Editorials

Smart drugs:

implications for general practice

The familiar landscape of substance misuse in the UK is changing. Recently a briefing in the *BJGP* highlighted two newer misuse scenarios: legal highs and 'chemsex'.[1] Another new misuse scenario generally escapes the attention of health professionals and others because it does not fit our concept of the term 'recreational drugs', since motivation for use is to enhance performance in exams or at work. However, so-called 'smart drugs' are prescription-only medicines; some being class B drugs. After becoming aware of this emerging issue the BMA Occupational Medicine Committee published a report.[2] This editorial aims to distil the evidence most relevant for primary care specialists.

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PRESCRIBED USE OF PHARMACOLOGICAL COGNITIVE ENHANCERS

Pharmacological cognitive enhancers are licensed for use in three disorders: attention deficit hyperactivity disorder (ADHD), dementia, and narcolepsy. There is no evidence of misuse of drugs used to treat patients with dementia, such as, acetylcholinesterase inhibitors (donepezil, galantamine and rivastigmine) and memantine hydrochloride. Those misused are modafinil, licensed to treat narcolepsy-related excessive daytime sleepiness; and the class B drug methylphenidate licensed to treat patients with ADHD. The class B drugs dexamfetamine and mixed amfetamine salts (Adderall®), used as second-line treatment for ADHD and narcolepsy are also misused as smart drugs. Modafinil[3] and methylyphenidate[4] are prescribed off-label, for example for refractory depression, narcolepsy, and Parkinson's disease, and modafinil additionally for multiple sclerosis.

ADVERSE SIDE EFFECTS

Off-label use in patients with comorbid conditions and concurrent medications raises concerns about potential for adverse events.[3] Methylphenidate is associated with, for example, drug dependence, overdose, and suicide attempts. In France, 43% of reported methylphenidate adverse drug reactions are attributable to off-label prescribing (children 30%; adults 88%).[4] Modafinil is associated with psychiatric disorders, cardiovascular symptoms, and serious skin and multiorgan hypersensitivity reactions, and so on; 49% of adverse events relate to off-label prescriptions.[5] In 2011, the European Medicines Agency concluded that the benefits of modafinil could only be considered to outweigh the risks when treating narcolepsy; and recommended that other previous indications (obstructive sleep apnoea, shift-work sleep disorder and idiopathic hypersomnia) be removed from the product information.[5]

STUDIES IN HEALTHY INDIVIDUALS

One robust systematic review and meta-analysis of healthy individuals used two search engines, discussed the methodological quality of included studies, and presented an evidence synthesis.[6] For methylphenidate there was no consistent evidence for neuroenhancement, although there was some evidence for memory enhancement, notably spatial working memory in laboratory tests. Modafinil had moderate enhancing effects on individuals who were not sleep-deprived, namely on attention. A single dose maintained wakefulness, memory, and executive functions in moderately sleep-deprived individuals. However, repeated doses did not prevent cognitive decrement for prolonged sleep deprivation and simply maintained wakefulness. The effect of modafinil depends partly on the individual baseline performance, having greater effect on those with a lower IQ. It appeared that modafinil induced overconfidence, interfering with the ability to accurately self-assess cognitive performance.[6] Indeed, dexamfetamine given to the US military as 'go-pills' have been associated with 'friendly-fire' incidents.[2]

Most research involves small experimental studies and not large scale clinical trials; and most have no standardised method to assess adverse reactions or report dropouts due to side effects. Some, usually benign, side effects were reported leading to a few drop-outs. Adverse reactions common to both drugs included headache, dizziness, tachycardia, nervousness and insomnia. The reviewers concluded that since most of the studies were short-term single dose studies, no comment can be made on dependence development and drug tolerance.[6]

A recent review used a single search engine and provided a narrative description of the same and similar, mainly single dose studies; without describing critical appraisal or quality of included studies. The authors stated '*... modafinil has been extensively evaluated for cognitive modulation in healthy humans, and appears safe for widespread use*'.[7] This statement was made without reference to wider and more relevant evidence relating to the safety of medicines; including clinical trials and adverse drug reaction reporting schemes.

