Modafinil Has the Potential for Addiction
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Available online: 18 Apr 2012

To cite this article: Ahmed Dahir Mohamed (2012): Modafinil Has the Potential for Addiction, AJOB Neuroscience, 3:2, 36-38
To link to this article: http://dx.doi.org/10.1080/21507740.2012.666322

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ethical questions Victorian-era fiction poses are still relevant today, even if technology has changed. The contemporary BBC production *Sherlock*, which reinvents Sherlock Holmes as a 21st-century detective, has the modern sleuth unroll his sleeve to reveal beige nicotine patches. “This, Watson, is a three-patch problem” (BBC 2011). The two versions differ by a subtle distinction. In the original story Holmes asks Watson not to disturb him for 50 minutes, meaning that three pipes indicated a measure of time. In the new story Holmes applies all three patches at once to maximize the dose. Nicotine in the original story is an accompaniment to taking time to think through a problem. Nicotine in the new story is the means to compress the time required to think his way to a conclusion. One story values contemplation, the other, haste.

Whether *Sherlock* in subsequent episodes will avail himself of modafinil or other off-label neuroceuticals with the intention of enhancing his cognitive acuity will, one hopes, originate from artistic creativity rather than pharmaceutical-industry sponsorship.

REFERENCES

In their article “Lessons for Enhancement From the History of Cocaine and Amphetamine Use,” Stephanie K. Bell, Jayne C. Lucke, and Wayne D. Hall (2012) present an important historical overview of the abuse potential of psychostimulants and its relevance to the recent trends in pharmacological cognitive enhancement practices among healthy individuals. Their article is accurate and timely and should be welcomed.

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March 25--April 2, Volume 3, Number 2, 2012

AJOB Neuroscience

Volkow and Swanson (2008) have recently argued that cognitive enhancers can lead to addiction. Their statement was based on in-depth understanding of the neurobiology of addiction and substance abuse (Volkow et al. 2011). There is now evidence that explicitly supports their view. For instance, modafinil has recently been shown to be addictive in animals (Wuo-Silva et al. 2011), and several studies show that it might also be addictive in healthy humans (Volkow et al. 2009). Indeed, it has been placed under Schedule IV of the Controlled Substances Act and classified as having the potential to lead to psychological and physiological dependency (Cephalon 2009; Food and Drug Administration 2010).

The evidence for modafinil’s addictive potential comes from several levels of neuroscientific analysis. First, molecular studies show that modafinil requires the presence of dopamine (DA) transporters (DAT) and D1 and D2 receptors to exert its wakefulness- and attention-promoting effect (Qu et al. 2008). Second, imaging studies using positron emission tomography (PET) methods with healthy humans...
(Volkow et al. 2009) and animals (Madras et al. 2006) show that modafinil increases levels of DA, a neurotransmitter that amplifies motivational reinforcement and incentive salience of reward and pleasure, specifically in the caudate, putamen, and the nucleus accumbens (NAcc) (Mohamed and Sahakian 2011). Nguyen and colleagues (2011) have also shown that in the brains of modafinil-treated mice, DA receptor and transporter bindings were also significantly increased in these areas, which are involved in addiction (Volkow et al. 2011). Modafinil’s ability to induce increased DA in the NAcc, which is known to be specifically involved in drug-seeking behavior and addiction, should give us reason to be cautious of its use for enhancement purposes.

Third, behavioral studies using both animals and healthy humans report that, similar to amphetamines and cocaine (Volkow et al. 2011), modafinil has behaviorally rewarding and reinforcement effects that lead to conditioned place preferences (Bernardi et al. 2009; Nguyen et al. 2011). Drugs that induce reinforcement and increase salience of pleasure instate conditioned place preferences and inevitably lead to abuse and addiction (Volkow et al. 2011). A recent study showed that modafinil induced psychostimulant-like reinforcement effects and that, relative to placebo conditions, healthy individuals who took modafinil preferred to work significantly more on a mathematical problem-solving task in order to earn more modafinil tablets (Stoops et al. 2005). Furthermore, under both cognitive performance and relaxation conditions, individuals on modafinil reported significantly more subjective pleasure, liking of the drug, good feelings, and a “rush.” Another study comparing the subjective effects of modafinil with d-amphetamine and placebo demonstrated that modafinil significantly increased ratings on the well-known amphetamine and morphine benzodrine group scales of the addiction inventory, as well as ratings on the vigor and total positive scales of the profile of mood states (Makris et al. 2007). These behavioral reports suggest that modafinil engenders d-amphetamine-like subjective liking effects in healthy individuals, and indicate clear reinforcement and positive conditioning effects familiar in the behavioral neuroscience of addiction (Volkow et al. 2011). In drugs of abuse, subjective liking of drugs and high ratings on these scales indicate additive potential. Hence, the findings from these studies indicate that, similar to d-amphetamine, modafinil might have the potential for abuse (Volkow et al. 2009), especially among participants who are not sleep-deprived and do not have a history of drug abuse (Makris et al. 2007). Modafinil’s effects on the reinforcement and pleasure areas of the brain also lend empirical validity to anecdotal evidence from lifestyle use of modafinil, indicating that, similarly to other stimulants, the drug improves stamina and the ability to party longer. Given that the cognitive enhancing effects of modafinil in healthy individuals are due in part to increased overconfidence in their judgement on the performance of cognitive tasks (for a review see Mohamed and Sahakian 2011 and references therein), the results from these studies show the subtle way in which modafinil can elicit rewarding experiences that might lead to abuse, compulsive use, and finally addiction.

