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A Randomized Trial of Modafinil for the Treatment of Fatigue and Excessive Daytime Sleepiness in Individuals with Chronic Traumatic Brain Injury

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Background: This study examines the efficacy of modafinil in treating fatigue and excessive daytime sleepiness in individuals with traumatic brain injury (TBI). **Methods:** A single-center, double-blind, placebo-controlled cross-over trial, where 53 participants with TBI were randomly assigned to receive up to 400 mg of modafinil, or equal number of inactive placebo tablets. Main eligibility criteria were being at least 1 year post-TBI severe enough to require inpatient rehabilitation. The primary outcome measures were fatigue (Fatigue Severity Scale, FSS) and daytime sleepiness (Epworth Sleepiness Scale, ESS). **Results:** After adjusting for baseline scores and period effects, there were no statistically significant differences between improvements seen with modafinil and placebo in the FSS at week 4 (-0.5 ± 1.88; $P = .80$) or week 10 (-1.4 ± 2.75; $P = .61$). For ESS, average changes were significantly greater with modafinil than placebo at week 4 (-1.2 ± 0.49; $P = .02$) but not at week 10 (-0.5 ± 0.87; $P = .56$). Modafinil was safe and well tolerated, although insomnia was reported significantly more often with modafinil than placebo ($P = .03$). **Conclusions:** While there were sporadic statistically significant differences identified, a clear beneficial pattern from modafinil was not seen at either week 4 or week 10 for any of the 12 outcomes. There was no consistent and persistent clinically significant difference between treatment with modafinil and placebo. **Key words:** *brain injury*, *fatigue*, *modafinil*, *randomized clinical trial*

IN the United States today, an estimated 5.3 million Americans are living with a traumatic brain injury (TBI)-related disability.[1] While these individuals may face many issues, including impaired mobility and cognition, ongoing health problems, decreased productivity, behavioral changes, difficulty with personal care, and reduced quality of life, depending on the injury type and severity, fatigue is common to a strikingly large number of those who survive TBI.

In a general population study, fatigue had a current prevalence of 6% to 7% and a lifetime prevalence of 24%.[2] Fatigue is experienced by individuals with a wide range of conditions, including cancer, multiple sclerosis, Parkinson's disease, fibromyalgia, depression, and hysterectomy.[3] In a population-based study of individuals hospitalized for TBI in Colorado, at 1 year post injury, 41% reported getting tired more easily than before their injury[4]; however, the proportion of individuals reporting fatigue varies considerably across studies and is often reported in conjunction with other symptoms, with reported prevalence ranging from 37% to 98%.[5–9] Other studies have documented higher levels of fatigue in individuals with TBI compared to normal controls[10] and that individuals with TBI reported a significantly greater impact of fatigue on their lifestyle, and reported activities requiring physical and mental effort as more frequent causes of fatigue.[11]

Despite the clearly ubiquitous presence of fatigue after TBI, the precise definition and measurement of fatigue remains enigmatic. Fatigue has been described as "an overwhelming sense of exhaustion and decreased capacity for physical and mental work regardless of adequate sleep."[12] It has been construed both as a single discrete experience and as a multicausal phenomenon that exists

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along a continuum of severity.[13] Moreover, there appears to be 2 types or dimensions of fatigue. For example, fatigue has been described as a condition characterized by a subjective feeling of decreased energy with both physical and psychological aspects.[14] *Physical* fatigue has been defined as the end result of excessive energy consumption, depleted hormones or neurotransmitters, or diminished ability of muscle cells to contract. *Psychological* or mental fatigue, on the other hand, is defined as a subjective state of weariness related to reduced motivation, prolonged mental activity, or boredom. In TBI, the "coping hypothesis"[7,15] proposes that psychological fatigue could be related to the mental effort necessary to overcome attention deficit and slowed processing, or that individuals with TBI expend greater psychophysiological costs to maintain stable performance over time, and that these costs are also associated with subjective increases in fatigue.[15] Despite the difficulties in definition, etiology, and measurement, it is also clear that excessive fatigue can lead to or be accompanied by mood disturbances, decreased energy, severe limitations in the ability to function, and negatively affect self-care, social activities, and quality of life.[16]

Reports of interventions for fatigue in individuals with TBI are few. Several TBI studies have shown that physical conditioning programs reduce physical fatigue.[6,17–19] Amantadine has been used to treat fatigue associated with multiple sclerosis, and has been used in single case studies of fatigue in TBI; however, no objective research evidence exists.[20]

Modafinil is a wakefulness-promoting agent, initially approved and indicated by the Food and Drug Administration (FDA) for patients with excessive daytime sleepiness (EDS) associated with narcolepsy,[21,22] with subsequent expansion to EDS in other conditions (eg, obstructive sleep apnea–hypopnea syndrome,[23,24] and shift work sleep disorder).[25] In addition, modafinil has been found to improve health-related quality of life in individuals with narcolepsy.[26] Reported by up to 31% of the adult population, consequences of EDS can include accidents, negative economic and public health outcomes, reduced work and school performance, and impaired psychological functioning.[27] While less studied than fatigue, individuals with TBI also experience an array of sleep disturbances including EDS. The prevalence of sleep disturbances of any kind (eg, insomnia, sleep apnea, periodic limb movement disorder) has ranged from 29% to 80%,[28–33] with one study finding that 80% of those also reported problems with fatigue.[34] One study looked at EDS specifically in 71 brain-injured individuals in a residential/day rehabilitation program, with excessive daytime sleepiness reported in 65% of subjects; among these, 11% had sleep apnea–hypopnea, 25% had periodic limb movement disorder, and 1 subject had narcolepsy.[35] With respect to treatment of EDS after TBI, one study suggested that daytime sleepiness was reduced by methylphenidate but not sertraline.[36]

