Risks of Stimulant Use for Attention Deficit Hyperactivity Disorder on the Developing Brain: *Primum non nocere*

Clinical Pediatrics
1–6

DOI: 10.1177/0009922817706148
journals.sagepub.com/home/cpj
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H. Patrick Stern, MD[1], Jonathan Lipman, PhD[2,3], Susan L. Andersen, PhD[4,5], John B. Bossaer, PharmD, BCPS, BCOP[6], and Jim Thigpen, PharmD, BCPS[6]

The prognosis of attention deficit hyperactivity disorder (ADHD) continues to "show heightened risk of multiple mental health and social difficulties as well as premature mortality in adult life" after nearly 50 years of primary pharmacological treatment.[1] If the prognosis of ADHD is not changed by stimulants, then 2016 research that stimulants may cause cardiac arrhythmia and myocardial infarction associated with subsequent death in children younger than 17 years prescribed methylphenidate (MPH)[2] raises the question of whether stimulants should be used. Furthermore, a 2015 Cochran Review found 98·6% of ADHD randomized clinical trials were considered high risk for bias and the remaining trials could also have been considered high risk by using a stricter definition.[3] Has medicalization and marketing of the diagnosis and treatment of ADHD become the basis of putting children at risk by using stimulants, especially in the United States?[4,5]

History of ADHD

Attention deficit hyperactivity disorder, which today is the most common neurobehavioral disorder of childhood, was historically considered to be within the normal range of childhood behaviors.[6] The 1954 edition of *Nelson's Textbook of Pediatrics* stated that children entering school are "naturally restless and overactive . . . inattentive and noisy" recommending that there "not be unduly long periods of work or sitting quietly in one place."[7] The 1975 edition of Nelson's introduced the term *hyperkinetic syndrome* and stated,

> difficulties in managing the active toddler mostly reflect inconsistent discipline by the parents . . . the normally exuberant activity of young grade school boys may present problems for teachers in the early school years . . . as a general principle, it may be wise not to have boys begin their first grade experience before the age of six, or at times closer to seven.[8]

Medication, dextroamphetamine or methylphenidate (MPH), was recommended, "at times to be a helpful adjunct in the management of children with learning disabilities."[8] By 1979, Nelson's brought up a concern related to the use of psychoactive medication, stating, "ethical issues are being raised regarding the 'behavioral control' of young children."[9] The 2004 edition of Nelson's stated that ADHD, diagnosed with symptoms of increased activity, decreased attention, and impulsivity, is the most common neurobehavioral disorder of childhood, with 80% of affected children continuing with symptoms into adolescence and adulthood.[6]

Prevalence of ADHD and Stimulant Use

A dramatic increase in the daily use of stimulants, higher stimulant dose, and longer-acting formulations leading to increased adherence has occurred with the increase in prevalence of ADHD and its comorbidities.[10] It is noteworthy that the prevalence of ADHD increased by an average of 4% per year from 1997 to 2006.[11,12] This increase was found in children 12 to 17 years old with no significant increase in children 6 to 11 years old, suggesting that earlier exposures to stimulants may have been related to the increased prevalence.[11,12] There was a 7-fold increase in the number of prescriptions written for ADHD treatment between 1987 and 2008.[13] Forty-nine percent of young children with ADHD in the United States are being treated only with medications.[14] In a report reviewing prescriptions for more than 15 million insured patients, 9% of boys between the ages of 12 and18 years were using stimulant medication in 2012,

[1]Developmental-Behavioral Pediatrician (Retired), Telford, TN, USA
[2]Neuroscience Consulting, Inc, Unicoi, TN, USA
[3]Quillen College of Medicine, East Tennessee State University, Johnson City, TN, USA
[4]Harvard Medical School, Boston, MA, USA
[5]McLean Hospital, Belmont, MA, USA
[6]Bill Gatton College of Pharmacy, East Tennessee State University, Johnson City, TN, USA

Corresponding Author:
James C. Thigpen, Bill Gatton College of Pharmacy, East Tennessee State University, Box 70657, Johnson City, TN 37614-1704, USA.
Email: thigpen@etsu.edu

an increase of 18% since 2008.[15] The prevalence of ADHD in adults is reflected in the remarkable rise in the use of stimulant medication during this same time period by 53·4%.[15]

