MIDAS (Modafinil in Debilitating Fatigue After Stroke)
A Randomized, Double-Blind, Placebo-Controlled, Cross-Over Trial

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Background and Purpose—This study aimed to assess the efficacy of modafinil, a wakefulness-promoting agent in alleviating post-stroke fatigue ≥3 months after stroke. We hypothesized that 200 mg of modafinil daily for 6 weeks would result in reduced symptoms of fatigue compared with placebo.

Methods—This single-center phase 2 trial used a randomized, double-blind, placebo-controlled, crossover design. The key inclusion criterion was a multidimensional fatigue inventory score of ≥60. Patients were randomized to either modafinil or placebo for 6 weeks of therapy, then after a 1 week washout period swapped treatment arms for a second 6 weeks of therapy. The primary outcome was the multidimensional fatigue inventory; secondary outcomes included the Montreal cognitive assessment, the Depression, Anxiety, and Stress Scale (DASS), and the Stroke-Specific Quality of Life (SSQoL) scale. The multidimensional fatigue inventory is a self-administered questionnaire with a range of 0 to 100. Treatment efficacy was assessed using linear regression by estimating within-person, baseline-adjusted differences in mean outcomes after therapy. This trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12615000350527).

Results—A total of 232 stroke survivors were screened and 36 were randomized. Participants receiving modafinil reported a significant decrease in fatigue (multidimensional fatigue inventory, −7.38; 95% CI, −21.76 to −2.99; $P<0.001$) and improved quality of life (SSQoL, 11.81; 95% CI, 2.31 to 21.31; $P=0.0148$) compared with placebo. Montreal cognitive assessment and DASS were not significantly improved with modafinil therapy during the study period ($P>0.05$).

Conclusions—Stroke survivors with nonresolving fatigue reported reduced fatigue and improved quality of life after taking 200 mg daily treatment with modafinil.

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Stroke is the leading cause of adult disability in the developed world; however, there are no available pharmacotherapies outside the acute period to improve the outcome or quality of life of stroke survivors. Fatigue affecting the activities of daily living after a stroke or transient ischemic attack is a common problem, with many series reporting over 50% of patients complaining of fatigue for months or years post stroke. [1] Post-stroke fatigue is a predictor of dependency in activities of daily living and is also associated with increased morbidity and mortality.[2] Persisting fatigue impairs concentration, motivation, and mood and can interfere with engagement in physical and cognitive rehabilitation, limiting the effectiveness of rehabilitation strategies.[3,4]

Post-stroke fatigue may result from one or multiple overlapping mechanisms, such as sleep apnea,[5] decreased cortical excitability,[6] pain,[7] or decreased cardiorespiratory fitness.[8] Current strategies to assist patients manage post-stroke fatigue generally involve conventional physical rehabilitation approaches, which have limited evidence to support their effectiveness in clinical practice.[9]

Modafinil is a wakefulness-promoting agent that stimulates monoaminergic pathways to increase the release of histamine, norepinephrine, serotonin, dopamine, and orexin.[10] Modafinil has also been hypothesized to have neuroprotective properties through enhancement of antioxidative processes to reduce free radical formation in neurons[11] as well as being a central nervous system stimulant that increases the cortical pool of neurotransmitters, which may, in turn, promote neural recovery.[12] Modafinil has limited known drug interactions and side effects, making it a potentially attractive therapeutic option

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for elderly individuals. It has been licensed for the treatment of sleep disorders. Modafinil has been tested in clinical trials to alleviate fatigue in multiple sclerosis and inpatient stroke patients with mixed results in small or incomplete studies.[13,14]

The aim of this trial was to assess the effects of modafinil in strokes survivors, 3 or more months after their event with significant fatigue as measured by the multidimensional fatigue inventory (MFI). Patients with recognized causes of fatigue including a diagnosis of sleep apnea were excluded. We hypothesized that in this population, where fatigue was not self-resolving, 200 mg of modafinil daily for 6 weeks would reduce the symptoms of fatigue compared with placebo.

