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Modafinil and orexin system: interactions and medico-legal considerations

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1. ABSTRACT

Modafinil (Mo) is increasingly being used as an enhancement drug rather than for its therapeutic effects. The effects of this drug have been examined in attention deficit disorders, depression, mental fatigue, and in enhancing concentration. The drug possesses wakefulness-promoting properties which are mediated through the interaction of orexinergic system with the activated sympathetic nervous system. Mo exerts a synergistic effect on the orexin system, controls energy expenditure and strengthens the ability of the individual to exercise. Some view Mo as a drug that enhances sports performance, since it induces a prolonged wakefulness and decreasing the sense of fatigue. These characteristics being similar to conventional stimulants have allowed Mo to emerge as a novel stimulant requiring medico-legal considerations. However, more studies are needed to better understand the mid and long-term effects of the drug on user/abuser.

2. INTRODUCTION

Cognitive enhancement comprises the utilization of different techniques, behavioral therapies, devices, substances, and applications, to improve cognitive and executive functioning skills. It is considered a common practice in many medical fields, and it is obtained stimulating memory, attention, learning, tasking, speed processing, motor behavior, motor control and vigilance.

Currently, the devices used in cognitive enhancement includes the transcranial direct current stimulation (tDCS) (1, 2, 3, 4), and the transcranial magnetic stimulation (TMS), (5, 6, 7, 8; 9, 10), both used in all ages groups (11, 12, 13, 14, 15).

Behavioral therapies used for cognitive enhancement have shown interesting results. Amongst them, meditation training, mnemonics and retrieval practice demonstrated an improved, selective,

executive attention, and sustained attention abilities (16). Regular physical exercise can also be considered as a good method to improve cognitive abilities (17; 18; 19; 20; 21).

Certain food and dietary supplements are utilized to increase the overall body energy and reduce fatigue. Dietary supplement like glucose and caffeine may also act as acute cognitive enhancers, whilst Omega-3 fatty acids, ginseng, and ginkgolide are considered to improve cognitive performances (22, 23, 24, 25). These substances are considered as nootropics (from the ancient Greek words *noos* for 'mind', and *tropein*, meaning 'towards'), also known as smart drugs (26, 27).

Nootropics/smart drugs are pharmaceuticals, herbal products or nutrients, which enhance cognitive functions by stimulating the nervous system, and by modulating the cellular release/ uptake of neurotransmitters. These drugs were initially developed to restore cognitive function in individuals with neuropsychiatric or mental disorders (28). Cognitive impairment or cognitive decline is a typical characteristic of numerous diseases, such as narcolepsy, Alzheimer's disease, mental retardation, and other neuropsychiatric diseases associated with accidental brain damage and aging (27). In addition to their therapeutic uses, smart drugs are also utilized by healthy individuals in order to: improve their cognition, increase the brain metabolism, protect the brain from oxidative damage, to become smarter, more efficient, stay awake, and counteract fatigue and loss of concentration (29). The use of smart drugs to enhance cognitive skills is not a new concept, since psychostimulants are readily available, ranging from caffeine, nicotine to methylphenidate and Modafinil (Mo). Several studies reported the use of these substances to improve working memory and planning in healthy adults (26; 30).

Mo is a wakefulness-promoting agent used to treat excessive daytime somnolence syndrome, such as narcolepsy, as well as to prevent sleepiness among soldiers and pilots in order to optimize alertness for a prolonged period of time without sleep (31, 32). Furthermore, trials conducted on healthy volunteers show that non-sleep deprived subjects treated with Mo, demonstrated better results on tests of planning, learning, attention, delayed and working memory (33). Mo is also used for off-label indications as a nootropic agent by professional athletes to enhance performance at a greater intensity and to reduce physical fatigue (34, 35). It shows specificity for areas in the brain related to wakefulness, such as the posterior and lateral hypothalamus (tuberomammillary nucleus and orexin cells) (36, 37), as well as regulates catecholamines, serotonin, glutamate, gamma-aminobutyric acid, orexin, and the histamine cerebral systems (36, 38).

3. MODAFINIL

3.1. Pharmacokinetic profile

Mo was initially developed in France in the 1970s for excessive daytime sleepiness in narcoleptic patients (38, 39). It is currently approved by the US Food and Drug Administration (FDA) as medication with awakening-promoting properties. Furthermore, there are a number of off-label indications for Mo use, which includes: treating obstructive sleep apnea syndrome (OSAS), depression, attention deficit hyperactivity disorder (ADHD), jet lag and shift-working sleep disorders (28; 36).

