

Cognitive Enhancement: Promises and Perils

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The potential use of drugs to enhance cognition, emotion, and executive function has engendered controversy despite the fact that few such agents exist today. Here, I provide a context for discussions based on medical, regulatory, and ethical concerns that have been raised by the possibility that enhancers will emerge from current efforts to discover drugs for neuropsychiatric disorders.

To prosper and flourish in a rapidly changing world, we must make the most of all our resources—both mental and material. Globalization and its associated demands for competitiveness are increasing the pressures in our working lives. Added to this are the demands from evolving family structures and increased care responsibilities, both for children and for older relatives. (Beddington et al., 2008)

What exactly is it about “man’s estate” that most calls for relief? Just sickness and suffering, or also such things as nastiness, folly, and despair? Must “improvement” be limited to eliminating these and other evils, or should it also encompass augmenting our share of positive goods—beauty, strength, memory, intelligence, longevity, or happiness itself? ...even assuming that we could agree on which aspects of the human condition call for improvement, we would still face difficulties deciding how to judge whether our attempts at improving them really made things better—both for the individuals and for the society. (President’s Council on Bioethics, 2003)

The controversy swirling around possible—and indeed current—uses of biotechnology (drugs, stem cells, brain-machine interfaces) to enhance human cognition, emotion, and executive function is illustrated by contrasting two government sponsored reports, one from the UK and one from the US. (Neither of the sponsoring administrations are still in office). Beddington et al. (2008), in

announcing the Foresight Mental Capital and Wellbeing Project (Government Science Office, 2008), call directly for efforts to boost what they call mental capital, i.e., cognitive abilities and emotional and behavioral regulation. The report does not make a direct recommendation for technological approaches to enhancement, focusing instead on prevention and early intervention in conditions that impair mental capital formation and well-being. A fair reading, however, could find the implication that enhancement strategies could play a role as part of an integrated strategy to improve productivity and well-being in an increasingly competitive and unforgiving world.

In contrast, the President’s Council on Bioethics (2003) chaired by Leon Kass worried that the very attractiveness of technologies to enhance performance and well-being in an increasingly competitive world, might lead individuals and societies to lose sight of the significant hidden costs of such interventions. In the Council’s view the potential costs are many, including acceptance of short-cuts (much like anabolic steroid use in sports) that undermine the intrinsic value of toil and self-improvement, and ultimately the instrumentalization of human beings as performance machines. It should be noted that performance enhancement in school or at work has significant differences, as well as similarities, to the situation in sports. In most organized sports, there are rules and sanctions grounded in the notion that sports fans pay to see the results of talent and training rather than the cleverness of one’s pharmacist. In most other areas of life, however, there are no such rules beyond the basic laws that require prescriptions for some drugs and rule others illegal.

In school and the workplace, performance enhancement can be quite seductive. Faced with limited places in prestigious schools or the high-stakes multitasking of modern work life, who would not consider a few extra cups of coffee during the day to enhance alertness and cognitive performance? As an ever-greater premium is placed on performance whether in school or in the workplace, prescription stimulants (albeit not always legally prescribed) such as modafinil, methylphenidate, and amphetamine derivatives are increasingly supplementing caffeine-containing beverages (Sahakian and Morein-Zamir, 2007). Militaries have long employed stimulants, including amphetamines, to increase alertness and performance in the face of fatigue (Caldwell and Caldwell, 2005; Moreno, 2006).

The Treatment-Enhancement Distinction

Extensive (and generally unenlightening) discussions have been dedicated to definitions and distinctions among prevention, treatment, and enhancement—unenlightening because, for the hard cases that policy makers may face when issuing practice guidelines or deciding what insurance should pay for, the distinctions often prove quite slippery. Given the brevity of this essay, I will therefore eschew definitions in favor of an example.

Based on studies of safety and efficacy, prescription of statin drugs (inhibitors of HMG-CoA reductase, the rate limiting enzyme in cholesterol biosynthesis) is no longer limited to individuals with the very highest levels of LDL cholesterol. Indeed prescription of these drugs has been broadly extended to healthy people whose cardiovascular risk would, not

long ago, have been considered acceptable. Statin drugs substantially improve blood lipid profiles in almost all people and decrease LDL cholesterol to levels that could not generally be achieved or realistically sustained by diet and exercise. Some grumpy public health figures may harbor grievances about the moral hazards of statins: for example, some slovenly individuals may feel entitled to an extra portion of dessert. Among most physicians and policy makers, however, there is appropriately very little hand wringing about statin use. Here is the definitional slipperiness: instead of saying that statins are used as enhancements that make people who have always been considered healthy “better than well” (extending longevity beyond what can be achieved without biotechnology), medicine altered the criteria for desirable LDL cholesterol levels so that statins can be used as bona fide treatments for a risk state (and thus, *inter alia*, their use can be covered by many insurance policies).

