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BETTER BRAINS

As part of the Foresight Brain Science, Addiction and Drugs project a state of science review was carried out into current knowledge in the area of cognitive enhancers. These are factors that improve functions such as memory, learning and attention. The review concluded there would be significant improvements in our understanding of this area in the next twenty years, and that these would lead to an increase in the development of cognitive enhancers. It raised the possibility of otherwise healthy individuals using enhancers to boost their cognitive abilities. This POSTnote reviews existing methods of cognitive enhancement along with likely future developments, and considers the regulatory and ethical questions that they pose.

Background

Interest in the area of cognitive enhancement stems from an expected increase in our knowledge of the mechanisms involved in skills such as learning, memory and attention, together with a deeper understanding of the relationship between these functions and brain chemistry. The Foresight review indicated that in the first instance these enhancers might involve nutritional and pharmaceutical agents[1]. Some dietary factors associated with cognitive enhancement are summarised in Box 1. These are generally considered less controversial than the use of novel drugs; for instance stimulants such as caffeine are widely accepted and used as a means of enhancing cognitive abilities. Many drugs have already been developed to treat specific cognitive impairment disorders and these could be used to treat less severely impaired, or even healthy individuals. This would raise ethical and regulatory issues which are discussed later. The area of pharmaceutical cognitive enhancement has already been the subject of a number of academic reviews[2]. The Foresight report also considered the potential for cognitive enhancers to be developed using mechanisms as diverse as computer-brain interfacing and genetic manipulation, but such approaches are longer-term and beyond the scope of this briefing.

Box 1 The role of nutrition in cognitive abilities

There is a general lack of large scale, robust trials investigating the role of diet in cognition. Furthermore, most current research is related to deficiencies of nutrients in particular disorders rather than enhancing cognitive function. However there is growing evidence from small scale studies that there may be a link between cognitive abilities and particular nutritional factors:

- Omega-3 essential fatty acids have specific roles in the brain and deficiencies have been linked to a risk of developing a variety of cognitive impairment disorders;
- Eating wholegrain foods that are slowly broken down and release a sustained supply of glucose into the bloodstream is thought to maintain optimum brain function;
- There is some evidence to suggest that dietary supplements of B vitamins, folic acid or foods rich in antioxidants such as blueberries improve cognitive function, and several larger trials are underway to investigate this.

Current pharmacological cognitive enhancers

A range of cognitive enhancing drugs are available which have been developed for therapeutic needs. The availability of these treatments has led to academic research trials which demonstrate cognitive improvements in healthy people. It is generally agreed that not enough is known about the long term effects of these drugs to advocate their use in healthy individuals at the present time.

Memory

Drugs to improve memory generally work by altering the balance of particular chemicals (neurotransmitters) in the brain that are involved in the initial learning of a memory or its subsequent reinforcement. The drug donepezil, which inhibits the cholinesterase neurotransmitter, is a common treatment for Alzheimer's Disease but has also been shown to have an effect on otherwise healthy individuals. Studies carried out with healthy middle-aged airline pilots showed that donepezil enhanced their performance after flight simulator training[3].

Executive function
Executive function refers to a broad range of abilities that allow us to carry out tasks and to select and use the appropriate information from a range of competing stimuli. This is a difficulty for those diagnosed with Attention-deficit Hyperactivity Disorder (ADHD) and is often treated by stimulants such as methylphenidate[4] which alter the balance of neurotransmitters in the brain (see Box 2). Studies on healthy volunteers show improved accuracy in completing a problem-solving task after receiving methylphenidate[5].

Wakefulness
The most commonly used drug in this area is another stimulant called Modafinil. This is licensed for the treatment of sleep disorders such as narcolepsy but also for the treatment of (healthy) workers who find their shift patterns difficult. Experiments with healthy volunteers have shown that Modafinil can improve abilities in a range of cognitive tests[6] and allow subjects to function better after periods of sleep deprivation. It is thought to have potential as a cognitive enhancer as it appears to avoid some of the side-effects and dependence usually associated with stimulant use.