Neuropsychiatric Symptoms Caused by Stimulants

The increase in ADHD may result from a greater awareness of the disorder, as has been speculated with the increased prevalence of autism.[16] An alternative hypothesis that merits consideration is whether early treatment with stimulants actually worsens the underlying symptoms long term. There is a wealth of research regarding the neuropsychiatric effects of stimulants when used in humans[17-22] and animals.[23-27] Importantly, the clinical symptoms of ADHD, including hyperactivity, impulsivity, and short attention span, are reported side effects of stimulants treating ADHD at therapeutic doses.[10] Amphetamine and MPH have both been found to induce ADHD-like symptoms, including increased activity and decreased attention, in animals.[23,24] The clinical symptoms of ADHD are reported as side effects of stimulants in the *Diagnostic and Statistical Manual of Mental Disorders: Primary Care Version* (DSM-IV-PC).[28] In primates, the chronic administration of D-amphetamine has been shown to cause hypervigilance and tracking of and responding to nonapparent stimuli—symptoms similar to those of paranoid schizophrenia in humans.[23,25,29] In these animal studies, symptoms cognate with psychotic symptoms have been reported as side effects of stimulant medications at therapeutic doses.[21,22]

Neuronal Imprinting

Human research and collateral animal studies, some using standard prescribed doses, raise the question of an association between the increasing prevalence and chronicity of ADHD and the use of stimulants.[24,30,31] Exposure to a drug can influence neuronal function even when the drug itself is no longer present, a phenomenon known as "neuronal imprinting."[32] This results from the drug redirecting the course of neuron development. Neuronal imprinting persistently alters inter-neuronal communication parameters in the brain, resulting in altered baseline behavior, a different behavioral response to stimulation, and an altered response to drugs. The process does not involve cellular death; it results from interference with the rapid course of natural developmental processes of synapse formation and axonal sprouting and pruning. Chronic stimulant use can lead to neuronal imprinting.[32,33] We hypothesize that stimulants are contributing to ADHD changing from a time-limited maturational delay into a chronic lifetime disorder in a subset of patients and propose long-term research, as done with chemotherapy, be conducted.

Need For Caution and Long-Term Studies

Amphetamines and MPH were initially approved by the US Food and Drug Administration (FDA) in 1955, prior to the 1962 Kefauver-Harris Amendment, which made safety and efficacy studies a prerequisite prior to marketing drugs for use in humans.[34] Current FDA protocol requires that extensive animal and human studies be conducted before stimulants are prescribed in humans, especially young children. The need for caution regarding the safety of stimulants was expressed when they were first introduced to treat ADHD. The *New England Journal of Medicine* (*NEJM*) published an article in 1973 questioning the use of stimulants to treat ADHD and urging that long-term safety studies be performed.[35] In spite of this insightful proposal, a 2014 review of safety and efficacy trials submitted to the FDA found the median trial length for ADHD medication in children for premarket studies to be 4 weeks and the median number of participants per drug was only 75.[36] Furthermore, current FDA postmarketing requirements did not exist prior to 2007.[36] The importance of long-term studies is exemplified by the experience of diethylstilbestrol (DES). DES was prescribed for 34 years (1937-1971) before the FDA issued a warning for physicians to stop prescribing the drug due to severe adverse effects on the offspring of women who took the drug during pregnancy.[37] Serious long-term side effects of medications prescribed with good intentions can take decades to discover.[37]

The ability to detect long-term effects of medications is dependent on the system that is designed to detect them. The Childhood Cancer Survivor Study (CCSS) conducted research on the long-term effects of chemotherapy in survivors of pediatric malignancies.[38] The CCSS included 25 institutions resulting in a cohort of more than 14 000 individuals diagnosed with childhood cancer from 1970 to 1986, with 4000 siblings serving as controls. The CCSS was able to provide critical information regarding long-term effects from pediatric cancer treatment, which included adverse neuropsychiatric effects and secondary cancers. Similar research investigating long-term neuropsychiatric and other adverse side effects in the use of stimulants to treat ADHD has not been conducted.[39] Neuropsychiatric effects and secondary cancers from chemotherapy would not have been discovered if safety studies by the CCSS had not been continued for many years following exposure.[38]

