Published in final edited form as:

Cancer. 2010 July 15; 116(14): 3513–3520. doi:10.1002/cncr.25083.

A Phase III Randomized, Placebo-Controlled, Double-Blind Clinical Trial of the Effect of Modafinil on Cancer-Related Fatigue among 631 Patients Receiving Chemotherapy: A URCC CCOP Research Base Study

Pascal Jean-Pierre, PhD, MPH¹, Gary R. Morrow, PhD, MS¹, Joseph A. Roscoe, PhD¹, Charles Heckler, PhD¹, Supriya Mohile, MD, MS¹, Michelle Janelins, PhD¹, Luke Peppone, PhD¹, Amy Hemstad, RN, BSN, MPH², Benjamin T. Esparaz, MD³, and Judith O. Hopkins, MD⁴

¹University of Rochester Cancer Center

²Metro Minnesota CCOP, Minneapolis, MN

³Central Illinois CCOP, Decatur, IL

⁴SCCC CCOP, Winston-Salem, NC

Abstract

Background—Cancer-related fatigue (CRF) is a debilitating symptom affecting psychosocial functioning and quality of life in 70 to 100% of cancer patients during and following treatment. We examined the effect of 200 mg of modafinil daily on the severity of CRF.

Methods—We conducted a multicenter, randomized, double-blind, placebo-controlled Phase III clinical trial to examine the effect of modafinil on patient-reported fatigue in cancer patients undergoing chemotherapy. A sample of 877 cancer patients beginning chemotherapy at 23 geographically separate URCC CCOP affiliates were assessed for fatigue. Patients who reported fatigue (N=867) were randomly assigned to receive either 200 mg of oral modafinil (PROVIGIL®) daily or a placebo. Treatment began on Day 5 of Cycle 2 and ended after Day 7 of Cycle 4. Fatigue and depression were assessed during Cycles 2 to 4 using psychometrically valid measures. Group differences (treatment versus control) in the worst level of fatigue during the previous week at Cycle 4 were examined using an analysis of covariance (ANCOVA) adjusting for baseline fatigue (Cycle 2).

Results—631 patients (315 modafinil, 316 placebo) provided evaluable data. ANCOVA showed a significant interaction between treatment condition and baseline fatigue ($p = 0.017$), where patients with severe baseline fatigue ($n=458$) benefited from modafinil while patients with mild or moderate fatigue did not. Modafinil had no statistically significant effect on depression ($p > 0.05$).

Conclusion—Modafinil may be useful in controlling CRF in patients presenting with severe fatigue but not in patients with mild or moderate fatigue.

Send correspondence and reprint requests to: Dr. Pascal Jean-Pierre, Ph.D., M.P.H., University of Rochester Medical Center, James P. Wilmot Cancer Center, Radiation Oncology Department/BMU, 601 Elmwood Avenue, Box 704, Rochester, NY 14642, Telephone: (585) 273-2545, Fax: (585) 461-5601, Pascal_Jean-Pierre@urmc.rochester.edu.

Financial Disclosures: No financial Disclosures from any authors.

Keywords

Cancer-Related Fatigue; Cancer Side Effects; Symptom Management; Cancer; Chemotherapy; Cancer; Behavioral Oncology

INTRODUCTION

Most cancer patients experience cancer-related fatigue (CRF) during the course of their disease and its treatment. For many patients, the distressing effects of CRF persist long after treatment is completed.^{1,2} CRF is one of the most common and most frequently anticipated side effects of cancer treatment³; previous studies reported CRF incidence rates up to 100%.^{4,5} Ninety-five percent of a large ($n > 1000$) multi-site sample from our University of Rochester Community Clinical Oncology Program affiliates expected fatigue as a side effect of cancer treatment. These patients had a variety of cancer types, including hematologic, lung, breast, alimentary tract, gynecologic, and genitourinary tract neoplasms.⁶

CRF can be a debilitating symptom that affects important areas of psychosocial functioning and quality of life.^{7,8} A key distinguishing feature between CRF and the fatigue experienced by healthy people is that CRF is not relieved by rest or sleep.⁹⁻¹¹

