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Further discussion of the Commentary and these Correspondence contributions is welcome at Nature Network. Please cisit http://tinyurl.com/6nyu29.

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Correspondence: A Medical View of Potential Adverse Effects

Abstract
These letters respond to the Commentary 'Towards responsible use of cognitive-enhancing drugs by the health' by Henry Greely and colleagues. (*Nature* 456, 702-705; 2008)

Comments
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CORRESPONDENCE

These letters respond to the Commentary 'Towards responsible use of cognitive-enhancing drugs by the healthy' by Henry Greely and colleagues (*Nature* **456,** 702–705; 2008).

Risks and benefits may turn out to be finely balanced

SIR — This Commentary is the latest in a series of expert-led deliberations on the prospects and implications of cognitive-enhancing drugs (see, for example, refs 1–3). Much of the debate on enhancement, as illustrated by the Commentary, is highly speculative and rests on assumptions that are not well grounded in evidence or experience. There are three key problematic areas.

First, efficacy — the claimed and assumed benefits are often exaggerated. Careful analysis of trial data suggests that any cognitive-enhancing effects of these drugs in healthy humans are at best modest and mixed, and at worst little better than placebo.

Second, safety — very few drugs are completely without adverse effects, especially when used chronically. In the absence of data on the long-term safety implications of these drugs, it is premature to be helping society "accept the benefits of enhancement" when the balance between risk and benefit might be much narrower than assumed.

Third, demand — there is little empirical evidence that large numbers of people will use (or are interested in using) enhancers on a routine basis. There is partial or anecdotal evidence of use in specific situations (for example, examinations), but equally, other partial or anecdotal evidence suggests considerable resistance to chronic use among the general public.

If enough positive assumptions are made about these key issues, then almost any technology can look attractive or inevitable. The speculation offered in the Commentary may be of interest to academic debates in philosophy. But what is needed is realism, based on a more sober evidence-based assessment that does not create unrealistic expectations about either the potential benefits, or the threats, to individuals and society.

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1. Academy of Medical Sciences *Brain Science, Addiction and Drugs* (AMS, 2008).
2. British Medical Association *Boosting Your Brain Power: Ethical Aspects of Cognitive Enhancements* (BMA, 2007).
3. Foresight *Drugs Futures 2025?* (UK Department of Trade and Industry, 2005).

Much ado about cognitive enhancement

SIR — Henry Greely and colleagues call for answers to several controversial questions regarding the use of drugs by healthy people to boost cognitive performance. The most important scientific and ethical concern they raise is safety, not least because the pressure that leads people to enhance their performance might also be a crucial trigger to mental disorder. This is particularly likely when combined with sleep deprivation and anxiety caused by aggressive competition, as we have already learned from the indiscriminate use of amphetamines.

However, it would not be surprising if the repurposing of these drugs has less of an impact than expected by some and feared by others. Myriad personality traits are just as important as memory or 'intelligence' in the overall scheme of a successful life. Studies of gifted or 'savant' children show that self-confidence, discipline, focus, drive, resilience and social skills are highly complex personality traits, often found in successful people (see, for example, E. Winner *Gifted Children: Myths and Realities*; Basic Books, 1996).

Using medications to improve cognitive performance might be relevant in the short term. But a fully successful future will always depend on two very singular human features: eagerness to excel and setting a high standard of achievement.

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A medical view of potential adverse effects

SIR — Most seasoned physicians have had the sobering experience of prescribing medications that, despite good intentions, caused bad outcomes. They would call for louder notes of caution than those expressed in this Commentary when considering the safety of 'cognitive-enhancing' drugs such as Ritalin and Adderall.

The authors do not mention the US Food and Drug Administration warning on the packets of both of these drugs. Printed in capitals in a black box, it includes phrases such as: "amphetamines have a high potential for abuse. Administration of amphetamines for prolonged periods of time may lead to drug dependence ... Misuse of amphetamine may cause sudden death and serious cardiovascular adverse effects."

This warning does not cover other rare but serious side effects, such as Stevens–Johnson syndrome (a serious skin reaction) or toxic psychosis. Furthermore, the incidence of serious cardiac arrhythmias is likely to be higher in older people with incipient cardiovascular disease — likely consumers of 'healthy' enhancement.

Further reason for caution in advocating neuroenhancers is the disproportionate advantage the

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Early scientific visitors found mammalian fossils awaiting discovery in apothecary shops
Xu Xing on the discovery of the Peking Man fossils, page 538

drugs, if effective, would confer on the wealthy. The authors' acknowledgment of existing disturbing inequities does not mean that we should add more.