Box 2. Attention-deficit hyperactivity disorder

Disease and prevalence
ADHD is characterised by 'core' signs of inattention, hyperactivity and impulsiveness, although all three need not be present for a diagnosis to be made. Its biological basis is not fully understood. Estimates of prevalence vary within and between countries but it is estimated to effect between 3–9% of children and adolescents in the UK and about 2-4% of adults worldwide. In some US schools prevalence is thought to be as high as 17%. One of the reasons for this disparity is that different diagnostic criteria are used. Not all those diagnosed with ADHD should require drug treatment. It is thought that only 1–2% of young people in the UK have the severest form of the disorder.

Treatment
The National Institute for Health and Clinical Excellence (NICE) is currently reviewing guidelines for treating ADHD. At present NICE recommends use of one of three drugs. Methylphenidate and dextroamphetamine directly stimulate the central nervous system (CNS) to change the balance of neurotransmitters in the brain. The newer drug atomoxetine has a similar effect but works by blocking the reuptake and breakdown of a neurotransmitter[7].

Use of CNS stimulants, particularly in children, has been controversial. Prescription rates have been steadily rising from 220,000 prescriptions of CNS stimulants in England in 1998, to 418,300 in 2004. There is also increasing concern that some prescriptions are being abused (methylphenidate is classified as a Class B controlled substance). However, there is conflicting information as to whether the disorder is under-diagnosed or whether more people receive drugs than necessary[8]. It is generally agreed that more research is needed to determine the long term effects of taking these drugs over an extended period of time.

Expected developments in cognitive enhancers
Pharmaceutical companies are currently exploiting increased knowledge of how the brain works to target novel drugs for a range of cognitive impairment disorders, such as Alzheimer's Disease and ADHD. Currently no new drugs are being developed specifically for cognitive enhancement of healthy individuals but evidence for this may arise as a consequence of therapeutic developments. Many cognitive impairments are spectrum disorders, in that they exist on a scale from very mild to severe. While drugs are usually developed to treat patients at the severe end of the spectrum, once they are on the market, there may be a tendency to seek extensions to the licence which allow them to be prescribed to people with less severe disorders. Pressure for this to occur can come both from drug manufacturers and consumers. Companies would like their drugs to be available to a wider market and potential patients may also want to avoid 'missing out' on a perceived benefit. This could result in a shift in the boundary between what is considered normal and what is considered a medical condition. Some suggest that this can already be observed in the diagnosis of new disorders such as shift work sleep disorder and the rise in diagnoses of ADHD (see Box 2).

In the near future, the focus is likely to be on cognitive domains such as memory, alertness and planning, which involve specific neurochemicals and/or where there is already a large body of knowledge. Longer-term research may focus on pharmacological targeting of wider areas such as deleting unwanted memories and improving group bonding and cooperation. Looking even further ahead, "electromagnetic" interventions, such as brain-computer interfaces and direct brain stimulation, could be developed that may have greater potential for affecting the higher cognitive abilities. Similar techniques have already been shown to improve complex abilities like creativity and "savant-like" skills. These methods may be more routinely used by healthy individuals, especially if drugs continue to be developed solely to treat disease.

Issues

As a follow up to the state of science reviews in the Foresight *Drugs Futures 2025?* report, the Academy of Medical Sciences is conducting a consultation with experts and members of the public. This aims to canvass views on the societal, health, safety and environmental issues raised by advances in cognitive enhancers, in addition to drugs to treat addiction and for mental health. The final report is due to be published by the end of the year. Regulatory and ethical issues raised by the use of cognitive enhancers are discussed below.

Illegal drugs
Several medicines that are used to treat cognitive dysfunction, such as methylphenidate (see Box 2), have the potential to be abused and are therefore listed as controlled substances under the Misuse of Drugs Act 1971. There is concern about children taking drugs into school that may be traded for their recreational value. As a result, slow-release formulas, such as Concerta, have been developed to allow children to take one morning dose under parental supervision.

