

*Law, Ethics, and Gender***Cognitive Enhancements in Human Beings**

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*Proskauer Rose LLP, New York, New York***ABSTRACT**

In the area of genometry—the nascent field of science and technology that proposes to apply enhanced understanding of the human genetic code to reshaping our individual and collective destinies—research and development directed toward improving the function of the human brain has not advanced at the same rate as studies focused on physical enhancement. This article describes developments in the area of cognitive enhancement, including the rise in nonmedical uses of prescription drugs. As those without medical ailments continue to take prescription drugs for their cognitive-enhancing side effects, social policy questions about the fairness of such actions will arise. This article also examines the regulation of cognitive enhancers, both by US law and the rules of international competition. (*Gend Med.* 2009;6:338–344)
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INTRODUCTION

The primary aim of biomedical and pharmaceutical research on brain function is to reverse losses or declines due to injury, disease, or natural aging. However, a number of pharmaceutical products originally developed to alleviate specific neurologic conditions have found application in healthy people. For example, the use of certain off-label cognitive performance-enhancing drugs, including modafinil and mixed amphetamine salts,* has gained popularity on college campuses and is beginning to penetrate the workplace as well. Fast-acting drugs that can augment cognitive function in an applied context and measurably improve a person's academic or professional abilities have obvious appeal in competitive environments.

Our previous article in this journal explored advances in genometry—the nascent field of science and technology that proposes to apply enhanced understanding of the human genetic code to reshaping our individual and collective destinies—for the potential physical enhancement of the human body.¹ From that discussion, we arrived at two interesting conclusions regarding the extensive and growing use of regulation directed at physical enhancements. First, there was a dearth of scientifically based statistical evidence that the genometric advances in the field of physical enhancement were, in fact, real. Second, it was unclear whether we currently have the measurement tools necessary to monitor compliance with the regulations being promulgated, and thus, the apparent “overreaction” of governmental and self-regulatory bodies would seem to need moderation over time.

*For example, Adderall®, a registered trademark of Shire US Inc., Wayne, Pennsylvania.

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We believe that the same two conclusions garnered from our exploration of physical enhancements are also justified with respect to cognitive enhancements. In addition, the mechanism of action of cognitive enhancers is poorly understood, and the potential long-term adverse effects on brain function resulting from repeated or habitual use are unknown.

COGNITIVE ENHANCEMENT

In contrast to physical enhancement, cognitive enhancement can be defined as the nontherapeutic application of technologies derived from various scientific disciplines to augment brain function. The general aim of cognitive enhancement is to restore or improve brain function such as memory, concentration, and attention span, as well as to refine and accelerate decision-making processes. A variety of technologies are in development to improve cognition, including specially adapted gene therapy techniques for brain disorders²; transcranial magnetic stimulation, in which specialized electromagnets generate short magnetic pulses that pass through the skull to stimulate the underlying brain cells; augmented cognition devices, which couple computers to human physiological indicators to enhance the interaction between humans and computers³; and neurochips, such as the silicon chip implant that functions as a prosthetic hippocampus, an area of the brain known for creating memories. Besides replacing the function of a diseased hippocampus, the chip can also enlarge memory capacity in healthy individuals, increasing their accessible memory, and with it perhaps their general intelligence.⁴

Although these are promising therapeutic modalities, by far the most popular category of cognitive enhancers is that of pharmaceutical drugs. A 2008 working group report from the Academy of Medical Sciences in England estimated that of the >600 compounds being assessed worldwide as treatments for neurodegenerative disorders, a large number of cognitive enhancers will likely emerge over the next few decades.⁵ Some of the cognition-enhancing psychopharmaceutical products that are already on the market include prescription drugs, such as mixed amphetamine salts, that were originally

developed to treat attention-deficit hyperactivity disorder (ADHD) but have a known off-label use as a study aid that decreases the need for sleep, increases focus and concentration, and apparently improves productivity.⁶ Similarly, modafinil, a pharmaceutical originally developed to treat narcolepsy, has prompted off-label usage to improve the working memory of healthy individuals. Modafinil has also been found to improve visual pattern recognition, spatial planning, and reaction time.⁷

Not much is known about the molecular basis of the effect that cognition-enhancing drugs exert on brain cells. It is believed that these drugs alter the balance of brain chemicals either by regulating the release of neurotransmitters that are involved in the processing of information, by modulating receptors and ion channels, or by affecting neuronal gene expression. However, precisely how they accomplish the ultimate task of augmented cognition remains largely unexplained.

