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**Modafinil** ([INN](/wiki/International_Nonproprietary_Name), [USAN](/wiki/United_States_Adopted_Name), [BAN](/wiki/British_Approved_Name), [JAN](/wiki/Japanese_Accepted_Name)) is a [wakefulness-promoting agent](/wiki/Wakefulness-promoting_agent) (or *eugeroic*) used for treatment of disorders such as [narcolepsy](/wiki/Narcolepsy), [shift work sleep disorder](/wiki/Shift_work_sleep_disorder), and [excessive daytime sleepiness](/wiki/Excessive_daytime_sleepiness) associated with [obstructive sleep apnea](/wiki/Obstructive_sleep_apnea).[[1]](#cite_note-1) It has also seen widespread [off-label use](/wiki/Off-label_use) as a purported cognition-enhancing agent. In English-speaking countries it is sold under the brand names **Alertec**, **Modavigil**, and **Provigil**. In the United States modafinil is classified as a [schedule IV controlled substance](/wiki/Controlled_Substances_Act) and restricted in availability and usage, due to concerns about possible addiction potential. In most other countries it is a prescription drug but not otherwise legally restricted.

Although the [mechanism of action](/wiki/Mechanism_of_action) of modafinil was initially unknown, it now appears that the drug acts as a selective, relatively weak, atypical [dopamine reuptake inhibitor](/wiki/Dopamine_reuptake_inhibitor). However, it appears that other additional mechanisms may also be at play.

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## Uses[[edit](/index.php?title=(none)&action=edit&section=1)]

### Medical[[edit](/index.php?title=(none)&action=edit&section=2)]

Modafinil is a [wakefulness-promoting agent](/wiki/Wakefulness-promoting_agent) (or *eugeroic*) used for treatment of [narcolepsy](/wiki/Narcolepsy), [shift work sleep disorder](/wiki/Shift_work_sleep_disorder), and [excessive daytime sleepiness](/wiki/Excessive_daytime_sleepiness) associated with [obstructive sleep apnea](/wiki/Obstructive_sleep_apnea).[[1]](#cite_note-1)<ref name=SleepAcademy2007>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>[[2]](#cite_note-2)<ref name=2015MetaRev>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

Because of the risk for development of skin or hypersensitivity reactions and neuropsychiatric disorders, the [European Medicines Agency](/wiki/European_Medicines_Agency) has recommended that new patient prescriptions should only be to treat sleepiness associated with narcolepsy.[[3]](#cite_note-3)

#### Off-label use for fatigue[[edit](/index.php?title=(none)&action=edit&section=3)]

Modafinil has also found off-label use with the [neurological fatigue](/wiki/Neurological_fatigue) reported by some with [multiple sclerosis](/wiki/Multiple_sclerosis).[[4]](#cite_note-4) In 2000, Cephalon conducted a study to evaluate modafinil as a potential treatment for MS-related fatigue. A group of 72 people with MS of varying degrees of severity tested two different doses of modafinil and an inactive placebo over nine weeks. Fatigue levels were self-evaluated on standardized scales. Participants taking a lower dose of modafinil reported feeling less fatigued and there was a statistically significant difference in fatigue scores for the lower dose versus the placebo. The higher dose of modafinil was not reported to be significantly more effective.[[5]](#cite_note-5)[[6]](#cite_note-6) Modafinil is also used off-label to treat sedation and fatigue in many conditions, including depression,[[7]](#cite_note-7)[[8]](#cite_note-8) [fibromyalgia](/wiki/Fibromyalgia), [chronic fatigue syndrome](/wiki/Chronic_fatigue_syndrome), [myotonic dystrophy](/wiki/Myotonic_dystrophy),[[9]](#cite_note-9) [opioid](/wiki/Opioid)-induced sleepiness,[[10]](#cite_note-10) spastic [cerebral palsy](/wiki/Cerebral_palsy),[[11]](#cite_note-11) and [Parkinson's disease](/wiki/Parkinson's_disease).[[12]](#cite_note-12) Modafinil has been shown to improve excessive daytime somnolence and fatigue in [primary biliary cirrhosis](/wiki/Primary_biliary_cirrhosis).[[13]](#cite_note-13)

##### Military and astronauts[[edit](/index.php?title=(none)&action=edit&section=4)]

Militaries of several countries are known to have expressed interest in modafinil as an alternative to [amphetamine](/wiki/Amphetamine)—the drug traditionally employed in combat situations where troops face [sleep deprivation](/wiki/Sleep_deprivation), such as during lengthy missions. The [French](/wiki/France) government indicated that the [Foreign Legion](/wiki/French_Foreign_Legion) used modafinil during certain covert operations.[Template:Citation needed](/wiki/Template:Citation_needed) The [United Kingdom's](/wiki/United_Kingdom) [Ministry of Defence](/wiki/Ministry_of_Defence_(United_Kingdom)) commissioned research into modafinil[[14]](#cite_note-14) from [QinetiQ](/wiki/QinetiQ) and spent £300,000 on one investigation.[[15]](#cite_note-15) In 2011, the [Indian Air Force](/wiki/Indian_Air_Force) announced that modafinil was included in contingency plans.[[16]](#cite_note-16) In the [United States](/wiki/United_States) military, modafinil has been approved for use on certain [Air Force](/wiki/U.S._Air_Force) missions, and it is being investigated for other uses.[[17]](#cite_note-17) As of November 2012, modafinil is the only drug approved by the Air Force as a "go pill" for fatigue management.<ref name=AF48>[Air Force Special Operations Command Instruction 48–101](http://static.e-publishing.af.mil/production/1/afsoc/publication/afsoci48-101/afsoci48-101.pdf) (sects. 1.7.4), U.S. Air Force Special Operations Command, November 30, 2012.</ref> The use of [dextroamphetamine](/wiki/Dextroamphetamine) (a.k.a., Dexedrine) is no longer approved.<ref name=AF48/>

