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Understanding the 36-Month MTA Follow-Up Findings in Context

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THE NATIONAL INSTITUTE OF MENTAL HEALTH (NIMH) Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder is usually called the MTA. The MTA is a large study that compared three different treatments for childhood AD/HD. The MTA team has been following the children since treatment ended over ten years ago. A special section in the *Journal of the American Academy of Child and Adolescent Psychiatry* in the summer of 2007 described the 36-month outcomes in four articles. The findings have been widely cited, but often misunderstood, partly because it is difficult to interpret results spread over four papers—and partly because these follow-up findings deal with examining the children's outcome nearly two years after the study treatment phase ended. This article is intended to clarify the meaning and limitations of the findings.


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Background information

To understand the 36-month findings, it is important to keep the study design in mind. The study treatments were provided to children only during the first 14 months of the study, when they were 7 to 9 years old. Although we had wanted to provide two full years of treatment—knowing that AD/HD is not a "short-term" disorder—our budget limited the treatment phase to 14 months. We randomly assigned families to receive one of four treatments: (a) medication management, (b) intensive behavior therapy, (c) the combination of medication and behavior therapy, or (d) treatment as usual in the community (the community comparison group).

The MTA medication management differed from the way medication is usually managed in the community by including several features: a careful initial comparison of different doses of medication to a placebo to make sure the medication was really working and to find the best dose, a trial of different medications and doses if the first medication did not work, telephone interviews with the child's teachers, and half-hour monthly office visits with the child and family to monitor the continued effectiveness of the medication.

Rather than letting families pick their own treatment of choice, our random assignment of families to different treatments ensured that comparisons of treatments were unbiased (fair and scientifically valid). We know, for example, that certain types of families may be likely to pick certain types of treatments for their children, and the characteristics of the families or children rather than the treatments may influence their outcomes. The design of the MTA (with random assignment) prevented this situation from occurring during the first 14 months of treatment. However, after that treatment period ended, the MTA became a "naturalistic" follow-up study: The MTA staff no longer provided treatment, and families were free to choose whatever treatment they wanted and could afford. Even so, we have continued to follow these children and to evaluate how they and their families are doing since that time.

It may be the case that our randomly assigned treatments would "work" only as long as they were delivered by the MTA staff. Over time, families might or might not stay with the treatment to which they had been assigned for the first 14 months. So, for our follow-up studies, we looked not only at the randomly assigned MTA treatment for each family but also at the treatments they actually received from community providers

during the follow-up time period. For example, some children originally assigned to medication management or combined treatment continued to take medication while others stopped, and some first assigned to behavioral therapy or community comparison started medication, even though they had not previously taken it.

So, our follow-up data are less scientifically "pure" because many things (such as insurance, transportation, parents' preferences, availability of treatment, and the like) may explain why a child received certain treatments beyond the initial phase of the MTA. We worked closely with statistical experts in order to control for the kinds of things that might explain patterns of treatment after the 14-month random assignment phase. Still, we must interpret the findings with caution. Finally, as with any scientific report, we have to remember that the results are based on averages across children, and few if any children are exactly average.

With these thoughts in mind, let's review the key findings from the beginning.

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MTA findings over time

First we summarize the initial findings from the MTA. At the end of the 14-month treatment phase, the two groups that were randomly assigned to receive MTA medication management—either alone or combined with behavior therapy—had improved significantly more in AD/HD symptoms and oppositional-defiant symptoms than the behavioral therapy alone or community comparison groups. (Note that two-thirds of the community comparison group also received medication, but not nearly as closely monitored as the MTA's medication management.) Also, those who received combined treatment did better than those who received medication management alone, particularly for non-symptom areas like family interaction patterns and academic achievement. The modest superiority of the combined treatment was achieved with significantly lower doses of medication than the medication management treatment alone. Overall, the community comparison group fared least well in social skills and academic achievement. Also, the presence of anxiety in addition to AD/HD made behavioral treatment relatively more successful than when children did not have anxiety. The presence of both anxiety and aggressive behavior made the combined treatment superior to all others.

