



Cognitive enhancing drugs and the workplace

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Executive summary

Cognitive enhancement or neuro-enhancement is the use by individuals of traditional or modern technologies to augment cognitive abilities. Education and physical exercise are two well-established cognition enhancers and there is growing interest in other factors such as diet. The US military have used pharmacological cognitive enhancers to promote performance during conflict since World War II and continued to research this area thereafter to aid performance in many military roles. Pharmacological cognitive enhancers are available and licensed to improve cognitive functioning in those suffering from specific medical disorders. These include anti-dementia drugs, eg acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) and memantine; drugs used to treat attention deficit hyperactivity disorder eg atomoxetine, dexamphetamine and methylphenidate; and the wakefulness agent – modafinil – indicated in the treatment of excessive daytime sleepiness associated with narcolepsy.

There is growing evidence that healthy individuals use pharmacological cognitive enhancers without a prescription for non-medical purposes. Currently such use appears to be largely restricted to students, with very little evidence for use in working populations. Media reports claim that pharmacological cognitive enhancers are used widely by students in the USA principally to aid memory and concentration. In colleges there is ready access to methylphenidate from fellow students who are prescribed it to treat attention deficit hyperactivity disorder. Modafinil and methylphenidate can be purchased easily (albeit illegally) online without a prescription, often from overseas. This is alarming because manufacture and supply are not subject to the same regulatory controls and because adverse drug events appear to be more common when used for reasons other than those indicated in their licenses.

In both healthy individuals and in many patient groups, the overall effects of pharmacological cognitive enhancers generally seem to be modest. However, there is evidence that there might be more significant effects in subgroups, such as those whose baseline performance is poorest or in individuals with a particular genotype. Currently available research suggests that pharmacological cognitive enhancers improve cognition in people at the lower end of the spectrum but they may impair people who are already at the optimum level of cognitive function – ie healthy people, in some cases leading to over confidence. The conclusion is that in healthy individuals, functioning at an optimum level, it is difficult to improve their cognition.

Healthy users of pharmacological cognitive enhancers may be unaware of the limited efficacy of these drugs, and users' expectations about the potential of these drugs often exceed their actual effects. Users are also likely to be unaware of the potential for adverse side effects or drug interactions, or the legal consequences of using or supplying them without a prescription. Ultimately pharmacological cognitive enhancers are short-term remedies that do not cause long-term improvement in cognitive function. Their efficacy and safety in healthy adults should be researched further.

On current evidence, healthy individuals who wish to protect or enhance their cognitive powers are best advised to avoid pharmacological cognitive enhancers and instead focus on leading a healthy lifestyle. This includes being physically, mentally and socially active; eating a healthy, balanced diet; drinking alcohol only in moderation; and maintaining good sleep habits.

Chapter 1 – Cognitive enhancement

1.1 Introduction

This publication aims to cite the most comprehensive and most recent sources of evidence. Where possible this citation is to a systematic review, which includes all earlier original studies in that area. Direct reference to original studies is made where there is no systematic review, where they are not included in the original review(s), or where they are necessary to support an important point.

Cognitive enhancement or neuro-enhancement is the use by individuals of traditional, scientific or medical technologies to augment cognitive abilities. There are well-established ways to enhance cognition in humans; eg education and physical exercise.¹ There is also growing evidence relating to lifestyle factors including diet, sleep and social interaction. These factors will be addressed briefly in this chapter to complete the overall picture; however, the main focus of this publication is the use of prescription only medicines to enhance cognition. There is also the potential for increased prescribed use in ageing populations for whom restoring and maintaining cognition will be increasingly important;¹ and possibly because of an increased awareness of misuse by healthy adults. Both of these trends are topics relevant to occupational physicians who may see increased prescribed or illicit use among working populations.

1.2 Pharmacological cognitive enhancement

Throughout history the military's need for technological innovation has proved a powerful stimulus to scientific research.² Consequently, cognitive enhancement has been a feature of military research since the 1940s. The potential to improve alertness, and therefore battlefield effectiveness, could enhance performance for those suffering from severe sleep deprivation. The United States Army Air Force (the predecessor of the United States Air Force) conducted extensive experimentation with drugs to assist pilots in an operational setting. Amphetamines, known as 'go pills', were used by pilots as early as World War II.³ The ultimate aim is for individuals to sustain a workload far beyond that which may have been previously experienced.² The non-researched use of amphetamines was also applied to special operations in World War II.⁴ Use continued in the Korean War,⁵ in the Vietnam War, during the strikes on Libya in 1986, and then again in operations Desert Shield and Desert Storm over Iraq and in later sustained military operations in the Middle East.⁶ Caffeine was considered to be extremely helpful maintaining capability with few, if any, adverse effects.⁷ Research has continued in this area, with further studies suggesting that some drugs may lead to overconfidence.⁸ The use of such drugs has been blamed for friendly fire incidents in Afghanistan⁹. Modafinil attenuates the effects of sleep deprivation, but vertigo, nausea and dizziness are significantly associated side-effects and are problematic for military personnel.¹⁰

Current use can be categorized as: prescribed use for patients with approved indications; off-license prescribed use for conditions for which pharmacological cognitive enhancers have no license; and misuse by healthy individuals. Most substances identified as pharmacological cognitive enhancers were originally developed for clinical use to treat conditions that are, at least partly, characterized by some observable cognitive defect: methylphenidate and modafinil were originally developed to treat the symptoms of attention-deficit hyperactivity disorder (ADHD) and narcolepsy respectively¹¹ and some acetylcholinesterase inhibitors are licensed for the treatment of dementia. Chapter 2 discusses the prescribed uses of pharmacological cognitive enhancers.

