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Academic doping or Viagra for the brain?

The history of recreational drug use and pharmacological enhancement can provide insight into these uses of neuropharmaceuticals

Jayne C. Lucke, Stephanie K. Bell, Bradley J. Partridge & Wayne D. Hall

Recent developments in neuroscience have raised the possibility that neuropharmaceuticals and other interventions could be used to enhance brain processes in 'normal' people who are not impaired by mental illness or disorder. The terms 'cognitive enhancement' and 'neuroenhancement' are often used interchangeably to describe this type of drug use—which is similar to doping in sports—that is not for treating impairments of clinical significance or for recreation.

Drug misuse studies have not, therefore, provided good evidence of widespread neuroenhancement

There is some evidence that drugs such as methylphenidate (Ritalin®) and modafinil (Provigil®) can enhance cognition to a small degree in people without cognitive deficits, but there are important caveats to this. Drugs that enhance one type of function might have a detrimental impact on another, or people who already function well might not experience any benefit, whereas those with less natural ability might experience only modest effects. Another important issue is whether statistically significant improvements in cognitive functioning can be translated into practical or clinically significant benefits in real-world contexts.

Notwithstanding these caveats, some proponents of neuroenhancement speculate that it will soon become normal practice (Greely *et al*, 2008). However, such speculation is supported by limited evidence of the prevalence of the use of neuroenhancers. For example, an informal poll of *Nature* readers (Maher, 2008) seems to support claims that neuroenhancement is quite common. One in five respondents stated that they had used drugs for non-medical reasons to stimulate their focus, concentration or memory: 62% had used methylphenidate, 44% had used modafinil and 15% had used beta-blockers such as propranolol. This was, however, an informal survey by *Nature*, not a scientific study, and its purpose was to stimulate debate, rather than to estimate the prevalence of neuroenhancement in the general population. Similarly, there is anecdotal evidence of the use of modafinil to treat the adverse effects of jet-lag among academics.

Empirical surveys about the misuse of prescription stimulants are often cited as evidence that neuroenhancement has become common (Wilens *et al*, 2008). However, these data probably overestimate the extent of neuroenhancement, as the use of a drug without a doctor's prescription might be not only for enhancement, but also for recreation, addiction and self-medication. Even if we assume that most stimulant misuse is for the purpose of neuroenhancement, there is no evidence from drug misuse studies that it is a widespread problem: recent and regular use of stimulants without a doctor's prescription is usually found to be low—for example, as few as 2% report using the drug in the past month (Teter *et al*, 2010). Drug misuse studies have not, therefore, provided good evidence of widespread neuroenhancement.

In fact, there is little empirical evidence for neuroenhancement (Lucke *et al*, 2010). A recent public engagement exercise in the UK concluded that the public's awareness of cognitive enhancers was extremely low, and that the idea of healthy people taking a drug to improve their cognitive capability was new to most participants (Academy of Medical Sciences, 2008). Despite the probably low prevalence of neuroenhancer use in the population, media coverage has nonetheless suggested that it is widespread, and that we will soon need a 'doping test' for university exams. Such coverage might unintentionally raise awareness of and increase interest in neuroenhancement among the general public. The popularity of 'lifestyle drugs'—particularly those aimed at delaying the effects of ageing—suggests that there might also be a potential market for neuroenhancers. There are many over-the-counter dietary supplements, and other substances such as ginkgo biloba, that are marketed as being able to improve cognitive function, despite there being no evidence for their efficacy. Moreover, research to develop treatments and preventative therapies for Alzheimer disease and other cognitive impairments might actually lead to the development of neuroenhancing drugs that people without cognitive impairment could use.

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Three questions are pertinent for the public debate about neuroenhancement. Should it be regarded as a form of cheating? Should it be regarded as a limited extension of medical treatment or as a legitimate lifestyle enhancement? What should we do

about it? In this article, we consider possible answers to these questions by comparing neuroenhancement with two other forms of enhancement: doping in sport and the enhancement of sexual performance using drugs that were developed to treat erectile dysfunction, such as sildenafil (Viagra®)—we will refer to these as 'Viagra' for simplicity. These comparisons might provide instructive examples of possible societal responses to neuroenhancement. Performance enhancement in sport is prohibited and there are well-established procedures for testing and enforcing compliance, whereas sexual enhancement using Viagra is regulated through the health-care system; drugs are available on prescription from a doctor or at pharmacies and they are publicly funded in some countries.

