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Health & Wellness

Do ADHD Drugs Take a Toll on the Brain?

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Research hints that hidden risks might accompany long-term use of the medicines that treat attention-deficit hyperactivity disorder

A few years ago a single mother who had recently moved to town came to my office asking me to prescribe the stimulant drug Adderall for her sixth-grade son. The boy had been taking the medication for several years, and his mother had liked its effects: it made homework time easier and improved her son's grades.

At the time of this visit, the boy was off the medication, and I conducted a series of cognitive and behavioral tests on him. He performed wonderfully. I also noticed that off the medication he was friendly and playful. On a previous casual encounter, when the boy had been on Adderall, he had seemed reserved and quiet. His mother acknowledged this was a side effect of the Adderall. I told her that I did not think her son had attention-deficit hyperactivity disorder (ADHD) and that he did not need medication. That was the last time I saw her.

Attention-deficit hyperactivity disorder afflicts about 5 percent of U.S. children - twice as many boys as girls - age six to 17, according to a recent survey conducted by the Centers for Disease Control and Prevention. As its name implies, people with the condition have trouble focusing and often are hyperactive or impulsive. An estimated 9 percent of boys and 4 percent of girls in the U.S. are taking stimulant medications as part of their therapy for ADHD, the CDC reported in 2005. The majority of patients take methylphenidate (Ritalin, Concerta), whereas most of the rest are prescribed an amphetamine such as Adderall.

Although it sounds counter-intuitive to give stimulants to a person who is hyperactive, these drugs are thought to boost activity in the parts of the brain responsible for attention and self-control. Indeed, the pills can improve attention, concentration and productivity and also suppress impulsive behavior, producing significant improvements in some people's lives. Severe inattention and impulsivity put individuals at risk for substance abuse, unemployment,

crime and car accidents. Thus, appropriate medication might keep a person out of prison, away from addictive drugs or in a job.

Over the past 15 years, however, doctors have been pinning the ADHD label on - and prescribing stimulants for - a rapidly rising number of patients, including those with moderate to mild inattention, some of whom, like the sixth grader I saw, have a normal ability to focus. **This trend may be fueled in part by a relaxation of official diagnostic criteria for the disorder, combined with a lower tolerance in society for mild behavioral or cognitive problems.**

In addition, patients are no longer just taking the medicines for a few years during grade school but are encouraged to stay on them into adulthood. In 2008 two new stimulants - Vyvanse (amphetamine) and Concerta - received U.S. Food and Drug Administration - indications for treating adults, and pharmaceutical firms are pushing awareness of the adult forms of the disorder. What is more, many people who have no cognitive deficits are opting to take these drugs to boost their academic performance. A number of my patients - doctors, lawyers and other professionals - have asked me for stimulants in hopes of boosting their productivity. As a result of these developments, prescriptions for methylphenidate and amphetamine rose by almost 12 percent a year between 2000 and 2005, according to a 2007 study.

With the expanded and extended use of stimulants comes mounting concern that the drugs might take a toll on the brain over the long run. Indeed, a smattering of recent studies, most of them involving animals, hint that stimulants could alter the structure and function of the brain in ways that may depress mood, boost anxiety and, contrary to their short-term effects, lead to cognitive deficits. Human studies already indicate the medications can adversely affect areas of the brain that govern growth in children, and some researchers worry that additional harms have yet to be unearthed.

Medicine for the Mind

To appreciate why stimulants could have negative effects over time, it helps to first understand what they do in the brain. One hallmark of ADHD is an underactive frontal cortex, a brain region that lies just behind the forehead and controls such "executive" functions as decision making, predicting future events, and suppressing emotions and urges. This area may, in some cases, be smaller than average in ADHD patients, compromising their executive abilities. Frontal cortex function depends greatly on a signaling chemical, or neurotransmitter, called dopamine, which is released in this structure by neurons that originate in deeper brain structures. Less dopamine in the prefrontal cortex is linked, for example, with cognitive difficulty in old age. Another set of dopamine-releasing neurons extends to the nucleus accumbens, a critical mediator of motivation, pleasure and reward whose function may also be impaired in ADHD.

