

COMMENTARY

Professor's little helper

The use of cognitive-enhancing drugs by both ill and healthy individuals raises ethical questions that should not be ignored, argue **Barbara Sahakian** and **Sharon Morein-Zamir**.

Today there are several drugs on the market that improve memory, concentration, planning and reduce impulsive behaviour and risky decision-making, and many more are being developed. Doctors already prescribe these drugs to treat cognitive disabilities and improve quality of life for patients with neuropsychiatric disorders and brain injury. The prescription use of such drugs is being extended to other conditions, including shift-workers. Meanwhile, off-label and non-prescription use by the general public is becoming increasingly commonplace.

Although the appeal of pharmaceutical cognitive enhancers — to help one study longer, work more effectively or better manage everyday stresses — is understandable, potential users, both healthy and diseased, must consider the pros and cons of their choices. To enable this, scientists, doctors and policy-makers should provide easy access to information about the advantages and dangers of using cognitive-enhancing drugs and set out clear guidelines for their future use. To trigger broader discussion of these issues we offer the following questions, to which readers can respond in an online forum. Now, on to the questions.

Should adults with severe memory and concentration problems from neuropsychiatric disorders be given cognitive-enhancing drugs?

We believe the answer is a resounding yes. A large debilitating aspect of many neuropsychiatric disorders is cognitive impairment. Thus, cognitive-enhancing drugs are a useful therapy option for several disorders, including Alzheimer's disease and Attention Deficit Hyperactivity Disorder (ADHD).

Alzheimer's disease is a neurodegenerative disease of the ageing mind characterized by a decline in cognitive and behavioural functioning, and in particular learning and memory. There are, at present, no treatments for Alzheimer's disease that can stop or reverse the decline in brain function, but cholinesterase inhibitors are being used to ameliorate the impaired neural transmission in the cholinergic system. Such drugs aim to increase the levels of acetylcholine, a neurotransmitter important for maintaining attention and in forming new memories, and may have

"The chief concern cautioning against the use of medications is adverse side effects."

additional neuro-protective effects.

Countries with ageing populations are seeing a surge in the number of people with Alzheimer's. The personal and social costs are staggering and in the United Kingdom, economic costs associated with dementias¹ are estimated to rise to £10.9 billion (US\$22 billion) by 2031. According to a report commissioned by the Alzheimer's Research Trust in Cambridge, UK, treatment that would reduce severe cognitive impairment in older people by just 1% a year has been estimated to cancel out all predicted increases in long-term care costs due to the ageing population¹.

For all medications, the chief concern cautioning against their use is adverse side effects that affect the individual's health and well being. These may range from mild, temporary physical symptoms, such as dry mouth and headaches, to more severe side effects such as vomiting and joint pain and even cardiac arrhythmia or psychosis. All medications also carry contraindications for certain conditions, such as high blood pressure, when one should not take the

drug. For patients with neuropsychiatric disorders, the benefits of the drugs must be weighed against the potential short-term and long-term side effects, and these factors should be discussed with the individual's doctor to ascertain the level of acceptable risk in each case.

If drugs can be shown to have mild side effects, should they be prescribed more widely for other psychiatric disorders?

We believe that cognitive-enhancing drugs with minimal side effects would also benefit many of the patients with schizophrenia, a condition for which they are not yet routinely prescribed. Currently, the disorder affects about 24 million people worldwide.

As with Alzheimer's, the personal and social costs are immense, with economic costs in the United States estimated in the tens of billions of dollars². It is common knowledge that people with schizophrenia typically have hallucinations and delusions, yet it is the long-term cognitive impairments that often impede everyday function and quality of life for many patients. Even small improvements in cognitive functions could help patients with schizophrenia



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Morning pick-me-up: will drugs that help you stay alert become as widely acceptable as coffee?

make the transition to independent living³.

Thus, cognitive-enhancing drugs are increasingly being considered as possible additions to antipsychotic medication, and long-term clinical trials are underway with drugs such as modafinil, which promotes wakefulness⁴. Although the mechanisms of modafinil are not fully understood, it has been found to have direct and indirect effects on various neurotransmitter systems. Behaviourally, an acute dose of modafinil has been found to increase alertness, memory and planning in healthy young adults and cognitive flexibility in patients with chronic schizophrenia⁵.

