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# An Overview of the Clinical Uses, Pharmacology, and Safety of Modafinil

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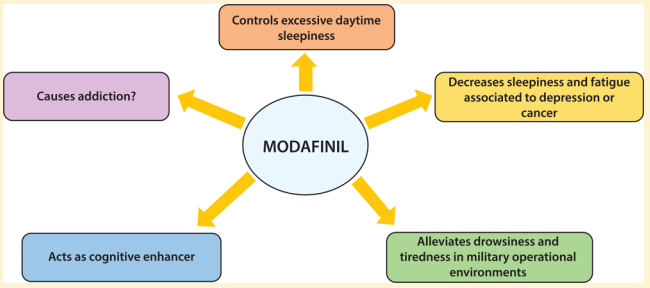
**ABSTRACT:** Modafinil (MOD) is a wakefulness-inducing compound prescribed for treatment of excessive daytime sleepiness as a consequence of sleep disturbances such as shift work sleep disorder, obstructive sleep apnea, restless leg syndrome, or narcolepsy. While providing effective results in patients with sleepiness, MOD also produces positive outcomes in the management of fatigue associated with different conditions including depression, cancer, or tiredness in military personnel. Although there is clear evidence of the stimulant effects of MOD, current data also show that administration of this drug apparently induces positive neurobiological effects, such as improvement in memory. However, serious concerns have been raised since some reports have suggested MOD dependence. Taken together, these findings highlight the need to characterize the changes induced by MOD which have been observed in several neurobiological functions. Moreover, further work should follow up on the likely long-term effects of this drug if used for treatment of drowsiness and tiredness. Here, we review and summarize recent findings of the medical uses of MOD in the management of sleepiness and fatigue associated with depression or cancer as well as exhaustion in military personnel. We also discuss the available literature related with the cognitive enhancing properties of this stimulant, as well as what is known and unknown about MOD addiction.




**KEYWORDS:** *Sleep, dopamine, hypocretin, treatment, drug, addiction*

## 1. INTRODUCTION

The sleep−wake cycle comprises the following neurobiological states: Wakefulness, slow wave sleep, and rapid eye movement sleep. For our purposes, sleep is defined as "...a recurring, reversible neuro-behavioral state of relative perceptual disengagement from and unresponsiveness to the environment. Sleep is typically accompanied (in humans) by postural recumbence, behavioral quiescence, and closed eyes...".[1] This definition of sleep emphasizes a relationship between concepts such as duration, efficiency, and timing which leads us to assume that sleep, like many other physiological phenomena, also displays pathological features with abnormal duration, altered efficiency and disrupted timing. Hence, sleep disturbances have been integrated for easier comprehension in the *International Classification of Sleep Disorders*.[2] The most common sleep problems among the population are insomnia and excessive daytime sleepiness,[3,4] the latter being characterized by the tendency to fall asleep during the day. This sleep

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alteration is present in approximately 20% of population.[5−7] The etiology of excessive daytime sleepiness comprises diverse factors and sometimes an underlying sleep disturbance is involved (e.g., insomnia, obstructive sleep apnea, narcolepsy, or restless leg syndrome).[8−12] There are behavioral, psychological, and pharmacological treatments aimed at managing excessive daytime sleepiness.[13−16] Although tiredness is a common problem in the population which can be mistaken for excessive daytime sleepiness, tiredness is a neurobehavioral reaction to physical and/or mental exhaustion which is usually relieved after rest or sleep.[17−21] A significant number of patients receiving treatments for depression or cancer report fatigue which differentiates from tiredness, compared to the rest of population.[22] Importantly, excessive daytime sleepiness (derived from obstructive sleep apnea, restless leg syndrome, or narcolepsy) or fatigue (associated with depression or cancer) is regulated by using modafinil (MOD). Given our increasing knowledge of the neuropsychopharmacological properties of MOD, it would indeed be ambitious to describe all available evidence. Thus, in this Perspective, we present a general overview of some recent publications available in PubMed regarding the uses of MOD to control excessive daytime sleepiness.[23−29] We also discuss the basic understanding of the uses of MOD to control fatigue associated with depression, cancer, or tiredness in military personnel. Next, we describe the putative cognitive enhancing abilities of MOD. Finally, we discuss what is known and unknown about MOD addiction. In-depth examination of the use of MOD for treatment of excessive daytime sleepiness is beyond the scope of this Perspective.