Doping in sport is defined as "the employment of prohibited means to enhance performance, with the intention to gain competitive advantage over the opponent" (Petroczi, 2007). The World Anti-Doping Agency, established in 1999, oversees the global governance of sports doping. There are lists of forbidden substances and drug tests are regularly performed to enforce the rules (Schermer, 2008).

A common concern about the use of drugs to improve physical or cognitive performance is that it gives an unfair advantage to those who take the drug over those who do not

Yet, the extent to which doping occurs in sport is difficult to estimate. Its prevalence probably depends on the type of sport, the success of drugs in enhancing performance, the age of the athlete, the level of competition and how professionalized is the sport, among other factors. The use of performance-enhancing drugs is not limited to elite athletes; it extends to amateur competitors including college students and school children. Specific sports such as weight-lifting have seen a high prevalence of drug use: the 1999 US Powerlifting Federations' National Championship found that 55% of competitors reported using steroids in the previous 12 months (Carpenter, 2007). In the UK it has been claimed that steroids are commonly offered to children and growth hormones have been tried by up to 5% of high-school children (Carpenter, 2007). At the elite sporting level, the US Office of National Drug Control Policy estimates that between 10 and 90% of all athletes use doping, depending on the sport. This wide range reflects the level of uncertainty about its prevalence (Holt *et al*, 2009).

Viagra is a selective inhibitor of phosphodiesterase type 5 (PDE5). It was developed by Pfizer and approved in 1998 for the treatment of erectile dysfunction, which is associated with ageing and other medical conditions, and which can have a profound impact on sexual relationships. One-half of all males over 40 years of age might experience erectile dysfunction at some time (Jackson *et al*, 2005). Viagra was considered a breakthrough in its treatment and efforts have been made to extend its use to female sexual dysfunction, premature ejaculation and cardiovascular dysfunctions (Jackson *et al*, 2005).

As with many new drugs, there was much optimism among the medical community and the general public, facilitated by extensive media attention, about the potential value of Viagra. By 2005, Viagra had proven to be safe and effective in treating erectile dysfunction that resulted from

many causes with a variety of co-morbid medical conditions. More than 700,000 doctors have prescribed Viagra and more than 23 million men are reported to have used it (Jackson *et al*, 2005). It has also been found to lead to a significant improvement in erectile function, self-esteem and sexual satisfaction in men without erectile dysfunction, and to enhance the sex lives of middle-aged men without erectile problems (Gruenwald *et al*, 2009).

Much debate in the bioethical literature is about whether neuroenhancement is a form of cheating. Cheating is the violation of an explicit rule—as in sports doping—or implicit rules, such as social norms or codes of conduct (Schermer, 2008). A common concern about the use of drugs to improve physical or cognitive performance is that it gives an unfair advantage to those who take the drug over those who do not. This concern might have less salience in cognitive enhancement than in sporting enhancement, because there is so far little evidence that drugs significantly enhance cognitive performance (Outram, 2010). Nonetheless, this perception of unfairness remains (Cakic, 2009).

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There is another perspective on this, namely that individuals using neuroenhancement are aiming to achieve something without effort—regardless of whether it involves competition—and that this therefore diminishes the value of their achievement. It is misleading to think that neuroenhancement might obviate the need for hard work or study; it is unlikely that drugs will produce a good exam mark if the subject has not studied. Instead, drugs might make the time spent studying more enjoyable or efficient, and these effects might be more marked in those of lower ability. If this was the case, those who are less disciplined or intelligent might gain an advantage from using drugs in conjunction with extra study.

Individuals who take cognitive-enhancing drugs would potentially have a competitive advantage, but this in itself assumes that they are in competition. College students who are

…young people might use cognitive enhancers or recreational drugs because they believe that others are doing so and that they must do so to remain competitive

measured against each other in examinations might be seen as being in competition, but it is not clear whether a medical resident who takes modafinil to increase alertness during a long shift is in competition with fellow residents. If the drug increases alertness, does this disadvantage non-enhanced residents? Even without competition, the perception that others are using cognitive-enhancing drugs might lead to cognitive enhancement becoming a requirement for the job.

Athletes who believe that most of their competitors are doping might think that they can only win with the assistance of performance enhancers. This could create indirect pressure to use drugs, regardless of personal concerns about their use. Similarly, young people might use cognitive enhancers or recreational drugs because they believe that others are doing so and that they must do so to remain competitive (Cakic, 2009). These processes illustrate a common theme in explanations of why athletes engage in sports doping: subjective norms (Petroczi, 2007). People's beliefs about the drug use of their peers have a large impact on their own willingness to use those drugs. This makes it important not to exaggerate the prevalence of a harmful behaviour.