Improvements in cognitive performance seen when pharmacological cognitive enhancers are used therapeutically have led to questions as to whether similar improvements might occur in healthy individuals with no clinical indication for these drugs.¹² The catecholamine-mediated effect of stimulants such as methylphenidate and mixed amphetamine salts (Adderal) in treating patients with ADHD led to improvement in executive cognitive function in patients, who became better able to focus their attention, manipulate information in working memory and flexibly control their response.¹² With rates of ADHD in the range of 4-7 per cent among US college students using DSM 4 criteria, and stimulant medication the standard therapy, there are plenty of these drugs on university campuses to divert to enhancement use.¹²

Buying prescription only medications without a prescription is illegal and possession with intent to supply is taken seriously in the UK. Yet there is growing awareness that pharmacological cognitive enhancers are commonly used illicitly by healthy adults especially among students groups.¹²⁻¹⁵ It is unclear whether off-license use is actually increasing and precisely who uses them and how often,¹⁶ however, methylphenidate and modafinil are presumed to be in widespread use as cognitive enhancers for non-medical reasons.¹⁷ Chapter 3 discusses the misuse of pharmacological cognitive enhancers by healthy individuals.

1.3 Non-pharmacological modalities of enhancing cognition

While non-pharmacological modalities of enhancing cognition are outside the scope of this publication it is useful to quickly review those of most interest across the spectrum of health ranging from enhancing performance in healthy individuals, to delaying or preventing the onset of dementia, and in the management of mild cognitive impairment and dementia.

Physical exercise

Exercise is one of the most effective means available to improve mental and physical health, without the side effects of many pharmacological treatments.¹⁷ Studies demonstrate that physical exercise is a lifestyle factor that might lead to increased physical and mental health throughout life.^{17,18} The data suggest that physical activity can have beneficial effects throughout the lifespan, even for individuals with neurodegenerative diseases.¹⁸ A meta-analysis of the effects of fitness training on cognition in older adults showed that the benefits on different cognitive tasks were significant. The effects were larger for some cognitive processes, in particular executive control processes.¹⁹ In people with mild cognitive impairment, there is strong evidence from meta-analyses that low to moderate physical activity used as a preventative measure can reduce cognitive decline by about 35 per cent²⁰ and reduce the development of dementia by 18 per cent.²¹ As a treatment, physical activity can improve memory, spatial awareness, and other tests of cognition in people who have already been diagnosed with impaired cognition, including those with dementia.²²

Diet and nutrition

Nutrition is an important modifiable risk factor that plays a role in preventing or delaying the onset of dementia. There is also considerable interest in the concept of enhancing cognition or slowing its decline through food supplements.¹⁵

Mediterranean diet is a predominantly plant-based diet, with olive oil being the main type of added fat.²³ Research suggests that better adherence to a Mediterranean diet is associated with less cognitive decline, dementia, or Alzheimer disease.²⁴ However, behaviours related to a Mediterranean lifestyle have also been shown to be associated with cognition, namely social interaction, participation in leisure activities, including physical activities, and sleep quality. The evidence indicates that these individual factors are important to cognitive function and decline; whether they inter-correlate or act synergistically is not known.²³

Omega-(n)-3 polyunsaturated fatty acids (n-3 FAs) are major components of neuronal membranes. Animal studies have consistently demonstrated that n-3 FAs are indispensable for proper brain development.²⁵ Higher intake of omega-3 fatty acids (n-3 FAs) is associated with a reduced risk of Alzheimer's disease and mild cognitive impairment without dementia; however, findings from interventional trials are inconsistent.^{25,26} A meta-analysis of ten randomized controlled studies including healthy adults, mild cognitive impairment, or Alzheimer's disease subjects suggest a small, but significant effect of n-3 FAs for immediate recall and attention and processing speed in people with mild cognitive impairment, but not in healthy or Alzheimer's disease subjects.²⁶

Antioxidant compounds contained in fruit, vegetables and tea, have been postulated to have a protective effect against age-related cognitive decline by combating oxidative stress. A recent systematic review reported that overall, findings from heterogeneous studies do not consistently show that habitual intake of dietary antioxidants (vitamins C, E, flavonoids, carotenoids), are associated with either better cognitive performance or a reduced risk for dementia.²⁷