Methods

This was a phase 2, single-center, randomized trial using a double-blind, placebo-controlled, crossover design. Patients were randomized 1:1 to either modafinil or placebo for the initial 6 weeks of treatment, then, after a 1 week, washout period were crossed-over into the alternate treatment arm for a second 6 weeks of therapy. This study was approved by the Hunter New England Area Health District Human Research Ethics Committee and the protocol published[15] and registered with the Australian New Zealand Clinical Trials Registry (ACTRN12615000350527). The trial was performed at the John Hunter Hospital, Australia, and participants provided written informed consent.

Study Population

Post-stroke patients were recruited from the Newcastle (New South Wales, Australia) community and from stroke clinics at John Hunter Hospital. Inclusion criteria were patients >18 years of age with a history of stroke at least 3 months previously and a score of ≥60 across all domains of the MFI-20, which has a healthy population mean score of 35 to 40.[16] All participants were required to provide informed consent. Exclusion criteria were known contraindications to modafinil: renal impairment, causes of other clinically recognized cause of fatigue such as narcolepsy, use of benzodiazepines or anti-epileptic drugs and pre-existing depression, dementia, or other neuropsychiatric disease. Patients with a recognized diagnosis of sleep apnea were excluded. Patients were excluded if the enrolling neurologist suspected possible sleep apnea due to patient reported snoring, difficulty breathing during sleep or sleeping during the day during a task.

Randomization and Masking

The study was conducted at the Hunter Medical Research Institute (HMRI) Clinical Trials Support Unit. Participants were randomized 1:1 to 200 mg modafinil per day or placebo. The placebo was manufactured to be physically identical to the modafinil tablets and contained rice powder. A computer-generated randomization schedule was developed by the HMRI Clinical Research Design, IT, and Statistical Support (CReDITSS) unit, and randomization was administered by the clinical trials pharmacy independent of study researchers.

Treatment

Patients were instructed to take one pill per day with breakfast or in the morning. All participants were provided with a 6 weeks supply of study drug after randomization. After 6 weeks, participants were asked to return to the study center for clinical assessments and to return any unused study drug to assess compliance. After the study drug had been returned, participants underwent a 1 week washout period. On completion of the washout period, participants again returned for outcome assessments and were crossed-over to the alternate study medication. After 6 weeks on the second round of study drug, participants again returned for outcome assessments and to return study drug bottles to assess compliance. Double blinding was maintained throughout the duration of the trial with only the clinical trials pharmacist aware of treatment allocation. All patient assessments were carried out in the morning.

Outcome Assessment

Assessments were carried out at baseline, in the last week of the first 6-week treatment arm, after a 1-week washout period, and in the last week of the second 6-week treatment arm (Figure 1). The assessments at each time point included the MFI, the Montreal cognitive assessment, the Fatigue Severity Scale (FSS), the Depression, Anxiety, and Stress Scale (DASS), and the Stroke-Specific Quality of Life (SSQoL) scale. All assessments were carried out by research staff blinded to treatment. Drug adherence was monitored through tablet return for each patient in each stratum (placebo or active drug).

The MFI is a 20-item self-administered fatigue questionnaire designed to measure 5 fatigue domains: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. Each item is scored from 1 to 5 with higher scores indicating greater fatigue. The scores within each domain are summed to a total of 20, with a whole MFI score of 100. The MFI has been developed[17] and validated[18] to demonstrate limited item redundancy, good reliability, strong construct viability, validity in disease, and healthy populations, with limited floor/ceiling effect.[13] The Montreal cognitive assessment is a 1 page, 30-point cognitive test designed to assess short-term memory recall, visuospatial abilities, executive function, attention, concentration, working memory, and language. The FSS is a 9-item self-administered questionnaire; each item is scored from 1 to 7 with higher scores reflecting more fatigue. The FSS has also been tested to demonstrate its validity, internal consistency, and discriminatory power to differentiate diseased and healthy populations[19,20] and is reported as a median. The DASS42 is a 42-item self-reported score consisting of statements, which participants must rate each item 0 to 3 and is designed to assess depression, anxiety, and stress. Finally, the SSQoL is a disease-specific quality of life measure consisting of 49 items assessing 12 domains, which include social roles, mobility, energy, language, self-care, mood, personality, thinking, upper extremity function, family roles, vision, and work/productivity. Each item of the SSQoL is ranked on a 5-point scale.

