The NIMH multimodal study of treatment for attention-deficit/hyperactivity disorder: A critical analysis

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Editorial note

On earlier occasions this Journal has devoted attention to the question of "Attention Deficit Hyperactivity Disorder". A not uncommon diagnosis in American children, the very existence of the condition is denied by many paediatricians and psychiatrists elsewhere, as is the propriety of treating these "hyperactive" children with stimulant drugs such as Ritalin® (methylphenidate, MPH). Late in 1999 the debate entered a new phase with the publication in the USA of the "MTA Study" which set out to examine the condition and its treatment and which was claimed to provide a vindication of the use of drugs in these young individuals. Bearing in mind the evident risks of widespread use of stimulants in children, the entire issue of "ADHD" deserves careful and ongoing attention. In this paper, Dr Peter Breggin examines the significance of this latest study. For those readers of the Journal concerned primarily with pharmaceuticals, the criteria against which he assesses the merits of this study will be familiar.

1. Background

After many months of positive publicity in the psychiatric and the general media, the results of the Multimodal Treatment Study for Attention-Deficit Hyperactivity Disorder (The MTA Study) were finally published in December 1999 [9,10]. The investigation study was sponsored by the (US) National Institute of Mental Health (NIMH). It deserves to be examined critically, since the topic to which it relates is a hotly disputed one. The aim of the NIMH study was to "resolve controversies and clinical quandaries about the relative value of medication and behavioural treatments" (National Institute of Mental Health, undated). The proponents of the study claim that it demonstrated the superiority of stimulant treatment over behavioural therapy and routine community treatment of ADHD. However, an examination of the MTA study reveals several serious methodological flaws that undermine its scientific validity, as well as other facets of the work which limit any conclusions that might be drawn from it concerning safety and efficacy.

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2. Method of analysis

When examining a study which is intended to define the therapeutic usefulness of a drug, one needs to devote attention to three crucial areas; long experience in clinical pharmacology and trials indicates that these are the areas in which the strengths or weaknesses of a study can most readily be detected. The first of these relates to the *study design*; there are many ways of undertaking a valid clinical trial, but unless the protocol meets certain fundamental criteria it is unlikely to produce trustworthy results. The second area concerns the avoidance of *bias* of any type, whether in the selection of participants or in the spirit in which the analysis is approached. The third area to be examined is naturally the *outcome* of the study: do the results point to a significant and useful effect of the drug or not? In considering the MTA study of the drug treatment of ADHD, as compared with behavioural therapy, all these aspects have to be reviewed.

3. Study design

This was a multi-centre trial, conducted at six different sites. At each of these sites, the study compared four different aspects of treatment or care of ADHD patients: (1) medication management alone, (2) combined medication management and behavioural therapy, (3) behavioural treatment, and (4) community care. The average age of the children was eight and 80% were boys. Already at this stage of study design, however, one finds that the investigation was seriously flawed in a number of respects.

3.1. The MTA was not a placebo-controlled, double-blind clinical trial

The MTA study fails to meet the commonly accepted criteria for a scientific study of medication efficacy or effectiveness. It was not a placebo-controlled double-blind clinical trial [9]. Firstly, there was no placebo control group and no non-treatment control group. Secondly, to reach their conclusions, the investigators relied almost exclusively upon evaluations made by teachers and parents who were not blind to the treatment. In other words, these raters whom the investigators relied upon knew whether or not the children were taking medication. In this respect, the MTA was an "open label" study. It could not be used, for example, for FDA approval of a drug. Bias, whether conscious or unconscious, on the part of researchers, observers or evaluators and research subjects often influences the outcome of such "open label" studies. Researchers commonly want to prove that the treatment under investigation is effective. Evaluators of efficacy often make observations that confirm what they anticipate finding, such as improvement in subjects treated with drugs. The research subjects themselves often give responses that they know will please their doctors. They also tend to respond to their own belief that the drug is safe and effective, and that it will help them or their children. Open label studies have therefore been discredited for purposes of evaluating effectiveness. As Nies and Spielberg [15, p. 45] observe, "Placebo effects, which occur in a large percentage of patients, can confound many studies, particularly those that involve subjective responses; controls must take this into account" (for additional discussions of placebo, double-blind procedures, and research standards, see [7]). One should add that to some extent the study did rely on blinded "classroom" raters whose findings one might expect to be more reliable; this aspect is discussed when considering the outcome of the study below.