Mo is a racemate with two enantiomers: Mo and its R-enantiomer, which are equipotent in behavioral effects. Doses ranging from 100 to 600 mg/day are clinically effective (40), with absorption being slowed (but not inhibited) by food in the gastrointestinal tract, and with a plasmatic peak level 2–4 hours after administration (41). Mo is lipophilic and bound to plasma proteins, mainly albumin. It is almost completely (around 90%) metabolized in the liver. The main remaining metabolites, such as Mo acid and Mo sulfone are excreted in the urine (40, 41). The primary reported side effects of Mo include headache, nausea, diarrhea, nervousness, anxiety, dyspepsia, and insomnia (even if they are lower than those of other amphetamine-like drugs) (38; 42). Mo is well-tolerated, with a low reported incidence for abuse, and has a wide-range of \ off-labeled indications worldwide (36, 38).

3.2. Modafinil as a wakefulness-promoting agent

Considering the wake-promoting properties of Mo in narcoleptic patients and its lower side effects profile with respect to other amphetamine-like drugs, a number of studies have extensively studied and evaluated the effects of Mo on cognitive skills, sport performance, mental fatigue and other off-label uses in healthy people. Different studies investigated the cognitive effects of Mo in healthy non-sleep-deprived humans suggesting that Mo may enhance attention, executive functioning, learning and vigilance/wakefulness (33, 42, 43, 44). During these studies, healthy volunteers reported feeling more alert, attentive and energetic during Mo administration (44, 45). In addition, Ghahremani *et al*. (46) suggested that Mo could be used as a pharmacological supplement to increase the efficacy of cognitive-based therapies in methamphetamine (MA)-dependent subjects (47).

3.3. Modafinil's mechanism of action

Studies on neurochemical and behavioral effects of Mo suggested that the mechanisms through which it carries out its clinical effects are complex (36).

Even though the mechanism of action is not completely known, in the seminal paper, it was reported that Mo has an affinity for numerous receptors and binding sites, such as: adenosine, dopamine, GABA, serotonin, NMDA, and others (48). The action of this drug is similar to the behavioral effects induced by amphetamine, but they are not suppressed by haloperidol, SCH 23390, or alpha-methyl-para-tyrosine. Another study (49) compared the effects of Mo on the sleep-wake EEG and locomotor activity. Mo induced a higher increment in locomotor activity. Both drugs increased wake time, but Mo produced more consolidated periods of wakefulness, suggesting that Mo is more effective in inhibiting sleep.

Mo can reduce the extracellular GABA concentrations, partially through the serotoninergic pathway, via the action of the $5HT_3$ receptor. Since GABA is an inhibitory neurotransmitter, this could disinhibit a number of wake-promoting sites like the tuberomammillary *neuron*s. By reducing GABA levels, Mo changes the subcortical electrophysiological oscillatory pattern in sensory evoked potentials (50, 51).

Another action mode of Mo is elicitated increasing the dopaminergic signaling. Dopaminergic innervations are the most prominent in the brain, involved in various vital central nervous system functions, such as voluntary movement, feeding, affect, reward, sleep, attention, working memory, and learning. Mo allows an increase in glucose utilization in several brain region, including the thalamus and hippocampus. Furthermore, it elicits a significant elevation in blood pressure and heart rate, together with sustained adrenomedullary activation.

3.4. Modafinil as a wakefulness-promoting agent

Studies on neurochemical and behavioral effects of Mo suggested that the mechanisms through which it carries out its clinical effects are complex and distinct from other known wakefulness agents (36). Certain psychostimulants such as cocaine, methylphenidate, and amphetamines tend to enhance dopamine levels in different parts of the brain by inhibiting dopamine reuptake via the dopamine transporter (DAT) compared to Mo which shows a low micromolar affinity for the DAT (45). In order to act as a wakefulness-promoting agent, Mo activates the orexin *neuron*s in the lateral hypothalamus and influences other brain regions involved in arousal system regulation. This is in contrast with the mode of action of the classical psychostimulants, which act by blocking the DAT (52, 53; 54).

