



The increasing lifestyle use of modafinil by healthy people: safety and ethical issues

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Pharmacological cognitive enhancers (PCEs) are used in the treatment of a variety of disorders, including targeting cognitive impairment and sleep abnormalities. Evidence suggests that PCEs also enhance cognition in healthy individuals. PCEs have attracted considerable interest recently, particularly from students, academics and the military. Proponents of PCE use in healthy people argue that these substances may be used to reduce fatigue-related and work-related accidents and improve learning outcomes. In this article, safety concerns as well as ethical issues of fairness and coercion are considered. Discussion amongst experts in the field, government officials and members of society on the topic of the increasing lifestyle use of PCEs in healthy people is urgently needed.

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Current Opinion in Behavioral Sciences 2015, 4:136–141

This review comes from a themed issue on **Cognitive enhancement**

Edited by **Barbara Sahakian** and **Arthur Kramer**

<http://dx.doi.org/10.1016/j.cobeha.2015.05.004>

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Introduction

Pharmacological cognitive enhancement is the practice of using drugs to enhance cognitive functions, including attention, learning, memory, planning and problem-solving. Some cognitive enhancers, like caffeine, have been around for a long time, but the development of drugs targeted at specific cognitive functions is relatively recent.

Pharmacological cognitive enhancers (PCEs) have received much interest in the media and in the reports of several professional bodies. There have been concerns over the growing use of PCEs in healthy populations, with some voices in support of unrestricted access and others wanting to restrict their use to disorders only, such as narcolepsy or attention deficit hyperactivity disorders.

There has also been some debate about their degree of efficacy and safety both in psychiatric conditions and in healthy individuals. Some authors have expressed concerns and have taken a very cautious response in regard to their usage by healthy people [1]. However, it is at least plausible that under some conditions the benefits of PCEs, for example increasing alertness in shift workers and reducing accidents, will outweigh its costs.

This article will review the actions and effects of modafinil, a recently synthesized wake-promoting drug, on healthy individuals. Modafinil was chosen as a representative PCE as it has been shown to be an effective cognitive enhancer with a relatively favorable side effect profile and no evidence to date of substance abuse potential compared to typical stimulants such as amphetamine. After a selective literature review of the effects of modafinil on healthy volunteers, a variety of oft-mentioned arguments against its use are examined. These include worries about safety, fairness and coercion. It will be argued that fair use of PCE technologies depend in large part on fair public policy.

Modafinil: effects and mechanism of action

Modafinil is a central nervous system wake-promoting drug that modulates multiple neurotransmitters, elevating levels of dopamine, noradrenaline, glutamate and serotonin, and decreasing GABA levels [2–4]. Modafinil also acts on histamine and orexin [2]. Modafinil does not appear to have abuse potential nor significantly interfere with sleep at low doses [5]. Possible side effects include headaches, dizziness, malaise, diuresis, palpitations, nervousness, insomnia, depression, anxiety, rashes, cardiovascular symptoms, suicidal thoughts and mania, although it is considered to be overall well-tolerated [6,7]. The exact mechanisms of action for the cognitive enhancing effects of modafinil remain unknown. However, it is highly likely from the published reports that the improvements in cognition are at least in part due to modafinil's effects on noradrenaline and dopamine.

Modafinil is indicated for use in narcolepsy, obstructive sleep apnea and shift work disorder by the Food and Drug Administration (FDA), but for narcolepsy only in Europe. It is widely prescribed for off-label use in conditions involving fatigue or cognitive dysfunction secondary to disease [8]. In 2008, the global market share of modafinil was more than 700 million US dollars per year [9]. Furthermore, it is estimated that approximately 90% of modafinil use is 'off-label' by healthy individuals [10].

In healthy individuals, modafinil improves performance on measures of digit span, visual pattern recognition memory, spatial planning and stop-signal reaction time [11]. In one study by Muller *et al.* [12^{••}], subjective ratings of enjoyment of task performance were significantly greater under modafinil compared with placebo, but mood ratings overall were not affected. In another very small study ($n = 6$), progressive ratio performance, a measure of sensation reward, was improved [13]. Increased ratings of confidence in task performance have been found in military fighter pilots given modafinil [14]. A recent review lists six further studies demonstrating significant improvements in measures of prefrontal function including the Wisconsin Card Sorting Test, Stroop, N-Back and Hayling Sentence Completion Task in sleep-deprived healthy individuals. It also lists three further studies showing improvements in working memory and vigilance [2]. Another review reported positive effects on attention in non-sleep-deprived individuals [15]. The magnitude of effects in the above studies is small to moderate. In no cases were deleterious effects on cognition reported.