Adverse events were followed closely by the Hunter Medical Research Institute clinical trials support unit by a research coordinator not otherwise involved in the study. All adverse events were registered by interview through monthly phone calls and review of patient files at each visit.

Statistical Analysis

The study was designed to have 80% power to detect a 10-point decrease in self-reported fatigue on the MFI after 6 weeks of modafinil treatment with a type I error rate of 0.05 and assuming a SD in the patient population of 14. A total sample size of 34 was required for a crossover study using previously reported effects of modafinil on fatigue for Parkinson's disease,[10] multiple sclerosis,[21] and a Cochrane review.[22] Assuming modest participant drop out and study drug compliance, we aimed to recruit 36 participants in total.

For the primary outcome, treatment efficacy was assessed by estimating within-person, baseline-adjusted differences in mean MFI after modafinil versus placebo. This involved fitting a linear regression with fixed effects for participants, treatment (modafinil or placebo) and the baseline outcome measure for each treatment. The treatment effect was expressed as the mean within-person, baseline-adjusted treatment effect with its 95% confidence interval and *P* value. Significance was assessed at the 0.05 level for the single primary outcome. The same significance level was used for each secondary outcome.[12]

For the primary outcome, a potential crossover effect was assessed via 2 sensitivity analyses: (1) estimating treatment effects using period 1 data only and (2) fitting the primary regression model to the data and including terms for treatment sequence and an interaction between treatment group and treatment sequence. The interaction

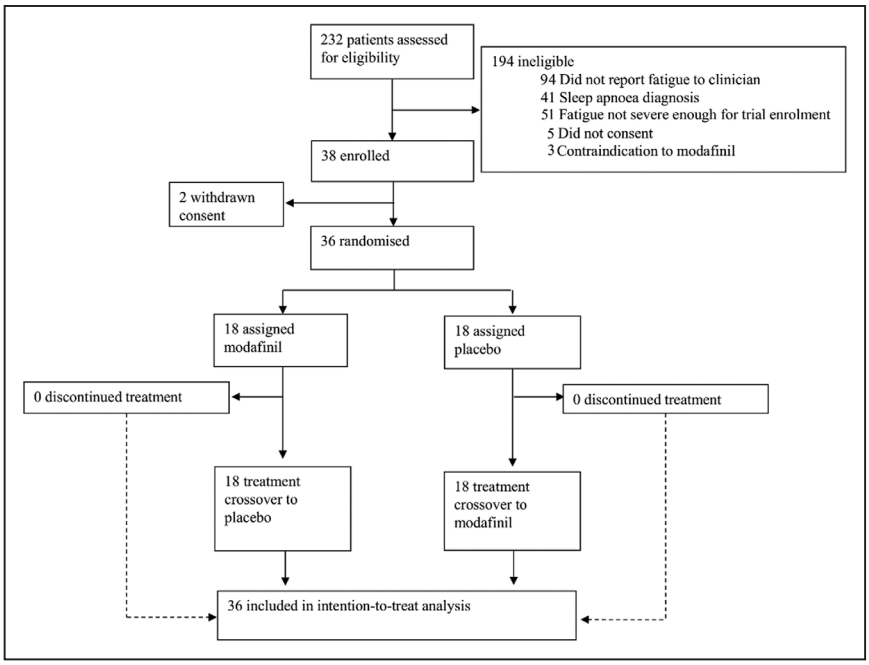

Figure 1. Patient flow for the MIDAS trial (Modafinil in Debilitating Fatigue After Stroke). Patients were enrolled after screening to target patients with severe fatigue and were then randomized to either placebo or modafinil for 6 weeks, and after a 1-week wash out period were crossed over treatment arms.

term was assessed for evidence of differential treatment effects by treatment sequence, using a significance level of 0.05. For all secondary outcomes, treatment effects were estimated using the same regression model as for the primary outcome and a significance level of 0.05. Statistical analyses were programmed using SAS v9.4 (SAS Institute, Cary, NC, USA).