In the case of cognition, emotion, and behavior, the boundary is heavily contested between enhancement and disorders that warrant treatment. This contestation reflects, in part, the lack of scientifically convincing demarcations between illness and such conditions of life as “normal” reactions to disappointments, losses, stress, and the like or having been born with a currently disfavored temperament, such as significant shyness. The Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IVTR, [American Psychiatric Association, 2000](#)) defines illnesses categorically (i.e., as entities discontinuous from each other and from normalcy, like pancreatic cancer or tuberculoses), not quantitatively or dimensionally (like hypertension or type II diabetes mellitus). As such, it stipulates precise thresholds for illness; thus major depression is diagnosed when a person has at least 5 of 9 listed symptoms for at least 2 weeks. In fact, these thresholds do not withstand much scientific scrutiny. A large and growing literature finds that most common neuropsychiatric disorders, including depression, attention deficit hyperactivity disorder (ADHD), and autism are actually better understood dimensionally with no bright line (or “point of rarity”) between illness and health ([Hyman,](#)

[2010](#)). This is not surprising for common disorders in which risk is heavily influenced by a very large number of common genetic variants of small effect (although autism can also result from highly penetrant mutations or copy number variants). Disease definitions, most significantly definitions of dimensional disorders, are comprised of a scientific component that stipulates the characteristic pathology, disordered function, or risk state, and a policy component that sets thresholds for diagnosis and for intervention. As noted, treatment thresholds for LDL cholesterol level have been changed in recent years—as have thresholds for diagnosis and treatment of hypertension.

Having elaborated on some of the reasons for the fuzziness of the line separating enhancement from treatment, I would propose a thought experiment. ADHD is characterized by abnormal attention, impulsivity, and hyperactivity. Children with ADHD tend to underperform their potential in school, to be extruded from prosocial peer networks, to generally annoy adults, and, when untreated, have an elevated risk of substance-use disorders. Many clinical trials using DSM-III, and later DSM-IV, diagnostic criteria have found stimulant drugs to be safe and effective at reducing the symptoms of ADHD, with the caveat, based on naturalistic follow-up, that most children do not receive optimal dosing. In the “real world,” there are marked variations in recognition of ADHD and stimulant treatment by region and by country. Many children who are treated with stimulants and appear to benefit do not actually meet DSM-IV criteria ([Angold et al., 2000](#)). Now, if we were to take seriously the Foresight Mental Capital and Wellbeing Project ([Government Science Office, 2008](#)) and recognize that ADHD (pace DSM-IV) differs from health only quantitatively on dimensions that measure attention, impulse control, and motoric activity, should we not consider lowering the diagnostic thresholds so that more children could be treated? In contrast to altering standards for cholesterol and blood pressure, I would predict that such a suggestion would create an uproar, only a small fraction of which would be based on issues of safety, efficacy, and cost. At a minimum one could conclude that controversies over enhancement of neu-

ropsychological function, especially in children, are treated very differently from interventions that influence organs other than the brain.

Safety and Efficacy

While less philosophically engaging than other aspects of the enhancement controversy, I would argue that questions of safety deserve serious attention. Unless surprising changes occur in global regulatory frameworks, all new drugs will continue to be developed and marketed for specific disease indications rather than to make healthy people better than well. Some drugs, such as lithium or most antimicrobials, only have therapeutic effects in the presence of certain disease states. For a drug to act as an enhancer, it must have a mechanism that permits its beneficial actions to occur in the absence of illness. Drugs such as the already discussed statins and stimulants have mechanisms that fulfill this latter criterion. (There is some evidence, however, that stimulants exert the greatest benefit on executive function for individuals who are initially impaired). Given current rules governing approvals, drugs come to be used for enhancement only after they are approved to treat an illness. Subsequently they are obtained through physicians prescribing “off label” or by diversion from other patients. I have no doubt that once drugs are approved that can also act as enhancers, people will find inventive, and not always legal, ways to obtain them.

