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Invited review

What should we do about student use of cognitive enhancers? An analysis of current evidence

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ABSTRACT

This article reviews current data on the use of cognition enhancers as study aids in the student population. It identifies gaps and uncertainties in the knowledge required to make a balanced assessment of the need for some form of regulation. The review highlights the weak evidence on the prevalence of use of such drugs, especially outside the US, and the ambiguous evidence for their efficacy in a healthy population. Risks are well documented for the commonly used drugs, but poorly appreciated by users. These include not only the side-effects of the drugs themselves, but risks associated with on-line purchase, which offers no guarantees of authenticity and which for some drugs is illegal. The case for urgent action to regulate use is often linked to the belief that new and more effective drugs are likely to appear in the near future. The evidence for this is weak. However, drugs are not the only possible route to neuroenhancement and action is needed to collect more data on the impact of existing drugs, as well as new technologies, in order to guide society in making a proportionate response to the issue.

This article is part of a Special Issue entitled 'Cognitive Enhancers'.

1. Introduction

The ISCD (Independent Scientific Committee on Drugs: www.drugscience.co.uk) is a UK organisation founded to investigate and review the scientific evidence relating to drugs, free from political concerns. Over the past year, it has been considering the issue of cognition enhancers (CEs) as a result of the extensive public and media interest in the field. It has established a working party to look at the current evidence of use of drugs as CEs among university students, as this has been the most widely publicised and debated, and encompasses an interesting mix of neuropharmacology, ethics and law.

The CE working party projects build on an earlier analysis conducted by the ISCD of harms caused by misuse of drugs in the UK (Nutt et al., 2010). This analysis was based on multicriteria decision analysis (MCA), an instrument that has been used to support decision making in complex issues characterised by conflicting objectives and influences (Dodgson et al., 2000). The analysis considered a number of harm criteria broadly divided into "harms to users" and "harms to others" and these two categories were further divided into physical, psychological and social harms. The overall harm of a particular drug relative to others was based on a weighted summation of the relative scores in each of the 16 categories of identified harm. The analysis ranked drugs in a way that is as objective as possible, although the concept of applying objectivity to drug user experience has been questioned (Rolles and Measham, 2011).

In principle, the method is also applicable to benefits, an aspect highly relevant to CEs. However, before a substantive analysis of CEs' harms and benefits can proceed using a tool like MCA, it is necessary to be clearer about the efficacy, safety and prevalence of CEs, as well as, more broadly, the landscape of their use in the United Kingdom. Specifically, the descriptions of benefits and harms need defining in the same way that the 16 categories of harm were identified for drugs of abuse. We maintain that while there are some data on efficacy and safety of CEs in the scientific literature, there is little understanding of CE prevalence in the UK, or indeed in the rest of Europe. Most estimates of CE prevalence are derived from US data. This means that the UK is far behind other countries in developing adequate measures to estimate prevalence of CE use in the population, and we have almost no understanding of other important factors, such as motivations for use and access to drugs.

Abbreviations: ISCD, Independent Scientific Committee on Drugs; CE, cognition enhancer or cognition enhancement; MCA, multi-criteria decision analysis; ADHD, attention deficit hyperactivity disorder; GABA, γ-aminobutyric acid; BCI, brain–computer interface; STOA, Science and Technology Options Assessment.

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While prevalence is a major consideration in estimating benefits and harms to others (e.g. family and society), measuring benefits and harms to users requires an understanding of the effects of different CEs on the individual. However, the debate on CEs conducted at the ethical level (e.g. British Medical Association, 2007; Bostrom and Sandberg, 2009) more often than not treats CEs as a single class of efficacious and safe drugs. This idealisation of CEs does not correspond at all to reality; it is the equivalent of considering all drugs of abuse as equal in their ability to cause harms. The relative effectiveness of the common CEs (methylphenidate, modafinil, caffeine and amphetamine, see below) in real world environments such as the student population is still largely anecdotal, but these drugs are pharmacologically quite distinct and it seems inherently unlikely that they would all have the same effects on cognition. In addition they differ in their side effect profiles and their legal status, all of which contribute to benefits and harms.

In this article, we outline the gaps in our knowledge of CEs, both in the specific context of the UK, and in the broader Euro-American context. We review the evidence in three areas critical to the debate on CEs among the student population: the prevalence of their use; their effectiveness (and risks) in enhancing cognition in domains relevant to student performance, and the need to "future-proof" society for new CEs expected in the years ahead.

