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Update the Multimodal Treatment of ADHD (MTA): twenty years of lessons

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Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder[1] and consists in a persistent pattern of inattention and / or hyperactivity - impulsivity that interferes with the functioning or development of the person who suffers from it. Because it is a disorder that is present since childhood, the treatment of these patients should be multimodal, and it should include doctors, therapists, teachers and parents[2].

The choice of a pharmacological treatment adjusted to the specific needs of the patient optimizes the results of the intervention programs. In 1997, the National Institute of Mental Health (NIMH) started the study of multimodal treatment of attention deficit hyperactivity disorder (MTA), and this constitutes a landmark in the history of treatment research in child psychopathology. MTA is the largest study of its kind ever undertaken. In the present article we intend to review the existing clinical evidence about the results of the MTA from the nineties to the current date.

Keywords: Attention-Deficit/Hyperactivity Disorder (ADHD), MTA, Follow-up

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Actualización del estudio del Tratamiento Multimodal en TDAH (MTA): dos décadas de aprendizajes

El Trastorno por Déficit de Atención e Hiperactividad (TDAH) se enmarca dentro de los trastornos del neurodesarrollo[1] y consiste en un patrón persistente de inatención, hiperactividad y/o impulsividad que interfiere con el funcionamiento o el desarrollo de la persona que lo padece. Es un trastorno que se encuentra presente desde la infancia y el tratamiento de estos pacientes debe ser multimodal, y debe incluir a médicos, terapeutas, profesores y padres[2].

La elección de un tratamiento farmacológico ajustado a las necesidades específicas del paciente, permite optimizar los resultados de los programas de intervención. En 1997 el Instituto Nacional de Salud Mental (NIMH, por sus siglas en inglés) inicia el estudio de tratamiento multimodal del trastorno por déficit de atención con hiperactividad (MTA según sus siglas en inglés) y éste constituye un hito en la historia de la investigación del tratamiento en la psicopatología infantil. Se trata del mayor estudio longitudinal de este tipo, con datos de seguimiento hasta nuestros días. En el presente artículo de revisión se revisan las evidencias clínicas existentes acerca de los resultados del MTA desde los años noventa hasta la fecha actual.

Palabras clave: Trastorno Déficit Atención/Hiperactividad (TDAH), MTA, Seguimiento

INTRODUCTION

Attention-deficit/hyperactivity disorder is one of the most common disorders that can affect the mental health of children, with a prevalence of around 5.3-7.1%[3] in school-age children. Beyond the interference of the disorder's core symptoms (inattention, hyperactivity and impulsivity), we find that different comorbidities and psychosocial environment are risk factors in the course of ADHD[3].

According to the main clinical practice Guidelines, the current consensus is that the multimodal approach is the gold-standard treatment for ADHD. These guidelines recommend using pharmacological treatment together with other measures, defined according to the particular needs of each case[4], a strategy that is based on the MTA study (multimodal treatment study of children with ADHD)[5].

In this review we concentrate on the scientific evidence regarding the results of the MTA study, which still continues to be the fundamental study and represents the gold stan-

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dard in the treatment of ADHD. We analyse the results not only at the end of the experimental phase but throughout these almost twenty years since it ended.

METHODOLOGY OF THE REVIEW

When writing this article, we performed a search on *PubMed*® using the search terms *"MTA, ADHD"*. Of the 141 articles identified using these criteria, all the articles published since 1997 by the *"MTA Cooperative Group"* and those which included the publication of an analysis of outcomes during follow-up of the study were selected (24 original articles).

STUDY DESCRIPTION

The MTA study[5,6] (multimodal treatment study of children with ADHD) was started by the National Institute of Mental Health (NIMH) in 1997 with the intention of assessing the different treatment options available for ADHD at that time. Initially it was a multicentre longitudinal study consisting of 14 months of follow-up, which included a total of 579 children (in the final sample), all with a diagnosis of ADHD, within an age range of 7 to 10 years (mean age 8.5 years). The study population came from different places (schools, paediatric departments and mental health centres), as six multidisciplinary teams took part in the study, and it also included patients with comorbid disorders: conduct disorder, oppositional defiant disorder and anxiety disorder.

