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Modafinil : its discovery, the early European and North American experience in the treatment of narcolepsy and idiopathic hypersomnia, and its subsequent use in other medical conditions

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Abstract

Adrafinil, a new molecule identified by a French drug company, L. Lafon Ltd, in 1974, turned out to cause a significant dose-dependent increase in motor activity in mice, without exerting peripheral sympathomimetic effects. As early as 1977-78, Michel Jouvet prescribed adrafinil to narcoleptic patients, but without consistent results. Meanwhile the kinetics of adrafinil led to the identification of an active metabolite, modafinil. In 1983, Jouvet and Bastugi prescribed modafinil to narcoleptic and idiopathic hypersomnia patients and obtained a significant decrease of excessive daytime sleepiness and sleep attacks in a majority of patients. L. Lafon Ltd was initially not interested in developing this molecule for market but, thanks to Jouvet's insistance, it decided to start clinical trials in both healthy volunteers and narcoleptic patients as well as to conduct animal studies. Results were excellent and lead to the use of modafinil by the French army during the Gulf War in January-February 1991, as well as to the official registration of the drug in France in 1992. Subsequent multicenter controlled clinical trials in North America confirmed the findings in Europe. Modafinil was later used to treat sleepiness, somnolence and fatigue in a large number of medical conditions.

1. The discovery of adrafinil and modafinil

The history of modafinil dates back to 1974 in France. While they were screening molecules in search of analgesics two chemists, Gombert and Assous, from L. Lafon Ltd, a pharmaceutical company based in Maisons-Alfort near Paris, identified a new molecule [benzhydryl sulfinyl-2 acetohydroxemic acid], called adrafinil. This molecule was later passed on to two pharmacologists, Duteil and Rambert, also from L. Lafon, Ltd. The intraperitoneal injection of adrafinil in male mice of the NMRI strain caused a significant dose-dependent increase in motor activity without exhibiting peripheral sympathomimetic effects [1].

As early as 1977-78, Michel Jouvet, working in the Clinical Neurophysiology Unit of the Neurological Hospital in Lyon, France, prescribed adrafinil to narcoleptic patients. He used a single

blind protocol, as he always refused to use a double-blind protocol in narcoleptic patients. The results were largely inconsistent.

2. Early animal studies

Adrafinil was subsequently provided to Jouvet for evaluation in the cat, and to Milhaud and Klein, from the *Centre d'Etudes et de Recherches de Médecine Aéronautique (CERMA)*, for evaluation in the rhesus monkey [2]. A decrease in sleep and increase in wakefulness were found in the cat, whereas the dose of 60 mg/kg doubled the monkeys' nocturnal activity, and doses of 90 and 120 mg/kg increased it fourfold, the activity level becoming practically identical to diurnal activity. Interestingly, no sedative effects on withdrawal were observed during the post treatment phase.

A later and more sophisticated study, also performed in male mice of the NMRI strain, caused an increase in locomotor activity, an antagonism of the hypnotic effect of barbital, a reduction of the duration of immobility in the forced swimming test, a slight reduction of electroshock-induced convulsions, no modification of rectal temperature, no stereotyped or climbing behavior, and no increase in lethality in aggregated mice [3]. Adrafinil, therefore, had behavioral-activating effects without the undesirable side effects of known stimulant**s.**

3. The evolution towards clinical trials

At that time, L. Lafon Ltd did not have the capacity to run a full study of adrafinil which would be needed to obtain official registration of the drug. However, Sandoz Ltd was in search of a molecule to replace hydergine, which was a combination of dihydroergocornine-dihydroergocretine and dihydroergocryptine, used to improve cognitive abilities and self-care functioning in aged persons. Clinical studies were conducted in France and published in French. The subjects examined in these studies were typically outpatients aged 45 years or older who had problems in focusing attention, sleep, memory, and mild depression [4-8]. The collective results of these studies were that adrafinil can be highly beneficial in the treatment of elderly patients showing deficits in vigilance, attention, behavior and mood. Adrafinil eventually reached the market in France in 1984.

