COMMENTARY

Towards responsible use of cognitive-enhancing drugs by the healthy

Society must respond to the growing demand for cognitive enhancement. That response must start by rejecting the idea that 'enhancement' is a dirty word, argue **Henry Greely and colleagues**.

Today, on university campuses around the world, students are striking deals to buy and sell prescription drugs such as Adderall and Ritalin — not to get high, but to get higher grades, to provide an edge over their fellow students or to increase in some measurable way their capacity for learning. These transactions are crimes in the United States, punishable by prison.

Many people see such penalties as appropriate, and consider the use of such drugs to be cheating, unnatural or dangerous. Yet one survey[1] estimated that almost 7% of students in US universities have used prescription stimulants in this way, and that on some campuses, up to 25% of students had used them in the past year. These students are early adopters of a trend that is likely to grow, and indications suggest that they're not alone[2].

In this article, we propose actions that will help society accept the benefits of enhancement, given appropriate research and evolved regulation. Prescription drugs are regulated as such not for their enhancing properties but primarily for considerations of safety and potential abuse. Still, cognitive enhancement has much to offer individuals and society, and a proper societal response will involve making enhancements available while managing their risks.

Adderall is one of several drugs increasingly used to enhance cognitive function.

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Paths to enhancement

Many of the medications used to treat psychiatric and neurological conditions also improve the performance of the healthy. The drugs most commonly used for cognitive enhancement at present are stimulants, namely Ritalin (methyphenidate) and Adderall (mixed amphetamine salts), and are prescribed mainly for the treatment of attention deficit hyperactivity disorder (ADHD). Because of their effects on the catecholamine system, these drugs increase executive functions in patients and most healthy normal people, improving their abilities to focus their attention, manipulate information in working memory and flexibly control their responses[3]. These drugs are widely used therapeutically. With rates of ADHD in the range of 4–7% among US college students using DSM criteria[4], and stimulant medication the standard therapy, there are plenty of these drugs on campus to divert to enhancement use.

A newer drug, modafinil (Provigil), has also shown enhancement potential. Modafinil is approved for the treatment of fatigue caused by narcolepsy, sleep apnoea and shift-work sleep disorder. It is currently prescribed off label for a wide range of neuropsychiatric and other medical conditions involving fatigue[5] as well as for healthy people who need to stay alert and awake when sleep deprived, such as physicians on night call[6]. In addition, laboratory studies have shown that modafinil enhances aspects of executive function in rested healthy adults, particularly inhibitory control[7]. Unlike Adderall and Ritalin, however, modafinil prescriptions are not common, and the drug is consequently rare on the college black market. But anecdotal evidence and a readers' survey both suggest that adults sometimes obtain modafinil from their physicians or online for enhancement purposes[2].

A modest degree of memory enhancement is possible with the ADHD medications just mentioned as well as with medications developed for the treatment of Alzheimer's disease such as Aricept (donepezil), which raise levels of acetylcholine in the brain[8]. Several other compounds with different pharmacological actions are in early clinical trials, having shown positive effects on memory in healthy research subjects (see, for example, ref. 9). It is too early to know whether any of these new drugs will be proven safe and effective, but if one is it will surely be sought by healthy middle-aged and elderly people contending with normal age-related memory decline, as well as by people of all ages preparing for academic or licensure examinations.

Favouring innovation

Human ingenuity has given us means of enhancing our brains through inventions such as written language, printing and the Internet. Most authors of this Commentary are teachers and strive to enhance the minds of their students, both by adding substantive information and by showing them new and better ways to process that information. And we are all aware of the abilities to enhance our brains with adequate exercise, nutrition and sleep. The drugs just reviewed, along with newer technologies such as brain stimulation and prosthetic brain chips, should be viewed in the same general category as education, good health habits, and information technology — ways that our uniquely innovative species tries to improve itself.

