Psychostimulants for Cancer-Related Fatigue

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Key Words
Cancer-related fatigue, fatigue, psychostimulants, wakefulness-promoting agents

Abstract
Fatigue is a highly prevalent and distressing symptom associated with significant psychological and functional morbidity and decreased quality of life among patients with cancer. Despite its impact on patients and caregivers, fatigue is underreported and unrecognized, and remains untreated among patients with cancer because of various patient- and clinician-related factors. In addition to assessment for potentially reversible medical causes or medications exacerbating fatigue, and the implementation of nonpharmacologic interventions, several pharmacologic treatment options have been considered for the treatment of cancer-related fatigue. Among traditional psychostimulants, methylphenidate has been studied the most and is effective and well tolerated among patients with cancer despite common side effects. Modafinil, a novel psychostimulant commonly referred to as wakefulness-promoting agents as a group, has also been studied and seems to be well tolerated among patients with cancer. A large placebo effect has been reported in most randomized controlled trials with psychostimulants. Thus, randomized placebo-controlled trials with large sample sizes are needed to further assess the efficacy and tolerability of psychostimulants in the treatment of cancer-related fatigue. This article presents a comprehensive review of the use of psychostimulant agents for fatigue among patients with cancer, including an overview of the clinical trials with psychostimulants and of the clinical guidelines available for treatment of cancer-related fatigue. (\textit{JNCCN} 2010;8:933–942)

Several pharmacologic agents have been considered and studied for the treatment of cancer-related fatigue, including psychostimulants, antidepressants, megestrol acetate, and amantadine.\textsuperscript{1} A recent meta-analysis of pharmacologic treatment options for cancer-related fatigue has concluded that based on current research evidence methylphenidate (a psychostimulant) seems to be effective in the treatment of fatigue among cancer patients.\textsuperscript{2} Evidence shows that treatment with hematopoietic agents relieved fatigue because of chemotherapy-induced anemia.\textsuperscript{2}

This article is a comprehensive review of psychostimulants, including the traditional psychostimulant medications and the wakefulness-promoting agents used in the management of cancer-related fatigue (Table 1). Table 2 presents a review of psychostimulant medication trials in the treatment of cancer-related fatigue. A review of other agents can be found elsewhere.\textsuperscript{1,3}

Psychostimulants
Psychostimulants are defined as drugs that increase levels of alertness or motivation. The term \textit{psychostimulant} is used to refer to traditional psychostimulants, including methylphenidate, dextroamphetamine, and pemoline (withdrawn from the market in the United States).

Methylphenidate and dextroamphetamine are sympathomimetic drugs. They both stimulate adrenergic receptors directly as agonists, and indirectly cause the release of dopamine and norepinephrine from presynaptic terminals.\textsuperscript{1} They are scheduled as controlled drugs because of their rapid onset of action, immediate behavioral effects, and tendency to develop tolerance with continued use, which leads to increased risk for abuse and dependence in vulnerable individuals (i.e., patients
Available data suggest that methylphenidate has pharmacokinetic properties that reduce its abuse potential compared with stimulant drugs of abuse, such as cocaine. 

Psychostimulants have been widely used in the treatment of medically ill patients with fatigue, including those with cancer, multiple sclerosis, Parkinson’s disease, opioid-induced sedation, and HIV. Psychostimulants have also been used to treat fatigue-related conditions, such as pain, depression, and cognitive impairment.

Agitation and insomnia are the most common side effects associated with the use of psychostimulants. Dose reduction and scheduling the medication early in the day may be helpful. Rare side effects include hypertension, palpitations, arrhythmias, confusion, psychosis, tremor, and headache. Most of the side effects are reversible with discontinuation of the medication. Methylphenidate and dextroamphetamine should be avoided in patients with uncontrolled hypertension, underlying coronary artery disease, and tachyarrhythmias.