Thus, the emerging theme from the molecular, imaging, and behavioral neuroscience evidence builds up an ever clearer picture strongly supporting the arguments of Bell and colleagues and gives us strong reasons to be cautious about the use of these drugs for enhancement. Most importantly, given that the beneficial effects of these drugs to healthy individuals are relatively small (Mohamed and Sahakian 2011), putting together all these levels of analysis gives us more reasons to be critical and skeptical about the reported enhancement effects of these drugs. Concerns about the safety of healthy individuals are even further amplified when modafinil is used regularly or in higher doses. There have been reported incidences of psychotic and manic episodes induced by modafinil.1 These reports indicate the need for awareness of the risks involved in modafinil use among healthy people.

This commentary supports Bell and colleagues’ article and is of the view that advocating for the use of these drugs for cognitive enhancement purposes is premature. Indeed, just as in the cases of cocaine and amphetamines, modafinil could potentially bring about deleterious effects in cognitive function in the vast majority of healthy individuals. Neuroscientists have an ethical obligation to demystify the inaccurate notions and opinions held by so many about these drugs. As Bell and colleagues argue, more robust neuroscientific evidence-based argument and real-world evidence showing that these drugs do actually enhance cognition in the healthy are urgently needed. As such evidence is currently lacking, we must learn from history and be more critical about the neuroenhancement bubble. 

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1. Several reports in the American Journal of Psychiatry indicate that modafinil can induce psychotic episodes (see Dequardo 2002; Mariani and Hart 2005); for more in-depth toxicity reports see Spiller et al. (2009).
Methylphenidate and Cigarettes

Peter Shiu-Hwa Tsu, Taipei Medical University

Stephanie Bell and colleagues (2012) contend that in the absence of evidence on the safety of its long-term use, bioethicists should not encourage the use of methylphenidate for cognitive enhancement purposes. As a bioethicist, my objection is as follows. While I agree that the authors’ contention is generally true, I don’t think that it is universally true. In this commentary, I argue that chain smokers who smoke cigarettes for cognitive enhancement purposes ought to be encouraged to switch from unmonitored chain smoking to monitored use of methylphenidate.

To begin with, it is an undeniable fact that some chain smokers smoke cigarettes for cognitive enhancement purposes. That artists, poets, or novelists rely on cigarettes as an important source of creativity is a commonplace. They smoke cigarettes for cognitive enhancement purposes to switch from unmonitored chain smoking to monitored use of methylphenidate. For the purpose of this paper, I use the term “cognitive enhancement” to refer to cognitive enhancement that is used to boost the cognitive performance of the normal, but not that of the cognitively deficit.

whereas, by contrast, there has been no solid evidence on the harm of long-term monitored use of methylphenidate. The emphasis here is laid on a monitoring system. The risks of harm can be relatively minimized when methylphenidate is used under the administration of a physician. The monitoring system will include specifics about when and how to use the drug and perhaps more importantly when to stop using it under the administration of a physician. By contrast, a monitoring system is nonexistent in the case of smoking.

Chain smokers can have unconstrained access to cigarettes and smoke freely, which might be more likely to cause harm to their own health, compared to the monitored use of methylphenidate. So other things being equal, I think that it is rational to encourage those chain smokers who smoke for cognitive enhancement purposes to switch from unmonitored chain smoking to monitored use of methylphenidate, as doing so reduces the risks of harm.

Moreover, in terms of efficacy, it is not clear that smoking is more effective than methylphenidate as a means to achieve the purpose of cognitive enhancement, if cognitive enhancement is so desired. True, there have been studies about nicotine that suggest that it is indeed effective for short-term cognitive enhancement (Heishman et al. 1994). But so is methylphenidate (Greely et al. 2008).

The author thanks John Benja and Yen-Chang Chen for their constructive comments. Part of this research is funded by Taiwan’s National Science Council (NSC 101-2410-H-038-001-MY2) and Taipei Medical University.

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To begin with, it is an undeniable fact that some chain smokers smoke cigarettes for cognitive enhancement purposes. That artists, poets, or novelists rely on cigarettes as an important source of creativity is a commonplace. They do chain smoking despite the well-confirmed evidence of its harm. Given their desire, or perhaps need, for cognitive enhancement, I think that they ought to be encouraged to switch from unmonitored chain smoking to the monitored use of methylphenidate instead. My reason is this: There has been well-confirmed evidence on the harm of chain smoking, whereas, by contrast, there has been no solid evidence on the harm of long-term monitored use of methylphenidate. The emphasis here is laid on a monitoring system. The risks of harm can be relatively minimized when methylphenidate is used under the administration of a physician. The monitoring system will include specifics about when and how to use the drug and perhaps more importantly when to stop using it under the administration of a physician. By contrast, a monitoring system is nonexistent in the case of smoking.

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April–June, Volume 3, Number 2, 2012