Of course, no two enhancements are equivalent in every way, and some of the differences have moral relevance. For example, the benefits of education require some effort at self-improvement whereas the benefits of sleep do not. Enhancing by nutrition involves changing what we ingest and is therefore invasive in a way

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that reading is not. The opportunity to benefit from Internet access is less equitably distributed than the opportunity to benefit from exercise. Cognitive-enhancing drugs require relatively little effort, are invasive and for the time being are not equitably distributed, but none of these provides reasonable grounds for prohibition. Drugs may seem distinctive among enhancements in that they bring about their effects by altering brain function, but in reality so does any intervention that enhances cognition. Recent research has identified beneficial neural changes engendered by exercise[10], nutrition[11] and sleep[12], as well as instruction[13] and reading[14]. In short, cognitive-enhancing drugs seem morally equivalent to other, more familiar, enhancements.

Many people have doubts about the moral status of enhancement drugs for reasons ranging from the pragmatic to the philosophical, including concerns about short-circuiting personal agency and undermining the value of human effort[15]. Kass[16], for example, has written of the subtle but, in his view, important differences between human enhancement through biotechnology and through more traditional means. Such arguments have been persuasively rejected (for example, ref. 17). Three arguments against the use of cognitive enhancement by the healthy quickly bubble to the surface in most discussions: that it is cheating, that it is unnatural and that it amounts to drug abuse.

In the context of sports, pharmacological performance enhancement is indeed cheating. But, of course, it is cheating because it is against the rules. Any good set of rules would need to distinguish today's allowed cognitive enhancements, from private tutors to double espressos, from the newer methods, if they are to be banned.

"We should welcome new methods of improving our brain function."

As for an appeal to the 'natural', the lives of almost all living humans are deeply unnatural; our homes, our clothes and our food — to say nothing of the medical care we enjoy — bear little relation to our species' 'natural' state. Given the many cognitive-enhancing tools we accept already, from writing to laptop computers, why draw the line here and say, thus far but no further?

As for enhancers' status as drugs, drug abuse is a major social ill, and both medicinal and recreational drugs are regulated because of possible harms to the individual and society. But drugs are regulated on a scale that subjectively judges the potential for harm from the very dangerous (heroin) to the relatively harmless (caffeine). Given such regulation, the mere fact that cognitive enhancers are drugs is no reason to outlaw them.

Based on our considerations, we call for a presumption that mentally competent adults should be able to engage in cognitive enhancement using drugs.

Substantive concerns and policy goals

All technologies have risks as well as benefits. Although we reject the arguments against enhancement just reviewed, we recognize at least three substantive ethical concerns.

The first concern is safety. Cognitive enhancements affect the most complex and important human organ, and the risk of unintended side effects is therefore both high and consequential. Although regulations governing medicinal drugs ensure that they are safe and effective for their therapeutic indications, there is no equivalent vetting for unregulated 'off label' uses, including enhancement uses. Furthermore, acceptable safety in this context depends on the potential benefit. For example, a drug that restored good cognitive functioning to people with severe dementia but caused serious adverse medical events might be deemed safe enough to prescribe, but these risks would be unacceptable for healthy individuals seeking enhancement.

Enhancement in children raises additional issues related to the long-term effects on the developing brain. Moreover, the possibility of raising cognitive abilities beyond their species-typical upper bound may engender new classes of side effects. Persistence of unwanted recollections, for example, has clearly negative effects on the psyche[18].

An evidence-based approach is required to evaluate the risks and benefits of cognitive enhancement. At a minimum, an adequate policy should include mechanisms for the assessment of both risks and benefits for enhancement uses of drugs and devices, with special attention to long-term effects on development and to the possibility of new types of side effects unique to enhancement. But such considerations should not lead to an insistence on higher thresholds than those applied to medications.

We call for an evidence-based approach to the evaluation of the risks and benefits of cognitive enhancement.

The second concern is freedom, specifically freedom from coercion to enhance. Forcible medication is generally reserved for rare cases in which individuals are deemed threats to themselves or others. In contrast, cognitive enhancement in the form of education is required for almost all children at some substantial cost to their liberty, and employers are generally free to require employees to have certain educational credentials or to obtain them. Should schools and employers be allowed to require pharmaceutical enhancement as well? And if we answer 'no' to this question, could coercion occur indirectly, by the need to compete with enhanced classmates and colleagues?