The [Canadian Medical Association Journal](/wiki/Canadian_Medical_Association_Journal) also reports that modafinil is used by [astronauts](/wiki/Astronauts) on long-term missions aboard the [International Space Station](/wiki/International_Space_Station). Modafinil is "available to crew to optimize performance while fatigued" and helps with the disruptions in [circadian rhythms](/wiki/Circadian_rhythms) and with the reduced quality of sleep astronauts experience.[[18]](#cite_note-18)

## Contraindications[[edit](/index.php?title=(none)&action=edit&section=5)]

Allergy and hypersensitivity are the only contraindications of the drug,[[19]](#cite_note-19) but literature distributed by [Cephalon](/wiki/Cephalon) advises that it is important to consult a [physician](/wiki/Physician) before using it, as problems may arise for people who are sensitive to constituents of the tablets, people with [cirrhosis](/wiki/Cirrhosis) (which may impair the metabolism of the drug), and people with various cardiovascular problems.[Template:Citation needed](/wiki/Template:Citation_needed)

## Adverse effects[[edit](/index.php?title=(none)&action=edit&section=6)]

According to documentation distributed by [Teva Pharmaceuticals](/wiki/Teva_Pharmaceuticals), one-third of participants in clinical trials reported experiencing headaches; 11% reported nausea; other negative side-effects such as nervousness, diarrhea, insomnia, anxiety, dizziness, and gastrointestinal problems were reported by less than 10% of participants.[[20]](#cite_note-20) Rare occurrences have been reported of more serious adverse effects, including severe skin rashes and other symptoms that are probably allergy-related. From the date of initial marketing, December 1998, to January 30, 2007, the US [Food and Drug Administration](/wiki/Food_and_Drug_Administration) received six cases of severe cutaneous adverse reactions associated with modafinil, including [erythema multiforme](/wiki/Erythema_multiforme) (EM), [Stevens–Johnson syndrome](/wiki/Stevens–Johnson_syndrome) (SJS), [toxic epidermal necrolysis](/wiki/Toxic_epidermal_necrolysis) (TEN), and [DRESS syndrome](/wiki/DRESS_syndrome), involving adult and pediatric patients. The FDA issued a relevant alert. In the same alert, the FDA also noted that [angioedema](/wiki/Angioedema) and multi-organ hypersensitivity reactions have also been reported in postmarketing experiences.[[21]](#cite_note-21) In 2007, the FDA ordered Cephalon to modify the Provigil leaflet in bold-face print of several serious and potentially fatal conditions attributed to modafinil use, including TEN, DRESS syndrome, and SJS.

The long term safety and effectiveness of modafinil have not been determined.[[22]](#cite_note-22) Modafinil may have an adverse effect on [hormonal contraceptives](/wiki/Hormonal_contraception), lasting for a month after cessation of dosage.[[23]](#cite_note-23)

### Addiction and dependence potential[[edit](/index.php?title=(none)&action=edit&section=7)]

The [addiction](/wiki/Addiction) and [dependence](/wiki/Drug_dependence) liabilities of modafinil are very low.[[24]](#cite_note-24)[[25]](#cite_note-25)[[26]](#cite_note-26) It shares biochemical mechanisms with addictive [stimulant](/wiki/Stimulant) drugs, and some studies have reported it to have similar mood-elevating properties, although to a lesser degree.[[26]](#cite_note-26) Monkeys will self-administer modafinil if they have previously been trained to self-administer cocaine.[[26]](#cite_note-26) Although modafinil does not produce reinforcing effects in mice at doses that are equivalent to those used therapeutically in humans, it does do so at higher doses.[[27]](#cite_note-27)[[28]](#cite_note-28) In accordance, although very rare, [case reports](/wiki/Case_report) of modafinil abuse exist.[[29]](#cite_note-29)[[30]](#cite_note-30) As such, modafinil is classified by the United States FDA as a [schedule IV controlled substance](/wiki/Controlled_Substances_Act#Schedule_IV_controlled_substances), a category for drugs with valid medical uses and low but significant addiction potential.[[25]](#cite_note-25)<ref name=Ballon>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

[Psychological dependence](/wiki/Psychological_dependence) upon modafinil has only been noted in [case reports](/wiki/Case_report) involving daily overdoses on modafinil for an extended period of time.[[24]](#cite_note-24) Reported [withdrawal symptoms](/wiki/Drug_withdrawal) include [anhedonia](/wiki/Anhedonia), [lethargy](/wiki/Lethargy), anxiety, and insomnia.[[24]](#cite_note-24)

### Tolerance[[edit](/index.php?title=(none)&action=edit&section=8)]

Large-scale clinical studies have found no evidence of tolerance with modafinil at therapeutic dosages even with prolonged use (for 40 weeks and as long as three years).[[31]](#cite_note-31)[[32]](#cite_note-32)[[33]](#cite_note-33)

## Overdose[[edit](/index.php?title=(none)&action=edit&section=9)]

In mice and rats, the [median lethal dose](/wiki/Median_lethal_dose) (LD50) of modafinil is approximately or slightly greater than 1250 mg/kg. Oral LD50 values reported for rats range from 1000–3400 mg/kg. Intravenous LD50 for dogs is 300 mg/kg. Clinical trials on humans involving taking up to 1200 mg/day for 7–21 days and known incidents of acute one-time overdoses up to 4500 mg did not appear to cause life-threatening effects, although a number of adverse experiences were observed, including excitation or agitation, insomnia, anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep disturbances, nausea, and diarrhea.[[1]](#cite_note-1) As of 2004, the FDA is not aware of any fatal overdoses involving modafinil alone (as opposed to multiple drugs, including modafinil).[[1]](#cite_note-1)

