Deflating the Neuroenhancement Bubble

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This article questions the evidence base for some commonly accepted assumptions among bioethicists about the prevalence of neuroenhancement among college students and the degree to which putative neuroenhancers in fact enhance cognitive functioning. We argue that the evidence on the prevalence of stimulant drug use does not support bioethicists' claims that neuroenhancement use of these drugs is widespread; that the evidence that putatively enhancing pharmaceuticals are truly neuroenhancing is much weaker than often supposed; that bioethicists have underestimated the challenges in assessing the safety and efficacy of putative neuroenhancers; and that the assumption that neuroenhancement is a novel development has deflected attention from historical experiences with other putatively enhancing pharmaceutical drugs such as cocaine and the amphetamines.

**KEYWORDS:** Cognitive enhancement, drug use, evidence, neuroenhancement, neuropharmaceuticals, smart drugs

There has been recent widespread interest among bioethicists, and in some high-profile cases, support for healthy individuals using pharmaceutical drugs for "cognitive enhancement" or "neuroenhancement." Some bioethicists have claimed that psychostimulant drugs such as modafinil (Provigil), methylphenidate (Ritalin), and dextroamphetamine/amphetamine (Adderall) are already being widely used for this purpose and suggested that such use is likely to become more common in the near future (Greely et al. 2008). Some commentators who have argued that allowing adults to use pharmaceuticals for cognitive enhancement would be consistent with respect for individual autonomy (Greely et al. 2008) have accordingly proposed policy responses that would arguably facilitate such use. These have included advising prescribers on how to respond to requests from healthy adults for prescriptions of drugs to be used for enhancement (Larriviere et al. 2009); suggesting ways of managing the enhancement use of psychotropic drugs by young people (Singh and Kelleher 2010); and proposing that the drug regulatory system allow pharmaceutical companies to develop and market prescription drugs for cognitive enhancement use (Greely et al. 2008). This article critically examines some key assumptions made in advancing these proposals. In doing so we support and extend the work of other critics (e.g., Outram 2010; Racine and Forlini 2009) who have also drawn attention to the poor quality of the empirical evidence used to support the neuroenhancement use of pharmaceuticals.

**WHAT IS NEUROENHANCEMENT?**

There is considerable diversity in the way that the terms “cognitive enhancement” and “neuroenhancement” are used in bioethics and medicine. “Cognitive enhancement” was originally used to describe the use of drugs to treat cognitive impairment in persons with dementia and later expanded to include their use to ameliorate mild cognitive impairment in persons with dementia and later expanded to include their use to ameliorate mild cognitive impairment. It now includes the use of psychoactive substances by healthy people (Jones, Morris, and Nutt 2007) for a variety of reasons: to improve cognitive performance when sleep-deprived or suffering from jetlag; to ameliorate the effects of declining memory capacity in aging or mild cognitive impairments in older adults that do not necessarily affect everyday functioning (Jones, Morris, and Nutt 2007); and to improve cognitive performance in people who are already functioning at their optimal level and want to perform even better (British Medical Association 2007).

In this article we use the terms “cognitive enhancement” and “neuroenhancement” interchangeably to cover any use of stimulant drugs in healthy adults that is clearly not intended to treat clinical impairment (such as attention deficit hyperactivity disorder [ADHD]) and not used for the purpose of experiencing a “high.” While we recognize that there is no bright, clear line between treatment and enhancement use in treating or preventing psychological and neurological disorders (Outram 2010), we think that this use of “neuroenhancement” covers the phenomenon most often discussed by bioethicists.

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HOW WIDESPREAD IS NEUROENHANCEMENT?

The claim that the neuroenhancement use of stimulant drugs is widespread and increasing is often made in bioethical discussions of neuroenhancement. We focus on the validity of this claim for the enhancement use of stimulant drugs that are used to treat ADHD (e.g., Ritalin and Adderall) and narcolepsy (e.g., Provigil) by college students as a “study aid.” These are the drugs that are routinely discussed in the literature, and empirical evidence on their use by U.S. college students is often cited in support of these claims (e.g., Farah et al. 2004; Greely et al. 2008; Singh and Kelleher 2010). Evidence for the enhancement use of stimulant drugs by academics who use modafinil to cope with the pressures of work and recover from jet lag is based on anecdotal reports of use by colleagues (Sahakian and Morein-Zamir 2007).