Questions of coercion and autonomy are particularly acute for military personnel and for children. Soldiers in the United States and elsewhere have long been offered stimulant medications including amphetamine and modafinil to enhance alertness, and in the United States are legally required to take medications if ordered to for the sake of their military performance[19]. For similar reasons, namely the safety of the individual in question and others who depend on that individual in dangerous situations, one could imagine other occupations for which enhancement might be justifiably required. A hypothetical example is an extremely safe drug that enabled surgeons to save more patients. Would it be wrong to require this drug for risky operations?

Appropriate policy should prohibit coercion except in specific circumstances for specific occupations, justified by substantial gains in safety. It should also discourage indirect coercion. Employers, schools or governments should not generally require the use of cognitive enhancements. If particular enhancements are shown to be sufficiently safe and effective, this position might be revisited for those interventions.

Children once again represent a special case as they cannot make their own decisions. Comparisons between estimates of ADHD prevalence and prescription numbers have led some to suspect that children in certain school districts are taking enhancing drugs at the behest of achievement-oriented parents, or teachers seeking more orderly classrooms[20]. Governments may be willing to let competent adults take certain risks for the sake of enhancement while restricting the ability to take such risky decisions on behalf of children.

The third concern is fairness. Consider an examination that only a certain percentage can pass. It would seem unfair to allow some, but not all, students to use cognitive enhancements, akin to allowing some students taking a maths test to use a calculator while others must go without. (Mitigating such unfairness may raise issues of indirect coercion, as discussed above.) Of course, in some ways, this kind of unfairness already exists. Differences in education, including private tutoring, preparatory courses and other enriching experiences give some students an advantage over others.

Whether the cognitive enhancement is substantially unfair may depend on its availability, and on the nature of its effects. Does it actually improve learning or does it just temporarily boost exam performance? In the latter

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case it would prevent a valid measure of the competency of the examinee and would therefore be unfair. But if it were to enhance long-term learning, we may be more willing to accept enhancement. After all, unlike athletic competitions, in many cases cognitive enhancements are not zero-sum games. Cognitive enhancement, unlike enhancement for sports competitions, could lead to substantive improvements in the world.

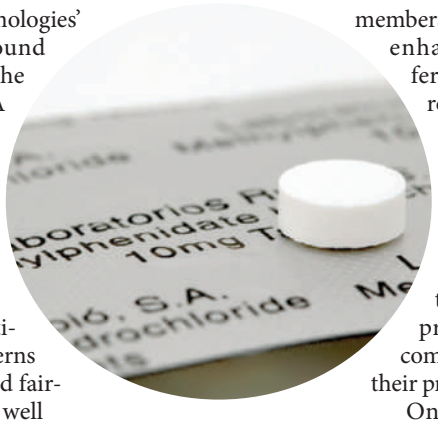
Fairness in cognitive enhancements has a dimension beyond the individual. If cognitive enhancements are costly, they may become the province of the rich, adding to the educational advantages they already enjoy. One could mitigate this inequity by giving every exam-taker free access to cognitive enhancements, as some schools provide computers during exam week to all students. This would help level the playing field.

Policy governing the use of cognitive enhancement in competitive situations should avoid exacerbating socioeconomic inequalities, and should take into account the validity of enhanced test performance. In developing policy for this purpose, problems of enforcement must also be considered. In spite of stringent regulation, athletes continue to use, and be caught using, banned performance-enhancing drugs.

We call for enforceable policies concerning the use of cognitive-enhancing drugs to support fairness, protect individuals from coercion and minimize enhancement-related socioeconomic disparities.

Maximum benefit, minimum harm

The new methods of cognitive enhancement are 'disruptive technologies' that could have a profound effect on human life in the twenty-first century. A laissez-faire approach to these methods will leave us at the mercy of powerful market forces that are bound to be unleashed by the promise of increased productivity and competitive advantage. The concerns about safety, freedom and fairness, just reviewed, may well seem less important than the attractions of enhancement, for sellers and users alike.



The prescription drug Ritalin is illegally traded among students.

SPL

Motivated by some of the same considerations, Fukuyama[21] has proposed the formation of new laws and regulatory structures to protect against the harms of unrestrained biotechnological enhancement. In contrast, we suggest a policy that is neither laissez-faire nor primarily legislative. We propose to use a variety of scientific, professional, educational and social resources, in addition to legislation, to shape a rational, evidence-based policy informed by a wide array of relevant experts and stakeholders. Specifically, we propose four types of policy mechanism.