## Interactions[[edit](/index.php?title=(none)&action=edit&section=10)]

Coadministration with modafinil alongside [opioids](/wiki/Opioid) such as [hydrocodone](/wiki/Hydrocodone), [oxycodone](/wiki/Oxycodone), and [fentanyl](/wiki/Fentanyl), as well as various other drugs, may experience a drop in plasma concentrations. The reasoning behind this action is because modafinil is an [inducer](/wiki/Enzyme_inducer) of the [CYP3A4](/wiki/CYP3A4) [enzymes](/wiki/Enzyme). If not monitored closely, reduced efficacy or withdrawal symptoms may and can occur.[Template:Mcn](/wiki/Template:Mcn)

## Pharmacology[[edit](/index.php?title=(none)&action=edit&section=11)]

### Pharmacodynamics[[edit](/index.php?title=(none)&action=edit&section=12)]

#### Dopamine transporter blocker[[edit](/index.php?title=(none)&action=edit&section=13)]

Initially, the [mechanism of action](/wiki/Mechanism_of_action) of modafinil was unknown.[[34]](#cite_note-34)[[35]](#cite_note-35) Research found that modafinil elevates [histamine](/wiki/Histamine) levels in the [hypothalamus](/wiki/Hypothalamus) in animals.[[36]](#cite_note-36) The locus of the [monoamine](/wiki/Monoamine) action of modafinil was also the target of studies, with effects identified on [dopamine](/wiki/Dopamine) in the [striatum](/wiki/Striatum) and, in particular, [nucleus accumbens](/wiki/Nucleus_accumbens),[[37]](#cite_note-37)[[38]](#cite_note-38) [norepinephrine](/wiki/Norepinephrine) in the [hypothalamus](/wiki/Hypothalamus) and [ventrolateral preoptic nucleus](/wiki/Ventrolateral_preoptic_nucleus),[[39]](#cite_note-39)[[40]](#cite_note-40) and [serotonin](/wiki/Serotonin) in the [amygdala](/wiki/Amygdala) and [frontal cortex](/wiki/Frontal_cortex).[[41]](#cite_note-41) Modafinil was screened at a large panel of [receptors](/wiki/Receptor_(biochemistry)) and [transporters](/wiki/Membrane_transport_protein) in an attempt to elucidate its pharmacology.[[42]](#cite_note-42) Of the sites tested, it was found to significantly affect only on the [dopamine transporter](/wiki/Dopamine_transporter) (DAT), acting as a [dopamine reuptake inhibitor](/wiki/Dopamine_reuptake_inhibitor) (DRI) with an [IC50](/wiki/IC50) value of 4 μM.[[42]](#cite_note-42) Subsequently, it was determined that modafinil binds to the same site on the DAT as [cocaine](/wiki/Cocaine), but in a different manner.[[43]](#cite_note-43)[[44]](#cite_note-44) In accordance, modafinil increases [locomotor activity](/wiki/Hyperactivity) and extracellular dopamine concentrations in animals in a manner similar to the selective DRI [vanoxerine](/wiki/Vanoxerine) (GBR-12909),[[45]](#cite_note-45) and also inhibits [methamphetamine](/wiki/Methamphetamine)-induced dopamine release (a common property of DRIs, since DAT transport facilitates methamphetamine's access to its intracellular targets). As such, "modafinil is an exceptionally weak, but apparently very selective, [DAT] inhibitor".[[46]](#cite_note-46) In addition to animal research, a human [positron emission tomography](/wiki/Positron_emission_tomography) (PET) imaging study found that 200 mg and 300 mg doses of modafinil resulted in DAT occupancy of 51.4% and 56.9%, respectively, which was described as "close to that of [methylphenidate](/wiki/Methylphenidate)".[[47]](#cite_note-47) Another human PET imaging study similarly found that modafinil occupied the DAT and also determined that it significantly elevated [extracellular](/wiki/Extracellular) levels of dopamine in the brain, including in the [nucleus accumbens](/wiki/Nucleus_accumbens).[[48]](#cite_note-48) Modafinil has been described as an "atypical" DAT inhibitor, and shows a profile of effects that is very different from those of other dopaminergic stimulants.[[49]](#cite_note-49)[[50]](#cite_note-50) For instance, modafinil produces wakefulness reportedly without the need for compensatory sleep, and shows a relatively low, if any,[[51]](#cite_note-51) potential for abuse.[[46]](#cite_note-46)[[49]](#cite_note-49)[[50]](#cite_note-50) Aside from modafinil, examples of other atypical DAT inhibitors include vanoxerine and [benztropine](/wiki/Benztropine), which have a relatively low abuse potential similarly to modafinil.[[49]](#cite_note-49) These drugs appear to interact molecularly with the DAT in a distinct way relative to "conventional" DAT blockers such as cocaine and methylphenidate.[[44]](#cite_note-44)[[49]](#cite_note-49)

