

Over the past year you may have seen preliminary reports of results from the Multimodal Treatment Study of Children with ADHD (MTA). This is the largest and most comprehensive treatment study of ADHD that has ever been conducted. Last month, the initial papers reporting the results from this study were published. This is a landmark study with a number of important implications.

The December issue of the Archives of General Psychiatry includes 2 papers that are based on this study. The first paper titled "a 14 month randomized clinical trial of treatment strategies for ADHD" presents the major findings from the study. The second paper, titled "Moderators and mediators of treatment response for children with ADHD" presents more fine-grained analyses in which factors that might have influenced response to the different treatments evaluated in the study were examined. In this summary, I will try to combine the findings that are reported in these two papers.

THE MTA STUDY

It is important to begin by providing an overview of how the study was conducted and the questions that it was specifically designed to address. The study represented the combined efforts of investigators at 6 different sites around the country and included 579 children ages 7 to 9.9 years who were diagnosed as having ADHD, Combined Type using state-of-the-art diagnostic procedures. (Children diagnosed with the hyperactive/impulsive subtype or inattentive subtype were excluded. This decision was made because the combined type is the most frequently diagnosed type of ADHD). Approximately 20% of the participants were girls and about the same percentage was African American.

After participants had been identified they were randomly assigned to 1 of 4 different treatment conditions. Fourteen months later, the participants were carefully evaluated so that the impact of the different treatments could be evaluated. Each treatment condition is described below.

MEDICATION MANAGEMENT - Children in the medication management condition received medication treatment only. This began with a 28-day, double-blind placebo-controlled trial in which the effects of 4 different doses of methylphenidate (the generic form of Ritalin) were evaluated. The doses tested were 5, 10, 15, and 20 mg. Children received a full dose at breakfast and lunch, and then a half-dose in the afternoon. Parent and teacher ratings of children's behavior on each dose were compared by a team of experienced clinicians, and the best dose for each child was selected by consensus. (In a double-blind placebo-controlled trial, the child is receiving real medication during some days and a placebo during other days. Neither the child, the teacher, nor the parent know when real medication is being received and when placebo is being received. Because of this, parent and teacher ratings of the child's behavior are not biased by the knowledge that the child is on medication.)

For children not obtaining an adequate response to methylphenidate during this initial trial, alternate medications were tested using non-double-blind procedures in the following order until a satisfactory medication and dose for the child was found: dextroamphetamine (the generic

version of dexedrine), pemoline (the generic version of Cylert), and imipramine (a tricyclic antidepressant).

Note: This study was begun before Adderall was available for use which is probably why it was not one of the medication options.

Of 289 participants initially assigned to receive medication in either the medication management condition or the combined condition (see below), 256 (88.6%) successfully completed this initial titration period used to select an effective medication. (For the remaining children, parents either refused to try their child on medication, there were intolerable side effects, or parents could not cooperate with the careful titration procedures.)

For about 69% of the children completing the initial medication trial, an adequate response was obtained with at least one of the doses of methylphenidate, and they began their treatment on this dose. Twenty-six children who did not respond to methylphenidate were found to do well on dextroamphetamine and began on this medication. A final 32 did not begin on any medication because they had such a strong placebo response that no clear benefits of medication could be demonstrated.

In addition to this VERY CAREFUL initial trial to determine the optimal medication and dose for each child, half-hour monthly visits were scheduled during which the provider for that child would review information about the child's behavior over the past month that was provided by parents and teachers. After carefully reviewing this information, dosage adjustments were made using predetermined guidelines. Adjustments that involved increases or decreases of more than 10 mg/dose needed to be approved by a cross-site panel of experts.

By the end of the study - 14 months later - about 74% of participants of the 289 in the medication or combined treatment groups were being successfully maintained on ethylphenidate, 10% on dextroamphetamine, and just over 1% on pemoline. Only two children were on any other type of medication. (As noted above, some children who were assigned to one of the medication groups never received medication either because their parents refused or could not follow the initial trial procedures.) Side effects had also been monitored monthly and over 85% of the sample were reported to show either no or mild side effects.

