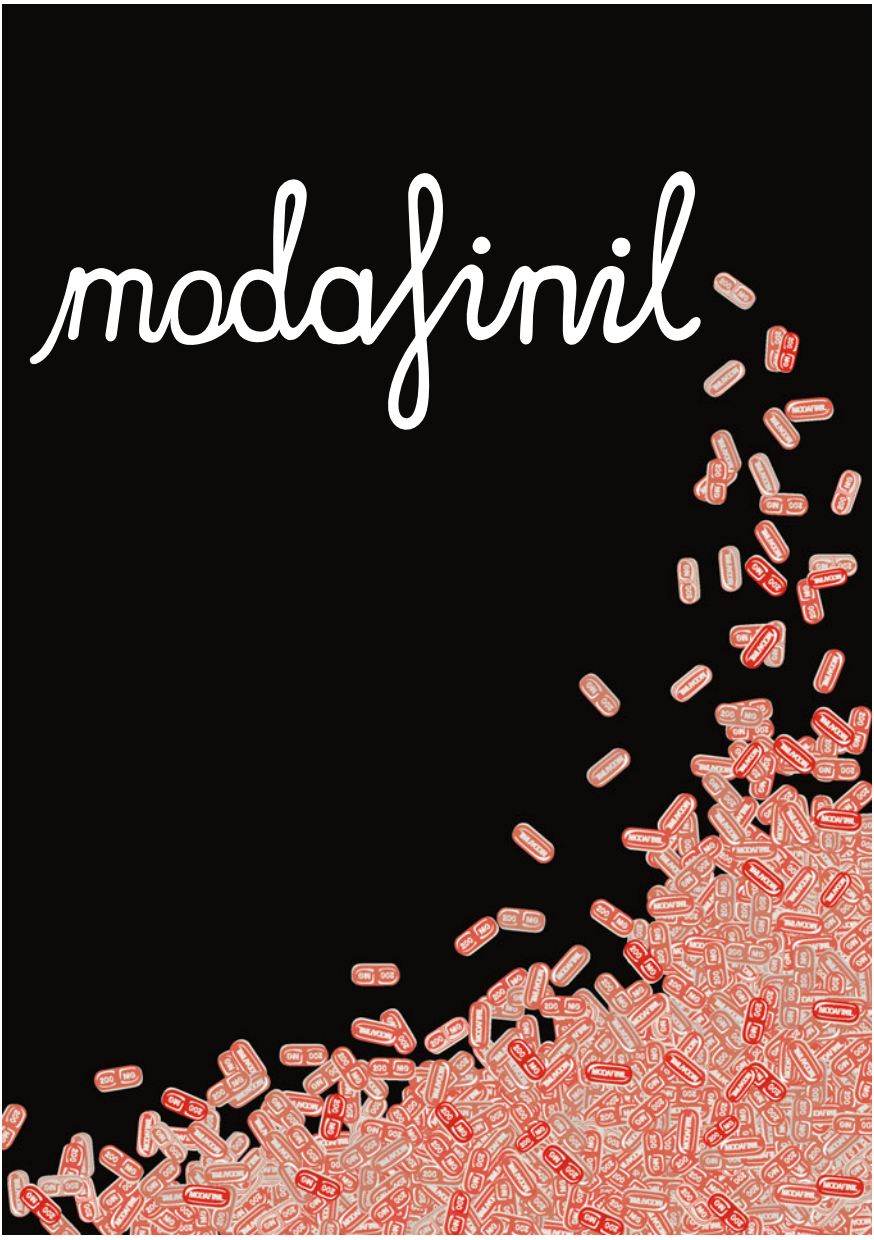
modafinil

Modafinil

Lorenza S. Colzato and Rebecca Mourits

Introduction

The atypical psychostimulant Modafinil is a drug that promotes wakefulness. For this reason, it is often used in the treatment of sleeping disorders such as narcolepsy and shift sleeping disorder. Modafinil belongs to a group of drugs named "eugeroic." These drugs mimic the effects of amphetamines by promoting the maintenance of wakefulness, but do so without the negative side effects typically associated with amphetamines (Whitmore et al. 2006; Minzenberg and Carter 2008; Mereu et al. 2013). Whereas amphetamines have a high risk of abuse (Kollins et al. 2001), Modafinil has fewer, milder side effects, and little evidence of dependence (Jasinski 2000).