Due to the stated economic and personal costs, the pharmaceutical industry is targeting drugs that would improve impaired cognition in specific neuropsychiatric disorders. Often when a drug is approved for one disorder, its efficacy in improving cognition in additional disorders is investigated and thus its use can be extended to multiple patient groups. In our view, the original justification for drug treatment improving quality of life still holds in these other disorders.

Do the same arguments apply for young children and adolescents with neuropsychiatric disorders, such as those with ADHD?

At present, children diagnosed with ADHD are routinely prescribed long-term medications including atomoxetine and stimulants, such as methylphenidate (Ritalin) and amphetamine. Both methylphenidate and atomoxetine increase the levels of the neurotransmitter noradrenaline. Generally, the therapeutic effects of these drugs include reductions in inattention, hyperactivity and impulsivity, although their widespread and long-term use in younger children has been controversial.

ADHD is a heritable and disabling condition characterized by core cognitive and behavioural symptoms of impulsivity, hyperactivity and/or inattention. ADHD affects 4–10% of children worldwide, and is the most prevalent neuropsychiatric disorder of childhood. ADHD is associated with increased levels of drop-outs from education, job dismissal, criminal activities, substance abuse, other mental illness and accidents⁶. Long-term drug treatment seems to be beneficial in many cases.

However, the side effects of chronic drug use may only become noticeable in the longer term, for example, with apparent reductions in normal growth rates in children with ADHD who are taking stimulant medication⁷. In fact, for many drugs there is limited information on long-term effects and in many areas the findings are inconsistent⁷. Consequently, in all the cases outlined above, we believe the medical consensus would be that medication choice, dose and timing, therapeutic effects and safety should be monitored for individual patients by a healthcare



Quick fix: but what are the long-term side effects?

professional. This is particularly important because of potential drug interactions, and so we do not advocate self-medication.

Would you boost your own brain power?

Cognitive-enhancing drugs are increasingly being used in non-medical situations such as shift work and by active military personnel. This is where the debate about their use begins in earnest. How should the use of cognitive-enhancing drugs be regulated in healthy people? Should their use always be monitored by healthcare professionals?

If offered by a friend or colleague, would you, the reader, take a pill that would help you to better focus, plan or remember? Under what conditions would you feel comfortable taking a pill, and under what conditions would you decline?

The answers to such questions hinge on many factors, including the exact drug being discussed, its short-term and long-term benefits and risks, and the purpose for which it is used. There are instances in which most people would agree that the use of cognitive-enhancing drugs should be prevented or at least regulated and monitored, such as by healthy



Is it cheating to use cognitive-enhancing drugs?

children or in competitive settings (including entrance exams to university).

There are also situations in which many would agree that the use of drugs to improve concentration or planning may be tolerated,

if not encouraged, such as by air-traffic controllers, surgeons and nurses who work long shifts. One can even imagine situations where such enhancing-drug-taking would be recommended, such as for airport-security screeners, or by soldiers in active combat. But there are no straightforward answers and any fruitful debate must address each situation in turn.

How would you react if you knew your colleagues — or your students — were taking cognitive enhancers?

In academia, we know that a number of our scientific colleagues in the United States and the United Kingdom already use modafinil to counteract the effects of jetlag, to enhance productivity or mental energy, or to deal with demanding and important intellectual challenges (see graphic opposite). Modafinil and other drugs are available online, but their non-prescription and long-term use has not been monitored in healthy individuals.

For many, it seems that the immediate and tangible benefits of taking these drugs are more persuasive than concerns about legal status and adverse effects. There are clear trends suggesting that the use of stimulants such as methylphenidate on college campuses is on the rise, and is becoming more commonplace in ever younger students⁸. Universities may have to decide whether to ban drug use altogether, or to tolerate it in some situations (whether to enable all-night study sessions or to boost alertness during lectures).

The debate over cognitive-enhancing drugs must also consider the expected magnitude of the benefits and weigh them against the risks and side effects of each drug. Most readers would not consider that having a double shot of espresso or a soft drink containing caffeine would confer an unfair advantage at work. The use of caffeine to enhance concentration is commonplace, despite having side effects in at least some individuals⁹. Often overlooked in media reports on cognitive enhancers is the fact that many of the effects in healthy individuals are transient and small-to-moderate in size. Just as one would hardly propose that a strong cup of coffee could be the secret of academic achievement or faster career advancement, the use of such drugs does not necessarily entail cheating.