It is important to emphasize how different this approach to medication management was from what often occurs in community treatment. The primary differences are 1) the use of a double-blind trial to establish the best initial dose and medication for each child; and, 2) regular follow-up visits to evaluate ongoing medication effectiveness based on parent and teacher reports with systematic adjustments made as needed.

It is also important to note that almost all children were judged to be effectively managed on one of the standard stimulants (either methylphenidate or dextroamphetamine) and none were judged to require a combination of medications to effectively manage their ADHD symptoms. I think this underscores how rarely medications need to be combined to treat ADHD when a

careful procedure is used to test out the different types of stimulants that are available. This is discussed in another article in this issue of ADHD RESEARCH UPDATE that you will find below.

BEHAVIORAL TREATMENT - Behavioral treatment included parent training, child-focused treatment, and a school-based intervention. Parent training involved 27 group sessions and 8 individual sessions per family. The focus was on teaching parents specific behavioral strategies to deal with the challenges that children with ADHD often present.

The child-focused treatment was a summer treatment program that children attended for 8 weeks, 5 days a week, during the summer. This program employed intensive behavioral interventions that were administered by counselors/aides who were supervised by the therapists conducting the parent training. The basic model was one in which children were able to earn various rewards based on their ability to follow well-defined rules and meet certain behavioral expectations. Social skills training and specialized academic instruction was also provided.

The school-based treatment had 2 components: 10 to 16 sessions of biweekly teacher consultation focused on classroom behavior management strategies, and 12 weeks of a part-time paraprofessional aide who worked directly in the classroom with the child. Throughout the school year, a Daily Report Card was used to link the child's behavior at school to consequences at home. The Daily Report Card was a 1-page teacher-completed ratings of the the child's success on specific behaviors. This was brought home daily by the child to be reviewed by parents with rewards for a successful day provided as indicated.

Consistent with what occurs in actual clinical practice, the family and child's involvement in behavioral treatment was gradually tapered over the 14 month period. In most cases, contact had been reduced to once monthly or stopped altogether by the end of this period.

The main point to take away from this brief summary of the behavioral treatment that children received is that it reflects absolute state-of-the-art practice that would be virtually impossible to obtain in a typical community setting. Thus, if anything, one would expect that the benefits of behavioral treatment as implemented in this study would be likely to be greater than what would typically be obtained.

COMBINED TREATMENT - Children in the combined treatment group received all of the treatments that are outlined above. Individuals supervising the child's behavioral and medical treatments conferred regularly, and this was used to guide overall treatment decisions. Consistent with what has been found in prior studies, by the end of the study, children in the combined group were being maintained on lower daily doses of methylphenidate than children who received medication alone (Average doses were 31.2 mg/day for the combined group and 37.7 mg/day for the medication only group).

COMMUNITY CARE - It clearly would not be ethical to assign children with ADHD to a no-treatment control group for a study that persisted for 14 months. Instead, some children were randomly assigned to a group that received "community care". Following their child's diagnosis

of ADHD, parents of these children were provided with a list of community mental health resources and made whatever treatment arrangements they preferred.

Most of the 97 children in this group (over 2/3s) received medication from their own provider during the 14 months. Several things are interesting about the medication these children received compared to children who received medication as part of the study. First, community care children received less medication each day. For those treated with methylphenidate, the average daily dose was 22.6 mg/day compared to the average daily doses of 31.2 mg and 37.7 mg noted above. In addition, community care children received an average of 2.3 doses per day compared to the 3 times/day dosing for children in the study.

Finally, while none of the children receiving medication in the study were maintained on either clonidine or a combination of medications, 4 children seen by community physicians were treated with clonidine and 10 children received more than one medication. Thus, it appears that physicians in these communities were in some ways more conservative in their use of medication (i.e. prescribed lower doses of methylphenidate) and in some way less conservative (i.e. were more likely to use medications other than the widely used stimulants).