Modafinil promotes a number of neurochemical actions that may be related to primary effects on catecholaminergic systems (Madras 2006). Given that these primary effects on catecholaminergic systems are generally beneficial in improving cognitive functions, the efficacy of Modafinil administration as a way to enhance cognition has been studied under different circumstances. As Modafinil appears to be a candidate for enhancing cognitive function with very low abuse liability, it has already been introduced in various professions requiring prolonged wakefulness, such as workers in the forced army and health care. Indeed, approximately 90% of Modafinil users are healthy individuals with no sleep disorders aiming to enhance their attentional capacity (Baranski et al. 2004). Therefore, it is not surprising that Modafinil is mostly used by healthy on-call physicians and people within academia

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(Franke et al. 2013; Greely 2008). Given, the nature of people working in the army and health care and the safety of the people involved, thorough and meticulous research on Modafinil and how it affects cognitive processes of healthy adults is crucial. However, to date, both the mechanism of action and the effectiveness of Modafinil on brain and cognition are not yet well understood. This chapter provides a summary of the existing studies exploring how Modafinil administration affects cognitive processes in healthy adults. The aim of this chapter is to create better understanding of the circumstances under which Modafinil has a positive effect on cognition and to clarify whether the drug is indeed useful as a cognitive enhancer.

First, this chapter describes the mechanism of action thorough which Modafinil administration affects cognitive-enhancing mechanisms in the brain. Second, an overview of the available studies investigating the effect of Modafinil on cognitive performance of healthy non-sleep-deprived individuals will be given. For these people, Modafinil appears to increase specifically attention and cognitive control and this effect seems to be more pronounced in challenging task conditions and in low performing individuals. Lastly, studies investigating the effect of Modafinil on sleep-deprived individuals will be reviewed. In these people, Modafinil seems to maintain and restore performance on cognitive tasks, but at the possible costs of subjective overconfidence.

Mechanism of Action

Modafinil is synthesized from adrafinil, a psychostimulant used to promote vigilance (Fontan et al. 1990). When administered in single oral doses, plasma concentrations of Modafinil peak approximately 2.5 h after intake (McClellan and Spencer 1998; Keating and Raffin 2005). The half-time elimination (time necessary for plasma concentration of a drug to drop to 50% during the elimination phase) is approximately 12–15 h. After oral administration, Modafinil is primarily transformed in the liver to inactive metabolites (the minor metabolite Modafinil acid and major metabolite Modafinil sulphone), which are then excreted in the urine (Moachon et al. 1996). The pharmakinetics of Modafinil are linear for the doses ranging 200 and 600 mg and the terminal half-life (time necessary to eliminate 50% of the drug from the body) is 9–14 h (Whitmore et al. 2006; Mereu et al. 2013).

Unfortunately, the specific mechanism of action of Modafinil is not yet well understood (Ballon and Fiefel 2006). The administration of Modafinil has been found to increase levels of serotonin, extracellular dopamine (DA), glutamate, noradrenaline (NE), histamine, and orexin in various brain regions, but to decrease extracellular GABA (Minzenberg and Carter 2008). It has been suggested that both increased dopaminergic and noradrenergic transmission and decreased GABAergic activity may play important roles in the positive effect the psychostimulant has on wakefulness (Baranskiet al. 2004). Mechanistic studies of Modafinil have frequently focused on the involvement of the dopamine transporter (DAT) and norepinephrine transporter (NET) (Dunn et al. 2012; Louvet et al. 2012; Funayama et al. 2014). Modafinil binds to the DAT and NET. This results in a direct increase

of extracellular DA and NE and in an indirect rise of serotonin, glutamate, and histamine levels, while simultaneously decreasing GABA levels, see Fig. 1 (Mereu et al. 2013; Minzenberg and Carter 2008). As the effect of Modafinil on the release of DA in the nucleus accumbens is weak and dose-dependent, the probability of drug overdose, abuse, and tolerance is very small.