#### DAT-independent actions[[edit](/index.php?title=(none)&action=edit&section=14)]

Against the hypothesis that modafinil exerts its effects by acting as a DRI, [tyrosine hydroxylase](/wiki/Tyrosine_hydroxylase) [inhibitors](/wiki/Enzyme_inhibitor) (which deplete dopamine) fail to block the effects of modafinil in animals.[[52]](#cite_note-52) In addition, modafinil fails to reverse [reserpine](/wiki/Reserpine)-induced [akinesia](/wiki/Akinesia), whereas [dextroamphetamine](/wiki/Dextroamphetamine), a [dopamine releasing agent](/wiki/Dopamine_releasing_agent) (DRA), is able to do so.[[53]](#cite_note-53) Moreover, one of the first published [structure-activity relationship](/wiki/Structure-activity_relationship) studies of modafinil found in 2012 that DAT inhibition did not correlate with wakefulness-promoting effects in animals among modafinil analogues, and a variety of analogues without any significant inhibition of the DAT still produced wakefulness-promoting effects.[[54]](#cite_note-54) Furthermore, "[the] neurochemical effects [of modafinil] and anatomical pattern of brain area activation differ from typical psychostimulants and are consistent with its beneficial effects on cognitive performance processes such as attention, learning, and memory",[[51]](#cite_note-51) and a study found that modafinil-induced increases locomotor activity in animals were dependent on histamine release and could be abolished by depletion of neuronal histamine, whereas those of methylphenidate were not and could not be.[[36]](#cite_note-36) As such, although it is established that modafinil is a clinically significant DRI, its full pharmacology remains unclear and may be more complex than this single property (i.e., may also include DAT-independent actions, such as "activation of the [orexin](/wiki/Orexin) system").[[43]](#cite_note-43)[[51]](#cite_note-51) In any case, there is nonetheless a good deal of evidence to indicate that modafinil is producing at least a portion of its wakefulness-promoting effects by acting as a DRI, or at least via activation of the dopaminergic system. In support of modafinil acting as a dopaminergic agent, its wakefulness-promoting effects are abolished in DAT [knockout mice](/wiki/Knockout_mice) (although it is important to note that DAT knockout mice show D1 and D2 receptor and norepinephrine compensatory abnormalities, which might confound this finding), reduced by both [D1](/wiki/D1_receptor) and [D2 receptor](/wiki/D2_receptor) [antagonists](/wiki/Receptor_antagonist) (although conflicting reports exist),[[53]](#cite_note-53) and completely blocked by simultaneous inactivation of both D1 and D2 receptors.[[46]](#cite_note-46) In accordance, modafinil shows full stimulus generalization to other DAT inhibitors including cocaine, methylphenidate, and vanoxerine, and discrimination is blocked by administration of both [ecopipam](/wiki/Ecopipam) (SCH-39166), a D1 receptor antagonist, and [haloperidol](/wiki/Haloperidol), a D2 receptor antagonist.[[50]](#cite_note-50) Partial substitution was seen with the DRA dextroamphetamine and the D2 receptor agonist [PNU-91356A](/wiki/PNU-91356A), as well as with [nicotine](/wiki/Nicotine) (which indirectly elevates dopamine levels through activation of [nicotinic acetylcholine receptors](/wiki/Nicotinic_acetylcholine_receptor)).[[50]](#cite_note-50) Modafinil may possess yet an additional mechanism of action. Both modafinil and its [metabolite](/wiki/Metabolite), [modafinil sulfone](/wiki/Modafinil_sulfone), possess [anticonvulsant](/wiki/Anticonvulsant) properties in animals, and modafinil sulfone is nearly as potent as modafinil in producing this effect.[[55]](#cite_note-55) However, modafinil sulfone lacks any wakefulness-promoting effects in animals, indicating that a distinct mechanism may be at play in the anticonvulsant effects of both compounds.[[55]](#cite_note-55)

#### D<sub>2</sub> receptor partial agonist[[edit](/index.php?title=(none)&action=edit&section=15)]

The (*R*)-[enantiomer](/wiki/Enantiomer) of modafinil, known as [armodafinil](/wiki/Armodafinil), was also subsequently found to act as a [D2High receptor](/wiki/D2_receptor) [partial agonist](/wiki/Partial_agonist), with a [Ki](/wiki/Dissociation_constant) of 16 nM, an [intrinsic activity](/wiki/Intrinsic_activity) of 48%, and an [EC50](/wiki/EC50) of 120 nM, in rat [striatal](/wiki/Striatum) tissue.[[56]](#cite_note-56) The (*S*)-enantiomer is inactive with respect to the D2 receptor.[[56]](#cite_note-56) Modafinil has been found to directly inhibit the firing of midbrain dopaminergic neurons in the [ventral tegmental area](/wiki/Ventral_tegmental_area) and [substantia nigra](/wiki/Substantia_nigra) of rats via activation of D2 receptors.[[57]](#cite_note-57)

#### Miscellaneous[[edit](/index.php?title=(none)&action=edit&section=16)]

Modafinil's efficacy in improving vigor and well-being in sleep deprivation subjects is dependent on [catechol-O-methyl transferase](/wiki/Catechol-O-methyl_transferase) (COMT) status.[[58]](#cite_note-58) Research suggests that individuals with the Val/Val [genotype](/wiki/Genotype) experience a great improvement in their cognitive function, while those with the Met/Met [allele](/wiki/Allele) experience very little improvement.[[58]](#cite_note-58)