The principal investigators in the MTA study are quoted as claiming that it would have been unethical to use a placebo group because stimulants have been proven effective as a treatment for ADHD. In reality, placebo groups are commonly used in ADHD and stimulant research. For example, the present writer recently reviewed eight double-blind placebo controlled studies of stimulants for ADHD that were

conducted from 1990–98 [3,4], including clinical trials carried out by the National Institute of Mental Health [1,6]. A well-known double-blind placebo-controlled study of stimulants for children diagnosed with ADHD lasted over fifteen months [8]; it was not criticized for withholding medication from some of the children. Furthermore, placebo-controlled trials are routinely carried out in psychiatry for far more dangerous "disorders" than ADHD, including "major depression" and "mania". One might add that a number of the children in the MTA study went without medication while they were in the community and behaviour treatment groups. It would have been no more "unethical" to add an actual placebo group. Ultimately, the lack of a placebo control group marred the study regardless of the motivation behind omitting the group. If the study could not be done in a manner that generated useful data and valid conclusions, it should not have been done at all. Finally, there can be no ethical problem surrounding the use of double-blind procedures. Yet this basic methodology was also omitted.

3.2. There was no control group of untreated children

In some situations, rather than using a placebo group, one can validly take as comparator certain subjects who receive no treatment at all. In this investigation there was no non-treatment control group. The MTA compared various treatments, but did not compare treatment to no treatment. Two-thirds of the community-treated group received a variety of medications, as well as other interventions, and cannot be considered a non-treatment control group. Basically, the study compared three drug conditions to behavioural interventions, but failed to compare the drug treatment to absence of treatment.

3.3. Thirty-two percent of the Medication Management group was already on medication for ADHD at the start of the MTA

Table 3 of the report on the study (p. 1079) shows that of 144 medication management subjects, 46 (32%) were on medication for ADHD at the start of the selection process. This is generally not acceptable in a study of medication effects and would be expected to corrupt the study. Since the children were already receiving medication, it is highly probable that their parents had already determined to their own satisfaction that the drugs were helpful. They could not therefore participate objectively in a "random" drug study.

3.4. Entry into the Medication Management group was highly selective

The report does not clearly describe how participants entered the Medication Management Group, but it seems clear that entry was selective, and entrants were probably not typical of children who are brought for consultation or treatment in connection with "ADHD". The study initially screened 4,541 children. These children were referred from a variety of sources, such as recruitment through public advertisements, clinics, and schools. The aim was to draw from a broad spectrum of the kind of children whose parents bring them for services for "ADHD". Remarkably, of these 4,541 children, only 579 subjects (12.8%) were selected to enter the trials. The small percentage of applicants actually selected for the study suggests (in the absence of adequate explanation) that the children in the trials do not reflect a representative community group of children routinely treated for "ADHD". As already noted, many of the children were already taking stimulant medications. As a result, many of the children who entered the trials probably had parents who were already favourable toward medication.

3.5. The Medication Management group was relatively small

The actual medical management group is much smaller than might be suspected based on the seemingly large scale of the study. Of the 579 who entered the clinical trials, only 144 entered medication management, i.e., received medication alone (others received medication in combination with other treatments or behavioural therapy alone). Thirteen of these dropped out before starting, limiting the actual start group to 131. Eight more dropped out during the study, resulting in a total of only 123 finishers in medication management. Overall, of the 4,541 children originally screened, only 12.8 percent entered the study and only 2.7 percent (123) completed the medication management trial. In addition, many of the children were comorbid for other psychiatric diagnoses, so that the group of children diagnosed solely with ADHD was much smaller than the total of 123 finishers.

3.6. Most of the subjects were boys

Boys represent a disproportional number of the children who are medicated with stimulants. Stimulants are known to be temporarily effective in suppressing overall normal spontaneous behaviour in children and animals. This drug-induced suppression of socialization, play, autonomy, and spontaneity makes normal boys easier to manage under certain circumstances, such as a home or classroom setting that does not meet their needs for spontaneous activity or provide them adequate discipline and engaging education [3,4]. In part to counter the argument that stimulants are used for the behavioural or social control of normal boys, attempts were made to include more girls in the MTA studies. Despite efforts to recruit more girls, 80% of the subjects were boys. This focus on treating boys reconfirms that stimulants are used to suppress the relatively higher activity rates of normal boys compared to girls. So far as the validity of the study is concerned, the constitution of the patient group at all events means that it is unlikely to provide sufficient data on girls to be informative.

3.7. Drug treatment was continuous for fourteen months; behavioural treatments were stopped earlier

The MTA claims to have compared behavioural and medication treatments. However, it did not compare drugs and behavioural treatments for the same length of time. Only the drug treatment was maintained for 14 months. During the final few months of the study, behavioural treatments were spaced out to once a month or stopped. Furthermore, parental attendance was inconsistent. Continuing the drug treatment while discontinuing the behavioural treatment gives the drug treatment an unfair advantage.