Energy products are sometimes claimed by their manufacturers to enhance physical and cognitive performance, while users believe the products promote concentration, alertness, and fun.²⁸ Most of these products contain caffeine as their foremost active ingredient. However, they also contain additional ingredients, eg carbohydrates, amino acids, herbal extracts, vitamins, and minerals, often in unspecified amounts. It is not clear whether these additional ingredients provide any physical or cognitive enhancement beyond that provided by caffeine alone.²⁸

Social engagement

Socialization (in terms of social networks and social engagement) was included within the recent systematic review of the Mediterranean diet in order to try to understand those variables that might result in better cognitive performance.²³ Maintaining a lifestyle that is intellectually stimulating not only predicts better maintenance of cognitive skills, but is also associated with a reduced risk of developing dementia in later life;²⁹ as is social participation in leisure activities, including physical activities.²³

Sleep

There is growing evidence of an association between sleep quality and cognitive function.^{23,30} It is thought that sleep benefits neuronal plasticity, which supports brain function and cognition. Numerous studies show that sleep disturbance (particularly sleep duration, sleep fragmentation, and sleep-disordered breathing) results in learning and memory impairments.^{30,31} There is less consistent evidence for associations of insomnia and circadian rhythm dysfunction with cognition. By impairing hippocampal plasticity and function, chronically restricted and disrupted sleep contributes to cognitive disorders and psychiatric diseases.³¹ A recent systematic review reports studies that demonstrate increased risk of: incident cognitive impairment for low sleep quality; increased odds of cognitive decline for insomnia; and increased risk for mild cognitive impairment or dementia in subjects with sleep-disordered breathing.²³ Conversely napping has been shown to be negatively associated with incident cognitive impairment in healthy individuals; those who napped being less likely to become cognitively impaired at two and ten years follow up, whereas short sleep duration (≤ 6.5 h) and daytime sleepiness were associated with increased incident cognitive impairment.³²

Computer training programmes

The association between lifelong engagement in cognitively stimulating activities and enhanced late-life cognition has triggered interest in the potential of computer and video game based cognitive training that involves structured practice on standardized and cognitively challenging tasks.³³ Overall studies indicate that computerized training is comparable or better than more traditional, pencil and paper cognitive training approaches suggesting that computerized training is an effective alternative, at least in older adults.^{34,35} The available peer-reviewed literature provides moderate evidence that these methods can generalize to untrained cognitive abilities, but the complexity of the game or programme as well as individual factors play a large role. However, generalizability of improvements on trained tasks to valid everyday tasks or to improve cognition in well-functioning young adults has not been routinely examined. Additionally, many studies are hindered by methodological limitations ie lack of an adequate control group, long-term follow-up and valid outcome measures.³⁴ Unsupervised at-home training and training more than three times per week are specifically ineffective.³³ The role of electronic cognitive training warrants greater scientific scrutiny.^{33,34} While data is promising, there is consensus among reviewers that the evidence base is insufficient to support many claims of the efficacy of computerized cognitive training and that further research is recommended.^{29,33,34}

1.4 Summary

Several factors influence cognitive performance and the risk of cognitive impairment including genetic factors, dietary and lifestyle factors, physical activity and sleep. A substantial body of research argues for numerous long-term health benefits of regular exercise and a healthy diet. Such evidence highlights the importance of promoting healthy lifestyles across the lifespan to ensure good general health as well as to prevent or reverse cognitive decline. The evidence for the effectiveness of nutritional supplements in improving and enhancing cognitive ability is equivocal. Whilst there is no doubt that good nutrition is essential to good health, including optimising brain development and functioning, the best way to achieve this is through a balanced, healthy diet. Supplements may be useful in those whose diet is deficient but more research is needed to confirm this. The available evidence is that maintaining an intellectually engaged and physically active lifestyle promotes successful cognitive aging.

Pharmacological cognitive enhancers are intended to be medicines prescribed to patients with approved indications; and occasionally off-license for other conditions. There is growing awareness of widespread use of some pharmacological cognitive enhancers for non-medical reasons by healthy individuals. Prescribed and illicit use of pharmacological cognitive enhancers is discussed in the following chapters.

Chapter 2 – Prescribed use of pharmacological cognitive enhancers

2.1 Introduction

Only a small number of pharmacological agents are available to treat cognitive impairment in patients with specific neuropsychiatric disorders. The available pharmacological cognitive enhancing agents include those to improve wakefulness in patients with narcolepsy; and those which improve function in patients with disorders characterised by cognitive impairment, eg attention-deficit hyperactivity disorder (ADHD) and dementia. Treatments are also being assessed to enhance cognitive ability in chronic mental disorders such as schizophrenia and following stroke, although none have yet been established.³⁶ It is often the decline in cognitive abilities that inhibits patients with such disorders from returning to work. Cognitive enhancers can improve concentration, memory and other aspects of cognitive performance in those who have impaired functioning. Individuals who have memory problems without significant limitations in activities of daily living are often diagnosed as having mild cognitive impairment. A systematic review and meta-analysis concluded that pharmacological cognitive enhancers do not improve cognition or function among patients with mild cognitive impairment and are associated with a greater risk of gastrointestinal harms. These findings do not support the use of cognitive enhancers for mild cognitive impairment.³⁷

Like all drugs, those used to enhance cognition can have systemic side-effects, most often gastrointestinal upset or nausea, sometimes leading patients to discontinue medication altogether. This chapter does not intend to discuss side-effects or contra-indications but simply aims to inform readers of the drugs that are available to treat certain disorders and which consequently can be misused by healthy individuals, which is addressed in Chapter 3.

