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Practical Use and Risk of Modafinil, a Novel Waking Drug

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Objectives: Modafinil is a waking drug prescribed to narcolepsy patients, but its usage among healthy individuals is increasing to enhance their alertness or to mitigate fatigue. This study was conducted to investigate practical use and toxic effects on neuro-immune interaction of modafinil.
Methods: This study reviewed the significance of psychoactive drugs, and discussed the benefits and risks of the application of modafinil, which seems to be ideal as an anti-psychotic or anti-fatigue agent.
Results: Modafinil is known to have less or no adverse effects than those found in traditional psychostimulants such as amphetamine, methylphenidate or cocaine. It can be applied as an anti-psychotic or anti-fatigue agent. However, the waking mechanism of modafinil is yet to be fully revealed. Recent studies reported that modafinil may be subject to abuse and addiction. In addition prolonged sleeplessness induces stress responses and impairs immune function.
Conclusions: Modafinil can be used by anyone, who wishes to work late, stay awake, enhance their cognitive reactions, or brighten their moods. Users may already be under a great level of stress, i.e. cancer patients or soldiers in a battle field. A psychoneuroimmunological approach is thus needed to investigate the multi-functional effects of modafinil.

Key words: Alertness, Central stimulants, Fatigue, Modafinil, Stress

INTRODUCTION

Modafinil (2-[(diphenylmethyl) sulfinyl] acetamide) is an exclusive psychostimulant with a waking effect, and is a special medicine that can only be prescribed to shift workers and patients suffering from narcolepsy or sleep apnea (Figure 1)[1,2]. Modafinil has been commercialized as a waking drug in 2003 [3]. The normal half-life of modafinil in humans is between 12 to 15 hours [4]. Modafinil consists of R-enantiomer and S-enantiomer as a racemic compound, and the waking effect of R-enantiomer has a longer duration. Moreover, Armodafinil, which is a R-enantiomer, was commercialized as a waking drug [5,6]. Pharmacological profile is notably different from the traditional psychostimulants, such as amphetamines, cocaine or methylphenidate. Modafinil is less related to side effects such as excess locomotor activities, anxiety, jitteriness, or rebound effects than the traditional stimulants [7]. It not only has a waking effect but is also known for its mood-brightening and memory-enhancing effects. Modafinil has also been tried on disease-related fatigue, attention-deficit disorder, Alzheimer's disease, age-related memory decline, depression, idiopathic hypersomnia, cognitive impairment in schizophrenia, myotonic dystrophy, post-anaesthesia grogginess, everyday cat-napping, and jet-lag treatment [2, 8-12].

Modafinil is also of a high interest to the US military for enhancing alertness and reducing battle fatigue [8,13,14]. Availability of modafinil as a lifestyle drug is increasing, namely as a non-prescription medicine for healthy people. More students or hard-working professionals will use it for a late night's work, if it can easily be purchased. In fact, it is sold illegally in on-line shopping sites. Modafinil is distinct from other psychostimulants in that it does not seem to accompany any side effects, and this might encourage healthy people to use it whenever they want to. However, prolonged sleeplessness induces stress responses and impairs immune functions [15]. Sleep-deprivation translocates microbes from the gut to blood streams [16]. Animals observed in sleep-deprivation experiments eventually became victims of a massive bacterial infection in the blood.

The purpose of this review is to introduce practical

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application of modafinil as an alertness-enhancing and anti-fatigue drug, and to discuss pharmacological and immunomodulatory effects of modafinil, of which the first impression is harmless, even ideal.

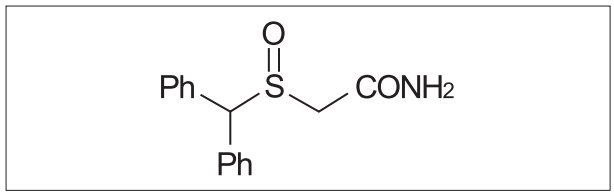

Figure 1. Modafinil structure.