Stimulants enhance communication in these dopamine-controlled brain circuits by binding to so-called dopamine transporters - the proteins on nerve endings that suck up excess dopamine - thereby deactivating them. As a result, dopamine accumulates outside the neurons, and the additional neurotransmitter is thought to improve the operation of neuronal circuits critical for motivation and impulse control.

Not only can methylphenidate and amphetamine ameliorate a mental deficit, they also can

enhance cognitive performance. In studies dating back to the 1970s, researchers have shown that normal children who do not have ADHD also become more attentive - and often calmer - after taking stimulants. In fact, the drugs can lead to higher test scores in students of average and above-average intellectual ability [see "*Smarter on Drugs*," by Michael S. Gazzaniga; *Scientific American Mind*, Vol. 16, No. 3, 2005].

Since the 1950s, when doctors first started prescribing stimulants to treat behavior problems, millions of people have taken them without obvious incident. A number of studies have even exonerated them from causing possible adverse effects. For example, researchers have failed to find differences between stimulant-treated children and those not on meds in the larger-scale growth of the brain. In January 2009 child psychiatrist Philip Shaw of the National Institute of Mental Health and his colleagues used MRI scans to measure the change in the thickness of the cerebral cortex (the outer covering of the brain) of 43 youths between the ages of 12 and 16 who had ADHD. The researchers found no evidence that stimulants slowed cortical growth. In fact, only the un-medicated adolescents showed more thinning of the cerebrum than was typical for their age, hinting that the drugs might facilitate normal cortical development in kids with ADHD.

Altering Mood

Despite such positive reports, traces of a sinister side to stimulants have also surfaced. In February 2007 the FDA issued warnings about side effects such as growth stunting and psychosis, among other mental disorders. Indeed, the vast majority of adults with ADHD experience at least one additional psychiatric illness - often an anxiety disorder or drug addiction - in their lifetime. Having ADHD is itself a risk factor for other mental health problems, but the possibility also exists that stimulant treatment during childhood might contribute to these high rates of accompanying diagnoses.

After all, stimulants activate the brain's reward pathways, which are part of the neural circuitry that controls mood under normal conditions. And at least three studies using animals hint that exposure to methylphenidate during childhood may alter mood in the long run, perhaps raising the risk of depression and anxiety in adulthood.

In an experiment published in 2003 psychiatrist Eric Nestler of the University of Texas Southwestern Medical Center and his colleagues injected juvenile rats twice a day with a low dose of methylphenidate similar to that prescribed for children with ADHD. When the rats became adults, the scientists observed the rodents' responses to various emotional stimuli. The rodents that had received methylphenidate were significantly less responsive to natural rewards such as sugar, sex, and fun, novel environments than were untreated rats, suggesting that the drug-exposed animals find such stimuli less pleasurable. In addition, the stimulants apparently made the rats more sensitive to stressful situations such as being forced to swim inside a large tube. Similarly, in the same year psychiatrist William Carlezon of Harvard Medical School and his colleagues reported that methylphenidate-treated preadolescent rats displayed a muted response to a cocaine reward as adults as well as unusual apathy in a forced-swim test, a sign of depression.

In 2008 psychopharmacologist Leandro F. Vendruscolo and his co-workers at Federal University of Santa Catarina in Brazil echoed these results using spontaneously hypertensive rats, which - like children with ADHD - sometimes show attention deficits, hyperactivity and motor impulsiveness. The researchers injected these young rats with methylphenidate for 16

days at doses approximating those used to treat ADHD in young people. Four weeks later, when the rats were young adults, those that had been exposed to methylphenidate were unusually anxious: they avoided traversing the central area of an open, novel space more so than did rats not exposed to methylphenidate. Adverse effects of this stimulant, the authors speculate, could contribute to the high rates of anxiety disorders among ADHD patients.