## 2. MODAFINIL

MOD is a drug that is commercially sold under the brand names of Alertec, Modavigil, or Provigil. Due to its possible addictive profile, this compound has been classified as a Schedule IV controlled substance in the United States of America. Decades of research have demonstrated that the wakefulness-promoting properties of MOD are present in multiple species, including humans.[23−28] Besides, the toxicology profile of MOD has shown fewer or no adverse effects compared to those reported in traditional psychostimulants such as amphetamine or cocaine.[29−31] In addition, MOD is generally well tolerated in animal models in contrast with other stimulants[32] and shows very low abuse liability (low reinforcing effects) in nondrug abusing individuals.[33] Finally, as in the case of other stimulants, official indications for MOD usage include the following critical information: "...serious side effects including a serious rash or a serious allergic reaction that may affect parts of your body such as your liver or blood cells. Any of these may need to be treated in a hospital and may be life-threatening..."[34]

Along with MOD, armodafinil (commonly known by the brand names of Artvigil and Waklert) is the enantiopure formulation of MOD which displays slightly more pharmacological potency and duration as a wakefulness-inducing compound compared to MOD.[35−41] Unlike the racemic formulation in 50/50 mix of both the (*S*) and (*R*) enantiomers, the molecular structure of armodafinil contains only the (*R*)-enantiomer of MOD. Despite the pharmacological characterization of armodafinil, sharing many behavioral effects with MOD,[35−41] the mechanisms of action of armodafinil remain to be described in detail. Lastly, it is worth mentioning that, in contrast to the positive therapeutic uses of MOD in controlling excessive daytime sleepiness, recent reports have suggested possible setbacks of abuse and addiction to this drug.[42,43]

## 3. MEDICAL USES OF MODAFINIL

**3.1. Positive Results Using Modafinil to Control Excessive Daytime Sleepiness.** There is evidence showing the positive outcomes of using MOD for treatment of excessive daytime sleepiness caused by sleep disturbances such as shift work sleep disorder, obstructive sleep apnea, or narcolepsy. There is both experimental and clinical data supporting the efficiency and efficacy of MOD in the management of excessive daytime sleepiness.[44−47] Moreover, several reports have indicated the positive uses of MOD for treatment drowsiness associated with nonsleep disorders.

The existence of evidence regarding the contribution of MOD to managing excessive daytime sleepiness has been widely recognized. Here, we have presented a general overview of the positive pharmacological benefits of MOD in treating excessive somnolence in some recent publications.[3−15,20,23−30,38,46−48] The data available suggest that MOD also controls excessive somnolence and fatigue in nonsleep disturbance circumstances. In the following sections, we present this evidence.

**3.2. Prescription of Modafinil Decreases Sleepiness and Fatigue Associated with Depression or Cancer.** Depression is a mood disorder characterized by distressing symptoms such as persistent sadness, thoughts of suicide, anxiety, loss of interest or pleasure in hobbies or usual activities, feelings of hopelessness, excessive sleepiness and fatigue. In addition, depression is prevalent in patients with health disorders, including cancer.[49] It is well established that cancer patients often report fatigue, which is defined as extreme tiredness caused by a deficit of energy as a consequence of chemotherapy.[50,51] Numerous reports have demonstrated that intake of MOD mitigates drowsiness in depressed patients and blocks the fatigue linked to cancer. In this regard, a daily dosage of 100−200 mg of MOD given to these patients promotes feelings of energy and alertness.[52−58] Although sleepiness and tiredness associated with depression or cancer are effectively controlled with MOD, further work is needed to distinguish the mechanism of action of this drug in the modulation of drowsiness and fatigue associated with both clinical conditions, with emphasis on subject characteristics, including comorbidity of depression or cancer.