Earlier, in 1976, kinetic studies of adrafinil had led to the identification of an active metabolite [2-(diphenylmethyl) sulfinylacetamide], also known as modafinil. In early 1983, Jouvet and Bastugi prescribed modafinil to narcoleptic and idiopathic hypersomnia patients, again in a single

blind protocol, and the results were excellent and surpassed all expectations [9-10]. However, Mr Louis Lafon was reluctant to develop modafinil for market, due to the orphan disease status of narcolepsy. It took Jouvet's insistence on the need to develop modafinil in order to convince Louis Lafon to start clinical trials in both healthy volunteers and narcoleptic patients, and also to run animal studies.

4. The first clinical testing of modafinil

The first studies of the effects of modafinil on both night sleep and daytime sleepiness in healthy volunteers were conducted by Goldenberg et al. in Paris [11] and by Saletu et al. in Vienna [12]. After a single evening dose of modafinil 200 mg or placebo in parallel groups, Goldenberg et al. found that modafinil led to a decrease in total sleep time, a decrease in NREM stages 3 and 4, no modification of REM sleep, and no rebound phenomena during the withdrawal period. In addition, the mean sleep latency on the Multiple Sleep Latency Test increased in every single session following a single dose of modafinil, 200 mg at 10 a.m. Saletu et al. compared the effects on night sleep of modafinil at 100 and 200 mg doses and to d-amphetamine at 10 and 20 mg, both to placebo, in young healthy volunteers. The decrease in sleep efficiency was much less with modafinil than with amphetamines.

Studies in patients with narcolepsy and hypersomnia and matched healthy volunteers were assessed using open-label trials. These studies were performed at the Pitié-Salpêtrière Hospital in Paris. Positive responses to modafinil were presented as free communications in sleep congresses by Garma et al. [13] and by Laffont et al. [14].

5. Modafinil studies in animals

Modafinil went through the same steps of development as did adrafinil in several animal species. These studies demonstrated a dose-dependent increased locomotor activity in mice [15-16], a wakening effect at the dose of 6 mg/kg in rhesus monkeys [17], an increase in nocturnal activity and in behavioural arousal without stereotyped behaviour in rhesus monkeys |18], an increase of wakefulness and a decrease of sleep in the cat |19], and a lack of pre-synaptic dopaminergic involvement with modafinil in anaesthetized mice using in vivo voltammetry studies [20].

6. Multicenter controlled randomized studies in patients with narcolepsy

The first multicenter, randomized, placebo-controlled trial of modafinil was subsequently conducted in 50 narcoleptic patients (33 men and 17 women) [21]. Modafinil was administered in a double-blind cross-over design, at a dosage of 300 mg compared to placebo. The duration of the study was 12 weeks and included a 2-week « run in » period with placebo, a first 4-week treatment period with either modafinil or placebo, a 2-week wash-out period with placebo, and a second 4-week treatment period with either placebo or modafinil.

Daily evaluation was based on a sleep log, visual analog scales, a sleep questionnaire and a clinical global index. Sleep laboratory evaluation took place on nights 1, 28, 42 and 70. It included one night of polysomnography preceded by a questionnaire on the therapeutic effect and side effects, and was followed by a Maintenance of Wakefulness Test (MWT). Sleep logs did not show any modification of night sleep, but there was a reduction of daytime sleepiness and sleep. Mood on awakening was not not modified. An overall clinical benefit was noted by both the physicians and the patients. Above all, there was a significant improvement in the results of the MWT for patients on modafinil compared to placebo ($p < 0.05$). In June, 1992, modafinil was officially registered for the treatment of narcolepsy in France . It became commercially available in September 1994. Further research including preclinical, phase I trials and multicenter, randomized, placebo-controlled,were conducted by Cephalon Ltd who originally leased the rights from L. Lafon Ltd in 1993, and eventually purchased the company in 2001.

7. The first military use of modafinil

During a press conference at an international NATO defense meeting in Lyon, France in March 1987, Jouvet claimed that modafinil had a potential military application since it has many characteristics which would make it preferable to the amphetamines as a stimulant medication. He asserted that modafinil « could keep an army on their feet and fighting for three days and three nights with no major side-effects ». It is therefore no surprise, that as the Gulf War (August 1990 – February 1991) was breaking out, and French troops were to be sent to Irak, the French Ministry of Defense demanded that L. Lafon Ltd, provide the French army with modafinil to test the drug in normal military subjects before a possible use in military operations. The drug was first tested in eight normal military subjects undergoing sleep deprivation for 60 h [25]. Modafinil 200 mg or placebo was given every 8 hours for 3 days. The results on cognitive tests were positive and no consistent adverse effects were noted.