The orexin *neuron*s are a cluster of *neuron*s located in the lateral hypothalamus that synthesize two orexin/ hypocretin neuropeptides (orexin A/ hypocretin-1 and orexin B/ hypocretin-2) (55, 56). Starting from a pre-pro-orexin gene, two orexins are obtained, orexin A and orexin B, consisting of 33 and 25 amino acids respectively (56). These neuropeptides act on two G- protein coupled receptors: orexin receptor 1, OXR1, which selectively binds OxA, and orexin receptor 2, OXR2, which binds to both orexins A and B with equal affinity (56). Orexin *neuron*s send axons to a wide range of areas in the central nervous system, including the major nuclei responsible for sleep regulation as well as those that play a role in central arousal (52). Orexin deficiency in the brain is associated with the onset of narcolepsy, a neurological disorder characterized by excessive sleepiness and abnormalities in rapid eye movement (REM) sleep, suggesting that orexin plays an essential role in regulating sleep/wakefulness states, as highlighted in previous literature (52, 57). Mo is found to be effective as a treatment for narcolepsy since it activates the orexin-containing *neuron*s (58, 59; 60). In fact, Mo increases Fos-immunoreactivity (an indicator of *neuron*al activity) in orexin *neuron*s, suggesting that the wakefulness-promoting properties of Mo may well be mediated by the neuropeptide (52). Furthermore, Mo is able to activate Fos in the TMN that contains wake-promoting histaminergic *neuron*s (37). Peripheral administration of Mo, instead of direct administration into the TMN, increases histamine levels in the hypothalamus, further supporting the notion that Mo's histaminergic effects are mediated by the orexin system (54). Moreover, orexins boost the release of histamine in the TMN, and its direct administration into the TMN may enhance the wakefulness state influencing arousal and regulating the sleep-wake cycle (61, 62). Using orexin *neuron*-deficient mice, Ishizuka *et al*. (62) demonstrated that Mo increases hypothalamic histamine release and c-Fos expression in the TMN through the orexinergic *neuron*s and this requires intact orexinergic *neuron*s. Furthermore, through the interaction with the orexin system, Mo increases wakefulness state by acting upon the noradrenergic and dopaminergic systems (63). Interestingly, orexin *neuron*s have a strong and direct excitatory effect on the cholinergic and non-cholinergic *neuron*s in the basal forebrain (BF), playing a role in central arousal and attention levels maintenance (53, 64, 65). In response to salient stimuli, orexin stimulation of the BF can promote cortical activation by acting on cholinergic and non-cholinergic *neuron*s (65). Therefore, we could hypothesize that orexin and the dopaminergic systems interact in the basal forebrain to promote wakefulness and attention following Mo administration (Figure 1). On the other hand, the Mo-induced wakefulness induces long-term potentiation (LTP) of glutamatergic synapses on orexin *neuron*s in the lateral hypothalamus, showing an indirect action of Mo on orexin receptors in memory and learning processes (66).

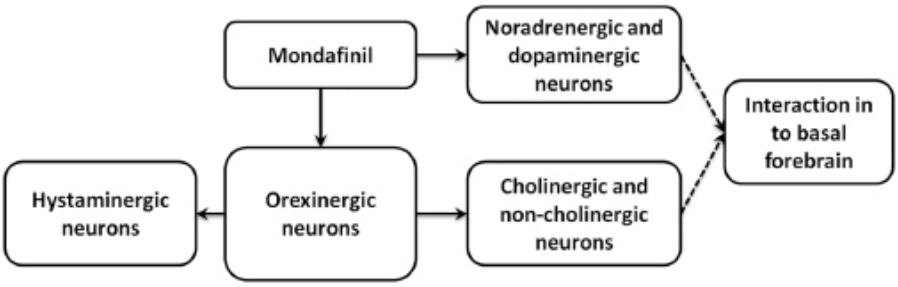

Figure 1. System interactions that may be involved in mediating the effects of Mo on arousal, enhancement of attention, executive functions, learning and regulation of the sleep-wake cycle. Solid lines indicate interactions demonstrated by studies, while dashed lines indicate interactions for which a mechanism has not yet been elucidated.

