

## Cognitive enhancement: a brief overview

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### Abstract

Cognitive enhancement involves the non-medical use of illicit and/or prescription drugs, such as agents prescribed for attention deficit/hyperactive disorder (ADHD) and narcolepsy, usually in order to stay awake and to counteract fatigue and loss of concentration, generally in the context of high workload and stress. Growing interest in taking prescription stimulant drugs for non-licensed purposes to improve academic, work and sporting performance has raised medical, ethical and regulatory issues.

**Keywords:** ADHD, attention deficit/hyperactivity disorder, cognitive enhancement, high workload, narcolepsy, stress

### Introduction

Recently, there has been considerable publicity surrounding “smart pills” having the potential to boost brain power in healthy people seeking greater productivity. Yet the concept of drug-induced cognitive enhancement is not new. Traditionally, people trying to stay awake and focused in order to manage excessive workloads and meet impossible deadlines have turned to caffeine and nicotine. “Burning the midnight oil” conjures up nostalgic images of a frantic individual hunched over a battered typewriter surrounded by mugs of strong coffee, overflowing ashtrays and clouds of stale cigarette smoke. These pharmacological strategies to stay awake and maintain cognitive function are not without merit. There is evidence that caffeine may improve cognitive performance,<sup>1</sup> that nicotine may enhance attention and spatial working memory,<sup>2</sup> and that nicotinic agonists are able to improve attention, learning and memory.<sup>3</sup> Increasingly however, in the context of perceived or real overwhelming internal and external academic, work-related and personal pressures, these non-prescription and easily accessible stimulants are being supplanted by or supplemented with more sophisticated prescription-only pharmacological alternatives; particularly drugs licensed for narcolepsy (modafinil) and ADHD (methylphenidate). Numerous sites devoted to the promotion of diverse cognitive-enhancing smart drugs or nootropics, such as piracetam, choline and adrafinil (“modafinil lite”), as well as information on where and how to acquire them, can be found using a cursory online search. It is this wider adoption and mainstream acceptance of the concept of neuro- or cognitive enhancement in healthy individuals that has prompted vigorous scientific debate, and raised complex ethical questions relating to accomplishment and the value of human effort.<sup>4</sup>

### Who and why?

The extent of drug use for cognitive enhancement in healthy individuals is difficult to establish, given the covert nature of acquiring, diverting and taking schedule 5 prescription-only medication for non-licensed purposes. Anecdotal reports suggest that the use of cognitive enhancers is possibly more common in people who naturally opt for the boost provided by stimulants because their working hours are long and their professional environment is conducive to substance taking. For instance, cocaine may be used extensively as a cognitive enhancer, and not merely as a recreational drug, in marketing and creative industries. Yet it is possible that this illicit agent is no longer the executive's drug of choice, given that prescription stimulant drugs may be perceived to be safer and enjoy wider social acceptability. If television series are to be believed, then even desperate housewives are turning to their children's ADHD medication simply to get through their day. Modafinil has been used when soldiers and pilots need to operate for long periods without sleep, and is now endorsed as the new “battlefield” drug in favour of the old-style amphetamines.<sup>5,6</sup>

Prevalence rates for cognitive enhancement in different spheres of surveyed employed adults are remarkably similar. For instance, an online Nature poll found a 20% lifetime prevalence of using “the professor's little helper” in senior academics who suffer a unique set of stresses and strains.<sup>7,8</sup> Fatigued doctors may also be partial to the idea of pharmacologically enhanced performance, working in situations which require efficient information processing, flexible thinking and decision-making under time pressure, and having easy access to these drugs.<sup>9,10</sup> A recent survey found that 20% of surgeons (who presumably need to maintain both high cognitive and fine motor function) use cognitive-enhancing drugs. This survey revealed that pressure to perform at work or in private life and gross income were positively

correlated with the use of these agents.<sup>11</sup> The authors noted that the misuse of stimulants for cognitive enhancement in the medical field may lead to addiction as well as an overestimation of one's capabilities, which places patients at risk. The apparent widespread use of cognitive-enhancing drugs in the medical profession has been publicly acknowledged by medical societies (the Royal Society and the Academy of Medical Sciences) and associations (the British Medical Association), who have held workshops and produced discussion papers on this issue.<sup>12</sup>