Benefits of use

The wake-and-vigilance promoting effects of modafinil make it particularly attractive to certain professional groups. For example, the use of PCEs is approved for use in the U.S. military if used to prevent decline of function rather than enhancement [16]. Caldwell and colleagues [14] reported that modafinil maintained flight accuracy within approximately 15–30% of baseline levels, whereas performance under the no treatment/placebo condition declined by as much as 60–100%. Although there have been concerns over explicit coercion in the military, the use of PCEs is thought to be justified so long as personnel are not dissociated from — and maintain moral culpability for their actions [17]. The use of PCEs may thus reduce errors in sleep-deprived soldiers.

PCEs are known to be used by students and academics. A qualitative study on the use of PCEs by students found that users reported being able to sustain higher productivity levels over a longer time, with greater task enjoyment and less expended effort [10]. In an online *Nature* poll, 20% of respondents admitted using PCEs for non-medical reasons [17]. Although this figure is typical of the literature, a review on the topic quoted prevalence rates ranging from 2.5% to 55% in college students [18]. The usefulness of these numbers is limited by variations in sample size, drug type and study design across prevalence studies.

Modafinil has been reported to increase performance on the Continuous Performance Task in sleep-deprived emergency room physicians [19]. A more recent study of sleep-deprived doctors found improvements on working memory and planning measures from the CANTAB

computerized tests (www.cantab.com) as well as improvements on measures of control of impulsivity and attentional flexibility with modafinil [20^{••}]. A review of the prevalence of physician errors estimated that mistakes by doctors are responsible for up to 98 000 unnecessary deaths and more than a million unnecessary injuries each year in the US alone [21]. Both studies cited above concluded that modafinil may reduce errors in sleep-deprived physicians.

In a survey of 9200 Norwegian drivers involved in road-traffic accidents, sleep deprivation was cited as the main cause in 18.6% of night time accidents, and 3.9% of accidents overall [22]. Although we were not able to find any concrete data on the extent of sleep deprivation and its effect on driving safety, or the extent to which it may be remediated by using PCEs, the above numbers warrant the assumption that the acute use of modafinil by sleepy drivers may reduce road-traffic-related accidents.

PCEs may also be of use in those who take decisions affecting others. For example, limitations of working memory are apparent in US jury deliberations, with many jurors not allowed access to a transcript of court proceedings and in some cases not being allowed to take notes [23]. It is still possible to be convicted solely by eyewitness testimony, which is known to be unreliable in some cases. Sandberg's paper [23] cites a survey finding juridical somnolence in up to 10% of cases. Likewise, legislators are required to sit still and listen to important information for hours on end. Therefore, PCEs in these groups might serve to reduce errors in decisions of great import.

Identifying Alzheimer's disease patients at an early stage results in cost savings and health benefits, compared with no treatment or treatment in the absence of early assessment [24]. The effects on task enjoyment and attention cited above warrant the assumption that using PCEs could lead to improvements in productivity. Thus, there exist sizeable financial and safety-related incentives for the use of PCEs, not only in patient groups, but also in parts of the workforce, in addition to the benefits to the individual of greater task-enjoyment and productivity.

Is it safe?

There appear to be no known cases of death attributed to modafinil [8,25]. In a recent study, Davies and colleagues [8] followed 1096 patients prescribed modafinil over six months. In their cohort, there were no cases of serious skin rashes; one case of depression; 11 cases of headache; 8 cases of nausea; 7 cases of malaise; 5 cases of dizziness and insomnia; 2 events of psychosis; one manic event and one overdose. Both cases of psychosis and the manic event were precipitated by doses of at least 400 mg, and symptoms receded after discontinuation. A study by Swanson

et al. [26] of modafinil in children and adolescents with attention deficit hyperactivity disorder (ADHD) reported on side effects in 189 patients. Modafinil significantly improved symptoms of ADHD, as shown by reductions in the ADHD-RS-IV School Version total score. No withdrawal symptoms were observed when modafinil was abruptly discontinued at the beginning of the two week observation period. Modafinil was generally well tolerated. Insomnia, headache and decreased appetite were the most commonly reported adverse events.