A responsible position would be to call for a moratorium on the use of enhancers until enforceable policies to minimize socioeconomic disparities are in place, research into the use and impact of these drugs is completed, information on risks and benefits is broadly disseminated — and physicians, educators and regulators have articulated professional normative positions.

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Recall of learned information may rely on taking drug again

SIR — Henry Greely and colleagues identify critical areas of public discussion about perceptions and use of drugs that are alleged or expected to improve cognition.

Stimulants and other drugs proposed as potential cognitive enhancers are known to create profound state dependence, a phenomenon in which information or associations learned while 'under the influence' of a drug will later be remembered or used only when the learner has again taken the drug. Thus, individuals who use amphetamines to improve their learning of new information may indeed learn slightly faster or with less effort than those who do not use such drugs. Later, however, they may not remember or use the learned information unless they take amphetamines or related drugs again.

How and when state dependence occurs has been studied extensively in humans and other animals, in well-controlled learning tasks in laboratory settings. State dependency of cognitive enhancers would dramatically influence drug use, the permanence of learning and the ability to use information in new conditions. Indeed, state dependence can complicate clinical use of pharmacotherapies for such disorders as anxiety and attention-deficit hyperactivity disorder.

Greely and colleagues note critical research and policy questions that societies must consider to shape expectations about putative cognitive enhancers. We urge that the discussion includes the known and profound state-dependent effects of these agents.

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Patterns of drug use have varied throughout history

SIR — Current issues are assessed by Henry Greely and colleagues, but their Commentary contains a bias consistent with current Western culture. The use of these drugs is probably older than recorded history. They have often been used regardless of social convention or rules — and have had impacts on societies.

In the 1960s, 'mind-altering drugs' had a different connotation from the present, exemplified by Timothy Leary's "Turn on, tune in and drop out" philosophy. Drugs such as marijuana and LSD were said to enhance individual thinking and creativity, but research both on the mental effects of these drugs and on their use has decreased. Since then, the use of mind-altering drugs has shifted towards enhancing performance, usually with amphetamine analogues. It seems that these are becoming acceptable when used for the goal of efficient production in standardized ways.

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The five preceding letters are a selection of many comments on this Commentary that were submitted to Correspondence. Many other reactions from readers have been posted in a long and lively online discussion forum at Nature Network, including the following anonymous contributions.

Careful use helps me do better research, and society benefits

SIR — I commend the authors of this Commentary on what I think is a fair and insightful piece. I suspect many of the negative commenters are guilty of default outrage without careful thought.

I find that my own occasional, metered use of these drugs can make astounding increases in my ability as a researcher — which results in tangible benefit to society. It's not a competition, I'm not taking an exam. I'm doing research; research that I hope may one day improve the lives of many. I exercise, sleep, eat well and I drink coffee. Yet sometimes that significant extra boost allows me to spend 12 hours successfully working through mathematics that for weeks I was previously unequal to solving. Why is this the act of a social criminal?

Current attitudes towards such drugs seem to be that they are good if you need them to become equal, but wrong if you want to become more than equal. Can we really be so quick to condemn a striving to better ourselves? Should we tell brighter students to hold back to the median? I think not. This issue is not black and white; it requires the careful grey-scale considerations the Commentary authors recommend.

It is true that many physicians and biomedical researchers have placed themselves in quite a tangled conflict-of-interest web, and that this compromise can be dangerous.

Some of the authors of this Commentary may have some conflict of interest, which thankfully *Nature* requires authors to disclose. However, that possible conflict of interest does not release you, the reader, from your obligation to rationally and carefully consider their argument. They are not wrong just because some of them consult for pharmaceutical companies.

Enhancement means a broader role for physicians

SIR — This Commentary raises a wider issue of perceived responsibility. The traditional role of physician as healer does not sit with the category of enhancement. Plastic surgery serves as a good analogy here, with views remaining varied on the ultimate responsibility. But with planned, novel, pharmacological intervention, physicians must surely be party to the cause, and thus a broadening of their role would be necessary.

Ultimately, the call for risk–benefit research and a fuller understanding of mechanisms is therefore welcome, but the real beneficiaries, at least in the short term, are likely to be dominated by the genuinely needy — neurological and psychiatric patients. These groups have had their needs for cognitive enhancement unmet for far too long.

Further discussion of the Commentary and these Correspondence contributions is welcome at Nature Network. Please visit http://tinyurl.com/6nyu29 to have your say.

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