MODAFINIL

THERAPEUTICS

Brands
- Provigil
- Alertec
- Modiodal

see index for additional brand names

Generic? Yes

Class
- Neuroscience-based Nomenclature: dopamine reuptake inhibitor (D-RI)
- Wake-promoting

Commonly Prescribed for
(bold for FDA approved)
- **Reducing excessive sleepiness in patients with narcolepsy and shift work sleep disorder**
- **Reducing excessive sleepiness in patients with obstructive sleep apnea/hypopnea syndrome (OSAHS) (adjunct to standard treatment for underlying airway obstruction)**
- Attention deficit hyperactivity disorder (ADHD)
- Fatigue and sleepiness in depression
- Fatigue in multiple sclerosis
- Bipolar depression

How the Drug Works
- Unknown, but clearly different from classical stimulants such as methylphenidate and amphetamine
- Binds to and requires the presence of the dopamine transporter; also requires the presence of alpha adrenergic receptors
- Hypothetically acts as an inhibitor of the dopamine transporter
- Increases neuronal activity selectively in the hypothalamus
- ✻ Presumably enhances activity in hypothalamic wakefulness center (TMN, tuberomammillary nucleus) within the hypothalamic sleep-wake switch by an unknown mechanism
- ✻ Activates TMN neurons that release histamine
- ✻ Activates other hypothalamic neurons that release orexin/hypocretin

How Long Until It Works
- Can immediately reduce daytime sleepiness and improve cognitive task performance within 2 hours of first dosing
- Can take several days to optimize dosing and clinical improvement

If It Works
- ✻ Improves daytime sleepiness and may improve attention as well as fatigue
- ✻ Does not generally prevent one from falling asleep when needed
- May not completely normalize wakefulness
- Treat until improvement stabilizes and then continue treatment indefinitely as long as improvement persists (studies support at least 12 weeks of treatment)

If It Doesn't Work
- ✻ Change dose; some patients do better with an increased dose but some actually do better with a decreased dose
- Augment or consider an alternative treatment for daytime sleepiness, fatigue, or ADHD

Best Augmenting Combos for Partial Response or Treatment Resistance
- ✻ Modafinil is itself an adjunct to standard treatments for obstructive sleep apnea/hypopnea syndrome (OSAHS); if continuous positive airway pressure (CPAP) is the treatment of choice, a maximal effort to treat first with CPAP should be made prior to initiating modafinil and CPAP should be continued after initiation of modafinil
- ✻ Modafinil is itself an augmenting therapy to antidepressants for residual sleepiness and fatigue in major depressive disorder
- Best to attempt another monotherapy prior to augmenting with other drugs in the treatment of sleepiness associated with sleep disorders or problems concentrating in ADHD
- Combination of modafinil with stimulants such as methylphenidate or amphetamine or with atomoxetine for ADHD has not been systematically studied
- However, such combinations may be useful options for experts, with close monitoring, when numerous monotherapies for sleepiness or ADHD have failed

Tests
- None for healthy individuals

SIDE EFFECTS

How Drug Causes Side Effects

- Unknown
- CNS side effects presumably due to excessive CNS actions on various neurotransmitter systems

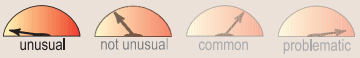
Notable Side Effects

- ✻ Headache (dose-dependent)
- Anxiety, nervousness, insomnia
- Dry mouth, diarrhea, nausea, anorexia
- Pharyngitis, rhinitis, infection
- Hypertension
- Palpitations

Life-Threatening or Dangerous Side Effects

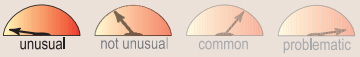
- Transient EKG ischemic changes in patients with mitral valve prolapse or left ventricular hypertrophy have been reported (rare)
- Rare activation of (hypo)mania, anxiety, hallucinations, or suicidal ideation
- Rare severe dermatologic reactions (Stevens-Johnson syndrome and others)
- Angioedema, anaphylactoid reactions, and multi-organ hypersensitivity reactions have been reported

Weight Gain



- Reported but not expected

Sedation



- Reported but not expected
- Patients are usually awakened and some may be activated

What to Do About Side Effects

- Wait
- Lower the dose
- Give only once daily
- Give smaller split doses 2 or more times daily
- For activation or insomnia, do not give in the evening
- If unacceptable side effects persist, discontinue use
- For life-threatening or dangerous side effects, discontinue immediately (e.g., at first sign of a drug-related rash)

Best Augmenting Agents for Side Effects

- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- 200 mg/day in the morning

Dosage Forms

- Tablet 100 mg, 200 mg (scored)

How to Dose

- Titration up or down only necessary if not optimally efficacious at the standard starting dose of 200 mg once a day in the morning

Dosing Tips

- ✻ For sleepiness, more may be more: higher doses (200–800 mg/day) may be better than lower doses (50–200 mg/day) in patients with daytime sleepiness in sleep disorders
- ✻ For problems concentrating and fatigue, less may be more: lower doses (50–200 mg/day) may be paradoxically better than higher doses (200–800 mg/day) in some patients
- At high doses, may slightly induce its own metabolism, possibly by actions of inducing CYP450 3A4
- Dose may creep upward in some patients with long-term treatment due to autoinduction; drug holiday may restore efficacy at original dose

Overdose

- No fatalities; agitation, insomnia, increase in hemodynamic parameters
- Postmarketing experience includes CNS symptoms, such as restlessness, disorientation, confusion, excitation, and hallucinations; digestive changes, such as nausea and diarrhea; and cardiovascular changes, such as tachycardia, bradycardia, hypertension, and chest pain

Long-Term Use

- Efficacy in reducing excessive sleepiness in sleep disorders has been demonstrated in 9- to 12-week trials
- Unpublished data show safety for up to 136 weeks