The majority of prevalence studies, however, have been conducted in the academic setting, where acceptance criteria are becoming more rigorous, ultimate job opportunities progressively limited, and expectations of having to perform at increasingly higher levels in order to succeed, obvious. Numerous surveys reveal that on average, 20% of university or college students use ADHD stimulants and modafinil in order to counteract tiredness and maintain academic performance.<sup>13,14</sup> Qualitative studies have shown that improved motivation is one of the most pronounced effects experienced by healthy students taking cognitive enhancers. In addition, students appear to perceive neuroenhancement as an acceptable means of coping with stress.<sup>15</sup> However, like doping in sport, underlying competitive drives are probably at play in this scenario too. Students may feel unfairly disadvantaged compared to their drug-using peers, and may be using prescription stimulants in order to level the playing field. This raises the critical question of whether cognitive-enhancing agents merely help people stay awake and maintain cognitive function, or actually enhance cognitive performance.

At the very least, stimulants for ADHD and modafinil have an immediate provigilant effect,<sup>11,16</sup> and may therefore be perceived as effective and easier alternatives to more time-consuming coping mechanisms. However, the issue of whether or not these agents increase academic performance is still undecided as consistent neuroenhancement in healthy, non-sleep-deprived individuals has not been demonstrated.<sup>17</sup>

Although the primary reason for using stimulant cognitive-enhancing drugs may differ other parallels may be drawn between doping in academia and in sport. A double-blind, randomised, placebo-controlled trial conducted in a small group of athletes ( $n = 16$ ) demonstrated that the acute ingestion of modafinil associated with greater physical endurance, higher oxygen uptake and lower subjective ratings of exertion, which suggests that increased performance relates to a reduced sensation of fatigue during exercise.<sup>18</sup> Methylphenidate has shown similar effects which has been attributed to increased dopamine levels.<sup>12</sup> Modafinil and methylphenidate appear on the 2016 World Anti-Doping Agency in competition list of prohibited substances.<sup>19</sup> Taken together, this suggests that stimulant drugs significantly reduce fatigue, thereby increasing training and/or learning capacity, and therefore enhancing ultimate performance, both physical (in athletes) and cognitive (in students), in addition to having a possible immediate "turbocharging" effect.

## Pharmacology

The use of cognitive-enhancing drugs appears to be relatively common in people under pressure to perform, where they are usually taken, at least initially, to combat fatigue. Fatigue is

linked to frequent lapses of attention and impaired functioning in several important cognitive domains, i.e. acquiring, selecting, understanding and retaining information; reasoning and co-ordination of motor output.<sup>20</sup> Modafinil and methylphenidate may modulate any of these core functions.<sup>21</sup>

However, the critical question is whether any of these drugs enhance cognitive function or merely restore function in the sleep deprived. Substances which increase dopamine, noradrenaline and glutamate enhance neural excitation in the memory and learning circuits, and therefore theoretically improve brain function in healthy individuals beyond their baseline functioning.<sup>6</sup> The most popular drugs used as potential cognitive enhancers include modafinil and methylphenidate, both of which increase these neurotransmitters.

### Modafinil

Modafinil, a schedule 5 stimulant-like drug, licensed in South Africa for the treatment of excessive daytime sleepiness in patients with narcolepsy, as defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*,<sup>22</sup> appears to be the most suitable agent for promoting wakefulness. Its mechanism of action is unknown, although it exhibits effects on brain dopamine, noradrenaline, serotonin, glutamate, gamma-aminobutyric acid, orexin and the histamine pathways, resulting in possible increased neuronal activation in cortical, rather than subcortical, regions of the brain.<sup>23,24</sup> Modafinil produces psychoactive and euphoric effects, alterations in mood, perception, thinking and feeling, typical of other central nervous system stimulants, such as cocaine, amphetamine, metamphetamine and methylphenidate. Although it is reinforcing, modafinil is believed to have a much lower potential for abuse compared to other cognitive-enhancing stimulant drugs. Incrementing dose or drug-seeking behaviour should alert the prescriber to the possibility of either addiction or drug diversion for off-label cognitive-enhancement purposes.