4 THE WIDESPREAD OFF-LABEL USE OF MODAFINIL

Mo is considered as a wakefulness-promoting agent and over the last decades has been used as an off-labeled drug to improve wakefulness, alertness, memory, and performance among healthy individuals in daily life. Surveys among university and college students showed the use of smart drugs, including Mo, as cognitive enhancers, in particular, to attain better learning (67, 68, 69). This is becoming a growing and alarming phenomenon. Students use Mo in order to counteract tiredness, maintain academic performance, improve memory and problem-solving skills (67, 70). Among medical professionals, surgeons who are generally exposed to a higher workload, tend to be Mo users in order to counteract fatigue and stress, and/or to enhance cognitive ability. In 2013, Franke *et al*. (71) distributed an anonymous questionnaire to surgeons and found that approximately 8.9.% of respondents, admitted to having used cognitive enhancers at least once during their lifetime in order to counteract fatigue and loss of concentration. Sugden *et al*, (72) evaluated the effect of Mo administration to healthy doctors after 1 night of supervised sleep deprivation. They found that Mo improved cognitive functions. They concluded that Mo may exert positive effects on doctors who work under immense pressure, and in situations that require efficient information processing and flexible thinking (72, 73). Mo may also reduce jet lag, and improve mood regulation among shift workers (36). Being a wakefulness-promoting agent, Mo was also tested as an alternative to amphetamines for military usage. In fact, it is provided by the military doctor to soldiers for Air Force missions in the US, UK and India to optimize alertness and combat against fatigue in sleep-deprivation or high stress situations that require prolonged periods of alertness without sleeping (74; 39). Apart from military use, Mo has also been used to enhance sport performance by athletes around the world (75, 76). Mo is also considered to be a 'mood enhancing psychostimulant' that may improve physical performance and counteract fatigue among athletes (33).

5. MODAFINIL, SPORT ACTIVITY AND MEDICO-LEGAL ASPECTS

Although the use of smart drugs is prohibited in sports, their illegitimate use is widespread among athletes. Even though a number of athletes have tested positive for Mo use, the first reported case of doping violation involving Mo was reported in 2003 at the Track and Field World Championships (TFWC) (35). In 2005, due to increased use of Mo among athletes, Mo was added to the World Anti-Doping Agency (WADA) list of forbidden substances for professional athletes (77). In 2011 Rossi and Botrè (78) evaluated the epidemiology of drug use among athletes by analyzing antidoping test results carried out on 100000 urine samples from 2000 to 2009 by the WADA. It showed a high prevalence of stimulants being used, mainly cocaine, followed by amphetamines and Mo, in order to allow these athletes to train for longer periods of time and in a more intense manner with lower fatigability (34). In a sporting context, Mo administration can lead to induction of an abnormal physical state of prolonged wakefulness (33). A double-blind, randomized, placebo-controlled trial was conducted by Jacobs and Bell (2004) to study the effect of Mo ingestion on the time it takes for a group of athletes to be exhausted. They demonstrated that acute ingestion of Mo prolonged exercise time to exhaustion at 85% VO2 max, and reduced ratings of perceived exertion (RPE) suggesting that the enhanced performance is due to a decreased sense of fatigue (79). Mo ingestion also results in elevations in heart rate, rectal temperature, and skin temperature both during rest and exercise (80). During continued wakefulness (72 hours), Mo increases thermoregulation, and total energy expenditure (TEE) (43, 79, 81, 82). A complex network of neuroendocrine and autonomic pathways can regulate energy homeostasis and physical activity, including the orexin system (83, 84, 85). Indeed, in these pathways, the hypothalamus plays a crucial role in monitoring the signals that reflect the energy status and initiate proper metabolic and behavioral responses (86). Thus, orexin is crucial for energy balance, and evidence from genetic murine models suggests its role in promoting energy expenditure through modulation

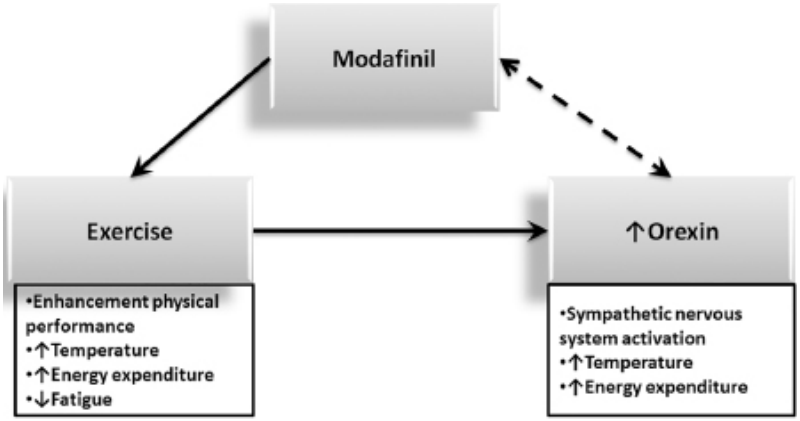

Figure 2. Interactions between Mo, exercise and orexin. Solid lines indicate interactions demonstrated by studies: Mo enhances physical performance, while exercise increases plasmatic orexin levels. Dashed lines indicate a possible synergistic combination between Mo and orexin system in the regulation of energy expenditure and strengthening exercise.