PSYCHOSTIMULANTS

Psychoactive drugs are commonly classified into four categories: tranquilizers, depressants, stimulants and hallucinogens (Figure 2). However, the bounds of these categories are not precisely delineated; rather, they have several effects that overlap or combine into a new, different one. Depressants and tranquilizers are used to relieve fear, anxiety or excessive tension, while stimulants relieve fatigue, stress or depression [9,17,18]. In particular, stimulants along with depressants or tranquilizers are medicated to treat sleep disorders or to maintain alertness for an extended period [8,19]. However, most psychoactive drugs have tolerance or dependence; in other words, they bring about addiction in varying degrees. Thus, these psychoactive drugs may cause problems when medicated repeatedly or continuously. Despite the side effects of psychoactive drugs, amphetamine and caffeine have been traditionally used as alertness-enhancing or anti-fatigue drugs.

Amphetamine, a kind of phenylethylamine, is a stimulant. Amphetamine maintains alertness by inhibiting the reuptake of norepinephrine and dopamine, and by that it stimulates the secretion of catecholamines preserved in the vesicle of neuronal cells [20]. The brain's reward circuits, which are related to dopaminergic transmission, are involved in pharmacological effects of amphetamine in the nervous system [21]. However, amphetamine has an adverse rebounding effect that causes depression or anxiety when the intended effects wear off [22]. As a clinical medication, amphetamine is used to treat traumatic brain injury, chronic fatigue syndrome, attention deficit hyperactivity disorder (ADHD), and hypnolesy [8,23,24]. It is also illegally prescribed as a mood enhancer or as a waking drug for daily life. Amphetamine is widely used for its comparative effectiveness and lasting duration, but when abused it becomes a highly addictive narcotic of rapid toleration rate and increasing dependence [25].

Caffeine, a methylxantine derivative, has been used as a psychoactive drug for a long period of time. For healthy adults, the halflife of caffeine is 5 hours and it can be extended up to 11 hours for pregnant women or women taking birth control pills [26]. Caffeine acts as an antagonist of adenosin receptors [27,28]. Pharmaceutically, caffeine is a stimulant of metabolism and the central nervous system but is also used as a lifestyle drug and a clinical drug to decrease physical fatigue and maintain alertness. Caffeine capsules brighten the mood for those with accumulated fatigue due to lack of sleep and enhance concentration and task performance. In daily life, caffeine is included in food or drinks to help to improve alertness and to recover from fatigue [29]. Medically, it is sold as a pill [8,19,24]. The effectiveness and duration of caffeine are not as great as amphetamine.

A novel class of psychostimulants is eugeroics under which modafinil, adrafinil, and ampakine are categorized. Eugeroic means good arousal; that is, eugeroics show no sign of common side effects of traditional psychostimulants,