The first mechanism is an accelerated programme of research to build a knowledge base concerning the usage, benefits and associated risks of cognitive enhancements. Good policy is based on good information, and there is currently much we do not know about the short- and long-term benefits and risks of the cognitive-enhancement drugs currently being used, and about who is using them and why. For example, what are the patterns of use outside of the United States and outside of college communities? What are the risks of dependence when used for cognitive enhancement? What special risks arise with the enhancement of children's cognition? How big are the effects of currently available enhancers? Do they change 'cognitive style', as well as increasing how quickly and accurately we think? And given that most research so far has focused on simple laboratory tasks, how do they affect cognition in the real world? Do they increase the total knowledge and understanding that students take with them from a course? How do they affect various aspects of occupational performance?

We call for a programme of research into the use and impacts of cognitive-enhancing drugs by healthy individuals.

The second mechanism is the participation of relevant professional organizations in formulating guidelines for their members in relation to cognitive enhancement. Many different professions have a role in dispensing, using or working with people who use cognitive enhancers. By creating policy at the level of professional societies, it will be informed by the expertise of these professionals, and their commitment to the goals of their profession.

One group to which this recommendation applies is physicians, particularly in primary care, paediatrics and psychiatry, who are most likely to be asked for cognitive enhancers. These physicians are sometimes asked to prescribe for enhancement by patients who exaggerate or fabricate symptoms of ADHD, but they also receive frank requests, as when a patient says "I know I don't meet diagnostic criteria for ADHD, but I sometimes have trouble concentrating and staying organized, and it would help me to have some Ritalin on hand for days when I really need to be on top of things at work." Physicians who view medicine as devoted to healing will view such prescribing as inappropriate, whereas those who view medicine more broadly as helping patients live better or achieve their goals would be open to considering such a request[22]. There is certainly a precedent for this broader view in certain branches of medicine, including plastic surgery, dermatology, sports medicine and fertility medicine.

Because physicians are the gatekeepers to medications discussed here, society looks to them for guidance on the use of these medications and devices, and guidelines from other professional groups will need to take into account the gatekeepers' policies. For this reason, the responsibilities that physicians bear for the consequences of their decisions are particularly sensitive, being effectively decisions for all of us. It would therefore be helpful if physicians as a profession gave serious consideration to the ethics of appropriate prescribing of cognitive enhancers, and consulted widely as to how to strike the balance of limits for patient benefit and protection in a liberal democracy. Examples of such limits in other areas of enhancement medicine include the psychological screening of candidates for cosmetic surgery or tubal ligation, and upper bounds on maternal age or number of embryos transferred in fertility treatments. These examples of limits may not be specified by law, but rather by professional standards.

Other professional groups to which this recommendation applies include educators and human-resource professionals. In different ways, each of these professions has responsibility for fostering and evaluating cognitive performance and for advising individuals who are seeking to improve their performance, and some responsibility also for protecting the interests of those in their charge. In contrast to physicians, these professionals have direct conflicts of interest that must be addressed in whatever guidelines they recommend: liberal use of cognitive enhancers would be expected to encourage classroom order and raise standardized measures of student achievement, both of which are in the interests of schools; it would also be expected to promote workplace productivity, which is in the interests of employers.

Educators, academic admissions officers and credentials evaluators are normally responsible for ensuring the validity and integrity of their examinations, and should be tasked with formulating policies concerning enhancement by test-takers. Laws pertaining to testing accommodations for people with disabilities provide