Both pharmacologic and non-pharmacologic interventions to control CRF have been studied. Minton and colleagues conducted a systematic and meta-analytic review of pharmacological treatment for CRF.¹² These authors concluded that methylphenidate and hematopoietic agents (for CRF due to chemotherapy-induced anemia) seem effective. Nonetheless, future studies need to confirm these preliminary findings. A recent review of non-pharmacological therapies for cancer patients reported that psychological interventions (e.g., cognitive behavioral therapy, supportive-expressive therapy and psychosocial interventions) and exercise (e.g., multimodal exercise, walking programs, and restorative approaches) had an effect on CRF.¹³

Despite significant recent attention to the management of cancer-related symptoms, CRF remains a persistent and distressing side effect of cancer and its treatment. The prevalence, debilitating characteristics and potential negative effects of CRF on treatment adherence, psychosocial functioning and quality of life (QoL) underscore the necessity to identify this symptom and develop effective interventions to control it. Based on clinical experience and positive results from an open-label pilot study¹⁴, the present study examined the effect of the non-amphetamine based stimulant modafinil on fatigue among cancer patients undergoing chemotherapy.

METHODS

We conducted a multicenter, randomized, double-blind, placebo-controlled Phase III clinical trial to examine the effect of modafinil on patient-reported fatigue in cancer patients undergoing chemotherapy. Eligibility criteria included being at least 18 years old, having a diagnosis of cancer with survival expectancy greater than six months, and being able to swallow medication. Patients were required to be starting a cancer treatment course of at least four planned cycles of chemotherapy with cycles at least two weeks apart without concurrent radiation or interferon treatment. Patients were excluded from the study if they had previously taken modafinil or any psychostimulant, such as amphetamines, methylphenidate (Ritalin) and pemoline (Cylert®) or a monoamine oxidase inhibitor on a regular basis within the past 30 days. Other exclusion criteria included being pregnant or nursing, having uncontrolled anemia, any history of clinically significant cardiac disease,

uncontrolled hypertension, any history of alcohol or drug abuse, severe headaches, glaucoma, seizure disorder, narcolepsy, or Tourette's syndrome or other psychiatric disorders. The Institutional Review Boards of the University of Rochester and the participating URCC CCOP affiliate sites approved the study protocol. All participants provided signed informed consent.

Intervention

Patients were contacted via telephone between the fifth and tenth day of their first chemotherapy cycle to assess their levels of fatigue using question 3 of the Brief Fatigue Inventory ("What is your worst level of fatigue during the past week?"). Responses were reported on a scale where '0' = no fatigue to '10' = worst possible fatigue. We choose worst level of fatigue because this state of CRF could have a higher likelihood of affecting psychosocial and activities of daily living and, perhaps, treatment adherence and outcome for cancer patients. Research also suggests that ratings of symptom at its worst have the highest predictive value for patients' ratings of symptom interference.^{15,16} Those who reported a score of at least 2 on the BFI question 3 were invited to participate in the study. This study is the first phase III randomized controlled trial using modafinil with this population. We selected a score of 2 on the BFI question 3 to provide as generous an entry as possible to facilitate greater likelihood of detection of improvement. Participants were randomized with equal probability to either modafinil or placebo using a random number generator program from SAS. Baseline assessments were taken following randomization and shortly after Cycle 2 of chemotherapy. Participants were then instructed to start with 100 mg of modafinil or placebo on Day 10 (before January 2005), or Day 5 (after January 2005) of Study Cycle 2, then increase to the full dose of 200 mg of modafinil or placebo after three days and continue on this regimen until Day 7 of Study Cycle 4, at which point all participants discontinued medication. The timing of the start dose was changed because accrual was inadequate. The change resulted in a better match to clinical practice in the private groups and tripled accrual with no change in baseline values and no effect on outcome. Cephalon, Inc. supplied modafinil and placebo tablets for the present study. Medication was discontinued in cases in which chemotherapy was discontinued or delayed longer than three weeks. Blinding was maintained throughout the study.