Modafinil, like the ADHD stimulants, is effective in attenuating the effects of fatigue in healthy, sleep-deprived individuals.<sup>10,25</sup> It improves function in several cognitive domains, including working memory and episodic memory, and other processes dependent on prefrontal cortex and cognitive control.<sup>23,26</sup> Side-effects in the cognitive enhancement population are difficult to assess, but in narcolepsy sufferers modafinil is well tolerated. The most commonly observed adverse events (> 5%) in controlled US and foreign studies include headaches, infection, nausea, tachycardia, nervousness, anxiety and insomnia.<sup>22</sup>

### Methylphenidate

Methylphenidate, in short-acting, intermediate-release and long-acting forms, is the only stimulant licensed in South Africa for ADHD.<sup>27</sup> It is thought to block the reuptake of noradrenaline and dopamine into the presynaptic neuron, and increase the release of monoamines into the extraneuronal space. Methylphenidate exerts its effects on cognition primarily by increasing the levels of these catecholamines in the prefrontal cortex, and in the cortical and subcortical regions projecting to it. This mechanism is thought to be responsible for improving cognition and behaviour in ADHD sufferers. Physical effects include activation of the sympathetic nervous system, producing increased heart

rate and blood pressure. Psychological effects are mediated by the activation of the nucleus accumbens, ventral striatum and other parts of the brain's reward system, producing feelings of pleasure and the potential for dependence. Methylphenidate has been found to enhance learning, and possibly working memory and cognitive control, but whether or not these effects translate to actual gains in cognition is equivocal.<sup>28</sup> Methylphenidate comes with serious warnings, including sudden death and hypertension, and may cause psychosis, bipolar illness, aggression, the suppression of growth, seizures and priapism, among others.<sup>29</sup>

Other physical, psychological and ethical costs may be incurred with cognitive enhancement. According to the Substance Abuse and Mental Health Services Administration, emergency room visits associated with the use of stimulants in young adults doubled between 2005 and 2010.<sup>30</sup> It appears that those who are most likely to use cognitive-enhancing drugs, i.e. high school and university students, and athletes, are the ones most vulnerable to potential long-term neurological sequelae because their brains are still developing. Changing glutamate function in healthy individuals may impair behavioural flexibility, which, in turn, impacts on interpersonal skills, as well as potentiate obsessive compulsive or addictive behaviours.<sup>6</sup> Dopamine and noradrenaline modulate cognitive and neuronal function on a bell-shaped, dose-response curve. Thus, healthy individuals run the risk of pushing themselves beyond optimal levels, thereby "paradoxically" impairing those aspects of cognitive function which they are trying to improve.<sup>6</sup>

### Recommendations and conclusion

While it may not be feasible to limit workloads, reducing unrealistic expectations may obviate the need for taking cognitive-enhancing drugs. It should be emphasised that these stimulant drugs counteract fatigue, but do not necessarily enhance performance directly. Relieving stress and optimising mental well-being may improve cognition, and can be achieved by nonpharmacological means. In addition, cognition may potentially be enhanced by a healthy lifestyle, including ensuring adequate sleep, increasing physical activity, maintaining a nutritious diet, and minimising stimulant drug and alcohol use.<sup>31</sup> In the meantime, clinicians should be aware that their patients, particularly those in academia and sport, are under enormous pressure to use cognitive-enhancing drugs, that the practice is common, and that adverse effects may be serious. Therefore, it is recommended that the complexities, nuances and issues associated with cognitive enhancement are embraced in order to promote overall patient well-being.

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