**3.3. Modafinil Intake Alleviates Drowsiness and Tiredness in Military Operational Environments.** Sleepiness and fatigue are critical problems faced by military personnel undergoing sleep deprivation as a consequence of prolonged waking in combat environments.[59,60] The effectiveness of stimulants such as caffeine and amphetamines in handling drowsiness and tiredness in military personnel has been previously studied.[61,62] For example, when oral doses of MOD were given to military operations personnel, their drowsiness was reduced compared to a control group.[63] One well-designed study has been carried out on helicopter pilots who received three doses of MOD (100 mg) at 4 h intervals during periods of 40 h of continuous alertness. After MOD intake, the subjects showed higher levels of alertness and improved cognitive functions.[64] In conclusion, current evidence suggests that MOD controls sleepiness and fatigue in military personnel.[61−64]



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## 4. MODAFINIL COULD BE MODULATING SLEEP HOMEOSTASIS MECHANISMS

While this compound promotes wakefulness by reducing sleepiness, we do not exclude the plausible possibility that MOD might exert an influence on sleep homeostasis. Under normal conditions, the homeostatic drive of sleep is enhanced when alertness is maintained beyond habitual bedtime, and it dissipates with an enhancement in the intensity and duration of sleep. This neurobiological feature is known as "sleep rebound".[65,66] Although long-term effects of MOD in patients with excessive daytime sleepiness have shown it to be effective and well tolerated,[67,68] sleep rebound effects caused by chronic use of MOD as a consequence of sleep homeostasis disruption are still unknown. Indeed, we do not yet know the effects that MOD might induce in sleep rebound. This intriguing but as yet unexplored observation raises questions about the properties of MOD in the control of neurobiological mechanisms of sleep homeostasis. Thus, these assumptions highlight the need for studies aimed to test whether MOD plays a role in sleep homeostasis control. Since many of the therapeutic uses of MOD are under a chronic schedule, it remains to be described whether MOD would induce undesirable effects derived from long-term consumption.

## 5. MODAFINIL AS A PRESUMED COGNITIVE ENHANCER

Memory is the neurobiological function whereby critical information is retained and recalled at a later time.[69] Cognitive improvements have been reported in experimental animals receiving MOD (200−300mg/kg),[70] and such changes have also been demonstrated in humans. In line with this, potential uses of MOD for improving memory in disorders such as neurodegenerative diseases or psychiatric conditions have been suggested. For example, Fernández et al. reported that students that used MOD improved their answers in the Stroop Test.[71] Similar findings were observed in patients with multiple sclerosis that received a single daily oral dose of MOD (200 mg). They showed an enhancement in working memory tasks tested in the Wechsler Adult Intelligence Scale-III.[72] In support of this, Lees et al. reported that MOD (200 mg) improved learning in patients with early schizophrenia.[73] Taken together, the emerging evidence suggests that MOD seems to promote cognitive enhancement.[73−79] These findings have been partially explained by neurobiological changes such as hippocampal neurogenesis.[80] However, it is worth noting that these results appear to be related to single doses, so prospective and/or longitudinal studies should be considered in the near future to investigate:

(i) What are the long-term neurobiological effects in learning and memory after chronic use of MOD?
(ii) What are the neuromolecular mechanisms activated by long-term MOD intake for memory improvement in healthy volunteers, multiple sclerosis patients, or schizophrenia patients?

To expand our knowledge, we should try to design new experiments aimed at addressing these unanswered questions.

## 6. MECHANISM OF ACTION OF MODAFINIL

It is widely accepted that MOD induces alertness by activating wakefulness-related systems such as hypocretin, histamine, $\alpha$-adrenergic, glutamate, and dopamine (DA).[81,82] Most of the evidence regarding the wakefulness-promoting properties of MOD has been obtained by studying the role of this drug in dopaminergic neurotransmission. Experimental studies have suggested that MOD blocks the activity of DA transporter (DAT) increasing the contents of DA.[83] Complementarily, MOD modulates norepinephrine (NET) or serotonin (SERT) transporter activity as well. For example, Madras and co-workers described how, in rhesus monkeys, MOD occupied striatal DAT sites (5 mg/kg, corresponding to 35% of occupancy), whereas in the thalamus MOD bound to NET at 16% (5 mg/kg).[84] Moreover, in vitro studies have reported that MOD inhibited [$^3$H]dopamine ($IC_{50}$ = 6.4 $\mu$M), [$^3$H]norepinephrine ($IC_{50}$ = 35.6 $\mu$M), and [$^3$H]serotonin ($IC_{50}$ > 500 $\mu$M) transport via human DAT, NET, and SERT.[85] The wakefulness-promoting effects of MOD might be produced by binding to allosteric sites on the DAT in similar fashion to cocaine.[86−88]