The first major weakness of the evidence on the putative enhancement use of ADHD medications by college students is that the surveys cited rarely ask students about their enhancement use of these drugs. Instead, they ask about the use of a stimulant “without a prescription of the individual’s own or simply for the experience or feeling the drugs caused” (Substance Abuse and Mental Health Services Administration 2010, 14). Such “nonprescription use” can include recreational use (e.g., to get high) or use to stay awake at night at dance or other parties. There is also some evidence that some nonmedical use of stimulants may be a form of self-treatment of symptoms in adults with ADHD (Peterkin et al. 2010; Upadhyaya et al. 2010). These uses are not the same as using a drug for the specific purpose of enhancing brain function in the context of study.

Second, the studies often cited do not support the claims made about widespread use. For example, Larrieviere and colleagues (2009) cite five articles to support their claim that people without a diagnosed disorder are “increasingly seeking and utilizing” prescription drugs such as those intended to treat ADHD to enhance memory or executive function. Two are commentaries on the ethics of neuroenhancement (Farah 2005; Farah et al. 2004), one is an online survey of enhancement use by readers of Nature (Maher 2008), and one is a survey of the nonmedical use of prescription opioids by college students (McCabe et al. 2005b). Only one of the studies cited estimated the prevalence of illicit Ritalin use but this was in high school students and no data were provided on the reasons given for such use (McCabe et al. 2004).

Third, the results of surveys of stimulant use among college students are not always accurately reported. For example, a survey by Babcock and Byrne (2000) has been cited in a number of prominent bioethical articles (e.g., Bush 2006; Farah et al. 2004; Koelch, Schnoor and Fegert 2008; MehLMAN 2004; Warren et al. 2009) as evidence that the enhancement use of stimulants is widespread in U.S. colleges. Babcock and Byrne (2000) asked 283 students at one U.S. college (MCLA), “Have you ever taken Ritalin for fun (non-medical purposes)?” (our emphasis), to which 16.6% of the sample answered “yes.” It was clear from the question asked and discussion in the paper that the authors were primarily concerned with the recreational use of Ritalin by college students. The only mention of neuroenhancement was one sentence in the discussion: “Personal communications with students at MCLA suggest that methylphenidate is sometimes used as a study aid for ‘pulling all-nighters’” (Babcock and Byrne 2000, 145).

Better assessments of prevalence are provided by surveys of larger, more representative samples of U.S. college students who were asked about nonmedical stimulant use in the past year rather than lifetime. These studies find much lower estimates of prevalence than the lifetime rate reported by Babcock and Byrne (2000). For example, McCabe and colleagues’ (2005a) survey of stimulant use among students in 119 U.S. colleges provides a median estimate of only 3% with a range between 0 and 25%. Only 3 colleges reported rates over 15%, but it was the 25% reported in one college that was cited to support the claim that neuroenhancement use of stimulants was widespread among college students (Greely et al. 2008).

We need better information on students’ motives for stimulant use before we conclude that most nonmedical stimulant use is for neuroenhancement purposes. Some surveys have asked students why they used drugs without doctor’s orders and many respondents have reported doing so to help with study, increase alertness, stay awake, or assist with concentration (Arria et al. 2008; DeSantis, Noar and Webb 2009; Novak et al. 2007; Teter et al. 2006; Upadhyaya et al. 2010). Even if we accept that these responses constitute enhancement use, overall rates of use among U.S. college students are much lower than is often implicitly assumed. A recent review of illicit methylphenidate (Ritalin) use reported that the most nationally representative U.S. survey showed only 4% of students had used these drugs in the past year without a prescription. Most reported that the primary reason for use was to improve academic performance but recreational use was also included (Bogle and Smith 2009). Much of this use was sporadic and infrequent. For example, in a recent survey of 3,639 U.S. undergraduates at one large U.S. university, 6% reported nonmedical use of prescription stimulants in the last year. However, only 1% had done so on 10 or more occasions in that year and only 76 individuals (around 2% of the whole sample) had done so in the last month (Teter et al. 2010).

These prevalence estimates suggest that somewhere in the range of 3–6% of the U.S. college population have used pharmaceutical stimulants probably for neuroenhancement purposes in the past year. Most of this use has been infrequent. The minority who regularly use these drugs are more likely to use other illicit drugs, to live in fraternities/sororities, and have lower grade point averages (McCabe 2008b; McCabe et al. 2005a).

Bioethicists are not the only ones who have overestimated the prevalence of stimulant drug use by U.S. college students. The same is true of college students themselves. For example, participants in McCabe’s (2008a) survey estimated that 20% of their peers engaged in nonmedical
stimulant use, when the self-reported rate in the same survey was only 6%.