In an analysis by the pharmaceutical company Cephalon [27], there were serious adverse events reported for 18 (2%) of 933 children and adolescent ADHD patients who received modafinil. Two patients reported 3 serious adverse events, including erythema multiforme, Stevens–Johnson syndrome and maculopapular rash. All of these skin rashes resolved without sequelae and none of which required medical intervention or hospitalization for treatment. Six additional subjects discontinued modafinil for concerns of rash, which subsequently resolved. Due to these reports, Cephalon reviewed in post-marketing data serious skin concerns. Five reports of severe adverse skin reactions have been made since 1999, during which time approximately 673 000 adults have taken modafinil worldwide [28]. These serious skin rashes, including Stevens–Johnson syndrome, are a concern, so should be monitored in future.

Carstairs and colleagues [25] reviewed all cases of modafinil intoxication reported to the California Poison Control Centre in the period 1998–2008. They identified 87 cases attributed to modafinil alone. Of these, 33 were intentional overdoses and the rest were due to accidental overdose or accidental ingestion. Doses ranged up to 16 100 milligrams; it should be noted that informal reports suggest that the typical dose used for acute cognitive enhancement is 100–200 mg. The authors stratified complaints according to severity: of 87 reported overdoses, 22 had no clinical effects, 54 had minor effects, and 11 had moderate effects. There were no cases of serious clinical effects or death caused by modafinil intoxication alone over the entire ten year period.

It seems clear that acute modafinil use at the doses of 100–200 mg, which are frequently used by healthy people, is relatively safe. However, no studies have examined effects of chronic use by healthy people. It is thus possible that modafinil may be benign in the short term but have serious long-term or cumulative effects. A study of the safety of long-term modafinil use in healthy people is urgently needed.

Is it fair?

Some argue that using PCEs is unfair because its use amounts to cheating, as with performance enhancing drugs in sports. The use of, for example, steroids in sports

is considered cheating because there are explicit rules against their use. Until recently, it appeared there were no explicit rules against the use of PCEs in universities. However, recently, Duke University in the USA specified on their website that the ‘unauthorized use of prescription medication to enhance academic performance’ amounted to cheating in the category ‘academic dishonesty’ of their academic conduct policy (Duke University: Policy on academic dishonesty; URL: <http://studentaffairs.duke.edu/conduct/zpolicies/academic-dishonesty>). While the long-term safety of PCEs in healthy people is unknown, it is not safe to purchase controlled substances and prescription only drugs, such as amphetamine and methylphenidate, via the internet. Whether or not a particular PCE is deemed fair to use will ultimately depend on whether the drug is approved by the regulatory bodies for use in healthy people.

The use of PCEs may still be considered unfair, even if it is not considered cheating. This concern about fairness is not just limited to PCEs, but indeed other enhancements, such as biotechnology [29]. The fear is that achievements of the enhanced are not attributable to their unenhanced state. However, PCEs are not unique in affecting the inner workings of an agent. Many currently accepted enhancement techniques causally influence brain function or structure, such as reading, sleep, nutrition and instruction [7]. Enhanced individuals experience a raised baseline of performance; this does not mean that their achievements are not due to training. For example, it may be the case that people take these drugs to improve the learning that they undertake in academic courses. Consider the use of trampolines by acrobats: a triple back-flip on hard ground is extremely challenging, but this does not mean that a trampoline acrobat performing this feat does not deserve praise or did not achieve it through training.

Another argument against using PCEs is that pharmaceuticals are inherently invasive, and whereas enhancements such as artificial light can easily be removed, it is not easy to remove the effects of a pharmaceutical drug once ingested. That is, one enhancement method may be more invasive than another. However, neural representation and adaptation to all stimuli are by definition internal, and the duration of effect of a PCE may be modulated by dose, type of drug and other factors. Furthermore, cognitive enhancement may be achieved through better nutrition, also invasive, yet this objection to enhancing cognition through nutrition is not raised. The ‘natural’ in the case of nutrition and the ‘unnatural’ in the case of drugs does not hold either, since many drugs can be derived from plants.

