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 aminobutyric 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.

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

Conflicts of Interest Statement: The authors have disclosed no relevant conflicts of interest.

Version History: First electronically published in August 2012. Significant revision occurred in November 2015 by Elizabeth L Thiel MD to reflect the evolution in the published literature on modafinil.

Fast Facts and Concepts are edited by Sean Marks MD (Medical College of Wisconsin) and associate editor Drew A Rosielle MD (University of Minnesota Medical School), with the generous support of a volunteer peer-review editorial board, and are made available online by the Palliative Care Network of Wisconsin (PCNOW); the authors of each individual Fast Fact are solely responsible for that Fast Fact’s content. The full set of Fast Facts are available at Palliative Care Network of Wisconsin with contact information, and how to reference Fast Facts.

Copyright: All Fast Facts and Concepts are published under a Creative Commons Attribution-NonCommercial 4.0 International Copyright (http://creativecommons.org/licenses/by-nc/4.0/). Fast Facts can only be copied and distributed for non-commercial, educational purposes. If you adapt or distribute a Fast Fact, let us know!

Disclaimer: Fast Facts and Concepts provide educational information for health care professionals. This information is not medical advice. Fast Facts are not continually updated, and new safety information may emerge after a Fast Fact is published. Health care providers should always exercise their own independent clinical judgment and consult other relevant and up-to-date experts and resources. Some Fast Facts cite the use of a product in a dosage, for an indication, or in a manner other than that recommended in the product labeling. Accordingly, the official prescribing information should be consulted before any such product is used.