2.2 Drugs used to treat attention-deficit hyperactivity disorder

Attention-deficit hyperactivity disorder (ADHD) is a common childhood condition characterised by inattention, hyperactivity and impulsiveness. Many affected children become socially isolated and in around 15 per cent the condition continues into adulthood. Drug treatment is only recommended for children who do not respond to psychotherapy. Atomoxetine and the psychostimulants dexamphetamine and methylphenidate are all recommended as possible choices and as part of a comprehensive treatment programme. The diagnosis of ADHD in children, young people and adults and the initiation and titration of treatment should take place in secondary care. Once treatment has been started it can be continued and monitored by a general practitioner.³⁸ Drug treatment is the first-line treatment for adults with ADHD with either moderate or severe levels of impairment. Methylphenidate is the first-line drug; where this is ineffective or unacceptable, atomoxetine or dexamphetamine can be tried.³⁸ There is potential for drug misuse and diversion in adults with ADHD, especially in some settings, such as prison, although there is no strong evidence that this is a significant problem.

Atomoxetine hydrochloride is licensed for the treatment of ADHD in children of six years and older, in adolescents and in adults. In adults, the presence of symptoms of ADHD that were pre-existing in childhood should be confirmed. Atomoxetine is a selective nor-adrenaline reuptake inhibitor, although the precise mechanism by which it works in ADHD is unknown.³⁹

Dexamphetamine sulphate is a central nervous system stimulant licensed for the treatment of ADHD in children of three years and older when remedial measures alone prove insufficient.³⁹ In adolescents whose symptoms persist into adulthood and who have shown clear benefit from treatment, it may be appropriate to continue treatment into adulthood. Dexamphetamine is not licensed for use in adults newly diagnosed with ADHD.

Methylphenidate hydrochloride is a piperidine derivative structurally and pharmacologically similar to amphetamine. It is indicated for ADHD in children aged six years of age and older and when other remedial measures alone prove insufficient.³⁹

Dexamphetamine and methylphenidate block the re-uptake of dopamine and nor-adrenaline, thus increasing the concentration of these neurotransmitters in the brain.

2.3 Drugs used to treat dementia

The central cholinergic neurotransmitter system involved in learning and memory is impaired in Alzheimer's disease. Medications such as cholinesterase inhibitors do not stop the neuro-degeneration from progressing, but can moderately improve cognitive functions, memory and daily life, and attenuate disease-related behaviour. Only specialists in the care of patients with dementia should initiate treatment with cognitive enhancers for the treatment of Alzheimer's disease. A meta-analysis showed a small but significant improvement in behavioural and psychological symptoms of dementia over placebo during six months of treatment,⁴⁰ but the improvement may not be clinically significant.⁴¹ Treatment should be continued only when it is considered to be exerting a worthwhile effect on cognitive, global, functional or behavioural symptoms. Patients who continue on treatment should be assessed regularly by an appropriate specialist team, unless there are locally agreed protocols for shared care.⁴²

NICE recommends three acetylcholinesterase inhibitors – donepezil, galantamine and rivastigmine – as options for managing mild to moderate Alzheimer's disease.

Donepezil hydrochloride is a second-generation acetylcholinesterase inhibitor structurally dissimilar from other established acetylcholinesterase inhibitors. Experimentally, donepezil inhibits acetylcholinesterase activity in human erythrocytes.

Rivastigmine is an acetylcholinesterase inhibitor with brain-region selectivity. Studies have shown that rivastigmine induces substantially greater inhibition of acetylcholinesterase in the central nervous system compartment than it does in the periphery. Rivastigmine also preferentially inhibits the G1 enzymatic form of acetylcholinesterase, which predominates in the brains of patients with Alzheimer's disease.

Galantamine modulates nicotinic cholinergic receptors to increase acetylcholine release as well as acting as an acetylcholinesterase inhibitor. Action of galantamine is on the most abundant nicotinic cholinergic receptors in the human brain.

NICE also recommends the use of memantine for severe disease and for patients with moderate Alzheimer's disease who are intolerant of or have a contraindication to acetylcholinesterase inhibitors.⁴²

Memantine hydrochloride is an N-methyl-D-aspartate receptor antagonist. It works by blocking the neurotransmitter glutamate, which is released in excessive amounts in people with Alzheimer's disease, causing brain cell toxicity.

2.4 Drugs used to treat narcolepsy-related excessive daytime sleepiness

Narcolepsy is a lifelong sleep disorder characterized by excessive daytime sleepiness, cataplexy, hallucinations and sleep paralysis. The exact cause is unknown, but there is evidence that hypocretin deficiency plays a role. The pharmacological treatment of excessive daytime sleepiness involves the use of central nervous system stimulants.