STUDY QUESTIONS

The MTA Study was designed to address 3 fundamental questions about the treatment of ADHD. These questions are as follows:

1. How do long-term medication and behavioral treatments compare with one another?
2. Are there additional benefits when they are used together?
3. What is the effectiveness of systematic, carefully delivered treatments vs. routine community care?

THE RESULTS

There is a tremendous amount of data presented in these papers and it is really not possible to summarize it all. Below, however, are what I found to be the most important findings.

First, let me list the variety of different outcomes that were assessed and reported. These include:

- * [Primary ADHD symptoms](#) - ratings provided by parents and teachers;
- * [Aggressive and oppositional behavior](#) - ratings provided by parents, teachers, and classroom observers;
- * [Internalizing symptoms \(e.g. anxiety and sadness\)](#) - ratings provided by parents, teachers, and children;

* **Social skills** - ratings provided by parents, teachers, and children;

* **Parent-child relations** - rated by parent;

* **Academic achievement** - assessed by standardized tests; (It is unfortunate, I think, that more frequent measures of academic performance in the classroom were not collected. These tend to be more sensitive to change than scores on standardized achievement tests. Thus, the reliance on achievement tests alone as the measure of academic performance may not have enabled important changes in academic functioning to be captured).

In considering the results presented below it is important to place them in this overall context:

Children in all 4 groups (i.e. medication only, behavioral treatment only, combined treatment, and treatment in the community as chosen by parents) showed significant reductions in their level of symptoms over time in most areas. Thus, even though some treatments were clearly superior to others in certain domains, overall, even children receiving the "least effective" treatment tended to show important improvement. Thus, these data should not be interpreted in a framework of "what worked" and "what did not work". Instead, it is a matter of what seemed to be most effective among treatments that all showed some positive effects.

1. How do long-term medication and behavioral treatments compare with one another?

For both parent and teacher ratings of primary ADHD symptoms (i.e. inattention and hyperactivity/impulsivity), medication management alone was clearly superior to behavioral treatment alone.

On all the other outcome measures reported, medication management and behavioral treatment did not differ significantly.

Thus, although medication was found to be superior to behavioral treatment on core ADHD symptoms, this did not extend to other important areas of children's functioning such as oppositional behavior, peer relations, and academic achievement.

2. Did participants receiving combined treatments show higher levels of improvement than participants receiving medication treatment alone or behavioral treatment alone?

Combined treatment and medication management treatment did not differ significantly in any of the 6 domains. This suggests that for most children with ADHD, adding behavioral intervention on top of well-conducted medication management is not likely to yield substantial incremental gains.

As can often be true with statistical analyses, however, this conclusion changes somewhat depending on how you look at the data. For example, when you look at the rank ordering on

different outcomes for children in the different groups, children in the combined treatment group did best on 12 of 19 outcome measures while those in the medication management group were best on only 4. In addition, when the individual outcome measures are combined into composite measures, or when children's outcomes are grouped into excellent response vs. less dramatic response categories, children receiving combined treatment did modestly, but significantly, better.

Compared to behavioral treatment alone, combined treatment was found to be superior on parent and teacher ratings of primary ADHD symptoms, on parent ratings of aggressive/oppositional behavior, on parent ratings of children's internalizing symptoms, and on results of the standardized reading assessment. Thus, adding medication to the treatment of a child already receiving behavioral intervention is likely to yield substantial benefits for most children.

3. Did participants assigned to each of the 3 MTA treatments (i.e. medication management, behavioral treatment, and combined treatment) show greater improvement than children receiving community care?

The answer to this question was clear and straight forward. Both combined treatment and medication treatment were superior to community care for parent and teacher reports of primary ADHD symptoms while behavioral treatment was not. In general, parents and teachers tended to report a decline of approximately 50% in inattentive and hyperactive/impulsive symptoms for children in the medication and combined treatment groups. For children receiving community care, the declines reported were in the 25% range and were comparable to those reported for children receiving behavioral treatment. In the non-ADHD domains, (e.g. oppositional behavior, internalizing symptoms, social skills, and reading achievement) combined treatment was always superior to community treatment, with particularly dramatic differences in parent reports of oppositional/ aggressive behavior. Medication management and behavioral treatment were superior to community treatment on a single domain only.