Neurotransmitter signaling pathways that are known targets for cognitive enhancers include those of the neurotransmitters glutamate and acetylcholine: glutamate and glutamate receptors play a key role in long-term potentiation (LTP), a process believed to underlie memory formation. Enhancing LTP and downstream pathways may provide a novel approach to the treatment of cognitive deficits.⁸ Ampakines, a newly discovered class of compounds, have been found to boost the activity of glutamate and thus enhance the formation of memories. An ampakine drug currently in development for Alzheimer's disease has been found to increase alertness in patients. Neurons that respond to acetylcholine, on the other hand, are involved in concentration, focus, and high-order thought processes as well as in new memory formation. Drugs that inhibit the breakdown of acetylcholine also offer cognitive benefits such as improved alertness.⁹ In addition, several cholinesterase inhibitors that have been used in the treatment of Alzheimer's disease have been reported to enhance learning and memory in healthy older individuals.¹⁰

Even if the mechanism of action of a cognition-enhancing psychopharmaceutical drug is currently well characterized at the molecular level, its role

in the functional organization of the brain has not been fully elucidated. That is so because the human brain comprises approximately 10 to 11 billion neurons that process information in a highly integrated fashion, communicating across various regions of the brain to perform mental tasks. Although modern neuroimaging techniques have made it possible to identify those areas of the brain that are activated during certain mental activities, neuroscience is only beginning to uncover the link between the activity of the individual neurons and the overall functioning of the mind. Research suggests that the relationship between cognitive performance and neurotransmitter function follows an inverted “U” curve: there is an optimal level of neurotransmitter function and deviations from this level—in either direction—will lead to inferior performance. Moreover, different types of cognitive tasks implicate different optimal levels of neurotransmitters.⁵ To complicate matters further, physiological states, including anxiety, depression, stress, and certain emotions, can profoundly influence memory encoding, recall, and possibly other neuronal signaling processes that underlie cognition.¹¹ Thus, not only might it be impossible to achieve enhancement across all aspects of cognition, but evidence is beginning to emerge that some types of cognition can be pharmaceutically enhanced only at the expense of impairing other, possibly higher cognitive functions.⁵

Regulation of Cognitive Enhancement

Whether or not the use of genometry to influence the cognitive capabilities of the human brain is well developed, increasing numbers of people nonetheless continue to look for a mental boost from drugs such as Adderall, Ritalin^{®,*} and Provigil^{®.†} Taking these drugs without a prescription (which is often done), in addition to being illegal, raises a host of questions regarding the

safety and fairness of such conduct. The safety of long-term use of cognitive enhancers is not yet known, and adverse effects that are not apparent in the short term could be debilitating years later. For those who take the drugs intermittently, what are the risks of abruptly stopping? Might these medications be as addictive as other drugs? Regarding fairness, could athletes gain a strategic advantage by “brain doping” to study the competition? In games of skill, such as bridge or chess, could advanced players improve by using these drugs to memorize hands or openings? Do students who take prescriptions to study all night have an unfair advantage over students who make do without the aid of pills? Despite the increase in use of cognitive-enhancing drugs, there is very little regulation from private bodies.

Cognitive Enhancers and the Law

Ritalin and Adderall, which are prescribed to help treat ADHD, are regulated by the federal government as Schedule II controlled substances.¹² Under the Controlled Substances Act, Schedule II substances must have a high potential for abuse, must have a currently accepted medical use in treatment in the United States (or a currently accepted medical use with severe restrictions), and, if abused, may lead to severe psychological or physical dependence.¹³ Schedule II substances may only be dispensed to the “ultimate user” with a prescription unless dispensed directly by the practitioner (excepting rare emergency situations).¹⁴ Provigil, a drug designed to improve wakefulness in adults who experience narcolepsy and other sleep disorders, is also used by those who do not suffer from any ailment so that they can boost their mental alertness, and stay awake and focused for long periods of time.¹⁵ Provigil is a Schedule IV controlled substance, a lower level of regulation than substances designated as Schedule II. Schedule IV substances have a lower potential for abuse and may lead to limited physical or psychological dependence relative to the drugs or other substances in higher schedules. Individuals unlawfully in possession of Adderall without a prescription face up to a year in prison and fines if convicted for a first offense of simple possession.¹⁶

*Ritalin (methylphenidate) is a registered trademark of Novartis Pharmaceuticals Corporation, East Hanover, New Jersey.