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

After screening 232 potentially eligible patients during the study period with stroke or transient ischemic attack ≥3 months previously, 38 patients met the eligibility criteria and consented to the trial. The great majority of screened patients were excluded because of an MFI score of <60 (Figure 1). Two of the 38 eligible patients were later excluded from the trial; one withdrew consent before receiving medication and one received alternative treatment before trial therapy commencement. The study analysis refers to the remaining 36 randomized patients. Participant baseline characteristics are presented in Table 1: the mean age was 63 years (SD, 15) and baseline fatigue severity was 72 on the MFI (SD, 8.7). Patients mean time post stroke was 9 months (range 3–38 months), with 61% being male (22 male and 14 female). Of the enrolled patients, 33 were initially diagnosed as ischemic stroke and three were hemorrhages. For the patients with ischemic stroke, the median baseline National Institutes of Health Stroke Scale (NIHSS) for the patients with stroke at admission was 13 (SD 4) and all 33 had received alteplase.

Participants receiving modafinil reported a significant decrease in fatigue compared with those receiving placebo (differences in means, modafinil–placebo −7.38; 95% CI, −21.76 to −2.99; P<0.001; Figure 2). Participants also reported a significant reduction in symptom severity for every MFI domain (Table 2). At the conclusion of treatment period 1, participants who had received placebo (n=18) had a mean MFI of 58 (SD, 11), whereas participants who had received modafinil (n=18) had a mean MFI of 50 (SD, 13). Participants who received modafinil for treatment period 1 saw a restoration of the mean MFI score after the washout period (mean MFI post-treatment period 1 50, SD 13, mean MFI postwashout in patients who received modafinil 59, SD 15). At the conclusion of treatment period 2, participants who had received modafinil in period 2 (crossing over from placebo after period 1) had a mean MFI of 48 (SD, 16), whereas those who had received placebo (crossing over from modafinil after period 1) had a mean MFI of 59 (SD, 15). Treatment effects were, thus, similar for the 2 treatment sequences, and there was no significant interaction between the treatment effect and treatment sequence (P=0.299), suggesting a lack of bias because of a crossover effect. The alternate self-reported fatigue assessment, the FSS was also significantly reduced with modafinil treatment (differences in means −6.31; 95% CI, −10.69 to −1.92; P=0.0048).

Participants also reported a significant improvement in quality of life (SSQoL differences in means, modafinil–placebo 11.81; 95% CI, 2.31–21.31; P=0.0148; Table 3). Within

Table 1. Participant Baseline Characteristics

Baseline Variable	Total (n=36), Mean (SD)	Placebo Then Modafinil (n=18), Mean (SD)	Modafinil Then Placebo (n=18), Mean (SD)
Age, y	63 (15)	65 (14)	60 (15)
MFI: Total	72.0 (8.7)	69.6 (7.5)	74.4 (9.3)
SSQoL: Total	152.6 (35.7)	162.7 (33.9)	142.4 (35.5)
DASS: Total	43.9 (30.6)	41.4 (27.6)	46.4 (34.0)
FSS: Total	50.3 (11.0)	49.1 (8.9)	51.4 (12.9)
MoCA: Total	22.4 (5.0)	22.4 (5.3)	22.5 (4.7)

DASS indicates Depression, Anxiety, and Stress Scale; FSS, Fatigue Severity Scale; MFI, multidimensional fatigue index; MoCA, Montreal cognitive assessment; and SSQoL, Stroke-Specific Quality of Life.

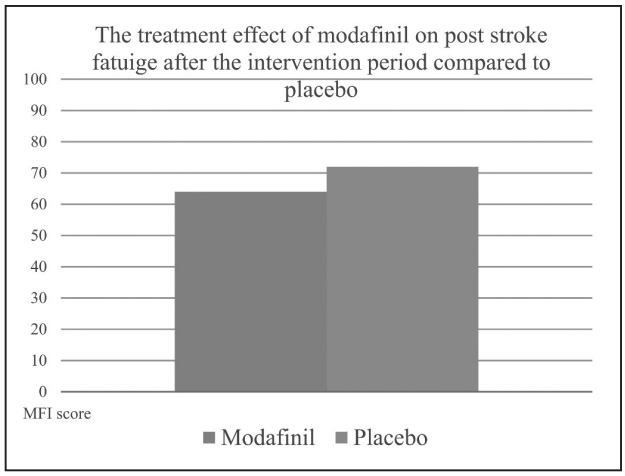

Figure 2. The primary outcome for the MIDAS trial (Modafinil in Debilitating Fatigue After Stroke). There was a statistically significant decrease in the self-reported fatigue score of patients randomized to modafinil during the trial period. MFI indicates multidimensional fatigue inventory.