In January 1991, military doctors accompanying the « Daguet » operation (the name given to the French participation in the international coalition) were allowed to prescribe modafinil. The

drug was also used during « Operation Desert Storm » (17 January - 28 February 1991), mainly by military air pilots and mechanics. Unfortunately, the prescribing of modafinil was not scientifically conducted, being inconsistent in terms of dosage and timing. Moreover, an aerial and ground combat zone is not the best environment to test a novel compound. In summary, the role of Michel Jouvet in the development of adrafinil and modafinil can be described as pivotal. He was the first to test adrafinil and modafinil in patients with narcolepsy or idiopathic hypersomnia. This was done as soon as pharmacologists revealed the increased in motor activity in mice and was long before any clinical trials occured. He was also the only researcher to test the activity of these drugs in the cat. His insistance in developing and marketing modafinil was determinant in convincing Louis Lafon to start clinical trials and animal studies. As well Michel Jouvet demonstrated the interest of modafinil for treating soldiers during military operations.

8. The first North American clinical trials of modafinil in narcolepsy

The first North American clinical trial of the effects of modafinil in narcolepsy in North America was a 9-center Canadian study published in 1997 [23]. Seventy-five patients meeting international diagnostic criteria were enrolled in a 6-week, three-period, randomized, crossover, placebo-controlled trial. Patients received placebo, modafinil 200 mg or modafinil 400 mg in divided doses, morning and noon. Patients were evaluated at baseline and at the end of each 2-week period. Modafinil at 200 and 400 mg per day both significantly increased the mean sleep latency on the Maintenance of Wakefulness Test (by 40% and 60%, respectively), but this difference between doses was not significantly different. Modafinil at both doses reduced the number of daytime sleep episodes and periods of severe sleepiness noted in sleep logs. The likelihood of falling asleep as measured by the Epworth Sleepiness Scale was reduced equally by both dosages of modafinil.

There were no significant effects on nocturnal sleep latency, sleep maintance or architecture, nor on co-existant sleep apnea or periodic leg movements. No effect was seen on the patients' ability to voluntarily nap during the daytime, nor for the amount or quality of nocturnal sleep. There were no effects on blood pressure or heart rate in either normotensive or hypertensive patients. The only significant adverse effects were seen at the 400 mg dosage which was associated with more nausea and more nervousness than placebo or the 200 mg dose. A small number of patients noted mild headache which usually disappeared in the second week of treatment. In sum the study confirmed earlier European studies by showing that modafinil is an effective and well-tolerated treatment for excessive daytime sleepiness in narcolepsy and lacked sympathomimetic autonomic effects.

The initial trial of modafinil in narcolepsy in the USA was published in 1998 [24]. It used a quite different protocol to assess patients suffering from narcolepsy on the effects of two doses of modafinil versus placebo. It was a placebo-controlled, double-blind, randomized, parallel-group, 18-center study involving 283 subjects with narcolepsy. They received either modafinil 200 mg or 400 mg, or placebo, for 9 weeks followed by an open-label treatment period. Subjective sleepiness was assessed using the Epworth Sleepiness Scale, objective sleepiness was measured using the Maintenance of Wakefullness Test, and intensity of illness was assessed by the Clinical Global Impression of Change. Modafinil significantly reduced all measures of sleepiness and significantly improved the intensity of illness. Adverse effects were few, dose-dependent and usually rated as mild to moderate. Modafinil taken once daily was a well tolerated and effective wake-promoting agent for treating excessive daytime sleepiness in narcolepsy. The open-label treatment period showed that modafinil had an excellent safety profile for up to 40 weeks and that efficacy was well maintained suggesting that tolerance will not develop in long-term use. It was concluded that modafinil was a promising compound for the treatment of pathological daytime somnolence.