Dexamphetamine sulphate is indicated in narcolepsy. First marketed in the mid-1930s, amphetamines were once widely available without prescription and, in addition to their ability to promote alertness, found their way into other medicines including weight loss and decongestant preparations. Recognition of the potential side effects coupled with reports of abuse, led to the drug being banned in the USA and the UK in the mid-1960s and restricted to prescription only usage.

Methylphenidate induces dopamine release similar to the action and clinical effect of amphetamines. Methylphenidate has been used off-license to treat narcolepsy for many decades.

Modafinil is a 'wakefulness-promoting' agent that is licensed in the UK for treating excessive sleepiness associated with narcolepsy with or without cataplexy. Its mechanism of action is not clear, although modafinil inhibits the reuptake of dopamine and norepinephrine in an area of the hypothalamus involved in sleep induction. Another possible mechanism is through activation of orexinergic neurones in the hypothalamus, which increase dopamine and norepinephrine levels. Modafinil has largely replaced other stimulants for treatment of narcolepsy-related excessive daytime sleepiness. Armodafinil is the longer-lasting enantiomer of modafinil.

Modafinil was previously licensed in Europe for treating conditions other than narcolepsy. In some countries outside of Europe, modafinil is licensed for treating insomnia or excessive daytime sleepiness caused by working at night (shift work sleep disorder). A Cochrane systematic review of three randomized controlled trials reported that modafinil and armodafinil increase alertness and reduce sleepiness to some extent in employees who suffer from shift work sleep disorder but they are associated with adverse events.⁴³ Modafinil can cause serious side effects including psychiatric disorders, cardiovascular symptoms, and serious skin and multi-organ hypersensitivity reactions. Almost half of all the adverse events reported for modafinil appear to be reported in use outside of the approved indications.⁴⁴ In January 2011, the European Medicines Agency's Committee for Medicinal Products for Human Use concluded that the benefits of modafinil could only be considered to outweigh the risks when used to treat narcolepsy. For obstructive sleep apnoea, shift work sleep disorder and idiopathic hypersomnia, the committee concluded that the benefit/risk profile not adequate and recommended that these indications be removed from the product information.⁴⁴

2.5 Off-license use of pharmacological cognitive enhancing drugs

The prescribing of pharmacological cognitive enhancing agents varies between different countries, not only because of differences in regulatory approved indications but also because of variations in off-license prescribing. It is beyond the scope of this document to describe licensed use outside of the UK or to describe any use other than the more commonly reported off-license use. Off-license prescribing appears to be on the increase. In the USA between 2002 and 2009 on-label use increased by less than three-fold, whereas off-license use increased more than fifteen-fold.⁴⁵ The rapid increase in off-license prescriptions were mostly for prescriptions for patients with depression or multiple sclerosis. In the UK, 34 percent of a cohort study group of patients prescribed modafinil had an indication of multiple sclerosis.⁴⁶ While Modafinil is used to treat fatigue in patients suffering from multiple sclerosis, a recent review concluded that rehabilitation interventions (both exercise and educational interventions) appear to have a stronger and more significant effect on reducing the impact or severity of patient-reported fatigue.⁴⁷ The use of modafinil in depression appears to be as an adjunct in refractory depression.^{48,49} Recent clinical studies have examined its use in the treatment of drug abuse, but have not shown consistent outcomes.⁵⁰ As noted earlier side effects commonly occur when modafinil is used off-license; the same has been reported for methylphenidate. In adults, methylphenidate has been prescribed for depression, a practice associated with serious adverse events of drug dependence, overdose and suicide attempt. A review of adverse reports to the French pharmacovigilance database revealed that more than 40 per cent of patients and 88 per cent of adults with adverse drug reactions received methylphenidate for off-license indications.⁵¹

2.6 Summary

Occupational physicians and other healthcare professionals might encounter working patients who have been prescribed pharmacological cognitive enhancers and for whom the presenting condition and/or their medication may affect their ability to work. Since these drugs act on the central nervous system they can cause side effects which may affect the ability to drive or operate machinery. Those workers who might be prescribed such drugs include those who have ADHD into adulthood and in whom stimulants were started in childhood; and patients suffering from excessive daytime sleepiness associated with narcolepsy. With an ageing population and longer working lives it is possible that more working patients will be prescribed cognitive enhancers in the early stages of dementia, however, there is no evidence of benefit for mild cognitive impairment without dementia. More rarely, occupational physicians (and other healthcare professionals) might encounter patients who have been prescribed pharmacological cognitive enhancers off-label eg. for refractory depression and multiple sclerosis. It is important to be aware of such patients since side effects appear to be more common in such patients.

