Psychostimulants as cognitive enhancers – the evidence for the use and abuse of smart drugs

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Abstract
While modafinil is licensed to treat narcolepsy as a psychostimulant, there is widespread use as a "smart drug" in the young to help study and interest in older populations as a cognitive enhancer. This review considers both the evidence for benefit and potential for harm. If it is as effective as it seems, should we all be using it? Should Neurologists recommend it, and should we worry if our patients are taking it? In this review the evidence base behind psychostimulants, in particular modafinil as a cognitive enhancer, is discussed.

Psychostimulants such as modafinil and methylphenidate are prescribed to treat CNS hypersomnias including narcolepsy and in the US, residual sleepiness due to obstructive sleep apnoea and shift work sleep disorder [1]. However, they are also widely used as smart drugs in those without sleep disorders to help concentration and memory, in particular modafinil. Modafinil is the most widely prescribed psychostimulant for narcolepsy and there is off-licence use in depression, older populations, and neurodegenerative disease for both alertness and cognition. Healthy individuals using modafinil as a stimulant report increased concentration and attention; facilitating harder and longer hours of study and work. Contrary to other traditional psychostimulants, like amphetamines, modafinil has few reported side effects, low potential for tolerance or dependence and is relatively safe to use [1]. It is widely available online.

What is modafinil?

Modafinil is a psychostimulant drug that increases wakefulness and has been licensed since 1994. The precise mechanism remains debated, but it acts as an atypical, selective and weak dopamine reuptake inhibitor alongside inhibition of noradrenaline reuptake. It also indirectly activates the release of orexin neuropeptides and histamine and inhibits GABA thereby increasing arousal and alertness. Elevated levels of circulating catecholamines are responsible for behavioural arousal [1].

Modafinil has chemical and physiological effects that differ from amphetamines. Amphetamines have far greater impact on motor activity with a shorter half life than modafinil [1]. This may explain why modafinil has fewer side effects than other traditional stimulants with very low potential for tolerance or dependence. It does have some unwanted side-effects including hypertension (dose initiation but no evidence for sustained increase in blood pressure compared to placebo), headache for up to 20% and increased anxiety with palpitations for some. Furthermore, the long 12-15 hour half-life undoubtedly increases the likelihood of insomnia [2]. Modafinil can decrease efficacy of the combined oral contraceptive pill and increase the risk of congenital malformation when used during pregnancy. These are notable interactions considering the potential overlap in users of modafinil and contraceptives [3]. The prescribed dose ranges from 100mg to 400mg a day in one or two divided doses.

Who is using it?

Almost a million prescriptions are currently issued in the United States per year and approximately 80,000 within the UK despite licensed use only for narcolepsy [4]. These patients are very likely to be the tip of the iceberg. In the UK it is legal to buy but not to sell modafinil. An abundance of websites can be found selling modafinil from around 60 pence a tablet with 5-star reviews accompanied with a word of warning about avoiding delivery direct to student halls of residence! A 2017 Global Drug Survey reported that 6.6% of participants used prescription pharmacological cognitive enhancing drugs (PCE) for non-medical purposes [5]. The most typical users of modafinil are employed, male, university graduates [6]. The unregulated nature of use means that it is not clear whether people are using it for an 'all-nighter' before an assignment is due or more frequently in the day to constantly enhance performance.

What is the evidence base for cognitive enhancement?

There have now been many randomised controlled trials studying cognitive measures in those using modafinil versus placebo, both in healthy non-sleep deprived individuals and those who were sleep deprived. Typically, this is a single dose of either 100mg-400mg. A wide variety of cognitive batteries have been used with variable results.

A meta-analysis and systematic review in 2019 looked at 19 trials and found a significant but small effect (hedges' g 0.10) across numerous cognitive domains. There was no difference across different cognitive domains and no difference between 100mg and 200mg [7]. Modafinil has been compared to the world's best loved stimulant caffeine and also to methylphenidate and dexamphetamine. Both modafinil and caffeine increase extracellular catecholamine concentrations to

promote wakefulness. Caffeine is an adenosine blocker, indirectly increasing catecholamine levels but with more widespread physiological effects alongside more variable peak plasma and elimination levels. A recent meta-analysis comparing modafinil, methylphenidate and dexamphetamine versus placebo in healthy, non-sleep deprived individuals looked at 47 studies [8]. There was no benefit from dexamphetamine, only a small benefit in sustained attention for methylphenidate and improved attention and some sub domains of memory for modafinil. Variability to both study design and results was highlighted by the authors.

