



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

Sebastian Porsdam Mann¹ and Barbara J Sahakian^{1,2}

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.

Addresses

¹ University of Cambridge, Department of Psychiatry, Addenbrooke's Hospital, Cambridge, UK

² University of Cambridge, MRC/Wellcome Trust Behavioural and Clinical Neuroscience Institute, Downing Site, Cambridge, UK

Corresponding author: Sahakian, Barbara J
(bjs1001@medschl.cam.ac.uk)

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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

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