Overall, these data indicate that although children treated in the community made modest gains over the course of the study, those receiving medication treatment in the MTA study - either alone or in combination with behavioral treatment - did significantly better. This was especially true for children receiving the combined treatments. Possible reasons for this will be discussed in the summary section below.

FOLLOW UP ANALYSES

In addition to the analyses reported above, the MTA research group was interested in whether the effect of the different treatments may have differed depending on certain characteristics of the children. Thus, they also looked at whether similar results were obtained:

1. for boys vs. girls - as noted above girls made up about 20% of the overall sample;

2. for children with and without an additional diagnosis of either *Oppositional Defiant Disorder (ODD)* or *Conduct Disorder (CD)*;

3. for children with and without a co-occurring anxiety disorder;

In general, there were no substantial differences in the effectiveness of the different treatments depending on these variables. Thus, similar treatment results were found for boys and girls and for children with and without a co-occurring behavior disorder. There was some indication, however, that for children with a co-occurring anxiety disorder, behavioral intervention alone was as effective as both medication management and the combined treatment. It is also worth noting, however, that children with anxiety disorders who received medication only did not have a poorer response to medication than other children. Thus, prior and less intensive studies in which it has been reported that children with ADHD and an anxiety disorder do not do as well on stimulant medication are contradicted by these results.

THE IMPACT OF TREATMENT ADHERENCE

In a final set of follow up analyses, the researchers also analyzed the results according to how children and parents were able to adhere to the prescribed treatments. Thus, children assigned to the medication management condition were divided into 2 groups depending on whether they or not medication treatment was implemented as recommended and whether the family attended at least 80% of the scheduled follow-up visits where the ongoing impact of the medication could be monitored. For behavioral treatment, children were divided into 2 groups depending on whether or not parents attended at least 75% of the scheduled parent group meetings, the child attended at least 75% of the summer treatment program, and whether the child and paraprofessional working with the child in the classroom were both present for 75% of the intended days. If any one of these 3 conditions were not met, the behavioral treatment was not considered to have been implemented as intended. For the combined treatment group, families had to adhere to the guidelines for both medication management and behavioral treatment to be placed in the "as intended" group. Otherwise, they were placed in a group that was judged to not have adhered to treatment as recommended.

HOW WELL WERE TREATMENT RECOMMENDATIONS FOLLOWED?

The first thing that is interesting to note is the percentage of families in the 3 MTA study treatment conditions that were able/willing to adhere to treatment as recommended. Acceptance/attendance was higher for the medication management treatment (78% of families completing treatment as intended) than in behavioral treatment (63%) or combined treatment

(61%). Thus, even when state of the art behavioral treatment was provided to families at NO CHARGE, almost 40% of families were unable and/or unwilling to fully take advantage of it.

In terms of the impact of treatment adherence on child outcome, significant effects were found only for the medication management group. Thus, for children where the recommended medication management procedure was followed more closely, the outcomes were significantly better. For the behavioral and combined treatment conditions, in contrast, no differences in child outcomes depending on treatment adherence were found. It seems reasonable that the absence of an effect of adherence for the combined treatment group is that most of the families in the non-adherent category were there because they failed to comply with the behavioral treatment procedure, and that these children did as well as the "adherers" because of the benefits they derived from the medication.

SUMMARY AND IMPLICATIONS

There is a LOT here to digest. Before trying to pull together what seem to me to be some of the fundamentally important implications of this study, it is important to note that many additional papers will be emerging from this work. In particular, although the children in this study are no longer receiving their treatment as part of the study, they do continue to be followed. This will enable the researchers to examine the sustained impact of different treatments beyond the 14 month outcome data that were presented in this initial paper. Thus, it is certainly possible that results based on 2 or 3 year outcomes may look somewhat different from what was found after 14 months.

