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ORIGINAL REPORT

Modafinil for the Treatment of Fatigue in Lung Cancer: Results of a Placebo-Controlled, Double-Blind, Randomized Trial

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ABSTRACT

Purpose
Fatigue is a distressing symptom occurring in more than 60% of patients with cancer. The CNS stimulants modafinil and methylphenidate are recommended for the treatment of cancer-related fatigue, despite a limited evidence base. We aimed to evaluate the efficacy and tolerability of modafinil in the management of fatigue in patients with non–small-cell lung cancer (NSCLC).

Patients and Methods
Adults with advanced NSCLC and performance status of 0 to 2, who were not treated with chemotherapy or radiotherapy within the last 4 weeks, were randomly assigned to daily modafinil (100 mg on days 1 to 14; 200 mg on days 15 to 28) or matched placebo. 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.

Results
A total of 208 patients were randomly assigned, and 160 patients (modafinil, n = 75; placebo, n = 85) completed questionnaires at both baseline and day 28 and were included in the modified intention-to-treat analysis. FACIT-Fatigue scores improved from baseline to day 28 (mean score change: modafinil, 5.29; 95% CI, 2.57 to 8.02; placebo, 5.09; 95% CI, 2.54 to 7.65), but there was no difference between treatments (0.20; 95% CI, −3.56 to 3.97). There was also no difference between treatments for the secondary outcomes; 47% of the modafinil group and 23% of the placebo group stated that the intervention was not helpful.

Conclusion
Modafinil had no effect on cancer-related fatigue and should not be prescribed outside a clinical trial setting. Its use was associated with a clinically significant placebo effect.

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INTRODUCTION

Fatigue is the most prevalent symptom experienced by patients with cancer, occurring in more than 60% of patients and more than 80% of those receiving cancer treatment.[1] Among primary cancer sites, patients with lung cancer have the most severe fatigue.[2] Cancer-related fatigue is reported to be the single most distressing symptom with the greatest negative impact on quality of life.[3] It starts before diagnosis and persists for months or years after treatment completion.

CNS stimulants are the only pharmacologic treatment for fatigue recommended by the National Comprehensive Cancer Network guideline on cancer-related fatigue.[4] The guideline states that modafinil or methylphenidate should be considered, when reversible causes of fatigue have been excluded, for patients during active cancer treatment and after completion of treatment.

Modafinil is a novel CNS stimulant licensed for the treatment of excessive sleepiness associated with narcolepsy. It is widely used among healthy individuals, such as pilots, for its cognitive and mood-enhancing effects, particularly after sleep deprivation.[5] Compared with traditional stimulant drugs, such as methylphenidate, it has a relatively selective site of action in the brain, with fewer adverse effects and lower abuse potential.[6]

Interest in modafinil as an agent for the treatment of fatigue emerged recently, after positive outcomes in a number of controlled trials in healthy individuals and in patients with conditions including multiple sclerosis, depression, and HIV.[7-10] In patients with cancer-related fatigue, several open-label studies have reported significant benefit from modafinil.[11-13] However, to date, there has been only one randomized controlled trial evaluating modafinil in cancer-related fatigue.[14] In a large study involving patients with cancer receiving chemotherapy, modafinil had a small impact only in a subgroup of patients with severe baseline fatigue.

In the context of increasing use of modafinil in patients with cancer, despite limited supporting evidence, the objective of this study was to establish its efficacy and tolerability in fatigued patients with advanced non–small-cell lung cancer (NSCLC). We also evaluated its impact on daytime sleepiness, depression, and quality of life.

PATIENTS AND METHODS

Study Design and Patients

We undertook a double-blind, placebo-controlled, randomized clinical trial. Patients were recruited from 24 hospitals across the United Kingdom. Eligible patients were adult outpatients with stage 3a/3b/4 NSCLC or recurrent disease after surgery or radiotherapy, WHO performance status of 0 to 2, and screening score of ≥ 5 on a 0-to-10 numeric rating scale (NRS) of fatigue severity (using question, "How would you rate your worst fatigue during the past week on a scale of 0 to 10, where 0 is 'no fatigue at all' and 10 is the 'worst fatigue imaginable'?").