Copying Cocaine?

The long-term use of any drug that affects the brain's reward circuitry also raises the specter of addiction. Methyl-phenidate has a chemical structure similar to that of cocaine and acts on the brain in a very similar way. Both cocaine and methamphetamine (also called "speed" or "meth") - another highly addictive stimulant - block dopamine transporters just as ADHD drugs do [see "*New Weapons against Cocaine Addiction*," by Peter Sergo; *Scientific American Mind*, April/May 2008]. In the case of the illicit drugs, the dopamine surge is so sudden that in addition to making a person unusually energetic and alert, it produces a "high."

Recent experiments in animals have sounded the alarm that methylphenidate may alter the brain in ways similar to that of more powerfully addictive stimulants such as cocaine. In February 2009 neuroscientists Yong Kim and Paul Greengard, along with their colleagues at the Rockefeller University, reported cocaine like structural and chemical alterations in the brains of mice given methylphenidate. The researchers injected the mice with either methylphenidate or cocaine daily for two weeks. Both treatments increased the density of tiny extensions called spines at the ends of neurons bearing dopamine receptors in the rodent nucleus accumbens. Compared with cocaine, methylphenidate had a somewhat more localized influence; it also had more power over longer spines and less effect on shorter ones. Otherwise, the drugs' effects were strikingly similar.

Furthermore, the scientists found that methylphenidate boosted the amount of a protein called ΔFosB, which turns genes on and off, even more than cocaine did. That result could be a chemical warning of future problems: excess ΔFosB heightens an animal's sensitivity to the rewarding effects of cocaine and makes the animal more likely to ingest the drug. Many former cocaine addicts struggle with depression, anxiety and cognitive problems. Researchers have found that cocaine has remodeled the brains of such ex-users. Similar problems - principally, perhaps, difficulty experiencing joy and excitement in life - could occur after many years of Ritalin or Adderall use.

Amphetamine and methylphenidate can also be addictive if abused by, say, crushing or snorting the pills. In a classic study published in 1995 research psychiatrist Nora Volkow, then at Stony Brook University, and her colleagues showed that injections of methylphenidate produced a cocaine like high in volunteers. **More than seven million people in the U.S. have abused methylphenidate, and as many as 750,000 teenagers and young adults show signs of addiction, according to a 2006 report.**

Typical oral doses of ADHD meds rarely produce such euphoria and are not usually addicting. Furthermore, the evidence to date, including two 2008 studies from the National Institute on Drug Abuse, indicates that children treated with stimulants early in life are not more likely than other children to become addicted to drugs as adults. In fact, the risk for severe cases of ADHD may run in the opposite direction. (A low addiction risk also jibes with Carlezon's earlier findings, which indicated that methylphenidate use in early life mutes adult rats' response to cocaine.)

Corrupting Cognition

Amphetamines such as Adderall could alter the mind in other ways. A team led by psychologist Stacy A. Castner of the Yale University School of Medicine has documented long-lasting behavioral oddities, such as hallucinations, and cognitive impairment in rhesus monkeys that received escalating injected doses of amphetamine over either six or 12 weeks. Compared with monkeys given inactive saline, the drug-treated monkeys displayed deficits in working memory - the short-term buffer that allows us to hold several items in mind - which persisted for at least three years after exposure to the drug. The researchers connected these cognitive problems to a significantly lower level of dopamine activity in the frontal cortex of the drug-treated monkeys as compared with that of the monkeys not given amphetamine.

Underlying such cognitive and behavioral effects may be subtle structural changes too small to show up on brain scans. In a 1997 study psychologists Terry E. Robinson and Bryan Kolb of the University of Michigan at Ann Arbor found that high injected doses of amphetamine in rats cause the major output neurons of the nucleus accumbens to sprout longer branches, or dendrites, as well as additional spines on those dendrites. A decade later Castner's team linked lower doses of amphetamine to subtle atrophy of neurons in the prefrontal cortex of monkeys.

