

# Adrafinil: A Novel Vigilance Promoting Agent

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## Introduction

Behavioral stimulants have widespread potential application in the treatment of affective disorders, disorders of vigilance, and disorders of sleep. Most behavioral stimulants, however, must be used with extreme caution because of undesirable side effects that include stereotypy, anxiolytic effects, and addiction. **Adrafinil**, developed in France by Louis Lafon Laboratories, is a novel pharmaceutical that has behavioral-activating effects but **lacks the undesirable side effects of other stimulants**. Peripheral sympathomimetic effects are also absent in subjects treated with adrafinil.

Jouvet (36) introduced the term *eugrégorique*. (eugregoric in English) to characterize this unique type of arousal-producing agent, but the term is not widely used in the scientific literature.<sup>1</sup> There have not been many published studies on adrafinil, and the large majority of studies have been published in French. **Human studies indicate that adrafinil has clinical efficacy as a vigilance-promoting and mood-enhancing agent** in the elderly. As an area for therapeutic intervention, vigilance enhancement has received much more attention in Europe than in North America. Somewhat surprisingly, perhaps, adrafinil is known to a larger nonscientific audience, where it is **considered to be a nootropic agent**.

## CLINICAL TRIALS

1. Israel et al. (35) examined the effects of adrafinil in ambulatory patients, aged 65 years or older, with problems in vigilance of sufficient severity to affect normal daily activities in a double-blind placebo-controlled study. The behavioral syndrome also consisted of moderate depression and loss of general motivation. The final analysis was based on 49 subjects in the placebo group and 50 subjects treated with adrafinil (3 tablets daily) over a 90-day period. Evaluations were made by general practitioners at baseline and days 45 and 90 using a series of tests that included the MacNair scale, the Dynamic Intellect scale, two questionnaires evaluating well-being, and the Sleep Intake Questionnaire from Duke University. The patients were also given a set of psychometric tests at baseline and day 90 to provide a measure of fluidity of cognitive function.

**The results showed marked improvements on the Dynamic Intellect Scale measures of confusion, attention, concentration, power of recall, forgetting, vigilance, and fatigue in the adrafinil group.** These improvements were generally established by day 45, and in many instances further improvement was seen at day 90. **The patients in the adrafinil group also felt happier, more energetic, and less sleepy by the end of the 3 months. In addition, the psychometric tests demonstrated a therapeutic efficacy of adrafinil on vigilance, perceptual acuity, and memory.** Three subjects had to have their treatment interrupted during the study because of nausea and dizziness. However, two of the three subjects were in the placebo-controlled group. Two subjects in the adrafinil group experienced light excitation but did not need to terminate treatment.

2. In an open trial, Kohler and Lubin (37) examined the effects of adrafinil in 304 patients, aged 45 to 88 years, who presented with difficulties in attention-concentration, affective troubles, and manifestations of depression. They also displayed problems with memory, anxiety, inactivity, and sleep. The patients received 900 mg/d of adrafinil (600 mg in the morning and 300 mg at noon) for 3 months. Evaluations were made by general practitioners at baseline and days 30 and 90 using Zazzo's test, which provides measures of vigilance, attention, concentration and perceptual-motor skills, Derouesne's scale, which assesses difficulties of daily life, and Zung's Depression and Anxiety scales.

**They found statistically significant improvements in all three measures, which was apparent within the first month of treatment and persisted for the duration of the study. This study specifically revealed improvements in vigilance, attention, and concentration. Daily activities improved with adrafinil treatment, which reflects improved memory functions and autonomy. Finally, adrafinil treatment resulted in improvements in the degree of depression and anxiety. No secondary effects were observed during the course of this study.**

3. Dewailly et al. (18) studied adrafinil in 86 hospitalized patients presenting with troubles of wakefulness or vigilance in a multicenter, double-blind, placebo-controlled study carried out at six hospitals. The SCAG scale revealed improvements in cognitive and relational troubles by day 30, which were maintained until day 60. The Nurse's Observation Scale for Inpatient

**Evaluation (NOSIE) showed that patients taking adrafinil were less depressed, less irritable, more patient, more sociable, more interested in their surroundings, more communicative, and adapted more easily to the hospital setting.** In some instances, these improvements were observed as early as day 15. One subject was reported to show increased aggressiveness by day 15 of treatment, but the subject was in the placebo group.

4. Boyer et al. (7) compared the effect of adrafinil with placebo controls in subjects aged 45.79 years who complained of problems with attention, concentration, memory and orientation. The analysis was based on a total of 548 patients

randomized into two treatment groups. **Adrafinil treatment resulted in highly significant improvements in daily activities, attention, orientation, and memory. There was no mention of secondary effects in this study.**

5. Defrance et al. (16) conducted a multicenter, placebo-controlled study of 49 patients aged 65 years or older from three different hospitals. Twenty-three subjects received adrafinil, while 26 subjects were given placebo. Each of the subjects was hospitalized for at least 1 month with deficits in wakefulness and vigilance. Treatment was most effective in the patients at Center 1. Since these patients were on the average 10 years younger than the patients in the other center, **the researchers concluded that this study justified early treatment with adrafinil (i.e., before any cognitive deterioration began).** No side effects were observed in the placebo group. Three of the adrafinil treated subjects were reported to show increased agitation and aggression. In one case, the daily dose had to be reduced.

6. Finally, Fontan et al. (29) found significant improvements in self-evaluations of vigilance and sleep in a multicenter, double-blind, placebo-controlled study. The 48 subjects were patients in senior residences, aged 65 years or older, and displayed troubles of vigilance and wakefulness. The subjects had difficulties in attention, concentration, ideation, and a lowered speed to learn and process information. Again, however, subjects were excluded if they had low MMSE scores (< 20). Half of the subjects were treated with adrafinil and half of the subjects were in the placebo-controlled group.