A Cochrane Collaboration systematic review reported that both modafinil and armodafinil increase alertness and reduce sleepiness to some extent in employees suffering from shift-work sleep disorder but are associated with adverse events; and that systematic reviews of adverse effects are needed.[8]

PREVALENCE AND DRIVERS OF MISUSE

Studies of use among high school and university students indicate prevalences of 11–25% in North America and 1–20% elsewhere, including the UK.[2] A student newspaper survey in *The Tab* reported that 20% of UK university students had tried modafinil; with Oxford students using it more than any other (26%).[9] Lowest use was among medical students (12%).

Little is known outside of student populations. An online poll of 1400 *Nature* readers reported a prevalence of 20%, with use driven by desires to improve concentration and focus; but also to party and counter jet lag. Methylphenidate was the most popular (62%) followed by modafinil (44%).[10] Half of users reported unpleasant side effects; some discontinued use for that reason. An anonymous questionnaire survey of around 1000 German-speaking surgeons revealed lifetime use of 8.9%;

amfetamine (2.6%) methylphenidate (2.5%), and modafinil (2.2%).[11] Prevalence was considerably higher (19.9%) using a randomised response technique which guarantees a higher degree of anonymity and confidentiality.[11]

Subjective effects motivate people to take a drug, not the objective results.[6] Pressure to achieve, word of mouth, and media reports help drive increasing use; whereas ready availability facilitates use. In the US most students obtain prescription stimulants from a peer with a prescription, usually methylphenidate for ADHD.[2] In the *Nature* survey one-third of drugs were purchased over the internet.[10]

Newspapers and websites reacted to the review that stated that modafinil appeared 'safe for widespread use'[7] with headlines for example, in *The Guardian* 'Drug developed to treat narcolepsy may be the world's first safe smart drug'.[12] These headlines persist and websites quoting the review often advise how to buy modafinil; providing web addresses for overseas suppliers. These suppliers operate outside of The Human Medicines Regulations 2012 governing the control, manufacture, and supply of human medicines.

A ROLE FOR PRIMARY CARE

GPs are the first medical point of contact for most patients, therefore occupy an unrivalled position to detect misuse and to provide evidence-based advice. GPs have a unique opportunity to influence the expectations and health of students in secondary and higher education, as well as shift workers, in this context. The following pointers could be useful when consulting students:

- be aware of the prescription-only medicines used by healthy people as 'smart drugs';
- be alert to the adverse effects of 'smart drugs' being a potential cause of unexplained symptoms for example, insomnia, especially in students and young graduates;
- be able to advise patients who use 'smart drugs' of the risk of side effects; concerns about the quality of drugs purchased through the internet from overseas; that the modest benefits are not necessarily long-lasting; and that they may negatively affect self-control to induce overconfidence;
- be aware of the fitness standards for healthcare students, which include a full awareness of their own health and the ability to communicate effectively about their health with their own doctors;[13]
- advise healthcare students not to take cognitive enhancers off-prescription and to declare health impairments arising from these substances since these impair fitness to train; and
- advise patients of risk-free methods of enhancing performance, for example a healthy lifestyle including exercise, diet, and the avoidance of excessive amounts of alcohol.

CONCLUSION

Generally less robust studies are more positive, whereas high-quality reviews are much more cautious about the effects of cognitive enhancers in healthy test subjects. Overall, expectations regarding the effectiveness of these drugs in healthy individuals exceed their actual effects. Together with safety concerns and a possible effect of overconfidence in one's cognitive performance, it is questionable whether repeated use could be of any practical benefit in healthy individuals.

Faced with websites and articles advocating smart drugs and a ready supply, vigilance to the growing misuse of pharmacological cognitive enhancers, especially by students, is important. GPs have an opportunity to advise patients not to misuse cognitive enhancers and to target healthcare students for particular advice in this context, related to fitness to train and fitness to practise. It will be helpful if GPs are aware of mandatory fitness standards for healthcare students, set by statutory regulatory bodies to ensure patient safety.[13] These standards include two gold health standards, namely a full awareness of their own mental health and the ability to communicate effectively about their own health. The capability to achieve and maintain these standards is essential for healthcare students to ensure patient safety. The misuse of cognitive enhancers is incompatible with these standards.

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