On the other hand, it has been also demonstrated that MOD enhances excitatory glutamatergic neurotransmission in several brain areas such as the ventromedial and ventrolateral hypothalamic nuclei, thalamus and hippocampus.[89−94] In addition, *c*-Fos expression in hypocretinergic neurons in hypothalamus in MOD-treated rats was found higher compared to respective controls.[95] In a later study, MOD administered to hypocretin null mice (10, 30, and 100 mg/kg) increased waking compared to wild-type animals.[96] At present, therefore, the hypocretinergic system also responds to MOD pharmacological challenge.[97,98] Finally, several observations have been reported regarding the influence of MOD in the modulation of sleep-inducing systems such as GABA.[91,99] Nevertheless, there are areas that require further research. For example, the progress that has been limited pertains to the field of sleep-inducing molecules, including adenosine (AD). In this regard, the results of one study showed that systemic administration of MOD (30 mg/kg) at the beginning of the lights-on period of rats, decreased extracellular levels of AD as determined by microdialysis and HPLC means.[100] Future studies should aim at providing an additional picture of the pharmacological properties of MOD in the modulation of sleep-promoting compounds.

## 7. ADDICTION TO MODAFINIL

Despite the efficacy of MOD for managing excessive daytime sleepiness and fatigue, and apparently improving cognitive functions,[3−15,20,23−30,38,46−64,67,68,70−80] critical studies are required to fully understand the likely risk of addiction to this drug (Table 1). In recent years, special attention has been given to a limited but growing body of evidence suggesting that MOD has a potentially addictive profile, since this drug promotes reward as described in cocaine-dependent animals.[101] In this regard, Dhillon et al. reported a case of MOD addiction in a 23-year old man who was under a schedule of using this compound (200 mg) during 6 weeks to treat daytime sleepiness and fatigue following methamphetamine withdrawal.[42] Similar findings of addiction to MOD have been reported in schizophrenic patients[102] as well as in experimental animals. For instance, Mereu et al. reported that systemic injections of MOD (17−300 mg/kg) in mice showed cocaine-like subjective effects.[76] Importantly, cocaine-treated animals showed an enhancement in dependence when cocaine and MOD were administered in combination. Despite these hazardous results, MOD has been proposed as a candidate for the treatment of cocaine addiction.[103,104] However, it is unclear if MOD would be considered as a pharmacological approach for managing


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**Table 1. Summary of some medical uses of modafinil to control excessive sleepiness and fatigue associated with depression or cancer, managing tiredness in military personnel or as a cognitive enhancer. No current evidence is available regarding the neuromolecular mechanism of action of modafinil in controlling fatigue linked to depression, cancer or tiredness in military staff as well as putative addiction to this compound**

| physiological condition | pharmacological effects of modafinil | neuromolecular mechanism of action | refs |
|---|---|---|---|
| sleepiness | decrease significantly the somnolence observed in sleep disorders such as narcolepsy | partially described: evidence of the activation of glutamatergic, dopaminergic, hypocretinergic, histaminergic, $\alpha$-adrenergic system and decreases activity of GABAergic neurotransmission | 3−15, 20, 23−30, 38, 46−48 |
| fatigue associated to depression | reduce significantly the fatigue and depressive symptoms in patients with depression | unknown | 52−58 |
| fatigue associated to cancer | diminish significantly the fatigue in patients with cancer under chemotherapy | unknown | 52−58 |
| fatigue associated to military combat | decline significantly fatigue and promotes well-being feelings in soldiers | unknown | 61−64 |
| cognition | facilitate learning and memory | unknown | 70−79 |
| addiction | potentially promote addiction | unknown | 42, 76, 105−108 |

