Modafinil #259

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Background

MODAFINIL IS A nonamphetamine psychostimulant approved for the treatment of excessive daytime somnolence associated with obstructive sleep apnea, narcolepsy, and shift work sleep disorder. Expanding research demonstrates potential indications for modafinil in cancer and non-cancer palliative care settings. This *Fast Fact* reviews use of modafinil for symptom management in the seriously ill.

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 two to four hours, with a half-life of 10 to 13 hours. It is primarily metabolized by the liver, with subsequent renal elimination of inactive metabolites. Compared to methylphenidate, modafinil has low-abuse potential and less rapid development of tolerance.³

Research Findings

- *In cancer populations:* One placebo-controlled trial with a 200 mg daily dose of modafinil resulted in significantly reduced excessive daytime sleepiness in patients with severe chemotherapy related fatigue.⁴ Modafinil has also been shown to be effective for specific symptoms in nonsmall cell lung cancer (fatigue, daytime drowsiness, depression); in breast cancer (fatigue); and in brain cancer (cognitive functioning, mood, and fatigue, and physical activity).^{5,6,7} Finally, in advanced-stage cancer patients with Karnofsky performance status of 50% to 70%, modafinil 200 mg daily improved attention and psychomotor speed as well as subjective scores of drowsiness and depression.²

- *In noncancer 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.^{8,9} However, recent studies have not shown significant improvement in fatigue in patients with multiple sclerosis, Parkinson's disease, and myotonic muscular dystrophy.^{10–12}

There are limited data comparing modafinil and methylphenidate in cancer and noncancer populations; one open-label pilot trial comparing modafinil with methylphenidate immediate release and methylphenidate sustained release in primary brain tumor patients found no significant difference in cognitive improvement between groups.¹³ Studies were sponsored by modafinil's manufacturer.^{4,6,7,10}

Dosage

Lower doses (50–200 mg, once daily in the morning) are generally prescribed for fatigue and concentration difficulties, and higher doses (up to 600 mg/day) are used for excessive sleepiness.¹⁴

Toxicity and Precautions

More common side effects include dose-related headaches (34%), nausea (11%), nervousness (7%), and diarrhea (6%). Hypertension rarely occurs, but monitoring of blood pressure is recommended.¹⁵

In patients with severe hepatic impairment, reduce dose by 50%. Safety and efficacy have not been evaluated for patients with renal impairment.¹⁵ Use cautiously in patients with bipolar disorder or preexisting psychosis (may stimulate mania/hypomania)¹⁶ and in patients with ischemic or structural heart disease (may precipitate palpitations, tachyarrhythmia, or chest pain).¹⁵

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Cost

Modafinil costs approximately \$608 for 30 100 mg tablets compared to \$33 for 30 tablets of methylphenidate 10 mg.¹⁷

Summary

Palliative care patients are often seriously debilitated by fatigue, excessive daytime somnolence, and depression; and modafinil may reduce these symptoms. Pending more conclusive randomized controlled trials, its use is likely limited by cost and availability. Nonetheless, even now modafinil may have a therapeutic niche when methylphenidate use is contraindicated or limited due to side effects.

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Opoid Use in Liver Failure #260

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Background

MOST OPIOIDS ARE at least partially metabolized by the liver, complicating their use in liver failure. This *Fast Fact* discusses the use of opioids in patients with liver failure (see also *Fast Facts* #161 about opioid use in renal

failure, #176 and #177 about managing ascites, and #189 about prognostication in end-stage liver disease: www.mcw.edu/eperc). While there are plenty of pharmacokinetic data about opioids and liver failure, all the clinical recommendations below are rational and empiric, but not based on clinical outcomes research.