Safety

The lack of clinical benefit inherent in cognitive enhancement of healthy individuals raises difficulties in licensing cognition enhancers as drugs under the current framework (see Box 3). Even where there is the potential for more substantial clinical benefit, assessing the safety of cognition enhancers is likely to be problematical. The precise mechanisms involved in currently available cognitive drugs are poorly understood and it may be difficult to examine different cognitive functions in isolation. There may also be difficulty in determining the long term risks of using these drugs and the way they effect individuals in real life situations. However, some researchers suggest that it may be possible to reach a consensus among regulatory bodies to control the safety and allowed risks in cognitive enhancement in a way similar to other non-therapeutic interventions such as cosmetic surgery or Botox™. Others argue that it may be impossible to predict the many subtle effects of cognitive enhancement, particularly as these may differ from one person to the next, and that they should not thus be advocated as a lifestyle choice.

Box 3 Current regulation

Medicines

The Medicines and Healthcare Products Regulatory Agency (MHRA) regulates medicinal products in the UK in line with EC regulations and the Medicines Act[9]. A medicinal product is generally defined as any substance presented as having properties for treating, preventing or curing disease. In order to be granted a licence the manufacturing company must provide evidence that the drug is efficacious, of good quality and safe based on robust clinical trials, and that the intended benefit outweighs any documented risks.

Foods and nutritional supplements

The Food Standards Agency (FSA) is responsible for regulating the safety of food and nutritional supplements on sale in the UK. In July 2007, Regulation 1924/2006 of the European Parliament and of the Council will apply to control nutrition and health claims that can be made on foods. It will define positive lists of authorised claims and the criteria a product must meet to use them. Companies can currently submit eligible health claims to the FSA, which will be considered for the authorised list following assessment of the supporting scientific evidence by the European Food Safety Authority. It is thought that this legislation will allow people to become more informed about the foods they choose to eat and provide a greater level of consumer protection. However, companies will continue to be prohibited from making any claims explicitly regarding the treatment, prevention or cure of a particular disease as these are only permitted for licensed medicines, which are thus regulated by the MHRA.

Access and information

In practice it might prove to be difficult to restrict access to cognition enhancers. For instance, drugs such as Modafinil can already be bought on the internet for as little as £35 for a month's supply. The MHRA enforcement team monitors internet sites based in the UK but cannot control the sale of prescription medicines from abroad. Hence the emphasis may be more on ensuring that individuals have access to good information on the likely risks and benefits so that they can make informed choices about whether to use cognitive enhancers on themselves or their children. It has been suggested that in the first instance it may be desirable to enforce some form of gate-keeping, for example through doctors or pharmacists. This would also allow for monitoring to assess the longer term effects of enhancers. However, this could raise ethical and legal questions for doctors who would be asked to prescribe drugs to healthy individuals. In the case of drugs such as Viagra, which may also be considered enhancing, it is considered preferable to allow access in a controlled and regulated environment through prescriptions so as not to encourage the use of drugs bought from illegal sources without any medical supervision or guarantee of quality.

Scientists suggest that cognitive enhancers available in the near future are unlikely to produce an overall improvement of brain function. It is possible to envisage a scenario where people can take a range of different enhancers depending on which improvements in cognitive function are desired. This may need specialists to advise on medication and to keep track of any negative drug interactions. It may also be necessary to determine a minimum age for the legal use of enhancers in the same way as alcohol or tobacco.

Coercion

Increased availability of cognitive enhancers could lead to greater pressure on individuals to use them. In the first instance, this could arise through pressure to compete with peers at school or in work. Indeed, legislation has already been introduced in the US to prevent school personnel promoting the use of cognitive enhancers[10]. There are also ethical questions as to whether employers would be within their rights to require employees in certain professions to use cognition enhancers in the workplace. For instance, QinetiQ are already investigating the use of enhancers such as Modafinil for potential applications in the military[11].

Morals, diversity and personal identity

The Office of Science and Innovation conducted a public dialogue on cognition enhancers as part of the Foresight *Brain Science, Addiction and Drugs* project. This highlighted concerns regarding the "unnatural" nature of pharmaceutical enhancers in comparison with food and herbal supplements which were regarded as natural and therefore harmless[12]. Opinion among researchers remains divided as to whether allowing pharmacological enhancement of healthy individuals is a step too far or merely the latest in a continuum of technologies that do not necessarily require special consideration.