Outcome Measures

Variables of interest were assessed using psychometrically valid and reliable measures used in previous studies of fatigue and found suitable for the present sample. CRF was assessed using Item 3 of the Brief Fatigue Inventory (BFI-3).¹⁷ We used BFI-3 because our pilot testing showed a single question was more sensitive than the full BFI or other multidimensional measures in detecting changes in CRF. Excessive daytime sleepiness was measured, using the Epworth Sleepiness Scale (ESS)¹⁸ as a manipulation check that a clinically active dose of modafinil was used, since we used a fixed dose, and ESS values have been reliably shown to change with modafinil.¹⁹ Depression was assessed with the Depression-Dejection subscale of the Profile of Mood States (POMS-DD)²⁰ and was included to further investigate the commonly reported high correlation between depression and fatigue. Previous findings that Paxil, a selective serotonin reuptake inhibitor antidepressant, significantly reduced depression in a study of 94 cancer patients without affecting fatigue, raised questions regarding any causal link between depression and fatigue.²¹ If fatigue was found to be reduced with modafinil without any corresponding reduction in depression, a causal link between depression and fatigue would be challenged. Internal consistency of the above measures, as indicated by Cronbach alpha coefficients, ranged from $\alpha = 0.85$ to 0.96 . Participants completed self-report measures of fatigue and psychological distress forms at home for one week following each chemotherapy cycle. The

primary outcome was the score on BFI-3 for Study Cycle 4, while the same score measured at baseline was used as a covariate in the ANCOVA.

Statistical Analyses

Analyses were performed on an intent-to-treat basis. Although the data were screened for factors, such as outliers, compliance, and other anomalies, no subjects were omitted from the analyses. Missing scores at Cycle 4 were imputed with scores from Cycle 3 for patients who completed the study and provided evaluable data only through Study Cycle 3 ($n = 58$ modafinil and $n = 29$ placebo). To confirm that biases were not introduced by this type of imputation, we repeated the primary analysis using multiple imputation²² and found the analysis confirmed the results reported here. The rate of missing value for the drug arm was numerically larger than that of the placebo arm (Figure 1). However, this difference was not statistically significant ($p = 0.11$). When excluding subjects that did not complete Cycle 4 questionnaire but remained on the study, the difference was also not statistically significant ($p = 0.80$).

Analysis of covariance (ANCOVA) was used to address the primary objective. BFI-3 at Cycle 4 was the response variable. The factor was drug (modafinil or placebo). The covariate was the baseline BFI-3 at Cycle 2 centered about the median. The model allowed for an interaction between the treatment effect and baseline fatigue. ANCOVA was also conducted to assess the drug effect for the secondary outcomes. Statistical significance was assessed with two-sided p -values using an alpha level of 0.05.

The planned sample size was 837 patients with up to 30% ($n = 251$) expected to be non-evaluable based on several previous symptom trials in cancer patients by this same multicenter group. The remaining sample of 586 participants would provide 90% power to detect a difference of 0.75 points between groups, based on an alpha-level of 0.05, two-sided t -test and standard deviation of 2.8.²³ This power calculation is conservative because the actual analysis included baseline fatigue as a covariate in an ANCOVA that accounts for variability from patient to patient. The assumptions underlying each of the analyses were thoroughly checked with graphical and regression diagnostics procedures. All statistical analyses were completed using SAS 9.1 and R 2.6.

Role of Funding Sources

This study was supported by a CCOP grant from the National Cancer Institute (NCI) to Dr. Gary R. Morrow. Cephalon, Inc. provided drug and placebo for the study without cost. Neither NCI nor Cephalon, Inc. had any role in the conceptualization, design, implementation, data analysis and interpretation of the study or in the development of this manuscript.

RESULTS

Participants

A total of 877 Cancer patients enrolled in the study. Of this sample, 431 were randomly assigned Modafinil and 436 were assigned a placebo. A total of 544 patients completed Study Cycle 4. Missing Cycle 4 data for 87 patients were imputed with Cycle 3 data as pretested in the protocol. Hence, data for 631 patients were available for analysis (Figure 1). Sixty-seven percent of the participants were females at baseline (Table 1). The majority of the sample was Caucasian and reported diverse marital status and educational levels. Participants also presented with various types of cancer (Table 1). Participants were drawn from 23 geographically distinct University of Rochester Cancer Center Community Clinical Oncology Program (URCC CCOP) affiliates across the United States. The URCC CCOP

Research Base developed and managed the study. The enrollment period for this study was from November 2002 until April 2007.