At 24 months (after a 10-month follow-up period), we found that children first assigned to the medication management or combined treatment groups still showed more improvement in AD/HD symptoms than children in the other two treatment groups—but their advantage at 14 months was fading. The continued advantage of medication management and combined treatments appeared to be largely, but not entirely, due to most families' continuing medication on their own, while the fading of advantage occurred when the medication was stopped. On the other hand, some children first assigned to behavior therapy alone increased their medication use after 14 months and showed a slight improvement by 24 months. An interesting finding at 24 months was that the earlier experience of behavior therapy seemed to protect against early substance use (mainly alcohol, tobacco, and marijuana), whether or not medication was used.

We also found that children who had been in MTA medication management or combined treatment groups grew significantly less in height than those assigned to behavioral treatment for the first 14 months. But by 24 months, the difference in height gain among the randomly assigned treatment groups dissipated, without rebound or "catch up." Overall, the difference in height gain was 0.8 of an inch between those who were never medicated and those who were medicated at both 14 and 24 months.

By 36 months, there was no longer any difference in AD/HD symptoms among any of the original randomly assigned treatment groups. That is, regardless of which treatment a child had been assigned during the 14-month treatment period, by 36 months—about two years after the MTA treatments stopped—the levels of AD/HD symptoms were identical. Whatever the initial advantage of medication management in the MTA, it was lost by that time. We then focused on "naturalistic" groups defined by patterns of actual treatment received during the follow-up period. We compared these groups not only to each other but also to a group of non-AD/HD classmates of the MTA children whom we had identified at 24 months to serve as a comparison group for follow-up studies.

We found something that at first may seem unusual: Children taking medication between the 24- and 36-month assessments got worse by 36 months compared to those not taking it—leaving no difference at 36 months. But this pattern would be expected if the most severe cases, as well as those who tended not to improve over time, either continued or started medication, while at the same time those who had improved tended to either stop or not start medication. (The same pattern was found for special education services: those who received these services between 24 and 36 months had worse outcomes at 36 months than those who did not receive such services during this time.) In other words, self-selection bias might explain the linking of worse outcome with medication use at 36 months.

But when we examined whether self-selection for medication at 36 months explained the lack of relative benefit of medication use at that point, our analysis failed to support this explanation. In fact, the idea that severity of symptoms was related to both medication use and worse outcomes was undercut by the observation that higher severity of symptoms before treatment began was linked to *less* medication at 36 months. This does not prove that self-selection was not a factor; it just means that we could not definitely show that it was operating.

In another analysis, to look beyond just the "average" findings, we regrouped children into three subgroups (or "classes") based on their pattern of change in symptoms over time. In one of these classes, about one-third of the sample, we found that consistent treatment with medication yielded benefit through 36 months, illustrating that some children differ from the average. Another class, just over half of the sample, had the best results, with immediate improvement from the randomly assigned treatment and maintenance of the improvement through 36 months. For this group, there was no advantage of the consistent medication at 36 months. Yet this class included more children originally randomized to medication management or combined treatment than to the other two treatments, raising the possibility that for some children, having the 14-month experience of rigorous medication management may have provided long-lasting benefit, whether or not ongoing use of medication still showed benefit. The third class, about a seventh of the sample, improved at 14 months and then deteriorated at 24 and 36 months. This group showed significant benefits of medication early, but not after 14 months. Experts disagree about how much confidence to put in these analyses of statistically derived subgroups, which are not protected by the initial randomization.

The overall pattern of change over time, regardless of treatment, showed substantial improvement in average symptom severity, but not to the level shown by the comparison group of classmates. That is, AD/HD symptoms continued to improve over time, but on average, the MTA children did not completely "normalize."

Although the randomly assigned groups showed no significant height differences at 24 and 36 months, when we examined the effects of growth by actual medication use—that is, based on consistent medication or lack of medication over the whole three years—we found some interesting findings. First, children with AD/HD who were never

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What Should Families and Doctors Do?