Patients were excluded if they had received radiotherapy or chemotherapy within the last 4 weeks. However, patients established on epidermal growth factor receptor tyrosine kinase inhibitors for at least 6 weeks were eligible. Other exclusion criteria included receiving a blood transfusion or having commenced steroids or antidepressants within the last 2 weeks, major psychiatric illness, uncontrolled hypertension, and history of arrhythmia or left ventricular hypertrophy.

The study received research ethics committee approval (Reference No. 08/H0604/171). Written informed consent was obtained from each patient before enrollment. The study was undertaken according to the Declaration of Helsinki, the International Conference on Harmonisation/Good Clinical Practice, and all applicable regulatory requirements.

Randomization and Masking

Patients were randomly assigned at a 1:1 ratio to either oral modafinil 100 mg or a matched placebo capsule using a central telephone system. The overencapsulated modafinil tablets and matched placebo capsules were manufactured and provided by an independent contract research organization. The randomization sequence was computer generated and stratified by WHO performance status and center, using a minimization algorithm. The first 30 patients were allocated by simple randomization to reduce the predictability of the early treatment assignments, and the remaining patients were randomly assigned to the treatment that minimized any imbalance with a probability of 0.8.[15] Patients, clinicians, and investigators were blinded to treatment allocation.

Procedures

The study period was 28 days. This was considered sufficient to avoid missing a treatment effect (seen within preliminary feasibility study within 14 days) but short enough to limit the high attrition rate likely in this study population. Patients took modafinil or placebo on a fixed-dose titration schedule, starting with one capsule daily for 14 days and increasing to two capsules daily for an additional 14 days. Treatment was discontinued after day 28. Baseline assessments were undertaken in clinic on day 0 and follow-up assessments in clinic or by telephone on days 14 and 28. Participants completed a questionnaire self-rating their symptoms at each time point. Adverse events and reactions were quantified using the National Cancer Institute of Canada Clinical Trials Group Expanded Common Toxicity Criteria. Patients were specifically questioned about headache, nausea and vomiting, and anxiety.

The primary outcome was fatigue, measured by Functional Assessment of Chronic Illness Therapy (FACIT) –Fatigue, a validated 13-item fatigue subscale of the FACIT measurement system.[16] FACIT-Fatigue gives a fatigue score between 0 and 52, where a low score indicates a high level of fatigue. The minimal clinically important difference has been defined as a change in score of 3 points.[17] Secondary outcomes were daytime sleepiness, depression, and quality of life, measured using validated scales: the Epworth Sleepiness Scale (ESS), the Hospital Anxiety and Depression Scale (HADS), and a quality of life linear analog scale (QOL-LAS).[18,19] QOL-LAS is a single-item measure of quality of life that has been found to be comparable to multi-item global measures and is recommended for use in lung cancer trials.[20]

Statistical Analyses

A sample size of 206 was required, based on a standard deviation of 11 points in the primary outcome measure from a previous pilot study, to have an 80% power to detect a difference in 5 points in the FACIT-Fatigue scale at 5% significance (two sided), allowing for 25% attrition.[11]

A modified intention-to-treat (ITT) analysis was performed for patients who completed assessments at baseline and day 28. This analysis was ITT with respect to treatment compliance, but fatigue scores were not explicitly imputed for missing end points. Changes in mean FACIT-Fatigue score at day 28 from baseline in the modafinil group were compared with those of the placebo group, using analysis of covariance (ANCOVA) with adjustment for baseline fatigue and performance status, with supplementary analyses adjusting for the additional prognostic factors of disease stage and age. We had intended to adjust for the stratification factor of trial center. However, this was not done, because the number of centers increased from eight to 24 to facilitate recruitment, with

