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Efficacy of Treatment With Armodafinil for Cancer-Related Fatigue in Patients With High-grade Glioma
A Phase 3 Randomized Clinical Trial

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IMPORTANCE Nearly 96% of patients with high-grade glioma (HGG) report moderate-to-severe fatigue. Armodafinil is a psychostimulant that might help cancer-related fatigue in patients with HGG.

OBJECTIVE To determine whether armodafinil reduces fatigue in patients with HGG and moderate-to-severe fatigue.

DESIGN, SETTING, AND PARTICIPANTS In this randomized multicenter, phase 3, double-blinded, placebo-controlled clinical trial, adults with HGG and moderate-to-severe fatigue who were clinically stable at least 4 weeks after completing radiation therapy were randomized to receive armodafinil daily (150 mg or 250 mg) or placebo over 8 weeks. A score of at least 6 out of 10 on severity scale for the brief fatigue inventory scale, with 10 being the worst, was required to suggest moderate-to-severe fatigue. Patients were allowed stable doses of corticosteroids but were excluded if they required increasing amounts of corticosteroids, were receiving some other treatment for fatigue, or had an uncontrolled seizure disorder. The study was conducted from June 2013 to December 15, 2019.

INTERVENTIONS Patients were randomized to 150 mg of armodafinil, 250 mg of armodafinil, or placebo for a total of 8 weeks with assessments at weeks 4 and 8.

MAIN OUTCOMES AND MEASURES The primary outcome was efficacy in treating cancer-related fatigue. Secondary outcomes included safety, neurocognitive function, and quality of life. Patients were evaluated at baseline and at weeks 4 and 8. Efficacy between the placebo and the 2 doses of study drug was determined by an improvement by 2 points on the 0 to 10 brief fatigue inventory scale. Kruskal-Wallis and χ^2 tests were used and followed by confirmatory analyses.

RESULTS A total of 328 patients were enrolled, of whom 297 had evaluable end point data. Of these, 103 received 150 mg of armodafinil (mean [SD] age, 58.5 [11.9] years; 42 women [40.8%]), 97 250 mg of armodafinil (mean [SD] age, 56.6 [12.5] years; 37 women [38.1%]), and 97 placebo (mean [SD] age, 57.1 [12.5] years; 39 women [40.2%]). There was no difference in the proportion of patients who achieved clinically meaningful fatigue reduction between arms (28% [95% CI 20%-30%] for 150 mg of armodafinil, 28% [95% CI 19%-38%] for 250 mg of armodafinil, and 30% [95% CI 21%-40%] for placebo). There was a statistically significant reduction in global fatigue for corticosteroid users compared with nonusers (−0.7 [95% CI, −1.5 to −0.3] vs −1.7 [95% CI, −2.1 to −1.3]; $P < .001$). More patients (2 vs 7) reported insomnia with treatment with 250 mg of armodafinil.

CONCLUSIONS AND RELEVANCE The results of this randomized clinical trial found no meaningful benefit of using treatment with armodafinil to reduce cancer-related fatigue in patients with HGG.

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Supplemental content

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Fatigue, commonly underrecognized, underdiagnosed, and undertreated,[1] is one of the most common and troublesome symptoms for patients with primary brain tumors throughout their disease trajectory.[2] Described as being a distressing, persistent, and subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion that is related to cancer that is not proportional to recent activity and interferes with usual functioning,[3] *cancer-related fatigue* is a concerning clinical problem.

Armodafinil, the R enantiomer of modafinil with a longer elimination half-life, works as a central nervous system stimulant. It is currently approved for use for treating the depression phase of bipolar disorder, narcolepsy, and other disorders.[4] Two prior studies have assessed the efficacy of armodafinil in treating fatigue in patients with glioma.[5,6] One of these studies reported that participants who had worse baseline fatigue scores experienced statistically significant improvements in fatigue and improvement in their quality of life scores with treatment with armodafinil.[6] This led to this phase 3 randomized double-blinded placebo-controlled clinical trial that was designed to assess the efficacy of armodafinil in patients with high-grade glioma and at least moderate baseline fatigue.

Key Points

Question Does armodafinil reduce fatigue in patients with high-grade glioma?

Findings In this randomized phase 3 double-blinded, placebo-controlled clinical trial of 328 patients with high-grade glioma, patients with moderate to severe fatigue who received 150 mg of armodafinil, 250 mg of armodafinil, or placebo did not experience a statistically significant reduction in fatigue.

