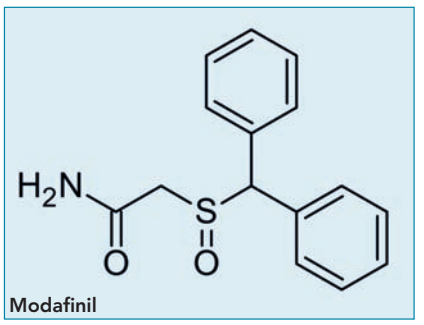
Modafinil Found to Have Little Effect on Fatigue in NSCLC

BY ROBERT H. CARLSON

The central nervous system stimulant modafinil has no effect beyond that of placebo in treating fatigue in patients with advanced non-small cell lung cancer (NSCLC), British scientists report in a study in the *Journal of Clinical Oncology* now online ahead of print (***doi: 10.1200/JCO.2013.54.4346***). Both modafinil and placebo led to a clinically significant improvement in fatigue score, but there was no significant difference between the groups.

The National Comprehensive Cancer Network guidelines for treating cancer-related fatigue recommend considering modafinil and methylphenidate, another CNS stimulant, after ruling out other causes of fatigue. Methylphenidate, however, has already been shown to have no effect compared with placebo, according to a study by Edward Bruera, MD, et al, published last year in *JCO* (***2013;31:2421-2427***). That study also found that a telephone intervention by nurses also did not help relieve fatigue when compared with placebo.



Modafinil

In the new study, a double-blind trial led by Anna Spathis, MSc, Consultant in Palliative Medicine at Addenbrookes Hospital in Cambridge, U.K., the researchers note that fatigue is the most prevalent symptom experienced by patients with cancer, occurring in more than 60 percent of patients and more than 80 percent of those receiving cancer treatment.


RONALD J. SCHEFF, MD: "The study shows that having randomized trial data is very important in establishing the efficacy of a drug. We have to be careful about prescribing medications that may not be as beneficial as we think."

Modafinil is licensed for the treatment of excessive sleepiness associated with narcolepsy. There had been only one previous randomized controlled trial evaluating modafinil in cancer-related fatigue, a U.S. study with 631 patients. Those researchers concluded that modafinil may be useful in controlling cancer-related fatigue in patients who present with severe fatigue, but not in those with mild or moderate fatigue (***Jean-Pierre et al: Cancer 2010;116:3513-3520***).

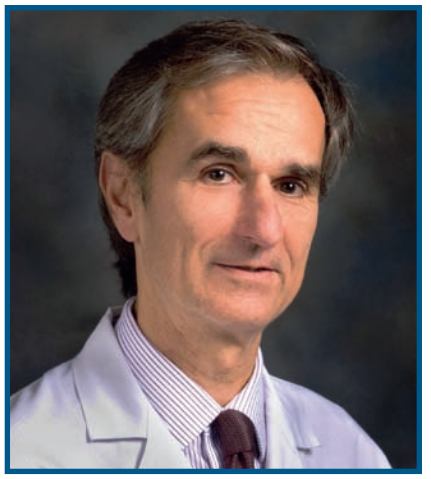
For the new study, Spathis and her colleagues randomly assigned treatment with modafinil to 75 patients (100 mg on days 1 to 14, 200 mg on days 15 to 18), and 85 to placebo. The patients, treated in outpatient clinics at 24 hospitals in the U.K. had stages 3a, 3b, or 4 NSCLC, or recurrent disease after surgery or radiation.

Spathis noted via email that modafinil has rarely been prescribed for cancer-related fatigue in the U.K., but an open-label feasibility study prior to this randomized, controlled trial was positive, with 10 out of 15 patients choosing to continue modafinil after the study.

In the randomized trial, the primary outcome was change in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score from baseline to 28 days, adjusted for baseline fatigue and performance status. Secondary outcomes included safety and patient-reported measures of depression, daytime sleepiness, and quality of life. The mean FACIT-Fatigue scores changed with modafinil from 24.64 to 31.28, and for placebo from 24.98 to 30.66.