Table 1. Baseline Patient Demographic and Clinical Characteristics

Characteristic	Modafinil Arm (n = 104) No.	Modafinil Arm (n = 104) %	Placebo Arm (n = 103) No.	Placebo Arm (n = 103) %
Age at random assignment, years				
Mean	68.60		69.18	
SD	9.10		9.46	
Sex				
Female	53	51.0	51	49.5
Male	51	49.0	52	50.5
WHO performance status				
0	10	9.6	10	9.6
1	56	53.9	57	54.8
2	38	36.5	37	35.6
Disease stage				
3a	8	7.7	12	11.6
3b	24	23.1	22	21.4
4	68	65.4	62	60.2
Recurrent	4	3.8	7	6.8
NRS screening fatigue score				
5-6	47	45.2	51	49.5
7-10	57	54.8	52	50.5
Haemoglobin at random assignment, g/dL				
Mean	12.35		12.64	
SD	1.69		1.84	
Corrected calcium at random assignment, mmol/L				
Mean	2.37		2.39	
SD	0.16		0.22	

Abbreviations: NRS, numeric rating scale; SD, standard deviation.

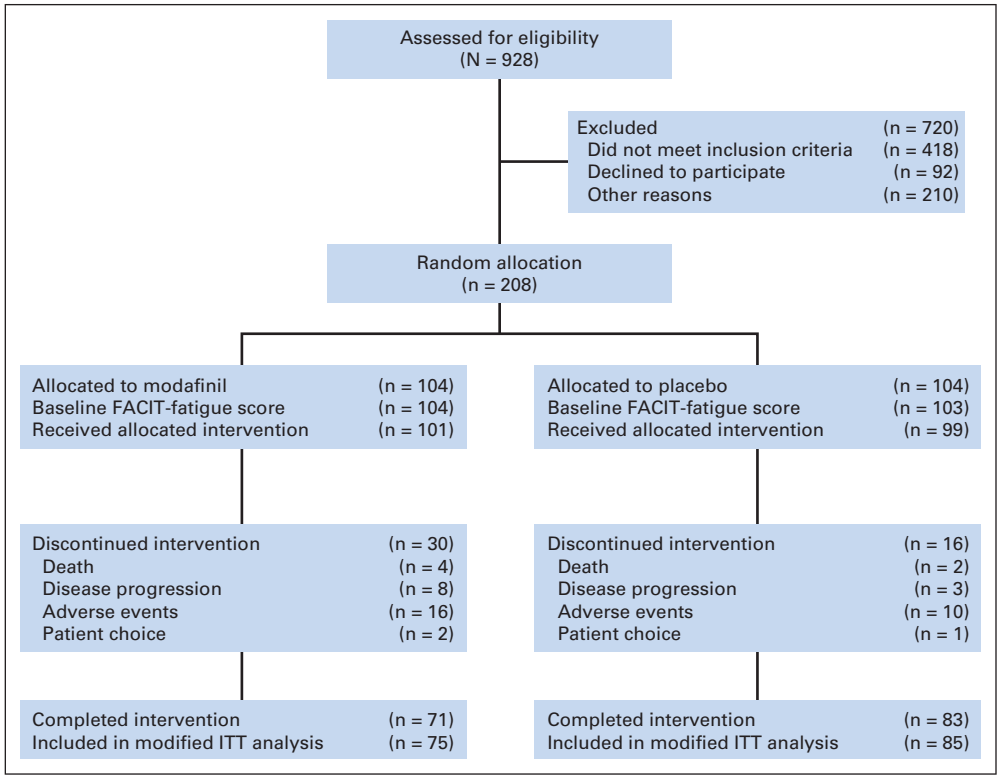

Fig 1. CONSORT diagram. FACIT, Functional Assessment of Chronic Illness Therapy; ITT, intention to treat.

resulting low patient numbers in many centers. A repeated measures ANCOVA was undertaken to assess individual variability in response and to include all available data from every time point. Secondary outcomes were analyzed by ANCOVA with adjustment for baseline fatigue and performance status if normally distributed or by Mann-Whitney U test when there were severe departures from normality. STATA software (version 12.0; STATA, College Station, TX) was used for all analyses.