†Provigil (modafinil) is a registered trademark of Cephalon, Inc., Frazer, Pennsylvania.

Some individuals who take these drugs without a prescription do so for their cognitive benefits. However, it has been reported that these pills may be crushed into a powder and snorted for a drug-induced high. One survey noted that 1 in 10 American teenagers has taken prescription stimulants without a doctor's order (for any reason, not just cognitive enhancement).¹⁷ Prosecution for small-scale possession or distribution is hampered by the way the pills are dispensed. The US Drug Enforcement Administration concedes that "youngsters have little difficulty obtaining methylphenidate from classmates or friends who have been prescribed it. Greater efforts to safeguard this medication at home and school are needed."¹⁸

Cognitive Enhancers in Competition

In the arena of international sports, authorities are concerned mostly with physical enhancements, whether achieved by gene doping or drugs. As discussed in our previous article, under the World Anti-Doping Code, which governs drug testing in every Olympic sport, stimulants such as amphetamine and modafinil are banned during competition only, whereas gene therapies are banned if they "enhance athletic performance."¹⁹ Interestingly, on reading the current Code, it appears that gene therapies that provide only cognitive benefits would not be outlawed, unless one could argue that enhancing cognitive performance is an indirect way of enhancing athletic performance. This argument seems like a stretch, frankly; athletic performance may be indirectly enhanced by many things (say, a good night's sleep), and we have not found any serious effort to ban those. It would stand to reason that, under current regulations, athletes could take Adderall during training, as long as the drug was out of their bloodstream by the start of the competition.

Banning the use of cognitive enhancers during competition does not make any more or less sense than banning physical enhancers. The science justifying regulation does not appear to be any more robust, nor are the measurement challenges any greater, in either context. Even if we set aside the physical enhancements that these drugs can elicit, artificially increasing the ability to focus for hours

on end would appear to provide a competitor with an advantage, for example, in Olympic sports such as archery (in which several rounds of competition can take place on a single day) or curling (in which matches last over 2 hours with multiple matches per day).

What is the argument for banning cognitive-enhancing gene therapies outside of competition? On the one hand, the benefits of cognitive enhancement for most sports seem limited and in all events far more indirect. To be sure, for team sports and certain individual sports such as tennis, the enhanced ability to focus and review game film of opponents or study strategy for extended time periods would again appear to be beneficial. But at the end of the day, cognitive aids cannot trump physical training—without athleticism and technical skill, all the strategy and tactics will be for naught.

In an attempt to gain inclusion into the Olympic Games, the governing bodies for several games—including chess, bridge, and billiards—have adopted the World Anti-Doping Code. These organizations test their competitors for drug use during international competitions. Although using designer steroids seems unlikely in chess, there would be a great benefit in being able to focus as intently during the endgame as at the opening move. At least one very successful professional poker player has discussed the beneficial effects of taking cognitive enhancers during poker tournaments (in which players may play for more than 10 hours a day).¹⁵ While poker remains unregulated, games that have embraced the Code have proscribed players from taking Adderall, Provigil, and other stimulants during competition, unless the players have a medical reason for taking the drug, in which case they may receive a therapeutic use exemption.

But the Code leaves a void when it comes to cognitive enhancers taken outside of competition. By taking cognitive enhancers in preparation for a tournament, a bridge player could spend extra time memorizing hands and card combinations, and then stop the medication just before the competition (despite the dangers of abruptly halting the medication). There is nothing in the rules that

would prohibit this, yet World Bridge Federation (WBF) officials are not concerned. The WBF currently does not perform out-of-competition drug testing (though it is engaged in discussions with the World Anti-Doping Agency about this issue). Furthermore, the WBF does not believe it is possible to increase “brain muscle” through out-of-competition doping. Chess officials take a similar view because of the complexity of their game (World Bridge and World Chess Federation officials, written communication, April and May 2009).

It is our belief that the distinction drawn between physical and cognitive enhancers will blur over time, and it is our further prediction that oversight bodies will begin treating the enhancers similarly—ban them equally, pre- and during competition, or not.

