

Study Update: Long-Term Effects of Stimulant Medications in AD/HD Children

By Benedetto Vitiello, M.D.

In early December 1999, the National Institutes of Mental Health hosted a research workshop to discuss ways to study the long-term efficacy and safety of stimulant medications. During the two-day meeting, basic neuroscientists and clinical researchers reviewed existing data and examined possible strategies for future research. The topic was timely, given the continuing interest in these medications, their increased use in our communities, and the recommendation of the 1998 NIH consensus conference on AD/HD. In fact, more is known about stimulants in children than about any other psychiatric or psychological treatment. Still, there is more to be known.

Stimulants such as amphetamine (Dexedrine, Adderall) and methylphenidate (Ritalin) have been used for over 50 years in the treatment of children with attention deficit hyperactivity disorder (AD/HD), making them one of the oldest pharmacological treatments in psychiatry. The efficacy and safety of these medications in decreasing the symptoms of AD/HD is supported by extensive literature of controlled studies (up to 24 months of treatment). The side effects, most commonly anorexia and insomnia, have also been well documented. With continuous use, a decrease in growth, both weight and height, can occur. The decrease in height growth is transient and does not change the ultimate adult height. Stimulants, however, do not "cure" AD/HD and symptoms usually re-emerge upon drug discontinuation.

Thus, because AD/HD is a chronic condition that is typically first apparent in preschool or early school years and can persist into adolescence and adult years, stimulants can be administered for many years. The exposure of children to chronic treatment with stimulants at a period when the brain undergoes major developmental changes can raise concern about the long-term safety of these medications. Because of their potential for abuse, the question has repeatedly been raised whether treatment with stimulants can sensitize the brain to future use of stimulants and, in this way, increase the risk of substance abuse and dependence.

On the other hand, AD/HD itself, when accompanied by conduct disorder, increases the risk for substance abuse, and treating AD/HD (with medication or other means) can be expected to reduce such a risk. Another concern relates to the possible effects of these drugs in children who may be at risk for mania, depression, or psychotic disorders. These disorders are often not clearly diagnosed until adolescence, but, in earlier years, symptoms of inattention, impulsiveness and hyperactivity can lead to a diagnosis of AD/HD and consequent treatment with stimulants. In these cases, it is not known if repeated exposure to stimulants can affect the presentation and course of mood and psychotic disorders.

Studies in animals indicate that the repeated administration of amphetamine or methylphenidate makes animals more sensitive to future administration of these drugs. That is, in these animals, a dose of stimulant becomes more and more active, with repeated use, at increasing motor activity and motivation. It is unclear if the results of these experiments in animals are relevant to the treatment of children with AD/HD. First, the doses of stimulants that were typically tested (amphetamine 2.5-20 mg/kg/day) are substantially higher than the AD/HD treatment doses (0.4-1.5 mg/kg/day). Second, the drugs were given to the animals by injection rather than by mouth. These discrepancies are due to the fact that these experiments were designed to study what happens during substance abuse, and not during treatment of AD/HD. Recent studies in adults suggest, however, that sensitization is a phenomenon that can occur also in adult humans and after brief exposure to relatively low oral doses of amphetamine (0.25 mg/kg/day). Data in children medicated with methylphenidate (Ritalin) for AD/HD seem to indicate that some tolerance (that is, the opposite of sensitization) may develop with repeated use.

Clearly, the most important question is whether substance abuse and/or dependence is more common in children with AD/HD who have been treated with stimulants compared to unmedicated children with AD/HD. A few follow-up studies of children treated for AD/HD have tried to address this question. Two of these studies found that medicated children were less likely to develop substance abuse as adolescents, whereas another study reported that previous treatment of AD/HD with medication was associated with increased use of tobacco and stimulants of abuse. These studies, however, which only follow up non-randomly assigned children over the years, have design limitations that prevent drawing definitive conclusions. In fact, because of selection biases, the more severe cases are more likely to be started on medications. Since severity of AD/HD is a risk factor for substance abuse, this selection bias can lead to a spurious association between medication for AD/HD and substance abuse.

On the other hand, it is also possible that families with more financial resources and social support seek medication treatment for their AD/HD children, thus possibly contributing to an opposite, but equally indirect, association between medication and reduced rate of substance abuse. Selection biases can be numerous and, what is worse, difficult to identify and control. Randomization is currently the best way of controlling for selection biases. It is not, however, possible, for practical and ethical reasons, to maintain children in a randomly assigned treatment for the 5-10 years that would be needed to study the relationship between treatment and outcomes such as substance abuse.

In addition to safety considerations, the potential therapeutic benefits of stimulants over the long-term (past 14 months) have not been systematically studied. In particular, it is not known whether suppression of AD/HD symptoms in childhood ultimately results in better educational achievement or social, occupational and mental health status. These questions are extremely important in understanding the value of diagnosing and treating children with AD/HD. Again, naturalistic follow-up studies are limited in their ability to provide definitive answers, but follow-up of randomized clinical trials can be of help.

The NIMH workshop gave an opportunity to researchers with different backgrounds, such as neuropharmacologists, experts in substance abuse, epidemiologists, and statisticians, to exchange views on which research approaches are more promising and worthy of attention. Because most of the animal studies used high doses and a route of administration that does not apply to the medical use in children, researchers agreed that new studies should be conducted using doses, route of administration, and measurements more relevant to the clinical use of these drugs. There was also an appreciation that imaging techniques, such as MRI, functional MRI, PET, and their more recent developments, have considerable potential to explain what happens in the brain upon administration of drugs. This technology could be applied to studying both short- and long-term effects of stimulants on the brain. Researchers also recognized that the recently completed Multimodal Treatment Study of Children with AD/HD (MTA) can offer a unique opportunity to follow up large groups of children randomly assigned to receive different treatments. MTA affords the possibility of testing whether treatments influence outcomes such as the rate of psychiatric disorders, substance abuse, antisocial behavior, accidents, educational achievement and social adjustment. Given the challenges and opportunities identified at the December meeting, we can expect a flurry of new research to clarify many of the issues discussed.

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