Several other caveats are important to note. First, in this study children with the inattentive subtype of ADHD were specifically excluded. Thus, these results can not be generalized to children with this subtype of ADHD.

Second, treatments investigated in this study were limited to those with the greatest empirical support to date: medication and behavioral treatment. This study thus sheds no light on the effectiveness of other types of treatment for ADHD such as dietary interventions, biofeedback, etc. Additional research on other treatment options that is as careful and well conducted as this study is certainly needed.

That being said, what are some of the important conclusions to be drawn from the data presented so far and what do these results mean for parents and health care providers who are concerned about doing the best they can for their child and their patients? (Please note that these are my opinions, and that other scientists, health care providers, and educators might reach somewhat different conclusions from those I present. Also, it is important to stress that conclusions about treatment are predicated on a careful evaluation of ADHD having been done in the first place, as was the case in this study).

For many children with ADHD, Combined Type, medication alone is likely to be an effective and perhaps even sufficient treatment when care is taken to determine the optimal medication/dose for each child and when the ongoing effectiveness of medication is carefully monitored.

I am aware that many people may find this conclusion to be distasteful, but I think it is a reasonable one to draw from these data. Remember, I am a Ph.D. not an M.D., and thus do not provide medication myself.

Although there was some indication for a mild to modest superiority for combined treatment on some outcomes, overall, children who received medication alone tended to do about as well as children who received the combined treatment. This was true even though the behavioral treatment provided in this study was far more intensive than would be routinely available in any community setting. In fact, I think it is reasonable to say that the behavioral treatment provided in the MTA setting could simply not be duplicated in any other context.

This does not mean that there is no place for behavioral treatment in the management of children with ADHD (see below). To me, however, it suggests that a reasonable approach may be to begin with carefully conducted medication trial to be certain that the maximum possible benefits from medication are being attained.

When this has been done, and there are still important difficulties in a child's behavioral, academic, and/or social functioning, adding behavioral or other psychosocial interventions that specifically target these residual problems should be pursued. These interventions can make an IMPORTANT difference for an individual child, even though the benefits at a group level are apparently not so dramatic.

It should also be noted that combining behavioral treatment with medication management did enable children to be maintained on a somewhat lower dose of medication. The authors note, however, that the actual significance of this difference is unclear. Many parents and physicians may regard this as quite important, however.

Thus, if maintaining your child on the minimum dose of medication required to yield optimum results is important to you, than combining medication treatment with carefully executed behavioral interventions is likely to be required.

Intensive and well-conducted behavioral treatment can also be an effective option for treating children with ADHD. For most children it will probably be less effective than careful medication treatment, however, and it may be hard for parents to implement as directed.

Once again, I think it is very important to note that the behavioral interventions implemented in this study were also associated with significant reductions in ADHD symptoms and some improvement in other domains. The

reductions in ADHD symptoms were not as great as for the medication management group, but in other areas, no statistically significant differences between these treatments were found.

There are, however, some important points to keep in mind here. First, as noted above, the intensity and quality of the behavioral treatment provided to children in this study could probably not be matched in any other context - it is just not available outside of a research setting. Whether a less intensive behavioral treatment would also be shown to produce significant gains over a 14-month period is thus unknown. Chances are, however, that behavioral treatment as typically practiced would probably not be as helpful as what was able to be provided in the study.

Second, it is very difficult for parents to persist with the type of behavioral treatment used in this study - about 40% were not able to adhere to the treatment even though it was offered in the study at no charge.

Finally, it should be noted that although not many statistically significant differences between behavioral treatment and medication management were found, 26% of the parents whose child was receiving behavioral treatment only as part of the study opted to add medication to their child's treatment. In contrast, only 2% of parents whose child was receiving medication opted to add behavioral treatment. This certainly suggests that many parents of children receiving behavioral treatment only were less likely to be satisfied with the results of their child's treatment.