Because EDS is associated with a number of other symptoms and conditions, modafinil has also been studied in a variety of other settings. The modafinil literature is replete with studies looking at a variety of outcomes, from symptoms of fatigue or sleepiness to neuropsychological test performance, in a variety of conditions including neurological conditions, breathing disorders, and psychiatric diagnoses.[37] To date, there has not been any controlled evaluation of modafinil use for the treatment of individuals with TBI. There have been some open-label, uncontrolled studies suggesting that modafinil may result in subjectively improved daytime function and quality of life.[38,39]

The purpose of this study was to determine the efficacy of modafinil in treating fatigue and EDS in individuals with TBI. The primary aim was to test the hypothesis that modafinil is more efficacious than placebo in treating fatigue and excessive daytime sleepiness in individuals with TBI. Additional analyses explored if modafinil would improve cognitive function and health-related quality of life in individuals with TBI.

METHODS

Study design

A single-center, randomized, blinded, placebo-controlled, crossover study design was used. Baseline testing consisted of all study measures in addition to a general physical examination performed by the research physiatrist. Participants' medical records were abstracted to collect demographic and injury-related information. This study was approved by the institutional review board of record for the study center.

Participants and recruitment

Recruitment for this study began in November 2002 when the first recruitment letter was mailed out, and continued through September 2004 when the final participant enrolled in the study. During this time period recruitment letters were mailed out 2 additional times (May 2003 and February 2004) to target individuals who were newly eligible because they met the criteria of being 1 year post-injury. Per study protocol, each participant was followed for at least 24 weeks (28 weeks if they opted for the open label portion of the study). The last follow-up evaluation was completed on the final participant in March 2005.

Individuals between the ages of 18 and 65 (inclusive) who had received inpatient rehabilitation for TBI (defined as injury to brain tissue caused by an external mechanical force as evidenced by loss of consciousness, posttraumatic amnesia, or objective neurologic findings

that can be reasonably attributed to TBI on physical or mental status examination)[40] at a single model system of care were identified from a hospital database. Approximately 1300 of those who were at least 1 year post injury were sent a recruitment letter describing the study and asking for those experiencing disabling symptoms of fatigue and/or excessive daytime sleepiness, which compromised their ability to function optimally, to consider participation in this study. Individuals who responded were then screened and excluded for the following: (1) presence of neurologic or neuropsychiatric diagnoses that would obscure the evaluation of the medication's effectiveness (eg, aphasia, brainstem dysfunction, a preinjury diagnosis of attention deficit hyperactivity disorder, Alzheimer's disease, stroke, other dementing illnesses, psychiatric disorder, or substance abuse or dependence); (2) a diagnosis by history of other likely causes of EDS (eg, narcolepsy or obstructive sleep apnea); (3) concurrent medication use and/or clinically significant systemic disease (eg, multiple sclerosis, fibromyalgia, bipolar disorder, chronically symptomatic respiratory disorders, congestive heart failure) that might cause fatigue and/or diminished arousal; (4) epilepsy (isolated seizures in the acute postinjury treatment period were not an exclusion); (5) cardiovascular disease or risks including hypertension requiring medical treatment; (6) history of severe renal or hepatic impairment; (7) significant psychiatric or behavioral disturbance that would obscure the evaluation of medication effectiveness; (8) non-English speaking (to the extent that would limit the ability to complete study measures); (9) pregnant females or females of childbearing potential unless acceptable double barrier contraceptives were in use.

One hundred fifty-six individuals responded to this recruitment letter and were screened for eligibility. Of these, 57 were excluded on the basis of study criteria and 48 chose not to pursue participation in the study. The remaining 51 individuals met study criteria, signed an informed consent form, and were enrolled in the clinical trial.

Intervention

The manufacturer (Cephalon, Inc, Frazer, PA) provided the study drug modafinil in 100-mg tablets, and matching placebo tablets. All instructions to patients referenced the number of tablets to be taken, without reference to dose or content. Subjects randomized to the DRUG FIRST protocol began taking 1 tablet (100 mg) of modafinil once a day at noon for 3 days, then increased to 1 tablet (100 mg) twice a day (200-mg total daily dose) for the next 11 days, followed by the maintenance dose for the trial of 2 tablets (200 mg total) twice a day in the morning and at noontime (400 mg total daily dose). This dosage was maintained for 8 weeks and was followed by a 4-week washout period in which the patient received neither modafinil nor placebo. Following the washout period, individuals in the DRUG FIRST group crossed over to begin taking placebo on the same time schedule as for the first 10 weeks of the trial.

Subjects randomized to the PLACEBO FIRST protocol were maintained in the same protocol timing of receiving placebo tablets, followed by washout and drug protocol. In the event that participants were unable to tolerate the 4-tablet (400 mg/d) dose, their dose was decreased back to 2 tablets (200 mg/d) and they remained in the trial. This could be done without breaking the study blinding by instructing the participant to only take 1 pill twice a day, without knowing the content of the tablets. Following the end of the randomized study protocol, both groups were offered a 4-week open label period where all participants could receive modafinil using individual clinically monitored titration and maintenance dosage.