2. Which are the common CEs?

Recent reviews have attempted to provide a comprehensive list of current and future CEs (Nutt et al., 2007; Academy of Medical Sciences, 2008), but attempts at a rational classification are hindered by the sheer diversity of claimed CEs and for many of these, the lack of real evidence for their efficacy. Most current interest focuses on those that have or have had medical use, meaning that their effects on cognitive functions are not in dispute and have been studied extensively in single- or double-blind randomized placebo controlled clinical trials (Arnold, 2000; Faraone et al., 2002, 2004; Greenhill et al., 2006; Turner et al., 2004; Minzenberg et al., 2008). They are: caffeine, amphetamine, methylphenidate and modafinil. These substances form an interestingly diverse group not only pharmacologically but also legally. Caffeine does not quite fit the medical use definition but qualifies by virtue of its significant recreational use, and a pharmacology as detailed as that of any medicinal drug (Huang et al., 2005; Ribeiro and Sebastião, 2010). It is also not a controlled or prescription substance in contrast to the others on the list and can be bought and sold legally without any restriction. Amphetamine (dexamphetamine, dexedrine) and chemically-related substances have a long history of both medical and non-medical use and abuse (Iversen, 2008). Amphetamine use is widespread in the US but less so in Europe (http://www.unodc.org/documents/data-and-analysis/WDR2011/World_Drug_Report_2011_ebook.pdf), despite the fact that most countries have signed up to the United Nations 1971 Convention of Psychotropic Substances that specifies amphetamine as a schedule II controlled substance (http://www.emcdda.europa.eu/publications/drug-profiles/amphetamine#control). The difference in use of amphetamine as a CE may be explained in part by the diversion of amphetamine formulations commonly prescribed for ADHD (Adderall and Vyvanse), which are available in the US but not in Europe. Methylphenidate, most commonly known as Ritalin, is prescribed in the US and in Europe for ADHD, and it shares some structural and mechanistic similarities with amphetamine itself (Iversen, 2008; Heal et al., 2009). Its legal status is the same as that of Adderall, but in normal clinical use, neither drug has high risk of dependence because the drugs are taken orally (Iversen, 2008). However, both drugs have both rapid and slow release formulations, which are thought to have different abuse liabilities (Arria et al., 2008). In addition, both drugs can be ingested nasally or injected, which significantly enhances the associated risks (Teter et al., 2006). As scheduled substances, Adderall and Ritalin are only available legally on prescription, and buying or selling of these drugs from on-line pharmacies is illegal. The last CE, one which has received much media attention, is modafinil (Provigil). Modafinil's mechanism of action remains somewhat obscure (Zolkowska et al., 2009; Seeman et al., 2009) and its pharmacological similarity to the other common CEs is unclear. Modafinil is a prescription-only drug, a schedule IV controlled substance in the US, but not in the UK, and on-line purchase is legal, although its sale is not.

The common CEs encompass at least three distinct pharmacological mechanisms with widely differing potential for effects on cognition, and mechanism and non mechanism-based side effects (including abuse and dependence liability).

In addition, they differ widely in their potential for involving users and distributors in breaking the law. The different means of access to these drugs, given their differing legal status, confer a range of risks to the user other than those associated with the drug itself.

3. Prevalence

Good empirical data about the prevalence of CE practices is crucial to making informed decisions about regulatory measures and to obtaining a balanced view of the risks and benefits of CEs to the individual and to society. This section will briefly discuss US studies, where most of the available findings originate, but will focus on data from outside the US, because these have not been reviewed anywhere previously.

While media reports sometimes describe the use of CEs by students in the US as an extensive phenomenon that has essentially become "the norm" (CBS, 2010), survey numbers indicate that use is more likely to be in the range of 5–15% (Smith and Farah, 2011). These figures suggest that use of CEs is occurring, but it is far from being a general practice amongst university students. Most US studies have looked at the phenomenon of CE in the context of the non-medical use of prescription stimulants such as methylphenidate and amphetamines, and some have included modafinil as well. Prevalence estimates vary greatly among different surveys and range from 5% to 35%. This raises questions about the representativeness of the samples used (Smith and Farah, 2011), and also about the comparability of different survey methods. Furthermore, as Schleim (2010) has pointed out, a number of studies have conflated psychostimulant use for recreational reasons and psychostimulant use for CE reasons. One example is the study conducted by Babcock and Byrne (2000), which included the question "Have you ever taken Ritalin for fun (non-medical purposes)?" to which 16.6% of respondents said "yes". While the question does not address CE use at all, in some highly prominent discussions (e.g. Farah et al., 2004) this figure is quoted as representing the proportion of students who use prescription stimulants without a medical indication to increase study performance.