### Pharmacokinetics[[edit](/index.php?title=(none)&action=edit&section=17)]

Modafinil [induces](/wiki/Enzyme_inducer) the [cytochrome P450](/wiki/Cytochrome_P450) enzymes [CYP1A2](/wiki/CYP1A2), [CYP3A4](/wiki/CYP3A4), and [CYP2B6](/wiki/CYP2B6), as well as inhibiting [CYP2C9](/wiki/CYP2C9) and [CYP2C19](/wiki/CYP2C19) [*in vitro*](/wiki/In_vitro).[[59]](#cite_note-59) It may also induce [P-glycoprotein](/wiki/P-glycoprotein) (Pgp), which may affect drugs transported by Pgp, such as [digoxin](/wiki/Digoxin).[Template:Citation needed](/wiki/Template:Citation_needed) The [bioavailability](/wiki/Bioavailability) of modafinil is greater than 80% of the administered dose. *In vitro* measurements indicate that 60% of modafinil is bound to [plasma proteins](/wiki/Plasma_protein) at clinical concentrations of the drug. This percentage actually changes very little when the concentration is varied.[[60]](#cite_note-60) Cmax (peak levels) occurs approximately 2–3 hours after administration. Food slows absorption, but does not affect the total [AUC](/wiki/Area_under_the_curve)[Template:Clarify](/wiki/Template:Clarify)(AUC – area under the curve – meaning, food may slow absorption, but the total amount of the chemical will be absorbed with or without food). [Half-life](/wiki/Half-life) is generally in the 10–12 hour range, subject to differences in CYP genotypes, liver function and renal function. It is metabolized in the liver, and its inactive metabolite is excreted in the urine. Urinary excretion of the unchanged drug ranges from 0% to as high as 18.7%, depending on various factors.[[60]](#cite_note-60) The two major circulating [metabolites](/wiki/Metabolite) of modafinil are [modafinil acid](/wiki/Modafinil_acid) (CRL-40467) and [modafinil sulfone](/wiki/Modafinil_sulfone) (CRL-41056).[[61]](#cite_note-61)[[62]](#cite_note-62) Both of these metabolites have been described as inactive,[[63]](#cite_note-63) and neither appear to contribute to the wakefulness-promoting effects of modafinil.[[61]](#cite_note-61)[[62]](#cite_note-62)[[64]](#cite_note-64) However, modafinil sulfone does appear to possess anticonvulsant effects, and this is a property that it shares with modafinil.[[55]](#cite_note-55)

## Physical and chemical properties[[edit](/index.php?title=(none)&action=edit&section=18)]

### Measurement in body fluids[[edit](/index.php?title=(none)&action=edit&section=19)]

Modafinil and/or its major metabolite, modafinil acid, may be quantified in plasma, serum or urine to monitor dosage in those receiving the drug therapeutically, to confirm a diagnosis of poisoning in hospitalized patients or to assist in the forensic investigation of a vehicular traffic violation. Instrumental techniques involving gas or liquid chromatography are usually employed for these purposes.[[65]](#cite_note-65)[[66]](#cite_note-66) As of 2011, it is not specifically tested for by common [drug screens](/wiki/Drug_test) (except for anti-doping screens) and is unlikely to cause false positives for other chemically-unrelated drugs such as substituted amphetamines.[[67]](#cite_note-67) [Reagent testing](/wiki/Pill_testing) can be used to screen for the presence of modafinil in samples.

|  |  |  |  |
| --- | --- | --- | --- |
| Colors produced by modafinil with various reagents | | | |
| **RC** | [**Marquis Reagent**](/wiki/Marquis_reagent) | [**Liebermann**](/wiki/Liebermann_reagent) | [**Froehde**](/wiki/Froehde_reagent) |
| Modafinil | Yellow/Orange > Brown[[68]](#cite_note-68)[[69]](#cite_note-69) | Darkening Orange[[68]](#cite_note-68) | Deep orange/red[[69]](#cite_note-69) |

## History[[edit](/index.php?title=(none)&action=edit&section=20)]

Modafinil was originally developed in [France](/wiki/France) by [neurophysiologist](/wiki/Neurophysiology) and [emeritus](/wiki/Emeritus) experimental medicine professor [Michel Jouvet](/wiki/Michel_Jouvet) and Lafon Laboratories. Modafinil originated with the late 1970s invention of a series of benzhydryl sulfinyl compounds, including [adrafinil](/wiki/Adrafinil), which was first offered as an experimental treatment for narcolepsy in France in 1986. Modafinil is the primary metabolite of adrafinil, lacking the polar -OH group on its terminal amide,<ref name=Ballas>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> and has similar activity to the parent drug but is much more widely used. It has been prescribed in France since 1994 under the name Modiodal, and in the US since 1998 as Provigil.

In 1998, modafinil was approved by the [U.S. Food and Drug Administration](/wiki/U.S._Food_and_Drug_Administration)[[70]](#cite_note-70) for the treatment of [narcolepsy](/wiki/Narcolepsy) and in 2003 for [shift work sleep disorder](/wiki/Shift_work_sleep_disorder) and obstructive [sleep apnea](/wiki/Sleep_apnea)/[hypopnea](/wiki/Hypopnea)[[71]](#cite_note-71) even though caffeine and amphetamine were shown to be more wakefulness promoting on the Stanford Sleepiness Test Score than modafinil.[[72]](#cite_note-72) It was approved for use in the UK in December 2002. Modafinil is marketed in the US by [Cephalon Inc.](/wiki/Cephalon), who originally leased the rights from Lafon, but eventually purchased the company in 2001.

Cephalon began to market the R-enantiomer armodafinil of modafinil in the U.S. in 2007. After protracted patent litigation and negotiations (see [below](/wiki/#Patent_protection_and_antitrust_litigation)), [generic](/wiki/Generic_drug) versions of modafinil became available in the U.S. in 2012.