There is some evidence that those most likely to use PCEs are those struggling to utilize alternative methods. A recent study found that students who were more likely to procrastinate, have high cognitive test anxiety, lower

intrinsic motivation to study and lowest internalization of prevalent moral norms were also most willing to use a hypothetical PCE [1]. Thus it may be that those most in need of a cognitive boost are the ones most likely to use PCEs. It is possible, therefore, given individual differences in attention, concentration and motivation, that some students are 'self-medicating' to increase task related motivation [12**].

The use of PCEs may be viewed as unfair because limited access to it would confer positional advantage to those with the most resources. For example, it is known that a high monetary price is associated with lower willingness to use PCEs [1]. Although valid, concerns about distributive justice can be seen as arguments of implementation.

Even if things were such that inevitable inequalities arise due to the large-scale use of PCEs, this is not an insurmountable objection against its use. Access to PCEs is certainly more limited at present than open access would be. At present, PCEs are restricted to those who can obtain them through prescription, who are willing and able to trade illegally. And if the benefits possible due to the use of PCEs are unfair on the grounds of inequality, then so are the larger benefits possible due to private schools, tutors, access to books in the home, preparation courses and many other educational luxuries over which the student has little control; yet these are tolerated for the strong argument that one should not be deprived of a benefit simply because it is not available to all. Nonetheless, cognitive enhancers and justice has been a concern of both the Presidential Commission for the Study of Bioethical Issues [30**] and the International Neuroethics Society [31**]. If PCEs can help disadvantaged members of society, it would be important to ensure access is not barred by cost.

Coercion

Coercion may exist, as in some militaries, or implicitly, through elevated levels of competition caused by enhanced competitors. Some who do not wish to take PCEs may feel or be compelled to do so. A recent study demonstrated the effect on an individual of others using PCEs. The study found that students were significantly more likely to use a (hypothetical) PCE when more peers used PCE drugs [1].

Furthermore, a study by Franke *et al.* [32] stated that only 15.6% of people surveyed stated that they would not use cognitive enhancers under any condition. These authors concluded that the disposition to use cognitive enhancers among high school and university students in Germany is high, as long as the substances are safe. However, a fear of addiction and doubts about fairness result in most participants abstaining from stimulant use.

An example of coercion was illustrated from the data obtained in the Nature Survey [17]. When respondents

were asked whether healthy children under the age of 16 should be restricted from taking PCEs, 86% thought that they should be restricted. Nonetheless, 33% of respondents said they would feel pressure to give PCEs to their children if other children at school were taking them.

Despite the existence of educational supplements, there are rarely complaints by students feeling coerced to attend summer schools, eat better, exercise, sleep more, meditate, spend time in nature, purchase books or work beyond their homework, despite the fact that PCEs and educational supplements are similar in that their use is associated with unattractive costs (e.g. loss of free time, unintended side effects, monetary and opportunity costs) yet beneficial to educational achievement. In response to pressure to use any of these educational supplements, whether pharmacological or not, the option exists of using a different enhancement strategy or accept relative disadvantage if the costs are thought to outweigh the benefits. Although implicit coercion to use PCEs is a legitimate concern, it does not warrant differential treatment of PCEs to other educational supplements unless it poses unacceptable additional risks to health or well-being.

Explicit coercion is a serious matter as the options of choosing alternative methods or accepting relative disadvantage are not available. Coercion maybe deemed acceptable in certain situations: for example, the extensive physical and/or mental training required of military personnel in order for them to perform better in their work, which involves harm to themselves or other military colleagues.

Discussion

Many countries, universities and employers do not have guidelines about the acceptable use of PCEs. As it stands, those who wish to use PCEs but do not have a prescription use the internet or buy them from friends with prescriptions. In Maher's poll [17], a third of respondents obtained PCEs through the internet. Those purchasing through internet sources run the risk of contamination of the product that they are purchasing.