**Table 1 Psychostimulant Medications Used in the treatment of Cancer-Related Fatigue**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Starting Dose</th>
<th>Dose Range</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychostimulants</strong></td>
<td></td>
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</tr>
<tr>
<td>Methylphenidate</td>
<td>2.5–5 mg daily or twice daily</td>
<td>5–30 mg/d, usually divided as twice daily</td>
<td>Longer-acting forms are available</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Capsule forms can be sprinkled in food</td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>2.5–5 mg daily or twice daily</td>
<td>5–30 mg/d, usually divided as twice daily</td>
<td>Longer-acting formulations are available</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Capsule forms can be sprinkled in food</td>
</tr>
<tr>
<td>Dexmethylphenidate</td>
<td>2.5–5 mg daily or twice daily</td>
<td>5–20 mg/d, usually divided as twice daily</td>
<td>Longer-acting formulations are available</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Capsule forms can be sprinkled in food</td>
</tr>
<tr>
<td><strong>Wakefulness-Promoting Agents</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Modafinil</td>
<td>50–100 mg daily</td>
<td>50–400 mg/d, may be divided as twice daily</td>
<td>High cost</td>
</tr>
<tr>
<td>Armodafinil</td>
<td>50–150 mg daily</td>
<td>150–250 mg/d</td>
<td>High cost; there have been no studies for its use in cancer-related fatigue</td>
</tr>
</tbody>
</table>

Methylphenidate

Methylphenidate has been used since the 1950s in the treatment of children with attention deficit-hyperactivity disorder. Methylphenidate is usually administered twice a day, at breakfast and lunch, to minimize insomnia. Peak plasma concentration occurs within 1 to 3 hours, with an average half-life of 2 hours. Sustained-release formulations have approximately 4 to 6 hours of clinical action. Newer sustained-release formulations have an early peak, followed by 8 hours of action. Close monitoring for common side effects, such as agitation and insomnia, is recommended, especially in the first few days of treatment initiation.

Breitbart et al. conducted the first randomized, double-blind, placebo-controlled trial with psychostimulants for the treatment of fatigue in ambulatory patients with HIV disease. In this study, methylphenidate and pemoline were found to be equally effective and significantly superior to placebo in decreasing fatigue severity with minimal side effects. Of 109 ambulatory patients with HIV randomized to treatment with methylphenidate, pemoline, or placebo, 15 of 37 (41%) taking methylphenidate and 12 of 33 (36%) taking pemoline experienced clinically significant improvement, compared with 6 of 39 (15%) taking placebo. Improvement in fatigue was shown to correlate with improved quality of life, decreased depression, and decreased psychological distress. Jitteriness and hyperactivity were the only side effects that occurred more frequently in the medication arm, reported by 31.8% of patients taking methylphenidate and 25.6% taking pemoline. Pemoline is no longer
### Table 2  Review of Studies with Psychostimulants in the Treatment of Cancer-Related Fatigue

<table>
<thead>
<tr>
<th>Sample</th>
<th>Design</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarhill et al.(^9)</td>
<td>Patients with advanced cancer (n = 11)</td>
<td>Prospective, open-label</td>
<td>Methylphenidate, 10 mg, twice daily for 7 d</td>
</tr>
<tr>
<td>Sugawara et al.(^12)</td>
<td>Patients with advanced cancer (n = 16)</td>
<td>Prospective, open-label</td>
<td>Methylphenidate 5–30 mg/d, for a mean duration of 8 d</td>
</tr>
<tr>
<td>Schwartz et al.(^13)</td>
<td>Patients with melanoma receiving interferon (n = 12)</td>
<td>Prospective, open-label</td>
<td>Exercise and methylphenidate, 20 mg, daily</td>
</tr>
<tr>
<td>Bruera et al.(^16)</td>
<td>Patients with advanced cancer (n = 30)</td>
<td>Prospective, open-label</td>
<td>Patient-controlled methylphenidate, 5 mg, every 2 hours, maximum 4 caplets a day</td>
</tr>
<tr>
<td>Hanna et al.(^14)</td>
<td>Patients with breast cancer experiencing remission for 6 mo to 5 y (n = 37)</td>
<td>Open-label, phase II</td>
<td>Methylphenidate, 5 mg, twice daily for 6 wk</td>
</tr>
<tr>
<td>Johnson et al.(^15)</td>
<td>Women with recurrent gynecologic cancer (n = 32)</td>
<td>Open-label, prospective</td>
<td>Methylphenidate, 5 mg, twice daily for 8 wk</td>
</tr>
<tr>
<td>Bruera et al.(^17)</td>
<td>Patients with advanced cancer (n = 52 in medication arm; n = 53 in placebo arm)</td>
<td>Randomized, double blind, placebo-controlled</td>
<td>Patient-controlled methylphenidate (5 mg every 2 hr, up to 4 caplets per d) vs. placebo for a total of 7 d</td>
</tr>
</tbody>
</table>
Table 2  Review of Studies with Psychostimulants in the Treatment of Cancer-Related Fatigue (cont.)