A further methodological problem with US surveys is the definition of non-medical use. In some studies non-medical use includes use with a prescription, while in others it does not. As Arria et al. (2008) highlighted, for the sake of comparability it seems necessary to arrive at a consensus on terminology. The issue of gauging prevalence accurately is further confused because those with a prescription are known to share their medication with others (Rainer et al., 2009), and because some students fake symptoms in order to get a prescription (Outram, 2010) while others may obtain these drugs from on-line pharmacies.

There are few empirical studies on CE prevalence outside the US. Table 1 provides an overview of findings from five European countries and Iran. The analysis of these findings is complicated by the fact that studies come from a variety of sources, which include an annual health insurance report about employees (DAK, 2009), academic journal articles (Franke et al., 2010; Habibzadeh et al., 2011; Holloway and Bennett, 2012), a Cambridge student newspaper survey (Lennard, 2009), an on-line newspaper survey (Humle and Friislund, 2010) and a report from a major initiative to inform drug prevention activities at university level. Different studies have used varying definitions of the type of non-medical use they investigated and while some defined clearly the exact substances they considered (Franke et al., 2010; Humle and Friislund, 2010; Habibzadeh et al., 2011), other studies used less precise definitions, such as "ADHD medications" (DAK, 2009; Rosiers et al., 2010), "stimulants" (Holloway and Bennett, 2012), or "drugs without prescription" (Lennard, 2009).

Drug use motivations were also differently specified across studies. Franke et al. (2010) asked about cognitive enhancement explicitly, the Cambridge survey inquired about drug use "to help work" (Lennard, 2009), and a survey of Welsh university students and staff by Holloway and Bennett (2012) listed several possible purposes, including pleasure, weight loss, and studying. Humle and Friislund (2010) also asked about drug use in connection with studies. Rosiers et al. (2010) investigated the changing pattern of stimulant use throughout the academic year without defining drug use purposes and the DAK study did not clearly distinguish cognitive and mood enhancement. Habibzadeh et al. (2011) gauged knowledge about methylphenidate among medical students, finding low levels of knowledge and that most respondents believed the drug was used to improve concentration, but users in particular were not queried about their own motivations for use.

None of the seven studies inquired about perceived effects and efficacy. While Holloway and Bennett (2012), Franke et al. (2010), Habibzadeh et al. (2011) and the Cambridge survey (Lennard, 2009) have clearly distinguished prescription and non-prescription users, the other studies have not. The source of the drugs was investigated in three projects (Franke et al., 2010; Holloway and Bennett, 2012; Lennard, 2009). In these studies, friends and peers were found to be the primary source, but Lennard (2009) points out that some students may buy larger quantities of drugs on-line and sell them to peers. In general, these surveys have not looked for correlations between CE and other factors, such as polydrug use or ADHD symptoms.

Given the methodological diversity as well as the different purposes for these surveys, the results are difficult to compare, both across this set of studies and with the US data. Overall, however, CE prevalence appears to be lower outside the US.

4. Effects

Beyond prevalence, the actual and perceived effects of CEs need careful evaluation. We can categorize the literature on these effects into three groups. The first group comprises articles assessing the effects and efficacy of CEs in trials conducted in non-clinical populations. The second consists of studies looking at the perceived effects of the drug, while the third stems mainly from personal experiences found in journalistic descriptions and on-line forums.

4.1. Trials in healthy populations

The cognition enhancing effects of methylphenidate, amphetamine and modafinil in healthy volunteers have been assessed in a number of single- or double-blind randomised controlled clinical trials, which have been reviewed extensively by Repantis et al. (2010) and Smith and Farah (2011). These reviews indicate that across trials, the tests used to evaluate effects vary considerably and frequently yield conflicting results in terms of performance enhancement. Some studies find positive effects for cognitive enhancement, others show no benefits and still others show decreased performance. Based on a meta-analysis of 19 randomised controlled trials using single drug administration in the majority of cases, Repantis et al. (2010) found that methylphenidate has a large, distinguishable positive effect on long-term memory consolidation, especially when longer periods elapse between the actual learning and its recall. No significant effects on attention, mood or executive functions were found. Methylphenidate and amphetamine seem to increase cognitive control in individuals whose performance on placebo was lowest, or who reported more impulsiveness in everyday life (Smith and Farah, 2011).