The subjects were randomised into four follow-up groups: A: Immediate-release methylphenidate (three doses per day[7]) controlled by the investigators, with close monitoring. B: Intensive behavioural treatment. C: Combined treatment (options A and B together). D: Standard community care (which served as a control group)[5,6].

Over the 14 months of treatment, the patients were assessed monthly by applying a battery of psychometric examinations with the aim of measuring the following variables: core symptoms of ADHD, anxiety symptoms and mood, oppositional/aggressive symptoms, parent/child relationship and academic achievement[6].

FOLLOW-UP AT 14 MONTHS

At the end of the experimental phase of the MTA, it was seen that there was a significant reduction in the symptoms in all four groups, although groups A and C were statistically superior in terms of control of core symptoms of the disorder and oppositional/defiant behaviours[8]. Combined treatment did not offer a significant improvement of symptoms versus pharmacological management in monotherapy, but it did allow the dose of the drug to be reduced, as the behavioural intervention helped. A greater level of parent and teacher satisfaction was also observed with the combined treatment, in addition to an improvement in the children's social skills. If we analyse the results of the combined group with respect to the subjects who only received the behavioural treatment, we see an improvement in aggressive behaviour and parent-rated internalising symptoms, as well as reading achievement at school. In cases of comorbidity with anxiety symptoms and aggressive behaviour, combined treatment was superior to the other alternatives[9]. However, these outcomes do not mean that behavioural intervention alone cannot be used to manage ADHD in certain clinical situations, as recommended in Clinical Practice Guidelines[10,11].

Once the 14-month experimental phase had ended, the MTA became a "natural" follow-up study. The teams that collaborated in this study no longer supplied the families with the treatment, but rather they were free to decide what treatment they chose or could afford. That is why some children who were originally assigned to medication alone or to combined treatment continued to take medication while others stopped taking it, and others who initially only received behavioural therapy or community care started to take medication, despite not having done so previously. Even so, it is interesting to learn about these children's progression since that first intervention[12].

FOLLOW-UP AT 24 MONTHS

Ten months after the end of the intervention phase, we find that there continued to be a greater improvement in the core symptoms of ADHD in the children who had initially been assigned to the medication management or combined treatment groups than in the children in the other two groups (B and D), but the difference was smaller than it had been on completion of the 14-month phase.

It is likely that this ongoing improvement in groups A and C was because most of the families continued with controlled pharmacological treatment[13], while it was found that there was actually a reduction in the advantage when its use was stopped. Moreover, some of the children who only received behavioural therapy at first started to take the pharmacological treatment after the first 14 months of the study, which is given as the reason for an improvement after 24 months[14].

It was interesting to discover after 24 months that the patients who had received behavioural therapy did not show early onset of problems related to substance abuse (alcohol, tobacco and cannabis), regardless of whether or not they were taking medication[15].

The children included in the groups receiving pharmacological treatment (A and C) grew significantly less than those who were assigned to behavioural treatment during the first 14 months. However, if we observe the results after 24 months, this difference in height is dissipated among the different randomly assigned groups[16].

FOLLOW-UP AT 36 MONTHS

After 3 years, 485 of the 579 children (83.9%) initially included were still participating. At this point the patients' ages ranged from 10 to 13 years (mean age 11.9 years). Approximately two years after the end of the experimental phase, the significant differences in the core symptoms of ADHD had been diluted among the original groups.

The loss of advantage of the effect in the groups that had been superior may be due to typical age-related changes in ADHD symptoms, changes in the intensity of the treatment followed or even complete discontinuation of the initially indicated treatments[17].

An external comparison group of children without ADHD was also established with classmates of the children in the study. This control group would also serve to establish comparisons in subsequent follow-up studies (MTA n= 487; Control n=272)[18].

There was a somewhat unusual finding after 36 months; the children who took pharmacological treatment between 24 and 36 months showed a slight (although not significant) worsening after 36 months with respect to those who were not taking medication (they achieved worse academic results). This pattern could be explained by the fact that it is the most serious cases, and those who do not tend to improve, that continue to use medication. However, in cases where the patient improved, they more often stopped the treatment. Nevertheless, it was not possible to demonstrate that the personal choice of treatment was a significant factor in this relationship[17].