RESULTS

Patients

A total of 208 patients were recruited from July 2009 to April 2012 from 24 centers across the United Kingdom and

Table 2. Outcomes at Baseline, Day 14, and Day 28

	Modafinil Arm				Placebo Arm			
Scale	Mean	SD	No.	Range	Mean	SD	No.	Range
FACIT-Fatigue score								
Baseline	24.64	10.58	104	1-45	24.98	10.83	103	3-47
Day 14	30.58	12.17	88	1-52	29.43	11.57	90	3-49
Day 28	31.28	13.66	75	1-52	30.66	13.85	85	3-51
ESS score								
Baseline	8.61	5.18	103	0-21	9.31	5.17	100	1-21
Day 14	6.51	5.25	86	0-21	7.51	5.10	87	0-24
Day 28	6.45	5.15	74	0-22	7.27	5.45	84	0-24
HADS-Depression score								
Baseline	7.09	4.40	104	1-19	7.27	4.27	103	0-18
Day 14	5.94	4.14	88	0-16	6.11	4.10	90	0-18
Day 28	5.71	4.21	75	0-18	5.94	4.76	85	0-18
QOL-LAS score								
Baseline	6.00	1.84	104	0-10	5.83	1.72	103	2-10
Day 14	6.14	1.89	88	0-10	6.02	1.90	90	0-10
Day 28	6.15	1.93	75	1-10	6.02	2.27	84	0-10

NOTE. Higher FACIT-Fatigue score indicates less severe fatigue. Higher ESS and HADS scores indicate more severe symptoms. Higher QOL-LAS score indicates better quality of life. Score ranges: FACIT-Fatigue, 0-52; ESS, 0-24; HADS-Depression, 0-21; QOL-LAS, 0-10.

Abbreviations: ESS, Epworth Sleepiness Scale; FACIT, Functional Assessment of Chronic Illness Therapy; HADS, Hospital Anxiety and Depression Scale; QOL-LAS, quality of life linear analog scale; SD, standard deviation.

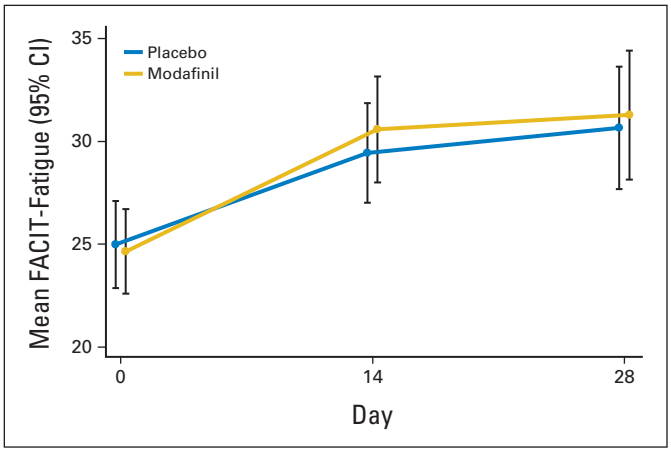

Fig 2. Change in fatigue over time in intervention and control arms. FACIT, Functional Assessment of Chronic Illness Therapy.

randomly allocated to modafinil (n = 104) or placebo (n = 104). The study groups were well balanced in terms of baseline characteristics (Table 1).

One patient in the placebo group was a protocol violator; no baseline data were collected, the intervention was not started, and the patient was not included in any data analyses. Of 207 randomly assigned patients, eight did not start study treatment, and 46 discontinued treatment early for reasons detailed in Figure 1. Some patients who discontinued treatment still completed the questionnaire at day 28. In total, 160 patients completed both baseline and day-28 FACIT-Fatigue questionnaires and were included in the modified ITT analysis for the primary end point.

Efficacy

Mean fatigue scores improved in both the modafinil and placebo groups across all time points (Table 2; Fig 2). The mean change in FACIT-Fatigue from baseline to 28 days, adjusted for baseline fatigue and performance status, was 5.29 (95% CI, 2.57 to 8.02) for the modafinil group and 5.09 (95% CI, 2.54 to 7.65) for the placebo group (Table 3). However, there was no statistically significant difference between the treatments (0.20; 95% CI, −3.56 to 3.97). No significant differences were found after additional adjustment for disease stage or age. On repeated measures ANCOVA, there was also no significant treatment effect ($P = .854$). Exploratory analyses showed these findings were consistent across subgroups defined by stage of disease, performance status, age, sex, and severity of baseline fatigue (Fig 3). There was no difference between treatments for any of the secondary outcomes, although there was an improvement in daytime sleepiness in both groups (Table 3).