### Patent protection and antitrust litigation[[edit](/index.php?title=(none)&action=edit&section=21)]

[Template:US patent](/wiki/Template:US_patent) was issued to [Laboratoire L. Lafon](/wiki/Laboratoire_L._Lafon) on May 22, 1990, covering the chemical compound modafinil. After receiving an interim term extension of 1066 days and [pediatric exclusivity](/wiki/Pediatric_exclusivity) of six months, it expired on October 22, 2010. On October 6, 1994, Cephalon filed an additional patent, covering modafinil in the form of particles of defined size. That patent, [Template:US patent](/wiki/Template:US_patent) was issued on April 8, 1997, but was reissued in 2002 as RE 37,516, which surrendered the 5618845 patent. With pediatric exclusivity, this patent expired on April 6, 2015.[[73]](#cite_note-73)[[74]](#cite_note-74) On December 24, 2002, anticipating the expiration of exclusive marketing rights, generic drug manufacturers Mylan, Teva, Barr, and Ranbaxy applied to the FDA to market a generic form of modafinil.[[75]](#cite_note-75) At least one withdrew its application after early opposition by Cephalon based on the '516 patent. There is some question whether a particle size patent is sufficient protection against the manufacture of generics. Pertinent questions include whether modafinil may be modified or manufactured to avoid the granularities specified in the new Cephalon patent, and whether patenting particle size is invalid because particles of appropriate sizes are likely to be obvious to practitioners skilled in the art. However, under United States patent law, a patent is entitled to a legal presumption of validity, meaning that in order to invalidate the patent, much more than "pertinent questions" are required.

As of October 31, 2011, U.S. Reissue Patent No. RE 37,516 has been declared invalid and unenforceable.[[76]](#cite_note-76) The District Court for the Eastern District of Pennsylvania ruled that RE 37,516 was invalid because it: (1) was on sale more than one year prior to the date of the application in violation of 35 U.S.C. section 102(b); (2) was actually invented by someone else (the French company Laboratoire L. Lafon); (3) was obvious at the time the invention was made to a person having ordinary skill in the art under 35 U.S.C. section 103(a); and (4) failed the written description requirement of 35 U.S.C. section 112.[[77]](#cite_note-77) The patent was also found to be unenforceable due to Cephalon's inequitable conduct during patent prosecution.[[77]](#cite_note-77) Cephalon made an agreement with four major generics manufacturers [Teva](/wiki/Teva_Pharmaceutical_Industries), [Barr Pharmaceuticals](/wiki/Barr_Pharmaceuticals), [Ranbaxy Laboratories](/wiki/Ranbaxy_Laboratories), and [Watson Pharmaceuticals](/wiki/Actavis) between 2005 and 2006 to [delay](/wiki/Reverse_payment_patent_settlement) sales of generic modafinil in the US until April 2012 by these companies in exchange for upfront and royalty payments.[[78]](#cite_note-78) Litigation arising from these agreements is still pending including an FTC suit filed in April 2008.[[79]](#cite_note-79) [Apotex](/wiki/Apotex) received regulatory approval in Canada despite a suit from Cephalon's marketing partner in Canada, [Shire Pharmaceuticals](/wiki/Shire_Pharmaceuticals).[[80]](#cite_note-80)[[81]](#cite_note-81) Cephalon has sued Apotex in the US to prevent it from releasing a genericized armodafinil (Nuvigil).[[82]](#cite_note-82) Cephalon's 2011 attempt to merge with Teva was approved by the FTC under a number of conditions, including granting generic US rights to another company;[[83]](#cite_note-83) ultimately, [Par Pharmaceutical](/wiki/Par_Pharmaceutical) acquired the US modafinil rights as well as some others.[[84]](#cite_note-84) In the United Kingdom, [Mylan Inc.](/wiki/Mylan_Inc.) received regulatory approval to sell generic modafinil produced by [Orchid](/wiki/Orchid_pharma) in January 2010; Cephalon sued to prevent sale, but lost the patent trial in November.[[85]](#cite_note-85)

## Society and culture[[edit](/index.php?title=(none)&action=edit&section=22)]

### Legal status[[edit](/index.php?title=(none)&action=edit&section=23)]

Modafinil is [Template:As of](/wiki/Template:As_of) classified as a [Schedule IV controlled substance](/wiki/Controlled_Substances_Act) under United States federal law; it is illegal to import by anyone other than a [DEA](/wiki/Drug_Enforcement_Administration)-registered importer without a prescription.[[86]](#cite_note-86) However, one may legally bring modafinil into the United States in person from a foreign country, provided that he or she has a prescription for it, and the drug is properly declared at the border crossing. U.S. residents are limited to 50 dosage units (e.g., pills).[[87]](#cite_note-87) Under the US [Food and Drug Act](/wiki/Food_and_Drug_Act), drug companies are not allowed to market their drugs for [off-label uses](/wiki/Off-label_use) (conditions other than those officially approved by the FDA);[[88]](#cite_note-88) Cephalon was reprimanded in 2002 by the FDA because its promotional materials were found to be "false, lacking in fair balance, or otherwise misleading".[[89]](#cite_note-89) Cephalon pleaded guilty to a criminal violation and paid several fines, including [Template:Nowrap](/wiki/Template:Nowrap) and [Template:Nowrap](/wiki/Template:Nowrap) fines to the U.S. government in 2008.[[90]](#cite_note-90)[[91]](#cite_note-91) The following countries do not classify modafinil as a controlled substance:

* Canada (not listed in the [Controlled Drugs and Substances Act](/wiki/Controlled_Drugs_and_Substances_Act), but it is a Schedule F prescription drug,[[92]](#cite_note-92) so it is subject to seizure by [Canada Border Services Agency](/wiki/Canada_Border_Services_Agency))
* [Mexico](/wiki/Mexico) (Not listed as a controlled substance, in the National Health Law)[[93]](#cite_note-93)\* [United Kingdom](/wiki/United_Kingdom) (not listed in [Misuse of Drugs Act](/wiki/Misuse_of_Drugs_Act_1971) so possession not illegal, but prescription required) [[94]](#cite_note-94)\* [Australia](/wiki/Australia) (listed as a Schedule 4 prescription drug)
* In [Germany](/wiki/Germany) the classification has been changed from controlled substance (BtM) to prescription drug (RP) effective March 1, 2008.
* In [India](/wiki/India), generic retailing as Modalert is available from [Sun Pharmaceuticals](/wiki/Sun_Pharmaceuticals); Indian firms are not required to respect [patents filed before 1995](/wiki/Pharmaceuticals_in_India#Patents).

