PALLIATIVE CARE NETWORK OF WISCONSIN

**FAST FACTS AND CONCEPTS #259**
**MODAFINIL**

**Jennifer Cheng MD, Elizabeth L Thiel MD, and Hunter Groninger MD**

**Background** Modafinil is a non-amphetamine psychostimulant approved for the treatment of excessive daytime somnolence associated with obstructive sleep apnea, narcolepsy, and shift work sleep disorder. This *Fast Fact* assimilates major findings from the published medical literature on the use of modafinil for symptom management in the seriously ill. See *Fast Facts* #173 for additional information on cancer related fatigue (CRF) and *Fast Fact* #51 for information on psychostimulants in general.

**Pharmacology** Although the exact mechanism is unclear, modafinil's action may involve enhanced catecholaminergic signaling and decreased gamma aminobutryic acid (GABA) release, primarily at the anterior hypothalamus (1,2). Rapidly absorbed after oral ingestion, the drug reaches peak plasma levels in 2-4 hours, with a half-life of 10-13 hours. It is primarily metabolized by the liver, with subsequent renal elimination of inactive metabolites. Compared to other commonly prescribed psychostimulants (e.g. methylphenidate or dextroamphetamine), it has low-abuse potential and less rapid development of tolerance (3). Consequently, modafinil is a scheduled IV controlled substance whereas methylphenidate and many other psychostimulants are controlled II substances.

**Research Findings**

- In cancer populations: A preliminary placebo-controlled trial resulted in significantly reduced daytime sleepiness in patients with severe CRF treated with daily modafinil (4). In other pilot studies, modafinil was shown to be effective for specific symptoms in a) non-small cell lung cancer (CRF, daytime drowsiness, depression), b) breast cancer (CRF), c) brain cancer (cognitive functioning, mood, and CRF), and d) advanced cancer with Karnofsky performance status of 50-70% (improved attention and psychomotor speed; reduced drowsiness and depression) (2, 5-7). Subsequently, two double-blind, placebo-controlled trials have suggested that modafinil is not associated with any additional benefit over placebo in the management of CRF nor in secondary outcomes such as daytime sleepiness, depression, and quality of life (8,9). Because these studies also associated modafinil with more nausea and vomiting, the National Comprehensive Cancer Network has removed modafinil from its guidelines on CRF management (10).
- In non-cancer conditions: Generally, these smaller controlled trials have generated conflicting results. Compared to placebo, use of modafinil may reduce fatigue in patients with HIV/AIDS and amyotrophic lateral sclerosis (11,12). However, recent studies have not shown significant improvement in fatigue in patients with multiple sclerosis, Parkinson's disease, and myotonic muscular dystrophy (13-15).
- Comparative data: There are limited data comparing modafinil and methylphenidate in cancer and non-cancer populations; one open label pilot trial comparing modafinil with methylphenidate in primary brain tumor patients found no significant difference in cognitive improvement between groups (16).

**Dosage** Lower doses (50-200 mg, once daily in the morning) are generally prescribed for fatigue and concentration difficulties;higher doses (up to 600 mg/day) are used for excessive sleepiness (17).

**Toxicity and Precautions**

- More common side effects includes dose related headaches (34%), nausea (11%), nervousness (7%), and diarrhea (6%). Hypertension rarely occurs, but monitoring of blood pressure is recommended (18).
- In patients with severe hepatic impairment, reduce dose by 50%. Safety and efficacy have not been evaluated for patients with renal impairment (19). Use cautiously in patients with bipolar disorder or preexisting psychosis (may stimulate mania/hypomania) and in patients with ischemic or structural heart disease (may precipitate palpitations, tachyarrhythmia, or chest pain) (20).

**Cost** Generic modafinil costs approximately $650 for thirty 100 mg tablets compared to about $70 for a comparable month long supply of sixty tablets of 10 mg tablets of generic methylphenidate (20).

**Use in Pediatrics** Modafinil's most established pediatric role is for ADHD management. However, reports of serious dermatologic adverse effects and psychiatric events led the FDA to limit it as a second

or third-line treatment for ADHD. Therefore, the off-label use of modafinil to treat CRF in children should be strongly cautioned against.

**Summary** Palliative care patients are often seriously debilitated by fatigue, excessive daytime somnolence, and depression. There is conflicting evidence about the usefulness of modafinil in improving CRF. Pending more conclusive randomized controlled trials, its use is likely limited by cost, gastrointestinal side effects, and availability.

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**Authors' Affiliations:** Johns Hopkins University School of Medicine, Baltimore, MD (JC); Medical College of Wisconsin; Clinical Center, National Institutes of Health, Bethesda, MD (HG).
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