Overall, I think a reasonable conclusion is that behavioral intervention - when used in isolation - is likely to be less effective than medication management, harder for parents to implement, and more expensive. To me, this suggests that the most appropriate use of behavioral treatment for many children may be not as the sole intervention, but as something that is carefully incorporated into a child's treatment to address problems that are not sufficiently helped by medication alone.

How medication is prescribed makes a difference and parents need to insist that their child's physician have an objective procedure in place to determine the optimum medication/dose for their child, and to carefully monitor the ongoing effectiveness of medication treatment for their child.

An inescapable conclusion from this study is that children who received medication from the MTA staff did significantly better than children who received medication from community physicians. Although the reasons for this can not be determined with certainty, it seems quite likely that this was because of the care that was taken initially to determine the optimum dose for each child, and to then carefully monitor how the child was doing and to make adjustments as needed. Parents need to insist that this be done for their child. Physicians need to begin using more objective procedures for evaluating medication response on a routine basis. This is not hard to do but it does take a bit of time. (Remember, you can easily use the ADHD Monitoring System that you received when you subscribed to evaluate the ongoing effectiveness of your child's treatment).

There are some differences in medication treatment in the MTA group and the community care group that we do know with certainty.

1. ***Children treated by community physicians may be routinely under- medicated.***

Children treated with medication alone in the MTA study who did well on methylphenidate received an average of almost 38 mg/day in 3 separate doses. Children treated with methylphenidate in the community received an average of about 23 mg/day - a dose reduction of about 40% - spread over 2 doses per day. Even though children receiving medication as part of the combined treatment were on lower doses than the medication only group, they still received a substantially higher dose than the community treated participants. Because MTA-treated children did much better, it seems reasonable to conclude that many children treated in the community were not receiving enough medication to obtain the maximum possible benefit.

Please do not interpret these data to mean that every child should be on the average dose used in the MTA study. Remember, some children do better on lower doses and some on higher, and the best dose for each child needs to be determined using a careful trial.

Also, it is important to remember that the daily total dose and 3 administration per day figure noted above was for methylphenidate and would certainly be different for other medications. For example, recent data suggests that Adderall - not used in this study because it was not available when the study was conducted - can produce at least comparable benefits to methylphenidate with fewer administrations per day. 2.

Children treated by community physicians are often put on non-stimulant medications and/or combinations of medications that are not necessary.

I think this is a really important point.

Recall that virtually every MTA participant receiving medication was able to be managed effectively on either methylphenidate or the generic version of dexedrine.

Very few needed to be prescribed a different class of medication like an antidepressant and not a single child was prescribed a combination of meds (e.g. methylphenidate and clonidine). In contrast, over 10% of children treated by community physicians were on multiple medications and over 16% were treated with an antidepressant.

What I conclude from these data is that when stimulant medication is prescribed carefully, there will be VERY few cases where another class of medication needs to be used and ALMOST NO CASES where multiple medications are needed.

I think that what may often happen in the community is that physicians give up on stimulants before an adequate dose has been tried, or before alternative stimulants have been tried. Instead, a switch is made to a different type of drug or a new drug is combined with the stimulants.

This is problematic for several reasons. First, no other class of drugs has been shown to be as effective as stimulants for treating ADHD. Second, despite the concerns that many people have about possible adverse health consequences of stimulant medications, available support for the long-term safety of these medications is greater than for the other medications that are often switched to or added.

So, if I were a parent of a child with ADHD, I would ask LOTS of questions of my child's physician before I switched him or her to a non-stimulant medication or had my child take multiple medication. (e.g. "Why don't we try a higher dose first?" "Why don't we test the effect of another type of stimulant first?")

If you are a provider of medication, I think these data should be carefully considered before such a switch is recommended.

This summary has been quite long and I hope it has been clear enough to give you a good feel for the results and significance of this important study. As noted earlier, there will be many more papers that emerge from this project, and I will be sure to include them in **ATTENTION RESEARCH UPDATE** as they are published.

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