<table>
<thead>
<tr>
<th>Sample</th>
<th>Design</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roth et al.\textsuperscript{18}</td>
<td>Ambulatory patients with prostate cancer (n = 16 in the placebo arm; n = 16 in the medication arm)</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>Methylphenidate vs. placebo</td>
</tr>
<tr>
<td>Mar Fan et al.\textsuperscript{22}</td>
<td>Women with breast cancer undergoing adjuvant chemotherapy (n = 29 d-methylphenidate; n = 28 placebo)</td>
<td>Randomized, placebo-controlled</td>
<td>Dexamethylphenidate, up to 10 mg, twice daily for a duration of 20–140 d</td>
</tr>
<tr>
<td>Butler et al.\textsuperscript{23}</td>
<td>Patients with primary or metastatic brain tumors undergoing radiation treatment (n = 33 d-methylphenidate; n = 29 placebo at study entry)</td>
<td>Randomized, placebo-controlled</td>
<td>Prophylactic use of d-methylphenidate or placebo up to 15 mg twice daily for 4–12 wk</td>
</tr>
<tr>
<td>Lower et al.\textsuperscript{21}</td>
<td>Adult patients with cancer who completed chemotherapy 2 mo before study entry (n = 78 placebo; n = 76 dexamethylphenidate)</td>
<td>Randomized, placebo-controlled, phase III</td>
<td>Dexamethylphenidate, 10–50 mg/d, for more than 2 wk; mean dose of 25.5 mg/d</td>
</tr>
<tr>
<td>Auret et al.\textsuperscript{25}</td>
<td>Patients with advanced cancer undergoing palliative care (n = 50)</td>
<td>Randomized, placebo-controlled</td>
<td>Dexamphetamine, 10 mg, twice daily or placebo for 8 d</td>
</tr>
<tr>
<td>Morrow et al.\textsuperscript{31}</td>
<td>Women with breast cancer, all completed treatment 2 y previously (n = 82)</td>
<td>Prospective, open-label</td>
<td>Modafinil, 200 mg/d, for 1 mo</td>
</tr>
</tbody>
</table>
available in the United States because of reports of liver failure and death associated with its use.

In a prospective, open-label pilot study, Sarhill et al.\textsuperscript{9} showed that 9 (82%) of 11 patients with advanced cancer were successfully treated for cancer-related fatigue with methylphenidate. Notably, more than half of the patients experienced side effects, such as insomnia, agitation, anorexia, dry mouth, nausea, and vomiting.

In an open-label study examining the efficacy of methylphenidate in the treatment of fatigue among 16 patients with advanced cancer, 2 patients withdrew from the study because of insomnia. The remaining 14 completed a mean duration of 8 days of treatment with methylphenidate, with a statistically significant decrease in fatigue scores on the visual analog scale for fatigue ($P = .01$).\textsuperscript{12}

A pilot study examining the effects of exercise and methylphenidate on fatigue, functional ability, and cognitive function in patients with melanoma compared the exercise and methylphenidate intervention groups with historical controls who underwent usual care while on interferon (IFN)-\textalpha. Twelve patients with melanoma entered and completed the study. Patients were instructed to take 20 mg daily of sustained-release methylphenidate and follow an aerobic exercise program 4 days a week for 15 to 30 minutes. Fatigue ratings were lower among the exercise and methylphenidate groups than among historical controls. The researchers concluded that the combination of aerobic exercise and methylphenidate may be effective in improving fatigue, cognitive functioning, and functional ability among patients with melanoma.\textsuperscript{13}

A phase II study evaluated the effects of methylphenidate on cancer-related fatigue in breast cancer survivors who scored 4 or higher on the Brief Fatigue Inventory (BFI), and those with less-than-moderate

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**Table 2**  
Review of Studies with Psychostimulants in the Treatment of Cancer-Related Fatigue (cont.)