the domains of the SSQoL, modafinil therapy significantly improved self-reported energy (differences in means 1.37; 95% CI, 0.16–2.58; *P*=0.0269), mobility (differences in means 2.07; 95% CI, 0.57–3.57; *P*=0.0069), social roles (differences in means 1.66; 95% CI, 0.07–3.26; *P*=0.0413), vision (differences in means 0.8; 95% CI, 0.11–1.49; *P*=0.0234), and thinking (differences in means 0.96; 95% CI, 0.09–1.83; *P*=0.0314; Table 3). The remaining SSQoL domains of family, language, mood, personality, work, self-care, and upper extremity did not significantly improve with modafinil therapy (*P*>0.05).

Mood assessment using the DASS did not change significantly in those randomized to modafinil (differences in means 0.87; 95% CI, −0.75 to 2.49; *P*=0.2916), nor did the DASS subdomains change significantly (*P*>0.05; Table 4). Overall cognitive performance assessed using the Montreal cognitive assessment also did not alter significantly with modafinil (differences in means 0.32; 95% CI, −0.37 to 1.00; *P*=0.365). However, the Montreal cognitive assessment subdomains of abstraction (differences in means 0.12; 95% CI, 0.01–0.22; *P*=0.0266), and visuospatial ability (differences in means 0.2; 95% CI, 0.04–0.36; *P*=0.0121; Table 4) showed improvement with modafinil.

During the trial period of 13 weeks, there were 12 adverse events (modafinil=5, placebo=7), but no serious adverse events. The adverse events included headache (4), nausea (1), anxiety (2), agitation (3), and dizziness (2).

Table 2. Trial Results on the Primary Outcome of the MFI

Outcome	Difference in Means: Modafinil–Placebo	95% CI	*P* Value
MFI: Total	−7.38	−21.76 to −2.99	<0.0001
MFI: Activity	−3.82	−5.22 to −2.42	<0.0001
MFI: General	−4.10	−5.06 to −3.14	<0.0001
MFI: Mental	−2.86	−3.68 to −2.03	<0.0001
MFI: Motivation	−2.96	−4.02 to −1.90	<0.0001
MFI: Physical	−3.63	−4.71 to −2.55	<0.0001
FSS:	−6.31	−10.69 to −1.92	0.0048

Treatment with modafinil resulted in a significant decrease in participant self-reported MFI score (multidimensional fatigue index). Each MFI domain also saw a significant decrease in symptom severity. The secondary fatigue measure, the FSS (Fatigue Severity Scale) also saw a significant reduction in participant self-reported fatigue with modafinil therapy.

Table 3. Trial Results on the Secondary Outcome of the SSQoL

Outcome	Difference in Means: Modafinil–Placebo	95% CI	*P* Value
SSQoL: Total	11.81	2.31 to 21.31	0.0148
SSQoL: Energy	1.37	0.16 to 2.58	0.0269
SSQoL: Family	0.70	−0.12 to 1.51	0.0927
SSQoL: Language	0.10	−0.88 to 1.07	0.8490
SSQoL: Mobility	2.07	0.57 to 3.57	0.0069
SSQoL: Mood	0.67	−0.86 to 2.19	0.3922
SSQoL: Personality	1.06	−0.11 to 2.23	0.0759
SSQoL: Social Roles	1.66	0.07 to 3.26	0.0413
SSQoL: Vision	0.80	0.11 to 1.49	0.0234
SSQoL: Work	0.39	−0.62 to 1.39	0.4524
SSQoL: Self Care	1.18	−0.24 to 2.60	0.1023
SSQoL: Thinking	0.96	0.09 to 1.83	0.0314
SSQoL: Upper Extremity	0.83	−0.42 to 2.08	0.1908

Treatment with modafinil resulted in a significant decrease in participant SSQoL score (Stroke-Specific Quality of Life). Within the domains of the SSQoL, modafinil therapy significantly improved self-reported energy, social roles, vision, and thinking. The remaining SSQoL domains of family, language, mood, personality, work, self-care, and upper extremity did not significantly improve with modafinil therapy (<0.05).