**HOW ENHANCING ARE “NEUROENHANCERS”?**

Recent scientific reviews have highlighted how limited the evidence is that putative neuroenhancers do enhance cognitive performance in healthy people (de Jongh et al. 2008; Kumar 2008; Outram 2010). For example, the review by the British Academy of Medical Sciences identified 27 agents that may offer benefit to healthy individuals (British Medical Association 2007). Ten were dietary supplements, but most of the rest were pharmaceutical drugs that work by affecting neurotransmission. The report concluded that while some drugs may have produced some cognitive enhancement in impaired individuals (for example, those with Alzheimer’s disease), the evidence that they enhanced cognitive performance in healthy individuals was very limited. Effects on vigilance, verbal learning, and long-term memory were often small and observed in laboratory conditions rather than everyday life (Academy of Medical Sciences 2008).

The likely enhancement potential of these drugs has probably been overestimated in several ways. First, it has been assumed that drugs that improve cognitive performance in impaired individuals (e.g., those with Alzheimer’s disease) will do the same in healthy individuals. This is uncertain. There are even doubts that stimulant drugs improve cognitive functioning in people with intellectual and neurological disorders (Advokat 2009; Quednow 2010). A recent review of the effects of modafinil concluded that it improved working and episodic memory and other processes dependent on prefrontal cortex and cognitive control in rodents, healthy adults, and patients with several psychiatric disorders (Minzenberg and Carter 2008). However, it is important to be clear that this review only advocated the use of modafinil as a treatment for cognitive dysfunction.

A recent study of methylphenidate in healthy young men (Tomasi et al. 2010) found that while functional magnetic resonance imaging suggested it increased activation in the dorsal attention network, these patterns of activation were not associated with improved accuracy in working memory or visual attention tasks.

Second, evidence for the neuroenhancing effect of drugs shares a weakness with assessments of the effectiveness of therapeutic drugs—it is based on trials of short-term use. The fact that these drugs have positive effects in healthy adults in short-term laboratory tests is an uncertain indication of their likely benefits in everyday life when used regularly over extended periods. Differences in study outcomes and limited studies in healthy individuals make it difficult to assess the efficacy of methylphenidate in real-world situations (Outram 2010). It is also uncertain whether the small statistically significant improvements in cognitive functioning reported in laboratory studies (Turner et al. 2003) translate into improvements of practical significance in everyday situations (Academy of Medical Sciences 2008).

**THE REGULATORY CHALLENGES IN ASSESSING PUTATIVE NEUROENHANCERS**

Greeley and colleagues (2008) proposed that the current regulation of psychoactive prescription drugs should be relaxed in order to make it easier to use pharmaceuticals for enhancement purposes and to avoid treating those who do so as criminals (Greeley et al. 2008). This, they argue, would bring drug regulatory systems into line with emerging social norms. It was also proposed that pharmaceutical companies should be allowed to develop and market cognitive enhancing drugs to healthy adults if they are able to provide the necessary data to satisfy regulatory requirements for safety and efficacy (Greeley et al. 2008).

The trust shown in the existing regulatory systems by those who welcome pharmaceutical neuroenhancement is at odds with bioethical critiques of the performance of regulation of therapeutic pharmaceuticals (Elliott 2004; Healy 2006). Big pharmaceutical companies have been especially criticized for unethical conduct and dubious marketing strategies such as ghostwriting scientific articles, suppressing negative or inconclusive findings, and engaging medical professionals involved in regulatory processes as consultants, thus producing less than objective regulatory decisions (Elliott 2004; Healy 2006). Why should pharmaceutical companies behave differently if the drugs are to be marketed for enhancement rather than therapeutic purposes?