Widespread use of enhancers would raise interesting questions for society. Currently individuals with above average cognitive performance in areas such as memory, reasoning, etc., are valued and rewarded. Making such performance readily available to all individuals could reduce the diversity of cognitive abilities in the population, and change ideas of what is perceived as normal. However, researchers suggest that although currently envisaged cognitive enhancers may raise the baseline of cognitive abilities they will not effect talents

such as creativity or the need to work hard to excel. Even a small upward shift in cognitive abilities may have a beneficial economic impact with more people able to work and fewer losses due to negligence.

Many issues to do with morality and sense of self would depend on the culture that develops around the use of cognitive enhancers. It is unclear whether this would more closely resemble the widely accepted use of coffee in society or whether it would have more parallels with illegal recreational drug use.

Regulation

One of the main issues raised by cognitive enhancers is the question of how they might be regulated. The first wave of such products will have been developed as medicines to be given to patients with some form of severe cognitive impairment. As outlined in Box 3, companies wishing to market a medicine must provide evidence of its safety, efficacy and quality. Regulatory bodies such as the MHRA then weigh the clinical benefits against any potentially harmful effects in deciding whether to allow the drug to be marketed. The less severe the cognitive impairment, the smaller the clinical benefit and the more certain a regulator has to be regarding the drug's safety. It is by no means clear that regulators would be willing or able to license cognition enhancing medicines for use in people who are healthy.

If cognition enhancers are categorised as foods or nutritional supplements they would need to comply with the relevant legislation and, as outlined in Box 3, companies are then constrained about the claims they can make for such products. Some argue that wider claims on foods and supplements should be allowed to educate the public and encourage people to make healthy choices. For this reason the Food and Drug Administration in the US enacted the Dietary Supplement Health and Education Act in 1994. This allows manufacturers of food supplements to make claims of effect on the structure and function of the body, provided there is sufficient scientific evidence, and there are some calls that the UK should follow a similar line.

Another potential regulatory model is that used to regulate herbal remedies which make medicinal claims. Currently, these are not required to be regulated by the MHRA or the FSA, so their efficacy, quality or safety cannot be guaranteed. To rectify this the MHRA introduced the Traditional Herbal Medicines Registration Scheme in October 2005 which requires companies to register their products as meeting specific safety and quality standards. Manufacturers have until April 2011 to register their products.

Overview

- There are a number of substances that have been shown to be effective in enhancing cognitive function, both in cognitively impaired patients and healthy individuals.
- It is generally considered that, although the role of nutrition in cognitive enhancement is not well understood, it is less risky and likely to be more widely accepted than pharmaceutical enhancement.
- Pharmaceutical enhancers developed for healthy individuals do not easily fit into the current regulations for foods, medicines or drugs of abuse. Specific regulations may be needed to govern areas such as safety, age and use in schools and workplaces.
- A range of issues may need to be considered by society before the use of cognitive enhancers became widespread. These include access, the potential for coercion, individual choice and questions surrounding identity and what is normal.

Endnotes

1 The Foresight state of science review on Cognition Enhancers is at www.foresight.gov.uk/Previous_Projects/Brain_Science_Addiction_and_Drugs
2 Rose SPR, *Nature Reviews Neuroscience*, 3 (2002), 975–79; Farah MJ *et al.*, *Nature Reviews Neuroscience*, 5 (2004), 421–25
3 Yesavage JA. *et a*, *Neurology*, 59 (2002), 123 – 25
4 Methylphenidate is marketed under a number of trade names, the most common of which are Ritalin and Concerta
5 Mehta, MA *et al*, *The Journal of Neuroscience*, 20 (2000), RC65 1–6
6 Sahakian, BJ *et al*, *Psychopharmacology*, 165 (2003), 260–69
7 National Institute for Health and Clinical Excellence Technology Appraisal 98, March 2006, www.nice.org.uk/TA098
8 "Use of stimulants for attention deficit hyperactivity disorder: For and Against", *British Medical Journal*, 329, 907–09
9 Directive 2001/83/EC, amended by Directives 2002/98/EC, 2003/63/EC, 2004/24/EC and 2004/27/EC
10 Legislative Commissioners' Office, *General Statutes of Connecticut*, Title 10, Ch 169, section 10-212b
11 Science & Technology Committee, Second Report of Session 2006–07, *Human Enhancement Technologies in Sport*, HC 67 Ev 17
12 HC (2006 – 07) 67, Ev 56

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