There are two populations in which the use of PCEs is generally considered acceptable: those with cognitive dysfunction due to illness and the military. PCEs have many different actions and we need novel, more effective ones to improve cognitive deficits in those with neuropsychiatric disorders and brain injury [33,34]. Implicit in the acceptance of PCEs in these groups is a normative judgment about its permissibility under certain circumstances. People with neuropsychiatric disorders who have their functionality, quality of life and wellbeing improved by PCEs should have access to them. This is not only of benefit to the individual, but also to society since, for example, each Alzheimer's disease patient who receives

early assessment and treatment saves society £7741, compared no early assessment and treatment. Of this, £3600 is in direct healthcare costs [24].

One reason is an altered risk/benefit ratio. Those with cognitive dysfunction suffer a variety of deficits some of which may be treated with PCEs. Although the risks of medication are likely to be similar in this population, the benefits are greater. The second reason is the importance and nature of the work carried out. The military operates in small, tight-knit groups, and any one soldier may be responsible for the safety of many others. Their alertness is crucial for their own survival and the safety of those who depend upon them.

Some groups, like soldiers, operate in highly dangerous environments or carry out very important functions. This also includes heads of state or members of the transport industry in times of jetlag or greater need for attentional capabilities. Furthermore, the increasing aging population may have to work for longer due to increased retirement age or lack of pension and some may experience problems, such as staying awake and alert, in the workplace. Some of the benefits and costs of PCEs in these populations are outlined above. The act of weighing up the risk and benefits is necessarily subjective, but a few additional remarks may put the matter in perspective.

It is important to keep analogous practices in mind. The use of non-steroidal anti-inflammatory drugs (NSAID) such as aspirin is a good example. NSAID are sold over the counter and used to ameliorate mild pains. Their use for this purpose is culturally accepted, and it is thus safe to assume that the risk/benefit ratio of such drugs is judged acceptable, despite the lack of benefits to others. Yet 40 000 yearly deaths are attributable to the use of NSAID in the US alone [35].

A reduction in professional errors even of small magnitude may translate into saved lives and improved efficiency. A possible requirement of PCEs in certain populations, for example train or bus drivers and medical doctors working shifts at night, would have to be considered carefully. Similarly, the risk/benefit ratio of PCE use in the healthy is dynamic. It may be favorable only in circumstances of excessive fatigue or pressure not manageable by lifestyle factors.

Conclusion

On the basis of this analysis, several conclusions may be drawn. PCEs have been demonstrated to increase cognitive performance in healthy populations [36]. The magnitude of improvement is generally small to moderate, and is subject to considerable inter-individual variation [36]. Deleterious cognitive effects of modafinil have not been reported at doses normally used for cognitive enhancement (e.g. 100 mg or 200 mg) in acute studies.

However, there is a serious lack of research into the long-term efficacy and safety of PCEs in healthy individuals. Nonetheless, there is reason to believe that acute PCE use may increase productivity and safety in certain populations, particularly where shift-work, jet-lag or highly dangerous work is involved (e.g. the military) [37^{**}]. Thus, it seems fair to conclude that in some circumstances, the benefits of using PCEs use may outweigh its costs. Therefore, if long-term studies in healthy volunteers of specific PCEs demonstrate successfully safety and efficacy, then it is recommended that these specific PCEs be marketed safely through a pharmacy following consultation with a medical doctor, such as a General Practitioner, at least for certain subgroups of the healthy population. Finally, future discussions by experts, government officials and the public on the topic of the use of PCEs by healthy people and its effects on society, including distributive justice, are urgently required.

Conflict of interest statement

Barbara Sahakian consults for Cambridge Cognition, Peak (Brainbow), Servier, Otsuka and Lundbeck. She holds a grant from Janssen/J&J. She has share options in Cambridge Cognition.

Acknowledgements

We thank Jonathan Shepherd for his comments on this manuscript.

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- of special interest
- of outstanding interest

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- The human enhancement and the future of work report explored potential enhancements arising from advances in science and engineering that are likely to impact on the future of work. This report was particularly important because it was the first time that the four Academies (the Academy of Medical Sciences, the British Academy, the Royal Academy of Engineering and the Royal Society) produced a joint report and because the report emphasized the urgency for considering pharmacological cognitive enhancement, since there was an increasing lifestyle use by healthy people.