In an intent-to-treat analysis, no significant differences between modafinil and placebo were found after adjustment for disease stage, performance status, gender, or severity of baseline fatigue. Interestingly, when patients were asked to rate how helpful the study treatment was on a four-point verbal scale, 47 percent of the patients in the modafinil group said treatment was not helpful, whereas only 23 percent of the placebo group did. And approximately twice as many patients withdrew from the modafinil group compared with the placebo group.

"Cancer-related fatigue is relatively neglected, beset by therapeutic nihilism on the part of both clinicians and patients, and simply allocating the time within a clinical consultation to acknowledge and discuss fatigue may benefit many patients experiencing this distressing symptoms," the researchers wrote.


EDUARDO BRUERA, MD: "This negative study of a mild stimulant is not surprising since a number of recent have found similarly disappointing results with methylphenidate."

Spathis added that "part of the benefit in the placebo arm of our trial may have been simply from clinicians or researchers taking the time to acknowledge and discuss patients' fatigue, and we suggest this is a simple approach that may help and would be unlikely to harm."

> "In patients with sedation and mild cognitive changes, methylphenidate can improve fatigue, but in the majority of patients with cancer-related fatigue modafinil and methylphenidate are not likely to be effective."

'Don't Be Dogmatic'

Asked for his opinion for this article, Ronald J. Scheff, MD, Assistant Attending Physician at New York-Presbyterian Hospital and Assistant Professor of Clinical Medicine at Weill Cornell Medical College, who treats

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FATIGUE

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both lung cancer and brain cancer patients, said the study is very important, "because it shows that having randomized trial data is key to establishing the efficacy of a drug.

"We have to be careful about being dogmatic in prescribing medications that may not be as beneficial as we think," he said.

Fatigue is definitely an issue, especially with lung cancer patients, and the symptom increases as treatment progresses, he said, noting, though, that he could recall only one patient he has ever treated with modafinil for fatigue, and that was a patient with a brain tumor, who did report that the drug was helpful.

Scheff said he and colleagues do not generally use medical therapy to treat fatigue, other than low-dose steroids — prednisone 10-20 mg daily—which helps some patients.

Scheff said they do use antidepressants regularly to treat cancer patients suffering from depression, and he thought that may reduce fatigue symptoms as well. "And sometimes physical therapy helps, or setting goals for physical activity — walking for instance," he said.

> "Part of the benefit in the placebo arm of our trial may have been simply from clinicians or researchers taking the time to acknowledge and discuss patients' fatigue, and we suggest that this is a simple approach that may help and would be unlikely to harm."

Scheff said he thought it noteworthy that the improvement in fatigue scores in this study were the same with placebo as with modafinil: "That raises important questions about making interventions of any type. Just addressing fatigue and showing concern might be beneficial."

'Outcomes Not Surprising'

Also commenting, Eduardo Bruera, MD, Professor and Chair of the Department of Palliative Care & Rehabilitation Medicine at the University of Texas MD Anderson Cancer Center, said he thought the paper was a very good study in a well-defined population using valid outcomes.

"This negative study of a mild stimulant is not surprising, since a number of recent studies [including the one he led, cited above] have found similarly disappointing results with methylphenidate," he said in an e-mail exchange.

Modafinil and methylphenidate have been found to be effective in the management of opioid-induced sedation, he noted. "In patients with sedation and mild cognitive changes, methylphenidate can improve fatigue, but in the majority of patients with cancer-related fatigue modafinil and methylphenidate are not likely to be effective."

In advanced cancer patients with fatigue, Bruera said, corticosteroids are superior to placebo, but these drugs have considerable side effects when used for prolonged periods of time. Exercise and counseling are important and safe interventions in these patients, he added.

New ASCO Guideline

Coincidentally, the American Society of Clinical Oncology recently issued new guidelines on cancer-related fatigue (***OT, 5/25/14 issue***). The guideline recommends that all patients be evaluated for symptoms of fatigue upon completion of primary treatment, be offered strategies for fatigue management, and that health care providers should assess fatigue history, disease status, and treatable contributing factors and offer management strategies that include physical activity, psychosocial interventions, and mind-body interventions.

The guideline adds, though, that there is limited evidence for use of psychostimulants in the management of fatigue in patients who are disease free after active treatment.