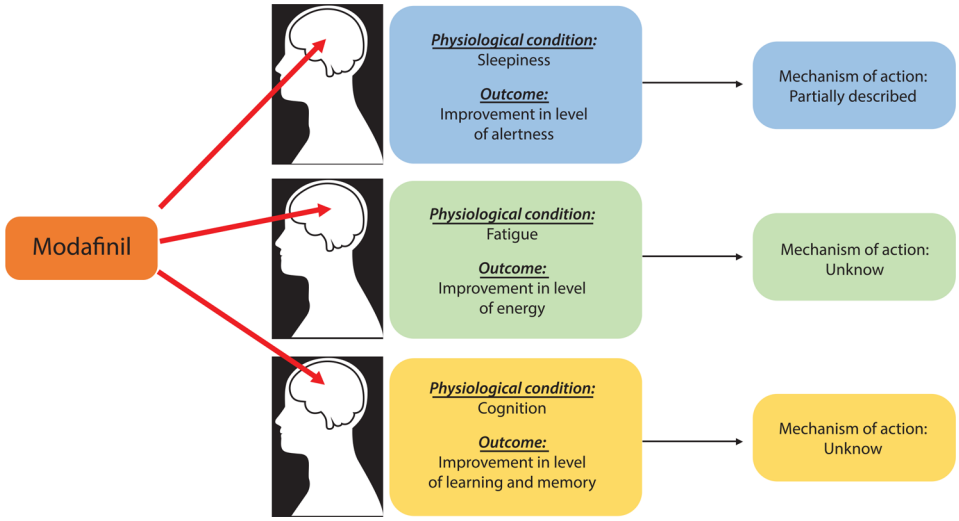


**Figure 1.** Modafinil combats sleepiness and fatigue, and enhances learning and memory. Despite the positive outcome of MOD, further evidence is needed to describe the neurobiological mechanism of action of this drug in control of fatigue and cognition.

cocaine addiction. Whether MOD is addictive, it should be under vigilance as suggested.[105−108] Altogether, it is difficult to predict whether addiction to MOD represents a public health problem based on few and limited studies (Table 1). In particular, there are individual case reports but no long-term pharmacovigilance studies or dependence/tolerance data. Approaches to elucidating the probability of addiction to MOD should consider an integrative perspective addressing the behavioral disorder profile (by drug self-administration procedures), brain reward circuitry activity (neurobiochemical studies or electrophysiological experiments using the novel technique of optogenetics) and gene expression (including analysis of CREB [cAMP response element binding protein]).[109,110]

## 8. CONCLUSIONS AND FUTURE DIRECTIONS

As mentioned, MOD manages excessive daytime sleepiness and fatigue, and improves learning and memory.[3−15,20,23−30,38,46−64,67,68,70−80] However, there is evidence that suggests the putative risk of developing addiction to this drug.[42,101,102,105−108] To fully understand the pharmacological effects of MOD on the control of fatigue and improvement in cognition, the mechanism of action of this drug should be described (Figure 1). On the other hand, along with evidence showing the positive outcomes of MOD in controlling sleepiness and fatigue associated with depression or cancer, as well as drowsiness reported in military personnel, missing data regarding its positive effects in controlling drowsiness in diseases such as fibromyalgia, anemia, diabetes, and burnout syndrome, among others, is required. Moreover, it remains to be demonstrated whether MOD is able to improve cognitive impairment in learning disabilities, including attention deficit hyperactivity disorder, executive dysfunction, and dyslexia, just to mention a few. Our knowledge of the possible long-term effects of using MOD is extremely limited, partially because of associated factors such as dosage (low or high dose), frequency of usage (daily vs intermittently), and route of administration (central of peripheral), among other circumstances. Lastly, several randomized, double-blind, placebo-controlled studies have determined the efficacy of MOD for the treatment of excessive daytime sleepiness, fatigue, and cognitive functioning.[109−115] However, this body of evidence is still incomplete since there is the need for external validity of data as well as longitudinal studies that follow up on whether the positive outcomes of medical uses of MOD persist across time and whether addiction to this drug can be discounted.

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E.M.-R. designed, and wrote the manuscript. A.B.V., N.B.R., H.B., and S.M. revised the manuscript sections. All authors revised the whole paper and approved the final version of the manuscript.

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### Notes

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## ■ ABBREVIATIONS

AD, adenosine; CREB, cAMP response element binding protein; DA, dopamine; DAT, DA transporter; MOD, modafinil; NET, norepinephrine transporter; SERT, serotonin transporter

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