**The researchers found that adrafinil improved attention and concentration. They also found significant improvements on psychometric tests involving visual masking and reaction time.** Performance on the Stroop test was not modified. **According to the authors, the most improved factor was immediate mental apprehension of information.** Two subjects receiving adrafinil experienced dryness of the mouth, while one placebo subject experienced a bitter taste.

**The collective results of all of these studies show an impressive degree of consistency; they indicate that adrafinil can be highly beneficial in the treatment of elderly patients showing deficits in vigilance, attention, behavior, and mood.**

### **Deficits Associated with Motor Organization**

Boyer et al. (8) examined the effect of adrafinil on ideomotor deficits, which included general suppression in voluntary movements, deficits in organizing motor sequences, paralysis of decision, and paralysis of functional motor action. A total of 81 subjects participated in a multicenter, placebo-controlled study. None of the patients were institutionalized. The treatment consisted of adrafinil 600 mg/d (300 mg in the morning and 300 mg at noon) or placebo for 28 days. Evaluations were made at baseline and on days 7 and 28. The AMDP system (4th and 5th scale),

General Somatic and Psychopathological Scale, Motor Activity Scale, Sheehan Scale of Social Incapacitation (anxiety), Visual Analogic Scales, and 3 global instruments [efficacy, tolerance and the Clinicians Global Impression (CGI) index] were used as the evaluation tools.

**Adrafinil treatment resulted in significant improvements in 3 factors of the AMDP system: depression, apathy-retardation, and somatic symptoms. The paralysis of motor action and the 3 components of the Sheehan scale were significant in the adrafinil group,** confirming the possibility of a reorganization of action. The analysis of the factors of change under adrafinil confirmed the existence of the first factor of change in the adrafinil group. This factor consists of the global score of the CGI index, the 3 components of the Sheehan scale, the 4 types of inhibition of action, the total score of the Motor Activity scale, the score of the Visual Analogic scale of motor activity, and the anxiety, depression and neurovegetative scales of the AMDP. Handicap tied to troubles of action, mood, motor, and social interactions is a general factor of change. This factor of change was not found in the placebo group. **The researchers concluded that adrafinil has therapeutic efficacy on ideomotor deficits,** which is independent of diagnostic category. Two subjects in the adrafinil group were removed from the study due to nausea and arrhythmia. One subject in the placebo group was removed because of somnolence.

### **Treatment of Depression**

Mild behavioral depression was a common characteristic of many of the subjects studied in the vigilance-promoting studies described previously. The term .depression. does not refer to the clinical syndrome as defined in DSM-IV but rather to a milder type of depression that is common in the elderly. The clinical effect of adrafinil on depression was the focus of a study by Guyotat (32). Adrafinil (600 mg/d) was compared to clomipramine (40 mg/d) and placebo in a group of 70 depressed patients over a 2-mo period. Clinical efficacy was evaluated using conventional rating scales: the Hamilton Depression Rating scale, Psychomotor Retardation, Raskin Depression scale, and COVI-Anxiety scale.

**Statistically significant improvements in depression were obtained for both adrafinil and clomipramine when compared to placebo. Adrafinil, however, also had a higher efficacy on psychomotor retardation than clomipramine. The clomipramine group suffered from frequent side effects (50% of patients), while adrafinil was well tolerated.** In the placebo group, undesirable effects (somatic or psychological) were observed in 25% of the subjects (e.g., tremors, dry mouth, stomach pain, agitation). Secondary effects were less noticeable in the adrafinil group, although they were reported to exhibit a transient period of psychological agitation and irritability.

## SUMMARY AND CONCLUSIONS

Adrafinil is a novel drug that is not well known outside of France, where it is used primarily as a vigilance-enhancing agent. **Clinical studies strongly indicate that adrafinil has efficacy in improving attention, memory, as well as other deficits resulting from decreased vigilance.**

**Given the effectiveness of adrafinil in improving performance on psychometric tests and motor function in people with mild cognitive impairment,** it is surprising that neither adrafinil nor modafinil have been used in trials with demented patients. In fact, two possible applications deserve careful consideration. **One possible application is the treatment of age-associated memory impairment (AAMI).** This term was introduced to describe medically, neurologically, and psychiatrically healthy persons over 50 years of age who have experienced a gradual decline in the ability to perform certain tasks of daily life dependent on memory. (14,15).

A second possible application for adrafinil would be in the treatment of subjects with dementing disorders, such as Alzheimer's disease. This application is not directly suggested from the studies performed thus far, which have precluded examination of severely demented patients because of the subject selection criterion used. In fact, research with canines provides limited support for this possibility. Adrafinil improved discrimination learning in a group of aged dogs; the dogs that showed the greatest improvement in cognitive functioning were those that showed the greatest overall impairment (42). The evidence that modafinil can have neuroprotective effects provides another compelling reason for testing adrafinil in patients with dementing disorders. **This study raises at least the possibility that long-term treatment with adrafinil can arrest or even reverse neurodegenerative processes that contribute to dementia.** Clearly, however, further preclinical studies are needed before this potential application can be evaluated.

Three other therapeutic applications of adrafinil warrant further study. The first application is as a potential therapeutic drug in treatment of Parkinson's and another is as a potential treatment for deficits associated with movement disorders (8). Finally, further investigations of the antidepressive effects of adrafinil are warranted.

**In summary, adrafinil is a novel stimulant that lacks the adverse effects associated with other psychostimulants.** It directly affects CNS function, but its mechanism of action is not completely understood. **Clinical studies have demonstrated that adrafinil has efficacy as a vigilance-promoting agent. It has also cognitive enhancing potential,** and trials on patients with dementing disorders appear warranted.