Discussion

This study, the first of its kind in chronic stroke, has demonstrated that self-reported post-stroke fatigue is significantly reduced after 6 weeks of modafinil therapy compared with placebo. In addition to the reduction in fatigue, it was observed that there was a significant improvement in participants' quality of life. The secondary fatigue measure, the FSS, also showed a significant reduction in participants' self-reported fatigue, confirming the primary end point. However, no significant change was reported for mood or cognition with modafinil therapy. These positive findings are encouraging, but preliminary, owing to the small size of the study.

The reported significant improvement in patient quality of life was due mainly to improvement in the subdomains of energy, mobility, social roles, vision, and thinking, which are critically important aspects of post-stroke life. Although there was no statistically significant improvement in the subdomains of family, language, mood, personality, work, upper limb

Table 4. Treatment With Modafinil Did Not Result in Improved Mood as Measured on the DASS or Cognition as Measured on the MoCA for This Trial

Outcome	Difference in Means: Modafinil–Placebo	95% CI	*P* Value
DASS: Total	−0.76	−5.80 to 4.29	0.7688
DASS: Anxiety	0.87	−0.75 to 2.49	0.2916
DASS: Depression	−0.06	−2.33 to 2.21	0.9608
DASS: Stress	−1.43	−2.98 to 0.11	0.0684
MoCA: Total	0.32	−0.37 to 1.00	0.3650
MoCA: Abstraction	0.12	0.01 to 0.22	0.0266
MoCA: Attention	0.08	−0.25 to 0.40	0.6509
MoCA: Language	−0.13	−0.31 to 0.06	0.1872
MoCA: Naming	−0.02	−0.13 to 0.10	0.7937
MoCA: Orientation	0.03	−0.16 to 0.23	0.7288
MoCA: Recall	−0.23	−0.49 to 0.04	0.0949
MoCA: Visuospatial	0.20	0.04 to 0.36	0.0121

There was some evidence for a reduction in DASS measured stress and the MoCA subdomains of abstraction and visuospatial did significantly improve with modafinil therapy. DASS indicates Depression, Anxiety, and Stress Scale; and MoCA, Montreal cognitive assessment.

mobility, or self-care, this may be because of the small study sample size or that these aspects of post-stroke life require additional interventions. These results also suggest that there is some specificity of the effects of modafinil. A recent study of modafinil therapy in a more acute population of patients with stroke in hospital, which did not recruit to target, was not able to show a treatment effect of modafinil on the MFI.[14] Of note is that the placebo group in this study also had a decline in fatigue during their hospital stay, something often observed in the initial recovery phase after acute stroke.[23] Importantly, our study assessed patients more than 3 months post-stroke, rather than in the in-hospital setting. By limiting our study recruitment to patients with established and persisting fatigue, we were able to observe a treatment effect. Finally, the number of adverse events presented in this trial was much lower than a previous trial.[20] This may also relate to the differences between patient populations, one was an in-hospital patient cohort, ours a subacute community-dwelling patient population. In this subacute post-stroke population, our data suggest that modafinil is not associated with any significant increase in adverse events.

A cross-over design can help reduce the influence of potential confounding, where patients have unrecognized causes of fatigue, in that each participant acts as their own control. This study design also allowed for a reduction in the required sample size because of a within-patient assessment. A potential disadvantage, however, is that if significant patient drop out occurs, this can result in a severe statistical penalty. Fortunately, this did not occur. Finally, the study dose of 200 mg daily for 6 weeks is half the maximum safe daily approved dose for modafinil in sleep disorders. For this study, 200 mg was chosen, in part, because there is not noticeable gain in therapeutic benefit over 200 mg, and also because of the older patient population studied (compared with previous studies in multiple sclerosis where 400 mg was used).