3.8. The behavioural treatments were flawed

It is significant that the study utilized behavioural treatments developed by Russell A. Barkley. Dr Barkley has used these techniques for decades as part of a long-term effort to demonstrate that drugs are better than behavioural treatments. His consistent conclusion that drugs are superior is not surprising when one bears in mind that in his work they were compared, not with well-established and generally recognized methods of behaviourial therapy, but with his own methods, which can fairly be regarded as inadequate. Barkley's behavioural approach makes the error of approaching the child as a defective object suitable for control by parents and teachers rather than as a sentient being in conflict with adults at home and/or at school. Such a behavioural approach ignores everything that is known about family systems and the necessity of changing the overall patterns of relationship in the family, starting with the parents [5].

3.9. There were no trained observers for ADRs

Adverse Drug Reactions were recorded by teachers and parents on a two-page check list. There was no apparent training for this process. In addition, parents and teachers were reassured in writing that the drug was safe and that ADRs were not serious, creating a bias in favour of the drug's safety. Furthermore, many ADRs – such as behavioural suppression, loss of spontaneity, apathy, and increased obsessive behaviour – can be mistakenly interpreted by parents and teachers as constituting improvement. The use of aware, experienced professionals, rather than parents and teachers, is absolutely necessary in order to determine the frequency and severity of ADRs (Borcherding, Keysor, Rapoport, Elia and Amass [1]; studies reviewed in Breggin [3,4]). In clinical practice, one finds that asking children about any potential adverse drug reactions is central to the assessment. Often the child is having drug-related problems, such as headaches or "blah" feelings, but does not understand their source or tell anyone about them until questioned by the doctor. The MTA study made no effort to ask the children what drug effects they might be experiencing. Overall, from the opening statement in the paper to its conclusion, it is obvious that the investigators did not fully evaluate the single most important issue surrounding the long-term use of stimulant drugs – the risks they pose to the children.

One should add that the study failed to carry out an objective evaluation of long-term adverse effects that have already been demonstrated in short-term studies. For example, the study should have gathered data on physical parameters such as height and weight (growth), blood pressure, cardiac status and abnormal movements, as well as on psychological parameters such as cognitive and affective functioning, including over-focusing (perseveration) and depression.

4. The need to avoid bias

Next, in examining such a study, one must consider the possible influence of bias on the entire process of design, performance and outcome. In this respect too, the MTA study leaves much to be desired.

4.1. All the principal investigators were well-known drug advocates

How could so many experienced professionals produce a study with so many flaws? There appears to be an answer. The framer of the MTA studies, Peter Jensen (then at NIMH), and all the principal investigators are drug advocates who touted the positive results of the study even before it was completed or published. The six principal investigators included Laurence Greenhill, C.K. Conners, William Pelham, Howard Abikoff, James Swanson and Stephen Hinshaw [9, p. 10077]. They have devoted their careers to encouraging the concept of ADHD and the drugging of children. Some, like Conners, have been doing so for four decades. Laurence Greenhill of the New York State Psychiatric Institute and Columbia University represents the kind of conflict of interest that exists among MTA researchers. Before the data were later removed from the internet during controversy over dangerous research on children at the institute and the university, the New York State Psychiatric Institute and Columbia University web site originally listed the funding of its researchers as of December 21, 1998 [18]. Greenhill had research funds or other financial support from six drug companies: Richwood, Bristol-Myers, Solvay, Wyeth-Ayerst, Glaxo, and Eli Lilly. Receiving support from pharmaceutical companies raises a suspicion of drug-oriented preferences which needs to be allayed.

4.2. The parents and teachers were exposed to pro-drug propaganda

The families and teachers were exposed to the pro-drug biases of these investigators in the materials given to them before they enrolled in the study. The "Teacher Information" for the MTA study presents the usual claims about how much harm ADHD causes children [16]. It states that the children will be treated with a "safe and effective dose of medication. . ." (a statement featuring in bold type in the original). This kind of built-in bias among the teachers can only invalidate observations subsequently made by them as regards safety and efficacy, especially in an open label study. The "Information for Parents" handout had similar built-in biases, including a reference to biochemical imbalances and genetic factors in "ADHD" [16]. In fact, based on the information handouts given out by Columbia and the NYSPI for the MTA, the parents in this study were not given the opportunity for informed consent for the risks posed to their children by the drugs.