Alternative Diagnoses Presenting With ADHD Symptoms

ADHD symptoms may result from a multitude of etiologies. Many of these are amenable to non-medication therapies, which have lower risk than drug treatments.[39-41] The differential diagnosis of ADHD symptoms is very extensive, including neurodevelopmental-learning, psychosocial-psychiatric, and general medical problems.[42] Hearing and vision disorders must be ruled out. Autism, Tourette's syndrome, neurodegenerative disorders, learning disorders, language disorders, and perceptual disorders must be identified for proper treatment.[42] Normal children, especially preschoolers, intellectually gifted students, and an average child in a high-achieving family may present with ADHD symptoms.[42] In addition, psychosocial stressors, including inconsistent parenting, child abuse, and parental psychopathology, must also be considered.[42] Research has also found that other exogenous environmental influences,[43-49] including parental divorce,[50] may cause ADHD symptoms.

The constellation of symptoms constituting ADHD can originate from a myriad of psychiatric disorders, most of which are remedial if properly diagnosed and treated. These include posttraumatic stress disorder, oppositional defiant disorder, depression, and substance abuse syndromes, among others.[42] Psychiatric comorbidities have been reported to occur in up to 90% of children with ADHD.[28,40,43-46] It is thought-provoking that ADHD symptoms from early childhood almost disappear when other comorbid disorders emerge.[51]

Numerous medical disorders may also present with ADHD symptoms. Side effects of many drugs, including prescription medication such as stimulants, chemotherapy, systemic corticosteroids and over-the-counter drugs such as caffeine, may present with these symptoms.[28,52,53] Lead toxicity and iron deficiency, as measured by ferritin, have been found to present with ADHD symptoms.[54,55] Because a sleep disorder may cause ADHD symptoms, a sleep history must be obtained and possibly a sleep study performed.[56] Findings consistent with a subtle seizure warrant an electroencephalogram. Additional testing should be done based on the comprehensive history and physical examination, including a detailed neurological evaluation.[42]

Treatment Options Besides Stimulants

Behavioral therapy and medications other than stimulants, have been shown through evidence-based research to be effective for treatment of ADHD in children.[44] Behavioral therapy, which does not have adverse drug side effects, may exert greater effects on functional improvement than simply treating the symptoms and has been found to be as effective as the use of stimulants in treating ADHD.[51] The American Academy of Pediatrics (AAP) has recommended, especially in young children, that non-pharmacological treatments should be used as first-line treatment of ADHD.[57,58] Behavioral therapy is preferred by some parents over medication alone.[59] Promoting self-control in children, not pharmacological control, has been found to predict physical, economic and behavioral success in adults, which has long-term social and economic implications.[60] Reducing screen time and increasing physical activity may also reduce ADHD symptoms.[61,62] Primary caregivers, especially parents and teachers, are the most important therapists for children and adolescents with ADHD symptoms. Books and Internet sites, such as the Buffalo Treatment Algorithm, offer quality behavioral intervention techniques.[63-67] Pediatricians may offer behavioral therapy to assist caregivers or collaborate with a multidisciplinary team.[68]

Medical treatments should be started for any medical disorder that could cause ADHD symptoms. Any drug that may cause ADHD symptoms should be discontinued or changed. Treating high lead levels and low ferritin levels, which were 23 ng/mL in patients with ADHD symptoms to 44 ng/mL in normal controls, may reduce the symptoms.[55] Sleep interventions should be started if warranted by sleep history or a sleep study when indicated. Subtle seizures should be treated with an appropriate anticonvulsant. A healthy lifestyle, including nutrition, sleep, play, and work activities, must also be ensured. Appropriate treatment determined by a comprehensive evaluation should be started to reduce ADHD symptoms before considering stimulant medication.

Conclusion

Quality research has not been conducted and demonstrated that stimulants are not increasing the prevalence and chronicity of ADHD in children and adults.[4] We concur with previous recommendations that nonpharmacological treatments be used as first-line treatment of ADHD.[51,58] We recommend that Risk Evaluation and Mitigation Strategy (REMS) licensing be utilized for prescribing ADHD medication to track and possibly reduce the risk of chronic adverse effects of these drugs in children.[69] If medications are used to treat ADHD, we recommend requiring parents to give informed consent as is done in the treatment of childhood cancer and REMS programs, and as has been proposed when imipramine is used to treat ADHD.[70] We also recommend that if medication is used, a low dose of a short acting

product with drug holidays be employed for as brief a duration as possible.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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