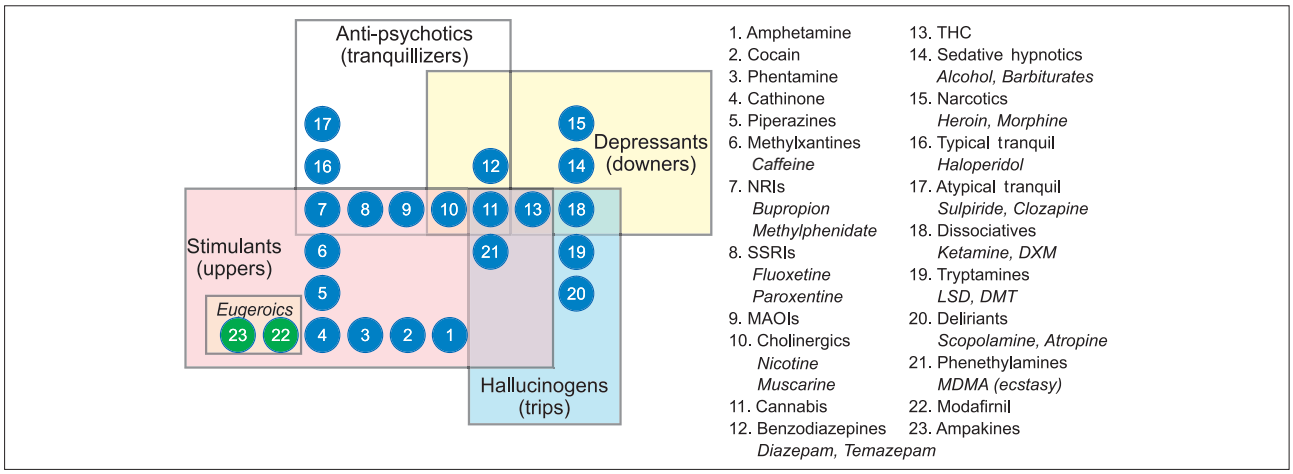

Figure 2. Classification of the psychoactive drugs.

NRIs, noradrenaline reuptake inhibitors; SSRIs, Selective serotonin reuptake inhibitors; MAOIs, Monoamine oxidase inhibitors; THC, Tetrahydrocannabinol; DXM, Dextromethorphan; LSD, Lysergic acid diethylamide; DMT, Dimethyltryptamine; MDMA, Methylenedioxymethamphetamine.

such as interference in recovery sleep, psychiatric disturbance, and addiction [5,30,31].

PHARMACOLOGICAL MECHANISM OF MODAFINIL

Modafinil has been clinically proven as an effective medication in treating narcolepsy, a disabling neurological disorder characterized by permanent and uncontrollable daytime sleepiness. Orexin, which is a family of wakefulness-promoting and sleep-inhibiting peptides, is involved in inducing narcolepsy [32]. The orexin neurons are found exclusively in the lateral hypothalamus and the orexin neurons in the hypothalamic area projects to the entire central nervous system [33]. Orexin neurons may be activated by modafinil. Thus modafinil may induce wakefulness by its action in the anterior hypothalamus [34]. However, the waking mechanism of modafinil on orexin neurons yet to be fully elucidated.

In a cat study, equal doses of amphetamine and methylphenidate increased c-fos gene expression in entire brain region including the caudate, but modafinil induced selectively and prominently the c-fos expression in hypothalamus of the brain [35]. Modafinil did not bind to most receptors related to sleep and wake cycle and did not inhibit monoamineoxidase or phosphodiesterase activities [36]. However, some other mechanisms of waking effects were proposed experimentally. Modafinil activates central alpha 1-adrenergic receptor as an agonist [37]. The currently proposed mechanism of modafinil suggests that modafinil induces alertness through alpha-adrenergic receptor. However, alpha-adrenergic transmission can not fully explain why the alpha-adrenergic receptors in only a specific part of the brain are activated for enhancing or maintaining wakefulness. Modafinil inhibits the reuptake of noradrenalin in the noradrenergic nerve endings. Therefore, the noradrenalin signal between sleep-promoting neurons of ventrolateral preoptic nucleus is amplified. An increase of excitatory glutamatergic signaling by a decrease in the local γ-amino butyric acid transmission is also a significant effect of modafinil [31,38,39]. Modafinil also amplifies cortical serotonin release [40]. Amplification of the electro-neurosecretory coupling mechanisms is preferentially involved in serotonin release by modafinil, while via reuptake process does not relate to serotonin release. Modafinil increases histamine release significantly in the anterior hypothalamus. However, modafinil did not induce histamine release in the orexin knockout mice [41,42]. That is, increase of histamine release by modafinil requires orexinergic transmission.

It has been known that modafinil may not be involved in dopamine release in the brain including the nuclear accumbens [37,43], although it seems that modafinil interacts with multiple molecular targets in the brain. However, in a recent research, addictive potential of modafinil has been reported [44,45]. There is substantial evidence that modafinil, just like other addictive drugs, is sensitive to dopamine signaling in the brain [30,45-47]. Modafinil preempts dopamine transporter (DAT) and norepinephrine transporters in a living primate brain [44]. It inhibits dopamine reuptake through DAT [48,49]. Therefore modafinil administration increases extracellular levels of dopamine in the brain [50-52], and wake-promoting actions are absent in the DAT-knock-out mice [50]. Modafinil blocks DAT and causes an increase of dopamine in the animals and human brain including the nucleus accumbens, thus inducing the same response as other waking drugs [45,49,52]. An increase of dopamine in the nucleus accumbens may be connected to drug abuse. The results of the experiment mentioned above are insufficient for a definitive evidence of addiction, since the main focus of those experiments was not addiction. However, these results lead to the possibility of addiction and have set the basis of prohibition on long-term medication of modafinil.