There is more convincing evidence that modafinil improves attention and executive function in sleep deprived subjects [9]. Sleep deprivation causes deficits in alertness and attention but also executive function. Executive functions include the cognitive abilities necessary to plan and coordinate actions, to monitor and adjust behaviour as necessary, and to focus attention and suppress distractions. Total sleep deprivation reduces many of these functions, including the ability to think divergently and to switch flexibly among semantic categories. Results demonstrating benefit of modafinil have been replicated over several simple task studies, particularly those that test sustained attention and reaction speed, for example the psychomotor vigilance test (PVT). The PVT is a simple reaction speed test to visual stimuli that is one measure of alertness. A delayed reaction is seen with sleep deficit.

Some have pointed out that those using modafinil as a study drug are unlikely to be performing simplistic tasks. For example, synthesising information and using it to write an essay may be completed quicker and to a higher standard with modafinil, but this is difficult to reproduce in research.

Executive function and processing speed has a small but significant improvement after taking modafinil. There is less evidence for different domains of memory including problem solving tasks and creativity, which in some studies was worse [10]. If the intended outcome of taking modafinil is an enhanced processing speed to aid completion of an occasional project started too close to a deadline, it may have a use. However, modafinil may offer less benefit when studying for prolonged periods and there is simply far less data that has tested this.

Cognition of course includes executive function but also encoding, sorting, retrieving and then linking up initially fragile short-term memories. Creative thinking is not clearly enhanced by psychostimulants [10]. Long-term side effects accompanying frequent usage may include hypertension but possibly more importantly either cause or allow chronic sleep deprivation. There is increasing interest in poor sleep as an independent risk factor for worse cardiometabolic health and possibly as a dementia risk factor [2]. There is a lack of data regarding the long-term effects of modafinil, particularly in populations without prescription. Most research also concentrates on sleep-disordered subjects, which is not representative of all consumers.

It is also impossible to be certain that drugs ordered online from unregulated sites are authentic. The MHRA estimate that 10% of people in the UK last year purchased 'fake' medical products online [11].

The potential role of modafinil in neurodegenerative disease

Cognitive enhancing drugs such as modafinil may provide therapeutic compensation for the neuronal degeneration seen in an ageing brain. Common symptoms of neurodegenerative disease include excessive daytime somnolence, cognitive decline, and decreased alertness. Modafinil has been used for these symptoms due to its alerting and potentially neuroprotective qualities. Some feel it may have a role in prevention of neurological decline and maintenance of optimal functioning, particularly in the elderly.

The total cost of dementia care in the UK is estimated to be $26 billion with an ongoing search for novel therapies. Catecholamine deficiency is characteristic of many dementias and modafinil triggers an elevation in catecholamine levels - hence its role in controlling symptoms of dementia has been postulated.

Trials in patients with Dementia with Lewy bodies (DLB) showed improvements in subjective attention-span and alertness with modafinil compared to placebo. A preliminary study of 9 patients with DLB or Parkinson's Disease Dementia (PDD) showed mild to moderate improvement in performance in cognitive assessment following modafinil consumption. Investigations included the psychomotor vigilance test, assessment of reaction and reflexive attention tasks [12]. Although there is some evidence for symptomatic improvement, clinicians report limited changes seen in practice at this stage and most trials are preclinical [13]. Some case reports also describe exacerbation of psychotic symptoms due to dopaminergic effects of modafinil [14]. The extent of drug interaction in dementia patients remains unclear.

Modafinil has demonstrated neuroprotective effect in animal models of Parkinson's disease. MPTP induces degeneration of the substantia nigra and is used to model Parkinsonian lesions. MPTP was injected into a primate model and half were also given a dose of modafinil. Animals treated with modafinil had reduced neurotoxin induced neuronal loss and reduced Parkinsonian symptoms, suggesting that modafinil may have roles other than as a psychostimulant [15].

Is there a better smart drug available?

Sleep has been proven to play a key role in memory consolidation and encoding new memories, [16,17]. Anatomical and chemical changes occur during sleep that lead to synaptic downscaling to strengthen new memory formation as the brain is taken off-line. In zebrafish, modafinil increased the number of wake bouts occurring throughout the night, meaning less time spent in a plastic memory-promoting state. Modafinil therefore may aid longer, but not necessarily smarter studying. Following sufficient hours of sleep, the drive to take modafinil may also be reduced. There is a trade-off between the benefits of occasional modafinil use and the detrimental effects of persistent sleep deprivation. Would it be smarter for students to simply utilise the body's free smart drug and power nap before they start writing?

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