Meaning Despite prior smaller heterogenous trials suggesting that there may be a population of patients with glioma who benefit from treatment with armodafinil, no efficacy was seen among patients in this trial.

Methods

Participants/Eligibility and Exclusion Criteria

Enrolled patients were at least age 18 years, had an Eastern Cooperative Oncology Group performance status of 0 to 3, and had a grade 3 to 4 glioma that was clinically stable between 1 to 24 months after completing radiation therapy (Supplement 1). A score of at least 6 of 10 on the severity scale for the worst fatigue on the Brief Fatigue Inventory (BFI) scale was required.[7] Concomitant use of chemotherapy, tumor-treating fields, and stable doses of corticosteroids were allowed. Patients were excluded if they were receiving some other treatment for fatigue or had an uncontrolled seizure disorder. Participants were required to read and respond to questionnaires in English.[8-15] Race and ethnicity categories were collected by questionnaire based on patient self identification. Ethnicity categories included Hispanic vs non Hispanic. The following racial categories were included in the questionnaire: American Indian/Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Black or African American, and multiracial. Approval by an appropriate institutional review board was obtained at each site. Each participant signed an informed consent document in accordance with federal and institutional guidelines.

Trial Design/Treatment

Eligible patients were randomized with equal probability to receive 1 of 2 different dose levels of oral armodafinil (150 mg and 250 mg) or placebo. Randomization was stratified by sex, age group (<60 years; ≥60 years), concomitant therapy (yes; no), and corticosteroid use (yes; no). After randomization, treatment continued for 8 weeks or until unacceptable adverse events or patient refusal to continue participation. The primary objective was to determine the efficacy in treating fatigue between the 2 doses of armodafinil and placebo. Secondary objectives included assessment of tolerability, effect on cognitive function, and quality of life. The study was conducted from June 2013 to December 15, 2019.

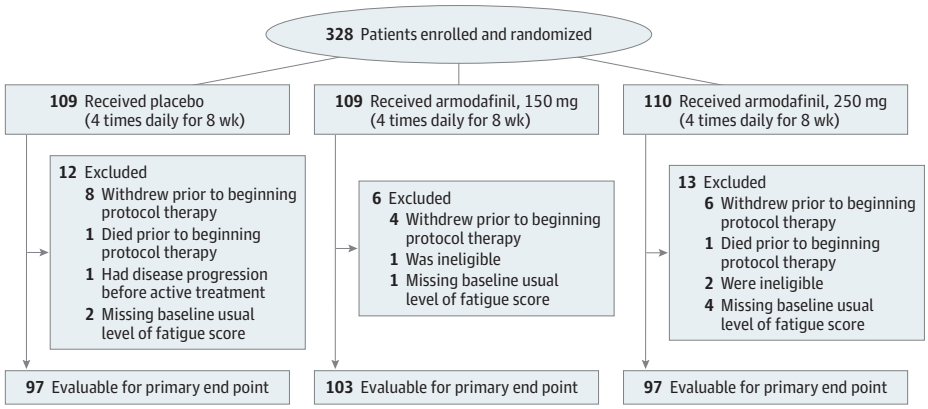
Outcome Measures

The patient self-report measures were collected by paper consistently across sites at baseline and after weeks 4 and 8 of treatment. Fatigue was measured by 2 questionnaires: the BFI and the Patient-Reported Outcomes Measurement Information System fatigue short form.[16] Other patient self-report measures included the Linear Analogue Self-Assessment, Functional Assessment of Cancer Therapy-Cognition, and the Godin Leisure Time Exercise Questionnaire.[17-23] Objective cognition was assessed using the Symbol Digit Modalities Test, the Controlled Oral Word Association test, and the Trail Making test,[20,24] which were administered by trained, certified site study team members who were masked to the assigned protocol treatment.

Statistical Analysis

The primary end point of this study was the proportion of patients who achieved a clinically meaningful improvement (defined as at least a 2-point improvement in the 0-10-point BFI usual fatigue item at 8 weeks after treatment initiation compared with baseline) in patient-reported fatigue. The primary end point was assessed by comparing each armodafinil arm with the placebo arm. This study was designed as a modified intent-to-treat study in which all patients who met the eligibility criteria and signed a consent form, began treatment, reported a baseline usual fatigue score, and had not had a major treatment violation within the first cycle of treatment were evaluable for the primary end point. Evaluable patients who were missing usual fatigue scores at week 8 were treated as not having a clinically meaningful improvement. Comparison of the primary end point between arms was based on a binomial point estimate computed for each arm by a χ^2 test. Based on previous work, 10% of patients in the placebo arm were expected to achieve this clinically meaningful reduction. We expected that 25% of patients in each of the armodafinil arms would achieve this reduction. Based on these assumptions, a sample size of 300 patients (100 per arm) provided 80% power at a 2-sided type 1 error rate of 5% to detect a difference in the reduction rate between each armodafinil arm compared with placebo using the χ^2 test. Planned accrual included an additional 30 patients to account