of locomotor activity and brown adipose tissue (BAT) thermogenesis (56, 87, 88). Orexins are required for BAT development, differentiation, and function (89). Lack of orexins' action may impair energy balance regulation and orexin-knockout mice are more susceptible to diet-induced obesity compared to wild-type mice (89, 90). Orexin-A also induces changes in body temperature. In rats, intracerebroventricular (ICV) injection of orexin-A enhances sympathetic discharge to the interscapular brown adipose tissue (IBAT), resulting in an increase in IBAT and colic temperatures (89). At the same time, ICV administration of orexin A causes tachycardia and hyperthermia, suggesting that orexin-A may modulate the widespread stimulation of the sympathetic nervous system (92, 93). In humans, an increase in the level of plasmatic orexin-A during exercise, suggests a possible association between exercise and orexin-A induced stimulation of specific cerebral areas that control sympathetic activation (94). Physical activity induces sympathetic activation as well as hormonal changes. It is possible that the increase in plasmatic orexin-A may be involved in the control of cortisol secretion. In fact, an orexin-A/cortisol relationship has been described by Wenzel *et al*. in 2009 (95) demonstrating that in human adrenocortical cells, orexin causes an enhancement of the expression of steroidogenic enzymes, suggesting a putative influence of orexin-A on cortisol secretion enhanced during physical activity. The precise mechanisms through which Mo exerts these effects remains unclear, but we can only speculate a synergistic relationship which exists between Mo and the orexin system in the regulation of energy expenditure and strengthening exercise (Figure 2).

An important aspect of the use of Mo, is the medico-legal implication with its use. Several studies reported adverse events that occurred after Mo assumption, such as cases of psychosis, mania, and suspected serious skin reactions, including Stevens-Johnson syndrome (96).

6. CONCLUSIONS AND FUTURE PERSPECTIVE

Increasing training interval and/or learning capacity may well be attributed to smart drugs, which also reduces fatigue, and consequently, enhance physical and cognitive performances both in athletes and healthy students (97). Since Mo is often administered and consumed without proper medical follow-up and, in some cases, its chronic use, it is important to evaluate and determine the potential adverse effects, toxicity and the addiction potential of Mo (45). Moreover, it is important to understand that cognitive enhancement is only attainable through the synergistic combination of different factors related to a healthy lifestyle, including adequate sleep and supply of nutrients, reduced use of drugs and alcohol and, most importantly, increased physical activity (98, 99, 100). Therefore, understanding the exact role of the orexin system in the physiology and pharmacology of sleep-wake regulation, cognitive and performance enhancement associated with external stimuli, and physical exercise, may shed some light into the current and future uses of Mo. Moreover, the scientific community may contribute to the definition of ethical policy on pharmacological cognitive enhancers use, adopting a "personalized" approach, identifying specific risks and benefits (30).

In conclusion, a multidisciplinary approach and middle and long-term clinical trials are required to evaluate the properties of Mo in athletes through measuring different parameters and mimic conditions during competitions.

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Abbreviations: Mo: Modafinil; tDCS: transcranial direct current stimulation; TMS: transcranial magnetic stimulation; FDA: Food and Drug Administration; OSAS: obstructive sleep apnea syndrome; ADHD: attention deficit hyperactivity disorder; DAT: dopamine transporter; OXR1: orexin receptor 1; OXR2: orexin receptor 2; REM: rapid eye movement; BF: basal forebrain; LTP: long-term potentiation; TFWC: Track and Field World Championships; WADA: World Anti-Doping Agency; RPE: reduced ratings of perceived exertion; TEE: total energy expenditure; BAT: brown adipose tissue; IBAT: interscapular brown adipose tissue; ICV: intracerebroventricular.

Key Words: Modafinil, Cognitive Functions, Enhancement Drugs, Mental Fatigue, Orexin System

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