

Cognitive enhancement in the pharmacy

As bodies like the British Medical Association and the UK Government's Office for Science grapple with how to respond to the increasing demand for cognitive enhancers, what should pharmacists be considering? **Danielle Turner** reports

Be it having cup of coffee to kick-start the morning or completing the fiendish sudoku in *The Times*, the chances are that most people will have experimented with trying to improve their mental performance. Certainly, pharmacists will be familiar with the plethora of nutraceuticals and dietary supplements claiming to improve cognition.

Effective cognitive performance requires the co-ordinated involvement of numerous neuronal pathways and neurotransmitter systems — all readily manipulable with drugs. Cognitive enhancement refers to the use of pharmacological agents to improve mental functioning. Functions such as memory, attention, problem-solving and mental flexibility are key nootropic targets. These capabilities are crucial for the successful execution of many everyday procedures, such as prioritising tasks and using important information.

Most cognitive enhancers have been developed by the pharmaceutical industry to target conditions, such as Alzheimer's disease, Korsakoff's syndrome and schizophrenia, with the aim of ameliorating the debilitating effects of impaired cognition. Brain disorders cause a substantial human and economic burden to communities, healthcare systems, caregivers and wider society. Critically, there are many disorders, such as schizophrenia, where the cognitive difficulties are now known to be the core limiting factor to full rehabilitation (eg, returning to work) and acceptable quality of life, even after the more florid clinical symptoms have remitted.

Frequently the benefits of cognitive enhancers in healthy individuals are discovered as a result of psychological studies. For example, in the laboratory where I work research aimed at identifying cognitive enhancers for therapeutic use, led to the discovery that a single dose of modafinil (100–200mg; licensed for the treatment of narcolepsy) can induce reliable improvements in short-term memory and planning abilities in healthy adult male volunteers.¹ Studies such as these are useful for profiling the psychological effects of a drug, free from any confounding disease that might be present in a patient population. They also enable a greater understanding of the neurochemical mechanisms of cognitive abilities, such as memory and attention. Although this work in healthy volunteers is vital in furthering our understanding of underlying brain mechanisms, it is also the most contentious owing to the ethical issues that arise when drugs that enhance functions of the healthy brain are found.²



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How cognition is measured

When considering how to respond to requests for cognitive enhancers, it is helpful to be aware of the methods used to evaluate cognition in the laboratory. The use of intelligence quotient tests is generally considered too non-specific to tease out the psychological effects of drugs and much of the research that relies on subjective assessments of cognition (such as asking participants to rate whether they feel that their performance has improved) has been superseded by more objective measures.

The gold standard currently is to use batteries of tests designed to measure individual aspects of cognition. These are intended to facilitate comparative assessment of cognitive

performance across different groups of patients and volunteers, as well as to assess the processes underlying particular cognitive functions, such as visual memory, working memory, planning, or attention.

The tests can be exquisitely sensitive to the effects of drugs and detect changes that the volunteer is unaware of. Nevertheless, despite the advances made in evaluating cognition in the laboratory, relatively little progress has been made in terms of being able to measure the real world impact of taking cognitive enhancers. For example, it is relatively straightforward to determine whether a particular drug influences a laboratory test of planning (eg, where subjects are asked to perform a series of moves in a game designed to see how

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well they plan ahead). It is less easy to examine whether it has a significant bearing on a person's ability to plan his or her weekly shopping effectively or to project manage a successful enterprise at work.

The evidence

Many purported methods are available to people interested in enhancing their cognition. They range from environmental enrichment (ie, making the environment more interesting) to psychological strategies, nutrients, drugs and more recent inventions, such as electromagnetic brain stimulation.

In terms of drugs, caffeine holds the title as the world's most popular cognitive enhancer. Despite this, the evidence for its cognitive enhancing effects is controversial, with some data suggesting it only enhances cognition in caffeine-dependent individuals during withdrawal.³⁻⁵ It is also known that high doses can cause side effects in vulnerable people and withdrawal effects include headaches and tiredness. Nevertheless, it is widely available and often consumed in a pharmaceutical form (eg, Pro-Plus tablets).

Dietary supplements and herbal products are also widely used to enhance cognition and are available in many different combinations throughout the UK. But again, there is a relative paucity of evidence suggesting efficacy. Cochrane reviews of vitamins E, B₆ and B₁₂, folate, thiamine, lecithin, dehydroepiandrosterone (DHEA), alpha-lipoic acid, acetyl-L-carnitine and *Ginkgo biloba* found no strong evidence to recommend their use as cognitive enhancers, although some small scale studies suggested that future research may be warranted.⁶

In 2006, the Food Standards Agency published a review of controlled trials into the effects of diet (including omega-3 long-chain polyunsaturated fatty acids) on learning and educational performance in school children.⁷ They concluded that good nutrition may have a positive impact on cognitive ability, but that a lack of large-scale trials, together with inconsistencies in the quality of available research, means that further research is needed before decisions can be made as to the wide-scale use of supplements such as omega-3s.