In a randomised double-blind, between-subjects study involving 60 healthy, young adult male volunteers modafinil produced significant CE effects on neuropsychological trials of memory (digit span, visual pattern recognition), spatial planning

Table 1
Prevalence of CE use.

Reference	Country	Population	CEs studied	Prevalence found	Comment
DAK, 2009	Germany	Representative sample, 3000 employees aged 20–50	Methylphenidate and modafinil	Lifetime prevalence: 0.5% for men; 0.19% for women	
Franke et al., 2010	Germany	1035 pupils; 512 students	Methylphenidate, modafinil, amphetamines	Lifetime prevalence: 1.55% pupils; 0.78% students	Excluded respondents with ADHD
Lennard, 2009	UK	1000 students at Cambridge University assessed by student newspaper Varsity	"Medication without prescription to help work"	10%	Prevalence and other details not disclosed
Holloway and Bennett, 2012	UK	1614 students and 489 staff members at a university in Wales	Unspecified prescription stimulants	33% had used some prescription drug without a prescription, of which 0.5% used stimulants "to study"	
Humle and Friislund, 2010	Denmark	1898 students	Methylphenidate, amphetamines, modafinil, caffeine, anxiety reducing medications "in connection with studies"	1.8% have taken prescription drugs, 6% have used prescription drugs or caffeine pills, 7% have used beta-blockers	Prevalence and prescribed/non-prescribed use not recorded
Rosiers et al., 2010	Belgium	3539 students from Ghent and Antwerp	Unspecified ADHD stimulant medications	4% took stimulants during exam period. Rates were considerably lower for other periods.	Study did not distinguish students with and without a prescription
Habibzadeh et al., 2011	Iran	310 medical students	Methylphenidate	7.7% used methylphenidate without a prescription	Most common motive for methylphenidate use was to increase concentration (41.7% of users)

and also improved the inhibition of pre-potent responses (Turner et al., 2002). Similarly, a single dose, double-blind, randomised and balanced crossover study with 16 participants found that modafinil greatly reduced error rates on maintenance and manipulation processes in trials of working memory (Müller et al., 2004). Wakefulness and working memory-enhancing properties have also been found in sleep-deprived individuals without any effects on attention, mood or motivation (Repantis et al., 2010). In a double-blind, randomized clinical trial of 37 sleep-deprived healthy, male doctors, modafinil was shown to be effective in improving working memory, and respondents made less impulsive decisions and could more flexibly redirect their attention. However no improvement was seen in basic motor tasks on a virtual reality surgical motor skills task (Sugden et al., 2012).

A counterbalanced, placebo controlled, double-blind crossover study with 18 healthy volunteers investigated the CE effects of modafinil and methylphenidate on visual attention capacity. The study found that both drugs improved processing speed in low-performing individuals. Based on blood plasma analysis, the authors suggest that higher doses of methylphenidate may be more effective in low-performing individuals, while those with higher baseline scores might benefit from lower doses (Finke et al., 2010).

Based on extensive reviews of the literature in healthy populations, both Smith and Farah (2011) and Repantis et al. (2010) conclude that to date, evidence for the efficacy of CEs is somewhat inconclusive and ambiguous. Individual baseline characteristics seem to make a considerable difference to outcomes, and enhancement in some individuals might be negated by no effects on other trial participants, therefore much more detailed analyses of individual effects seem indicated. The identification of CE effects would need to be based on optimization in terms of dose, individual genetic and personality characteristics, ability levels and the nature of the specific task and would also need to investigate the effects of CEs on motivation, in addition to cognitive effects. Furthermore, there is little evidence for CEs from placebo-controlled studies in real life scenarios (Smith and Farah, 2011).

4.2. Studies on perceived effects

Very few data exist about students' perceived effects of CEs on their cognitive and academic performance. A study by Hall et al. (2005) found that while the most prevalent reason for taking prescription stimulants was for study purposes, there were no reported long-term academic benefits from their use, and the most commonly reported effect was short-term improved alertness and energy levels. This last effect is unsurprising, considering that the drugs in question are potent stimulants. Rainer et al. (2009) have found that the most common motivations of non-medical use were to concentrate better while studying, to study longer and to feel less tired, and students perceived the drugs to be very effective in facilitating these effects. In-depth interviews with university students have shown that most users consider psychostimulants as relatively harmless and safe substances (DeSantis and Hane, 2010), while being rather ill-informed about actual health risks associated with these drugs, and the legal ramifications of using or supplying them without a prescription (DeSantis et al., 2010).