Outcomes

Primary outcome measures

There were 3 primary outcomes measures used in the study, 2 for fatigue, and 1 for daytime sleepiness. The 2 measures of fatigue included the *Fatigue Severity Scale* (FSS)[41] and the *Modified Fatigue Impact Scale* (MFIS).[42] Daytime sleepiness was measured by the *Epworth Sleepiness Scale* (ESS).[43]

The FSS is a popular one-dimensional fatigue/function measure that has been used in studies of individuals with chronic fatigue syndrome (CFS)[44] and has been found to be an accurate and comprehensive measure of fatigue-related severity, symptomatology, and functional disability for individuals with CFS-like symptomatology.[13] The FSS has been used in a population of individuals with TBI[45] and has also been used in trials of modafinil.[46] The FSS is composed of 9 Likert-type items, each ranging from 1 (*no impairment*) to 7 (*severe impairment*), yielding scores from 9 to 63, with higher scores indicating more severe fatigue.

The MFIS is a short, multidimensional subjective fatigue measure that has been found to be valid and reliable[42] and has been used successfully in individuals with TBI.[45] It is a 21-item self-report instrument in which subjects are asked to rate the extent to which fatigue has caused problems for them (0 = no problem, to 4 = extreme problem), yielding scores from 0 to 84, with higher scores indicating a greater impact of fatigue. Subscales for cognitive, physical, and psychosocial functioning can also be calculated.

The ESS is a simple and reliable self-administered 8-item questionnaire, which is shown to provide a measurement of the subject's general level of daytime sleepiness.[43,47,48] This measure has been tested in a

variety of applications, including individuals with TBI.[35] Each of the 8 items rates a routine daytime situation on a 4-point scale from 0 = would never doze to 3 = high chance of dozing. Subjects who score 10 or more are considered to have excessive daytime sleepiness.

The *FSS* and *ESS* were collected weekly, and the *MFIS* was collected at 8 time points during the study period. Study participants completed these measures during a phone interview with the study coordinator. During these interviews, the study coordinator also asked participants about any adverse reactions or side effects they might be experiencing.

Secondary outcome measures

Health-related quality of life was measured using the physical summary score and mental summary score from the Medical Outcome Study 12-Item Short Form Survey (SF-12).[49] The 12 items are a subset of items in the SF-36 and include 1 or 2 items from each of the 8 health concepts commonly represented in widely used surveys: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality (energy/fatigue), social functioning, role limitations due to emotional problems, and mental health.[49] This measure has been validated in a TBI population[50] and has been used in modafinil trials.[26] The SF-12 (along with all secondary outcomes) was administered at 5 time points during the study period, at baseline, week 4, week 10, and weeks 4 and 10 after crossover. A baseline measurement was not repeated after the washout phase.

The cognitive functions of interest in this study were reaction time, attention, memory, and vigilance. Reaction time, visual motor speed, and memory were measured using the Immediate Post Concussion Assessment Cognitive Testing (ImPACT), a computerized cognitive test battery with 6 alternate forms that is designed for repeated administration.[51–60] The test battery contains 6 cognitive testing modules: (1) Word Memory; (2) Design Memory; (3) X's and O's; (4) Symbol Matching; (5) Color Match; and (6) Three Letters. Performance on these individual modules are combined to yield the 4 composite scores, Verbal Memory, Visual Memory, Visual Motor Speed, and Reaction Time, used in this study.

The cognitive function of vigilance was measured using the Conners' Continuous Performance Test II (CPT II) computer program,[61] a computerized assessment tool that measures sustained visual attention and was developed for use in individuals with attention deficit hyperactivity disorder. The CPT II can be used repeatedly to monitor changes in sustained attention over time.[62] All measures of cognitive function were administered at 5 time points during the study period.

The Beck Depression Inventory II (BDI II)[63] was administered to assess for the presence of depression, which has been found to be associated with both fatigue and excessive daytime sleepiness.[14,64] This measure has been found to be valid and reliable,[63] has had its psychometric properties tested with individuals with TBI, and been found to be an effective tool for self-reported depression in TBI.[65,66] The BDI II may be used repeatedly to monitor changes in depressive symptoms over time. It consists of 21 four-choice questions, with scores ranging from 0 to 3, where higher scores indicate more depressive symptomatology. This measure was administered at 5 time points during the study.

Participants completed these secondary study measures in-person at the hospital with the study coordinator. Pill containers were also checked by the pharmacy at the time of the in-person visits to monitor medication compliance.

Randomization and blinding

A computer-generated randomization sequence was created for the total expected enrollment for the study, without blocking or stratification, and was provided to the pharmacy as a list. Once patients provided informed consent, the study coordinator alerted the hospital pharmacy to randomize the participant by assigning them the next group assignment (drug or placebo first) according to the randomization sequence. The pharmacy was responsible for maintaining the study blinding. Investigators, study coordinator, data collectors and analysts, as well as the study participants were blinded to which protocol (drug or placebo) subjects received first. The success of blinding was evaluated by asking participants at the end of each phase which pill they felt they were receiving.

Statistical methods

The target sample size for the study was 44 patients, which was selected so that a paired *t*-test would have approximately 90% power to detect a half-standard deviation difference between treatment conditions. Approximately 50 patients were enrolled in order to allow for some incomplete data. There were no interim analyses or plans for early termination of the trial. All study data were entered into a Microsoft Access 2002 database, and were analyzed in SPSS Version 13 and SAS Version 9.1.