Chapter 3 – Use of pharmacological cognitive enhancers by healthy individuals

3.1 Introduction

Both the general media and bio-medical literature report increasing use of pharmacological cognitive enhancers by healthy adults in order to increase performance. Much of the current data on prevalence of use derives from surveys and epidemiological investigations in student populations. A review of surveys of non-prescription stimulant use among college and university students in Canada and the USA between 1998 and 2007 experienced difficulty reaching precise quantitative conclusions because of differences in substances studied; definitions of non-medical use; methods of sampling; and the length of time for which prevalence was reported (lifetime/past year/past month).⁵² Excluding outliers and results from smaller studies, prevalence of use among university students was most commonly in the range 2-16 per cent.⁵² The majority of high school and college students obtained prescription stimulants from a peer with a prescription, who diverted their medication.⁵² More recent studies report prevalences of 11-25 per cent.⁵³⁻⁵⁸ It was thought that use was less prevalent in other countries; however, recent surveys indicate prevalence of the order of 1-20 per cent in France,⁵⁹ Germany,⁶⁰⁻² Iran,⁶³ Italy,⁶⁴ the Netherlands,⁶⁵ Switzerland^{66, 67} and the UK.^{68, 69} The true frequency of use among students is unknown since reported rates are beset with reporting, recall and selection biases, and conflation of the data with use for recreational purposes or with other stimulant drugs.

Little is known about the prevalence of prescription stimulant use for cognitive enhancement outside of student populations.⁵² *Nature* conducted an online poll which elicited responses from 1400 readers in 60 countries.¹³ One in five respondents had used pharmacological cognitive enhancers, mostly to improve concentration and focus. Other reasons included partying, house cleaning and to counter jet lag. Methylphenidate was the most popular (62 per cent) followed by modafinil (44 per cent) and beta-blockers (15 per cent). Use did not differ greatly across age-groups. There was an even distribution between those who took them daily, weekly, monthly, or no more than once a year. Half of users reported unpleasant side effects, and some discontinued use for that reason. One-third of drugs were purchased over the internet.¹³ A survey of over 1,200 German-speaking surgeons attending conferences in 2011 enquired about use of any prescription or illicit drug as a cognitive enhancer without medical need. Lifetime use was 8.9 per cent by anonymous questionnaire and 19.9 per cent using a more anonymous randomised response technique.⁷⁰ The questionnaire revealed that the commonest prescription stimulants were amphetamine (2.6 per cent) methylphenidate (2.5 per cent) and modafinil (2.2 per cent). As will be discussed later, apart from the risk of dependence, a key concern is over-estimation of personal capability associated with use of these drugs.

While non-medical use of such drugs might be vogue among students there is little evidence to support their use as 'smart pills' to enhance cognitive performance in healthy, well-performing adults. Systematic reviews for neuroenhancement in healthy individuals conclude that expectations exceed actual effects for modafinil and methylphenidate;⁷¹ and for acetylcholinesterase inhibitors and memantine.⁷² Primary studies are small or of low quality, often single dose studies; and produce conflicting or contradictory findings. There have been few studies outside the laboratory to investigate effects in occupational groups in normal working conditions. The following text summarises the evidence for enhancing memory, increasing performance in executive function, and in countering fatigue and promoting wakefulness and attentiveness for the three most investigated drugs: methylphenidate; modafinil; and donepezil.

3.2 Memory enhancement

The ability to encode new memories and to retain and recall these appears desirable, but evidence of the effect of cognitive enhancers on memory is conflicting.

Methylphenidate is reported to have a positive effect on memory in healthy individuals but there is no consistent evidence for other neuroenhancing effects. The most prominent positive effect is on spatial working memory.⁷¹ Studies on repeated doses are scarce and most studies used low doses (10–20mg).

Modafinil has no effect on memory in available studies of healthy subjects, all of which are single dose studies.⁷¹ It appears to maintain memory in sleep deprived individuals compared to placebo. However, with prolonged sleep deprivation repeated doses of modafinil do not prevent deterioration of cognitive performance; and instead maintain wakefulness and impair self-control – inducing overconfidence.

Donepezil might improve verbal memory; episodic memory and the retention of training on complex aviation tasks but results are inconsistent especially for episodic memory.⁷² In a sleep deprivation study, donepezil had no effect when participants were well rested, but reduced memory deficits following 24 hours of sleep deprivation, and only in those whose performance declined the most, having no such effect on rested individuals.⁷²

3.3 Enhancement of executive functions

Executive functions manage and control complex cognitive processes ie attention, decision-making, discriminating information relevance, novel problem solving, self-control and working memory. These functions might deteriorate with tiredness or low arousal.