The recommended daily dose of Modafinil is 200–400 mg, given once or twice a day. Modafinil seems to be well tolerated with little side effects, the tolerability profiles of 200–400 mg doses are generally similar to that of placebo (McClellan

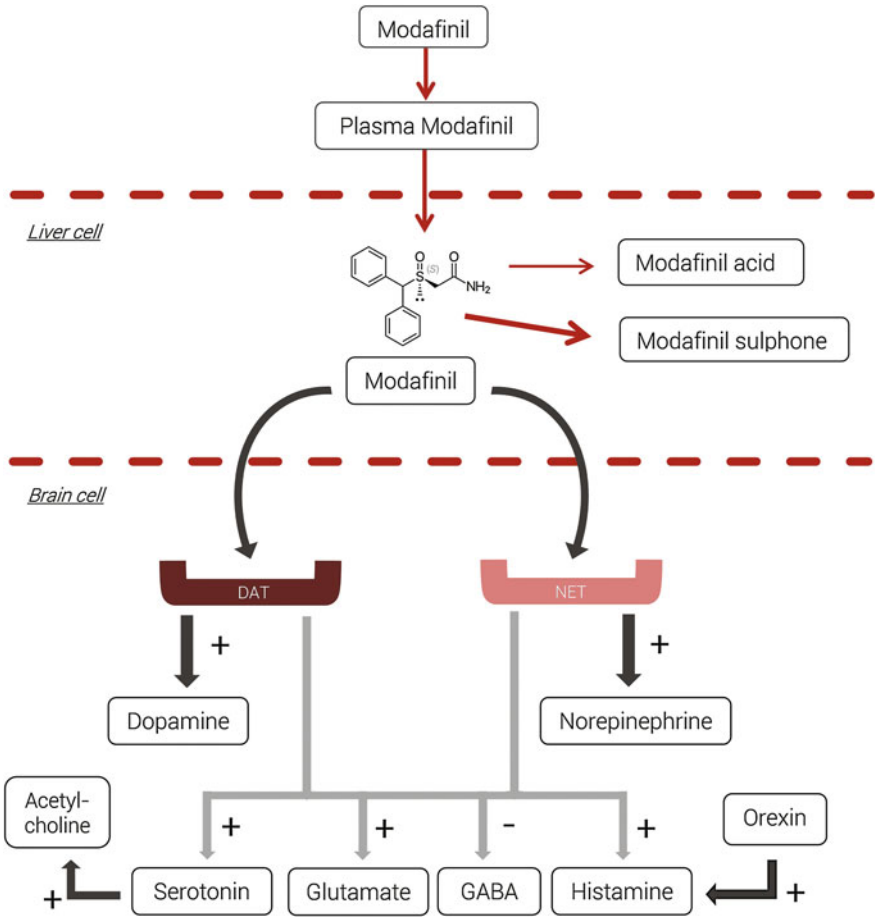

Fig. 1 Schematic representation of Modafinil metabolism. In the liver Modafinil is transformed to inactive metabolites: Modafinil acid and Modafinil sulphone. After having crossed the blood–brain barrier, Modafinil binds to the dopamine transporter (DAT) and norepinephrine transporter (NET). This result in a direct increase of extracellular dopamine and norepinephrine and in an indirect rise of serotonin, glutamate, acetylcholine, histamine, and Orexin levels, while simultaneously decreasing GABA levels

and Spencer 1998). However, higher doses of 400–600 mg may cause headache, nervousness, dizziness, or nausea. Other possible side effects, such as increased urinary frequency, hypertension, and hallucination, are rarely found.

Enhancing Effect in Healthy Non-sleep-Deprived Individuals

Although originally used for the treatment of narcolepsy and other sleep disorders, but given that users are mostly healthy individuals, Modafinil has become the focus of scientific interest for its allegedly cognitive-enhancing properties. This section provides an overview of recent studies on the effect of Modafinil on healthy adults who are not sleep-deprived. Given some findings were mixed, we will discuss factors that may be responsible for the contradictory results.

Several studies indicate that Modafinil enhances various cognitive functions, primarily those that highly depend on cognitive control and processes involving the prefrontal cortex (Geng et al. 2013). These beneficial effects include improvements in planning and decision-making, working memory, inhibitory control, and proactive cognitive control. For instance, a placebo-controlled, randomized, single-dose study evaluated the cognitive enhancement potential of Modafinil using a battery of neuropsychological tests (Turner et al. 2003). Sixty adults were given a single dose of either 100 or 200 mg. In general, the effects were not dose-dependent, that is, the higher dose of Modafinil did not induce better performance, with the only exception of inhibitory control (as indexed by the stop-signal task). The study showed that Modafinil selectively augments performance on spatial planning, visual recognition memory, response inhibition, and working memory (as indexed by the digit span). However, there was no beneficial effect on spatial memory, attentional set-shifting and rapid visual information processing. This selective effect of Modafinil may be explained by the fact that the effectiveness of Modafinil may dependent on the level of task difficulty. Several studies indicate that the beneficial effects of Modafinil were most prominent or even solely present when the difficulty of the tasks was high (Müller et al. 2013; Marchant et al. 2009). This indicates that Modafinil may primarily increase performance in non-sleep-deprived individuals but only when tasks are rather challenging.