Participants were asked to rate how helpful the study treatment was on a 4-point verbal rating scale; 47% of the modafinil group and 23% of the placebo group stated that the treatment was not helpful ($P = .13$).

Safety

Modafinil seemed to be well tolerated, with similar frequency and severity of adverse events occurring in the modafinil and placebo groups (Table 4). Adverse events were experienced by 55.8% of patients taking modafinil and 54.4% of those taking placebo ($P = .84$). Twenty-four serious adverse events were reported (modafinil, n = 14; placebo, n = 10). Most serious adverse events were considered unrelated to study treatment and to be expected in this patient group. However, six patients (modafinil, n = 4; placebo, n = 2) did experience serious adverse events that may have been related to the treatment. More patients withdrew from the modafinil than the placebo group (modafinil, n = 30; placebo, n = 16), and the differential withdrawal rate reached statistical significance ($P = .02$).

DISCUSSION

Modafinil and placebo led to a clinically significant improvement in fatigue score in patients with advanced NSCLC, but there was no significant difference between the two groups. There are a number of potential explanations for the significant change within both treatment groups. It could be the consequence of a placebo effect from receiving an intervention or another aspect of taking part in a clinical trial; it may represent the natural history of the symptom over time; or it could be an artifact related to recruiting only a subgroup of patients with fatigue above a certain level (biasing selection toward those experiencing worse-than-usual fatigue on day of screening). However, the latter two explanations are unlikely to be important contributors to the improvement in fatigue seen in this trial. Patients with advanced NSCLC have a poor prognosis and will tend to experience fatigue that worsens, rather than improves, over time. The selection artifact would

Table 3. Difference Between Treatments

Scale	Modafinil Arm			Placebo Arm			Adjusted Mean Difference	95% CI	*P*
	Change	95% CI	IQR	Change	95% CI	IQR			
FACIT-Fatigue*	5.29	2.57 to 8.02		5.09	2.54 to 7.65		0.20	−3.56 to 3.97	.92
FACIT-Fatigue†	5.78	3.72 to 7.84		4.33	2.29 to 6.36		1.45	−1.47 to 4.36	.33
ESS*	−1.84	−2.91 to −0.77		−1.78	−2.79 to −0.77		−0.06	−1.54 to 1.43	.94
HADS-Depression‡	−1		−3 to 1	0		−3 to 2			.39
QOL-LAS‡	0		−1 to 1	0		−1 to 1			.60

Abbreviations: ANCOVA, analysis of covariance; ESS, Epworth Sleepiness Scale; FACIT, Functional Assessment of Chronic Illness Therapy; HADS, Hospital Anxiety and Depression Scale; IQR, interquartile range; QOL-LAS, quality of life linear analog scale.
*Adjusted mean change from baseline to day 28, analyzed using ANCOVA adjusted for baseline fatigue and performance status.
†Adjusted mean change from baseline to day 14, analyzed using ANCOVA adjusted for baseline fatigue and performance status.
‡Unadjusted median change from baseline to 28 day, analyzed using Mann-Whitney U test.