The neurophysiological mechanisms causing post-stroke fatigue have yet to be fully elucidated; however, previous studies in patients with stroke,[24,25] and others having chronic fatigue,[26] have provided some insight. Electrophysiological and functional magnetic resonance imaging studies have demonstrated the presence of a striato-thalamic-frontal "facilitation" circuit that acts to increase output from the primary motor cortex to compensate for fatigue and maintain performance during activity. Chronic fatigue syndrome has been shown to be associated with dysfunction of the motor facilitation circuit and sensitization of a counteracting "inhibition" circuit centered in the insular cortex and posterior cingulate cortex. Both of these processes could also play a role in post-stroke fatigue. In particular, disruption of the motor facilitation circuit would translate to reduced physical tolerance, which is widely described in survivors with stroke,[23] as has a reduction in motor cortex excitability.[27] While this was a small cohort and care should be taken in extrapolating such results, it is conceivable that restoring some functions to the facilitation circuits through a central nervous system stimulant such as modafinil would improve subjective fatigue.

For this trial, several limitations should be noted. This study excluded patients with a clinically suspected diagnosis of sleep apnea, a well recognized but treatable cause of sleepiness and fatigue. However, specific measures of sleepiness were not assessed at baseline or post intervention, thus, we cannot exclude that this study may still have included some patients with sleep apnea. Finally, despite assessing participant pill returns to ensure trial medication compliance, we cannot guarantee that participants consumed all trial medication that was not returned.

In conclusion, this study, a randomized, crossover, single-center, double-blinded, placebo-controlled trial of post-stroke fatigue treatment with 6 weeks of 200 mg daily modafinil therapy, has demonstrated a significant reduction in fatigue and improvement in quality of life during therapy. The results of this study suggest that it is appropriate to proceed to a phase 3 trial of longer-term modafinil therapy with the aim of alleviating post-stroke fatigue and improving quality of life.

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Disclosures

None.

References

1. Lerdal A, Gay CL. Fatigue in the acute phase after first stroke predicts poorer physical health 18 months later. *Neurology*. 2013;81:1581–1587. doi: 10.1212/WNL.0b013e3182a9f471.