Methylphenidate had no statistically significant effect on attention and executive functions in a meta-analysis of single dose studies.⁷¹ Small numbers and heterogeneity of studies of repeated dose trials and sleep deprivation studies make statistical analyses impractical.⁷¹ Primary studies have reported that methylphenidate improves spatial working memory;^{73,74} one observing that improvement is greatest in subjects with lower baseline spatial working memory capacity.⁷⁴ Methylphenidate may influence performance in two conflicting ways; enhancing executive aspects of spatial function on novel tasks, but impairing performance on previously learned spatial tasks and increasing speed of response before information is processed.⁷³

Modafinil moderately improved attention in a meta-analysis of single dose studies in rested individuals; while it significantly maintained executive functions in sleep deprived individuals.⁷¹ There were no statistically significant effects on attention and executive functions in repeated dose studies for prolonged sleep deprivation. A retrospective pooled analysis of two small studies demonstrated significant modafinil IQ interactions particularly in tests for sustained attention and speed of response. Improvements were only observed in the group of 'lower' IQ, not in the 'higher' IQ group.⁷⁵ In a recent small randomised controlled trial relative to placebo, participants administered modafinil were significantly slower in the performance of sentence completion tests.⁷⁶

Donepezil has not been shown to improve executive function in the few relevant studies in healthy subjects.⁷² These studies report on varying aspects of executive function in experimental studies with no common outcome measures.

3.4 Wakefulness and countering fatigue

As most cognitive enhancers are stimulants it is reasonable to anticipate that they will have a positive short term effect on alertness.

Methylphenidate and its effect on wakefulness and fatigue in healthy subjects is a topic that has scant research. For single dose studies lack of baseline measurements do not allow for statistical analysis.⁷¹ Two repeated dose studies report contradictory findings; one reported significantly reduced self-assessed ratings of fatigue in healthy volunteers; while another reported no effect on sleepiness during sustained sleep deprivation.⁷¹

Modafinil maintains wakefulness in sleep deprived individuals. A meta-analysis of repeated drug administration studies in healthy people undergoing sleep deprivation showed that wakefulness was the only outcome to be significantly changed by modafinil with improvements in self-ratings for sleepiness and fatigue.⁷¹ In studies which yielded sufficient extractable data there was no effect on other outcomes, ie executive functions and attention. Improved alertness is only advantageous while people wish to stay alert. Modafinil was associated with complaints of restlessness and sleep disturbances and especially in studies with non-sleep deprived individuals, insomnia.⁷¹

Donepezil has no effect on subjective sleepiness ratings in experimental studies of sleep deprived subjects.⁷²

3.5 Summary

Most cognitive enhancing drugs yield only moderate effects in the healthy, and enhance only a subset of cognitive abilities in a subset of individuals. Existing research is confined to experimental studies involving very small numbers of subjects (eg doctors and pilots) that are not representative of real tasks and the general population. Some findings have only been observed in one study and have not been assessed in other studies. Elsewhere the findings from many studies are contradictory. Consequently many reported observations are not generalizable and therefore have not been detailed in this text, but are available in the cited meta-analyses for readers who wish to read further.

There are practical limitations to the use of cognitive enhancing drugs by healthy subjects. Any drug-induced improvement may be related to baseline capacity, such that it is unlikely that cognitive performance can be improved in highly performing individuals. Additionally improvements in one cognitive function may be offset by impairment in others. Many studies find that user expectations greatly exceed actual enhancements, and that anticipated results motivate people to use. There is also the risk that the over-confidence induced by use might outweigh any performance enhancing benefit. The benefit for real people, performing everyday work tasks in the real world is dubious. Longer term effects are uncharacterised. There will be unwanted side-effects from taking these drugs which may be accepted or tolerated less well by healthy individuals compared to their use for treating illness in patients.

Given the current state of knowledge, uncertainties over effects and risks arising, users might be better directed toward improving work-life balance, exercise, diet and optimising shift schedules, strategies that have been shown to have a greater effect on cognitive performance with less risk.

Chapter 4 – Legal aspects

4.1 Introduction

Those who use pharmacological cognitive enhancers without a prescription may not be aware of the applicable laws and regulations; nor that some of these medicines are controlled drugs. This chapter aims to outline the major legislation governing the prescribing and usage of medicines and controlled drugs.

4.2 Drugs legislation

The *Human Medicines Regulations 2012* implement European Directive 2001/83/EC relating to medicinal products for human use and consolidate and replace most of the *Medicines Act 1968* and other regulations governing the control, manufacture and supply of human medicines. The Regulations define three categories of medicine: prescription only medicines (POM) available only from a pharmacist if prescribed by an appropriate practitioner; pharmacy medicines (P) available only from a pharmacist but without a prescription; and general sales list (GSL) medicines obtainable from any shop without a prescription. All pharmacological cognitive enhancers described in Chapter 2 are prescription only medicines; but two are additionally controlled drugs covered by further legislation.