Figure. CONSORT Diagram



for patient cancellations, ineligibility, or major treatment violations. As a supplemental analysis, a repeated measures analysis using data from baseline and weeks 4 and 8 was applied. The mixed model included the interaction term between the intervention and period and was adjusted by age, sex, concomitant chemotherapy, and corticosteroid use.

Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center. Data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chairperson following the center's policies. *P* values are 2-sided and reported as continuous quantities. All analyses were based on the study database that was frozen on December 11, 2019, and were conducted using SAS, version 9.4 (SAS Institute). Statistical significance was set at $P < .05$.

Results

Patient Accrual and Study Compliance

A total of 328 participants were enrolled and randomized from June 2013 to March 2019 (**Figure**). Baseline patient characteristics were well balanced between the study arms (**Table 1**) with the exception of the BFI usual level of fatigue in the past 24 hours and BFI global fatigue scores (supporting data reported in eTable 1 in Supplement 2).

Treatment per protocol criteria was completed by 195 participants (59.5%) (eTable 2 in Supplement 2). The most common reasons for discontinuation of participation in the trial included withdrawal or refusal to continue treatment after initiation (20 [18%], 19 [17%], and 20 [18%] for the armodafinil, 150 mg, armodafinil, 250 mg, and placebo arms, respectively). Discontinuation because of adverse effects was seen among 14% of participants who were enrolled in the armodafinil, 250 mg, arm compared with 8% in the armodafinil, 150 mg, and 4% in the placebo arms. This difference was statistically significant ($P = .03$).

Fatigue

There was no statistically significant difference for clinically meaningful improvement in the primary end point, BFI usual level of fatigue from baseline to end of week 8, between the 150 mg armodafinil, 250 mg armodafinil, and placebo arms: 28% (95% CI 20%-38%); 28% (95% CI 19%-38%); and 30% (95% CI, 21%-40%), respectively ($P = .94$; **Table 2**). The repeated measures analysis from the linear mixed model for change in BFI global fatigue score from baseline showed no interaction between intervention and time and no intervention effect. The mean change in BFI global fatigue score from baseline had a smaller reduction for corticosteroid users than nonusers (−0.7; 95% CI, −1.5 to −0.3; vs −1.7; 95% CI, −2.1 to −1.3; $P < .001$) and a larger reduction for patients younger than 60 years than those 60 years or older (−1.5; 95% CI, −2.0 to −1.1; vs −0.9; 95% CI, −1.6 to −0.6; $P = .02$) (**Table 3**). Additional analyses using complete cases were conducted and confirmed the original results (Table 2). As a supplemental analysis, multiple imputation was applied for all randomized patients under the assumption that these data were missing at random. Although the magnitude of the intervention effect in both analyses was modestly larger compared with the magnitude of the intervention effect obtained from the complete case analysis sample, the conclusion based on the complete case analyses remained unchanged. Additionally, within each planned subgroup, the results were consistent with the results obtained from the primary analysis.

Quality of Life

There was no statistically significant difference for change in total Linear Analogue Self-Assessment score from baseline to end of week 4 or end of week 8 between arms. There was no statistically significant difference for change in the weekly leisure time activity score from baseline to the end of weeks 4 or 8 between arms. The mean change in the weekly leisure time activity score (Godin Leisure Time Exercise Questionnaire) from baseline had a larger reduction at end of week 4 than end of week 8 (−3.3; 95% CI, −8.0 to 1.4; vs 1.2; 95% CI, −4.4 to 6.8; $P = .04$).