4.3. Personal accounts

The question remains to be answered whether and how the results of trials in non-clinical populations can be translated to real world settings, such as the academic environment. This question is all the more interesting when we consider that experience accounts are somewhat incongruent with scientific findings, in that perceived effects of CEs are greater than the effects shown in research studies. This could be due to a number of factors, including placebo effects, or that experimental conditions are inadequately modelling real-life practices. Placebo effects could be driven up by increasingly widespread attention to CEs as an effective means of boosting cognitive performance. Media accounts (CBS, 2010; Nixey, 2010; Talbot, 2009) have highlighted CEs' effects on wakefulness, attention and concentration, as opposed to improving learning and memory, and have described modafinil in particular as a wakefulness-promoting agent that positively affects motivation for studying (Nixey, 2010).

Another source of personal accounts of CE effectiveness is on-line information. While on-line accounts of drug user experiences represent a biased sample, the internet provides ample first-person descriptions of drug effects. Though CE accounts have not been analyzed systematically, scholars have begun to study on-line drug forums as a source of information (Wax, 2002). Research funded by the National Institute on Drug Abuse has very favourably reviewed the websites of the Erowid Centre (Murguia et al., 2007), a non-profit educational organization (www.erowid.org), which has contributed to scientific publications (Baggott et al., 2004) and hosts drug-related information and the most comprehensive list of user-generated experience accounts. These accounts include information about drug combinations, doses, routes of administration and the person's body weight. Erowid's websites feature 214 reports of caffeine, 126 accounts of methylphenidate, and 107 accounts for modafinil. On-line accounts also mention modafinil analogues such as adrafinil and the R-enantiomer, armodafinil (Nuvigil), whose legal status is the same as modafinil itself. For amphetamines there are a total of 387 reports, 54 of which describe experiences with Adderall. While not all of these accounts describe use aimed at CE, a significant proportion of them do. The websites represent a self-selected sample of a small group of individuals, but analysis of these data would still be highly useful given that such on-line forums are among the primary sources of information for students and young people.

5. The urgency of a societal response to CEs

This issue certainly polarises commentators on CEs, who range from those who believe the potential impact on the individual and society is already great enough to require a response in the form of some kind of regulation (Academy of Medical Sciences, 2008), to those who claim that it is all a "phantom debate" hyped by the media and over-enthusiastic scientists (Quednow, 2010). In between there are those who admit that the current crop of CEs may not set the world alight but that we need to be prepared for the arrival of a new generation of more powerful CEs (Jones et al., 2007; Nadler and Reiner, 2010; Robbins, 2011). The urgency to take action therefore depends on an understanding of three factors: the current benefits and harms to individuals, the current benefits and harms to society and future opportunities or threats.

We have already considered the evidence for the efficacy of CEs, and while it is clear that these drugs do have effects on cognition, the impact in real world settings is still ambiguous. The evidence for harms to the individual is more obvious but less frequently taken into consideration. All these drugs have extensive toxicological histories, and their side effects may not always be psychiatric and linked to the mechanism of the cognitive effects. To give one example, modafinil was recently reviewed by the European Medicines Agency, who concluded that its benefit/risk profile was not adequate for conditions other than narcolepsy, a potentially life-threatening condition (European Medicines Agency, 2010). They advised that the drug should not be prescribed for obstructive sleep apnoea, shift-work sleep disorder and idiopathic hypersomnia because the risks of serious skin reaction, suicidality,

depression, psychosis and adverse cardiovascular events outweighed the benefits for these less severe conditions. Presumably the European Medicines Agency would not have approved the drug for cognitive enhancement of healthy individuals. However, it is unfair to single out modafinil. Caffeine poisoning causes vomiting and other gastric disturbance as well as neurological effects such as anxiety, tremor and hallucinations. The identification of caffeine as the main constituent of some legal highs bought on-line makes this risk more than just theoretical (Davies et al., 2011). Finally, the ISCD ranked amphetamine only just below tobacco in its ranking of harms (Nutt et al., 2010). Some have argued that mentally competent adults should be free to use CEs assuming the development of safe drugs and appropriate regulation (Greely et al., 2008). While this seems a justifiable proposition, the history of the development of medicines tells us that there is no such thing as a safe drug, only a drug whose benefits outweigh its drawbacks. When the benefits are non-medical this becomes a very difficult task and logically the benefit/risk balance for all the CEs should be much lower. It is doubtful that users adequately assess the risk/benefit ratio for CEs (DeSantis and Hane, 2010; DeSantis et al., 2010).