Summaries of the outcomes at Baseline and Cycle 4 are presented in Table 2. The ANCOVA conducted for the primary outcome (BFI-3 at Cycle 4) showed an interaction between treatment effects and baseline BFI-3 score ($p = 0.017$). The interaction is important because it measures the size of the dependency of the drug effect on baseline. Modafinil significantly reduced fatigue only for patients with high baseline fatigue (Table 3). To further interpret this interaction, we divided the patients into three categories based on the severity of their baseline fatigue^{24,25} to mimic clinical impressions: “Mild” (BFI-3 score = 2 to 4) 10.6%, “Moderate” (BFI-3 score = 5 to 6) 16.8% and “Severe” (BFI-3 = 7 and above) 72.6%. T-tests comparing mean scores for modafinil and placebo were conducted for each severity group (Table 4). The results showed a statistically significant group difference ($p = 0.033$) for those in the severe fatigue category. Patients on modafinil had an average BFI-3 of 7.2, while those on placebo had an average of 7.6. There were no significant differences in BFI-3 in the Mild or Moderate categories.

Daytime sleepiness, as measured by ESS as a check that a clinically active dose of modafinil had been administered, showed a significant improvement in the modafinil group ($p = 0.002$). The differences in depression-related outcomes were not statistically significant (all $p > 0.05$).

The proportion of patients experiencing any adverse event was similar ($p = 0.46$) for the modafinil and placebo groups: 46 (11%) of 431 and 39 (9%) of 436, respectively. The proportion of patients experiencing a severe adverse event was also similar for the modafinil and placebo groups: 37 (8.6%) and 34 (7.8%), respectively, for a total of 71 severe adverse events. A total of 16 adverse events were judged to be possibly due to the treatment: Ten occurred in patients taking modafinil (i.e., 1 allergic reaction, 2 cardiac arrhythmia, 1 dyspnea, 2 headaches and dizziness, 3 mood changes, and 1 myalgia) and six occurred in patients taking placebo (i.e., 3 fever, 1 diarrhea, 1 dyspnea, 1 abdominal pain, and 1 cardiac arrhythmia). Three of these adverse events were judged to be definitely associated with the treatment (allergic reaction, dyspnea, and headaches), and all three occurred in patients taking modafinil. All three related adverse events judged to be related to modafinil subsided when the drug was discontinued.

DISCUSSION

The primary aim of this randomized controlled trial was to examine the effect of the non-amphetamine-based stimulant modafinil on CRF among patients undergoing chemotherapy. Previous open label studies reported that modafinil helped alleviate CRF following cancer treatment in 30 brain cancer patients²⁶ and 51 breast cancer patients.¹⁷ The findings of the present study confirm these preliminary data and support the use of 200 mg of modafinil as an effective treatment for severe CRF in patients undergoing chemotherapy.

Modafinil is a eugeroic agent that has been associated with minimal toxicities and a low susceptibility for misuse. If tolerable, modafinil could be utilized effectively to alleviate CRF and consequently improve QoL for patients with severe CRF. Modafinil has been shown to significantly reduce excessive daytime sleepiness.¹⁹ In the present study, the significant effect found on daytime sleepiness as defined by the Epworth Sleepiness scale (ESS) shows that the fixed 200 mg dose given was biologically active and produced the same significant clinical effects on sleepiness in cancer patients as shown in previous studies of various medical populations.¹⁹

Despite increasing knowledge of the negative effect of CRF on psychosocial functioning and treatment outcome for cancer patients, few studies have examined the effectiveness of pharmacologic interventions to control this side effect. The present study addresses this paucity of relevant data. The findings show that modafinil could be a useful agent to control CRF and also characterize the severity level of CRF (i.e., severe CRF) for which modafinil could be most useful. The heterogeneity and size of the present sample indicate the likelihood that these findings will be generalizable for a wide variety of cancer patients undergoing treatment.

Modafinil had an effect on CRF but not on depression. Our previous research showed that paroxetine hydrochloride (Paxil®) alleviated depression but had no significant effect on CRF.^{27,21} This contrast might indicate that hypotheses of a common underlying pathway for CRF and depression are debatable.^{14,17} The association between fatigue and depression has always been correlational. Both the previous RCT and the present study are randomized studies where one part of the associated pairing was changed with no effect on the other. While these findings do not suggest a disconnection between CRF and depression, they do, however, bring into question the association between these two symptoms.

Our previous findings are that the more individual questions added to a fatigue measurement scale, the more it correlates with depression.²⁸ This could be suggesting that the consistently high correlations previously reported between fatigue and depression may be measurement artifacts. This study and the previous paroxetine hydrochloride study support this view: fatigue and depression were each effectively treated without affecting the other. When measured properly by a single item scale, fatigue is not clinical depression by another name.