A report published in 2005 by neurologist George A. Ricaurte and his team at the Johns Hopkins University School of Medicine is even more damning to ADHD meds because the researchers used realistic doses and drug delivery by mouth instead of by injection. Ricaurte's group trained baboons and squirrel monkeys to self-administer an oral formulation of amphetamine similar to Adderall: the animals drank an amphetamine-laced orange cocktail twice a day for four weeks, mimicking the dosing schedule in humans. Two to four weeks later the researchers detected evidence of amphetamine-induced brain damage, encountering lower levels of dopamine and fewer dopamine transporters on nerve endings in the striatum - a trio of brain regions that includes the nucleus accumbens - in amphetamine-treated primates than in untreated animals. The authors believe these observations reflect a drug-related loss of dopamine-releasing nerve fibers that reach the striatum from the brain stem.

One possible consequence of a loss of dopamine and its associated molecules is Parkinson's disease, a movement disorder that can also lead to cognitive deficits. A study in humans published in 2006 hints at a link between Parkinson's and a prolonged exposure to amphetamine in any form (not just that prescribed for ADHD). Before Parkinson's symptoms such as tremors and muscle rigidity appear, however, dopamine's function in the brain must decline by 80 to 90 percent, or by about twice as much as what Ricaurte and his colleagues saw in baboons that were drinking a more moderate dose of the drug. And some studies have found no connection between stimulant use and Parkinson's.

Stimulants do seem to stunt growth in children. Otherwise, however, studies in humans have largely failed to demonstrate any clear indications of harm from taking ADHD medications as prescribed. Whether the drugs alter the human brain in the same way they alter that of certain animals is unknown, because so far little clinical data exist on their long-term neurological effects. Even when the dosing is similar or the animals have something resembling ADHD, different species' brains may have varying sensitivities to stimulant medications.

Nevertheless, in light of the emerging evidence, many doctors and researchers are recommending a more cautious approach to the medical use of stimulants. Some are urging

the adoption of strict diagnostic criteria for ADHD and a policy restricting prescriptions for individuals who fit those criteria. Others are advocating behavior modification - which can be as effective as stimulants over the long run - as a first-line approach to combating the disorder. Certain types of mental exercises may also ease ADHD symptoms [see "*Train Your Brain*," by Ulrich Kraft; *Scientific American Mind*, February/March 2006]. For patients who require stimulants, some neurologists and psychiatrists have also suggested using the lowest dose needed or monitoring the blood levels of these drugs as a way of keeping concentrations below those shown to be problematic in other mammals. Without these or similar measures, large numbers of people who regularly take stimulants may ultimately struggle with a new set of problems spawned by the treatments themselves.

Growing Problems

So far the best-documented problem associated with the stimulants used to treat attention-deficit hyperactivity disorder (ADHD) concerns growth. Human growth is controlled at least in part through the hypothalamus and pituitary at the base of the brain. Studies in mice hint that stimulants may increase levels of the neurotransmitter dopamine in the hypothalamus as well as in the striatum (a three-part brain structure that includes part of its reward circuitry) and that the excess dopamine may reach the pituitary by way of the bloodstream and act to retard growth.

Recent work strongly indicates that the drugs can stunt growth in children. In a 2007 analysis of a National Institute of Mental Health study of ADHD treatments involving 579 children, research psychiatrist Nora Volkow, who directs the National Institute of Drug Abuse, and her colleagues compared growth rates of unmedicated seven- to 10-year-olds over three years with those of kids who took stimulants throughout that period. Relative to the unmedicated youths, the drug-treated youths showed a decrease in growth rate, gaining, on average, two fewer centimeters in height and 2.7 kilograms less in weight. Although this growth-stunting effect came to a halt by the third year, the kids on the meds never caught up to their counterparts.