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TITLE: The Use of Modafinil in Operational Settings: Individual Difference Implications

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ADP010453 thru ADP010473
The use of modafinil in operational settings: individual differences implications

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Abstract

Disruptions in wake-sleep rhythms, particularly induced by SUSOPS and CONOPS, are limiting factors for military personnel in operation. Pharmacological aids, such as hypnotic or stimulant substances can be effective countermeasures. Modafinil (MODIODAL®, PROVIGIL®) is a synthetic molecule prescribed for the treatment of narcolepsia and idiopathic hypersomnia. The wakening effect is potent: modafinil allows healthy volunteers to stay awake and efficient for more than 60 hours, without side effects. Its mechanism of action is complex, and it could induce wakefulness by different mechanisms, as compared with other classical vigilance enhancing drugs such as amphetamines. A neuroprotective effect against neurotoxic organophosphate agents was recently discovered. Modafinil seems to be a powerful and safe countermeasure in the management of sleep-wake rhythm during operational situations.

Introduction

The use of drugs in sleep-wakefulness management during operational settings is changing a lot according to the fast development of new generation of psychotrops. During the second world war, the use of amphetamines was widely spread in the military personal, especially US army (16). Later during Falklands conflict, benzodiazepines were used, in a controlled manner, by the pilots of the Royal Air Force (13). During the Persic Golf war, a new and original substance, called modafinil, was used for the first time by french military personal under a very strict medical control (while american military personal used dextedrine) (5). Before the presentation of modafinil properties, we will see why we have to use a stimulant and what kind of stimulant to use.

The choice of a stimulant

The choice of a psychotrop and especially of a stimulant to manage the vigilance come from the antinomia between physiological requirements and operational requirements.

Globally, each subject must respect his own quota of sleep, his own sleep type and his circadian rhythms. Generally, most people need between seven and eight hours of sleep. But some of them, sleep five hours or ten hours; we called them small and big sleepers and it is an inborn characteristic. The specific type of sleep is also a physiological requirement. Some people are morningness type, it is to say that they are very operational during the morning and are out of order after 10 p.m. We called them "skylark". On another hand, some people are eveningness type, they have the maximum of their capacity in the evening and are able to stay available and efficient very late, but they can not awake up early in the morning. We called them "barn-owl".

The result of circadian propensity to drowsiness is also very important. Everybody has two pics of drowsiness, one during the day located just after the lunch in a post-meridian period, the other during the night between 02 a.m. and 06 a.m. in the early morning. At the opposite, during the morning, around 10 a.m. and in the
afternoon between 6 p.m. and 10 p.m., we have a top level of vigilance. This daily fluctuation is found again with the level of performance (cognitive, psychomotor and physical performance). If we respect all these physiological requirements, we will have the maximum of efficiency.

But the problem is induced by operational requirements. During sustained operations (SUSOPS) it is impossible for the soldier to sleep, sometimes during one or two consecutively days. During continuous operations (CONOPS) the soldier can sleep but not in a usual way, it is to say sometimes during the day and not during the night, sometimes two or three hours i.e. a disrupted sleep, and sometimes in a disturbed environment (noise, heat, light, etc...) This operational environment induces a decrease in vigilance and performance levels with fatigue, which can provoke a dramatically decrease of security and efficiency:

### OPERATIONAL REQUIREMENTS

<table>
<thead>
<tr>
<th>SUSOPS</th>
<th>CONOPS</th>
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<tbody>
<tr>
<td>Vigilance and performance</td>
<td>Security and efficiency</td>
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Troops deployment (transmeridian flights, sleep deprivation,...)

To help the subject to maintain a good level of vigilance and performance and to preserve his security, some counter measures must be proposed. Some of them concern the physiological management with recommendations about how to take a nap or what kind of meal to eat. Others concern pharmacological management and are used when the previous one are inefficient or inapplicable. It could be substances to induce sleep (hypnotics) or substances to prolong wakefulness.

**• THE CHOICE OF AN ORIGINAL SUBSTANCE**

To prolonge wakefulness, as to induce sleep, we follow a pharmacological concept which presents three main points:
- this substance has to preserve the subject from deleterious effects of sleep disturbancies,
- it can be easy to use,
- the administration of this substance has not to induce side effects.

For these reasons, we eliminate drugs with side effects as amphetamines and amphetamine-like substances and also caffeine solution in case of repeated administration with a dose superior to 600 mg. The choice was given to a new and original waking substance called modafinil (MODIODAL® or PROVIGIL®) studied in our laboratory since 1981 and classed by Jouvet (2) as an eugregoric substance (in grec : eu = good and gregor = wakefulness).