This US publication was followed in 2000 by publication of a companion study by the same multi-center trial group [25]. It was a 9-week randomized, double-blind, placebo-controlled study in which 271 narcolepsy patients naive to modafinil who were randomized to receive fixed daily doses of modafinil 200 mg, modafinil 400 mg, or placebo. A 2-week placebo-controlled discontinuation phase was included to evaluate the effects of withdrawal on patients who had been receiving modafinil. The full cohort of 271 patients received the study medication in the 9-week trial, and 240 patients received study medication in the discontinuation period. Treatment with modafinil significantly improved two measures of EDS : the Multiple Sleep Latency Test and the Maintenance of Wakefulness test. The Epworth Sleepiness Scale showed significant improvement of subjective sleepiness, and the intensity of illness assessed by the Global Impression of Change showed a significant reduction. Polysomnographic recordings of nightime sleep was essentially unchanged on modafinil compared to placebo. The most frequent adverse effect was headache, but this was not significantly greater on modafinil compared to placebo. During treatment discontinuation, the EDS of individuals who had been receiving modafinil returned to baseline levels and patients did not experience any of the effects of an amphetamine withdrawal syndrome. There was no evidence of development of dependence during the 9-week period of daily modafinil.

The efficacy of modafinil for narcolepsy and idiopathic hypersomnia being solidly proven in these acute European and North American trials was rapidly followed by a number of long-term studies which showed that its effect was well maintained across time, that drug dependance did not develop, and that there were no new side effects from extended exposure (27-31). As obstructive

sleep apnea is the most frequent diagnosis which leads to referal to a sleep medicine facility, and is regularly associated with excessive daytime sleepiness, due mainly to the high fragmentation of night sleep, a number of studies of the effectiveness of modafinil to alleviate sleepiness in sleep apea were published (32-35).

9. Rapid spread of the use of modafinil in the treatment of other medical conditions

Subsequent to the use of modafinil to treat the neurological conditions of narcolepsy, idiopathic hypersomnia and obstructive sleep apnea, its efficacy in reducing excessive sleepiness, somnolence, and fatigue, has led to its assessent in a a large number of other medical contitions. Beginning around 2002 there began an almost exponential growth in the number of published articles on modafinil to the extent that, in 2017, over 1000 such articles were listed on PubMed. It is beyond the range of this article to reference all those medical conditions in which trials of modafinil have show significant benefits. Many are referenced in the 2006 excellent modafinil review of Ballon and Feifel (36). The relevant articles, which are typically off-label studies, can be found rapidly by doing an internet search for the medical condition of interest using the key words: modafinil plus the disease name. Some of conditions are listed in Table 1.

Table 1. Conditions for which modafinil has shown benefits

Neurological	**Psychiatric**	**Other**
Narcolepsy types 1 and 2	Endogenous depression	Chronic fatigue syndrome
Idiopathic CNS hypersomnia	Bipolar disorder	HIV infection
Symptomatic hypersomnias	Schizophrenia	Dementia
Parkinson's disease	Opioid dependency	Chronic pain
Attention Deficit Hyperactivity Disorder	Autism	Cirrhosis
Cerebral palsy		Post-anaethesia somnolence
Multiple sclerosis		Shift work sleep disorder
Post polio		Jet Lag sleep disorder
Myotonic dystrophy		
Myasthenia gravis		
Amyotrophic lateral sclerosis		

The number and variety of conditions in which modafinil has proven useful continues to grow. The compound has never been shown to develop tolerance and has very few side effects which are often idiosyncratic and due to prolonged use or abuse. Very rare potentially serious dermatological side effects have included cutaneous eruptions and Steven Johnson syndrome which

have mainly been reported from India (37, 38). Modafinil appears to be helful in virtually all conditions with excessive sleepiness, significant somnolence, or intense fatigue, whether somatic or mental. As it causes no significant sympathosomatic activation, modafinil is uniqually different from amphetamine-based stimulants, and has consequently been characterized as a *wake-promoting substance,* rather than as a stimulant.

The list of conditions in Table 1 illustrates that modafinil has revolutionized the treatment of a large number of medical conditions. This underlines Michel Jouvet's very significant direct, and indirect, contributions not only to sleep medicine, but also to clinical medicine in general.

Conflict of interest

Michel Billiard….

Roger Broughton was a consultant with Draxis Canada which marketed modafinil as Alertec at the time of and since the 9-center Canadian study of modafinil in the treatment of narcolepsy-cataplexy. Draxis also supported the study financially.

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