The second category of risk to the individual is linked to how CEs are sourced. The waters are muddied by off-label prescribing, which is legal, and faking symptoms in order to get a prescription (Outram, 2010), which is not. But buying methylphenidate and amphetamine without a prescription is most certainly not legal and penalties for possession vary from a fine to imprisonment, depending on the country. Possession with intent to supply is taken very seriously however and in the UK can lead to up to 14 years imprisonment (www.homeoffice.gov.uk/drugs/drug-law/). Nevertheless it only takes seconds to find on-line pharmacies willing to supply these drugs and their websites offer a reassuring but entirely spurious air of medical respectability and professionalism. The extent of on-line sales and whether the legal status of the drugs is a factor in such sales is unclear. There is a real risk that what is bought is something else entirely. It might be an unknown legal high, it might be caffeine, it might be entirely innocuous, but the risk to the purchaser is currently unknown as there are few data on the prevalence of counterfeiting of these drugs simply because it is illegal to buy them for testing. Furthermore, although most offences pertaining to drugs require proof that the substance in question is what it purports to be, there can be circumstances where a person commits an offence even if the substance turns out to be innocuous. This may apply whether the person is buying or selling the drug.

There is also evidence of on-line legal highs used as CEs. Ethylphenidate, an analogue of methylphenidate, is a controlled substance in the US, but not in the UK, and on-line experiences refer to its use as a study aid (www.erowid.org/experiences/exp.php?ID=95093). This is another risk of on-line purchase; access to analogues not covered by generic legislation, but whose pharmacology and side-effects are much less well understood than the parent drug. Chemists ingenuity is boundless but these analogues, by their very nature, are unlikely to stray too far from their pharmacological roots into entirely new mechanisms of action. For true innovation in the development of new CEs one would look to the pharmaceutical industry, whose perspective and activity is considered below.

The benefits and harms to society have been extensively reviewed in discussions of the ethics of CE use. The perceived or potential benefits to society depend very much on the prevalence: while the prevalence is still low, the benefit, such as it is, rests with the individual. However, that is not true of the harms, and there has been much consideration of concerns about fairness and peer pressure (Scheske and Schnall, in press). Interestingly, the ethical debate is largely divorced from considerations of individual benefits and harms because it treats all CEs alike. We have the impression that the numerators and denominators in the benefit/risk equation, whether for the individual or for society, have been treated as separate entities. What society should do, if anything, about CEs requires consideration of all factors and for that, we need more data.

The urgency of a societal response depends also on a third factor: the evidence that in the near future, CEs with novel mechanisms, greater efficacy and improved safety are going to become available. A survey of pharmaceutical industry views on CEs concluded that new drugs affecting attention, memory, executive function and other aspects of cognition might become available in the next 10 years, but only as the result of work on defined and recognised medical conditions (Ragan, 2007). The hurdles to developing and testing drugs specifically for non-medical use are considerable, perhaps insuperable, unless society develops totally different attitudes to benefit/risk, and to the ethical issues around medicalising normal behaviour, the conduct of clinical trials and animal experimentation. Consequently, the industry is reluctant to invest directly in the development of life-style drugs, even though they would, of course, accept the off-label use of medicines for "real" illnesses in other settings, in the way that methylphenidate, amphetamine and modafinil are currently being used.

The question is then whether current research efforts in the pharmaceutical industry to develop drugs for brain disorders are likely to result in the next generation of off-label CEs. A recent review considered cognitive dysfunction in a wide range of brain disorders and provided an exhaustive list of possible drug targets (Millan et al., 2012). Not all of these will result in effective treatments for these conditions and logically, an even smaller subset will turn out to be useful as CEs for the general population. We have compared the list of 34 molecular targets in this paper with the published late stage pipelines (phases II, III and submitted for approval) of the top ten pharmaceutical companies by sales (Arrowsmith, 2012). It seems a reasonable assumption that these companies will be fully aware of all the possible targets for improving cognitive function and therefore that their pipelines should reflect their views on the likelihood of therapeutic and commercial success.