Baseline differences in demographic and clinical attributes across the 2-groups were compared using independent samples *t* tests for continuous variables and χ^2 tests for categorical variables. Crude treatment effects were analyzed using a paired *t* test of the difference between modafinil and placebo in the 4-week change in outcome (and separately for the difference in 10-week

change). In addition, treatment effects within each treatment period were analyzed separately using 2-sample *t* tests.

The primary analysis was specified a priori as the difference between treatment groups in the 4-week change in the outcome measures after adjusting for the baseline value of the outcome and period effects. The primary analysis was conducted in a linear mixed-effects regression analysis of the 4-week change in each of the 2 periods for each subject with treatment group, period, and baseline score as explanatory variables and a random subject effect. The potential for carryover effects was assessed by adding a period-by-treatment interaction term to this regression model. Secondary analyses evaluated treatment effects on secondary endpoints and at 10 weeks. Preliminary descriptive plots were used to determine if transformations were necessary (they were not), and the robustness of the conclusions to potentially influential data points was evaluated by sequentially deleting subjects and evaluating whether there were substantial changes to the estimated treatment effects or to their statistical significance.

RESULTS

Participant flow and number analyzed

Fifty-one subjects were randomized to receive either modafinil first ($n = 27$) or placebo first ($n = 24$). Forty-six individuals completed the entire study and were included in the per-protocol analysis (Fig 1). However, the number of participants included in each analysis varied because of incomplete data.

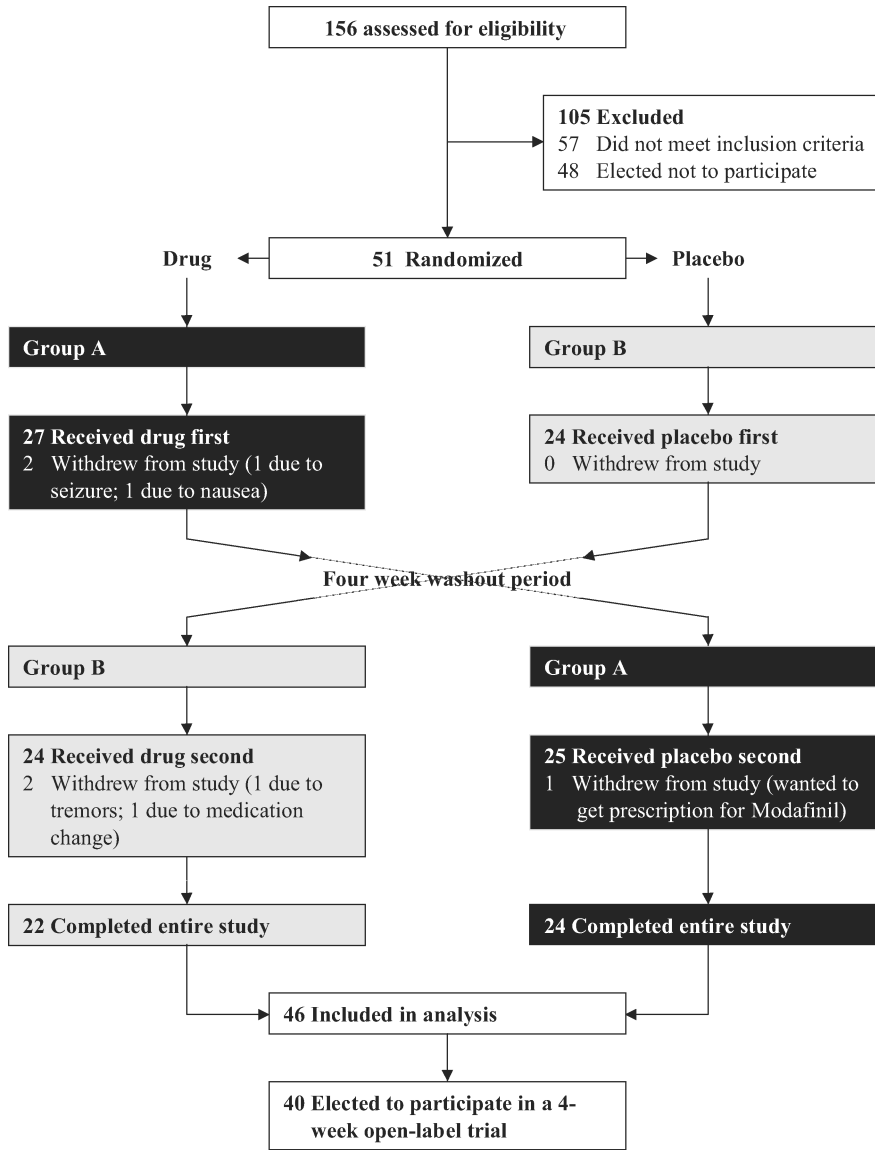

Figure 1. Participant flow.