What is true is that if we analyse the MTA study population with respect to the control population, we do find that these children have a greater risk of delinquency and early substance use[18]. At 36 months of follow-up, this finding was not observed to be more closely related to any of the original randomised treatment groups. However, in terms of clinical practice, this underlines the need for continuous control of these outcomes as the children enter adolescence. The parents of children with ADHD should be informed about this risk and about strategies to improve supervision and minimise negative influences[19].

With regard to the general pattern of change in the core symptoms of ADHD, over time a change in the average severity of the symptoms has been observed as the child matures, but not to the same degree as in their classmates without ADHD (control group). This means that, although the symptoms of ADHD gradually improved over time, on average, the children in the MTA study did not become "normal"[20-22].

Although no significant differences were found in the patients' height at 24 or 36 months in terms of the initially assigned groups, differences are observed when we examine the effects of medication on growth. This analysis is based on adherence to pharmacological treatment: consistent use of medication, inconsistent use of medication or no medication over the three full years[23].

The first finding in this respect is that the children in the group that was never treated with medication grew taller than the national average and were even taller than their classmates without ADHD (control group) in all the periods evaluated. The second finding was that the medication slightly delayed growth in the patients who had not taken it previously (not assigned to the pharmacological treatment groups, A or C, in the experimental period), but did take it after that first 14 months. They grew ¾ of an inch (1.9 cm) less than those who never received medication. The third finding was that those taking medication throughout MTA follow-up had a lower-than-average height in all the assessments. We are talking about averages, so each individual child could show a different degree of delayed growth[23].

OUTCOME 6 AND 8 YEARS LATER

If we analyse the outcome for these patients after 6 and 8 years of follow-up (age range from 13 to 18 years), the continuity of the sample in the MTA group is 78% and 75%, respectively, with respect to the initial n. At neither assessment point were any significant intergroup differences observed in the core symptoms of ADHD or in the new variables that were analysed, e.g. school grades, arrests, psychiatric hospitalisations and other clinically relevant outcomes. The use of medication decreased by 62% after the 14-month controlled trial but adjusting for this did not modify the results. The ADHD symptom trajectory in the first 3 years predicted 55% of the outcomes[24].

The control group sample, classmates without ADHD, corresponded to 87% of the n initially recruited for follow-up after 6 years and 90% after 8 years. MTA participants obtained worse results than this local normative comparison group in 91% of the variables assessed[24].