Cognitive Enhancement Among Students

Stimulants have long been a staple of college life. Whether the jolt comes from a pot of coffee, a couple of Vivarins,* or something procured on the street, the ability to study and write long into the night (and into the morning) is coveted (and exploited) by students and faculty alike. It is not surprising, then, to learn that the use of cognitive-enhancing drugs is common on college campuses. Faculty use them to stay up late grading papers or to complete labyrinthine grant proposals. Students use these drugs as study aids to help them write papers and prepare for exams, and even recreationally. A 2005 survey found that 6.9% of college students had ever taken a prescription stimulant for nonmedical use, while 4.1% had done so within the past year. At 12 schools, more than 10% of students had used stimulants within the past year—at one school, the rate was 25%.²⁰ With such frequent usage, ethical questions can be easily overlooked. But is it fair for people who do not have ADHD or sleep disorders to take drugs designed to treat those ailments so that they can increase the amount of time and the efficiency with which they work?

Students may receive the drugs legally via a prescription for the treatment of ADHD, or, more

easily, from a friend or roommate. Some students sell their prescription pills. While students who do have ADHD or narcolepsy need medications so that they may work at the same baseline level as their peers without these ailments, they are critical of their “healthy” friends who take the drugs. One Ivy League student who had attention deficit disorder (ADD) expressed frustration on this issue: “It gives people an unfair academic advantage. For people with ADD, it just makes them normal, and for people without ADD, it makes them above average. If both me and someone without ADD were both on Adderall, I could never outdo them.”²¹

The fairness issues are not just limited to the differences between those who have a medical reason to take Adderall and those who do not. McCabe et al’s 2005 survey noted that rates of nonmedical use of prescription stimulants differed based on race.²⁰ Certain characteristics of colleges and universities also correlated with higher rates of use among students. For example, colleges located in the northeastern United States had higher rates of stimulant use than did schools in other regions. Students who attended colleges with competitive or highly competitive admissions criteria were more than 2 times more likely to report nonmedical use within the previous year than were students who attended less competitive colleges. Commuter schools had less than one fourth the rate of past-year use compared with residential campuses, and at the 3 historically black colleges in the sample, there were no reports of nonmedical use within the past year. Overall, the characteristics of students who were most likely to have used stimulants in the past year were male sex, white race, residence in a fraternity or sorority house, and grade-point average of B or lower.

If we assume for the sake of argument that students attending highly competitive colleges are, on average, wealthier than those attending commuter schools, then this survey provides at least cursory evidence that nonmedical use of stimulants is more common among the affluent. Concerns about this unfair advantage have led some to advocate for “[s]elective use of neuroenhancers amongst those with lower intellectual capacity, or those from deprived backgrounds who do not have the benefit of additional tuition, [which] could

*A caffeine product manufactured by GlaxoSmithKline, Research Triangle Park, North Carolina.

enhance the educational opportunities for those groups.”¹⁵ Others, such as Dr. Martha Farah, a professor of psychology at the University of Pennsylvania and director of the school’s Center for Cognitive Neuroscience, note that the risk of cognitive-enhancing drugs fostering inequality is remote, because there is a “pretty clear trend across the studies that say neuroenhancers will be less helpful for people who score above average.” Nonetheless, bright and able students at some of America’s top universities turn to prescription drugs for a boost that might not be available to their peers.

Schools lack effective detection and enforcement mechanisms to prevent healthy students from taking cognitive enhancers without a prescription. Will schools begin testing students for drugs in the days before an exam? Would legal stimulants like caffeine be outlawed as well? Although many schools have honor codes, some of which require students to report breaches of the code, banning the use of cognitive enhancers seems counterproductive. The purpose of higher education, in part, is to encourage students to learn and to expand their learning capacities. If taking Adderall permits a student to learn more than he could otherwise, is that necessarily bad? Some have argued, including a Stanford professor who is head of the school’s Center for Law and the Biosciences, that use of cognitive enhancers by the healthy should be permitted, as long as sufficient safety regulations are in place.²²

CONCLUSIONS

Like physically enhancing drugs, those associated with cognitive enhancement have not been the subject of sufficient study to permit generalized conclusions about either efficacy or safety for non-prescribed uses. Yet, like physically enhancing drugs, those associated with cognitive enhancement are being used in ever-increasing quantities. We have not found solid evidence that gene-based cognitive enhancers are at all effective for such uses. For both physical and cognitive enhancers, regulatory oversight is alive and well, at least in connection with competition and sport. But it is unclear whether banning such substances, for example, in the field of competitive sports or at universities, is either necessary or sufficient.

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