Currently, use of modafinil is controversial in the sporting world, with high-profile cases attracting press coverage since several prominent American athletes have tested positive for the substance (see [modafinil as a doping agent](/wiki/#Doping_agent)). Some athletes who were found to have used modafinil protested that the drug was not on the prohibited list at the time of their offenses. However, the [World Anti-Doping Agency](/wiki/World_Anti-Doping_Agency) (WADA) maintains that it was related to already banned substances. The Agency added modafinil to its list of prohibited substances on August 3, 2004, ten days before the start of the [2004 Summer Olympics](/wiki/2004_Summer_Olympics).

### Brand names[[edit](/index.php?title=(none)&action=edit&section=24)]

Modafinil is sold under a wide variety of brand names worldwide, including:

* **Alertec** – Canada, Ecuador
* **BravaMax** – Egypt, Morocco
* **Carim** – El Salvador, Guatemala, Honduras, Colombia, Ecuador, Uruguay
* **Provake** – India (also **Modalert, Modapro, Modafil, Modvigil, Modatec**)
* **Modasomil** Austria, Switzerland
* **Modavigil** – Australia, New Zealand
* **Modiodal** – Mexico, Philippines, Spain, France, Denmark, Iceland, Greece, Cyprus, Netherlands, Portugal, Sweden, Norway, Turkey, Japan, Iran
* **Modiwake** – Turkey
* **Provigil** – Belgium, Ireland, Italy, South Korea, United Kingdom, United States, South Africa, Israel, Finland
* **Resotyl** – Chile (also **Mentix, Alertex, Zalux**)
* **Stavigile** – Brazil
* **Vigia** – Colombia
* **Vigicer** – Argentina
* **Vigil** – Germany

### Doping agent[[edit](/index.php?title=(none)&action=edit&section=25)]

Modafinil has received some publicity in the past when several athletes (such as sprinter [Kelli White](/wiki/Kelli_White) in 2004, cyclist [David Clinger](/wiki/David_Clinger)[[95]](#cite_note-95) and basketball player [Diana Taurasi](/wiki/Diana_Taurasi)[[96]](#cite_note-96) in 2010, and rower Timothy Grant in 2015[[97]](#cite_note-97)

### Motion sickness[[edit](/index.php?title=(none)&action=edit&section=35)]

Modafinil has been evaluated alone and in combination with [scopolamine](/wiki/Scopolamine) as an anti-motion sickness medication. It did not help by itself, but appeared to help in combination with scopolamine, acting to reduce symptoms of drowsiness associated with scopolamine.[[135]](#cite_note-135)

### Modafinil analogs[[edit](/index.php?title=(none)&action=edit&section=36)]

[Template:Multiple image](/wiki/Template:Multiple_image)

Modafinil is a highly researched compound, with many derivatives created and studied, some examples and their differences between dopamine, serotonin & norepinephrine affect is given in bundled table form below.