Neurocognitive Function

There were no statistically significant differences between arms for any of the objective measures of cognitive function

Table 1. Baseline Characteristics of Evaluable Patients by Arm

Characteristic	No. (%)			P value
		Armodafinil		
	Placebo (n = 97)	150 mg (n = 103)	250 mg (n = 97)	
Race				
White	92 (94.8)	97 (94.2)	92 (94.8)	>.99[a]
Racial minority group	5 (5.2)	6 (5.8)	5 (5.2)	
Ethnicity				
Hispanic or Latino	6 (6.2)	1 (1.0)	2 (2.1)	.11[a]
Not Hispanic or Latino	91 (93.8)	102 (99.0)	95 (97.9)	
Concomitant chemotherapy				
Yes	80 (82.5)	82 (79.6)	77 (79.4)	.83[b]
No	17 (17.5)	21 (20.4)	20 (20.6)	
Age, y				
<60	48 (49.5)	48 (46.6)	49 (50.5)	.85[b]
≥60	49 (50.5)	55 (53.4)	48 (49.5)	
Corticosteroid use				
Yes	39 (40.2)	42 (40.8)	37 (38.1)	.92[b]
No	58 (59.8)	61 (59.2)	60 (61.9)	
Sex				
Male	58 (59.8)	61 (59.2)	60 (61.9)	.92[b]
Female	39 (40.2)	42 (40.8)	37 (38.1)	
Age, y				
Mean (SD)	57.1 (12.5)	58.5 (11.9)	56.6 (12.5)	.52[c]
Median (range)	60.0 (22.0-81.0)	60.0 (27.0-83.0)	59.0 (20.0-85.0)	
Worst level of fatigue during the past 24 h (BFI) (inclusion criterion ≥6)				
Mean (SD)	7.5 (1.16)	7.7 (1.21)	7.7 (1.19)	.26[c]
Median (range)	7.0 (6.0-10.0)	8.0 (6.0-10.0)	8.0 (6.0-10.0)	
Is this a woman whose age is within reproductive years?				
Yes	5 (5.2)	8 (7.8)	7 (7.2)	.77[a]
No	92 (94.8)	95 (92.2)	90 (92.8)	
ECOG performance status				
0	22 (22.7)	17 (16.5)	23 (23.7)	.30[a]
1	55 (56.7)	58 (56.3)	53 (54.6)	
2	14 (14.4)	22 (21.4)	20 (20.6)	
3	6 (6.2)	6 (5.8)	1 (1.0)	
Status of primary tumor				
Resected with no residual	36 (37.1)	37 (35.9)	32 (33.0)	.45[a]
Resected with known residual	38 (39.2)	44 (42.7)	41 (42.3)	
Unresected	14 (14.4)	6 (5.8)	11 (11.3)	
Recurrent	9 (9.3)	16 (15.5)	13 (13.4)	
Months from end of prior radiotherapy to registration				
No. of participants	92	103	97	.49[c]
Mean (SD)	7.9 (9.33)	8.6 (16.38)	8.3 (10.10)	
Median (range)	5.3 (0.7-64.8)	4.5 (0.5-130.4)	4.8 (0.6-69.7)	
Months from end of prior radiotherapy to registration				
<6	51 (55.4)	55 (53.4)	55 (56.7)	.89[b]
≥6	41 (44.6)	48 (46.6)	42 (43.3)	
Missing	5	0	0	
Prior chemotherapy				
Yes	78 (80.4)	82 (79.6)	80 (82.5)	.87[b]
No	19 (19.6)	21 (20.4)	17 (17.5)	
Months from end of prior chemotherapy to registration				
No.	69	75	72	.78[c]
Mean (SD)	6.7 (12.21)	9.4 (19.49)	6.1 (6.90)	
Median (range)	3.7 (0-89.5)	4.1 (0.3-118.8)	3.1 (0.2-35.8)	

(continued)

Table 1. Baseline Characteristics of Evaluable Patients by Arm (continued)

Characteristic	No. (%)			P value
		Armodafinil		
	Placebo (n = 97)	150 mg (n = 103)	250 mg (n = 97)	
Prior concurrent chemotherapy				.85[b]
Yes	77 (79.4)	79 (76.7)	74 (76.3)	.85[b]
No	20 (20.6)	24 (23.3)	23 (23.7)	

Abbreviations: BFI, Brief Fatigue Inventory; ECOG, Eastern Cooperative Oncology Group.

[a] Fisher exact *P* value.

[b] χ^2 *P* value.

[c] Kruskal-Wallis *P* value.