- The need for continued treatment should be reevaluated periodically

Habit Forming

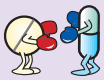
- Schedule IV; may have some potential for abuse but unusual in clinical practice

How to Stop

- Taper not necessary; patients may have sleepiness on discontinuation

Pharmacokinetics

- Metabolized by the liver
- Excreted renally
- Elimination half-life 10–12 hours
- Inhibits CYP450 2C19 (and perhaps 2C9)
- Induces CYP450 3A4 (and slightly 1A2 and 2B6)



Drug Interactions

- May increase plasma levels of drugs metabolized by CYP450 2C19 (e.g., diazepam, phenytoin, propranolol)
- Modafinil may increase plasma levels of CYP450 2D6 substrates such as TCAs and SSRIs, perhaps requiring downward dose adjustments of these agents
- Modafinil may decrease plasma levels of CYP450 3A4 substrates such as ethinyl estradiol and triazolam
- Due to induction of CYP450 3A4, effectiveness of steroidal contraceptives may be reduced by modafinil, including 1 month after discontinuation
- Inducers or inhibitors of CYP450 3A4 may affect levels of modafinil (e.g., carbamazepine may lower modafinil plasma levels; fluvoxamine and fluoxetine may raise modafinil plasma levels)
- Modafinil may slightly reduce its own levels by autoinduction of CYP450 3A4
- Modafinil may increase clearance of drugs dependent on CYP450 1A2 and reduce their plasma levels
- Patients on modafinil and warfarin should have prothrombin times monitored
- Methylphenidate may delay absorption of modafinil by an hour
- ✻ However, coadministration with methylphenidate does not significantly change the pharmacokinetics of either modafinil or methylphenidate
- ✻ Coadministration with dextroamphetamine also does not significantly change the pharmacokinetics of either modafinil or dextroamphetamine
- Interaction studies with MAOIs have not been performed, but MAOIs can be given with modafinil by experts with cautious monitoring

Other Warnings/ Precautions

- Patients with history of drug abuse should be monitored closely
- Modafinil may cause CNS effects similar to those caused by other CNS agents (e.g., changes in mood and, theoretically, activation of psychosis, mania, or suicidal ideation)
- Modafinil should be used in patients with sleep disorders that have been completely evaluated for narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS), and shift work sleep disorder
- In OSAHS patients for whom continuous positive airway pressure (CPAP) is the treatment of choice, a maximal effort to treat first with CPAP should be made prior to initiating modafinil, and then CPAP should be continued after initiating modafinil
- The effectiveness of steroidal contraceptives may be reduced when used with modafinil and for 1 month after discontinuation of modafinil
- Modafinil is not a replacement for sleep

Do Not Use

- If patient has severe hypertension
- If patient has cardiac arrhythmias
- If there is a proven allergy to modafinil

SPECIAL POPULATIONS

Renal Impairment

- Use with caution; dose reduction is recommended

Hepatic Impairment

- Reduce dose by half in severely impaired patients

Cardiac Impairment

- Use with caution

- Not recommended for use in patients with a history of left ventricular hypertrophy, ischemic EKG changes, chest pain, arrhythmias, or recent myocardial infarction

Elderly

- Limited experience in patients over 65
- Clearance of modafinil may be reduced in elderly patients

Children and Adolescents

- Safety and efficacy not established under age 16
- Can be used cautiously by experts for children and adolescents

Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Intrauterine growth restriction and spontaneous abortion have been reported with armodafinil and modafinil
- In animal studies, developmental toxicity was observed at clinically relevant plasma exposures of armodafinil and modafinil
- Use in women of childbearing potential requires weighing potential benefits to the mother against potential risks to the fetus

✻ Generally, modafinil should be discontinued prior to anticipated pregnancies

Breast Feeding

- Unknown if modafinil is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk

✻ Recommended either to discontinue drug or bottle feed

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Selective for areas of brain involved in sleep/wake promotion
- Less activating and less abuse potential than stimulants

Potential Disadvantages

- May not work as well as stimulants in some patients

Primary Target Symptoms

- Sleepiness
- Concentration
- Physical and mental fatigue

Pearls

✻ Anecdotal usefulness for jet lag short-term (off label)

✻ Modafinil is not a replacement for sleep

✻ The treatment for sleep deprivation is sleep, not modafinil

- Controlled studies suggest modafinil improves attention in OSAHS, shift work sleep disorder, and ADHD (both children and adults), but controlled studies of attention have not been performed in major depressive disorder

✻ May be useful to treat fatigue in patients with depression as well as other disorders, such as multiple sclerosis, myotonic dystrophy, HIV/AIDS

- In depression, modafinil's actions on fatigue appear to be independent of actions (if any) on mood
- In depression, modafinil's actions on sleepiness also appear to be independent of actions (if any) on mood but may be linked to actions on fatigue or on global functioning
- Several controlled studies in depression show improvement in sleepiness or global functioning, especially for depressed patients with sleepiness and fatigue
- May be useful adjunct to mood stabilizers for bipolar depression
- May be useful in treating sleepiness associated with opioid analgesia, particularly in end-of-life management
- Subjective sensation associated with modafinil is usually one of normal

wakefulness, not of stimulation, although jitteriness can rarely occur
- Anecdotally, some patients may experience wearing off of efficacy over time, especially for off-label uses, with restoration of efficacy after a drug holiday; such wearing off is less likely with intermittent dosing

✻ Compared to stimulants, modafinil has a novel mechanism of action, novel therapeutic uses, and less abuse potential, but is often inaccurately classified as a stimulant
- Alpha 1 antagonists such as prazosin may block the therapeutic actions of modafinil
- The active R enantiomer of modafinil, called armodafinil, is also available

Suggested Reading

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