The findings have important clinical implications for cancer-related symptom management. Questions related to the etiology and assessment of CRF in divergent cancer types, stages, and clinical settings remain open, and the mechanism of action of modafinil remains unclear. Nevertheless, modafinil seems a promising agent to diminish CRF for patients with severe baseline CRF. Future studies should focus on describing ways to maximize the benefits of this agent and also evaluate whether and how modafinil could facilitate the effects of behavioral interventions to alleviate CRF.

Acknowledgments

Supported by National Cancer Institute grant U10CA37420 and Cephalon, Inc.

References

1. Curran SL, Beacham AO, Andrykowski AM. Ecological momentary assessment of fatigue following breast cancer treatment. *J Behav Med*. 2004; 27:425–444. [PubMed: 15675633]
2. Schwartz AL, Nail LM, Chen S, et al. Fatigue patterns observed in patients receiving chemotherapy and radiotherapy. *Cancer Invest*. 2000; 18:11–19. [PubMed: 10701362]
3. Jean-Pierre P, Figueroa-Moseley C, Kohli S, Fiscella K, Palesh O, Morrow GR. Assessment of cancer related fatigue: Implications for clinical diagnosis and treatment. *The Oncologist*. 2007; 12(Supplement 1):11–21. [PubMed: 17573452]
4. Ahlberg K, Ekman T, Gaston-Johansson F, Mock V. Assessment and management of cancer-related fatigue in adults. *Lancet*. 2003; 362:640–650. [PubMed: 12944066]
5. Gaston-Johansson F, Fall-Dickson JM, Bakos AB, et al. Fatigue, pain and depression in pre-autologous breast cancer patients. *Cancer Pract*. 1999; 7:240–247. [PubMed: 10687593]
6. Hofman M, Morrow GR, Roscoe JA, et al. Cancer patients' expectations of experiencing treatment-related side effects: a University of Rochester Cancer Center–Community Clinical Oncology Program Study of 938 patients from community practices. *Cancer*. 2004; 101:851–857. [PubMed: 15305419]