Baseline data

Demographic and clinical characteristics for study participants are shown in Table 1. Average age for all participants was 38.25 years (SD = 12.20). Thirty-five participants were male (68.6%), and 16 were female (31.4%). At the time of enrollment, average time post injury was 5.77 years (SD = 4.97). Initial Glasgow Coma Scale (GCS) scores were in the severe range (GCS 3–8) for 26 participants (51%), in the moderate range (GCS 9–12) for 12 participants (23.5%), and in the mild range (GCS 13–15) for 13 participants (25.5%). Demographic and clinical characteristics for the 27 participants who were allocated to Group A (modafinil first), and the 24 participants who were allocated to Group B (placebo first) are likewise shown in Table 1. Although the groups show significant differences in their Rancho Level class, overall the groups did not show any important imbalances that have the potential to affect trial results. Baseline scores on the various outcome measures are reported in Table 2. While BDI–II scores suggest elevated levels of depressive symptoms, they were not substantially different between the 2 groups.

TABLE 1 *Baseline characteristics*

	Total ($N = 51$)	Group A ($n = 27$)	Group B ($n = 24$)	P
Age				.279*
Mean	38.25	36.49	40.23	
Standard deviation	12.20	11.59	12.80	
Years postinjury				.810*
Mean	5.77	5.61	5.95	
Standard deviation	4.97	4.76	5.29	
Sex				.776
Male	68.6%	70.4%	66.7%	
Female	31.4%	29.6%	33.3%	
Initial GCS score				.197†
Mild (13–15)	25.5%	33.3%	16.7%	
Moderate (9–12)	23.5%	14.8%	33.3%	
Severe (3–8)	51.0%	51.9%	50.0%	
Rancho level (DC)				.047†
V	5.9%	0.0%	12.5%	
VI	17.6%	25.9%	8.3%	
VII	58.8%	63.0%	54.2%	
VIII	9.8%	3.7%	16.7%	
Missing	7.8%	7.4%	8.3%	
Cause of injury				.413†
Vehicular	72.5%	66.7%	79.2%	
Fall	17.6%	18.5%	16.7%	
Other	9.8%	14.8%	4.2%	
Marital status				.597†
Single	49.0%	55.6%	41.7%	
Married	37.3%	33.3%	41.7%	
Separated/ divorced	13.8%	11.1%	16.7%	
Employment status				.648†
Student	7.9%	11.1%	4.2%	
Employed	49.0%	44.4%	54.2%	
Homemaker	3.9%	3.7%	4.2%	
Special employment	3.9%	7.4%	0.0%	
Retired	23.5%	18.5%	29.2%	
Unemployed	11.8%	14.8%	8.3%	
Caregiver				.835†
No	80.4%	81.5%	79.2%	
Yes	19.6%	18.5%	20.8%	
Race				.155†
White	84.3%	85.2%	83.3%	
Hispanic origin	9.8%	14.8%	4.2%	
Black	3.9%	0.0%	8.3%	
Native American	2.0%	0.0%	4.2%	

*Independent samples t test.
† χ^2 Test.

Primary and secondary outcomes

Table 2 shows mean scores in period 1 for those taking modafinil and placebo at baseline, week 4, and week 10, as well as the average unadjusted difference between the modafinil group and the placebo group at weeks 4 and 10. There was a substantial placebo effect with improvements in a variety of outcomes between baseline and 4 weeks when taking either pill. For example, when compared to baseline, mean 4th-week FSS scores improved by 5.8 points when taking modafinil and 6.7 points when taking placebo. However, when comparing changes on modafinil versus placebo at weeks 4 and 10 in period 1, there were no statistically significant differences in any of the primary outcome measures. There was one statistically significant finding in period 1, with the change from baseline in the ImPACT Visual Motor Speed Composite score at week 4 being 3.4 points larger in the placebo group than the modafinil group (P = .04). This was entirely due to an increase between baseline (21.4 points) and week 4 (25.2 points) in the placebo group, while the modafinil group showed essentially no change (23.9–23.5). At week 10, during period 1, there were no statistically significant differences between the modafinil and placebo groups.

Table 3 shows mean raw scores and difference in changes during period 2, after the crossover. The group taking modafinil second had a 10.9 point larger reduction in the MFI than the placebo group at week 4 (P = .03), although the MFI difference was reduced to 8.1 points at week 10 and was no longer significant (P = .14). The only other statistically significant finding was in the ImPACT Verbal Memory Composite scores, which decreased while on modafinil from 80.3 points at baseline to 77.4 at week 10, and increased in the placebo group from 78.1 at baseline to 87.1 at week 10. The difference between the changes in the 2 groups was statistically significant at weeks 4 and 10 in period 2. However, these