Considering the MTA findings, the results of other studies, and clinical common sense, the following may be considered:

- First, don't panic because of sensational headlines that may be misinterpreting the data.
- Plan each child's treatment individually and monitor it carefully.
- Follow-up should be frequent enough (e.g., every two months) and informed enough (e.g., with school input) to adjust medication dosages for optimal benefit and minimal side effects.
- The risk-benefit ratio of medication has to be considered for each child individually.
- Because side effects seem related to dose, adding behavioral therapy that allows reducing the dose of medication may also reduce side effects and improve daily life functioning in non-symptom areas such as social skills and academic performance.
- Keep growth charts to check on possible drop-off of growth rate. Keep in mind that children often grow in spurts, so consider at least six months of data (preferably a year) before drawing any conclusions.
- "Drug holidays" can test whether the medication is still needed and may decrease any growth lag. Medication should be continued as long as the benefit outweighs the risk. Many children in the MTA showed symptomatic improvement over time, despite stopping medication.
- In most instances, medication should be considered only as part of a comprehensive treatment plan. It may provide relative benefits (compared to other treatments) but cannot substitute for good teaching, supervision, and support provided by parents and teachers to maintain motivation.

treated with medication tended to be much taller than national averages and larger than their classmates at all times assessed. Second, stimulant medication mildly but significantly slowed growth in those not taking it before: those who had no previous medication use before the study began but took it throughout the 36 months of the study grew about ¾ inch less than those who never took medication. Third, those who took stimulant medication before entering the MTA study and consistently used it throughout had below-average size at all times assessed. They were much smaller than the group never treated with medication even before entering the MTA. These are averages, and individual children could have more or less slowing of their growth.

The full amount of growth slowing for those who first started medication in the MTA and continued it for 36 months, compared to those who never took it, was about ¾ inch on average, and that occurred in the first 24 months. That is, after 24 months of continuous medication, there was no further growth slowing even with continued medication use, nor was there rebound or catch-up growth (accelerated growth making up for the prior reduction in growth rate). The growth rate after 24 months paralleled that of the never-medicated group from that point on, even if medication was continued over the additional year. Will the residual growth loss eventually be "caught up"? We don't know yet, but we continue following the MTA participants, who are now in early adulthood. The answer will be determined from the 12-year data we are currently collecting. We will evaluate adult height relative to their expected size based on their parents' size.

Other studies and practical conclusions

Other studies have reported that stimulant medication for AD/HD is effective through two years. This is consistent with the MTA finding at 24 months: both those assigned to medication provided by the MTA and those having actual treatment with medication were doing relatively better than those assigned to groups without medication or not actually receiving medication. Beyond 24 months there are not good data from which to draw conclusions with confidence. The MTA was not designed to test the effect of medication for 36 months or longer. A different design would be necessary to test the effect of medication over longer periods, such as 36 months.

Taking all the available data into consideration, the following conclusions seem reasonable:

- In treatment of children with combined-type AD/HD, the inclusion of systematic medication management results in better relief of AD/HD and other symptoms than intensive behavioral therapy alone or low intensity medication. The medication effect may be enhanced when combined with behavioral treatment. The 14-month superiority of MTA medication management is still evident at 24 months.
- After 24 months there are considerable individual variations from child to child in the relative benefit of medication, and there is not a good evidence base for general conclusions about average benefit beyond 24 months.
- Benefits of medication management may remain or increase for a minority of children (about one-third) after several years of treatment.
- Regardless of treatment, the general trend of symptoms is to improve over time.
- At 36 months, the symptom level was greatly improved on average, including for those who stopped medication. But even if symptoms improve, there is no guarantee that improvements occur in other important areas of impairment.
- However, the average level of AD/HD symptoms did not reduce to that of a classmate comparison group, indicating that on average, children with AD/HD remain symptomatic relative to children without the disorder.
- It is possible that behavioral therapy, either with or without medication, may have a protective effect against very early substance use, but it is doubtful whether medication imparts either protection or risk regarding substance use.
- Continuous stimulant medication use seems on average to result in a slowing of height growth, confined to the first two years of treatment and accumulating to about ¾ inch, and after that there is no further slowing and no immediate catch-up of growth. This is an average and could be more or less for individual children.
- Intermittent medication use was accompanied by less slowing of growth compared to continuous use, so planned drug holidays, resulting in intermittent use, may mitigate growth slowing (but this was not tested in the MTA).

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