<table>
<thead>
<tr>
<th>Sample</th>
<th>Design</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
</table>
| Kaleita et al.\textsuperscript{32}  
Adult brain tumor patients (n = 30) | Phase III, open-label, extension phase | Modafinil, mean dose 225 mg/d, at wk 8; 258 mg/d at wk 12 | Mean fatigue score change at wk 8 and 12 was significantly higher in the intervention arm  
Well-tolerated  
Only results from the open-label extension phase were reported in this abstract  
Final data analysis has not been published yet |
| Blackhall et al.\textsuperscript{33}  
Adult cancer patients (n = 27) | Open-label trial | Modafinil, 100 mg/d, for 2 wk, and 200 mg/d on wk 3 and 4 | BFI score was improved in 46% of patients at 2 wk and 75% at 4 wk ($P = .025$)  
Modafinil was well tolerated  
During the study period, there was a rapid and statistically significant reduction in the primary outcome, fatigue ($P = 0.001$) based on FACT-F subscale |
| Spathis et al.\textsuperscript{34}  
Patient with non-small cell lung cancer (n = 20) | Open-label trial | Modafinil, 100 mg/d, for 7 d, followed by 200 mg/d | Patients receiving modafinil had a statistically significant decrease in fatigue levels than those receiving placebo  
This study has not been published, and the numerical results of fatigue assessments have not been reported |
| Morrow et al.\textsuperscript{35}  
Adult patients with cancer receiving chemotherapy (n = 320 on modafinil; n = 322 on placebo) | Phase III, double-blind, randomized, controlled | Modafinil, 200 mg/d, or placebo |

Abbreviations: BFI, Brief Fatigue Inventory; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue Subscale; FACT-F, Functional Assessment of Cancer Therapy–Fatigue; VAS, visual analog scale.
decrease significantly on day 8 in both the methylphenidate and placebo groups. However, no significant difference was noted in fatigue improvement between the intervention (n = 52) and placebo (n = 53) groups. Approximately 90% of patients receiving methylphenidate or placebo chose to continue the medication beyond 8 days. Improvement in fatigue scores was sustained during the open-label methylphenidate phase at days 15 and 36. Researchers concluded that, in the absence of a placebo-controlled group, determining whether these findings reflect an independent result or an extension of the placebo effect would not be feasible. The mean daily number of capsules of methylphenidate and placebo taken by the patients between days 1 and 8 was 2.3 (± 1.0) and 2.1 (± 1.0), respectively (P = not significant). In a double-blind, randomized, placebo-controlled study evaluating the benefits of methylphenidate compared with placebo in ambulatory patients with prostate cancer, Roth et al.18 were able to recruit 32 patients (16 in the placebo group, 16 in the methylphenidate group), with 23 patients completing the study (13 in the placebo arm, 10 in the intervention arm). BFI total scores significantly decreased for both groups; however, patients in the methylphenidate group, compared those in the placebo group, reported greater decrease in BFI severity scores (P = .03). A greater number of subjects in the methylphenidate group showed clinically significant improvement in fatigue on total BFI scores (7/10 vs. 3/13) and BFI severity scores (8/10 vs. 3/13). The placebo response rate was higher than expected. Six men in the methylphenidate arm withdrew from the study because of cardiovascular side effects.

Johnson et al.15 evaluated the effects of methylphenidate on cancer-related fatigue among 32 women with recurrent gynecologic cancer. Patients were prescribed methylphenidate, 5 mg, twice daily over an 8-week period, and completed the Fatigue Symptom Inventory (FSI) along with assessments of quality of life and mood at baseline and weeks 2, 4, and 8 to determine changes in levels of fatigue experienced. Patients reported significant declines in fatigue (P = .0001) and improvement in both mood (P = .0020) and quality of life (P = .03) when comparing baseline scores to those at study end.