7. Jacobsen PB, Hann DM, Azzarello LM, et al. Fatigue in women receiving adjuvant chemotherapy for breast cancer: characteristics, course and correlates. *J Pain Symptom Manage.* 1999; 19:14–27.
8. Maughan TS, James RD, Kerr DJ, et al. Comparison of survival, palliation, and quality of life with three chemotherapy regimens in metastatic colorectal cancer : A multicentre randomized trial. *Lancet.* 2000; 359:1555–1563. [PubMed: 12047964]
9. Mock, V.; Abernathy, AP.; Atkinson, A., et al. Jenkintown, PA: National Comprehensive Cancer Network; 2006. NCCN clinical practice guidelines in oncology: cancer-related fatigue v.1.2006. Available from: www.nccn.org/professionals/physician_gls/PDF/fatigue.pdf.
10. Morrow GR, Hickok JT, Andrews PL, Stern RM. Reduction in serum cortisol after platinum based chemotherapy for cancer: a role for the HPA axis in treatment-related nausea? *Psychophysiology.* 2002a; 39:491–495. [PubMed: 12212641]
11. Morrow GR, Andrews PL, Hickok JT, et al. Fatigue associated with cancer and its treatment. *Support Care Cancer.* 2002b; 10:389–398. [PubMed: 12136222]
12. Minton O, Richardson A, Sharpe M, Hotopf M, Stone P. A Systematic Review and Meta-Analysis of the Pharmacological Treatment of Cancer-Related Fatigue. *JNCI.* 2008; 100:16, 1155–1166.
13. Kangas M, Bovbjerg DH, Montgomery GH. Cancer-related fatigue: A systematic and meta-analytic review of non-pharmacological therapies for cancer patients. *Psychological Bulletin.* Sep; 2008 134(5):700–741. [PubMed: 18729569]
14. Morrow GR, Shelke AR, Roscoe JA, et al. Management of cancer-related fatigue. *Cancer Invest.* 2005a; 23:229–239. [PubMed: 15945509]
15. Cleeland, CS. Measurement of pain by subjective report. In: Chapman, CR.; Loeser, JD., editors. *Issues in Pain Measurement.* New York: Raven Press; 1989. p. 391–403. *Advances in Pain Research and Therapy*; Vol. 12
16. Shi Q, Wang XS, Mendoza TR, Pandya KJ, Cleeland CS. Assessing persistent cancer pain: a comparison of current pain ratings and pain recalled from the past week. *J Pain Symptom Manage.* 2009; 37(2):168–174. [PubMed: 18676116]
17. Morrow GR, Gillies LJ, Hickok JT, Roscoe JA, Padmanaban D, Griggs JJ. The positive effect of the psychostimulant modafinil on fatigue from cancer that persists after treatment is completed. *Journal of Clinical Oncology*, 2005b ASCO Annual Meeting Proceedings. June 1.2005 23(16S): 8012. Supplement.
18. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep.* 1991; 14:540–545. [PubMed: 1798888]
19. Anonymous. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy: US Modafinil in Narcolepsy Multicenter Study Group. *Neurology.* 2000; 54.5:1166–75. [PubMed: 10720292]
20. Norcross JC, Guadagnoli E, Prochaska JO. Factor Structure of the Profile of Mood States (POMS): Two Partial Replications. *J Clin Psychol.* 1984; 40:1270–1277. [PubMed: 6490926]
21. Roscoe JA, Morrow GR, Hickok JT, et al. Effect of paroxetine hydrochloride (Paxil) on fatigue and depression in breast cancer patients receiving chemotherapy. *Breast Cancer Res Treat.* 2005; 89:243–249. [PubMed: 15754122]
22. Rubin DB. Inference and Missing Data. *Biometrika.* 1976; 63:581–590.
23. Mendoza TR, Wang XS, Cleeland CS, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. *Cancer.* 1999; 85:1186–96. [PubMed: 10091805]
24. Cleeland CS, Mendoza TR, Wang XS, Chou C, Harle MT, Morrissey M, Engstrom MC. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. *Cancer.* 2000 Oct 1; 89(7):1634–46. [PubMed: 11013380]
25. Chang YJ, Lee JS, Lee CG, Lee WS, Lee KS, Bang SM, Wang XS, Mendoza TR, Cleeland CS, Yun YH. Assessment of clinical relevant fatigue level in cancer. *Support Care Cancer.* 2007 Jul; 15(7):891–6. [PubMed: 17318593]
26. Kaleita TA, Wellisch DK, Graham CA, et al. Pilot study of modafinil for treatment of neurobehavioral dysfunction and fatigue in adult patients with brain tumors. *J Clin Oncol.* 2006 ASCO Meeting Abstract 1503.
27. Morrow GR, Hickok JT, Roscoe JA, et al. Differential effects of paroxetine on fatigue and depression: a randomized, double-blind trial from the University of Rochester Cancer Center

- Community Clinical Oncology Program. J Clin Oncol. 2003; 21(24):4635–4641. [PubMed: 14673053]
28. Sloan JA, et al. Integrating patient-reported outcomes into cancer symptom management clinical trials supported by the National Cancer Institute-sponsored clinical trials networks. Journal of Clinical Oncology. 2007; 25.32:5070–77. [PubMed: 17991923]

Figure 1.
Participant Flow

Table 1

Demographic and clinical characteristics of the trial groups at baseline.

Characteristic	Modafinil Group	Placebo Group
Number of Participants n, (%)	426 (50%)	434 (50%)
Age Mean (Min-Max), Years	61 (18-90)	60 (22-90)
Gender n, (%)		
Male	137 (32.2%)	148 (34.1%)
Female	289 (67.8%)	286 (65.9%)
Race n, (%)		
White	398 (93.7%)	393 (91.0%)
Nonwhite	27 (6.3%)	39 (9.0%)
Marital Status n, (%)		
Married	297 (70.0%)	287 (67.1%)
Not Married	127 (30.0%)	141 (32.9%)
Highest level of education achieved n, (%)		
Bachelor degree or higher	100 (23.6%)	84 (19.6%)
Partial college training (<4 years)	114 (27.0%)	126 (29.4%)
High school graduate	171 (40.4%)	170 (39.7%)
Non high school graduate	38 (9.0%)	48 (11.3%)
Cancer Type n, (%)		
Alimentary	110 (26.1%)	101 (23.5%)
Breast	156 (37.0%)	145 (33.8%)
Genitourinary	18 (4.3%)	17 (4.0%)
Gynecologic	24 (5.7%)	44 (10.3%)
Hematologic	37 (8.8%)	36 (8.4%)
Lung	68 (16.1%)	69 (16.1%)
Other	9 (2.1%)	17 (4.0%)
Previous tamoxifen treatment n, (%)	36 (8.5%)	37 (8.6%)
Previous chemotherapy n, (%)	242 (57.1%)	248 (57.9%)
Previous radiation therapy n, (%)	101 (23.8%)	96 (22.4%)
Fatigue at baseline, BFI-3 Mean (SD)	7.3 (2.17)	7.4 (2.06)