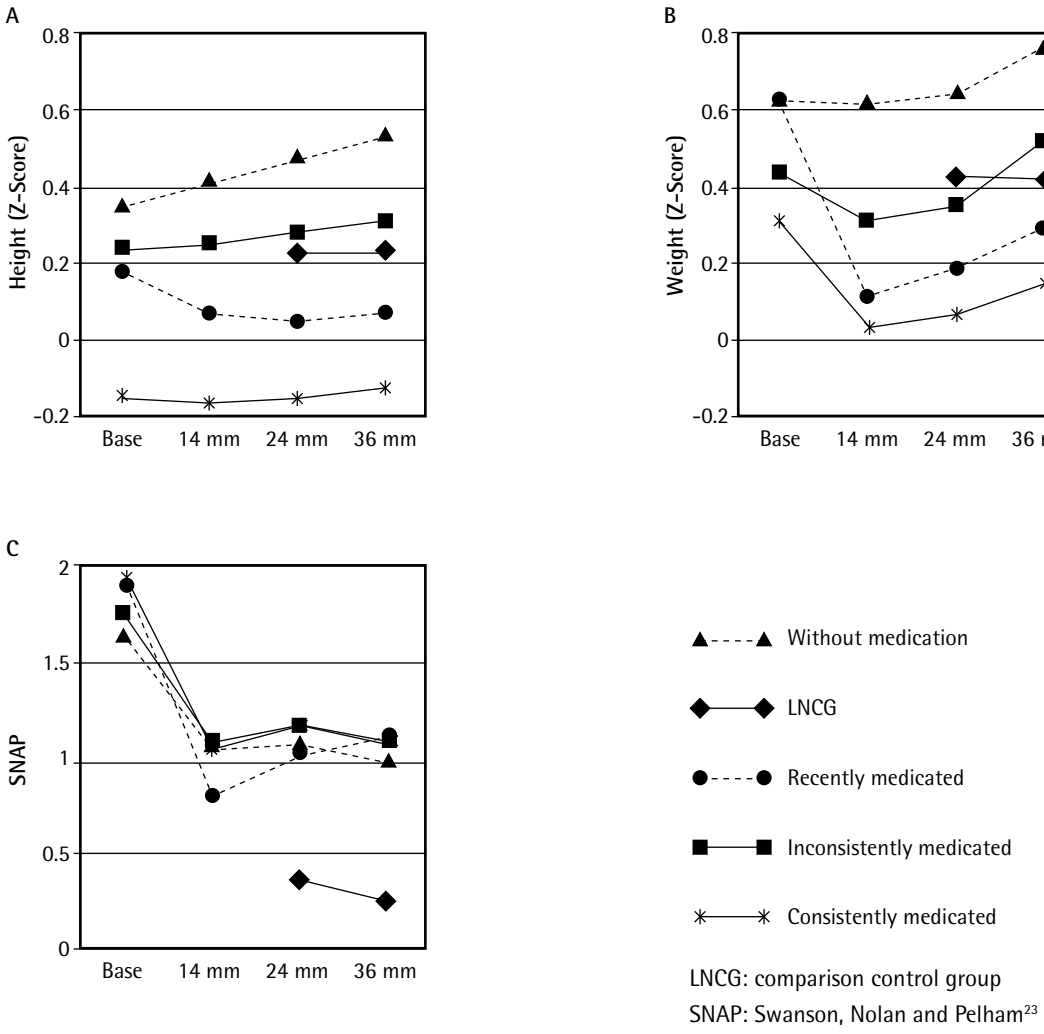

Figure 1 — *Naturalistic group profiles showing standardised size measurements (height [A] and weight [B]) and efficacy (average rating in SNAP [C]). The figure shows the four subgroups based on history of medication use before MTA (baseline), at the end of the MTA treatment phase (14 months), at the first assessment point (24 months) and at the second assessment point (36 months)*

OUTCOME UP TO 16 YEARS LATER

Data were collected 10, 12, 14 and 16 years after the start of the study (average age of 24.7 years 16 years after the start of the study) for 476 participants in the initial MTA group and 241 peers in the control group. The participants were grouped according to persistence of symptoms according to DSM-5 ADHD symptom criteria for adults. According to this definition 50% (n=226) had persistent symptoms, while the other 50% were asymptomatic (n=227). They were in turn compared with the non-ADHD control group, taking into account that 23 cases were excluded due to missing parent reports[25].

An orthogonal comparison was performed between the aforementioned groups. Thus, the following variables were analysed first: completion of secondary education, jobs lost/left, current income, unemployment benefits and risky sexual behaviour. In all the measures the control group showed the best pattern of outcomes, followed by the asymptomatic ADHD group and finally the ADHD group with persistent symptoms. In a second analysis of emotional outcomes (emotional lability, neuroticism, anxiety and mood disor-

ders) and substance use[25,26], there were no differences between the control group and the asymptomatic ADHD group, but both did better than the symptom-persistent ADHD group. In the third pattern analysed, related to jail time (uncommon) and alcohol use disorder (common), the differences between the groups were not significant. There were 10 deaths in the ADHD group (initial MTA) compared with one in the control group[25].

Additionally, with the intention of analysing whether there are factors in childhood that are related to persistence of symptoms in adulthood, a retrospective analysis was performed of 453 participants (mean age= 25 years) in the MTA study. It related IQ in childhood, total number of comorbidities, parenting practices perceived by children, parent-child relationship perceived by children, parental mental health problems, parents' marital problems, level of family income and parents' education at the start of the study (mean age of participants 8 years). Persistence of ADHD in adults was defined according to the DSM-5 criteria and the mean ADHD symptom score on the Conners' Adult ADHD Rating Scale (CAARS). It was thus determined that the most important and significant childhood predictors of persistence of ADHD symptoms in adulthood were: initial severity of ADHD symptoms, the existence of comorbidities and parental mental health problems. The other variables showed no association with persistence of ADHD symptoms in adulthood[27].