The effects of stimulants taken for enhancement do not differ markedly from their effects for approved indications (ADHD and disorders of excessive sleepiness): Stimulants increase arousal, improve attention, increase motivation, and improve aspects of learning and memory. Other drugs being sought for several other disease indications may eventually prove to have properties that would permit their use as enhancers. These include several different mechanisms being investigated for the symptomatic improvement of memory in Alzheimer’s disease as well as drugs (that might be similar or identical) to enhance extinction learning in anxiety disorders. The currently available antidepressants have only modest positive effects in healthy people, (and only moderate

efficacy in people who are depressed), but ultimately antidepressant drugs might be developed that safely elevate mood not only in depressed but also in distressed or pessimistic people who are healthy. Another interesting possibility might come from drugs to treat social deficits in autism spectrum disorders. Extrapolating from studies with the hormone oxytocin in healthy volunteers, it is imaginable that drugs targeted to social cognition could enhance trust or feelings of interpersonal closeness. Another, perhaps farther off, possibility includes drugs to disrupt memory reconsolidation. In combination with carefully selected stimuli to call up the memories to be targeted, such drugs would be used to wipe out traumatic memories in posttraumatic stress disorder or drug cues that propel relapses in addiction. (Extinction learning leaves such memories intact, but suppresses them, leaving a risk of relapse.) Drugs that disrupt memory reconsolidation would have significant safety hurdles to pass—there would be a significant risk of wiping out important adaptive memories—but if approved, one could imagine (and worry about) “off label” attempts to remove unpleasant memories that detracted from a person’s happiness or self-esteem. In a nightmare scenario, such drugs might be misused by criminal perpetrators to overwrite unwanted intrusions of misdeeds and thus, perhaps conscience—such a drug is what Shakespeare has Lady Macbeth asking for. In the context of such musings, it is important to recall just how difficult it has been to develop such drugs with the unimpeachable goal of treating serious illnesses, including treatment refractory depression, posttraumatic stress disorder, addiction, and dementias. If problems arise with respect to use of such agents for enhancement, it will mean that we finally possess much needed treatments for neuropsychiatric disorders, treatments that have long remained stubbornly out of reach.

Of course, all drugs and technologies have risks. For regulators and from a public health point of view, an acceptable ratio of risk to benefit is far different when people have a life-threatening illness as opposed to when they have milder symptoms or when they are well to begin with. For example, drugs with

the severe side effect profiles of cytotoxic cancer chemotherapies would not be approved for mild disorders like allergic rhinitis. Greely et al. (2008) have called for a program of research on cognitive enhancers in healthy individuals. To date, studies of stimulants in healthy people have been limited largely to single-dose laboratory experiments; longer-term clinical trials to investigate whether there is significant and lasting efficacy for cognitive enhancement have not been performed. The problem with conducting such trials is precisely the risk of producing any serious harm in people with no illness. Stimulant drugs have some cardiovascular risks, and the amphetamine derivatives, and possibly methylphenidate, pose real risks of addiction. The libertarian in me suggests that informed consent should remove a major obstacle to clinical trials. The realist in me wonders who might then accept the responsibility, if not the liability, for producing and marketing them. The public health-oriented physician in me sadly recognizes that clinical trials data often fail to inform practice and that in any case most psychotropic drugs performed are prescribed by generalist physicians with little training about their effects or side effects and little time to monitor for dosage escalation.

Fairness and Implicit Coercion

Health insurance is highly unlikely to pay for enhancements. Thus a concern often raised about making drugs available to enhance cognition, emotion, and executive function is the possibility of increasing the “opportunity gap” between the rich and educated (who are more likely to request antidepressants and stimulants as treatments) and the poor and less educated. It is possible that chemical “haves,” whose children already have the benefit of lessons and tutors, better health care, and better nutrition, will gain for their offspring an even greater educational advantage than the children of the chemical “have-nots.” The substantial, and by many indices growing, economic and educational gaps between rich and poor are not likely to be conducive to the long-term flourishing of our society. While the enhancement issue should not be glibly declared irrelevant, it is hard to imagine that the problem of disparities,

which already plague US health care and public education will be worsened materially based on the question of who will request and who can pay for enhancing drugs. A more fruitful first step for decreasing disparities in health care and education would be to improve the recognition and treatment of impairing mental illnesses among the disadvantaged.

Another concern about enhancement is that of implicit coercion and thus the risk of an arms race. I am no expert on the current state of performance enhancement in sports, but an arms race problem can be at least hypothetically illustrated by the predicament of a fictional interior lineman playing US football in a time or place with little effective antidoping enforcement. A player who did not want to take anabolic steroids or growth hormone when nearly everyone else, including his own teammates, was taking such drugs, would be at a significant disadvantage, “playing naked” as it has been said. If an athletic scholarship or a high salary were at stake, it might be very difficult to resist the unfortunate community norm. This scenario can be extended to performance enhancement with psychotropic drugs. Given that the rates of stimulant prescription tend to be highest in affluent schools (and in some documented cases well above the prevalence of DSM-IV ADHD), it is reasonable to surmise that some parents have already entered their progeny in a pharmacologic performance arms race. One wonders whether students will one day have to provide a urine sample before taking a high stakes exam if truly effective memory enhancing drugs are ever developed and marketed.

