What remain to be examined in other studies is the type and duration of behavioral interventions that are needed to achieve clinically significant results in a cost-effective manner. In addition, community care with stimulant medication needs to include more frequent monitoring and consistent, titrated dosing in order to obtain results similar to those seen in the MTA.

Almost ten years after randomized treatment in the MTA study ended, clinically relevant information continues to be generated. Data are currently being collected on 12 year outcomes, with analyses of 6 and 8 year data to be submitted for publication shortly. Future findings are expected to help generate new ideas about treatments for ADHD and new theories about the pathogenesis, course, and sequelae of ADHD.

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* These four articles are considered “of importance” as they include the key 36-month findings that provide the content for the body of this article. These are the most recently published outcome data for the MTA.

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Table 1

Moderators and Mediators of MTA Treatment Effects

Moderator	**Effect**
Comorbid Anxiety	Responded equally well to behavioral treatment and medication; most treatment responsive subgroup
Comorbid ODD/CD	Medication required for benefit; worse outcomes than ADHD alone
Comorbid Anxiety + ODD/CD	Greater benefits from Comb treatments than other groups
Comorbid manic symptoms	No effect on medication response or side effects
Receipt of Public Assistance	Benefit more from Comb than medication alone; may be related to poorer treatment attendance
Minorities	African-Americans responded better to behavioral treatments alone; Hispanics responded better to Comb thanMedMgt; BUT no differences after controlling for public assistance. Minorities in general responded better to Comb than to MedMgt even after controlling for SES.
Maternal Depression + Severe ADHD	Lower rates of excellent response (48% vs. 73%)
Maternal Depression +Severe ADHD +IQ<100	Lowest rates of excellent response (10%)
Female Gender	Overall few differences, but Comb needed for effect on hyperactivity-impulsivity
Prenatal Exposure to Maternal Smoking	Increased growth suppression in children with early and persistent stimulant exposure
Mediator	Effect
Attendance at Medication Visits	80%+ related to better treatment response
Attendance at Behavioral Treatment Visits	Unrelated to treatment response as defined in this study
Changes in Parental Discipline Practices	Improved teacher-rated social skills

Note. The only long-term predictor effect maintained at 36 months was socio-economic status (e.g., low status predicted worse outcomes). Girls also had better long-term outcomes.