One retrospective analysis study (n = 89), combining two earlier studies on the effectiveness of Modafinil on a battery of cognitive tests in healthy university students (Randall et al. 2005), found that the effectiveness of Modafinil depends on the individual performance baseline levels (as indexed by IQ). The results indicated both doses of 100 and of 200 mg improved response speed and target sensitivity in a sustained attention test, but only for individuals with lower IQ. This suggests that primarily suboptimal performing individuals can benefit from Modafinil intake. Consistent with these findings on attention, the beneficial effect of Modafinil on

working memory was also limited to participants that originally exhibited poorer baseline performance (Müller et al. 2004).

In some cases, Modafinil seems to have adverse effects on higher order cognitive processes. Modafinil was found to impair creativity in terms of convergent thinking especially in participants who were highly creative, whereas it reduced divergent thinking in all participants (Mohamed 2014). However, a double-blind, placebo-controlled study by Müller et al. (2013) replicated beneficial effects of Modafinil administration on planning, memory, and decision-making only in the most demanding conditions, but failed to find any effects on creativity.

In sum, in healthy non-sleep-deprived individuals, Modafinil appears to increase specifically attention and cognitive control and this effect seems to be more pronounced in challenging task conditions and in low performing individuals.

Enhancing Effect in Healthy Sleep-Deprived Individuals

In this section, we will review studies investigating the effect of Modafinil on cognitive functions in sleep-deprived, but otherwise healthy adults. These studies involve sleep deprivation ranging in their total period from 40 to 85 h and typically fall into one of two categories: maintenance and recuperation. In maintenance studies, participants are given smaller doses on a more frequent basis, for example, 100–200 mg every set amount of hours. The aim here is to determine if cognitive performances are maintained throughout a period of wakefulness. In recuperation studies, participants are typically administered a single, larger dose, e.g., 300–400 mg, after becoming extremely fatigued due to lack of sleep. The aim is to determine if cognitive performances can be restored to or near baseline levels.

One placebo-controlled, double-blind maintenance study on six healthy volunteers examined cognitive performance in terms of speed and accuracy in detecting a target using the visual search paradigm (Stivalet et al. 1998). Modafinil was administered three times a day in doses of 100 mg during 60 h of sleep deprivation. The results indicated Modafinil compensated for the slowing of serial processes and the increase of errors due to sleep deprivation. The relative effects of three different doses of Modafinil were examined during a sleep deprivation period of 64 h in a third double-blind, placebo-controlled maintenance study (Baranski et al. 1998). A dose-related effect was found: a total dose of 300 mg in a 24 h period, administered as 100 mg every 8 h, kept cognitive performance near or even at baseline levels; 150 mg of Modafinil, administered as 50 mg every 8 h, maintained performance to a lesser degree; 50 mg administered as 16.7 mg every 8 h did not substantially differ from the placebo.

Further, a seminal study by Bodenmann et al. (2009) showed that effects of Modafinil on waking functions after sleep loss are determined by catechol-O-methyltransferase (COMT) genotype. COMT is an enzyme that catalyzes the breakdown of DA in the cerebral cortex. Given that Modafinil increases DA level in the brain, the authors investigated whether the functional $Val^{158}Met$

polymorphism contributes to individual differences in the reactivity to Modafinil administration. The findings revealed that Val/Val homozygotes (i.e., individuals potentially associated with lower frontal DA level) showed larger beneficial effects of Modafinil administration than Met/Met homozygotes (i.e., individuals potentially associated with higher frontal DA level), suggesting that genetically determined differences in DA function may explain inter-individual differences in response to Modafinil administration.