Although performance enhancement in sport is widely condemned by the media, sporting officials and government bodies, factors such as prize money, sponsorship, widespread coverage of sporting events and a desire to win encourage doping at all levels of competition (Holt *et al*, 2009). Athletes still engage in doping and there is evidence that at least some members of the general public are not concerned by the practice. Recent studies suggest that young people do not hold extremely negative views of doping, unlike sporting bodies and governments. In one study, more than 50% of 18–34-year-old sporting fans had 'little or no objection' to doping and 19% were in favour of legalizing it under medical supervision (Morgan, 2009). Other evidence suggests that students who take stimulants regard cognitive enhancement as acceptable (DeSantis & Hane, 2010).

A study in the 1990s that asked athletes about their willingness to use performance-enhancing drugs found a pervasive 'win at all costs mentality' (Ehrnborg & Rosen, 2009). Of the athletes, 98% said that they would take a performance enhancer if they would not be caught. One-half said that they would use a performance enhancer if they would win every competition for the next five years, even if they could die from the side effects (Ehrnborg & Rosen, 2009).

Public attitudes toward the use of neuroenhancing drugs are less clear. There is some evidence suggesting that although healthcare providers and parents are reluctant to condone the practice, students are less concerned about long-term health effects (DeSantis & Hane, 2010). For example, students using illegal stimulants justified their use as a way of achieving good marks; they either believed that moderate use would not harm them, that they were self-medicating for undiagnosed symptoms, or they equated stimulant use with drinking coffee (DeSantis & Hane, 2010).

Many regard taking drugs for neuroenhancement as a lifestyle choice, similar to the non-medical use of Viagra, which is considered one of the first lifestyle drugs

Schermer (2008) suggests that neuroenhancement is different from sports doping because there are no explicit rules that prohibit it in examinations. However, many people have a moral intuition that there is something wrong with it, which would require a ban on such drug use (Sabini & Monterosso, 2005). One option would be to allow everyone access to enhancers to minimize cheating. If the process of education is about gaining cognitive skills that can be used in the workplace rather than to perform in exams (Schermer, 2008), we need to consider the social consequences of neuroenhancement in a broader context, beyond its impact on a particular examination.

Many regard taking drugs for neuroenhancement as a lifestyle choice, similar to the non-medical use of Viagra, which is considered one of the first lifestyle drugs. The effects, predictably, include higher levels of sexual satisfaction as well as improvements in

emotional well-being and mental health (Salonia *et al*, 2003).

There were initial concerns there would be excessive demand for Viagra for both therapeutic and 'lifestyle' uses, that doctors would be inundated with requests, and that the cost of the drug would strain health budgets (Ashworth *et al*, 2002). However, this did not occur. Ashworth and colleagues (2002) conducted an observational study the year after Viagra was introduced in the UK and found that it was discussed in only 0.5% of consultations. A prescription was given in 43% of these consultations and doctors generally followed the prescribing guidelines. Doctors did not feel under pressure to prescribe it, and they generally felt it was justifiable to prescribe a lifestyle drug through the UK National Health Service. However, one-quarter of British doctors believed that there were no circumstances in which such a prescription was justified.

Different substances might need different types of regulation, as might different uses of the same substances

An obvious difference between sports doping and Viagra use is that Viagra was developed as a treatment for a distressing condition: erectile dysfunction. The framing of Viagra as a medical treatment allowed it to be regulated as a pharmaceutical product within the medical system. However, there are many types of erectile function and it might be difficult to decide whether a patient has a medical disorder or is within the normal range. Men who expect to achieve an erection several times a day and those who expect to achieve one once a week obviously have different expectations about normal functioning. Santtila and colleagues (2007) found that recreational users of Viagra had lower confidence in their ability to achieve an erection than non-users, even though they had significantly better erectile function. There was an indication that regular Viagra users became psychologically dependent on it and were less confident about their ability to function without it.

The role of expectations is probably important for neuroenhancement too; a student who expects to be top of the class will have different expectations about acceptable cognitive performance than a student who is satisfied with passing the course. Similar concerns could also arise among regular users of neuroenhancing drugs; they might lose confidence in their ability to do well without medication.