Controlled drugs are psychoactive substances whose distribution is forbidden by law or limited to medical and pharmaceutical channels. Substances subject to control differ between countries. At international and national levels, controlled drugs are commonly classified according to a hierarchy of schedules, reflecting different degrees of restriction of availability.⁷⁷ The *Misuse of Drugs Act 1971* controls drugs considered dangerous or otherwise harmful, and which have potential for diversion and misuse. These drugs are listed in the Act and are termed 'controlled drugs' which are classified according to their harmfulness into Class A, B or C drugs, with Class A drugs being the most harmful. Under the Act it is an offence to: possess a controlled drug unlawfully; to possess with intent to supply; to supply or offer to supply a controlled drug (even where no charge is made); and to allow premises to be used unlawfully for the purpose of taking or trafficking in controlled drugs. Hence if an employer knowingly permits the production, supply or possession of any controlled drugs to occur on their premises they could be committing an offence.⁷⁸ Amphetamines and methylphenidate are Class B drugs. While the Act specifies the penalties attracted by offences associated with different classes of drugs, the police and courts retain a degree of discretion in policing and sentencing. The penalties for Class B drugs defined by Schedule 4 of the *Misuse of Drugs Act 1971* are:

- for possession – up to five years in prison, or an unlimited fine or both
- for dealing – up to 14 years in prison, or an unlimited fine or both

Any Class B drug in injectable form is treated as Class A and carries more severe penalties ie up to seven years in prison for possession and up to life imprisonment for dealing; or an unlimited fine or both in each situation.

Since many controlled drugs have legitimate medical uses, the *Misuse of Drugs Regulations 2001* control activities which would otherwise be illegal under the *Misuse of Drugs Act 1971*. The Regulations define the health care professionals who may legitimately possess and supply controlled drugs and lay down conditions under which these activities are performed. The Regulations categorise controlled drugs into five schedules, which dictate the degree of control according to each drug's medicinal or therapeutic benefit balanced against its harm when misused. Schedule 1 drugs are subject to the highest level of control and include substances that are not available for medical purposes ie LSD and cannabis. Possession and supply are prohibited without specific Home Office approval. Amphetamines and methylphenidate are Schedule 2 drugs that, because of their harmfulness, are subject to special requirements relating to their safe custody, prescription, destruction and the need to maintain registers relating to their acquisition and use.

4.3 Summary

Pharmacological cognitive enhancers are prescription only medicines subject to the *Medicines Act 1968*. Dexamphetamine and methylphenidate are Class B Schedule 2 controlled drugs for which prescription and use in the UK is subject to the *Misuse of Drugs Act 1971* and the *Misuse of Drugs Regulations 2001*. Drugs are classified according to their perceived harmfulness into 'Classes' for the purposes of criminal offences with class A drugs being subject to the most severe penalties, and 'Schedules' for the purposes of legal supply, with schedule 1 and 2 drugs having the most restricted use.

Chapter 5 – Practice based recommendations

5.1 Introduction

At first glance, the issues arising from the use of pharmacological cognitive enhancers by those in work seem esoteric and of little relevance to all but a few practising occupational physicians. However, this guidance does describe the use of cognitive enhancers in students, doctors and the military. Their dubious benefits might also seem attractive to others working shifts and/or in safety critical roles, such as in transport, healthcare, emergency services and utilities, to improve focus, wakefulness and performance, when fatigued. Graduate recruits may have a history of use through their student years or at examination time and may continue use when entering the world of work, and possibly recommend them to others. Despite the uncertainties around prevalence of use, evidence from the USA suggests doctors are increasingly being asked to prescribe cognitive enhancing medications,¹⁶ and in England, prescriptions for stimulants nearly doubled over the period 1998-2004.¹ Thus it is not unlikely that occupational physicians and physicians who prescribe pharmacological cognitive enhancers will be called upon at some point to provide information and guidance on workplace implications.

5.2 Recommendations

Occupational physicians and others who care for patients who work should:

1. Be aware that a proportion of the workforce may be prescribed pharmacological cognitive enhancers for specific medical conditions, ie ADHD and narcolepsy, who may require informed occupational health guidance and assessment of fitness to work.
2. Understand the law and regulations relating to human medicines in order to advise employees and employers accordingly.
3. Be aware of the licensed indications for pharmacological cognitive enhancers, their benefits, potential side-effects and drug interactions, and their impact on ability to work safely.
4. Be aware that pharmacological cognitive enhancers are increasingly being used by healthy people and can be bought (illegally) over the internet.
5. Consider routinely asking about the use of pharmacological cognitive enhancers in patients who are students or in social groups likely to use such drugs.
6. Be able to advise employees and managers of the risks of misuse, and ensure employees have easy access to information about the advantages and dangers of using pharmacological cognitive enhancers.
7. Be able to advise employees and managers of other risk-free methods of enhancing performance eg education, exercise, diet, stress management techniques and the avoidance of excessive amounts of alcohol.
8. Explore with any employees who request information about pharmacological cognitive enhancers the reason for their request and discuss the indicated medical uses for employee/patient uses, including:
 - a. The specific indications for use ie ADHD, dementia, narcolepsy.
 - b. The legal position on using the drugs without clinical indication by healthy individuals.
 - c. The uncertain long term risk profile in healthy individuals.
 - d. The fact that the known modest benefits are not necessarily long-lasting.
 - e. That high cognitively performing individuals, and those with higher IQs, are unlikely to derive any benefit
 - f. Usage may be associated with a negative effect on self-control, and may induce overconfidence
 - g. Purchase of any drugs over the Internet can result in substances of dubious quality.
9. Be able to advise on designing shift work schedules to minimise circadian disruption, sleepiness and fatigue.

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