Participants were also screened for psychotic symptoms at 6, 8, 10, 12, 14 and 16 years of follow-up and a group of 509 participants in the MTA group (88% of the original sample) was compared with 276 participants in the control group (96% of the original sample). These data were available when the participants had a mean age of 25.1 years in the MTA group and 24.6 years in the control group after 16 years. Associations between positive screening and the consumption of alcohol or other substances were also taken into account. Twenty-six patients in the MTA group (5%) and 11 in the control group (4%) screened positive, although most of the psychotic symptoms were transient. The prevalence of psychotic symptoms (confirmed by a specialist) was 1.1% in the MTA group and 0.7% in the control group. Greater cannabis use was recorded in those who screened positive for psychotic symptoms and in whom it was subsequently confirmed[28]. There was no evidence that ADHD increases the risk of psychotic symptoms, while cannabis consumption was associated with a greater probability of experiencing psychotic symptoms[28].

In the final height assessment (16 years after the start of the MTA) 88% of the initial sample of patients with ADHD and 92.1% of the first sample of the local normative comparison group were compared. It was found that the ADHD group was statistically significantly shorter than the control group ($p<0.01$, $d=.21$), but with relative clinical relevance; a difference of 1.29 ± 0.55 cm was observed. Moreover, within the ADHD group, a significantly lower height was observed in the group that was consistently medicated with respect to those whose use of medication was inconsistent[29].

DISCUSSION

The MTA is one of the most major studies on the treatment of ADHD, and it has been fundamental in defining the multimodal approach as the gold standard. This project has yielded some important findings, as testified by the articles cited in this review. The findings of the MTA study at 24 months of follow-up are consistent with other studies that have concluded that stimulant medication is highly effective for ADHD[30,31]. The superiority of the effect with pharmacological treatment in the MTA at 14 months continued to be evident after 24 months of follow-up. Beyond 24 months, it is not possible to draw any reliable conclusions regarding the effect of medication because the MTA study was designed with a specific set of objectives and a methodology that was in line with those objectives. A different design would be needed to test the effect of the treatments over longer periods of time. However, this does not mean that the longitudinal findings from 14 months after the end of the intervention phase of the MTA are not clinically valid. The truth is that, from that point on, the MTA became a naturalistic study from which we can draw important conclusions for the management of patients with ADHD in standard clinical practice, as we have seen in this review.

It is important to highlight the significant risk of developing comorbidities associated with ADHD, as has been found in other studies[32], since it can also be deduced from these works that the ADHD group is at increasing risk of developing complications or comorbidities throughout the course of their disorder when compared with the children without ADHD in the control group. Of the most important problems experienced during follow-up by the patients in the MTA it is known that substance use is more common in young adults with ADHD in childhood, in addition to greater initial exposure at an early age and a slightly faster escalation of substance use. Early prevention and screening are critical before this escalates to untreatable levels. It is therefore important to carry out a clinical follow-up of these patients throughout the course of their disorder, adapting the treatment as necessary and anticipating any complications that may arise.

There was no evidence that ADHD increases the risk of psychotic symptoms. In both the ADHD group and the normative control group, cannabis use was the factor associated with greater likelihood of experiencing psychotic symptoms.

The prospective findings also indicate that initial severity of ADHD symptoms, parental mental health problems and the existence of comorbidity are correlated with persistence of ADHD symptoms in adulthood. Addressing these areas from the start could help reduce persistence of the symptoms, dysfunctionality and functional problems associated with ADHD in adulthood. Other studies consider emotional variables as predictors of quality of life and persistence of symptoms in patients with ADHD when they reach adulthood[33].

In terms of safety and adverse effects, the MTA provides safety data on the long-term use of methylphenidate. According to the outcomes described, extended use of stimulant medication could, on average, result in a reduction in final expected height of 1.29 ± 0.55 cm in long-term follow-up[29]. From the clinical point of view and in terms of the risk-benefit ratio, the impact on height seems reasonable, taking into account other risks associated with ADHD.

The MTA study has shown us to think long-term about ADHD, in that a treatment that may be effective now will not necessarily be effective in a few years. Hence the importance of long-term follow-up of patients with ADHD and, although the multimodal approach is still the ideal strategy, the medication and objectives must be personalised according to each patient's needs at each point in their development. It also highlights the importance of making an early diagnosis and prescribing an effective, personalised treatment based on each patient's situation in order to avoid greater risks in adulthood.

CONFLICT OF INTERESTS

BMN: Has no conflict of interests.

JQ: Has participated as a speaker or consultant for Lilly, Shire, MSD, Janssen & Ferrer, and has received research grants from ISCIII and Otsuka.

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