Table 2. Change in Usual Level of Fatigue (BFI) From Baseline to Week 8 by Arm

Characteristic	Placebo (n = 97)	Armodafinil		Total (n = 297)	P value
		150 mg (n = 103)	250 mg (n = 97)		
Usual level of fatigue during the past 24 h (BFI) (end of week 8)					
No.	69	65	59	193	.30[a]
Mean (SD) [95% CI]	5.2 (2.33) [4.6 to 5.7]	5.0 (2.52) [4.4 to 5.7]	4.5 (2.37) [3.9 to 5.1]	4.9 (2.41) [4.6 to 5.3]	
Median (range)	5.0 (0 to 10.0)	5.0 (0 to 10.0)	5.0 (0 to 9.0)	5.0 (0 to 10.0)	
Change in usual level of fatigue during the past 24 h (BFI) from baseline to end of week 8					
No.	69	65	59	193	.81[a]
Mean (SD) [95% CI]	−1.3 (2.66) [−1.9 to −0.6]	−1.6 (2.73) [−2.2 to −0.9]	−1.4 (2.94) [−2.2 to −0.6]	−1.4 (2.76) [−1.8 to −1.0]	
Median (range)	−1.0 (−8.0 to 4.0)	−1.0 (−9.0 to 5.0)	−1.0 (−8.0 to 7.0)	−1.0 (−9.0 to 7.0)	
Clinically meaningful improvement from baseline to end of week 8, No. (%)					
No	68 (70.1)	74 (71.8)	70 (72.2)	212 (71.4)	.94[b]
Yes	29 (29.9)	29 (28.2)	27 (27.8)	85 (28.6)	
95% CI, %	21.0 to 40.0	19.7 to 37.9	19.2 to 37.9	23.6 to 34.1	
LVCF-imputed usual level of fatigue during past 24 h (BFI) (end of week 8)					
No.	97	103	97	297	.28[a]
Mean (SD) [95% CI]	5.4 (2.22) [4.9 to 5.8]	5.5 (2.52) [5.0 to 6.0]	5.0 (2.47) [4.5 to 5.5]	5.3 (2.41) [5.0 to 5.6]	
Median (range)	6.0 (0 to 10.0)	6.0 (0 to 10.0)	5.0 (0 to 10.0)	5.0 (0 to 10.0)	
Change in LVCF-imputed usual level of fatigue during the past 24 h from baseline to end of week 8					
No.	97	103	97	297	.75[a]
Mean (SD) [95% CI]	−0.9 (2.43) [−1.4 to −0.5]	−1.2 (2.62) [−1.7 to −0.7]	−1.1 (2.65) [−1.6 to −0.5]	−1.1 (2.56) [−1.4 to −0.8]	
Median (range)	0 (−8.0 to 4.0)	−1.0 (−9.0 to 7.0)	0 (−8.0 to 7.0)	0 (−9.0 to 7.0)	
LVCF-imputed clinically meaningful improvement from baseline to end of week 8, No. (%)					
No	64 (66.0)	65 (63.1)	64 (66.0)	193 (65.0)	.89[b]
Yes	33 (34.0)	38 (36.9)	33 (34.0)	104 (35.0)	
95% CI, %	24.7 to 44.3	27.6 to 47.0	24.7 to 44.3	29.6 to 40.7	
Complete case usual level of fatigue during past 24 h (BFI) (end of week 8)					
No.	68	59	56	183	.14[a]
Mean (SD) [95% CI]	5.2 (2.34) [4.6 to 5.7]	4.9 (2.33) [4.3 to 5.5]	4.3 (2.22) [3.7 to 4.8]	4.8 (2.32) [4.5 to 5.1]	
Median (range)	5.0 (0 to 10.0)	5.0 (1.0 to 10.0)	5.0 (0 to 8.0)	5.0 (0 to 10.0)	
Change in complete case usual level of fatigue during the past 24 h from baseline to end of week 8					
No.	68	59	56	183	.77[a]
Mean (SD) [95% CI]	−1.3 (2.67) [−1.9 to −0.6]	−1.6 (2.54) [−2.3 to −0.9]	−1.5 (2.96) [−2.3 to −0.7]	−1.5 (2.71) [−1.8 to −1.1]	
Median (range)	−1.0 (−8.0 to 4.0)	−1.0 (−7.0 to 5.0)	−1.0 (−8.0 to 7.0)	−1.0 (−8.0 to 7.0)	
Complete case clinically meaningful improvement from baseline to end of week 8, No. (%)					
No	41 (58.6)	36 (57.1)	31 (53.4)	108 (56.5)	.84[b]
Yes	29 (41.4)	27 (42.9)	27 (46.6)	83 (43.5)	
95% CI, %	29.8 to 53.8	30.5 to 56.0	33.3 to 60.1	36.3 to 50.8	

Abbreviations: BFI, Brief Fatigue Inventory; LVCF, last value carried forward.