Further Considerations

In my view, a serious problem for science is the dearth of truly efficacious new drugs to treat neuropsychiatric disorders. It would be a terrible error to impede progress in drug discovery and development (as some critics of biotechnology have suggested) in order to avoid managing their possible use as enhancements (Fukuyama, 2002). Aside from concerns about safety, social justice, and implicit coercion, discussed above, other difficult, unresolved issues arise that justify fuller discussion than is possible here.

As noted by Greely et al. (2008), we really do not know how useful stimulants are in regular use for enhancement. Some worry that the prescription of these drugs to children ingrains in them malign lessons about taking short-cuts, elevating performance over other values, or believing that learning or self-control come from a pill bottle. The evidence for this dark view is lacking (Singh, 2008). The question is often raised about the possibility of terrible, still unknown, long-term side effects of stimulants—we do know about appetite suppression, growth delay, and insomnia. One should not be cavalier, but these drugs have been in use for decades, and long-term cohorts have been followed for a variety of reasons, making it unlikely that we are missing some truly awful long-term side effect. The lack of solid empirical knowledge on all these points opens the arena for noisy disagreements (Singh, 2008).

From a policy point of view, however, I do not think that societies have been really tested yet. The existing cognitive enhancers are simply not so potent as to tilt the scales of advantage overmuch. If truly safe and effective memory enhancement becomes possible, I believe that it will be incumbent on society to develop the right regulatory regime. It is difficult to predict whether that regime will be one of restriction, or, imagining years of experience that demonstrates the possibility of safe transient use in discrete settings (e.g., not when there is risk of injury or danger), a regime of wider distribution. Wide distribution of truly

effective cognitive enhancers will make our world different in unpredictable ways that are well worth discussing ahead of time.

Perhaps the most concerning drugs to me are those that alter what are called moral emotions such as trust. Drug for memory erasure fall into this category because they could be used to obliterate selected life lessons, including moral lessons, connected as they most often are to shame and guilt. Such drugs, if truly effective could lead to manipulation of others and highly problematic even dangerous individual behavior.

In a free society people, including the kinds of people who read this journal, have always found ways to experiment with drugs, legal or not, in order to banish pain, distress, fatigue, and a sense of limitation (Sahakian and Morein-Zamir, 2007). Arguments that people must passively accept their draw in the genetic-developmental lottery, if safe and effective enhancements are possible, can be seen as paternalistic if not cynical. People have always sought advantage for themselves and their family and friends, which is why our economic system (some large recent hiccups notwithstanding) has been so successful. In short, I believe that if drugs discovered and developed for medical purposes also increase self-mastery, provide a competitive edge, or increase happiness (or decrease unhappiness) in healthy people, they will find such uses. Despite the frustrating difficulty of developing new generations of drugs to treat neuropsychiatric disorders for which there is

a powerful medical need, it is not too early to begin to think about the kind of research, education, and enlightened regulation that we will need should such drugs turn out to function also as enhancers.

REFERENCES

- American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (Washington, DC: American Psychiatric Association).
- Angold, A., Erkanli, A., Egger, H.L., and Costello, E.J. (2000). *J. Am. Acad. Child Adolesc. Psychiatry* 39, 975–984, discussion 984–994.
- Beddington, J., Cooper, C.L., Field, J., Goswami, U., Huppert, F.A., Jenkins, R., Jones, H.S., Kirkwood, T.B., Sahakian, B.J., and Thomas, S.M. (2008). *Nature* 455, 1057–1060.
- Caldwell, J.A., and Caldwell, J.L. (2005). *Aviat. Space Environ. Med.* 76 (7, Suppl), C39–C51.
- Government Office for Science. (2008). *Foresight Mental Capital and Wellbeing Project* (London: The Government Office for Science).
- Fukuyama, F. (2002). *Our Posthuman Future* (New York: Farrar, Straus, and Giroux).
- Greely, H., Sahakian, B., Harris, J., Kessler, R.C., Gazzaniga, M., Campbell, P., and Farah, M.J. (2008). *Nature* 456, 702–705.
- Hyman, S.E. (2010). *Annu. Rev. Clin. Psychol.* 6, 155–179.
- Moreno, J.D. (2006). *Mind wars: Brain research and national defense* (New York, NY: Dana Press).
- President's Council on Bioethics. (2003). *Beyond Therapy. Biotechnology and the Pursuit of Happiness* (New York: Dana Press).
- Sahakian, B., and Morein-Zamir, S. (2007). *Nature* 450, 1157–1159.
- Singh, I. (2008). *Nat. Rev. Neurosci.* 9, 957–964.