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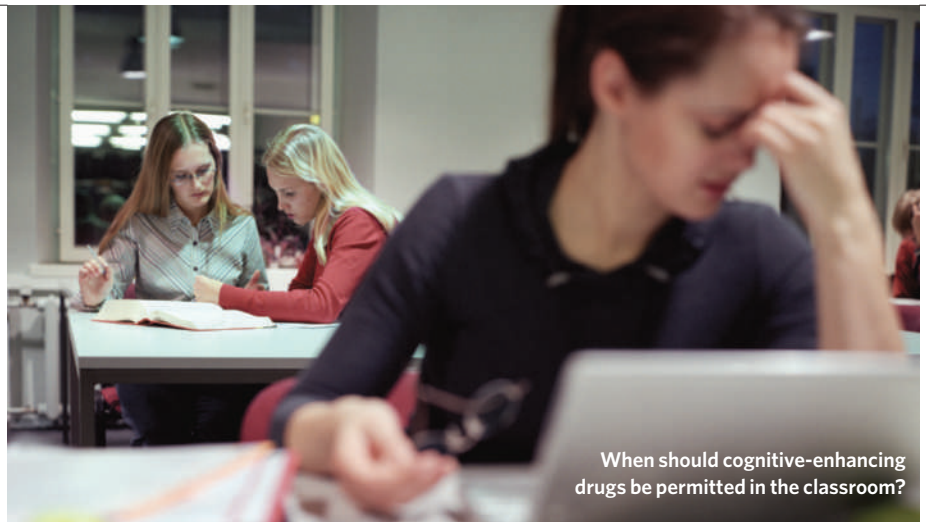

When should cognitive-enhancing drugs be permitted in the classroom?

a starting point for discussion of some of the key issues, such as how and when enhancements undermine the validity of a test result and the conditions under which enhancement should be disclosed by a test-taker.

The labour and professional organizations of individuals who are candidates for on-the-job cognitive enhancement make up our final category of organization that should formulate enhancement policy. From assembly line workers to surgeons, many different kinds of employee may benefit from enhancement and want access to it, yet they may also need protection from the pressure to enhance.

We call for physicians, educators, regulators and others to collaborate in developing policies that address the use of cognitive-enhancing drugs by healthy individuals.

The third mechanism is education to increase public understanding of cognitive enhancement. This would be provided by physicians, teachers, college health centres and employers, similar to the way that information about nutrition, recreational drugs and other public-health information is now disseminated. Ideally it would also involve discussions of different ways of enhancing cognition, including through adequate sleep, exercise and education, and an examination of the social values and pressures that make cognitive enhancement so attractive and even, seemingly, necessary.

We call for information to be broadly disseminated concerning the risks, benefits and alternatives to pharmaceutical cognitive enhancement.

The fourth mechanism is legislative. Fundamentally new laws or regulatory agencies are not needed. Instead, existing law should be brought into line with emerging social norms and information about safety. Drug law is one of the most controversial areas of law, and it would be naive to expect rapid or revolutionary change in the laws governing the use of controlled substances. Nevertheless, these laws should be adjusted to avoid making felons out of those who seek to use safe cognitive enhancements. And regulatory agencies should allow pharmaceutical companies to market cognitive-enhancing drugs to healthy adults provided they have supplied the necessary regulatory data for safety and efficacy.

We call for careful and limited legislative action to channel cognitive-enhancement technologies into useful paths.

Conclusion

Like all new technologies, cognitive enhancement can be used well or poorly. We should welcome new methods of improving our brain function. In a world in which human workspans and lifespans are increasing, cognitive enhancement tools — including the pharmacological — will be increasingly useful for improved quality of life and extended work productivity, as well as to stave off normal and pathological age-related cognitive declines[23]. Safe and effective cognitive enhancers will benefit both the individual and society.

"Many kinds of employee may benefit from enhancement."

But it would also be foolish to ignore problems that such use of drugs could create or exacerbate. With this, as with other technologies, we need to think and work hard to maximize its benefits and minimize its harms. ■

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improving a standardized technical core that already exists.

Scientific understanding related to a standardized core is much easier to apply than science aimed at elucidating the theoretical foundations, causes or dynamics of a problem. When knowledge is not largely embodied in an effective technology, but must instead be applied to practice through, say, training, institutional incentives, organizational structures or public policies, the difficulty of improving outcomes is greatly amplified. Now the task involves moulding, coordinating and governing the activities of practitioners, who themselves must acquire judgement and skill that may not be easily translatable from one context to another. Interpreting the results of management or policy innovations is difficult because of the many variables involved, few of which are directly related to the actual technology deployment. When the results of applying knowledge to practice are uncertain, the value of the new knowledge itself becomes subject to controversy.