2. Mücke M, Cuhls H, Peuckmann-Post V, Minton O, Stone P, Radbruch L. Pharmacological treatments for fatigue associated with palliative care. *Cochrane Database Syst Rev*. 2015;5:CD006788
3. Ingles JL, Eskes GA, Phillips SJ. Fatigue after stroke. *Arch Phys Med Rehabil*. 1999;80:173–178.
4. Wu S, Kutlubaev MA, Chun HYY, Cowey E, Pollock A, Macleod MR, et al. Interventions for post-stroke fatigue. *Cochrane Database of Systematic Reviews* 2015; 7:CD007030.
5. Arzt M, Young T, Peppard PE, Finn L, Ryan CM, Bayley M, et al. Dissociation of obstructive sleep apnea from hypersomnolence and obesity in patients with stroke. *Stroke*. 2010;41:e129–e134. doi: 10.1161/STROKEAHA.109.566463.
6. Kuppuswamy A, Clark EV, Turner IF, Rothwell JC, Ward NS. Post-stroke fatigue: a deficit in corticomotor excitability? *Brain*. 2015;138(pt 1):136–148. doi: 10.1093/brain/awu306.
7. Naess H, Lunde L, Brogger J, Waje-Andreassen U. Fatigue among stroke patients on long-term follow-up. The Bergen Stroke Study. *J Neurol Sci*. 2012;312:138–141. doi: 10.1016/j.jns.2011.08.002.
8. Egerton T, Chastin SF, Stensvold D, Helbostad JL. Fatigue may contribute to reduced physical activity among older people: An Observational Study. *J Gerontol A Biol Sci Med Sci*. 2016;71:670–676. doi: 10.1093/gerona/glv150.
9. Kutlubaev MA, Mead GE, Lerdal A. Fatigue after stroke–perspectives and future directions. *Int J Stroke*. 2015;10:280–281. doi: 10.1111/ijs.12428.
10. Gerrard P, Malcolm R. Mechanisms of modafinil: a review of current research. *Neuropsychiatr Dis Treat*. 2007;3:349–364.
11. Xiao YL, Fu JM, Dong Z, Yang JQ, Zeng FX, Zhu LX, et al. Neuroprotective mechanism of modafinil on Parkinson disease induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Acta Pharmacol Sin*. 2004;25:301–305.
12. Piérard C, Satabin P, Lagarde D, Barrère B, Guezennec CY, Menu JP, et al. Effects of a vigilance-enhancing drug, modafinil, on rat brain metabolism: a 2D COSY 1H-NMR study. *Brain Res*. 1995;693:251–256.
13. Brioschi A, Gramigna S, Werth E, Staub F, Ruffieux C, Bassetti C, et al. Effect of modafinil on subjective fatigue in multiple sclerosis and stroke patients. *Eur Neurol*. 2009;62:243–249. doi: 10.1159/000232927.
14. Poulsen MB, Damgaard B, Zerahn B, Overgaard K, Rasmussen RS. Modafinil may alleviate poststroke fatigue: A Randomized, Placebo-Controlled, Double-Blinded Trial. *Stroke*. 2015;46:3470–3477. doi: 10.1161/STROKEAHA.115.010860.
15. Lillicrap T, Krishnamurthy V, Attia J, Nilsson M, Levi CR, Parsons MW, et al. Modafinil In Debilitating fatigue After Stroke (MIDAS): study protocol for a randomised, double-blinded, placebo-controlled, cross-over trial. *Trials*. 2016;17:410. doi: 10.1186/s13063-016-1537-4.
16. Lin JM, Brimmer DJ, Maloney EM, Nyarko E, Belue R, Reeves WC. Further validation of the multidimensional fatigue inventory in a US adult population sample. *Popul Health Metr*. 2009;7:18. doi: 10.1186/1478-7954-7-18.
17. Smets EM, Garssen B, Bonke B. *Manual; Multidimensional Fatigue Inventory*. Amsterdam, the Netherlands: Medical Psychology, Academic Medical Center; 1995.
18. Smets EM, Garssen B, Bonke B, De Haes JC. The multidimensional fatigue inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res*. 1995;39:315–325.
19. Valko PO, Bassetti CL, Bloch KE, Held U, Baumann CR. Validation of the Fatigue Severity Scale in a Swiss cohort. *Sleep*. 2008;31:1601–1607.
20. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The Fatigue Severity Scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol*. 1989;46:1121–1123.
21. Ledinek AH, Sajko MC, Rot U. Evaluating the effects of amantadin, modafinil and acetyl-L-carnitine on fatigue in multiple sclerosis–result of a pilot randomized, blind study. *Clin Neurol Neurosurg*. 2013;115(Suppl 1):S86–S89. doi: 10.1016/j.clineuro.2013.09.029.
22. Sheng P, Hou L, Wang X, Wang X, Huang C, Yu M, et al. Efficacy of modafinil on fatigue and excessive daytime sleepiness associated with neurological disorders: a systematic review and meta-analysis. *PLoS One*. 2013;8:e81802. doi: 10.1371/journal.pone.0081802.
23. Duncan F, Greig C, Lewis S, Dennis M, MacLullich A, Sharpe M, et al. Clinically significant fatigue after stroke: a longitudinal cohort study. *J Psychosom Res*. 2014;77:368–373. doi: 10.1016/j.jpsychores.2014.06.013.
24. Kuppuswamy A, Clark EV, Turner IF, Rothwell JC, Ward NS. Post-stroke fatigue: a deficit in corticomotor excitability? *Brain*. 2015;138(pt 1):136–148. doi: 10.1093/brain/awu306.
25. Kuppuswamy A, Clark EV, Sandhu KS, Rothwell JC, Ward NS. Post-stroke fatigue: a problem of altered corticomotor control? *J Neurol Neurosurg Psychiatry*. 2015;86:902–904. doi: 10.1136/jnnp-2015-310431.
26. Tanaka M, Ishii A, Watanabe Y. Neural mechanisms underlying chronic fatigue. *Rev Neurosci*. 2013;24:617–628. doi: 10.1515/revneuro-2013-0035.
27. Liepert J, Mingers D, Heesen C, Bäumer T, Weiller C. Motor cortex excitability and fatigue in multiple sclerosis: a transcranial magnetic stimulation study. *Mult Scler*. 2005;11:316–321. doi: 10.1191/1352458505ms1163oa.

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