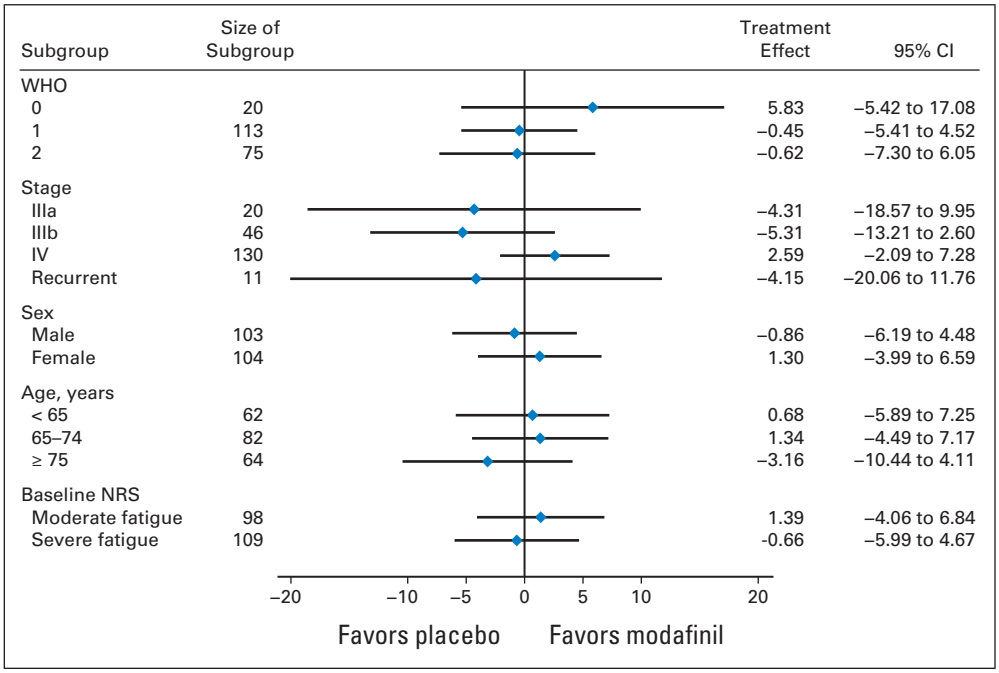

Fig 3. Exploratory subgroup analyses. Moderate fatigue is 5 to 6 and severe fatigue is 7 to 10 on screening 0-to-10 fatigue severity numeric rating scale (NRS).

have been minimized by our use of a different fatigue scale for screening and trial assessments and by recruiting patients with a relatively broad range of fatigue severity (moderate as well as severe fatigue).

Therefore, we argue that the clinically significant benefit seen in both arms of this trial is likely related to the placebo effect. Fatigue is a highly subjective symptom, established as being amenable to the placebo effect. In patients with nonmalignant disease, 11 controlled trials have evaluated modafinil for fatigue in a heterogeneous group of conditions, including multiple sclerosis, HIV, and traumatic brain injury. Although four studies had positive outcomes, which led to the initial interest in evaluating modafinil in cancer, five of the seven negative studies reported a strong placebo effect.[21-25] Of the eight studies evaluating the alternative stimulant, methylphenidate, three of the five negative studies revealed a significant response to placebo.[26-28]

An important finding in this study is the significantly greater withdrawal rate in patients taking modafinil. As detailed in Figure 1, there were more withdrawals related to death (modafinil, n = 4; placebo, n = 2), disease progression (modafinil, n = 8; placebo, n = 3), and adverse events (modafinil, n = 16; placebo, n = 10). The overall frequency and severity of adverse events during the trial were similar between the two treatment groups, suggesting that the differential withdrawal rate may have occurred by chance. However, it is conceivable that some adverse events judged as being expected, because of the presence of malignant disease, were in fact related to modafinil. Furthermore, modafinil-related deterioration could have been misattributed to disease progression in the context of advanced disease. Therefore, the safety of modafinil in this patient group has not been established.

To date, only one controlled trial has been published evaluating modafinil for cancer-related fatigue. Jean-Pierre et al[14] undertook a large controlled trial evaluating the impact of modafinil in 631 patients receiving chemotherapy (baseline: breast cancer, 35%; alimentary cancer, 25%; lung cancer, 16%). Modafinil did not improve fatigue significantly. Using an 11-point NRS, fatigue was reduced by 0.50 in the modafinil group and 0.33 in the placebo group. For the subgroup of 458 patients with severe fatigue (≥ 7 on 11-point NRS), the mean