TABLE 2 *Mean raw scores and differences in period 1*

Period 1 Outcome	Modafinil			Placebo			Difference Modafinil – Placebo			
							Change W4 – BL		Change W10 – BL	
	Baseline est (SD)	Week 4 est (SD)	Week 10 est (SD)	Baseline est (SD)	Week 4 est (SD)	Week 10 est (SD)	est (SD)	$P^* > \|t\|$	est (SD)	$P^* > \|t\|$
Fatigue severity (high = fatigued)	45.22 (11.82)	39.36 (15.61)	37.13 (18.33)	44.46 (12.17)	37.70 (12.55)	36.91 (14.08)	2.33 (12.96)	.5370	0.44 (15.31)	.9226
Epworth sleepiness (high = sleepy)	9.63 (5.34)	6.65 (4.71)	6.96 (6.23)	9.92 (4.71)	7.83 (4.44)	6.92 (4.85)	−0.61 (4.28)	.6232	0.56 (5.59)	.7274
Modified fatigue impact (high = fatigued)	46.56 (19.28)	38.65 (16.09)	35.63 (20.00)	47.17 (15.53)	36.45 (15.03)	33.55 (18.16)	5.68 (14.79)	.2097	4.03 (16.93)	.4289
SF-12 physical (high = more QOL)	44.61 (10.38)	46.96 (12.09)	46.92 (11.00)	45.24 (9.94)	48.40 (10.02)	47.24 (10.91)	−2.18 (7.56)	.3287	−0.54 (8.90)	.8359
SF-12 mental (high = more QOL)	36.84 (7.42)	39.05 (7.32)	40.13 (7.18)	36.91 (8.59)	36.95 (7.20)	39.15 (5.94)	1.95 (8.95)	.4594	0.41 (8.48)	.8682
Beck depression II (high = depression)	18.15 (7.81)	14.50 (8.83)	13.54 (8.70)	18.78 (7.97)	14.18 (10.11)	13.09 (10.49)	1.63 (9.03)	.5404	−0.52 (8.30)	.8358
ImPACT verbal memory composite	78.07 (11.96)	79.88 (14.12)	83.40 (12.51)	80.26 (12.95)	80.95 (15.05)	80.22 (18.19)	1.42 (10.66)	.6505	4.11 (10.05)	.1687
ImPACT visual memory composite	61.70 (17.78)	61.08 (14.22)	61.52 (16.24)	62.09 (16.44)	63.91 (13.45)	63.87 (19.99)	0.25 (12.38)	.9458	−1.61 (13.27)	.6796
ImPACT visual motor speed composite	23.92 (5.52)	23.49 (5.36)	24.90 (6.87)	21.44 (8.93)	25.22 (7.19)	24.09 (8.31)	−3.44 (5.43)	.0354	−1.43 (5.62)	.3882
ImPACT reaction time composite	0.82 (0.20)	0.79 (0.24)	0.76 (0.20)	0.80 (0.19)	0.74 (0.18)	0.80 (0.27)	0.01 (0.11)	.6668	−0.03 (0.10)	.3031
CCPT-II No. of omissions	4.74 (8.52)	5.96 (12.76)	5.08 (12.34)	9.54 (31.24)	5.74 (17.73)	4.88 (16.44)	5.21 (11.47)	.1189	5.15 (11.60)	.1274
CCPT-II No. of commissions	13.59 (7.34)	12.04 (7.87)	10.64 (5.96)	16.83 (6.76)	13.30 (6.84)	11.67 (7.12)	1.65 (5.10)	.2633	2.33 (4.67)	.0878

* *P* values from a 2-sample *t* test.

TABLE 3 *Mean raw scores and differences in period 2*

Period 2 Outcome	Modafinil			Placebo			Difference Modafinil – Placebo			
							Change W4 – BL		Change W10 – BL	
	Baseline est (SD)	Week 4 est (SD)	Week 10 est (SD)	Baseline est (SD)	Week 4 est (SD)	Week 10 est (SD)	est (SD)	$P^* > \|t\|$	est (SD)	$P^* > \|t\|$
Fatigue Severity (high = fatigued)	38.17 (15.23)	31.38 (10.66)	28.90 (14.03)	35.92 (16.82)	33.74 (16.16)	30.95 (16.25)	−2.55 (11.07)	.4499	−3.70 (14.60)	.4279
Epworth Sleepiness (high = sleepy)	8.00 (4.74)	6.42 (3.69)	6.23 (4.19)	6.73 (4.88)	7.23 (4.22)	6.22 (4.59)	−2.08 (3.83)	.0603	−1.59 (3.95)	.1827
Modified Fatigue Impact (high = fatigued)	39.73 (20.82)	28.91 (19.06)	28.27 (16.06)	36.27 (17.67)	37.74 (17.51)	31.20 (19.44)	−10.9 (15.93)	.0323	−8.07 (16.61)	.1434
SF-12 Physical (high = more QOL)	45.24 (9.94)	48.41 (10.82)	50.05 (8.81)	44.61 (10.38)	49.18 (11.08)	51.10 (7.42)	−0.55 (9.70)	.8439	−1.65 (9.74)	.5872
SF-12 Mental (high = more QOL)	36.91 (8.59)	40.13 (5.40)	39.24 (5.62)	36.84 (7.42)	37.30 (7.55)	38.65 (7.47)	3.41 (9.09)	.2008	1.09 (8.15)	.6670
Beck Depression II (high = depression)	18.78 (7.97)	12.13 (8.52)	10.52 (7.77)	18.15 (7.81)	12.96 (8.29)	11.68 (8.13)	−1.18 (8.53)	.6384	−1.66 (7.38)	.4764
ImPACT Verbal Memory Composite	80.26 (12.95)	76.58 (18.18)	77.41 (16.52)	78.07 (11.96)	85.36 (11.84)	87.09 (12.01)	−9.29 (11.09)	.0057	−8.83 (9.43)	.0038
ImPACT Visual Memory Composite	62.09 (16.44)	58.08 (20.08)	58.18 (18.53)	61.70 (17.78)	61.80 (15.83)	65.36 (16.26)	−3.44 (13.34)	.3769	−2.18 (12.14)	.5602
ImPACT Visual Motor Speed Composite	21.44 (8.93)	24.28 (8.54)	25.76 (9.52)	23.92 (5.52)	25.48 (7.16)	26.24 (6.53)	1.97 (5.56)	.2256	2.71 (5.68)	.1256
ImPACT Reaction Time Composite	0.80 (0.19)	0.81 (0.36)	0.81 (0.30)	0.82 (0.20)	0.79 (0.24)	0.77 (0.21)	−0.03 (0.11)	.4007	0.01 (0.08)	.7407
CCPT-II No. of Omissions	9.54 (31.24)	8.08 (17.67)	7.71 (18.91)	4.74 (8.52)	5.64 (16.72)	11.76 (31.41)	−2.50 (12.97)	.5034	−10.3 (27.05)	.2230
CCPT-II No. of Commissions	16.83 (6.76)	12.50 (6.48)	12.43 (7.62)	13.59 (7.34)	10.64 (5.27)	8.67 (5.95)	−1.49 (5.30)	.3293	0.52 (6.66)	.8000