A number of pharmaceutical products that improve concentration, memory and other aspects of cognitive performance are available. The cholinesterase inhibitors, the monoamine modulators and modafinil show the most promise, albeit with still relatively little psychological research in healthy individuals. Two cholinergic drugs, donepezil and nicotine, have both been shown to have enhancing effects in healthy volunteers, with the largest effects in tests of sustained visual attention.^{8,9} Some evidence also exists for the cognitive-enhancing effects of nicotine in healthy old people¹⁰ and smokers.¹¹

It is well recognised that the monoamine neurotransmitters dopamine, serotonin and noradrenaline all have substantial and complex effects on cognition. Of the drugs that manipulate these systems, methylphenidate is,

perhaps, the most well-known. When tasks are novel, a single dose of methylphenidate can improve spatial working memory and planning performance in healthy young volunteers,¹² but not in healthy elderly participants performing the same tasks.¹³ Similarly, the amphetamines, including dexamfetamine, have been shown to enhance several measures of cognition in healthy volunteers, including verbal memory and response speed.^{14,15}

Cerebral adrenoreceptors have been implicated in arousal and attention, and are known to impact on sensory processes such as emotion and working memory (where information is kept at the front of the mind while performing a task). The alpha₂-receptor agonist clonidine has been shown to improve working memory in several small studies,^{16,17} although no effect of another α_2 -receptor agonist, guanfacine (which has been used in hypertension and attention deficit hyperactivity disorder), has been observed.¹⁸

Modafinil is a novel wakefulness-promoting agent that does not yet have a well-defined biochemical mechanism of action. Nevertheless, recent evidence suggests that modafinil might be acting via the newly discovered neuropeptides orexin-A and -B to promote histamine release. Unlike amphetamines and methylphenidate, the psychomotor effects of modafinil do not appear to be mediated via a catecholamine mechanism. In healthy adults, modafinil significantly improves spatial planning, visual pattern recognition memory, working memory, and response inhibition.¹ It is interesting that modafinil appears to cause slowing on several tasks, suggesting that it may be exerting its effects through reducing impulsivity.

There are a considerable number of cognitive enhancers in development, predominantly for use in clinical populations. Of these, the main class worth mentioning is the novel memory-modulating group of drugs called ampakines.

Ampakines are thought to act as allosteric modulators of AMPA-type glutamate receptors, facilitating hippocampal long-term potentiation, which is associated with memory storage and consolidation. One example, farampator, has been shown to improve short-term memory in healthy elderly volunteers, although it also impaired episodic memory in the same group,¹⁹ and another ampakine, CX717, has been shown to have some enhancing properties in small studies in healthy volunteers,²⁰ although the effects are not unequivocal.²¹

Who is using cognitive enhancers?

We live in a society with increasing expectations of productivity and a work hard, play hard ethos, and this reflected in the prevalence of the use of cognitive enhancers in the community. Impaired cognition and alertness affects millions of people, often as a result of ageing, jet lag, shift work and stress.

The cognitive performance and alertness deficits that result from monotonous activities or sleep loss are recognised as a considerable

threat to productivity and safety in a variety of settings, including industry and the military. It is also well known that musicians and actors avail themselves of enhancing agents before performances. However, they are not the only people looking to enhance their mental abilities. The large number of elderly people experiencing age-related cognitive decline in the absence of dementia or depression, is another potential market, while students and young professionals have become some of the most recognised users of cognitive enhancers.

Researchers at the University of Michigan showed that just over 8 per cent of university undergraduates reported having illegally used prescription stimulants in 2005.²² These findings were backed by reports from the National Institute on Drug Abuse in the US that, in 2004, 2.5 per cent of 13- and 14-year-old children abused methylphenidate, as did 3.4 per cent of 15- to 16-year-olds and 5.1 per cent of 17- to 18-year-olds.²³ The most common motive given by students for the use of such stimulants was to help with concentration and increase alertness, not a desire to get high.

In addition, a recent informal poll by *Nature* revealed that one in five respondents had used drugs for non-medical reasons to stimulate their focus, concentration or memory.²⁴ Of the drugs used, the most common was methylphenidate (62 per cent of users reported taking it), followed by modafinil (44 per cent) and beta-blockers (15 per cent). Other drugs mentioned included dexamfetamine, piracetam, and various alternative products, such as ginkgo and omega-3 fatty acids.

A cognitively-enhanced future?

Aside from the ethical issues relating to the increasing use of cognitive enhancers (see article on p694), there are a number of practical points worth considering. In particular, the effects of smart drugs are not homogeneous, nor entirely predictable. For example, in healthy young university undergraduates the cognitive-enhancing effects of methylphenidate are limited to novel situations, with detrimental effects being seen when the psychological tasks are familiar.¹²

It is also known that improvements in performance may depend on the individual's baseline level of performance. In the laboratory at Cambridge, we found that volunteers with the poorest memory capacity showed the greatest improvement on methylphenidate.²⁵ In contrast, other drugs demonstrate a classic inverted-U shaped function of enhancement, causing impairments at low and high doses and enhancements at intermediate doses.

Cognitive-enhancing drugs also do not improve all aspects of cognition equally. For example, a single dose of modafinil improves short-term memory and planning abilities, but has no effect on the ability to sustain attention in healthy individuals.³ Methylphenidate, however, primarily affects attention but not short-term memory.¹⁴



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A cognitively enhanced future?

People might, therefore, feel the need to experiment with several different cognitive enhancers to target all the functions they want to improve, with a risk of drug interactions and increased side effects.

Perhaps of all the concerns for the future the most important is that we do not know yet know the long-term effects of regular use

of cognitive enhancers. Until we do, it may be wise to err on the side of caution. It would be devastating to discover, for example, that a youth of regular enhancement was followed by an old age of subtle but irreversible brain damage.

Increasingly effective and safer drugs are likely to be developed but, for the moment,

the agents available to us are neither wonder drugs nor entirely benign. As we understand more about the neural basis of the human brain, it is imperative that we carefully consider how to react to the increasing physical control we can exert over our minds.

If pharmacists can be involved in these discussions, so much the better.

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