Because of the rapid onset of action and short half-life of methylphenidate, Bruera et al.16 proposed that methylphenidate may be effective in relieving fatigue when taken on an as-needed basis throughout the day, also referred to as patient-controlled dose administration. An open-label pilot study was initially conducted using patient-controlled methylphenidate to manage cancer-related fatigue. Among 30 patients with fatigue, treatment with methylphenidate was associated with improvement in fatigue, overall well-being, and depression. It was well tolerated and none of the patients had to discontinue the medication because of toxicity. After the open-label study, Bruera et al.17 conducted a double-blind, randomized, placebo-controlled trial comparing patient-controlled methylphenidate with placebo (5 mg methylphenidate or placebo every 2 hours as needed, up to 4 tablets a day for 7 days). Fatigue assessments were completed at baseline and at days 8, 15, and 36. All of the patients were offered open-label methylphenidate for 4 weeks. Fatigue intensity decreased significantly on day 8 in both the methylphenidate and placebo groups. However, no significant difference was noted in fatigue improvement between the intervention (n = 52) and placebo (n = 53) groups. Approximately 90% of patients receiving methylphenidate or placebo chose to continue the medication beyond 8 days. Improvement in fatigue scores was sustained during the open-label methylphenidate phase at days 15 and 36. Researchers concluded that, in the absence of a placebo-controlled group, determining whether these findings reflect an independent result or an extension of the placebo effect would not be feasible. The mean daily number of capsules of methylphenidate and placebo taken by the patients between days 1 and 8 was 2.3 (± 1.0) and 2.1 (± 1.0), respectively (P = not significant).
mg daily was well tolerated. Side effects related to methylphenidate use seemed to improve spontaneously with continued treatment. Depression and fatigue also improved at lower methylphenidate doses than those recommended in other clinical conditions.

Dexmethylphenidate is the d-isomer of methylphenidate, with a longer duration of action (about 6 hours) than methylphenidate. A randomized, double-blind, placebo-controlled study evaluated the potential therapeutic effect and safety of dexmethylphenidate in the treatment of patients with chemotherapy-related fatigue. Change from baseline in the Functional Assessment of Chronic Illness Therapy-Fatigue Subscale (FACT-F) total score at week 8 was the primary outcome measure. Of the 154 patients (predominantly with breast and ovarian cancers), those treated with dexmethylphenidate showed a significant improvement in fatigue symptoms at week 8 according to the FACT-F \( (P = .02) \) and the Clinical Global Impression-Severity scores \( (P = .02) \), without clinically relevant changes in hemoglobin levels. Cognitive function was not significantly improved. Patients treated with dexmethylphenidate had a higher rate of study drug–related adverse events \( (48 \text{ of } 76 [63\%] \text{ vs. } 22 \text{ of } 78 [28\%]) \) and a higher discontinuation rate from adverse events \( (8 \text{ of } 76 [11\%] \text{ vs. } 1 \text{ of } 78 [1.3\%]) \) than for placebo. The most commonly reported adverse events in patients treated with dexmethylphenidate were headache, nausea, and dry mouth, compared with headache, diarrhea, and insomnia for placebo. Dexmethylphenidate was found to be well tolerated and shown to be more effective than placebo in improving fatigue symptoms.

Mar Fan et al.\(^\text{22}\) studied efficacy and tolerability of dexmethylphenidate among women undergoing chemotherapy. All participants took placebo for 1 cycle to ensure compliance, and then study medication until completion of chemotherapy. Subjects were assessed at baseline, end of chemotherapy, and at approximately 6 months follow-up with the High Sensitivity Cognitive Screen (HSCS), the Hopkins Verbal Learning Test-Revised (HVLT-R), the self-report Functional Assessment of Cancer Therapy-General (FACT-G), and the FACT-Fatigue (FACT-F) questionnaires, evaluating cognition, quality of life, and fatigue. A total of 57 women were randomized to either dexmethylphenidate \( (n = 29) \) or placebo \( (n = 28) \). Both dexmethylphenidate and placebo were well tolerated. No significant differences were seen between the randomized groups in classification of cognitive function by HSCS or in summed FACT-F scores (the primary end points of the study) at any of the assessments, nor were differences seen in HLTV-R scores or quality of life.\(^\text{22}\)