APPLICATION FOR THE COUNTERMEASURE OF FATIGUE

I. Anti-fatigue Agent for Cancer and Depression Patients

Fatigue is a usual symptom among cancer patients, which degrades their quality of life. Depression in cancer patients may also come with tiredness. In regard to treatment of cancer-related fatigue, methylphenidate has long been studied to be very effective, despite its side effects [9,53]. Modafinil was also well-tolerated and effective against fatigue in cancer patients when self-administrated for four weeks [10]. The mood and quality of life of those patients were improved. Modafinil has been applied effectively to treat fatigue associated with depression, amyotropic lateral sclerosis, and multiple sclerosis [11,54]. Modafinil is effective in lowering the elevated fatigue level of cancer or multiple sclerosis patients, but positive effects in cognitive dysfunction associated with diseases are still controversial [54,55].

II. Military Use of Modafinil as a Countermeasure of Combat Fatigue

Fatigue is a significant problem in a combat environment. Combat fatigue come mainly from sleep deprivation caused by extended duty periods, unpredictable work hours, circadian disruption, fear, anxiety, and many more. Combat fatigue by continuous sleep deprivation or sleep disorder can be mitigated by medication. Pharmacological countermeasure is

Table 1. The effectiveness of modafinil, amphetamine, caffeine against fatigue

	Restoring alertness	Duration of action (order)[a]	Subjectively reported adverse effects (order)[b]	Recovery sleep adverse effects
Modafinil	Effective	2	3	No
Amphetamine	Effective	1	2	Yes
Caffeine	Effective	3	1	No

[a] Duration of alertness-enhancing effect measured through psychomotor vigilance test was 13.5 hours for amphetamine, 11.5 hours for modafinil, and 5.5 hours for caffeine.
[b] More than 50% of caffeine group reported symptoms of nervousness, excitation, abdomen pain, dry mouth, tremor, nausea, and jitteriness. More than 50% of amphetamine group reported symptoms of excitation, happiness, and dry mouth. Modafinil group was not significantly different from placebo group in adverse effects.

to use hypnotics for deep sleep and sleep-control and/or waking drugs for enhancing alertness and improving psychomotor activities [26]. Modafinil along with the traditional psychostimulants, such as amphetamines and cocaine, has alertness-enhancing effect and mitigate the accumulated fatigue in combat environment [13,14,27].

The effectiveness of caffeine, modafinil, and amphetamine has been directly compared in a few studies, and the doses of equal effectiveness in enhancing alertness and vigilance for each of these three compounds were specified [22,27,56]. Administration of a single dose of caffeine 600 mg, modafinil 400 mg, dextroamphetamine 20 mg, or placebo after 44 hours of continuous wakefulness restored psychomotor vigilance effectively compared to placebo in healthy adults [27]. The duration of this effect was longest for dextroamphetamine and shortest for caffeine. At above doses, caffeine turned out to have the most "subjectively reported side effects", followed by dextroamphetamine. Dextroamphetamine was the only stimulant that had adverse effects on subsequent recovery sleep. Modafinil did not show significant, subjectively-reported side-effects nor subsequent recovery sleep compared to placebo. The effectiveness of these three stimulants is arranged in Table 1.