Some have argued that there is no clear line between treatment and enhancement in relation to psychological and neurological disorders (Outram, 2010). For both Viagra and neuroenhancement, there is no relevant life-threatening medical condition; these drugs are taken to enhance lifestyle. Furthermore, a prescription could be obtained for lifestyle use of these drugs by exaggerating or feigning symptoms of erectile dysfunction for Viagra, or attention deficit hyperactivity disorder (ADHD) for neuroenhancing drugs.

Media discussions of policy responses to enhancement often contrast two extreme positions: either we should prohibit enhancements or we should make them freely available. Advocates of the latter argue that bans on use will not stop the development of enhancers or the misuse of existing drugs, and will only make it more difficult to regulate their safety and efficacy. Concurrent with this, Greely and colleagues have recently suggested that the current regulation of psychoactive prescription drugs should be relaxed (Greely *et al*, 2008).

However, neither strategy is likely to be fully effective. The regulation of addictive drugs shows that prohibition can decrease their misuse, but rarely completely prevents it. Demand for the drug can create a black market, thereby amplifying the problems caused by illicit use and resulting in an increased cost to society from enforcing the law. The usual regulatory response to recreational drugs is precautionary: to prohibit their use to prevent potentially harmful consequences, which are often initially unknown. Substances that are eventually considered to be less harmful have generally been controlled through the regulatory processes for pharmaceutical products, or by restricting access, as for nicotine and alcohol. Such regulation can limit consumption and the number of potential users. For pharmaceuticals, regulation also aims to ensure that safety and efficacy claims are justified.

The way in which drugs are regulated depends on their specific characteristics. It is therefore not helpful to discuss neuroenhancing drugs as a homogeneous category. Different substances might need different types of regulation, as might different uses of the same substances. Larriviere *et al* (2009) have recently provided guidance for neurologists on how to respond to requests for neuroenhancers, assuming that neurologists will encounter patients without a diagnosed illness who request medication to improve their memory, cognitive focus or attention span. This approach is in line with arguments that neuroenhancing drugs could be regulated through prescriptions and used under the supervision of health-care professionals (Greely *et al*, 2008).

An examination of the way in which Viagra has been managed and regulated illustrates some of the potential issues in regulating neuroenhancers through the pharmaceutical regulatory system. Sildenafil was first approved by the US Food and Drug Administration and equivalent organizations in most other nations as a prescription-only medication. It is now available in the UK as a pharmacy medication that can be obtained over the counter under the supervision of a trained pharmacist. This change was mostly made in response to concerns about users who could suffer adverse cardiovascular effects after purchasing the drug over the internet without a prescription and without medical supervision (Aronson, 2009). Indeed, the recreational use of Viagra has been eased by access to it on the internet (Smith & Romanelli, 2005; Fox & Ward, 2008). This makes it difficult to monitor non-prescribed or off-label use, particularly if drugs are registered for the treatment of medical conditions (Schermer *et al*, 2009).

The absurdity of students and academics submitting urine samples is often cited as the logical conclusion of any suggestion that neuroenhancement should be regulated

The use of performance-enhancing substances in sport is prohibited, and the regulation of banned substances is vigorously enforced. The initial reason for banning performance enhancers in sport was concern for the health and well-being of athletes (Petroczi, 2007), which is the same as the rationale for banning illicit recreational drugs. There is a similar debate about the safety of drugs for cognitive enhancement—particularly in the long term—which provides support for the argument that their use should not be allowed.

It has been argued that anti-doping measures to keep performance-enhancing drugs out of sport have not achieved their goals because there is still widespread abuse of these drugs (Cakic, 2009). Interestingly, this argument is often invoked against any attempt to regulate the use of cognitive-enhancing drugs. The absurdity of students and academics submitting urine samples is often cited as the logical conclusion of any suggestion that neuroenhancement should be regulated. This perpetuates a false policy choice between prohibition and drug testing, or adopting a *laissez-faire* attitude. Neither position is helpful: neuroenhancing drugs should be assessed on their merits, and regulated according to the risks that they pose and the feasibility of regulating or restricting their use.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

Academy of Medical Sciences (2008) *Brain Science, Addiction and Drugs*. UK: Academy of Medical Sciences

Aronson JK (2009) From prescription-only to over-the-counter medicines ('PoM to P'): time for an intermediate category. *Br Med Bull* **90:** 63–69