Not included are drugs specifically targeted to disease-modification for neurodegenerative conditions such as Alzheimers disease. These drugs, while still requiring proof of concept, work through interacting with the pathological processes believed to be involved in disease-progression, and are therefore most unlikely to have any effects in normal individuals. But even taking the most inclusive view of the symptomatic treatments in development for psychiatric diseases, we are still left with a rather thin list (Table 2). Of the possible 34 targets, only eight are currently in clinical development by the major companies. Tellingly, only two are in phase III and therefore have good supporting efficacy data, and one of these, preladenant, is targeted to the motor symptoms of Parkinson's disease. The drugs in phase II lack clinical data to support the six remaining mechanisms. The probability is, therefore, that only a minority of these drugs will prove effective and safe in the clinic against the targeted disease, even fewer will turn out to be more effective or safer than current marketed treatments, and perhaps a very small subset will find a niche in the hands of those who currently take CEs. Also significant perhaps is the poor representation of molecules acting on glutamate or GABA (γ-aminobutyric acid) receptors which have long been popular on lists of future CEs (e.g. Jones et al., 2007; Academy of Medical Sciences, 2008; Robbins, 2011). Technical difficulties in making selective compounds may have played a part in delaying their development.

If drugs face problems as a major source of CE in the future, a more realistic path that cognitive enhancement could take is

Table 2
Drugs that could be used as cognition enhancers in development by the top ten companies.

Company	Drug	Target	Disease	Phase
Johnson & Johnson	None to be approved before 2016			
Pfizer	PF-02545920	PDE10 inhibitor	Schizophrenia	II
GSK	742457	5HT6 antagonist	Dementia	II
Novartis	None to be approved before 2016			
Roche	RG1678 (bitopertin)	Glycine (GlyT-1) reuptake inhibitor	Schizophrenia	III
	RG7090	mGluR5 antagonist	Treatment-resistant depression	II
Merck	Preladenant	Adenosine A2A antagonist	Parkinson's disease	III
Sanofi	SAR110894	H3 antagonist	Alzheimer's disease	II
Abbott	ABT-126	Nicotinic a7 agonist	Schizophrenia and Alzheimer's disease	II
AstraZeneca	AZD3480	Nicotinic a4b2 agonist	Alzheimer's disease	II
Bayer	None			

The drugs listed are from the most recent pipelines published on the companies' websites.

through novel neurodevices, which are already on the market and in development. Currently, brain–computer interfaces (BCIs) are the most likely source of CE application. Like drugs, BCI technology has been developed primarily with therapeutic or clinical applications in mind (e.g. neuroprosthetics), but commercial and military interests are driving the development of BCIs that have potentially wide applications, e.g. video games that promise to improve focus, attention, and memory among children, soldiers or the elderly (British Medical Association, 2007; Engber, 2006). Non-invasive brain stimulation may also have a future as a CE technology; an early study suggests that transcranial direct current stimulation improves mathematics learning ability (Kadosh et al., 2012). However at present, application of brain stimulation technologies for CE purposes must be viewed as a speculative endeavour.

6. Needs assessment and forward look

In this section we review the key findings of the preceding discussion and consider what is needed to move forward constructively across the range of arenas concerned with CE.

6.1. Scientific studies of CE

In their review of current research on CEs, Smith and Farah (2011) rightly point out that facts alone cannot resolve ethical dilemmas; however, ethical dilemmas cannot be fruitfully discussed in the absence of facts either. We conclude that there is still great need for more and better data on all aspects of CE than what is currently available. In particular, comparable datasets are necessary that distinguish between various types of drug use purposes, record prevalence and frequency data, as well as perceived efficacy and correlations with other factors, such as socio-demographic indicators, academic standing, and other drug and alcohol use habits. Research indicates that a significant proportion of non-medical prescription stimulant users are symptomatic for ADHD (Peterkin et al., 2010). Future research needs to investigate this possible correlation further and find ways of addressing the problem of self-medication. Furthermore, research should also study the influences on students' perceptions of smart drugs and their relative willingness to use them. More trials of CE in healthy individuals are likely to become necessary if CE prevalence increases. Therefore funding bodies should consider how best to promote scientific studies that are rigorous as well as socially and ethically responsible.