* *P* values from a 2-sample *t* test.

analyses assumed that all participants returned to their original baseline scores at period 1 for all of the neuropsychological tests.

Table 4 shows the results of the mixed-effects regression analyses. Participants averaged a 1.2 point greater decrease in the ESS when on modafinil versus placebo, after controlling for their baseline scores and whether they took the modafinil first or second ($P = .02$). However, this difference had decreased to 0.5 points at week 10 and was no longer statistically significant ($P = .56$). Statistically significant findings on the ImPACT Verbal Memory Composite ($P = .03$) and CCPT-II Omissions ($P = .03$) were seen at week 4, but not at week 10, where CCPT-II Commissions was significant ($P = .05$).

The sensitivity analyses showed that results were not influenced by extreme values or missing data. There was no evidence of significant carryover effects as measured by the magnitude of the period-by-treatment interaction. Since subjects had elevated baseline depression scores (BCI-II) we also adjusted the primary results for baseline depression score, and (separately) checked for interaction between treatment effects on fatigue and baseline BDI-II score. Neither analysis showed any significant associations nor required alteration of our conclusions.

Adverse events

Owing to the cross-over study design, all participants were given both modafinil and placebo during the course of the study. Thus, adverse events data were available for all 51 participants under each treatment modality (Table 5). With the modafinil treatment, 5% or more of the 51 participants reported a total of 6 adverse events. Headaches were the most commonly reported adverse event, with 15 (29.4%) participants reporting a total of 51 headaches. Insomnia was reported by 10 (19.6%) participants, who experienced a total of 13 occurrences during the 12 weeks that they were taking modafinil. Fatigue was reported by 5 participants (9.8%), dizziness was reported by 4 participants (7.8%), and nausea and tremor were reported by 3 (5.9%) participants. With placebo treatment, 2 adverse events were reported by 5% or more of the 51 participants. Like with modafinil, headaches were the most commonly reported adverse event. Ten (19.6%) participants reported a total of 33 headaches during the 12 weeks that they were taking placebo. Nasopharyngitis (common cold) was reported by 3 (5.9%) participants under the placebo treatment modality. Insomnia was reported significantly more with modafinil than with placebo ($P = .03$; chi-square test).

Blinding

In the first period, 15/24 (62.5%) of the placebo patients and 13/25 (52%) of the modafinil patients

TABLE 4 *Unadjusted and adjusted mean differences on modafinil vs placebo for both periods combined*

	Week 4			Week 10		
Scale	**One-sample *t* test Mean (95%CI)**	***P*> |*t*|**	**Mixed model* Modafinil vs Placebo†**	**One-sample *t* test Mean (95%CI)**	***P*> |*t*|**	**Mixed model* Modafinil vs Placebo†**
FSS Total	0.00 (−5.45, 5.45)	1.000	−0.48 ± 1.88 (.7977)	−1.34 (−9.29, 6.60)	.7341	−1.40 ± 2.75 (.6129)
ESS Total	−1.43 (−3.05, 0.19)	.0831	−1.15 ± 0.49 (.0245)	−0.55 (−2.98, 1.89)	.6540	−0.51 ± 0.87 (.5623)
MFI Total	−3.39 (−11.7, 4.92)	.4134	−1.34 ± 3.08 (.6664)	−2.28 (−12.0, 7.40)	.6358	−1.35 ± 3.91 (.7319)
SF-12 Physical	−1.30 (−4.35, 1.75)	.3954	−1.40 ± 1.46 (.3439)	−0.83 (−4.17, 2.50)	.6167	−0.91 ± 1.49 (.5444)
SF-12 Mental	2.19 (−0.59, 4.98)	.1199	2.56 ± 1.37 (.0683)	1.09 (−1.45, 3.62)	.3918	0.81 ± 1.22 (.5071)
BDI-II Total	0.30 (−2.12, 2.73)	.8018	0.08 ± 1.17 (.9430)	−0.68 (−3.17, 1.82)	.5881	−0.93 ± 1.15 (.4244)
ImPACT Verbal Memory	−3.67 (−7.09, −0.26)	.0355	−3.76 ± 1.70 (.0318)	−1.81 (−4.41, 0.79)	.1670	−2.29 ± 1.26 (.0760)
ImPACT Visual Memory	−1.46 (−5.16, 2.25)	.4324	−1.67 ± 1.76 (.3484)	−3.07 (−6.44, 0.30)	.0727	−2.89 ± 1.66 (.0898)
ImPACT Visual Motor Speed	−0.91 (−2.25, 0.43)	.1802	−1.02 ± 0.64 (.1190)	0.35 (−1.26, 1.96)	.6654	0.44 ± 0.74 (.5524)
ImPACT Reaction Time	−0.01 (−0.03, 0.02)	.6465	−0.00 ± 0.01 (.7142)	−0.01 (−0.03, 0.02)	.5698	−0.01 ± 0.01 (.5297)
CCPT-II No. of Omissions	1.25 (−0.43, 2.93)	.1418	1.66 ± 0.72 (.0252)	−2.05 (−8.79, 4.69)	.5429	1.72 ± 1.49 (.2543)
CCPT-II No. of Commissions	−0.04 (−1.49, 1.41)	.9541	0.02 ± 0.72 (.9822)	1.36 (−0.08, 2.80)	.0638	1.36 ± 0.66 (.0462)

*Estimated treatment effect adjusted for baseline value and period effects.
†Parameter estimates are: estimate ± standard error (*P* value).