**Assessing Safety**

There has been a conspicuous lack of attention in bioethical discussions to the safety of using psychotropic drugs for neuroenhancing purposes. If there are many people using psychotropic substances off-label, or without medical supervision (and in combination with other licit and illicit substances, as has been noted), the potential for negative short- and long-term side effects increases. It is also likely that some people will use the drugs more frequently than may be advisable, or in larger than recommended doses, especially if tolerance develops with regular use, as it often does with stimulant drugs. We cannot assume that the harm/benefit ratio observed in using lower doses of these drugs therapeutically will apply to their enhancement use by healthy adults. As Schermer and colleagues explain:

> When drugs that have been tested and admitted for serious diseases and complaints, come to be used more and more by those who are less seriously afflicted, the risks-benefit ratio that used to be acceptable in the serious cases, may shift to unacceptable. (Schermer et al. 2009, 81)

The addictive potential of neuroenhancing drugs with stimulant effects is an underappreciated concern. There is little evidence of addiction to methylphenidate when it is used appropriately for ADHD (Diller 1996), but it is a dependence-producing drug when used in larger doses for its euphoric effects (Keane 2008). Indeed, its manufacture, distribution, and prescription were legally controlled (Svetlov, Kobeissy and Gold 2007) after widespread recreational
use and abuse of methylphenidate in Sweden in the 1960s (Diller 1996).

HOW NEW IS NEUROENHANCEMENT?

The creation of a new term “neuroenhancement” inadvertently suggests that the enhancement use of pharmaceuticals is a novel phenomenon. The rise and fall of psychoactive stimulant pharmaceuticals in the late 19th and 20th centuries shows that the term may be new but the use of pharmaceuticals for enhancement is not. It is surprising that the bioethical debate about neuroenhancement has not referenced historical examples of stimulant pharmaceuticals used for enhancement purposes. Nor does it recognize that many stimulant drugs that are now illicit street drugs were initially introduced as therapeutics and later came to be used by healthy people for their enhancing effects (Rasmussen 2008). The history of patterns of drugs like cocaine and the amphetamines demonstrates that therapeutic drug use, misuse, and enhancement use are often tightly interwoven.

Rasmussen suggests that cocaine was the first antidepressant because it was the first specific medicine for mood disorders (Rasmussen 2008). During the early 1900s cocaine was seen as a miracle medical breakthrough alongside insulin and penicillin. Amphetamines were viewed in much the same way from the 1930s and used for enhancement purposes in much the same way that it is claimed that stimulants are used today. For example, university students used Benzedrine, an early amphetamine, to “aid the time-honoured practice of last minute ‘cramming’ for exams” (Rasmussen 2008, 30). Pharmaceutical companies promoted this use by claiming that amphetamines produced “mental performance enhancement” and increased intelligence test scores, as reported in The Lancet in 1936 (Sargent and Blackburn 1936). Later studies showed they improved efficiency in simple mental tasks and psychomotor problem solving, but this was related to increased confidence and optimism, initiative, and aggression, rather than enhancement of cognitive ability (Rasmussen 2008).

By the end of 1938 student misuse and worries about addiction blocked the marketing of amphetamine for mental enhancement. Benzedrine sulphate was approved in 1937 for treatment of narcolepsy and Parkinson’s disease and for mood elevation in depression and other psychiatric conditions. Its use by healthy people was explicitly excluded because of media stories of Benzedrine as “brain fuel” and the reported death of a student during an examination after allegedly using Benzedrine “brain tablets” (Smith 1939). Despite concerns about their addictive risk, amphetamines were widely used for depression in the 1950s, and healthy people were still able to use them off-label for neuroenhancement purposes. By the late 1960s, one in 20 U.S. adults used amphetamines by prescription and at least half as many were doing so without a prescription. Amphetamines were used on university campuses during the 1960s as a study aid and a party drug in much the same way that it is claimed students currently use Ritalin (Svetlov, Kobeissy, and Gold 2007). Thus, the contemporary use of stimulants by students fits into an historical pattern of enthusiasm for using stimulant drugs as study aids. These experiences over the last century highlight the need for more caution when looking benignly upon the contemporary use of prescription stimulants for neuroenhancing purposes.

SOME CONCLUSIONS

The use of stimulant drugs to enhance human functioning is not a new phenomenon but arguably a recent manifestation of a common cycle of enthusiasm and disillusionment with the enhancement use of drugs with stimulant effects. The support for the current phenomenon is based on an overestimation of the extent of stimulant use by college students and the efficacy of these drugs in enhancing cognitive performance in healthy adults. The media repetition of claims about stimulant use has amplified the perceived extent of their use beyond that which is indicated by closer examination of the survey evidence. There are few studies assessing the safety or efficacy of the enhancement use of these drugs, so individuals who use them do so at their own risk. The guidelines advising doctors on how to respond to requests for enhancement prescriptions are premature. Well-conducted empirical research on the prevalence and reasons for the nonmedical use of stimulant drugs by young adults is essential to inform public debate about policy responses to the neuroenhancement use of stimulant and other pharmaceutical drugs.

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