MODAFINIL

**THERAPEUTICS**

**Brands**
- Provigil, Alertec, Modiodal

**Generic?**
No

**Class**
- Wake-promoting agent

**Commonly Prescribed for**
*(FDA approved in bold)*
- Reducing excessive sleepiness in patients with narcolepsy or shift-work related sleep disorder
- Reducing excessive sleepiness in patients with obstructive sleep apnea (OSA)/hypopnea syndrome
- Treatment of fatigue in multiple sclerosis (MS)
- Fatigue in depression
- Attention deficit hyperactivity disorder
- Fatigue in cancer, HIV, or post-stroke patients

**How the Drug Works**
- Unlike traditional stimulants which act directly via dopaminergic pathways, it may also act in the hypothalamus by stimulating wake-promoting areas, or inhibiting sleep-promoting areas
- It may also have effects on dopamine transporter pathways similar to other stimulants, hypothetically inhibiting the dopamine transporter
- Increases neuronal activity selectively in the hypothalamus and activates tuberomammillary nucleus neurons that release histamine
- It also activates hypothalamic neurons that release orexin/hypocretin

**How Long Until It Works**
- Typically 1–2 hours, although maximal benefit may take days-weeks

**If It Works**
- Continue to use indefinitely as long as symptoms persist. Complete resolution of symptoms is unusual. Does not cause insomnia when dosed correctly

**If It Doesn’t Work**
- Change to most effective dose or alternative agent. Re-evaluate treatment of underlying cause (i.e., OSA) of fatigue. Consider other causes of fatigue (i.e., anemia, heart disease) as appropriate. Screen for use of CNS depressants that can interfere with sleep, i.e., opioids or alcohol

**Best Augmenting Combos for Partial Response or Treatment-Resistance**
- In treating OSA, modafinil is an adjunct to standard treatments such as continuous positive airway pressure (CPAP), weight loss and treatment of obstruction when possible
- In MS change drug regimen, i.e., antispasticity or disease-modifying agents when possible if they are significantly contributing to fatigue. Amantadine is an alternative treatment for MS-related fatigue
- Treat coexisting medical illnesses such as HIV, depression, or chronic pain disorders with appropriate agents

**Tests**
- None required

**ADVERSE EFFECTS (AEs)**

**How Drug Causes AEs**
- Unknown but most AEs are likely related to drug actions on CNS neurotransmitters

**Notable AEs**
- Nervousness, insomnia, headache, nausea, anorexia, palpitations, dry mouth, diarrhea, hypertension

**Life-Threatening or Dangerous AEs**
- Transient ECG changes have been reported in patients with preexisting heart disease
- Rare psychiatric reactions (activation of mania, anxiety)
- Rare severe dermatologic reactions

**Weight Gain**
- Unusual

*Unusual, not uncommon, common, problematic*
Sedation
- Unusual

What to Do About AEs
- Try lowering the dose or dividing doses. If insomnia, do not take later in the day

Best Augmenting Agents for AEs
- Most AEs do not respond to adding other medications

**DOsing and Use**

**Usual Dosage Range**
- 100–400 mg daily

**Dosage Forms**
- Tablets: 100, 200 mg (scored)

**How to Dose**
- Start at 200 mg in the morning
- In patients sensitive to medications, start at 100 mg in the morning
- When dividing dose, give the first dose in the morning, the second 4–6 hours later (i.e., at noon)
- If sleepiness does not improve on 200 mg/day dose, increase to 400 mg if no AEs

**Dosing Tips**
- Dose requirements can escalate over time due to autoinduction. A drug holiday may restore effectiveness of lower dose
- In general, patients with sleepiness do better with higher doses (200 mg or more) and patients with fatigue or inability to concentrate may do well at lower doses
- In patients with shift-work related sleep disorder, take 1 hour prior to beginning a shift

**Overdose**
- No reported deaths. Agitation, anxiety and hypertension are common

**Long-Term Use**
- Although most initial trials were only a few months, appears safe. Periodically re-evaluate need for use

**Habit Forming**
- Class IV medication, but rarely abused in clinical practice

**How to Stop**
- Withdrawal is not problematic, unlike traditional stimulants. Symptoms of sleepiness may recur

**Pharmacokinetics**
- Metabolized by CYP450 system including isoenzymes 2C19, 3A4, among others. Peak concentrations at 2 hours and elimination half-life is 10–12 hours. About 10% of drug is excreted unchanged in urine. Mild CYP3A4 induction

**Drug Interactions**
- Can increase plasma levels and effect of many drugs metabolized by 2C19 or 2D6 including phenytoin, diazepam, propranolol, tricyclic antidepressants, and SSRIs
- Can induce CYP450 3A4 reducing plasma levels of triazolam, and many steroidal contraceptives
- Carbamazepine can lower modafinil plasma levels and fluvoxamine and fluoxetine can increase levels
- Modafinil can affect warfarin effectiveness requiring closer monitoring of prothrombin times
- May interact with MAO inhibitors

**Other Warnings/Precautions**
- May adversely affect mood. Can cause activation of psychosis or mania

**Do Not Use**
- Known hypersensitivity to the drug, severe hypertension or cardiac arrhythmias

**Renal Impairment**
- No known effects. May require lower dose

**Hepatic Impairment**
- Reduce dose in patients with severe impairment

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MODAFINIL (continued)

Cardiac Impairment
- Do not use in patients with ischemic ECG changes, chest pain, left ventricular hypertrophy or recent myocardial infarction

Elderly
- No known effects

Children and Adolescents
- Not studied in children under 16. Not a first-line agent in ADHD

Pregnancy
- Category C. Generally not used in pregnancy

Breast Feeding
- Unknown if excreted in breast milk. Do not use

The Epworth sleepiness scale is a reliable way to measure daytime sleepiness and response to treatment. It is a self-administered 8 item questionnaire with scores of 0–24. A score of 10 or greater indicates excessive daytime sleepiness. A reduction of 4 or more points on the Epworth is considered a good response to treatment

Narcolepsy is characterized by excessive daytime sleepiness, uncontrollable sleep and observed cataplexy. Hypnagogic or hypnopompic hallucinations or sleep paralysis suggest the diagnosis. In sleep studies, a sleep latency of 8 minutes or less and quick onset of REM sleep confirms the diagnosis. The maintenance of wakefulness test can monitor response to treatment or be used to document safety in patients in which wakefulness is important for public safety (e.g., pilots). An increase of 1–2 minutes in maintenance of wakefulness is considered a good response to treatment

Dividing doses and giving a second dose at noon does not appear to affect sleep architecture

For MS-related fatigue, amantadine is another commonly used treatment. Modafinil is usually most effective at the 200 mg/day dose

May be effective in treating excessive sleepiness in Parkinson’s disease (at 200 mg/day dose) but does not usually improve motor scores

Technically not a psychostimulant and minimal abuse potential

THE ART OF NEUROPHARMACOLOGY

Potential Advantages
- Less risk of addiction, withdrawal and abuse compared to other stimulants

Potential Disadvantages
- Cost. May be less effective than other stimulants

Primary Target Symptoms
- Sleepiness, fatigue, concentration difficulties
Suggested Reading