6.2. Social science of stakeholder attitudes and expectations around CE

Cognitive enhancement is often discussed in relation to the expansion of the goals of medicine beyond the treatment of disease into the domain of improving wellbeing (Synofzik, 2009). Despite the fact that 'wellbeing' has become a policy buzzword in many western nations, it is unknown how cognitive enhancement fits into individuals' health concerns, expectations or desires. It is also unknown if CE will remain an interest only among particular groups; e.g. students, pilots, doctors; or whether it has broader public appeal. The perspectives of the medical profession on CE are particularly relevant but under-researched. The American Academy of Neurology has issued some guidelines about responding to patient requests for CE (Larriviere et al., 2009); however, the issue is still being debated in part because the medical profession is ambiguous about dispensing CEs to healthy individuals (Flower et al., 2010). Parents' and children's perspectives on CE would seem to necessitate a separate analysis (Singh and Kelleher, 2010) but existing guidelines make no comment on this issue. Finally, as we have reviewed here, we need to know more about current CE practices in order to assess the need for a regulatory response, to ensure relevant experimental models in drug trials, and to properly evaluate the societal and ethical impacts of CE.

6.3. Public engagement activities around CE

In 2009 the European Commission's Science and Technology Options Assessment (STOA) agency published a major report on the topic of human enhancement. The report identified cognitive enhancement as the most likely enhancement technology to find broad public appeal, and it discussed the lack of a normative framework for the research and distribution of enhancements as a key challenge (Coenen et al., 2009). The STOA study called for the creation of public engagement programmes that allow broad segments of society to deliberate this issue. To date, despite a continued focus on the societal impact of cognitive enhancement among high-level policy and scientific stakeholders, a programme of public engagement activities has not yet been enacted across EU countries. At the same time, social surveys suggest a public increasingly interested in cognitive enhancement (Gaskell et al., 2010), which further highlights the need for stakeholder engagement to move forward.

6.4. Regulation

Any future regulation of CEs would have to aim at minimizing the risks and harms of cognitive enhancement while maximizing the benefits. We suggest that this should involve a careful deliberative process involving an evaluation of scientific and social science evidence, ethical analyses, and the views of multiple stakeholders. We anticipate that this is the path that most governments will take. However there is an alternative regulatory route, via national medical organisations. This route effectively legalises the use of cognition enhancing substances for non-therapeutic purposes, by sanctioning off-label drug prescriptions for CE. The American Academy of Neurology first outlined this approach by arguing that patient requests for CEs be considered in line with existing guidelines for off-label drug use (Larriviere et al., 2009). The Israeli Medical Agency has taken the next step, to issue official guidelines to its practitioners, enabling them to dispense cognition enhancing substances for non-therapeutic purposes (personal communication to IB from Malke Borow, Director of the Division of Law and Policy, Israeli Medical Association). In its proposal for making enhancers more widely available, the Agency reasoned that medical

interventions can legitimately aim to improve wellbeing in the absence of disease and that "quality of life" should be judged according to patients' subjective views. Physicians examine each request to prescribe off-label individually and not all are approved. Systematic monitoring and evaluation of the impact of these guidelines would help to inform regulatory deliberations in other nations.

7. Conclusion

In the title of this article we asked what we should do about student use of cognitive enhancers. In assessing the need for society to take a stance on the use of CEs, and perhaps to consider how they should be regulated, we consider that the potential harms to individuals are real and should be taken seriously, regardless of the benefits, and that there is a case for some form of action. Estimation of societal benefits and harms really requires more information on effectiveness and prevalence, and issues of fairness need to be considered alongside other factors that contribute to an unequal playing field. Therefore we urge that more research in this area be funded and undertaken. Lastly, we maintain that while there is no evidence that society needs to prepare itself urgently for a new generation of pharmacological CEs, it is still necessary to engage in an anticipatory analysis of the social and ethical consequences of CEs, because other technologies, like neurodevices, are likely to emerge that have more immediate CE applications.

In the near term, researchers and science journalists should consider carefully what information they provide about the risks and benefits of CEs and how they present this information. Lab researchers should be careful not to generalise laboratory findings to real life scenarios in an oversimplifying manner. All research in this area needs to reflect upon the ethical aspects of raising awareness about potentially harmful and illegal behaviours by overemphasising the effectiveness or desirability of smart drugs for the purposes of cognitive performance enhancement.

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