Table 2

Descriptive statistics of the primary and secondary outcomes at Baseline, Cycle 4, and the change at Cycle 4 from Baseline.*

Outcome	Statistic	Baseline			Cycle 4			Change Cycle 4 - Baseline		
		Modafinil	Placebo	N	Modafinil	Placebo	N	Modafinil	Placebo	N
BFI-3	N	315	316	315	315	316	309	309	312	312
	Mean	7.39	7.43	6.87	7.09	7.09	-0.50	-0.50	-0.33	-0.33
	Std. Err.	0.11	0.11	0.14	0.13	0.13	0.14	0.14	0.13	0.13
ESS	N	315	316	315	315	315	308	308	313	313
	Mean	18.16	19.19	16.82	18.38	18.38	-0.98	-0.98	-0.73	-0.73
	Std. Err.	0.27	0.30	0.26	0.31	0.31	0.20	0.20	0.26	0.26
CESD	N	312	315	312	313	313	306	306	310	310
	Mean	16.90	17.79	15.89	16.12	16.12	-1.00	-1.00	-1.58	-1.58
	Std. Err.	0.54	0.57	0.56	0.58	0.58	0.47	0.47	0.50	0.50
POMS-DD	N	315	316	314	315	315	308	308	313	313
	Mean	3.87	4.09	3.37	3.56	3.56	-0.53	-0.53	-0.74	-0.74
	Std. Err.	0.22	0.22	0.20	0.22	0.22	0.20	0.20	0.19	0.19

* No mean change scores were statistically significant (all p-values > 0.05).

Table 3
Treatment and Treatment-by-Baseline interaction coefficients from the ANCOVA.

Category	Outcome	Median at Baseline (Range)	Coefficient, P-Value (95% Confidence Interval)			
			Treatment		Treatment by Baseline Interaction	
			Coeff.	P-Value	Coeff.	P-Value
Fatigue	BFI-3	8 (2 – 10)	-0.33	0.08	-0.22	0.02
			(-0.700, 0.037)		(-0.391, -0.038)	
Sleepiness	ESS	18 (8 – 32)	-1.03	0.002	0.13	0.054
			(-1.679, -0.380)		(-0.002, 0.253)	
Depression	CESD	16 (0 – 49)	0.34	0.60	-0.03	0.71
			(-0.943, 1.621)		(-0.154, 0.105)	
	POMS-DD	3 (0 – 18)	-0.04	0.87	-0.05	0.42
			(-0.550, 0.463)		(-0.176, 0.073)	

The treatment coefficient is the change in outcome level for modafinil relative to placebo at the median baseline. The interaction coefficient is the change in outcome level (modafinil relative to placebo) per unit change in the baseline. The interaction is important because it measures the size of the dependency of the drug effect on baseline. The negative sign for BFI-3 means that the drug reduces CRF more at higher baseline CRF. The P-values are associated with two-sided t-tests for the coefficients (testing whether the coefficient is zero). When the interaction is significant, as with BFI-3, it must be included (along with the Treatment effect) in the interpretation of the modafinil/placebo effect. See Table 4 for a practical interpretation.

Comparison of adjusted BFI-3 means¹ for modafinil vs. placebo with patients subdivided into fatigue severity at baseline.

Table 4

Category	%	Placebo		Drug		Difference	P-Value ²
		Mean	SE	Mean	SE	Drug - Placebo	Drug - Placebo
Mild (2, 3, 4)	10.6	1.86	0.31	2.60	0.31	0.74	0.090
Moderate (5, 6)	16.8	0.62	0.18	0.82	0.17	0.20	0.411
Severe (7, 8, 9, 10)	72.6	-0.87	0.14	-1.31	0.15	-0.44	0.033
Maximum (10)	100.0	-1.61	0.21	-2.37	0.21	-0.76	0.010

¹ Treatment arm means adjusted for baseline at the midpoint of the category interval.

² P-values are associated with the difference between drug and placebo adjusted means.