{| class="talk collapsed collapsible" |- ! Tables containing modafinil analogs & their values: click to |- style="text-align: left; style="font-size:smaller" |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Modafinil analogs and their effects on the central nervous system.[[136]](#cite_note-136) | | | | |
| **Structure** | **X1** | **X2** | **NR1R2** | **Action on CNS** |
| rowspan=10|[File:Modafinil substitution pattern 2nd analog series.png](/wiki/File:Modafinil_substitution_pattern_2nd_analog_series.png) |  |  |  |  |
| H | H | NHCH3 | Stimulating |  |
| H | H | NHCH(CH3)2 | Stimulating |  |
| H | H | NHC(CH3)3 | Stimulating |  |
| H | H | NHCH2CH3 | Sedative |  |
| H | H | Piperidine | Sedative |  |
| H | H | Morfoline | Sedative |  |
| 4-Cl | H | NH2 | Stimulating |  |
| 4-F | 4-F | NH2 | Stimulating |  |
| 4-F | H | NH2 | Stimulating |  |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Thio- & Sulfinylacetamide Modafinil analogs[[44]](#cite_note-44) | | | | | | |
| **Structure** | ***X* (di-benzene substitutions)** | ***Y* (CH2 substitution)** | ***R* (*N*-methyl terminating substitution)** | ***K*i [SE interval] (*nM*) @ DAT** | ***K*i [SE interval] (*nM*) @ SERT** | ***K*i [SE interval] (*nM*) @ NET** |
| Modafinil | H | S=O | H | 2600 (2430—2780) | *inactive* | *inactive* |
| rowspan=31|[File:Modafinil analog substitutions.png](/wiki/File:Modafinil_analog_substitutions.png) |  |  |  |  |  |  |
| H | S | H | 12400 (10800—14300) | 14500 (11800—17700) | *inactive* derived as 285000 (117000—690000)</small> |  |
| 3,3′-di-Cl | S | H | 275 (257—295) | *inactive* derived as 808000 (706000—924000)</small>||45400 (39600—52000) |  |  |
| H | S | Me | 19300 (17900—20800) | *inactive* derived as 656000 (302000—1420000)</small>||27200 (25700—28900) |  |  |
| 4,4′-di-Cl | S | Me | 4130 (3620—4710) | 10700 (7310—15700) | 9770 (9170—10400) |  |
| 4,4′-di-Br | S | Me | 3010 (2770—3260) | 5720 (5320—6150) | 11000 (9540—12600) |  |
| H | S | allyl | 8370 (6680—10500) | *inactive* derived as 303000 (267000—344000)</small>||*inactive* derived as 171000 (88300—332000)</small> |  |  |
| H | S | *n*-propyl | 20700 (20300—21100) | *inactive* derived as 419000 (240000—729000)||68000 (53200—86900) |  |  |
| 4,4′-di-F | S | *n*-propyl | 11700 (10300—13200) | 44200 (38700—50500) | 59700 (51200—69600) |  |
| 4,4′-di-Cl | S | *n*-propyl | 1240 (1120—1380) | 10100 (8900—11400) | 7540 (6830—8330) |  |
| 4,4′-di-Br | S | *n*-propyl | 590 (550—632) | 8900 (8150—9720) | 10600 (9980—11300) |  |
| H | S | cyclopropylmethyl | 13600 (11900—15600) | 20500 (17500—23900) | *inactive* |  |
| 4,4′-di-F | S | cyclopropylmethyl | 6700 (5730—7830) | 34000 (28800—40200) | 57000 (51500—63000) |  |
| 4,4′-di-Br | S | cyclopropylmethyl | 975 (852—1110) | 7030 (6040—8180) | *inactive* |  |
| H | S | *n*-butyl | 23600 (20500—27100) | *inactive* | *inactive* |  |
| 4,4′-di-F | S | *n*-butyl | 6400 (5820—7050) | 25500 (23300—28000) | 56100 (53900—58500) |  |
| 4,4′-di-Br | S | *n*-butyl | 722 (659—792) | 7090 (6990—8180) | 7580 (7210—7970) |  |
| H | S | 3-phenylpropyl | 2020 (1990—2050) | *inactive* | *inactive* |  |
| 4,4′-di-F | S | 3-phenylpropyl | 442 (385—509) | 3500 (2950—4160) | *inactive* |  |
| 4,4′-di-Cl | S | 3-phenylpropyl | 223 (191—260) | *inactive* | *inactive* |  |
| 4,4′-di-Br | S | 3-phenylpropyl | 238 (202—280) | 60700 (58400—63200) | 35500 (31700—39800) |  |
| H | S | 4-phenylbutyl | 1150 (1020—1290) | *inactive* | 7960 (7590—8350) |  |
| 4,4′-di-Br | S | 4-phenylbutyl | 405 (348—471) | *inactive* | *inactive* |  |
| 4,4′-di-CH3 | S=O | H | 12700 (12400—13100) | *inactive* | *inactive* |  |
| 4,4′-di-CF3 | S=O | H | 35400 (34100—36700) | not tested | not tested |  |
| 3,3′-di-F | S=O | H | 5930 (4990—7060) | *inactive* | *inactive* |  |
| 3,3′-di-Cl | S=O | H | 881 (763—1020) | *inactive* | *inactive* |  |
| H, 3-Br | S=O | H | 550 (542—557) | *inactive* | *inactive* |  |
| H | S=O | Me | 13100 (12600—13700) | *inactive* | *inactive* |  |
| 4,4′-di-Br | S=O | 3-phenylpropyl | 1280 (1160—1400) | 892 (787—1010) | *inactive* |  |
| 4,4′-di-Cl | S | H | 2200 (2060—2390) | 38800 (36400—41300) | 51400 (46000—57500) |  |

|}

## See also[[edit](/index.php?title=(none)&action=edit&section=37)]

[Template:Portal](/wiki/Template:Portal)

* [Adrafinil](/wiki/Adrafinil)
* [Armodafinil](/wiki/Armodafinil)
* [CRL-40,940](/wiki/CRL-40,940)
* [CRL-40,941](/wiki/CRL-40,941)
* [Fluorenol](/wiki/Fluorenol)

## References[[edit](/index.php?title=(none)&action=edit&section=38)]

[Template:Reflist](/wiki/Template:Reflist)

## Further reading[[edit](/index.php?title=(none)&action=edit&section=39)]

* [Template:Cite journal](/wiki/Template:Cite_journal)
* [Template:Cite news](/wiki/Template:Cite_news)

## External links[[edit](/index.php?title=(none)&action=edit&section=40)]

* [PROVIGIL – official website](http://www.provigil.com/)
  + [Medication Guide for Patients](http://www.provigil.com/media/PDFs/medication_guide.pdf)
  + [Full Prescribing Information](http://www.provigil.com/media/PDFs/prescribing_info.pdf)
* [RxList Patient Information](http://www.rxlist.com/cgi/generic2/modafinil_pi.htm) for modafinil users
* ["Mayo Clinic Proceedings Publishes Study of NUVIGIL in Patients with Shift Work Disorder"](http://ca.sys-con.com/node/1169081)
* [U.S. National Library of Medicine: Drug Information Portal – Modafinil](http://druginfo.nlm.nih.gov/drugportal/dpdirect.jsp?name=Modafinil)

[Template:Stimulants](/wiki/Template:Stimulants) [Template:Dopaminergics](/wiki/Template:Dopaminergics)

[Category:Acetamides](/wiki/Category:Acetamides) [Category:Anticonvulsants](/wiki/Category:Anticonvulsants) [Category:D2-receptor agonists](/wiki/Category:D2-receptor_agonists) [Category:Dopamine reuptake inhibitors](/wiki/Category:Dopamine_reuptake_inhibitors) [Category:Drugs with unknown mechanisms of action](/wiki/Category:Drugs_with_unknown_mechanisms_of_action) [Category:Nootropics](/wiki/Category:Nootropics) [Category:Stimulants](/wiki/Category:Stimulants) [Category:Sulfoxides](/wiki/Category:Sulfoxides) [Category:1994 introductions](/wiki/Category:1994_introductions)