Most research on Modafinil as a potential cognitive enhancer in healthy sleep-deprived people has been conducted in controlled laboratory conditions. However, given that Modafinil is often used by workers in the military and health care, who need to stay awake for prolonged periods of time, there is the need for field research or studies highly simulating real-life situations. This is particularly important given that these professions directly involve the safety not only of the individuals taking Modafinil but also of others. Caldwell et al. (2000) conducted one such study, focused on sustaining alertness and performance of six aviators. Throughout two 40 h periods of wakefulness, they were administered either three 200 mg doses or a placebo and their performances on a helicopter simulation flight were evaluated. Modafinil sustained both alertness and performance on four out of six flight maneuvers, especially in the time-span when fatigue was at the highest peak. The drug effects became more prominent as the period of sleep deprivation increased, a finding consistent with those by Lagarde and Batéjat (1995) and Pigeau et al. (1995). However, side effects such as nausea were more notable in this study, possibly due to the moving aspect of the flight simulation. Another placebo-controlled field study was conducted by Whitmore et al. (2006). Subjects participated in a simulated escape and evasion scenario and were administered doses of either 100 or 200 mg every 8 h during an 88 h period of wakefulness. Modafinil maintained cognitive performance, measured by math accuracy, during this period. These results were in line with an earlier field study by Whitmore et al. (2004) that was specifically set up to simulate the environment and workload that aircrew or special forces workers may experience during military ground operations.

Even though the results of studies described above plead in favor of the use of Modafinil as cognitive enhancer considering its low abuse risk and side effects, other findings suggest more cautious conclusions. Indeed, the drug may influence self-monitoring and metacognitive abilities. Recently, Mohamed (2015) proposed the idea that Modafinil did not enhance or maintain cognitive functions per se but it augments the individual perceived confidence and judgment in her/his own performance. Even though task performance may be objectively not improved, the overconfidence effect may be achieved by the increased salience of pleasure in performing such tasks under the influence of Modafinil. In line with this idea, Baranski and Pigeau (1997) reported that a single 300 mg dose of Modafinil, administered to individuals who were deprived of sleep in a recuperative paradigm, induced an overconfidence effect: subjects' estimates of their own cognitive performance exceeded their actual performance. In other words, the capability to assess one's own performance accurately may be negatively affected through the use of

Modafinil. This is in line with another study (Batejat and Lagarde 1999) reporting Modafinil to cause similar changes in self-confidence. A placebo-controlled study investigating driving simulator performance (Gurtman et al. 2008) also found that Modafinil may induce overconfidence in driving ability. The drug was administered as a single dose of 300 mg and increased subjective judgements of driving performance after participants remained awake overnight. However, a maintenance study that administered the drug in several smaller doses of 100 mg (Baranski et al. 2002) found no evidence of overconfidence. The overconfidence effect was also not found in a study on healthy, non-sleep-deprived individuals, even though participants in the Modafinil condition did overall display a nonsignificant tendency toward boldness in their judgement on their performance on the cognitive tests (Baranski et al. 2004). This indicates that the overconfidence effect may be a relative dose-dependent side effect (i.e., probable to appear only with high doses) that is present more in sleep-deprived individuals than in healthy, non-sleep-deprived individuals.

In sum, administration of Modafinil shows promising potential to maintain cognitive function in sleep-deprived individuals: however, caution may be needed given a possible overconfidence effect.

Conclusion

As it binds to DAT and NET, Modafinil has the potential to impact primarily the dopaminergic and noradrenergic system and secondarily other neurotransmitters critically relevant for cognitive functioning such as GABA. Even though more research is necessary to further elucidate the neurobiological underpinnings underlying the effect of Modafinil on cognition, in non-sleep-deprived healthy individuals Modafinil seems to improve mainly attention and cognitive control in challenging conditions and this effect seems to be limited to suboptimal performing individuals. Consequently, future studies that explore the cognitive-enhancing effects of Modafinil should consider individual variations in baseline performance.

In healthy sleep-deprived individuals Modafinil seems to maintain and restore performance on cognitive tasks, but at the possible costs of subjective overconfidence. That is, the use of Modafinil, especially in military and medical settings, raises significant ethical issues given that this drug augments the individual perceived confidence and judgment in her/his own performance. Accordingly, future studies need to shed light on the safety and efficiency of the administration of Modafinil and whether this drug increases human errors in decision-making in naturalistic environment.

Moreover, the effectivity of Modafinil seems to be determined by the COMT genotype. Future studies investigating the effect of Modafinil on cognition should consider genetic markers associated with DA availability in the brain. Indeed, genetic carriers associated with low DA baseline levels are the ones expected to profit the most from the administration of Modafinil. Therefore, we suggest that

genetic predisposition might modulate the effect of Modafinil in its role as cognitive enhancer.

In sum, even if more research is required, given its low liability to abuse and little side effects, Modafinil seems a promising tool for enhancing cognition.

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