The limits of technology

In the absence of an existing standardized core, therefore, R&D programmes aimed at solving particular social problems should neither be expected to succeed, nor be advertised as having much promise of succeeding, at least in the short and medium term. They should be understood and described as aiming at the creation of fundamental knowledge and the exploration of new approaches, with success possible only over the long term, and with a significant chance of failure.

We are not, of course, arguing against working hard to address social problems that are not amenable to technological fixes, but we are saying that R&D is unlikely to be the main source of short- or medium-term progress. So long as the teaching of reading, for example, cannot be condensed into an easily deployed technology or tightly specified routine, improvement will mostly come through context-dependent trial and error at the level of public policy and organizational management. This is more a process of effective politics than effective innovation, and typically progress will be slow, hard-fought and uneven. On the other hand, when a standardized technological core relevant to a particular problem is available, appropriate R&D investments have the potential to stimulate rapid progress.

How might these insights help guide innovation policies today? To illustrate the implications of our rules for decision-makers, we turn briefly to climate change.

The global energy system that lies at the heart of the climate-change problem is probably more complex and resistant to successful reform than the health-care and education systems discussed above. Despite enormous scientific, political and diplomatic efforts over the past two decades, no progress on reducing global greenhouse-gas emissions has been made[5,6]. In the absence of technological fixes, progress towards significant reductions of greenhouse-gas emissions will remain frustratingly slow, uneven and inconclusive.

What are the prospects for a technological fix? In principle, stabilizing atmospheric carbon dioxide concentrations at levels deemed acceptable by climate experts can be achieved through radically reduced emissions or through direct removal of CO_2 from the atmosphere. Most discussion and effort focuses on the former. The suite of promising possibilities for reducing emissions — from nuclear fission, to photovoltaics, to on-site carbon capture and storage — offers attractive targets for R&D investments[7] consistent with Rule III: existing technological capacities can leverage continued improvement. Nevertheless, successful transition to a low-emissions energy system requires effective management across all sectors of society and all uses of CO_2-emitting technologies. Within this system, no particular technology fully encompasses the go of the process — eliminating CO_2 in the atmosphere — just as no particular teaching technology encompasses the go of teaching children to read. Rule I is violated.

> "Technological fixes do not offer a path to moral absolution, but to technical resolution."

Moreover, because emissions-reducing technologies will compete with existing energy technologies supported by entrenched interests, and because there will be competition between the emerging technologies, we can expect ongoing technical and political debates about efficacy of specific technologies, as seen for biofuels today — a violation of Rule II. System-wide progress is therefore likely to be buffered by political processes similar to the ones that frustrate progress now.

In contrast, direct removal of CO_2 from the atmosphere — air capture[8] — satisfies the rules for technological fixes. Most importantly, air capture embodies the essential cause–effect relations — the basic go — of the climate-change problem, by acting directly to reduce CO_2 concentrations, independent of the complexities of the global energy system (Rule I). There is a criterion of effectiveness that can be directly and unambiguously assessed: the amount of CO_2 removed (Rule II). And although air-capture technologies have been remarkably neglected in both R&D and policy discussions, they nevertheless seem technically feasible (Rule III)[9–11].

Our rules do not allow us to predict if air-capture technologies will in fact help stabilize greenhouse-gas concentrations. Certainly these technologies face technical, political and economic obstacles. Our rules do, however, allow us to strongly predict that stabilization is unlikely to be achieved, except in the very long term, without something like air capture. Such technologies should therefore receive much greater attention in energy innovation portfolios.

The climate-change example illustrates an important final point: technological fixes do not offer a path to moral absolution, but to technical resolution. Indeed, one of the key elements of a successful technological fix is that it helps to solve the problem while allowing people to maintain the diversity of values and interests that impede other paths to effective action. Recognizing when such opportunities for rapid progress are available should be a central part of innovation policy, and should guide investment choices. ■

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Correction
The Commentary 'Towards responsible use of cognitive-enhancing drugs by the healthy' (*Nature* **456,** 702–705; 2008) described views derived from the report *Beyond Therapy* as solely those of Leon Kass. In fact, the work in question was by the President's Council on Bioethics, which at that time Kass chaired.

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