TABLE 5 *Adverse events*

	Modafinil		Placebo	
	n	%	*n*	%
Headache	15	29.41	10	19.61
Insomnia	10	19.61	2	3.92
Fatigue	5	9.80	2	3.92
Dizziness	4	7.84	2	3.92
Nausea	3	5.88	1	1.96
Tremor	3	5.88	0	0.0
Nasopharyngitis	1	1.96	3	5.88

correctly guessed their treatment group. In the second period, 13/24 (54.2%) of the placebo and 11/23 (47.8%) of the modafinil patients correctly guessed their treatment assignments. None of these percentages are significantly different from 50%; thus, participant blinding was considered to be effective. Data collectors and data analysts were also blinded to treatment allocation until after initial interpretation of the results.

DISCUSSION

This study provides evidence that in this small population of persons with chronic TBI, modafinil is safe and well tolerated but is not effective in treating fatigue. There were no statistically significant differences in a number of subjective and objective fatigue measures when participants were taking modafinil versus placebo. Our findings demonstrate that fatigue symptoms may exhibit a substantial placebo effect in pharmaceutical studies and questions the utility of open-label studies of fatigue. Our study suggests that modafinil does not exhibit any additional benefit.

Our results are consistent with the findings of other studies that have not found modafinil to be effective for the treatment of fatigue in multiple sclerosis,[67] schizophrenia,[68] Parkinson disease,[69] and postpolio syndrome.[70] Residual fatigue in patients with depression treated with selective serotonin reuptake inhibitors may be a possible exception.[71–73] Several uncontrolled studies have found significant improvements in fatigue,[74–76] although our study suggests that these findings may largely be explained by the substantial placebo effect. The results of our study, along with previous studies, suggest that fatigue after TBI is a complex, multifactorial phenomenon.

Several studies have found modafinil to be effective for the treatment of EDS in various populations and it may also be effective in chronic TBI. The relationship between fatigue and sleepiness is not straightforward,[77] and participants in this study did exhibit a statistically significant difference between modafinil and placebo on the ESS at 4 weeks. However, these differences were no longer present at 10 weeks, suggesting that only time-limited, short-term use of modafinil may be beneficial. Furthermore, although statistically significant, no correction for multiple comparisons was made and the clinical significance of these findings is unclear. One researcher has suggested that a difference in ESS total score of 6 points is needed for a change to be considered reliable.[78]

Likewise, on the objective neuropsychological tests, there were sporadic statistically significant differences between modafinil and placebo, but there was no consistent pattern of improvement when taking modafinil.

Overall, the adverse event profile resembled that seen in a larger 21-center trial in patients with narcolepsy, where headaches were most common on placebo and modafinil, while nausea and rhinitis were more common on modafinil than placebo.[22] In the present study, insomnia was significantly more common while taking modafinil, but in most cases the medication was well tolerated and did not result in discontinuation of the medication. There were 4 discontinuations while participants were taking modafinil, and 1 while taking placebo (see Fig 1). One withdrawal was for suspected, but not confirmed, seizures and one each for tremors and nausea.

There are several limitations to the study that affect both the internal validity and the generalizability of the findings. First, the study population was limited to a single center treating moderate to severe TBI. The findings may not apply to the larger number of individuals with mild TBI. Furthermore, the sample showed a high level of depressive symptoms, which may not be representative of the general population of individuals with TBI. Second, a number of outcomes were assessed and multiple statistical tests were performed, making it possible that statistically significant findings were due to random variation. Third, the clinical significance of our findings is complicated by the fact that most participants elected to continue with the open-label phase of the study. This may suggest that modafinil had unmeasured benefits, or simply reflect an eagerness to receive free medication. A clinical global impression measure may have helped clarify the issue. Anecdotally, participants suggested that the fatigue measures used in the study may not accurately reflect the fatigue experienced by individuals with TBI and may suggest the need for better measures. Finally, the validity of self-report measures in TBI may be questioned.

Although this study does not support the use of modafinil in treating fatigue in individuals with TBI, individual responses were certainly variable, and it is possible that certain subgroups may benefit more than others. We are currently doing exploratory analyses that may identify characteristics that could be used to help

guide future studies within specific subgroups of individuals with TBI.

CONCLUSION

In this randomized controlled study of fatigue in individuals with moderate to severe TBI, there was no significant difference between treatment with modafinil and placebo over a 10-week period. Although a statistically significant improvement in excessive daytime sleepiness was seen at 4 weeks, the clinical relevance of this finding is unclear. Future studies may consider the possibility of needing outcome measures that are specific to the fatigue experienced by individuals with TBI.

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