[a] Kruskal-Wallis *P* value.

[b] χ^2 *P* value.

Table 3. Repeated Measures Analysis for Change in Global Fatigue Score (BFI) From Baseline

Effect	*F* value				*P* value	
Type 3 tests of fixed effects						
Cycle	0.01				.92	
Arm	1.42				.24	
Concomitant chemotherapy	0.47				.49	
Age	5.41				.02	
Corticosteroid use	15.47				<.001	
Sex	0.28				.60	
Baseline global fatigue	92.72				<.001	
Least-squares means	**Level**		**Estimate (95% CI)**		**SE**	
Age, y	≥60		−0.8821 (−1.5461 to −0.5632)		0.2128	
	<60		−1.4702 (−2.0445 to −1.0706)		0.2100	
Corticosteroid use	Yes		−0.6522 (−1.4576 to −0.3126)		0.2480	
	No		−1.7001 (−2.1381 to −1.3162)		0.1772	
Differences of least-squares means	**Level**	**Reference**	**Estimate (95% CI)**	**SE**	***t* value**	**Pr>|t|**
Age, y	≥60	<60	0.5881 (−0.0831 to 1.0889)	0.2529	2.33	0.0209
Corticosteroid use	Yes	No	1.0479 (0.2262 to 1.4578)	0.2665	3.93	0.0001

Abbreviation: BFI, Brief Fatigue Inventory.

(Symbol Digit Modalities Test, the Controlled Oral Word Association test, Trail Making Test parts A and B) from baseline to end of weeks 4 or 8 either in terms of mean z score change or number of patients with *neurocognitive deterioration* (defined as at least 1 standard deviation drop in at least 1 test; eTable 4 in Supplement 2). At 4 weeks 36.6% (95% CI, 30.3%-43.2%) of patients met the operational definition of cognitive decline. At 8 weeks, 38.6% (95% CI, 31.5%46.0%) of patients experienced decline. In terms of cognitive decline by arm, at 4 weeks there was significant cognitive decline in 37.7% (95% CI, 26.3%-50.2%) in the 250-mg group, 38.5% (95% CI, 27.7%-50.2%) in the 150-mg group, and 33.8% (95% CI, 23.6%-45.2%) in the placebo group. At 8 weeks, there was decline in 43.1% (95% CI, 30.9%-56.0%) in the placebo group, 34.4% (95% CI, 22.7%-47.7%) in the 150-mg group, and 37.9% (95% CI, 25.5%-51.6%) in the 250-mg group. The percentage of patients showing cognitive decline was not significantly different across arms.

Regarding subjective cognitive function, there was no statistically significant difference for any of the 3 Functional Assessment of Cancer Therapy-Cognition subscales between arms (eTable 2 in Supplement 2). The mean diminishment in the Perceived Cognitive Impairments subscale score from baseline was greater for patients who had not undergone prior concomitant chemotherapy than those who had (8.8; 95% CI, 4.9-12.6; vs 4.5; 95% CI, 2.5-6.5; $P = .048$; eTable 3 in Supplement 2).

Toxic Effects (Common Terminology Criteria for Adverse Events, Version 4.0)

Headache was the most frequently self-reported symptom in the study, occurring in 41% (95% CI, 35%-47%) of all participants ($P = .28$; **Table 4**). There was a slightly increased frequency of headache in the armodafinil, 250 mg, arm (47%; 95% CI, 37%-57%) compared with 40% (95% CI, 31%-50%) in the armodafinil, 150 mg, arm and 35% (95% CI, 26%-46%) in the placebo arm, but this difference was not statistically significant. There was a statistically significant difference in the number of patients who reported experiencing insomnia during the treatment period between arms, in which more patients reported insomnia in the armodafinil, 250 mg, arm than the other 2 arms (eTable 4 in Supplement 2).

Discussion

The results of this phase 3 randomized clinical trial, to our knowledge the largest of its kind designed to determine the effect of armodafinil in this setting, are consistent with prior studies regarding the use of armodafinil in this setting.[5] Unlike the study by Page et al,[6] this study did not detect any trend toward an improved response for those patients with worse baseline fatigue.