Cognitive enhancers with small or no side effects but with moderate enhancing effects that alleviate forgetfulness or enable one to focus better on the task at hand during a tiring day at work would be unlikely to meet much objection. And does it matter if it is delivered as a pill or a drink? Would you, the reader, welcome a cognitive enhancer delivered in a beverage that is readily obtainable and affordable, and has a moderate yet noticeable effect



on your concentration and alertness?

How should society react?

When imagining the possible influences of efficient cognitive enhancers on society as a whole, there can be many positive effects. Such drugs may enable individuals to perform better and enjoy more achievements and success. However, cognitive enhancers may have a darker side. Fears have been raised of an overworked 24/7 society pushed to the limits of human endurance, or of direct and indirect coercion into taking such drugs. If other children at school or colleagues at work are taking cognitive-enhancing drugs, will you feel pressure to give them to your children or take them yourself? What if a perfectly safe and reliable cognitive enhancer existed, could society deny it to healthy individuals who may benefit from it?

At present, relatively safe cognitive enhancers with clear effects in healthy individuals are available. Today, in healthy individuals, most cognitive-enhancing drugs yield only moderate effects, and enhance only a subset of cognitive abilities. In the case of some drugs, such as methylphenidate, there are improvement in some domains such as attention, but there may be impairments in others, such as previously learned spatial tasks¹⁰. Consequently, we believe that current debates must focus on the risks and harms at the level of the individual.

In future, drug treatment may be better tailored to individuals through a better understanding of how genes influence the body's response to drugs. Because domain-specific effects vary between individuals depending on their genetic make-up, drug efficacy may ultimately be enhanced and side effects reduced. Many believe that with increasingly sophisticated and targeted treatments, truly smart drugs with moderate-to-large effects on cognition, will become feasible in the future. With the advent of such cognitive enhancers, the discussion must turn to

the effects on society as a whole.

There have been debates over the potential of such drugs to decrease or increase disparity in society. Even today many people benefit from their financial status to obtain a better education and nutrition that in turn can enhance brain power. Thus, the potential for cognitive enhancers to increase disparity in society would seem unavoidable.

We believe it would be difficult to stop the spread in use of cognitive enhancers given a global market in pharmaceuticals with increasingly easy online access. The drive for self-enhancement of cognition is likely to be as strong if not stronger than in the realms of 'enhancement' of beauty and sexual function.

Some agreement and regulation on supervised use requires urgent attention, particularly because of concerns in regards to healthy children and adolescents and the long-term consequences of stimulant use on the developing brain. For example, if young stimulant users were informed of the potential effects on their growth, would they continue with long-term use?

Rather than individuals purchasing substances over the Internet, we believe it would be better to ensure supervised access to safe and effective cognitive-enhancing drugs, particularly given potentially dangerous drug-drug interactions. Such regulation must be evidence-based and a product of active dialogue between scientists, doctors, ethicists, policy-makers and, importantly, the general public. This may necessitate a new form of regulation because the remit of the existing health and drug agencies are for the regulation of medicines for treatment, not for enhancement.

Regulations may also be proposed for particular situations in which the use of cognitive-enhancing drugs would impart an unfair advantage, such as in competitive situations, similar to existing regulations for sporting events.

Ultimately, our drug use is a reflection of our

society and should never be considered without the broader context of why healthy people choose to use the drugs in the first place. There are other options available for coping with everyday stresses, such as improving the work-life balance or relaxation. Sleep, psychological and behavioural problems can be addressed through alternative methods including psychological treatments, and enhanced cognition can be obtained through education and other means.

Similarly, drug treatment for patients with neuropsychiatric disorders should always be considered as part of a wider treatment programme (including psychological, rehabilitative and social components). Nevertheless, we believe that as we move into the twenty-first century, a key challenge for the pharmaceutical industry will be the development of more effective cognitive-enhancing drugs, so desperately needed by those who have impairments in cognitive and behavioural functioning due to neuropsychiatric disorders or brain injury. ■
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Competing financial interest statement

Barbara Sahakian consults for several pharmaceutical companies and for Cambridge Cognition. She also has shares in CeNeS.

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