Table 4. Adverse Events Summary

	Modafinil Arm								Placebo Arm							
	Grade 1 to 2		Grade3 to 5		Unknown		All		Grade 1 to 2		Grade 3 to 5		Unknown		All	
Adverse Event	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Headache	22	21.2	1	1.0	0	0.0	23	22.1	23	22.3	2	1.9	0	0.0	25	24.3
Nausea/vomiting	16	15.4	0	0.0	0	0.0	16	15.4	19	18.4	1	1.0	0	0.0	20	19.4
Anxiety	9	8.7	0	0.0	0	0.0	9	8.7	10	9.7	0	0.0	0	0.0	10	9.7
Other	28	26.9	15	14.4	2	2.0	45	43.3	23	22.3	11	10.7	1	1.0	35	34.0
Any							58	55.8							56	54.4

NOTE. Where more than one adverse event was experienced, worst severity reported. Patients may have experienced > one type of adverse event. Patients were specifically asked about headache, nausea and vomiting, and anxiety. Severity defined according to The National Cancer Institute of Canada Clinical Trials group Expanded Common Toxicity Criteria.

fatigue score at the study end point was 7.2 for patients receiving modafinil and 7.6 for patients receiving placebo. Although the difference between the group adjusted means was statistically significant (−0.44; $P = .033$), this small change is unlikely to be of clinical significance.[29,30] In comparison with this subgroup, our study population was less fatigued, because we used the 11-point NRS as a screening measure and recruited patients with a score of ≥ 5. However, our exploratory subgroup analysis in the patient group with a screening score of ≥ 7 showed no significant benefit from modafinil (Fig 3).

There has been one systematic review and meta-analysis of CNS stimulants for the management of cancer-related fatigue. Minton et al[31] updated the review in 2010 and concluded that there was equivocal evidence that methylphenidate improves cancer-related fatigue, based on a small statistically significant improvement in fatigue ($Z = 2.83$; $P < .001$), which did not reach clinical significance.[17,31] None of the studies evaluated modafinil.

On the basis of these two lines of evidence and a number of positive open-label studies, the National Comprehensive Cancer Network guideline on cancer-related fatigue management (2013) recommends consideration of modafinil and methylphenidate for patients with cancer during active treatment, after treatment, and at the end of life, when other causes of fatigue have been excluded.

In this context, our study provides important negative evidence. This trial and the one other controlled trial evaluating modafinil for cancer-related fatigue both found that modafinil has no benefit over placebo. We have shown a marked placebo effect of > 5 points on the FACIT-Fatigue scale, where a change of 3 points is of clinical significance.[17]

The main strengths of this study are its size (ie, second largest study evaluating any CNS stimulant drug for fatigue [primary outcome] in any disease group, powered to detect clinically significant difference); its double-blind, randomized, placebo-controlled design; its use of validated, multidimensional, patient-reported outcomes; and its relatively homogeneous study population. Important benefits from modafinil are unlikely to have been missed. A limitation is the attrition rate of 22.7% (although 25% was allowed for in sample size calculation). Another potential limitation is the differential withdrawal rate at 28 days. At day 14, the arms were balanced (modafinil, n = 88; placebo, n = 90), and it is noteworthy that analysis of the change in day-14 FACIT-Fatigue score from baseline also showed clinically significant improvement in fatigue in both arms, with no significant mean difference (Table 3). Therefore, it is unlikely that the differential withdrawal rate has had any substantial impact on the overall outcome of the trial.

There is insufficient evidence to prescribe modafinil for patients with cancer-related fatigue outside of a clinical trial context. Future trials need to have sufficient power to evaluate the effect in those patients with severe fatigue and could incorporate a placebo wash-in period to minimize the influence of the placebo effect. We argue that the clinically significant placebo effect found in this trial is, in itself, an important finding. Further research is needed to identify the precise component of being involved in a clinical trial and taking a placebo drug that improves this subjective symptom. Cancer-related fatigue is relatively neglected, beset by therapeutic nihilism on the part of both clinicians and patients. Simply allocating the time within a clinical consultation to acknowledge and discuss fatigue may benefit the many patients experiencing this distressing symptom.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Data analysis and interpretation: Anna Spathis, Kate Fife, Susan Dutton, Rose Wharton, Bee Wee
Manuscript writing: All authors
Final approval of manuscript: All authors

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GLOSSARY TERMS

non–small-cell lung cancer (NSCLC): a type of lung cancer that includes squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma.

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