Limitations

This study has several limitations. Referral tendencies, as well as self-reported questionnaires, could lead to biased results. Only 60% of the enrolled patients completed the trial, with attrition most commonly related to adverse effects and perceived limited efficacy. Despite this limitation, it is unlikely that the outcome of the trial would have been affected, given the power of the study. Furthermore, patients who did not complete treatment still had their fatigue assessed at 8 weeks. The number of patients using corticosteroids during the trial may have affected the results, considering that steroid dependence is seen as a poor prognostic factor in patients with high-grade glioma.

Conclusions

The phase 3 randomized clinical trial was unable to identify any meaningful benefit of armodafinil at either dose for treating fatigue in patients with high-grade glioma.

Table 4. Patient-Reported Adverse Events by Arm

MedDRA System Organ class (version 12.0)	CTCAE term (version 4.0)	Placebo (n=99)[a]	Armodafinil, 150 mg (n=104)[a]	Armodafinil, 250 mg (n=101)[a]	Total (n=304)[a]	*P* value
Blood and lymphatic system disorders	Anemia	0	1 (1.0)	0	1 (0.3)	>.99
Ear and labyrinth disorders	Vertigo	0	1 (1.0%)	0	1 (0.3)	>.99
Gastrointestinal disorders	Abdominal pain	0	0	2 (2.0)	2 (0.7)	.22
	Diarrhea	1 (1.0)	1 (1.0)	2 (2.0)	4 (1.3)	.85
	Dry mouth	0	0	1 (1.0)	1 (0.3)	.66
	Gastroesophageal reflux disease	0	0	1 (1.0)	1 (0.3)	.66
	Mucositis oral	0	3 (2.9)	1 (1.0)	4 (1.3)	.33
	Nausea	2 (2.0)	5 (4.8)	5 (5.0)	12 (3.9)	.54
	Oral pain	0	0	1 (1.0)	1 (0.3)	.66
	Stomach pain	0	0	1 (1.0)	1 (0.3)	.66
	Vomiting	2 (2.0)	1 (1.0)	2 (2.0)	5 (1.6)	.75
General disorders and administration site conditions	Edema limbs	0	2 (1.9)	1 (1.0)	3 (1.0)	.78
	Fatigue	2 (2.0)	9 (8.7)	9 (8.9)	20 (6.6)	.07
	Gait disturbance	0	1 (1.0)	1 (1.0)	2 (0.7)	>.99
	General disorders and administration site conditions; other, specify	0	1 (1.0)	0	1 (0.3)	>.99
	Pain	2 (2.0)	1 (1.0)	0	3 (1.0)	.43
Infections and infestations	Sepsis	0	0	1 (1.0)	1 (0.3)	.66
	Upper respiratory infection	1 (1.0)	1 (1.0)	2 (2.0)	4 (1.3)	.85
	Urinary tract infection	0	2 (1.9)	0	2 (0.7)	.33
Injury, poisoning, and procedural complications	Fall	1 (1.0)	2 (1.9)	1 (1.0)	4 (1.3)	>.99
	Hip fracture	0	1 (1.0)	0	1 (0.3)	>.99
	Spinal fracture	1 (1.0)	0	0	1 (0.3)	.33
Investigations	Alanine aminotransferase levels increased	1 (1.0)	0	1 (1.0)	2 (0.7)	.55
	Aspartate aminotransferase levels increased	1 (1.0)	0	0	1 (0.3)	.33
	GGT increased	0	0	1 (1.0)	1 (0.3)	.66
	Lymphocyte cell count decreased	1 (1.0)	0	1 (1.0)	2 (0.7)	.55
	Neutrophil cell count decreased	1 (1.0)	1 (1.0)	0	2 (0.7)	.78
	Platelet cell count decreased	2 (2.0)	2 (1.9)	0	4 (1.3)	.47
	White blood cell count decreased	1 (1.0)	3 (2.9)	0	4 (1.3)	.28
Metabolism and nutrition disorders	Anorexia	2 (2.0)	2 (1.9)	2 (2.0)	6 (2.0)	>.99
	Dehydration	1 (1.0)	2 (1.9)	0	3 (1.0)	.66
	Hyperglycemia	2 (2.0)	0	1 (1.0)	3 (1.0)	.21
	Hypoalbuminemia	0	0	1 (1.0)	1 (0.3)	.66
	Hyponatremia	0	0	1 (1.0)	1 (0.3)	.66
	Metabolism and nutrition disorders; other, specify	0	0	1 (1.0)	1 (0.3)	.66
Musculoskeletal and connective tissue disorders	Back pain	0	0	1 (1.0)	1 (0.3)	.66
	Generalized muscle weakness	2 (2.0)	2 (1.9)	6 (5.9)	10 (3.3)	.25
	Muscle weakness lower limb	1 (1.0)	0	0	1 (0.3)	.33
	Musculoskeletal and connective tissue disorders; other, specify	0	0	1 (1.0%)	1 (0.3)	.66
	Myalgia	0	0	1 (1.0)	1 (0.3)	.66
	Neck pain	1 (1.0)	0	0	1 (0.3)	.33
	Pain in extremity	0	0	1 (1.0)	1 (0.3)	.66
Neoplasms benign, malignant, and unspecified	Neoplasms benign, malignant and unspecified; other, specify	1 (1.0)	0	0	1 (0.3%)	.33