Modafinil is generally tolerated, and has few reported cases of adverse events. Modafinil improves task performance when medicated to people with normal living patterns. It is also more effective than amphetamine [57]. Modafinil may become a lifestyle drug without a restriction for narcoleptic patients. Also, the US military has shown interest in modafinil for increasing alertness and helping battle fatigue [8,13,14]. Moreover, when medicated to people with fatigue and lethargic reactions as symptoms of depression, modafinil generates a synergy by relieving fatigue as well as depression [11]. Modafinil has a great potential of becoming a combat-capability-enhancing drug due to its waking, mood-brightening, and fatigue relieving effects [2]. Elevated lethargy or fatigue under a combat environment or war can be decreased by modafinil, and this can also lead to an enhancement of combat capability through an improvement in vigilance, psychomotor activity, and self-regard.

III. Adverse Effects

In early studies, it has been known that modafinil is a well tolerated drug with a low probability of addiction. However, the possibility of addiction in modafinil was reported in recent papers mentioned above [44,45]. Modafinil induced the elevation of dopamine level in the nucleus accumbens, which could lead to drug abuse. Traditional waking drugs elicit dopamine in the nucleus accumbens of the brain. Modafinil increases dopamine in the nucleus accumbens through inhibition of DAT in the animal and human brain as other addictive waking drugs [44,49,52]. Classification of modafinil as an addictive is still controversial. Modafinil show possible setbacks of abuse and addiction even though no cases have been reported to date [45]. The pharmacological mechanism of modafinil must be further elucidated.

In general, we believe that sleep helps to build the immune system. Sleep deprivation induces stress responses and impairs immune functions [15,16]. However, reports for immunomodulating effects of modafinil for keeping wakefulness are quite limited. An investigation for immunomodulation effects of modafinil is a significant step in itself. The disruption of circadian rhythm and sleep control may influence the neuro-immune circuits [32,33]. A waking drug may have effects on neuro-immune circuits. If someone, who is a non-narcoleptic patient, wants to use modafinil for waking, enhancing their cognition, or brightening his mood, they may already be under a high level of stress, like soldiers in a battle field. It is possible that modafinil seekers already face quite a stressful situation. Stress responses via the hypothalamic-pituitary-adrenal axis start from corticotropin-releasing hormone (CRH) [58,59]. The waking effect of modafinil is related to CRH [60]. Modafinil cannot be excluded from investigation for immunomodulatory effects of stress. Serum C-reactive protein level, which indicates the inflammation level of an individual, was increased by a single dose of modafinil, while it reduced host resistance to *Listeria monocytogenes* infection [2].

Alertness-enhancing effect of modafinil may affect the autonomic nervous system in the periphery [61,62]. Modafinil increases resting heart rate and blood pressure. Modafinil elicits plasma and urine norepinephrine and urine epinephrine. Modafinil may induce sympathomedullary activation. Usage of modafinil could be restricted to patients with heart disease because it causes excessive peripheral autonomic activation. A few studies reported that modafinil impairs recovery sleep under sleep deprivation, although alertness-enhancing or cognitive-improving effect of

modafinil is significant among sleep-deprived individuals [12,63,64].

CONCLUSIONS

As modafinil gradually became known for its mood-brightening and memory-enhancing effects along with its waking effect, its usage has clearly increased as it is now medicated to treat memory loss due to dementia, ADHD, jet lag, and fatigue caused by extended work hours or illnesses. Also modafinil can be used by anyone who wishes to work late and/or concentrate for a long time. The demand for drugs is high among those in competitive environments such as high school students, examinees for new career development, and athletes. If someone who is not a narcoleptic patient wants to use modafinil for waking, enhancing their cognition, or brightening their moods, they may already be under great stress, like cancer patients or soldiers in a battle field. A psychoneuroimmunological approach is therefore needed to investigate multi-functional effects of modafinil. A psychoneuroimmunological approach may elucidate the immunomodulating effects of modafinil in the aspect of communication between the nervous and immune system.

In future studies, mechanism of modafinil will continue to be examined because modafinil may generate possible abuse and addiction and its waking mechanism has not been fully elucidated [36,45]. Also, its medication guidelines have to be revised because experiments on the dose and frequency of modafinil have shown different results under multiple simulations, and armodafinil, which is proven to be more safe and effective, has been commercialized as a substituent of modafinil.

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CONFLICT OF INTEREST

The author has no conflict of interest to declare on this study.

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