5. The outcome

5.1. The blind classroom raters found no difference in any of the treatment groups

As noted above, the MTA study did use one group of "blinded ratings of school-based ADHD and oppositional/aggressive symptoms..." [9, p. 1074]. The blind raters observed the children in the class-room only. The data from these raters are produced in Table 5 (pp. 1082–3) of the study. *It is notable that, when examined by the blinded classroom raters, outcomes in the two groups were the same, i.e., behavioural interventions were equal to medication interventions*. The blind raters found no difference between any of the treatment groups on any of the variables involving ADHD or oppositional behaviour. However, this extremely important finding, that the only potentially objective raters found no drug effect, was not considered in the study conclusions. Nonetheless, the findings of the blind classroom raters are the most important in the study, confirming that stimulant drugs offer no observable advantages over other interventions, including behavioural therapy and non-specific community treatments.

One may add at this point that even the defective behavioural techniques which were used in the study produced results which in the view of the these "blind" observers were similar to those attained with all the other treatments. Once again, therefore the study shows no advantage to drugs.

5.2. The children did not rate themselves improved

The children self-rated themselves on an anxiety scale (the MASC, Table 5 in the study). They did not rate themselves differently in any treatment category at any time. In other words, these children did not rate themselves as doing better on the drugs than on any other treatment. This outcome again supports the use of the safer non-drug treatment.

From unpublished information on this study it appears that the children also rated themselves on a depression scale. This information also appears in a handout provided by the Columbia project [14]. However, no data are reported in the study concerning the depression scale. Because stimulants commonly cause depression in children, the authors of the MTA study should publish any data they possess on this issue. If the children did rate themselves on a depression scale, one might validly raise the question: "Were the depression self-rating scales dropped because they indicated a worsening of the children's condition?"

5.3. There was very little effect on social skills

Social skill differences among the groups were limited to a significant difference favouring combined treatment over standard community care. Neither was better than behavioural or medical management treatment [9]. Of great importance is the fact that the peer group sociometrics analysis yielded no advantage to any of the treatment groups. The other children did not rate the medicated children as relatively improved.

5.4. There was no improvement in academic performance

In a note to Table 4 of the Report [9] the authors of the MTA study admit that there was no improvement or difference in academic performance in spelling or mathematics. The table itself seems to indicate that in some groups there was marginal improvement in reading. However, according to Bertram Karon (personal communication, January 24, 2000), the statistical analysis on this point was flawed, due to the use of a Bonferroni correction of 6 that was too small. Overall, no academic improvement was found as a result of any treatment and no differences were found among the treatments.

5.5. Most children suffered from adverse drug reactions (ADRs)

Sixty-four percent of children were reported to have some ADRs, 11.4% of them moderate and 2.9% severe. The authors of the study dismiss the severe reactions because 6 of 11 were in the category of "depression, worrying, irritability". They explain these "could have been due to non-medication factors". In reality, placebo-controlled double-blind clinical trials show that depression, worry and irritability are common adverse reactions to stimulant drugs (trials reviewed in [3,4]). Their dismissal of known stimulant-induced ADRs also points to the strong biases of the investigators.

6. Discussion

The MTA study has been highly promoted by advocates of drug therapy as a demonstration of the superiority of stimulant treatment for ADHD. In fact, as one discovers when one examines the manner in which it was designed and conducted, the study failed to meet the basic criteria for a drug trial. It was not placebo-controlled and lacked a non-treatment control group. It was not double blind. Teachers and parents provided ratings relied upon by the study, but both groups knew whether or not the children were taking medications. The MTA study was in this respect "open label" and would not have qualified, for example, as a study for the FDA-approval process. As research purporting to demonstrate the effectiveness of stimulant drugs, it is scientifically unsound.

Insofar as the study involved blind raters, who observed behaviour in the classroom, it found no difference over fourteen months between any of the treatment conditions. In other words, the observations generated by the most objective of the observers showed that the medicated children did no better than the other children in the study. Similarly, the peers of the subjects did not rate the children as improved in any of the treatment groups. Positive ratings for the medication groups came from the parents and teachers who were heavily indoctrinated in favour of the drugs and who knew which children were receiving them. In many cases, the children were already on the drugs, indicating teacher and parent biases in favour of medication. The study also failed to evaluate adverse drug effects in a scientific manner. Lacking observations by trained professionals, while relying upon potentially biased and untrained parents and teachers, the study is not a valid source of data concerning stimulant-induced adverse effects.

Unfortunately, the MTA study also failed to examine the kind of interventions that, in actual clinical practice, prove very effective in helping children labelled with ADHD. These interventions include individualized family counselling aimed at improving relationships in the family and individualized educational approaches that inspire children to engage themselves in school [2,5].

In summary, the MTA study failed to adhere to basic scientific standards for clinical trials and cannot be used to draw valid conclusions about stimulant safety or efficacy. The best of the data which it generated tends to indicate that stimulant medication produced no different results than any of the other intervention. The MTA study does not demonstrate the superiority, or even the safety and usefulness, of stimulant medication in the treatment of children labelled with ADHD.

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