(continued)

Table 4. Patient-Reported Adverse Events by Arm (continued)

MedDRA System Organ class (version 12.0)	CTCAE term (version 4.0)	Placebo (n=99)[a]	Armodafinil, 150 mg (n=104)[a]	Armodafinil, 250 mg (n=101)[a]	Total (n=304)[a]	*P* value
Nervous system disorders	Amnesia	1 (1.0)	0	0	1 (0.3)	.33
	Aphonia	0	0	1 (1.0)	1 (0.3)	.66
	Ataxia	0	1 (1.0)	1 (1.0)	2 (0.7)	>.99
	Dizziness	1 (1.0)	3 (2.9)	5 (5.0)	9 (3.0)	.25
	Dysarthria	0	0	2 (2.0)	2 (0.7)	.22
	Dysgeusia	0	0	1 (1.0)	1 (0.3)	.66
	Dysphasia	0	0	2 (2.0)	2 (0.7)	.22
	Edema cerebral	0	2 (1.9)	0	2 (0.7)	.33
	Headache	35 (35.4)	42 (40.4%)	47 (46.5)	124 (40.8)	.28
	Hydrocephalus	1 (1.0%)	0	0	1 (0.3)	.33
	Hypersomnia	0	1 (1.0%)	1 (1.0)	2 (0.7)	>.99
	Lethargy	0	0	2 (2.0)	2 (0.7)	.22
	Memory impairment	0	1 (1.0%)	0	1 (0.3)	>.99
	Movements involuntary	0	1 (1.0)	0	1 (0.3)	>.99
	Muscle weakness left sided	0	1 (1.0)	0	1 (0.3)	>.99
	Muscle weakness right sided	1 (1.0)	0	0	1 (0.3)	.33
	Paresthesia	1 (1.0)	0	0	1 (0.3)	.33
	Seizure	2 (2.0)	2 (1.9)	1 (1.0)	5 (1.6)	.87
	Syncope	1 (1.0)	0	0	1 (0.3)	.33
	Tremor	1 (1.0)	0	1 (1.0)	2 (0.7)	.55
Psychiatric disorders	Anxiety	1 (1.0)	0	1 (1.0%)	2 (0.7)	.55
	Confusion	0	1 (1.0)	3 (3.0)	4 (1.3)	.22
	Depression	1 (1.0)	0	2 (2.0)	3 (1.0)	.32
	Insomnia	0	2 (1.9)	7 (6.9)	9 (3.0)	.01
	Personality change	0	0	1 (1.0)	1 (0.3)	.66
	Restlessness	0	0	1 (1.0)	1 (0.3)	.66
Respiratory, thoracic, and mediastinal disorders	Dyspnea	0	0	2 (2.0)	2 (0.7)	.22
	Pneumonitis	0	1 (1.0)	0	1 (0.3)	>.99
	Productive cough	1 (1.0)	0	0	1 (0.3)	.33
	Voice alteration	0	0	1 (1.0)	1 (0.3)	.66
Skin and subcutaneous tissue disorders	Dry skin	0	0	1 (1.0)	1 (0.3)	.66
	Pruritus	0	1 (1.0)	1 (1.0)	2 (0.7)	>.99
	Skin and subcutaneous tissue disorders; other, specify	0	0	1 (1.0)	1 (0.3)	.66
Vascular disorders	Hypertension	0	1 (1.0)	3 (3.0)	4 (1.3)	.22
	Hypotension	1 (1.0)	0	0	1 (0.3)	.33
	Superficial thrombophlebitis	1 (1.0)	0	0	1 (0.3)	.33
	Thromboembolic event	2 (2.0)	0	2 (2.0)	4 (1.3)	.40

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; GGT, gamma-glutamyl transferase.

[a] No. (%).

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