**• THE MAIN PROPERTIES OF MODAFINIL**

- **Indications**
  Modafinil = (diphenyl-methyl) sulfinyl-2-acetamide is a vigilance enhancing drug indicated in the treatment of narcolepia and idiopathic hypersomnia. It is synthetized by L. LAFON laboratory (France).

- **In human healthy subjects (all references are in 15)**
  Modafinil was also used in human healthy subjects as control population for the study of the interest of the substance in narcoleptic people: Benoit et al. (1987), Goldenberg et al. (1987), or as healthy people submitted to a sleep deprivation period: Puech and Bensimon (1987), Saletu et al. (1989), Lagarde et al. (1993, 1995a, 1995b, 1997, 1999), Bourdon et al. (1994), Pigeau and Buguet (1995).

- **The awakening property**
  Modafinil presents a strong awakening effect during 60 hours of sleep deprivation. The performance is maintained at the same level than in reference period during 48 hours:

![Graph showing comparative changes in performance at the tracking test under placebo and modafinil](chart)

Comparative changes in performance at the tracking test under placebo and modafinil (from 7)

No side effect was found when a correct dose (200 mg) was administered every eight hours. One of the most interesting characteristic of modafinil is that it is not an anti-sleep substance but a vigilance enhancing drug. It is to say that it is possible to sleep, when the environment is available even if you took a pill, one or two hours before (3, 8). During a sleep deprivation period, this substance deletes microsleeps on EEG, increases the sleep latency (compared to placebo) and maintains the cognitive and psychomotor performance.

- **The neuroprotective effect**
  We examined the neuroprotective effect of modafinil agonist soman-induced hippocampus damage. In mice, modafinil administered at 600 mg.kg⁻¹ i.p. 2 hours before...
soman significantly reduced the density of hippocampus
$\omega_3$ peripheral benzodiazepine binding sites, an indirect
marker of neuronal damage, as compared to soman
control animals. This was confirmed in rats (10).
Similar results were found by another team on cerebral
cortical cultures (1).

**AN ORIGINAL MECHANISM OF ACTION**
The mechanism of action of modafinil is original and
complex. Studies realized showed that modafinil acts as
an agonist of $\alpha_1$-adrenergic post-synaptic receptors (4).
It binds to the dopamine uptake carrier site with low
affinity (12). At high doses, pimozide can partially
antagonize the behavioral and EEG effects of modafinil
(3). It increases turn-over of serotonin in striatum (14),
decreases cortical inhibitory aminoacids (glutamate)
outflow (14). It increases intracellular and decreases
extracellular level of excitatory aminoacids (aspartate
and glutamate), and also increases energetic pool
(creatine/phosphocreatine) and decreases metabolic
amino acids (14). Lin et al. in 1996 (11) showed that
modafinil could act upon anterior hypothalamus
nucleus.

To summarize it is possible to say that the $\alpha_1$-adrenergic
post-synaptic effects seem to be prominent; at high
doses, dopaminergic effects seem to appear. Moreover
(at high doses) aminoacids neurotransmission system
seems to be involved. Brain energetic effect could
participate in the pharmacological action.

**THE USED PROPOSALS**
Concerning only the wakening property, two kinds of
attitudes are or could be adopted. In peace time: no
drug must be used included training period: the
management of people must not include drug
administration. One exception is the crash of helicopter
or plane: to facilitate the waiting period between crash
and rescue, modafinil is available in the kit located
under the seat of the pilot. Like that the ejected pilot can
stay awake two days to wait for the rescue.

In war time, the order to use modafinil is only given by the
high command, the health service gives only
advices. The directions for use depend of the operational
situation and are confidential.

Concerning the individual differences implications, in
healthy subjects we never found differences related to
age or gender, but the differences observed concern the
weight and sometimes individual susceptibility (9). To
avoid these differences, a test could be done, starting
with one pill (100 mg), then trying two pills (200 mg).

**CONCLUSION**
Nowadays, SUSOPS and CONOPS are, unfortunately,
spread all over the world. The respect of the soldier's
physiology, to maintain his vigilance and performance
but also his security, seems to be now taken into account;
the operational sleep management is more and more
employed, because of new compounds as modafinil easy
to take, very powerful and very safe. Nevertheless, their
use has to be under control.

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