The prophylactic use of d-threo-methylphenidate HCl \( (d\text{-MPH}) \), another form of dexmethylphenidate, has been considered in patients with a brain tumor undergoing radiation therapy. One study randomized 68 patients with primary or metastatic brain tumors to receive \( d\text{-MPH} \) or placebo. The starting dose of \( d\text{-MPH} \) was 5 mg twice daily and was escalated by 5 mg twice daily to a maximum of 15 mg twice daily. The primary outcomes were fatigue and quality of life. Patients were assessed at baseline, the end of radiation therapy, and 4, 8, and 12 weeks after brain radiation using the FACIT-F brain and fatigue subscales, and the Center for Epidemiologic Studies Depression Scale and Mini-Mental Status Examination. The Mean Fatigue Subscale Score at baseline was 34.7 for the \( d\text{-MPH} \) arm and 33.3 for the placebo arm \( (P = .61) \). At 8 weeks after the completion of radiation treatment, no difference in fatigue was seen between patient groups. The adjusted least squares estimate of the Mean Fatigue Subscale Score was 33.7 for the \( d\text{-MPH} \) and 35.6 for the placebo arm \( (P = .64) \). Secondary outcomes were not different between the treatment arms. The prophylactic use of \( d\text{-MPH} \) in patients with brain tumors undergoing radiation therapy was not effective in preventing fatigue and was not associated with improvement in quality of life.\(^\text{23}\)

**Dextroamphetamine**

Dextroamphetamine is the d-isomer of amphetamine and is a more potent psychostimulant than methylphenidate. Dextroamphetamine has been studied in the treatment of HIV-related fatigue with favorable results.\(^\text{24}\) Despite its common use in the treatment of cancer-related fatigue, dextroamphetamine has not been extensively studied in cancer patients. Auret et al.\(^\text{25}\) conducted a randomized, double-blind, placebo-controlled trial with dextroamphetamine among patients with advanced cancer and fatigue. In this study, 50 patients with advanced cancer who were undergoing palliative care were randomized to dextroamphetamine, 10 mg, twice daily or placebo for 8 days. Effectiveness was assessed using the BFI and
the McGill Quality-of-Life Questionnaire, with 39 patients completing the trial. A transient improvement in fatigue levels was seen on day 2, but no significant difference in fatigue (P = .267) or quality of life (P = .579) occurred by the end of the study. These results suggest that dexmphetamine, 20 mg daily, although well tolerated, does not significantly improve fatigue or quality of life in patients with advanced cancer.

**Wakefulness-Promoting Agents**

Modafinil, a novel psychostimulant, commonly referred to as a wakefulness-promoting agent, was approved by the FDA for the treatment of excessive daytime sleepiness in patients with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shiftwork sleep disorder. Modafinil has been used to augment antidepressants in major depressive disorders, as an adjunct treatment of bipolar depression, and in patients with persistent fatigue and sleepiness despite antidepressant treatment. Compared with other psychostimulants, modafinil has a novel mechanism of action and has less abuse potential. Modafinil is well tolerated, with a good safety profile. The most frequent adverse events (35%) are headache, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness, and dyspepsia.

Modafinil’s mechanism of action is largely unknown. It presumably enhances activity in the hypothalamic wakefulness center (i.e., tuberomammillary nucleus), activates tuberomammillary nucleus neurons that release histamine, and activates other hypothalamic neurons that release orexin/hypocretin. The half-life of modafinil is approximately 15 hours, and a steady state is reached after 2 to 4 days of dosing. Higher doses (200–400 mg/d) of modafinil may be more effective for sleepiness; however, lower doses (50–200 mg/d) seem to be better for concentration problems and fatigue.