Ashworth M, Clement S, Wright M (2002) Demand, appropriateness and prescribing of 'lifestyle drugs': a consultation survey in general practice. *Fam Pract* **19:** 236–241

Cakic V (2009) Smart drugs for cognitive enhancement: ethical and pragmatic considerations in the era of cosmetic neurology. *J Med Ethics* **35:** 611–615

Carpenter PC (2007) Performance-enhancing drugs in sport. *Endocrinol Metab Clin North Am* **36:** 481–495

DeSantis AD, Hane AC (2010) "Adderall is definitely not a drug": justifications for the illegal use of ADHD stimulants. *Subst Use Misuse* **45:** 31–46

Ehrnborg C, Rosen T (2009) The psychology behind doping in sport. *Growth Horm IGF Res* **19:** 285–287

Fox NJ, Ward KJ (2008) Pharma in the bedroom... and the kitchen... the pharmaceuticalisation of daily life. *Sociol Health Illn* **30:** 856–868

Greely H, Sahakian B, Harris J, Kessler RC, Gazzaniga M, Campbell P, Farah MJ (2008) Towards responsible use of cognitive-enhancing drugs by the healthy. *Nature* **456:** 702–705

Gruenwald I, Leiba R, Vardi Y (2009) Effect of sildenafil on middle-aged sexually active males with no erectile complaints: a randomized placebo-controlled double-blind study. *Eur Urol* **55:** 969–978

Holt RIG, Erotokritou-Mulligan I, Sonksen PH (2009) The history of doping and growth hormone abuse in sport. *Growth Horm IGF Res* **19:** 320–326

Jackson G, Gillies H, Osterloh I (2005) Past, present, and future: a 7-year update of Viagra (sildenafil citrate). *Int J Clin Pract* **59:** 680–691

Larriviere D, Williams MA, Rizzo M, Bonnie RJ (2009) Responding to requests from adult patients for neuroenhancements: guidance of the Ethics, Law and Humanities Committee. *Neurology* **73:** 1406–1412

Lucke J, Bell S, Partridge B, Hall W (2010) Weak evidence for large claims contribute to the phantom debate. *Biosocieties* **5:** 482–483

Maher B (2008) Poll results: look who's doping. *Nature* **452:** 674–675

Morgan WJ (2009) Athletic perfection, performance-enhancing drugs, and the treatment-enhancement distinction. *J Philos Sport* **36:** 162–181

Outram SM (2010) The use of methylphenidate among students: the future of enhancement? *J Med Ethics* **36:** 198–202

Petroczi A (2007) Attitudes and doping: a structural equation analysis of the relationship between athletes' attitudes, sport orientation and doping behaviour. *Subst Abuse Treat Prev Policy* **2:** 34

Sabini J, Monterosso J (2005) Judgments of the fairness of using performance enhancing drugs. *Ethics Behav* **15:** 81–94

Salonia A, Rigatti P, Montorsi F (2003) Sildenafil in erectile dysfunction: a critical review. *Curr Med Res Opin* **19:** 241–262

Santtila P, Sandnabba NK, Jern P, Varjonen M, Witting K, von der Pahlen B (2007) Recreational use of erectile dysfunction medication may decrease confidence in ability to gain and hold erections in young males. *Int J Impot Res* **19:** 591–596

Schermer M (2008) On the argument that enhancement is "cheating". *J Med Ethics* **34:** 85–88

Schermer M, Bolt I, de Jongh R, Olivier B (2009) The future of psychopharmacological enhancements: Expectations and policies. *Neuroethics* **2:** 75–87

Smith KM, Romanelli F (2005) Recreational use and misuse of phosphodiesterase 5 inhibitors. *J Am Pharm Assoc* **45:** 63–72

Teter CJ, Falone AE, Cranford JA, Boyd CJ, McCabe SE (2010) Nonmedical use of prescription stimulants and depressed mood among college students: frequency and routes of administration. *J Subst Abuse Treat* **38:** 292–298

Wilens TE, Adler LA, Adams J, Sgambati S, Rotrosen J, Sawtelle R, Utzinger L, Fusillo S (2008) Misuse and diversion of stimulants prescribed for ADHD: a systematic review of the literature. *J Am Acad Child Adolesc Psychiatry* **47:** 21–31




Jayne C. Lucke [top left], Stephanie K. Bell, Bradley J. Partridge [bottom left] and Wayne D. Hall are at the University of Queensland, Centre for Clinical Research in Brisbane, Australia.
E-mail: j.lucke@uq.edu.au

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