Modafinil is commonly used for the treatment of severe fatigue in patients with multiple sclerosis, and has been considered a treatment option for patients with cancer-related fatigue. Morrow et al. conducted an open label study of modafinil, in which 82 breast cancer survivors with persistent fatigue received a modafinil dose of 200 mg daily for a month. Results showed that 83% of study participants reported reduction of fatigue, 7% dropped out of the study, and 10% had no improvement.

Kaleita et al. reported the fatigue-related outcomes of the open-label extension part of a phase II clinical trial. In their sample of 30 patients with brain tumors (malignant and benign), statistically significant differences (P ≤ .005) were observed in the mean score changes at weeks 8 and 12 compared with baseline on all fatigue self-ratings measures. The mean modafinil dose was 225 mg daily (range, 50–400 mg/d) at week 8, and 258 mg daily (range 50–600 mg/d) at week 12. Modafinil was generally well tolerated, with a low incidence of adverse events.

Blackhall et al. conducted an open-label pilot study to evaluate the safety and efficacy of modafinil in improving cancer-related fatigue. Modafinil was self-administered at a dose of 100 mg daily during weeks 1 and 2, and 200 mg during weeks 3 and 4 among 27 cancer patients. Assessments were performed at baseline and at 2 and 4 weeks. BFI score was improved in 46% of patients at 2 weeks and 75% at 4 weeks (P = .025). Significant changes in ECOG performance status were noted, with 40% of patients improving at least 1 level. Modafinil was well tolerated, and improvements were also seen in mood, quality of life, and functional status.

Spathis et al. conducted an open-label feasibility trial to assess the efficacy and safety of modafinil in treating fatigue in patients with lung cancer. In this study, 20 patients with non–small cell lung cancer were given modafinil in a fixed dose-titration schedule of 100 mg daily for 7 days, followed by 200 mg daily for 7 days; 15 patients completed the study. During the study period, a rapid and statistically significant reduction was seen in the primary outcome of fatigue (P = .001). The drug was well tolerated, and 10 patients chose to continue modafinil after the study.

In the largest study to date, the efficacy of modafinil was evaluated in a phase III, randomized, placebo-controlled, double-blind trial involving patients with cancer reporting fatigue while undergoing chemotherapy. Patients were randomized to receive modafinil, 200 mg daily, or placebo if they complained of fatigue levels greater than 1 on a 10-point scale. Of the 888 patients originally randomized, 642 completed the study (320 modafinil, 322 placebo). Patients receiving modafinil had a statistically significant decrease in fatigue levels compared with those receiving placebo. The authors concluded that
modafinil is useful in the treatment of cancer-related fatigue, particularly for patients with severe baseline fatigue. However, this study remains unpublished, and the authors have not reported the numerical results of the fatigue assessments from either group in the abstract, so the actual difference cannot be stated. Therefore, despite the improvements in achieving statistical significance, their clinical significance is difficult to determine.

Armodafinil is the longer-lasting isomer of modafinil. It was recently approved by the FDA as an adjunct to standard treatment for obstructive sleep apnea, shift-work sleep disorder, and narcolepsy in patients with excessive sleepiness. No studies have examined the use of armodafinil in the treatment of cancer-related fatigue.

Despite emergent use of wakefulness-promoting agents among patients with cancer-related fatigue, well-designed, randomized, placebo-controlled clinical trials are needed to further assess the role of these agents in the treatment of cancer-related fatigue.

**Conclusions**

Fatigue is a serious clinical problem in patients with cancer. It is highly prevalent in this population and is associated with decreased quality of life. Patients with cancer-related fatigue should be evaluated and treated for potentially reversible medical causes of fatigue, and for comorbid depression. Several therapeutic strategies are available for the treatment of cancer-related fatigue; however, randomized controlled trials with larger sample sizes are warranted to assess the efficacy and tolerability of psychostimulants. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) on Cancer-Related Fatigue (in this issue; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org) have concluded that evidence is insufficient to recommend pharmacologic therapy for cancer-related fatigue and that more research in this area is required before further recommendations could be made.

**References**


© Journal of the National Comprehensive Cancer Network | Volume 8 Number 8 | August 2010


